Section Four: Chapter 21: The Urinary System

Overview

Most people know some basic information about the kidneys, such as they act as a "filter" for the blood in our bodies. That is a very good start for understanding the kidneys. These relatively small organs work continuously to ensure that our blood is clean and stable by removing metabolic waste, toxins, any excess water and excreting them in urine. The entire blood supply of the body (about 5 liters) is filtered **30** to **40** times each day through the kidneys to maintain homeostasis. No machine ever devised could accomplish what the kidneys do. This begins to establish how important healthy kidneys are to the body.

Although urine is a waste by-product from cleansing the blood, in a healthy person it is **non-toxic** and **aseptic**. It typically contains **95% water**, **2.5% urea** and **2.5%** of other **mineral** salt mixtures and enzymes, and possibly trace amounts of other wastes depending on the diet and activity of the person.

The **urinary system** is also called the **renal system** and consists of **2 kidneys** (see **Figure 21.1** below), both of which constantly filter, cleanse and regulate the blood and body fluids. Each kidney has a **ureter** which is a tube that leaves the kidneys and carries the urine produced by the kidneys to the urinary **bladder** where it is stored. The **urethra** is a tube that transports the urine from the bladder to the external environment for the elimination or voiding of urine, termed **micturition**.

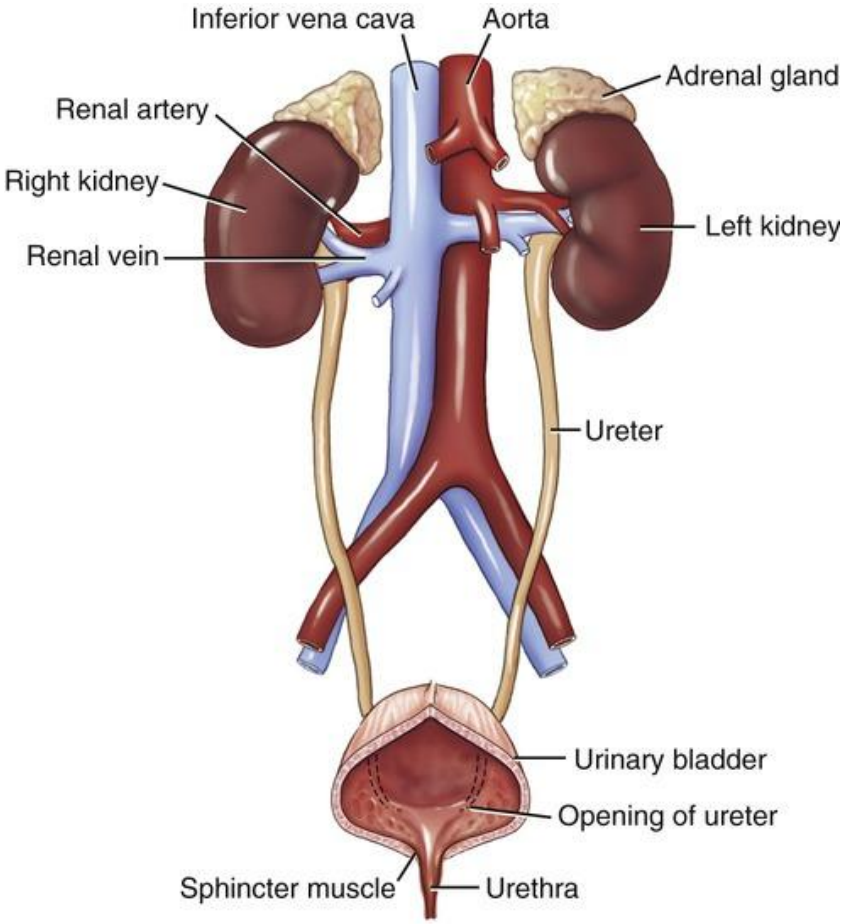


Figure 21.1 This diagram shows the renal system (kidneys, ureters, bladder and urethra) in context with the structures that are deeply integrated with it, including the significant vasculature and the adrenal glands.

In accomplishing its purpose, it will be seen that the renal system also closely regulates **blood volume** and **blood pressure**. It also maintains **osmolarity** of body fluids; regulates **blood pH**; and control levels of **electrolytes**. Although the urine eliminated is typically composed mostly of water, the composition of urine can be modified significantly as it is a direct reflection of the current state and needs of the body.

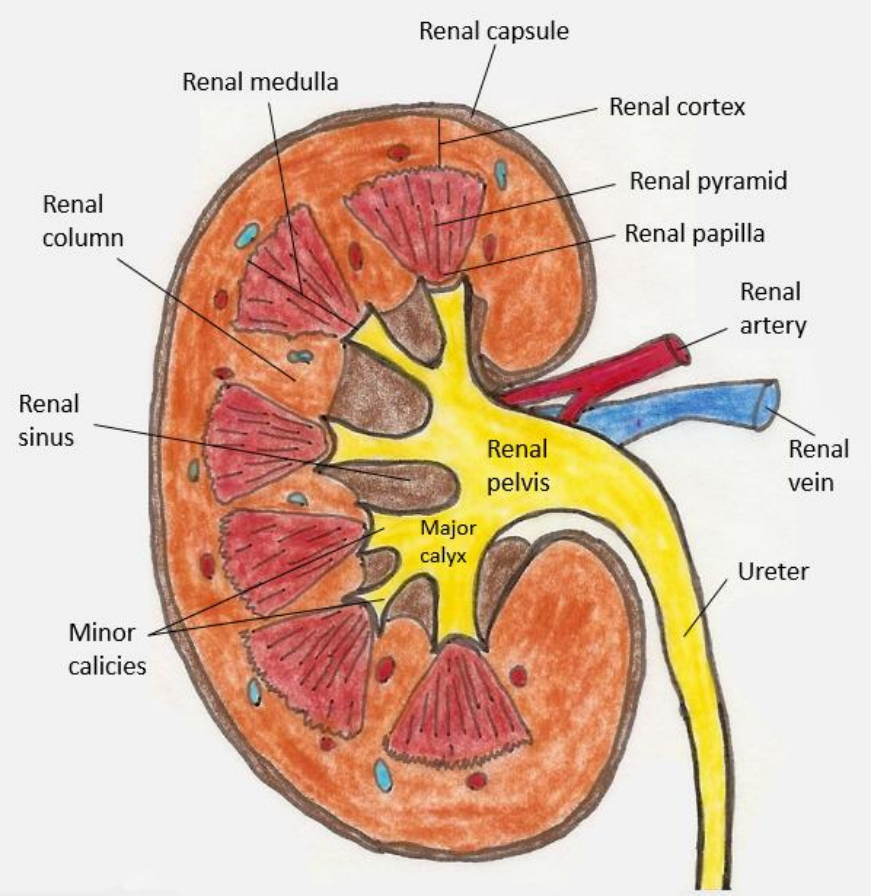
Urinalysis is an informative lab test process used to detect substances and cells in urine samples. This can assist in making an assessment of the function of the kidneys and the state of the entire body. A detailed exploration of urinalysis is described at toward the end of this chapter.

General Anatomical Location and Arrangement of the Urinary System

The 2 kidneys are situated on either side of the spine, just below rib 10 and so partially protected by ribs 11 and 12, just above the waist. Their location is described as ***retroperitoneal***, which means they are located behind the peritoneal lining of the abdominal cavity and are held in place by an adipose (fat) capsule and an outer renal fascia which secures their position. The kidneys receive **20-25%** of **cardiac output**, this is a large amount; consider that the brain only gets about 20% of cardiac output. This substantial amount reveals their critical filtration role. The **nephron** is the functional unit of the kidney.

Structure of the Kidney

The kidney, like all other organs in the body, is very well organized for its various functions. The basic anatomy (see **Fig. 21.2** below) shows how it is divided into the outer **renal cortex** portion and the inner **renal medulla** portion. The other major components and arrangements of the internal kidney are also seen, such as the renal pyramids and papilla, which deliver urine to the minor and major calicies. The urine then travels to the renal pelvis and exits the kidney via the ureter to be stored in the bladder.



Although the kidneys are fairly small, each one only weighing about **4.5 ounces**, they are very big with regard to their role in the body. The renal system is integrated one way or another into all the other systems of the body. Many of the concepts covered in previous chapters will re-present themselves in the amazing renal system. To give context to a real kidney, the image seen in **Fig. 21.2** to the left is a frontal section of the kidney, which is the same orientation seen in **Fig 21.3 b)** further below in the photo of a real kidney.

Figure 21.2 Frontal section drawing of a kidney showing the basic structures and regions including the renal capsule (outermost covering), the renal cortex (outer) and renal medulla (inner), as well as renal blood vessels and ureter.

In the drawing above, the systemic arterial blood can been seen as it arrives via the renal artery and leaves the kidney via the renal vein. Running in between these two vessels deep within the tissues of the kidney and not seen in any of these images, is an intricate network of arterioles and capillary beds that are arranged in a highly specialized way in order to **reabsorb 99% of the what is constantly filtered by the kidneys.** What this means is that when the kidneys filter this fluid (called **filtrate**), it returns 99% of it back to the blood before the blood vessels even leave the kidney. The vascular arrangement of the kidney's is incredibly precise and vital to human health, that is why it is an important focal point of renal function.

As we examine the detailed structure and function of the kidneys it will be seen that cleansing and carefully regulating the healthy composition of blood is a complex and elegant task that involves many of the elements we have previously covered in this physiology course.

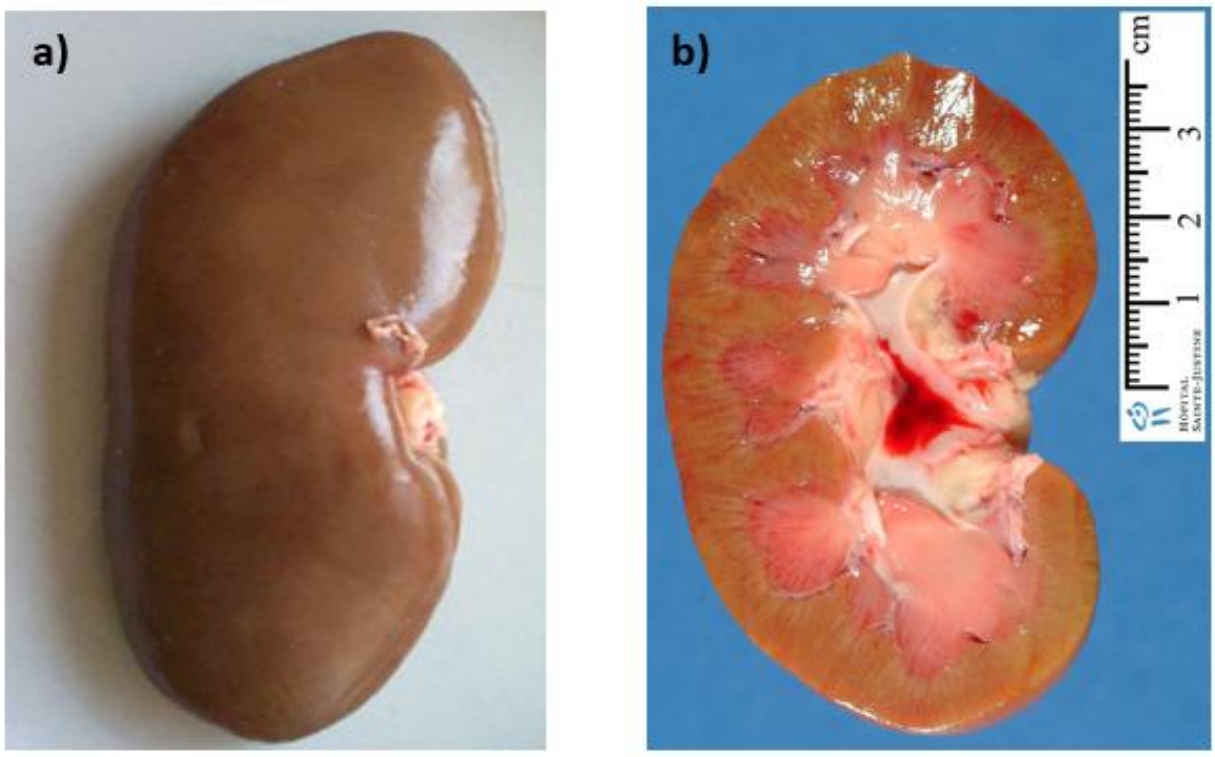
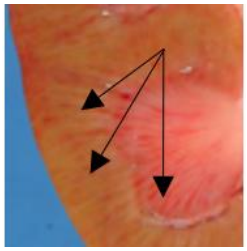


Figure 21.3 Shows photographs of **a)** the outer surface and **b)** a frontal section of a healthy kidney. Note the surface texture, colors and the highly vascular appearance of a healthy kidney. The scale in **b)** shows that these kidneys are about 3 inches (7.5 cm) in length.

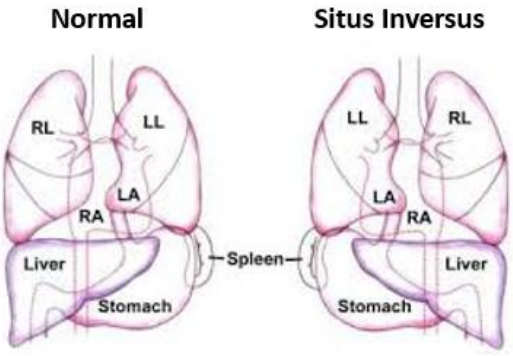
Typically (as seen in **Fig. 21.3** above) each kidney is about **4 to 5 inches long** (10 to 12 cm), maybe about 1.5 inches thick (3 to 4 cm), making it roughly the size of a large fist. The weight of kidneys varies, but each is usually from about **3 to 5 ounces** (from 100 to 150g). For the frontal section of the kidney, **b)** in **Fig. 21.2** above, notice the outer renal cortex is more brown and the inner medulla is pink and red. The renal hilus is where the renal blood vessels and ureter enter and exit the kidneys (at the dimple in the center).



The orientation of the many tubules and blood vessels of the kidney make patterns that can be seen in a real kidney with the naked eye (at left). The different colors of the tissue can also easily be seen. The outer renal cortex is a sort of **beige** color, with the inner renal medulla showing light **pink** where the renal pyramids are. Both of these region have tiny red blood vessels traveling across them (see arrows at left).

Finally, looking at the general anatomical placement of both kidneys in the body, **Fig. 21.1** notice that the right kidney is slightly lower than the left kidney. This is typical and normal, and is due to its slight downward displacement caused by the very large singular organ above it, the **liver**. Since the liver is usually always on the right side of the body, it is the right kidney that is pushed down by it.

There is a rare condition called **situs inversus** (viscerum) in which the internal organs in a person's chest and abdomen are 'inverted' as the etymology of the term implies. Situs inversus means 'inverted placing of the internal organs'. In this situation, the organs are positioned in a mirror image of normal human anatomy, in other words, they are reversed (see image at right). For example, a person's liver would be on their left side, their spleen and heart on the right side. Interestingly, nearly all organs in the chest and abdomen develop in the human body in the formation of left to right.



In a healthy human, the renal system produces from **1 to 2 Liters** of urine every day. That is essentially from 1 to 2 quarts! This amount varies according to fluid intake and kidney function. The female and male urinary systems are very similar, differing only in the length of the urethra.

Following the filtration of blood and further processing, **urine** is created containing various waste products that exit the kidney through the **ureters** which are tubes with smooth muscle enabling them to propel urine to the **bladder**, where it is temporarily stored. Urine is eliminated (expelled) from the urinary bladder by urination which is termed **micturition** (Latin micturire "to desire to urinate,") and is defined as the process of eliminating urine from the bladder via the **urethra**.

The *functional unit* of the kidney is the **nephron**, as it is the smallest structure that performs the function of the whole. There are approximately **1.25 million nephrons** in each kidney.

The 4 Processes of the Urinary System

The urinary system as a whole engages in **four (4) processes** that will be covered in very detailed ways as we examine this system. First though, here is a brief introduction to some important terms associated with the renal system, some simple descriptions of the 4 processes, followed by the *renal* specific definitions for these processes.

As will be explored fully in this chapter, it is a structure called the **nephron** that works to constantly filter the plasma of the body, recall that plasma is the fluid component of blood. As mentioned, the nephron is the ***functional unit of the kidney***, meaning it is the smallest structure that does the job of the whole.

In the process called **Filtration** (**F**) the kidneys produce filtrate at the rate **180L/day**, this is referred to as the **Glomerular Filtration Rate** (**GFR**). The substances the body needs to retain are recovered in a process called **Reabsorption** (**R**); additional substances can be added to the tubular filtrate by a process of **Secretion** (**S**) to fine tune and further regulate the blood; and finally, waste products we no longer need are eliminated by the process of **Excretion** (**E**) and this is voided in urine. These are each defined precisely in terms of renal processes below. Think of each of the 4 processes with the term renal before it, such as; **renal filtration**, **renal reabsorption**, **renal secretion** and **renal excretion**.

The Specific Definitions for the 4 Renal Processes:

- **Filtration** - the net movement of water and solutes from the glomerulus into the Bowman's capsule.
- **Reabsorption** - the net movement of water and solutes from the renal tubules into the peritubular and vasa recta capillaries (i.e., returned back to the body).
- **Secretion** - involves movement of substances from the peritubular or vasa recta capillaries of the body into the renal tubules (this material will be destined for elimination as urine if not reabsorbed).
- **Excretion** - this is the elimination of waste from the body by voiding it in urine.

Specific Functions of the Kidneys

1. Regulation of Extracellular Fluid Volume

Renal function contributes to **Mean Arterial Pressure** (MAP) by controlling the total volume of blood in the body. Remember this volume is about 5.0 L for a 150 lb. man. If blood volume become too high, for example after drinking a large amount of water, then more filtrate is created and therefore more fluid volume is excreted as urine; if blood volume is too low, fluid is conserved and urine excretion is decreased.

2. Regulation of Osmolarity

Osmolarity of body fluids should be between **295** and **310 mOsM** (a familiar range, right?). Principally, the osmolarity of blood is significantly controlled by altering the amount of water that is excreted in the urine. If excessive water intake decreases plasma osmolarity below about 280 mOsM, the kidneys remove the excess water by producing more dilute urine. If osmolarity of blood becomes hypertonic and goes up beyond 310 mOsM, the kidneys will act to conserve water, producing more concentrated urine.

3. Maintenance of Ion Balance

The concentrations of ions in the blood play a very important role in homeostasis and are therefore highly regulated. The renal system plays a significant role in constantly establishing ion balance in body fluids. The main ions discussed are: Na^+, K^+, Cl^-, Ca^{2+}, H^+, Mg^{2+} and PO_4^{3-}. However, there are many more ions, such as trace minerals, that are present in the body and regulated by the kidneys.

4. Homeostatic regulation of pH in body fluids

Selective secretion and reabsorption of $\mathbf{H^+}$ or $\mathbf{HCO_3^-}$ in the distal convoluted tubule of the nephron is the main way that the kidneys contribute to the maintenance of a stable pH of the body fluids.

5. Excretion of Metabolic Wastes Products

The renal system plays a fundamental role in the elimination of normal metabolic waste products that are always normally accumulating in the body. Substances like ***urea*** (a product of protein catabolism), ***uric acid*** (a product of nucleic acid catabolism) and ***creatinine*** (a waste product from muscle breakdown of a creatine) are continuously generates by the body, and therefore excreted in urine.

6. Excretion of Foreign Substances

The kidneys eliminate many unnatural **toxins** or **foreign substances** that may enter your body from a number of sources. These substances can include: Medications and other types of drugs; harmful chemicals such as pesticides, preservatives, additives, artificial colors, artificial flavors, poisons, etc., and even other organisms that might find their way into the bloodstream.

7. Production of Hormones

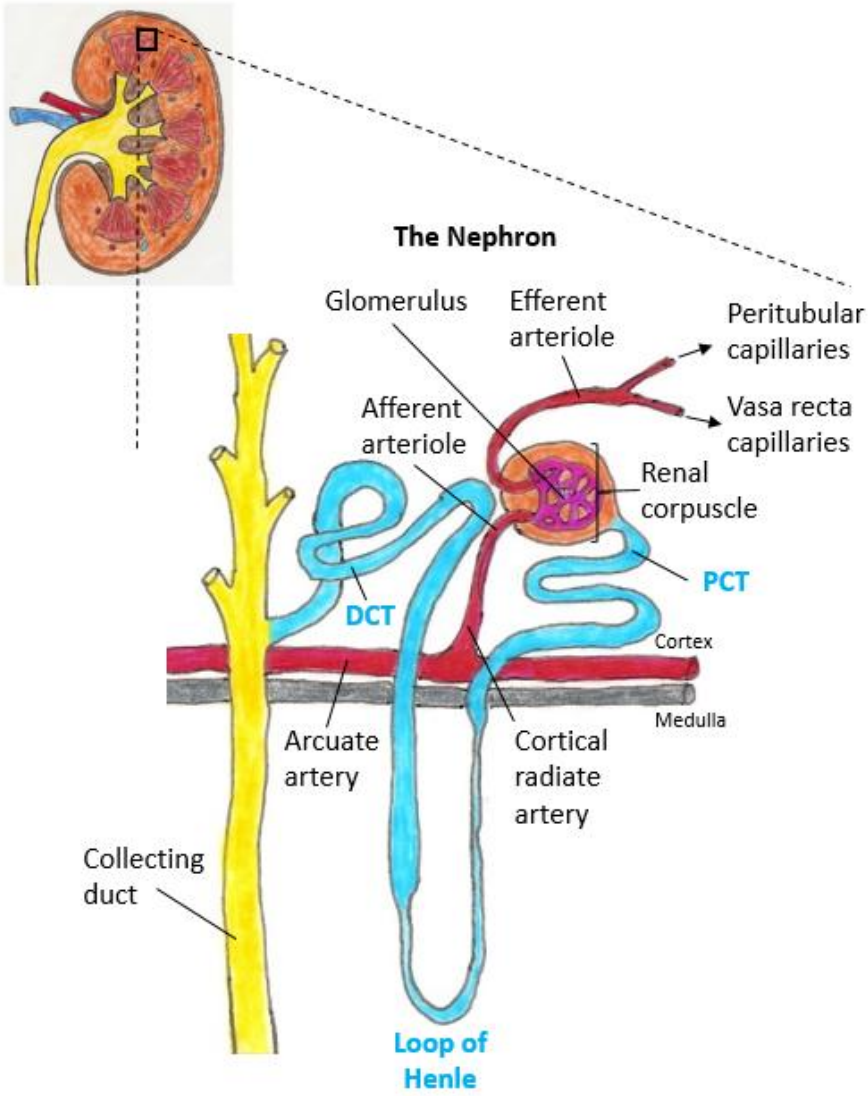
The renal system is considered a secondary **endocrine gland** because in addition to filtering the blood, it also releases <u>two hormones</u> which play a critical role in homeostasis. They are:

Renin – this is an enzyme/hormone made by the juxtaglomerular (JG) cells of the nephron, and released in response to a decrease in blood pressure, increases in blood osmolarity (hypertonicity) indicating the body's need to conserve water. The release of renin is the start of the **renin-angiotensin-aldosterone system** which impacts the entire body (see **Fig 21.19**).

Erythropoietin – released by peritubular cells of the renal cortex in response to **hypoxia** (low O_2 levels in the tissues) and it acts to stimulate red blood cell (RBC) production in the red bone morrow.

The Kidney

We have started to establish that the kidneys remove waste and extra water from the blood to create as a waste product called urine that is excreted from the body. They help to maintain the chemical balance of sodium, potassium, calcium, phosphates, etc. We also know that they act as a secondary endocrine gland, in that they make hormones that conserve water loss and maintain blood pressure (renin), and stimulate bone marrow to make red blood cells (erythropoietin). Since the **nephrons** are the functional unit of the kidneys, this small structure is where we will commence our focus. A zoom in of a diagrammatic depiction of a nephron is shown in **Fig. 21.4** at right.



There are two main components of the nephron, the **Renal Corpuscle** and the **Renal Tubule**. It is very useful to focus our examination of the nephron's function in these two regions because it will become clear that filtration occurs at the renal corpuscle and reabsorption and secretion occur in the renal tubules. The arrangement of these regions is clearly associated with their physiology, as we shall see.

Figure 21.4 From the base of a renal pyramid (inset at upper left) is a zoomed-in representation of a cortical nephron close to the juncture between the cortex and the medulla within the kidney. Seen in this representation is the relationship between the two components of the nephron, that is, the renal corpuscle (where the glomerulus is) and the 3 sections of the renal tubules that merge into the collecting duct.

The Nephron has 2 major Components

1. Renal Corpuscle: This is the proximal portion of the nephron in terms of renal function.

a) Glomerulus – this is a fenestrated capillary bed. It has pores in the endothelial cells which allows for a greater degree of filtration. The glomerulus is covered with podocytes that provide an additional layer of control to the glomerular filtration rate (GFR).

b) Bowman's space – the area around the glomerulus that captures the filtrate being produced.

c) Bowman's capsule – a capsule that is a modified continuation of the podocyte cells.

2. Renal Tubule: These three regions handle the filtrate made at the renal corpuscle.

a) Proximal Convoluted Tubule (PTC) – this is lined with cuboidal epithelial with microvilli called 'brush border' cells that create a vast surface area for absorption. This is the longest portion of the renal tubules and plays the most significant role in bulk reabsorption of filtrate.

b) Loop of Henle (LH) – this is lined with simple squamous and simple cuboidal epithelium without a brush border. It has a descending limb (with a thin and thick segment) and an ascending limb (with a thin segment and a thick segment that is impermeable to water).

c) Distal Convoluted Tubule (DCT) – this is lined with simple cuboidal epithelium and is shorter than the PCT. It specializes in secretion of substances into the filtrate. This is the last portion of the nephron and it leads into the collecting tubules and the collecting duct.

Regions of the Kidney and the 2 Types of Nephrons

It is useful to know some basic anatomy of the kidneys because the names of many structures are related to their anatomical location or arrangement. In terms of the general anatomy of the kidney, the outer portion is called the **renal cortex** and the inner deeper portion is called the **renal medulla**.

This basic distinction is important as it relates to the two different types of nephrons in humans. The two types of nephrons are:

1) Cortical nephrons – most common, these have the renal corpuscle higher up in the renal cortex and have a shorter loop of Henle.

2) Juxtamedullary nephrons – far less common, these have the renal corpuscle lower in the renal cortex, close to the medulla which is what "juxta medullary" means, and they have a longer loop of Henle.

In humans approximately **85%** of nephrons are **cortical**. They are characterized by having the renal corpuscle higher up in cortex and also have a much shorter loop of Henle in the renal tubules. The other **15%** are the **juxtamedullary** nephrons which have their renal corpuscle located closer to medulla (but still in the renal cortex), and they have a much longer loop of Henle that extends deep into renal medulla.

Each of these two types of nephrons has slightly different roles as will be explored. For all nephrons, both cortical and juxtamedullary (see in **Fig. 21.5** below), their renal corpuscles are always located in the renal cortex.

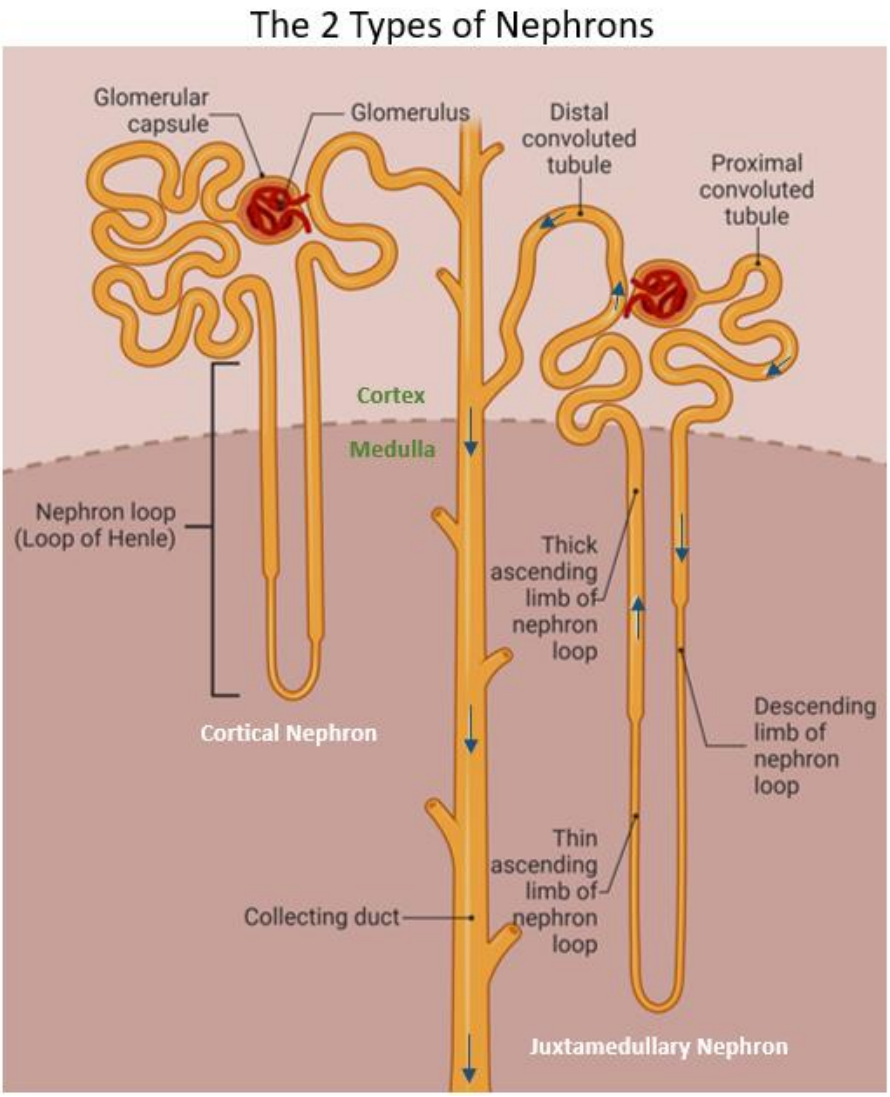
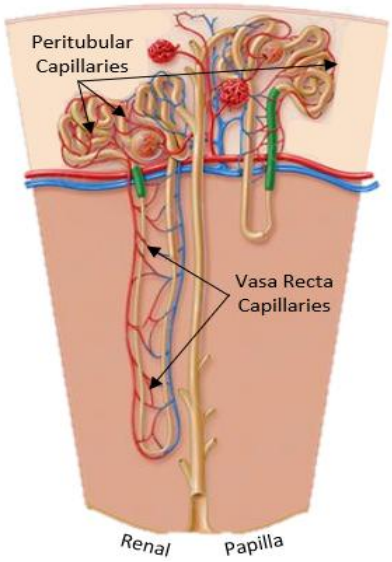


Figure 21.5 This shows the two types of nephrons in the kidney. On the left is the most common cortical nephron with the renal corpuscle higher up in the renal cortex, with a shorted loop of Henle. On the right is the less common juxtamedullary nephron with the renal corpuscle much closer to the renal medulla, with a much longer loop of Henle extending deep into the renal medulla.

It is important to know that as the renal medulla moves deeper (downward in **Fig. 21.5**), this area in the tissue is characterized by higher than normal ECF osmolarity, that is, it is very '***salty'*** there. As will be discussed ahead in more detail, this allows for water reabsorption to occur in the renal tubules that pass through this area. It is especially relevant in the loop of Henle and the collecting ducts as these structures go very deep into the renal medulla.

This arrangement is a key component of the renal system which allows for the formation of <u>very concentrated urine</u> if the body needs to conserve water. Before we continue it is also important to understand and visualize how filtrate inside the renal tubules is reabsorbed back into the body. There are 2 different types of capillaries that drape over the renal tubules, they are **1) peritubular** (meaning 'around the tubes'), and **2) vasa recta** (meaning 'straight vessels'). It is these 2 types of capillaries that 'pull' the filtrate that is needed back into the body.



In the section of the kidney shown to the left, there are 2 nephrons, can you tell which one is the cortical and which is the juxtamedullary nephron? Both nephrons are draped in capillaries. Notice that the capillaries branching from the efferent (outgoing) arteriole are the **peritubular** and the **vasa recta** capillaries. On the drawing the peritubular capillaries are in the cortex around the tubules of both types of nephrons, however, the vasa recta capillaries are **only** seen around the tubules of the long loop of Henles of the juxtamedullary nephrons.

The arrangement and importance of these 2 sets of capillaries is especially significant because all of the filtrate **reabsorbed** from the renal tubules must go into these capillaries - that is how we keep that material from being excreted. In making a connection to Figure **21.6** below, the peritubular and the vasa recta capillaries are not seen in that image, but at the efferent arteriole (where they would come from), note it is labeled 'peritubular capillaries' and 'vasa recta capillaries' to show their origins. These capillaries reabsorb **99%** of the filtrate.

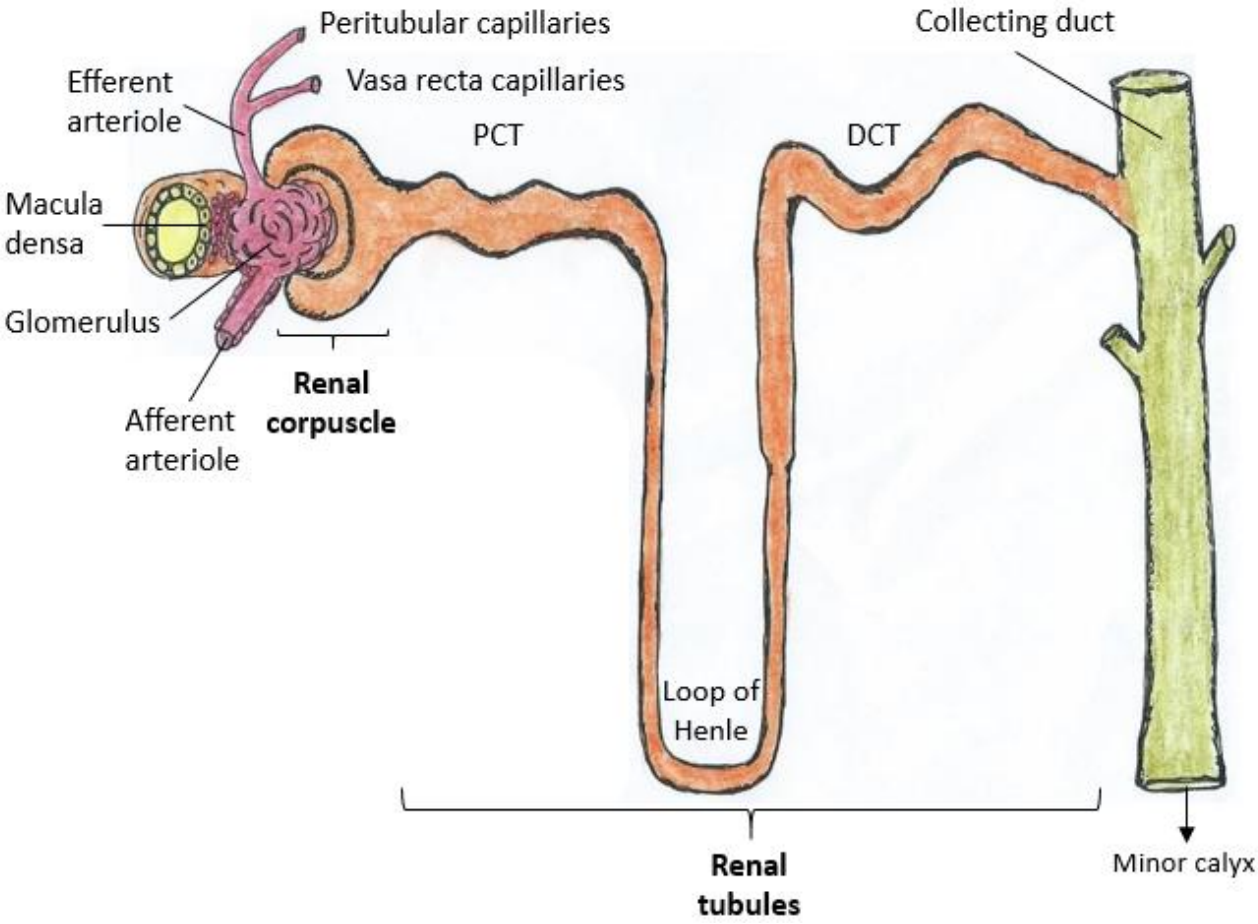


Figure 21.6 This drawing shows a linear or 'straightened out' illustration of a nephron, which is not anatomically correct but allows for clearer representation of the regions. The renal corpuscle is at the proximal end, and the renal tubules carry and modify the filtrate all the way to the collecting duct (green section). All the major structures of the nephron are labeled. The peritubular and vasa recta capillaries would normally drape over and cover all of the renal tubules to reabsorb the filtrate, but they are not shown in this image.

Juxtaglomerular Apparatus

The renal system has some elegant forms of **autoregulation** which will be examined in detail shortly. At this point we need to notice a very important component that each nephron has called the **juxtaglomerular apparatus**, see the drawing of this apparatus in **Fig. 21.7** below.

The juxtaglomerular apparatus is composed of these main structures:

1) **The Macula Densa** – this is a specialized portion of the **DCT** that passes in between the afferent and efferent arteriole of the nephron before merging into the collecting ducts. The cells of the macula densa can release **ATP** and **adenosine** which cause constriction of the afferent arteriole and thereby cause a decrease in GFR. These cells can also release **Nitric Oxide** (NO) which causes relaxation of the vascular smooth muscle (VSM) around the afferent arteriole and therefore increases GFR.

2) **The Juxtaglomerular (JG) Cells** – these are cells predominantly around the afferent arteriole to adjust the diameter of this vessel and are somewhat modified smooth muscle cells. These JG cells that have granules containing the enzyme/hormone **Renin**. When the body needs to conserve water, the kidneys release renin to start the 'renin-angiotensin-aldosterone' system (discussed later).

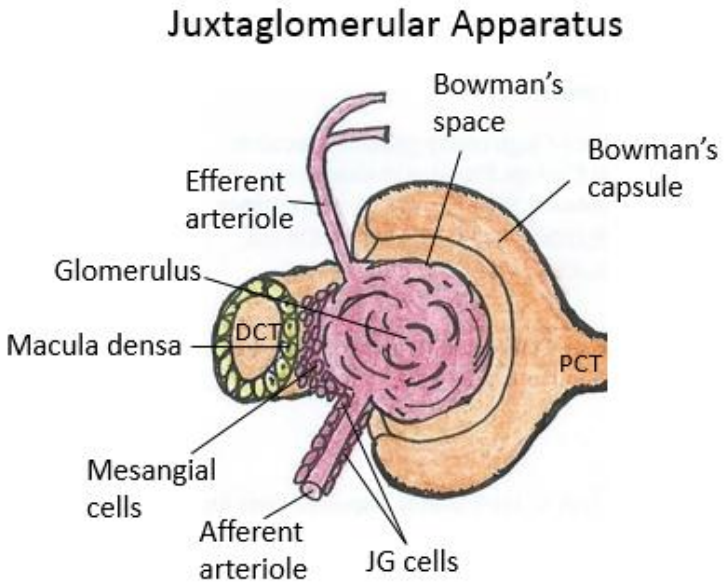


Figure 21.7 This is a zoom-in of the renal corpuscle of the nephron showing the constituents of the juxtaglomerular apparatus. It is composed of the macula densa, a segment of the distal convoluted tubule (DCT) in between the two arterioles and the juxtaglomerular (JG) cells, which encircle the afferent arteriole. The mesangial cells are located in between the DCT and the glomerulus. The juxtaglomerular apparatus operates as a paracrine form of communication to generate renal autoregulation and also has a role in homeostasis of the entire body.

Another vital component of the juxtaglomerular apparatus are additional cells called **mesangial cells**. These are sandwiched in between the afferent and efferent arterioles and the DCT and the glomerulus, see **Fig. 21.7** above. They contain contractile elements and can causes constriction of the afferent arteriole, thereby causing a decreases in GFR.

The Barriers to Filtration

Although renal filtration at the glomerulus is vital, it is not an unbridled event! There are actually significant and important **barriers to filtration** that keep this process balanced and ensure that only the appropriate elements and correct amounts are filtered from the blood into the tubules.

The key thing to remember is that not everything from the plasma is filtered into the renal tubules. The arrangement of the renal corpuscle is such that there are essentially **3** regions or barriers that molecules must pass through (like an obstacle course) in order to become filtrate. These **3 barriers** are listed below in the order that they would be encountered by the filtrate being made at the glomerulus.

1. The **endothelium** of the glomerular capillary provide a barrier by restricting the passage of cells. Remember that the glomerulus is a *fenestrated* capillary bed, so the endothelial cells have large **pores** which make them more 'leaky' than continuous capillaries. This allows a lot of the fluid from the plasma to be filtered but normally prevents any blood cells (red or white) from entering the renal tubules.

2. The **basement membrane** in between the fenestrated capillary bed and the podocytes is created by a basal lamina, and restricts the passage of most plasma proteins. This layer is acellular (has no cells) and acts as a coarse sieve (strainer) for larger molecules, see **Fig. 21.8** below. Also, the glycoproteins and collagen-like molecules in this area are slightly negatively charged, thus the basement membrane repels larger negatively charged proteins from moving into the filtrate.

3. Cells called **podocytes** ('**foot**' process cells) surround the capillaries and create narrow '**filtration slits**' which can cause changes to the glomerular filtration rate (GFR), see drawing in **Fig. 21.8** below. The width of these slits can change the surface area that is available for filtration. When podocytes *contract*, they *increase* the area available for passage of plasma, thus *increasing* the rate of filtration. When podocytes *relax*, they *decrease* the area available for passage of plasma, thus *decreasing* the rate of filtration.

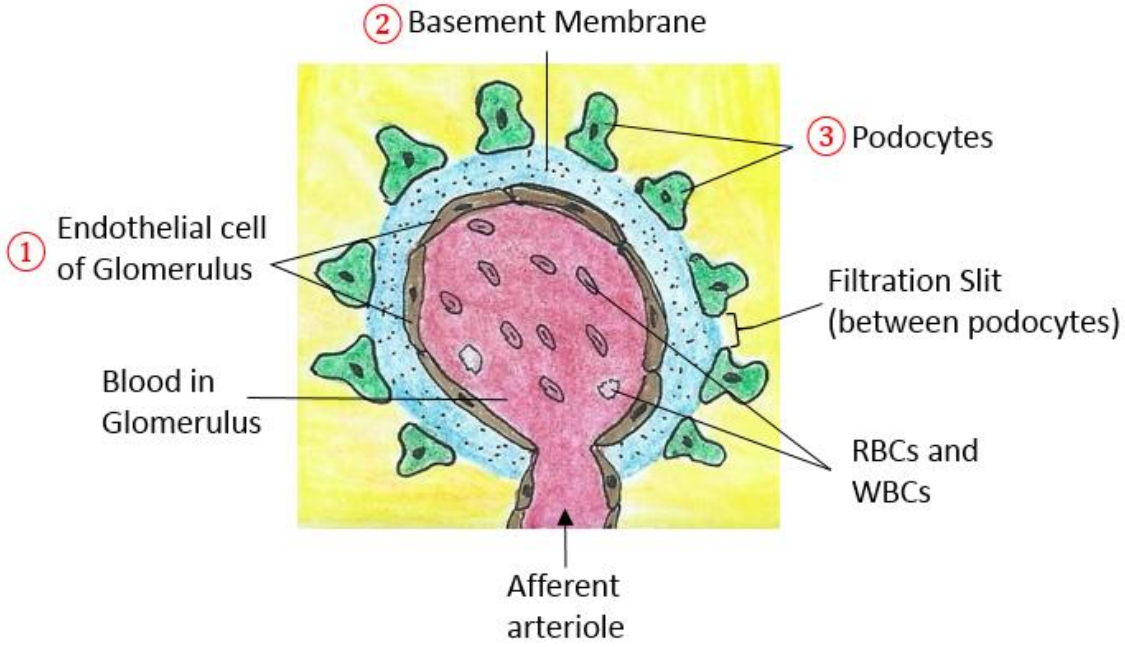


Figure 21.8 In this drawing the barriers to filtration are shown at the glomerulus. The endothelial cells of the glomerular blood vessel restrict the passage of cells. The basement membrane in between the fenestrated capillary bed and the podocytes restricts the passage of most large plasma proteins. The podocytes that surround the glomerulus and create narrow 'filtration slits' can changes glomerular filtration rate (GFR).

At first glance the process of filtration may seem like a relatively non-specific process. However, there is some degree of selection involved in how substances are moved across. The fluid called **filtrate** that is pushed into the renal tubules is essentially **like plasma but without large proteins**. Not all small molecules in the plasma will be filtered. For example, low molecular weight fatty acids and some Ca^{2+} ions bind to plasma proteins and therefore will not filter freely into the tubules.

What is the Filtration Fraction?

Only about **1/5** of the plasma volume flowing into the kidneys gets filtered by the glomerulus into the tubules of the nephrons. That is, only about **20%** of the blood (plasma) flowing into the glomerulus is filtered into the renal tubules, this is called the "**filtration fraction**".

The filtration fraction represents the faction (or percentage) of total plasma volume that is being filtered at any one moment. The remaining **4/5** or **80%** of the plasma of blood continues to move into the efferent arteriole and into one of either the **peritubular** or **vasa recta** capillary beds.

Of that 20% of plasma that is pushed into the renal tubules, 19% is reabsorbed and returned to the peritubular or vasa recta capillaries before even leaving the kidneys, that is, **99%** of what is filtered from blood is returned to the blood. In this way, a significant amount of plasma can be filtered and returned to the vascular system within the kidneys - this helps maintain a very stable total blood volume.

The relevance of this issue is that only about **20%** of the plasma in blood is 'out of commission' so to speak, at any one time, since it has to be taken out of circulation to be cleaned. This information is just to illustrate that the renal system is very balanced in its function, such that while cleansing the blood it ensures there is always plenty of blood circulating for the body's needs.

Filtration Occurs Because of Hydrostatic Pressure in the Capillaries of the Glomerulus

Glomerular filtration is similar to filtration out of systemic capillaries, however there is a significant difference in the hydrostatic pressure of the glomerulus that favors filtration. Shown below are the forces that **1)** Favor filtration, and **2)** Oppose filtration.

1. The Force that Favors Filtration

- The **Hydrostatic Pressure** (HP) of blood in the glomerulus is *unusually high* at a value of **55** mmHg. Considering that most other capillaries have a HP of about 10 to 20, the glomerulus is unique in its hydrostatic pressure and this is the force that is responsible for the high levels of filtrate out of the already leaky capillary epithelium (see **Fig. 21.9**).

2. Forces that Oppose Filtration

- The **Colloid Osmotic Pressure** (COP) in capillaries of the glomerulus is about **30** mmHg, which is very high compared to the COP of the fluid within the Bowman's space which is essentially zero. Therefore, this COP gradient opposes fluid movement into the Bowman's capsule, in other words it favors reabsorption back into capillaries, which is the opposite of filtration (see **Fig. 21.9**).

- The **Hydrostatic Pressure** (HP) of the fluid that is already in Bowman's space is about **15** mmHg, and this also opposes fluid filtration into the Bowman's space.

If we summate or add up these forces and give the one favoring filtration a **positive** (+) sign (the HP of the glomerulus) and give the two forces opposing filtration a **negative** (-) sign (the COP of the glomerulus and the HP of the Bowman's capsule), then when they are all added, overall, there is a net driving force of 10 mmHg in favor of filtration (see below).

Calculation:
+ 55 mmHg
- 30 mmHg
- 15 mmHg

+ 10 mmHg

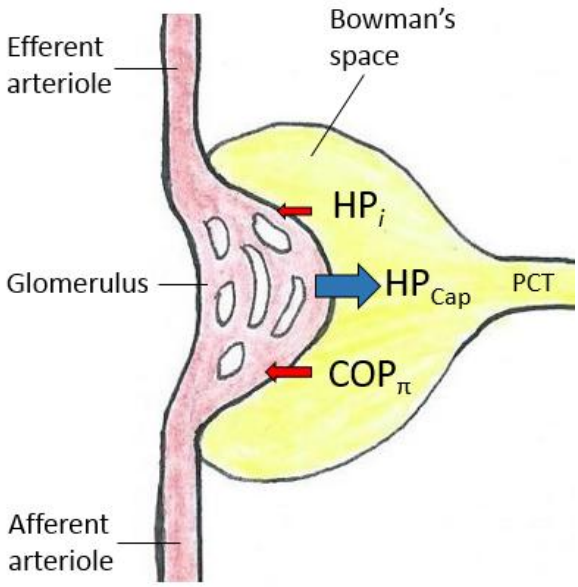


Figure 21.9 The drawing to the right shows the balance between the hydrostatic pressure of the capillary (HP_{Cap}) pushing fluid into the Bowman's space (blue arrow), compared to the hydrostatic pressure of the interstitium (HP_i) and the colloid osmotic pressures the glomerulus (COP_π), both of which draw fluid back into the glomerulus (red arrows) and therefore oppose filtration.

Glomerular Filtration Rate (GFR) is normally kept very Constant

We've seen that the normal forces allow for constant filtration, which is good because we need to keep filtering! In healthy kidneys the Glomerular Filtration Rate (**GFR**) remains remarkably constant over a large range of mean arterial pressure (**MAP**) values, ranging from of 80 to 180 mmHg.

As the graphs below in **Figure 21.10** shows, there can be significant increases in MAP without any increases in GFR. It is only when the MAP is extraordinarily high, at 180 mmHg, that GFR starts to increase from the steady 180 L/day.

However, the GFR is much more sensitive to **decreases** in MAP, as seen in the graph in **Fig. 21.10** below, a small decrease from the average MAP of 93 mmHg to 80 mmHg will instigate a decrease in GFR. In fact, GFR will rapidly and significantly drop in response to dangerous reductions in MAP.

This illustrates a clear protective mechanism by the renal system: When blood pressure drops the body cannot afford to lose any more vascular volume, and by shutting down glomerular filtration, that stops any more urine from being produced. Since urine is 95% water, this can prevent any further decrease in blood pressure by conserving water in the body.

The control of GFR is accomplished primarily by regulation of blood flow through the renal arterioles, most notably by **control of the afferent arteriole** (details below).

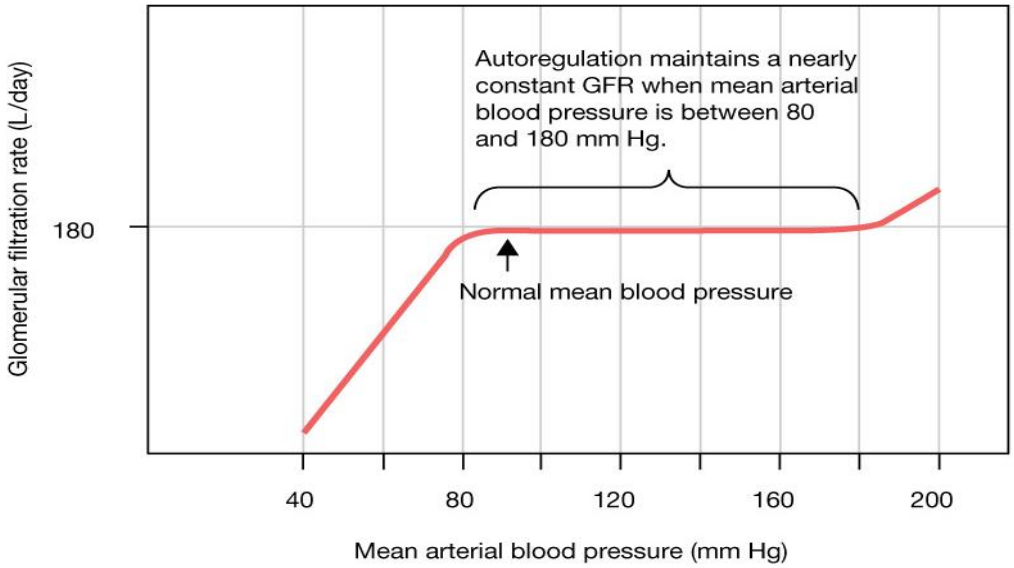


Figure 21.10 The graph above shows the remarkably constant Glomerular Filtration Rate (GFR) across a large range of mean arterial pressure (MAP) values from 80 mmHg to about 180 mmHg. Note that when there is even a relatively small decrease in MAP, there is an immediate and significant decrease in GFR.

GFR is Regulated by the Nephron Itself – this is called Autoregulation

Autoregulation, like its name indicates, means **self-regulation**. This is a very local control process in which the kidney maintains a relatively constant GFR in the face of normal fluctuations in blood pressure. There are two categories of renal autoregulation, the **Myogenic Response** and **Tubuloglomerular Feedback**.

1. Myogenic Response

The term myogenic, means myo (= muscle) and genic (= generate) such that it refers to the vascular smooth muscle (VSM) that surrounds both the afferent and efferent arterioles before and after the glomerulus. Effectively, the myogenic response is about the effect of stretching of the smooth muscle in the walls of the arterioles and what happens as a consequence of stretching these vessels. Spoiler alert: Concisely put, the **myogenic response** is this. If the afferent arteriole is **stretched**, its response is to **contract**. In direct terms, it usually opposes most attempts to stretch it!

Here are the details. If the MAP **increases**, this pressure increase would **stretch** the smooth muscle in the walls of the arterioles. In response to this stretching, the smooth muscle there contracts leading to **vasoconstriction** mostly of the afferent arterioles. The vasoconstriction of the afferent arteriole **reduces blood flow** through it and hence reduces blood flow to the glomerulus. This would **decrease GFR**, or more accurately prevents an increase in GFR when MAP is elevated, thus ensuring a very constant volume of filtrate is maintained even during changes in MAP. In simple terms the myogenic response is when the arterioles are stretched by an increase in blood pressure, they contract to 'push back' and negate any changes that an increase in blood pressure might have on their blood flow and hence GFR.

What this myogenic response ensures is that **GFR is held very constant at 180L/day** within a range of a MAP of 80 to 180 mmHg (this is often called the '*zone of regulation*'). As we saw above in the graph of **Fig. 21.10**, if MAP drops below 80 mmHg, this is indicative of a life threatening situation, such as of shock (e.g., from severe dehydration or significant hemorrhage), and this will result in a virtual shutting down of the kidneys in order to conserve and redistribute vascular volume.

2. Tubuloglomerular Feedback and the Juxtaglomerular Apparatus

As seen and discussed earlier, there is a portion of the distal convoluted tubule (DCT) that passes in between afferent and efferent arterioles of the nephron. Contained therein is a specialized area of the DCT called the **macula densa**, which are modified cells in the tubule wall, one part of the **juxtaglomerular apparatus**. The macula densa cells can detect and exchange information about the flow of filtrate in the renal tubules and relay this to the arterioles. The information from the macula densa stimulate the **juxtaglomerular (JG) cells**, which are predominantly around the afferent arteriole walls, and they synthesize and release **renin** in response to signals of dehydration of the body (discussed in detail later).

The basics of the tubuloglomerular feedback are that the fluid composition of the filtrate towards the end of the nephron (at the DCT) communicates information about the **osmolarity** (**salinity**) of filtrate to the beginning of the process, where filtration occurs. In a classic **Negative Feedback Loop** fashion, if there is a change in the condition of the filtrate that pushes it outside of the normal homeostatic range, this will be the stimulus to trigger mechanisms that will oppose the original stimulus and restore filtrate osmolarity to bring it back into a normal range in order to maintain homeostasis.

However, as seen below in **Figure 21.11**, there is a step by step sequence that can be seen in terms of regulation of how the nephron makes adjustments along the way to regulate the GFR.

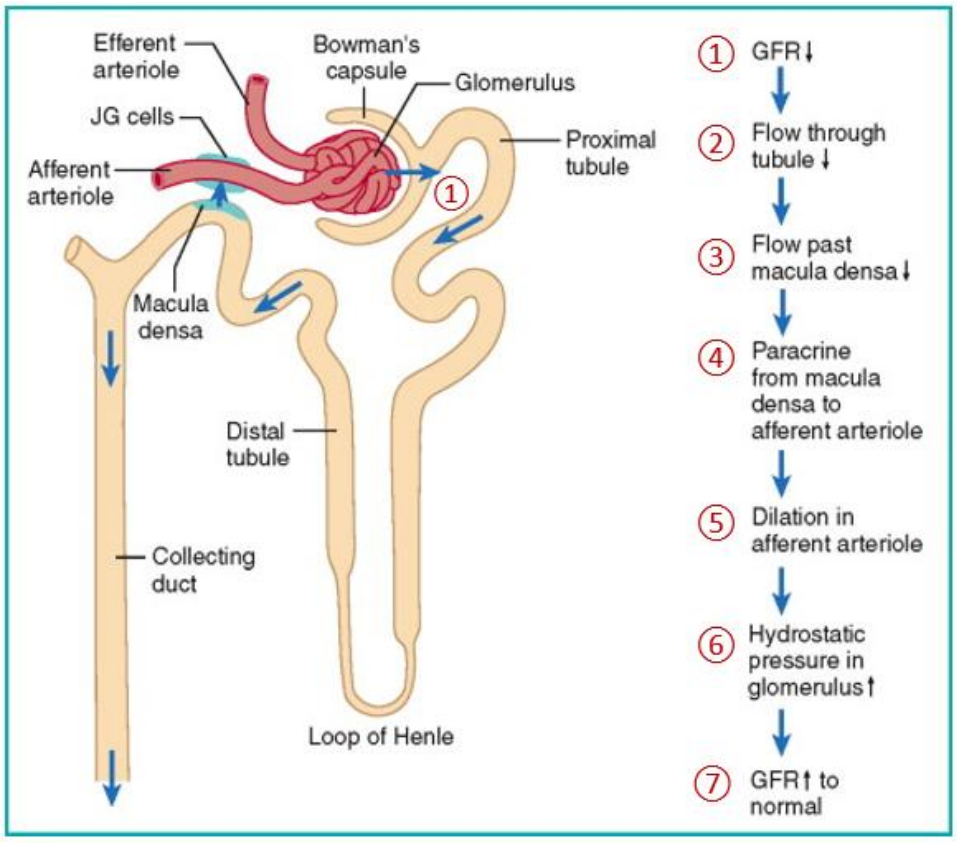


Figure 21.11 The example in this illustration exhibits a classic negative feedback loop. The stimulus is a decreased GFR, entailing a decreased DCT flow moving across in the macula densa region, which detects the change, then sends paracrine messages to the afferent arteriole, causing it to dilate, which decreases resistance and increases blood flow through the glomerulus. This elevated the amount of filtrate produced and increases GFR back to normal.

Example of the Feedback Loop (from start to end).
The details of the exact nature of the stimulus which initiates the macula densa's response is unclear, no one really knows what starts it off. This is actually true about many aspects of physiology, but that's OK. It is thought that the feedback loop may be related to an aspect of NaCl absorption in the macula densa region. It is also theorized that nitric oxide (NO) and adenosine act as paracrine signals within the juxtaglomerular apparatus to regulate GFR. It is just not clearly understood.

The GFR is also influenced by Autonomic Nervous System (ANS) and Hormones

Nervous System Control of GFR

The **Sympathetic** division of the **ANS** has a large role in innervating the renal system at the level of the nephron. Both the **afferent** and **efferent arterioles** (but particularly the afferent arteriole) are innervated by sympathetic neurons, see **Figure 21.12** to left. These vessels have **α_1 receptors** on their smooth muscle wall and sympathetic nerve endings release norepinephrine (NE) which bind to these α_1 receptors causing **vasoconstriction**. If the afferent arteriole constricts, this will decrease GFR. Typically, moderate sympathetic activity has little effect on GFR. However, if there are drastic changes in systemic blood pressure, it is the sympathetic division of ANS that can respond very quickly and *significantly decrease GFR*. Note there are scant α_1 receptors on the efferent arteriole as well.

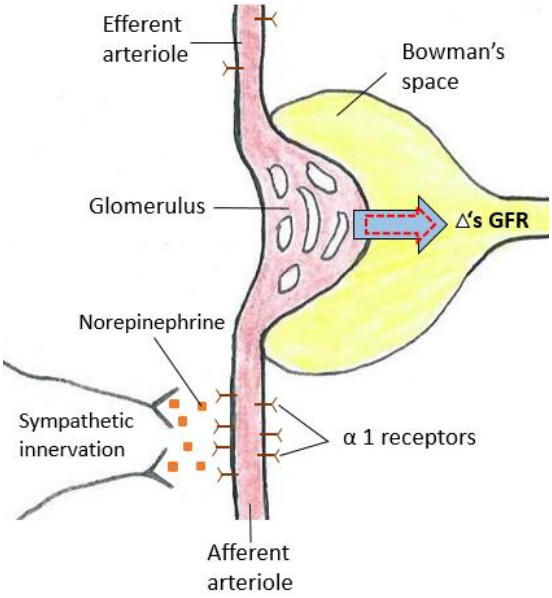


Figure 21.12 Sympathetic innervation of the afferent arteriole of the nephron occurs via stimulation by norepinephrine (NE) on alpha (α) 1 receptors present there. This results in vasoconstriction of this arteriole and a reduced flow of blood to glomerulus, which then causes a reduced glomerular filtrate rate (GFR).

Additional actions of Sympathetic Innervation
It is also important to know that the sympathetic stimulation of the renal system also increases **renin** secretion from the JG cells, which triggers the **renin–angiotensin–aldosterone system** to conserve water in the body (discussed in detail later). This same sympathetic stimulation which decreases renal blood flow also increases renal tubular **sodium absorption**. All of these actions prevent further fluid loss through urine production and at the same time stimulate vasoconstriction to maintain systemic blood pressure.

Endocrine System Control of GFR

As elsewhere in the body, there are several hormones that influence arteriolar resistance in the renal system, and as a consequence can also influence the GFR. Below are the major influential hormones.

a) Angiotensin II: This is a potent **vasoconstrictor**. It has effects not only on the afferent arteriole, whereby it decreases GFR, but it is also a powerful vasoconstrictor throughout the body. Its activation is set into motion by the release of **renin** by the JG cells of the kidney. It is a part of the **renin–angiotensin–aldosterone system**, which involves a powerful cascade of events that act to conserve water and maintain blood pressure in the body should it decrease. The details can be seen in **Figure 21.19** further ahead.

b) Prostaglandins: The group of molecules called prostaglandins are a collection of lipid molecules that are active signaling compounds. Prostaglandin E2 (PGE2) especially, as well as PGE1, and I2 (PGI2) are all

direct **vasodilators** of the afferent and efferent arterioles of the glomerulus capillary bed. In their actions they tend to increase GFR. This may be related to allowing more toxins to be eliminated via urine.

These prostaglandins also act on vascular smooth muscle systemically in other vascular tissue to cause vasodilation. Interestingly, in addition to acting as a vasodilator PGE2 also inhibits **platelet aggregation** and **suppresses T cell** receptor signaling and proliferation, demonstrating a role in resolving inflammation.

c) Other molecule interactions at the glomerulus may alter the **filtration slit** size by acting on **podocytes** or **mesangial cells**. In doing so, it can impact GFR. Overall consistency within the renal system is maintained by reflex control from the **Sympathetic** division of the ANS and several hormones that affect the diameter of the afferent and efferent arterioles going into and leaving the glomerulus. For example, if epinephrine (E) or norepinephrine (NE) are released as hormones, their ability to act as vasoconstrictors will depend on the presence of **cortisol** in blood, which has a permissive effect with E and NE and greatly enhances their vasoconstrictor effects.

Renal Reabsorption

As we have heard, the nephrons of the kidney produce about **180** liters of filtrate per day, and of that amount approximately **99%** of the filtrate is recovered by the kidneys and kept in the body by the process called **renal reabsorption**. Therefore, reabsorption is a very important process in the kidneys.

The process of reabsorption of filtrate occurs across <u>all the renal tubules</u> from the PCT, to the loop of Henle, the DCT, and also in the collecting ducts (which are not technically part of the nephron).

However, the vast majority of the filtrate, approximately **70%**, is reabsorbed in the **PCT**. This region of the renal tubule is the workhorse of reabsorption! The arrangement within the kidneys is very elegant and effective, wherein they get back most of what they filtered in the very first section of the renal tubules.

Various portions of the nephron differ in their capacity to reabsorb water and other specific solutes. While much of the reabsorption and secretion occurs passively based on concentration gradients, the amount of **water** that is reabsorbed or lost is tightly regulated.

If there is ever a need to conserve water in the body, the start of this regulation is initiated by the release of the enzyme/hormone **renin** by the JG cells of the juxtaglomerular apparatus. In a cascade of events that will be covered shortly, the *direct* control for water conservation in the renal tubules is exerted by **antidiuretic hormone** (**ADH**) made by the hypothalamus but stored in and released from the posterior pituitary. Another hormone **aldosterone** is also released from the adrenal cortex. Both of these hormones are triggered to act by the release of renin.

The vast majority of water is reabsorbed in the PCT, then in the loop of Henle and then in the DCT. Only about **10%** of the original filtrate (18 L) actually reaches the collecting ducts. The collecting ducts, when under the influence of ADH, can recover <u>*almost all of the water passing through them*</u> in cases of dehydration, <u>*or almost none of the water*</u>, in cases of overhydration.

We will see that the collecting ducts provide the kidneys with the last opportunity to modify (concentrate or dilute) the filtrate before it becomes urine. Once the renal filtrate leaves the collecting ducts it is called urine because it can no longer be modified. It is delivered to the urinary bladder and stored there until it is voided.

Mechanisms of Recovery – How are substances Reabsorbed?

The mechanisms by which substances move across membranes for reabsorption or secretion can be placed in two broad categories of passive and active transport.

- **Passive transport** mechanisms include diffusion, osmosis and facilitated diffusion.
- Primary and secondary **active transport**, and vesicular transport.

For a quick review, **passive** transport does not require energy or ATP and **active** transport requires energy typically in the form of **ATP** (the high E phosphate bond). This need for energy centers on the direction of movement of the substance and whether it will be going **up** or **down its electrochemical gradient**.

Simple diffusion is the movement of a substance down its concentration gradient. **Osmosis** is a special case of diffusion for water. **Facilitated diffusion** is also movement of a substance down its concentration gradient, the difference being that it requires a specific transporter protein to 'facilitate' this movement.

Primary and Secondary Transport

As we saw earlier, the perfect example of primary active transport is the Na^+/K^+ pump, whereby $3Na^+$ are ejected out of a cell and $2K^+$ are imported into a cell via a protein transporter, both being moved up/against their concentration gradients.

It is essential that most of the Ca^{2+}, Na^+, glucose, and amino acids that have been filtered are **reabsorbed** by the nephron to maintain homeostatic plasma concentrations. The vast majority of the transport mechanisms for these vital elements is **active transport**, usually involving **co-transport**! Recall the differences between uniport, symport and antiport:

- **Uniport** mechanisms move one substance in one direction.
- **Symport** mechanisms move two or more substances in the same direction at the same time.
- **Antiport** mechanisms move two or more substances in opposite directions across cell membrane.

Other substances, such as urea, K^+, ammonia (NH_3), creatinine, and some drugs are **secreted** into the filtrate as waste products. Acid–base balance is maintained through actions of the lungs and kidneys: The lungs rid the body of H^+, whereas the kidneys secrete or reabsorb H^+ and HCO_3^-.

Vesicular Transport From material in section one, vesicular transport is the movement of large molecules inside a vesicle across the membrane. This mechanism is predominant for the recovery of any small proteins and many lipids in the renal filtrate. Since even a small proteins and lipids are fairly large, they require vesicular transport in order to be recovered sufficiently from the renal tubules. This is an active form of transport. In this example it is transporting substances across the cells lining the renal lumen.

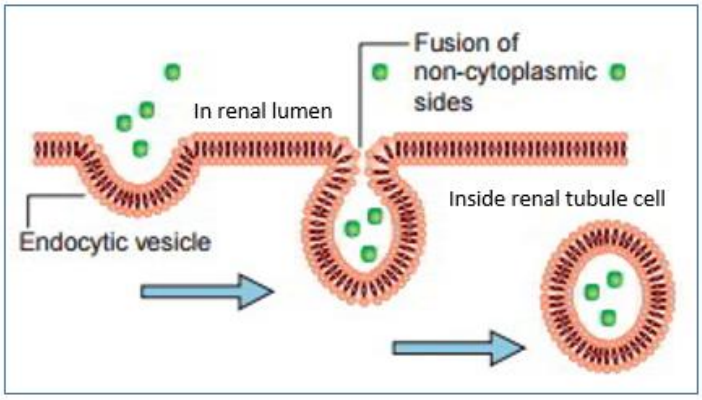


Figure 21.13 Endocytosis is an active transport mechanism (require ATP) that enables the movement of large quantities of a molecule or large macromolecule, to be transported across a membrane.

Often it is receptor mediated endocytosis, wherein the protein, for example, will bind to a receptor in the cell membrane of the tubule cells to instigate the formation of a vesicle for endocytosis and recovery by the body. See the example provided in **Figure 21.13** (above).

How Reabsorption Starts in the Proximal Convoluted Tubule

We have established that the proximal convoluted tubule (**PCT**) is the primary site for renal reabsorption. We've also seen that there is a lot to reabsorb and we've had a quick review of transport mechanisms across cells. Now we are ready to examine **how** this all occurs. Right from the word go - as filtrate is made and pushed into the renal tubules - the process of getting it back starts!

This entire process might seem a little bit like a waste of time, to push all this material into the renal tubules just to grab **99%** of it back as soon as possible. Not only that, but it costs the body metabolic energy to get many of the substances back from the renal filtrate. However, it turns out to be a very effective way of cleansing the blood. Additionally, all of this vascular cleansing, and the speedy return of 99% of the blood contents occurs before leaving the kidney. Therefore, when looking at the big picture, this method is incredibly effective and efficient.

Note: Any time we talk about 'renal reabsorption' it is the movement of a substance from the lumen of the renal tubules into the capillaries that surround and engulf those tubules. The capillary beds are either the **peritubular capillaries** (for both cortical and juxtamedullary nephrons) or **the vasa recta capillaries** (for juxtamedullary nephrons only).

The Sodium ions (Na^+)

It is the sodium ions (Na^+) that are the first key substance to be strategically drawn back into the body from the renal tubules. The Na^+ diffuses into the apical region of the cells lining the renal tubules, where [Na^+] is kept very low, thus this is **passive transport**.

Then at the basolateral (bottom) of the cells, Na^+ is ejected from the cell via the Na^+/K^+ pump against its gradient, thus this is **active transport**. Overall, Na^+ is pumped out of the PCT into the interstitial spaces and diffuses down its concentration gradient into the peritubular capillaries.

Water always goes to where it is Less

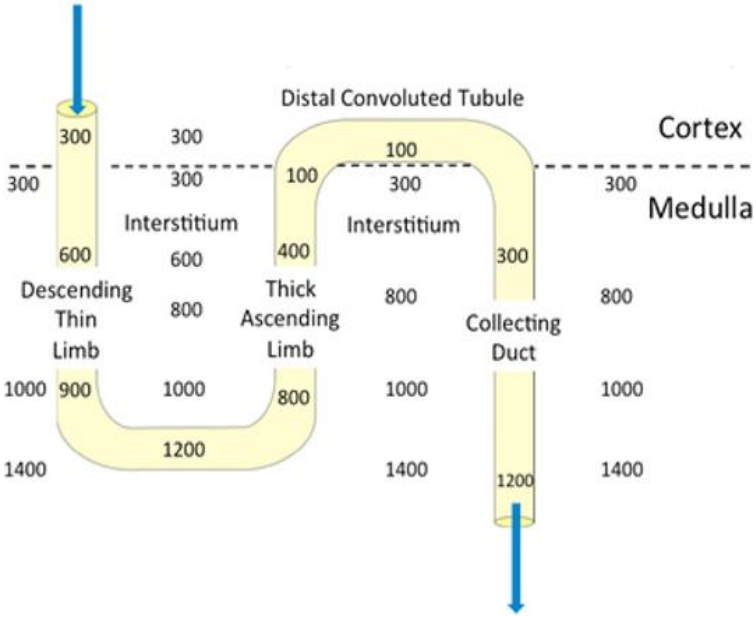
As Na^+ leaves the filtrate, the filtrate's osmolarity *decreases*, which effectively means the solution becomes more dilute (more watery) because of the *salt* leaving it. This causes the **water** in the in the filtrate in the renal tubules to follow the Na^+ and leave the filtrate passively, via **osmosis**, as water moves into the interstitium and peritubular capillaries down its concentration gradient to maintain an isotonic fluid environment inside the capillary. Therefore, **water is passively reabsorbed from the PCT** as it is obliged to follow its concentration gradient that was created by the departure of Na^+ from the filtrate.

Urea

There are significant quantities of urea in the renal filtrate. As more water is pulled out of the filtrate, the interstitium become more dilute, drawing urea out of the PCT and into the interstitium down its concentration gradient. Therefore, **urea is passively reabsorbed from the PCT**. Yes, **urea**, the metabolic waster product is reabsorbed by the body! In fact, about **50% of the urea** in the renal filtrate is passively reabsorbed in the PCT (**Fig. 21.14**). More urea is recovered in the collecting ducts as needed. So why would the kidneys reabsorb a waste product? Hold onto your hat, the kidney, like the rest of the body, is genius, watch this.

The urea that is reabsorbed in the PCT causes an increase in the medullary solute concentration, that is, it contributes significantly to the '**saline gradient**' seen the deeper we go down into the renal medulla.

The establishment of this steep gradient is critical for the reabsorption of water from the thin segments of the descending limb of the **loop of Henle** further along in the renal tubules. As the loop drops deeper into the renal medulla, more water is pulled out. In order to keep urea movements intact, some urea diffuses into the thin ascending limb, allowing it to be recycled, as seen in the image at right. The osmolarity of the medulla is shown by the increasing numbers down the medulla. This is also seen in **Fig. 21.14** and **Fig. 21.16** further below.



Glucose

The reabsorption of glucose in the kidneys is by **secondary active transport**, via the **Na^+/glucose symport**. Many of the transport mechanisms in the renal tubules use the protein transporters we have already seen, and as we know, these transporters exhibit the characteristics of saturation, specificity, and competition.

The **Na^+/glucose symport** transporter moves both Na^+ and glucose into the cell. The cotransporter moves glucose into the cell against its concentration gradient as Na^+ moves down the electrochemical gradient. This powerful Na^+ gradient is created by the basal membranes Na^+/K^+ pumps. Once inside the cell, the glucose then diffuses across the basal membrane by **facilitated diffusion** into the interstitial space and from there into peritubular capillaries. The Na^+/K^+ ATPase's on the basal membrane of a tubular cell constantly maintain the strong electrochemical gradient for Na^+ to move into the cell from the tubular lumen.

Amino acids are reabsorbed in the same fashion as glucose, that is, by **secondary active transport,** via the **Na^+/Amino Acid symport**. **Notes on PCT Transport:**

- More substances move across the membranes of the PCT than any other portion of the nephron.
- At least three ions, K^+, Ca^{2+} and Mg^{2+} diffuse laterally between adjacent cell membranes (transcellular) reabsorption. That is, they sneak into the body in between the cells.
- About 70% of water, Na^+, and K^+ filtered are reabsorbed in the PCT back to the circulation.
- Essentially 100% of glucose, amino acids, and other organic substances such as vitamins, lipids and small proteins are normally recovered here in the PCT.
- About 50% of Cl^- and variable quantities of Ca^{2+}, Mg^{2+} and HPO_4^{2-} are also recovered in the PCT.

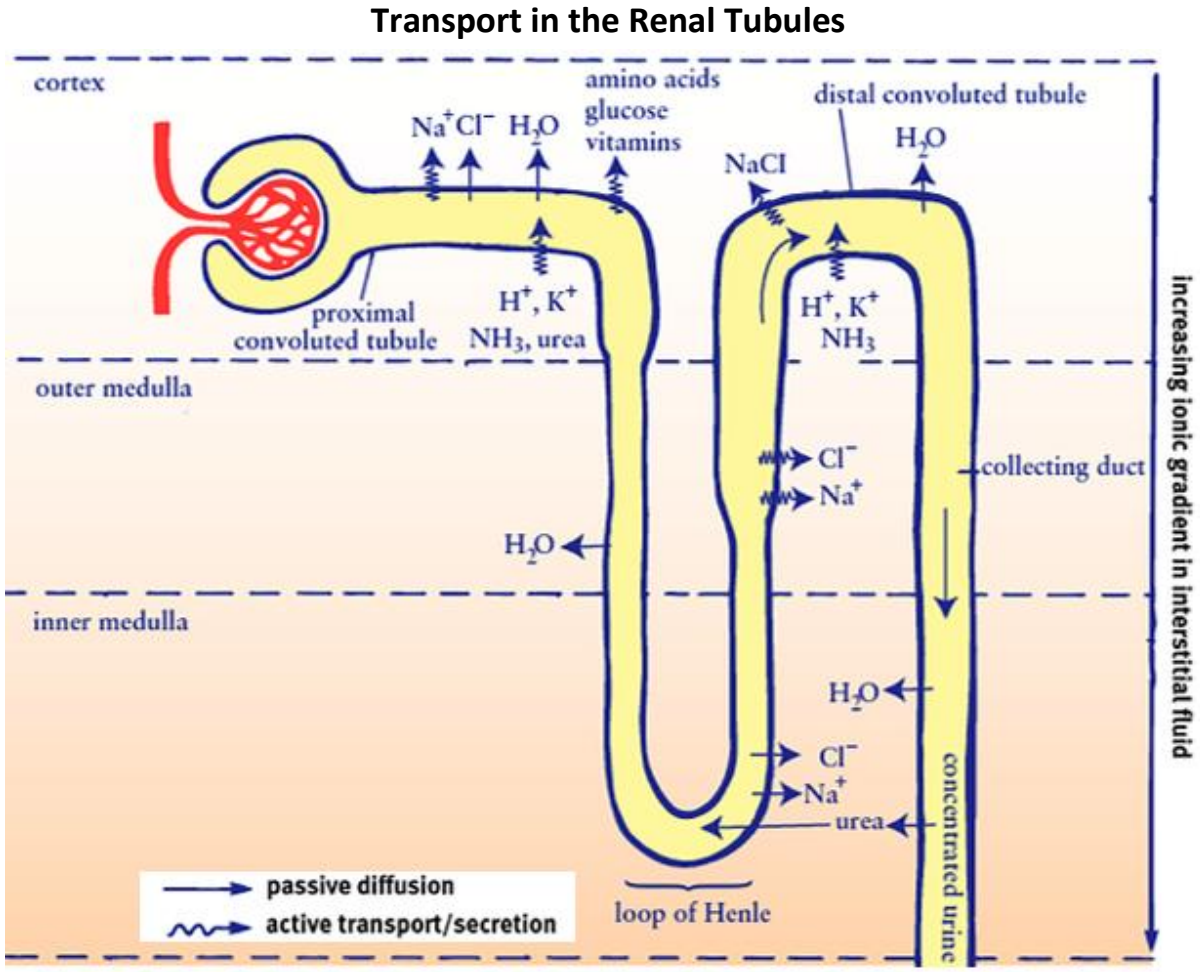


Figure 21.14 This diagram summarizes the passive and active transport mechanisms along the renal tubules and the collecting duct. The diagram key for the arrows indicates which transport mechanisms are passive and active. The coloration indicates the extracellular fluid (ECF) osmolarity within the kidneys, being pale in the renal cortex (indicating isotonicity) but getting darker moving deeper into the renal medulla (indicating hypertonicity).

Recovery of **bicarbonate** (HCO_3^-) is vital to the maintenance of acid–base balance, since it is a very powerful and fast-acting buffer. An important enzyme is used to catalyze this mechanism: **carbonic anhydrase** (CA) located within the luminal cell, but a small amount is bound to the brush border.

Aquaporins 1 and 2

Water reabsorption in the PCT moves through channels created by the **aquaporin 1** (**AQP1**) proteins. These can be referred to as 'water pores'. These proteins are found in most cells in the body in varying amounts, and their role is to help regulate water movement across membranes and through cells by creating a passageway across the hydrophobic lipid bilayer membrane.

The aquaporin 1 proteins are different from another type of water pore, **aquaporin 2** (**AQP2**), stimulated to be inserted by **antidiuretic hormone** (**ADH**), which is also known as **vasopressin**, in the collecting ducts. The term '*anti'* means against or opposed and '*diuretic'* means excessive urination, therefore '*antidiuretic*' means preventing excessive urination. ADH conserves body water by reducing urine production (see **Fig. 21.15** below). The ADH released from the posterior pituitary induces the insertion of aquaporin 2 proteins (and possibly others) into the collecting ducts (and in the DCT). This allows for the significant reabsorption of water back into the body from the filtrate when the signal to conserve water is triggered.

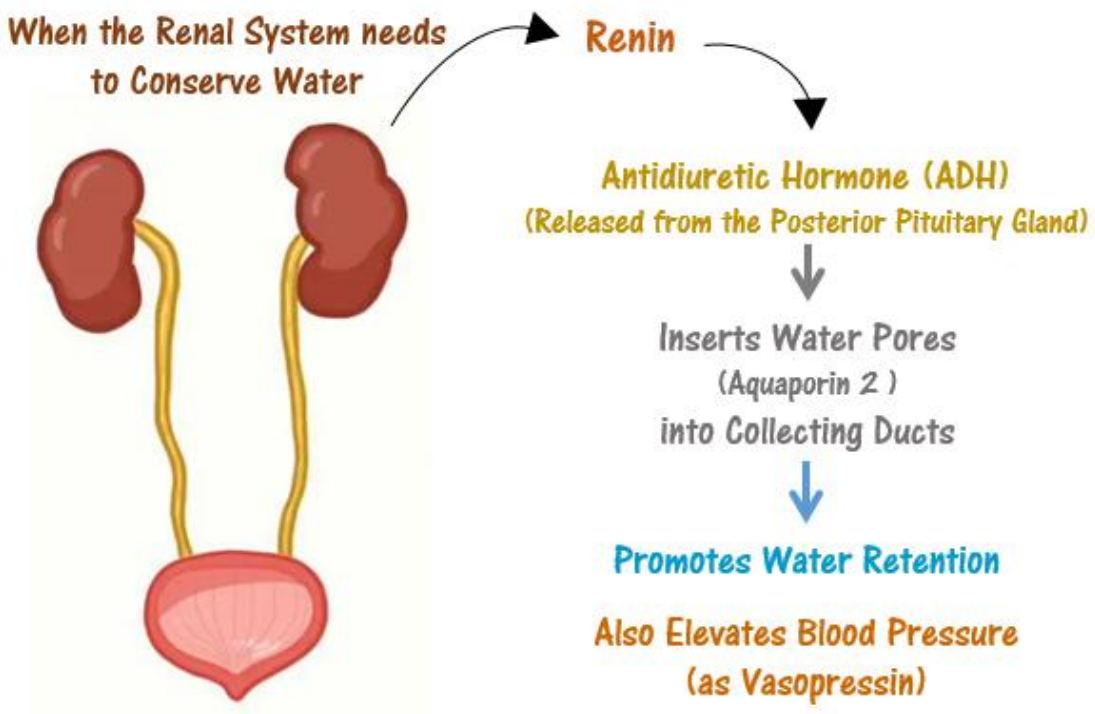


Figure 21.15 The release of renin from the kidneys sparks the release of antidiuretic hormone (ADH), which is important in the regulation of water throughout the body, but particularly in the renal system. ADH is released from the posterior pituitary and acts to insert aquaporin 2 (AQP2) proteins in the collecting ducts of the kidney. These AQP2 are a type of water pore which help the kidney retain more water within the body.

The Loop of Henle

The loop of Henle in the renal tubules consists of two sections:

a) The thick and thin **descending** segments.
b) The thin and thick **ascending** segments.

For **cortical** nephrons, the loops do not extend very far into the renal medulla. However, for the **juxtamedullary** nephrons, these have loops that extend variable distances, some very deep into the medulla. This feature of the loop of Henle in some nephrons which extends deep into the medulla has a big impact on the ability of the nephron to concentrate the filtrate as can be seen in **Figure 21.16** below.

The **descending** and **ascending** portions of the loop are highly specialized to enable the recovery of much of the Na^+ and water that were filtered into the renal tubules by the glomerulus.

Descending Loop

Most of the descending loop of Henle is lined with **simple squamous epithelium** and these cells have permanent aquaporin 1 channels in them that allow **unrestricted movement of water** out of descending loop into interstitium.

As the filtrate moves down the descending limb, the osmolarity of the ECF becomes more and more concentrated (from **300** mOsM to **1,200** mOsM) as seen in drawing below in **Fig. 21.16**, and this pulls more water out by osmosis (for reabsorption back into the body). This results in reabsorption of up to 15% of the water entering the loop. Solutes and water recovered from these loops are returned to the circulation by way of the **vasa recta** capillaries.

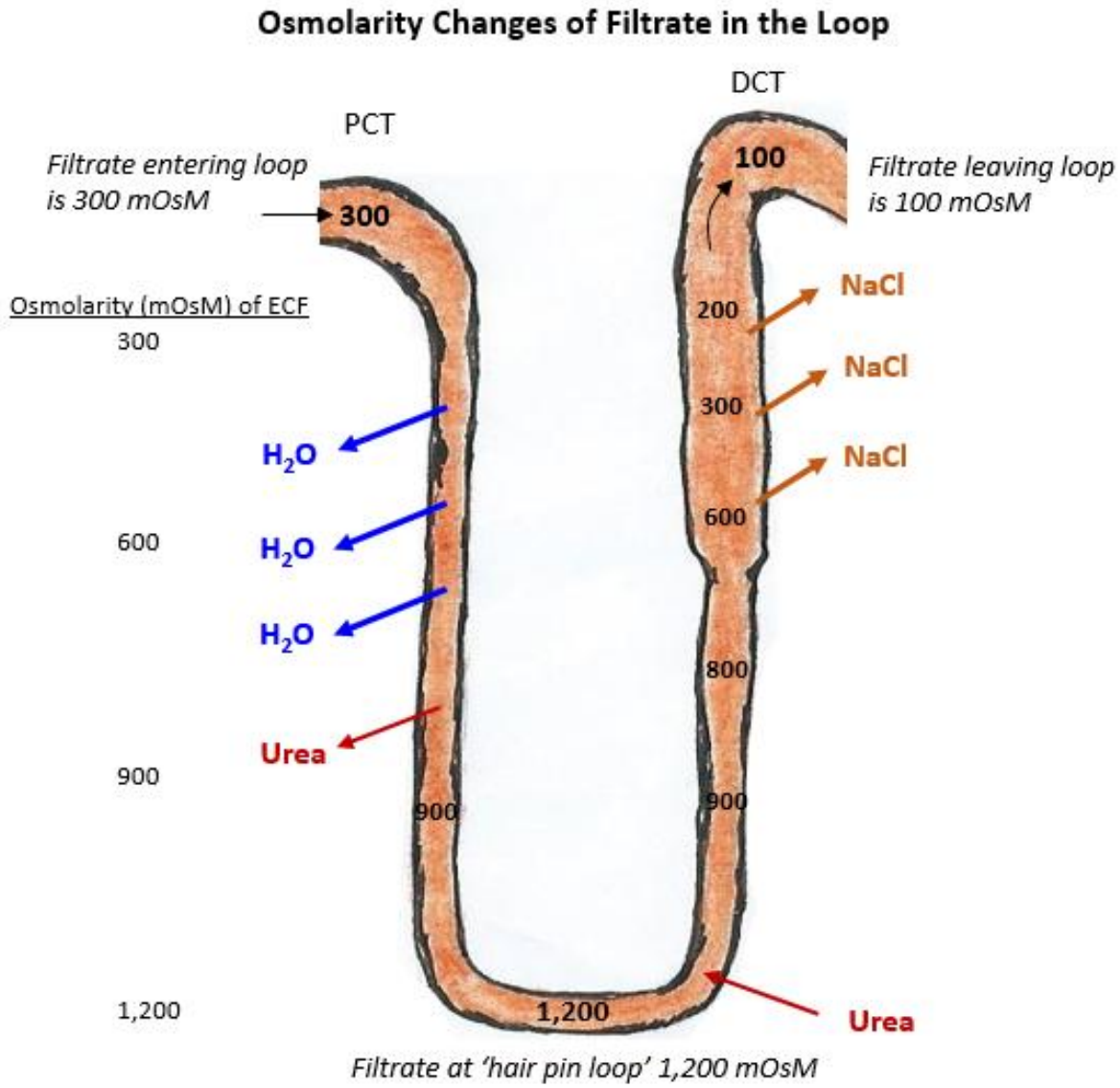


Figure 21.16 Shows the changes in osmolarity of filtrate as it enters and exits the loop of Henle, along with the osmolarity of the extracellular fluid (ECF) as it increases deeper into the medulla. This is called the 'saline gradient' of the renal medulla and assists in making the filtrate more concentrated at the bottom tip of the loop. The thick segment of the ascending portion of the loop of Henle is impermeable to water and only NaCl can be reabsorbed there, making the filtrate very dilute again by the time it gets to the start of the DCT.

Ascending Loop

The ascending loop of Henle has a short thin segment and longer thick segment, as seen in **Figure 21.16** above. The focus here is on **thick segment** which is lined with **simple cuboidal epithelium** without a brush border. This thick segment of the ascending loop **is completely impermeable to water!** This is due to the absence of aquaporin 1 in the epithelial cells lining this region. However, the ions **Na^+ and Cl^- are actively reabsorbed** by cotransport in this region. This has two crucial effects: **1)** It actively removes an enormous amount of NaCl from the filtrate allowing for the filtrate to become hypotonic (with an osmolarity of about 100 mOsM) by the time it reaches the distal convoluted tubule (DCT): and **2)** The pumping of NaCl into the interstitial space contributes to the **saline gradient** or hyperosmotic conditions going deeper into the renal medulla. This NaCl is reabsorbed by the vasa recta capillaries but its transit through the renal medulla contributes greatly to the salinity there.

The Countercurrent Multiplier System

As mentioned above, there is a steep **osmotic** or '**saline gradient**' in the ECF of the kidneys moving from isotonic (300 mOsM) in the renal cortex to extremely hypertonic (1,200 mOsM) deep in the renal medulla. This is a very important and a fundamental condition in the kidneys by which substances, particularly water, can be effectively reabsorbed by utilizing the power of this gradient. This force pulls water out via osmosis all along the descending loop of Henle.

The Hair Pin Loop

The steep saline or osmotic gradient exists due to the 'hair pin loop' of Henle where the adjacent loops have fluid flow in opposite (countercurrent) directions. The use of the term multiplier is due to the action of solute pumps that increase (multiply) the concentrations of urea and Na^+ deep in the medulla to over 1,200 mOsM (see **Fig. 21.17**). The descending and ascending flows form a ***countercurrent multiplier***. As the ascending loop **actively** reabsorbs NaCl from the filtrate. Note: Na^+ is actively pumped out of the ascending loop and Cl^- accompanies it.

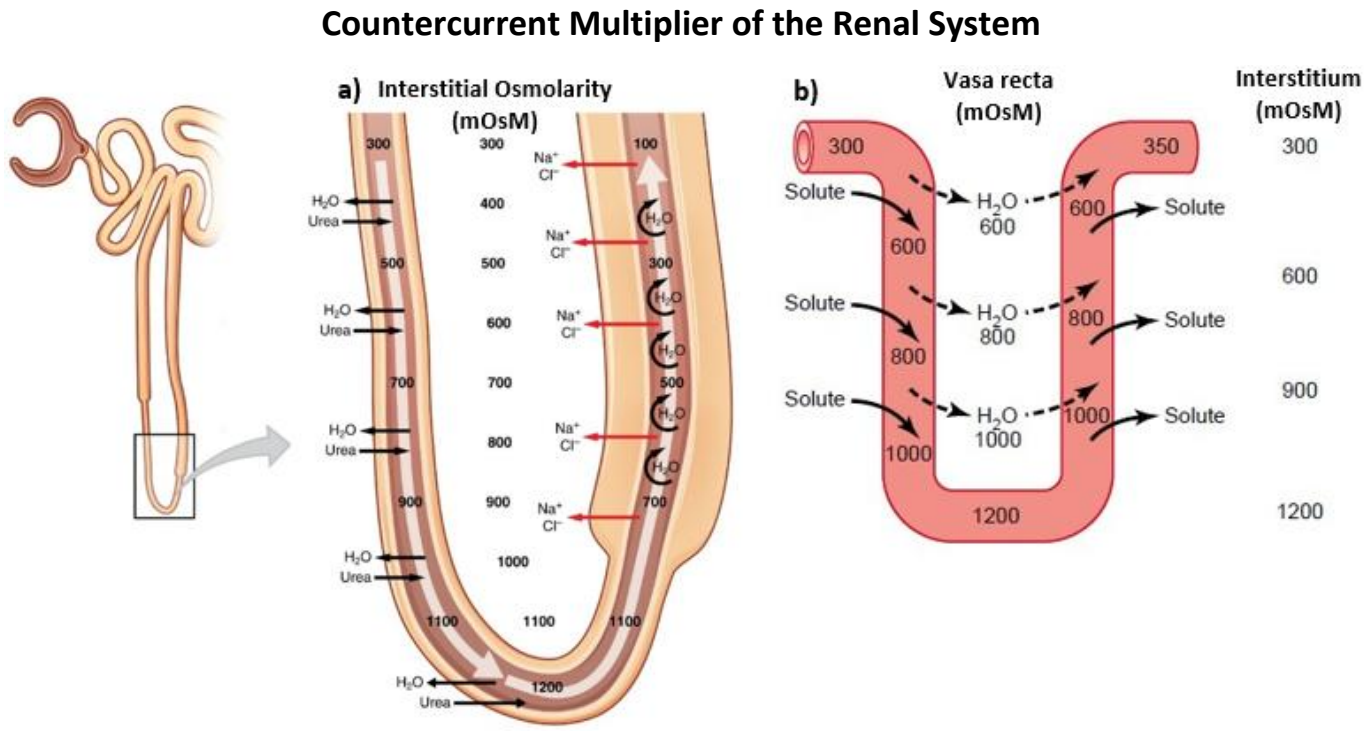


Figure 21.17. At left **a)** the Countercurrent Multiplier occurs from the arrangement of the descending and ascending limbs of the loop flowing countercurrent to each other, where both sides can take advantage of interstitial gradient to pull in more material from the tubules. At right **b)** the Countercurrent Exchanger involving the vasa recta capillaries where blood flows next to each other in opposite directions and especially augments water reabsorption.

As NaCl is being **actively** reabsorbed from the filtrate, at the same time, the collecting ducts actively pump **urea** into the interstitial spaces, some of which is secreted back into the descending loop. This results in the recovery of NaCl to the circulation via the **vasa recta** and creates a high osmolarity environment in the depths of the medulla. In this way, **urea is utilized as part of the gradient to aid in the recovery of water by the loop of Henle and collecting ducts**. The net result of this countercurrent multiplier system is to recover both water and Na^+ back in the circulation. Glomerular filtration constantly pushes new fluid into the tubule and the movements and gradients are maintained.

The Countercurrent Exchanger

The structure of the loop of Henle and associated vasa recta create a **countercurrent multiplier system**. Like the loop of Henle, the vasa recta capillaries have descending and ascending loops next to each other with blood flow in opposite directions (**countercurrent**). Within this vasa recta arrangement, the blood vessels can reabsorb both H_2O and NaCl yet can still maintain the osmotic gradient in the renal medulla.

Plasma flowing down the descending limb of the vasa recta becomes more hyperosmotic as the diffusion of water goes out of the blood, and the diffusion of solutes from the interstitium go into the blood. In the ascending limb of the vasa recta solutes diffuse back into the interstitium while water moves back into the vasa recta see **Fig. 21.17. b)**. This anatomical structure enables the reabsorption of large amounts of solutes.

Note about blood flow in the vasa recta:

In the vasa recta capillaries, not only does the slow flow rate allow time for exchange of nutrients and wastes, but it accommodates two other important factors. Firstly, the flow needs to be slow enough to allow blood cells to lose and regain water without either crenating (shrinking) or bursting. Secondly, too rapid a flow would remove too much Na^+ and urea from the blood, destroying the osmolarity gradient that is necessary for the recovery of solutes and water. Thus, the slow flow preserves the countercurrent mechanism, as the vasa recta descends, Na^+ and urea are able to enter the capillary freely, while water leaves freely; as they ascend, Na^+ and urea are secreted into the surrounding medulla, while water reenters the blood vessels and is reabsorbed.

The Distal Convoluted Tubule - Reabsorption and Secretion

At the transition from the Loop of Henle to the distal convoluted tubule (DCT), the osmolarity of the filtrate is now very low at about **100 mOsM** and approximately **80%** of the water has been recovered from the filtrate by the time it enters the DCT. The DCT will recover another 10–15 % before the filtrate enters the collecting ducts.

Actions of Parathyroid Hormone

The cells of the DCT also recover **Ca^{2+}** from the filtrate. It is here in the DCT that receptors for the **parathyroid hormone** (PTH) are found. The PTH acts to insert Ca^{2+} channels on the luminal surface which enhance Ca^{2+} recovery from what will shortly be urine. This is an effective way to conserve vital Ca^{2+}. This enables to body to retain more Ca^{2+} in the body because it loses less Ca^{2+} in the urine.

Vitamin D Synthesis

Our body makes vitamin D, and in truth it's really a hormone. Endogenous vitamin D production begins in the epidermis of the **skin** where the sun's ultraviolet radiation B (UVB) catalyzes 7-dehydrocholesterol (a precursor molecule derived from **cholesterol**) into **cholecalciferol** (Vitamin D_3). This is transported in the blood stream to the **liver** where it is processed into **calcidiol** which is 25-Hydroxycholecalciferol (25-Hydroxy Vitamin D_3). The final step occurs in the **kidneys**, where calcidiol is processed into the most active form, **calcitriol** which is 1, 25-Hydroxycholecalciferol (1, 25-Hydroxy Vitamin D_3).

The active form of vitamin D is very important for calcium recovery in the renal system. It induces the production of calcium-binding proteins that reabsorb Ca^{2+} back into the cell. These binding proteins are also important for the movement of calcium inside the cell and aid in exocytosis of calcium across the basolateral membrane. Any Ca^{2+} not reabsorbed at this point will be lost in the urine. It is also worth remembering that **Vitamin K2** is absolutely necessary for getting Ca^{2+} in the blood where it belongs, into

the bones. Vitamin K2 activated the enzymes **MGP** and **osteocalcin**, which takes excess Ca^{2+} out the blood (and arterial walls), and deposits it into bone tissue via MGP and osteocalcin respectively.

Collecting Ducts and Recovery of Water

When the filtrate moves from the DCT to the collecting duct, about 20% of the original water is still present, along with about 10% of the Na^{+}. If there were no other mechanism for water reabsorption after the DCT, about 20–25 liters of urine would be produced! Since we only have 5L of blood (about 3L of plasma) we know that this cannot occur.

The regulation of the final volume and osmolarity of the filtrate, and what will soon be urine, are major functions of the collecting ducts. The collecting ducts play a major role in maintaining the body's normal osmolarity, most significantly they do so by regulating the amount of water that is reabsorbed in this final stage. The various aquaporins within the renal tubules are indicated in **Fig. 21.18** below, highlighting the concentration of filtrate in the collecting ducts.

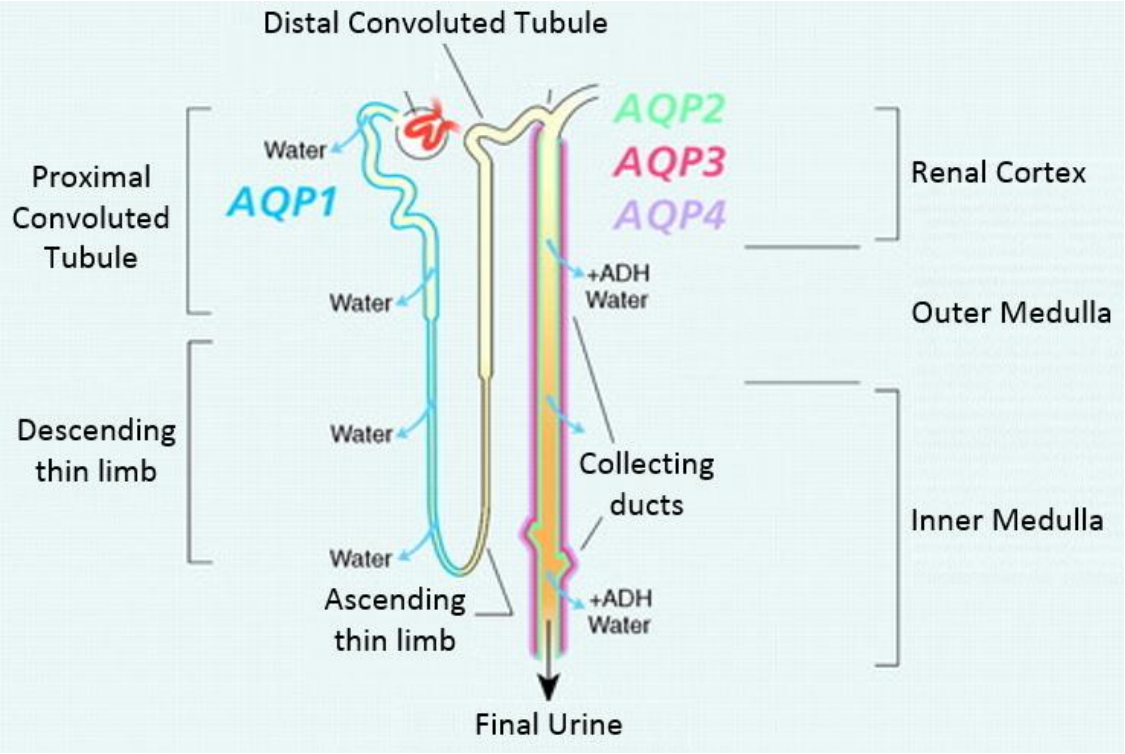


Figure 21.18 Shows the location and type of aquaporins (AQP's) in the renal tubules of the nephron. Aquaporins are water pores that allow the additional passage of water down its concentration gradient. A key site for control of water reabsorption in the nephron are the collecting ducts. Antidiuretic hormone (ADH) has its effects of drawing out more water from the filtrate at the collecting ducts, making a more concentrated urine.

Osmolarity of Blood is closely Monitored and Regulated

In another example of a negative feedback loop, when the blood becomes **hyper-osmotic** (above 310 mOsM), systems are in place that cause the collecting ducts recover more water, reduce urine output and bring the plasma osmolarity back into its homeostatic range.

If the blood becomes **hypo-osmotic** (below 295 mOsM), the collecting ducts will recover less of the water, eliminate more urine, which should lead to restoration of blood osmolarity. This regulation is achieved by interactions between several body systems as shown in detail in **Fig. 21.19** below.

Renin-Angiotensin-Aldosterone System

The kidneys are in the perfect position to monitor the condition of blood and to put into action mechanisms that can help maintain homeostasis. Not only does the **juxtaglomerular apparatus** monitor the osmolarity of the blood, but so too does the hypothalamus via **osmoreceptors**. In terms of the renal control of body fluid osmolarity, it starts when the **juxtaglomerular cells** release **renin** in response to an increased osmolarity of the incoming filtrate. This puts into motion the **Renin-Angiotensin-Aldosterone System** as outlined below.

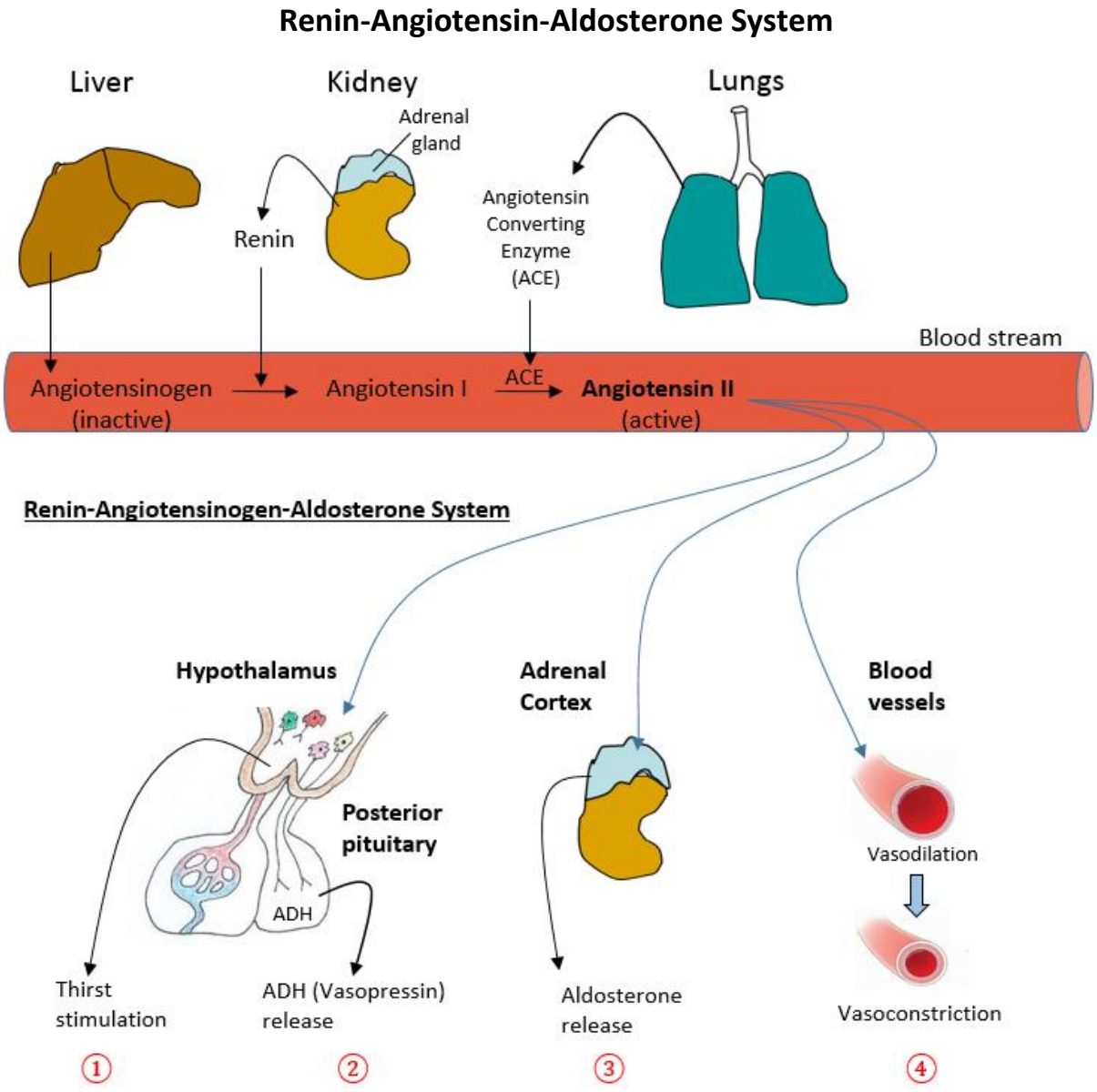


Figure 21.19 The renin–angiotensin–aldosterone system is a cascade to conserve water and maintain blood pressure. The liver synthesizes and secretes **angiotensinogen**, an inert (inactive) elongated peptide. If, due to a drop in blood pressure, **renin** is released by the kidneys into the bloodstream, it catalyzes the conversion of angiotensinogen into **Angiotensin I** via *proteolytic activation*. **Angiotensin Converting Enzyme** (ACE) then completes the activation by converting angiotensin I into **Angiotensin II**, which is the biologically active form of this hormone. As shown in 1 to 4, it is angiotensin II that stimulates thirst and the release of AHD by the hypothalamus, and triggers the release of aldosterone by the adrenal cortex, and it is also a powerful vasoconstrictor.

Summary of the diagram above:
The kidneys cooperate with the lungs, liver, and adrenal cortex via the renin–angiotensin–aldosterone system. The liver synthesizes and secretes the inactive precursor **angiotensinogen**, it is released by the liver into the bloodstream wherein contributes to the colloid osmotic pressure (COP) of the plasma, since it is released in its inert (inactive) elongated peptide form.

If **renin** is release by the kidneys into the bloodstream (for example, if blood pressure gets low), it catalyzes the conversion of angiotensinogen into **Angiotensin I** via *proteolytic activation*, wherein renin cleaves the "-ogen" off and begins the activation process from the formerly inert longer hormone.

Angiotensin Converting Enzyme (ACE) predominantly lining the alveoli of the lungs (but can come from many sources of epithelial tissue) then completes the activation by converting angiotensin I into **Angiotensin II**, which is the biologically active form of this hormone.

The actions of Angiotensin II are multifaceted (see **Figure 21.19** above) it stimulates:

1) The release of the steroid hormone **aldosterone** from the adrenal cortex (endocrine gland that sits on top of each kidney). The cells in the DCT and collecting ducts have receptors for aldosterone and this hormone is primarily involved in the regulation Na^+ recovery. Aldosterone stimulates Na^+ and K^+ channels as well as Na^+/K^+ ATPase pumps on the basal membrane of the cells. When aldosterone output increases, more Na^+ is reabsorbed (retained by the body) from the filtrate and the associated osmotic recovery of more water passively follows the Na^+.

2) The release of **Antidiuretic hormone** (ADH) which is also called **vasopressin**. This hormone is made in the hypothalamus but stored and released from the **posterior pituitary**. When the cells lining the collecting ducts (and the DCT) are stimulated by ADH, they insert **aquaporin 2** channels (**AQP2**) - also called "water pores" into these tubules. As the collecting ducts descend deeper into the medulla, the osmolarity surrounding them increases (due to the countercurrent mechanisms described previously). When the water pores are present within the collecting duct, water will move osmotically from the collecting duct into the surrounding interstitial space and into the peritubular and vasa recta capillaries – thus **increasing the amount of water reabsorbed**. This makes the filtrate more concentrated as it nears the end of the collecting duct where it enters the minor calyx, and can produce very **concentrated** urine

3) With mild dehydration, plasma osmolarity rises slightly. This increase is detected by **osmoreceptors** in the hypothalamus where it signals the **thirst center**, also located in the hypothalamus. **Angiotensin II stimulates the thirst center** and accentuates the thirst sensation, driving behaviors that can conserve and attain more water.

4) Finally, **angiotensin II is also an extremely potent vasoconstrictor**. It functions immediately to increase blood pressure systemically (across the body). It can vasoconstrict the afferent arteriole, and as we have already discussed, this will dramatically decrease GFR, and reduce urine output as a consequence. It also stimulates aldosterone production, providing a longer-lasting mechanism to support blood pressure by maintaining vascular volume (water recovery).

Osmolarity of Urine

With changes in plasma osmolarity come changes in urine osmolarity that reflect the needs of the body. When the body is dehydrated, renin will trigger the release of antidiuretic hormone (ADH). As a consequence, the actions of **ADH** will create a more concentrated urine. Conversely, if there is little to no ADH secreted, less water will be reabsorbed by the collecting ducts and the urine produced will be more dilute. In this way the **osmolarity of urine** has a very large range and can vary from **50 mOsM** (very dilute) to **1,200 mOsM** (very concentrated).

Intercalated Cells of the Renal Tubule

The **intercalated cells** of the renal tubules are epithelial cells that line specific regions of the lumen, and are associated with regulation of the acid-base homeostasis, primarily in the distal convoluted tubule (DCT). These cells play significant roles in **regulating the pH of blood**. Intercalated cells reabsorb K^+ and HCO_3^- (bicarbonate ions) while secreting H^+. This function lowers the acidity of the plasma while increasing the acidity of the urine. This is why usually the typical urine sample is acidic, with the pH value for urine at a **pH** of **5** or **6**, but it can vary from a pH of **4.5** to a pH of **8**. These cells also participate in potassium and ammonia transport.

Erythropoietin and Erythropoiesis

Erythropoietin (**EPO**) is a protein hormone released by **peritubular cells** and **interstitial cells** of the associated with the peritubular capillary and PCT. If cellular hypoxia is detected, the kidneys respond by releasing EPO in order to stimulate an increase in the formation of red blood cells in the red bone marrow. Erythropoietin is a 193-amino acid hormone with about 85% of it is produced by the kidney and the remaining 15% of circulating EPO being made by the liver.

If you start an aerobic exercise activity, your tissues will need more oxygen to cope, and the kidney will respond with more EPO. If erythrocytes are lost due to severe or prolonged bleeding, or under-produced due to imbalance or severe malnutrition, the kidneys spring into action by producing more EPO. If you move to a high altitude location the partial pressure of oxygen is lower, meaning there is less pressure to push oxygen across the alveolar membrane and into the red blood cell. One way the body compensates is to manufacture more red blood cells by increasing EPO production.

Regulations of Critical Elements by the Renal System

Regulation of Ca^{2+} and Phosphate

If Ca^{2+} levels in the blood drop too low, the parathyroid gland detects this and releases **parathyroid hormone** (PTH), which stimulates the DCT to reabsorb Ca^{2+} from the filtrate. This helps to retain more Ca^{2+} in the body. In addition, if Ca^{2+} levels are low, PTH inhibits reabsorption of HPO_4^{2-} so that its blood level drops, allowing Ca^{2+} levels to rise in relation to the phosphates. PTH also stimulates the renal conversion of calcidiol into **calcitriol** – which is the active form of **vitamin D**. Calcitriol then stimulates the intestines to absorb more Ca^{2+} from the diet. If Ca^{2+} levels are adequate or high, less PTH is released and more Ca^{2+} will be lost in the urine.

Regulation of Nitrogen Wastes

Metabolic nitrogenous waste products are handled by the kidneys (see **Fig. 21.20** at right). **Urea** is the most abundant nitrogenous waste and it is produced by the normal catabolism of proteins. Free amino acids from protein broken down are **deaminated** by having their nitrogen groups removed. This deamination converts the amino groups (NH_2) into **ammonia** (NH_3), ammonium ion (NH_4^+). Ammonia is extremely toxic, so most of it is very rapidly converted into urea in the liver.

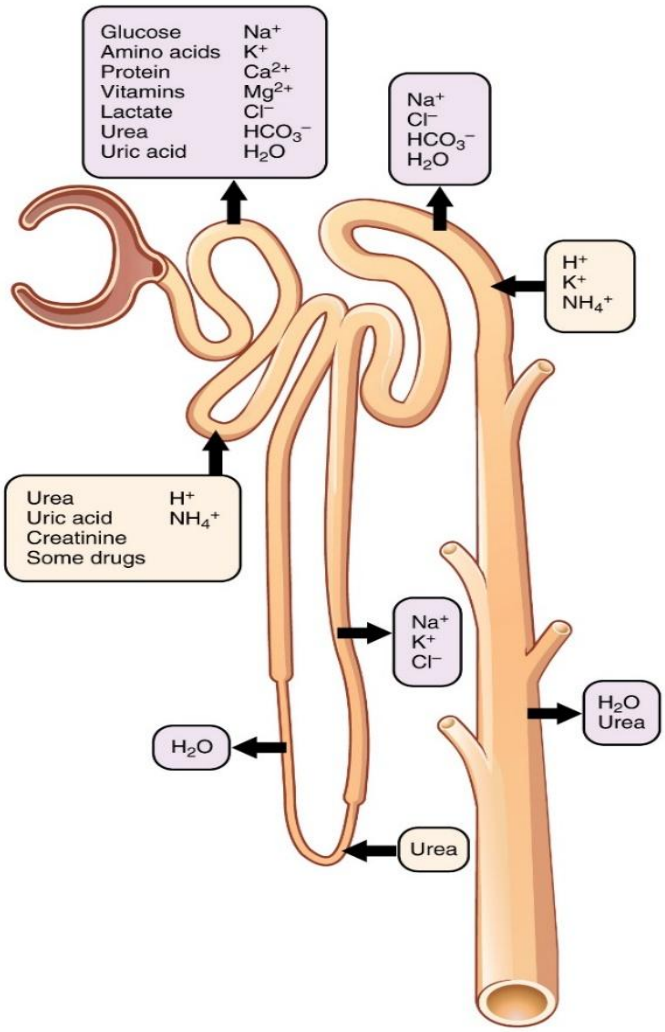


Figure 21.20 Above right is a summary of what normally moves into and out of the renal tubules. The elements that are reabsorbed (taken out of the renal tubules) are shown with an outward arrow, and the elements that are secreted (added into the renal tubules) are shown with an inward arrow and tan colored content box.

Uric acid is the product of normal catabolism of nucleic acids (such as ATP, GTP, DNA, RNA, etc.) and is filtered by the kidneys and removed from the plasma. **Creatinine** is the catabolic product of **creatine phosphate** in muscle tissue, and is also nitrogenous waste.

If the kidneys become impaired, creatinine level in the blood will rise due to poor clearance of creatinine by the kidneys. Thus, abnormally high levels of creatinine warn of possible kidney problems. In terms of nitrogenous waste, urine typically contains primarily urea with small amounts of ammonium creatinine and relatively smaller amounts of uric acid.

When **Blood Urea Nitrogen** (**BUN**) is measured it indicates the amount of urea nitrogen found in blood. The liver produces urea in the urea cycle as a waste product of the digestion of protein.

Normal human adult blood urea nitrogen should range from **6** to **20** mg/dL (1.8 to 7.1 mmol/L) of urea nitrogen and the BUN is an indication of renal health. Blood tests routinely check the amount of creatinine in the blood too, or a BUN-to-creatinine ratio.

Some reasons for elevated BUN are: High protein diet; decrease in glomerular filtration rate (GFR) (suggestive of renal failure); decrease in blood volume (hypovolemia); congestive heart failure; gastrointestinal hemorrhage; fever; and increased catabolism. Hypothyroidism can cause both decreased GFR and hypovolemia, and BUN has been found to be lowered in hypothyroidism and raised in hyperthyroidism. However, the main causes of a decrease in BUN are severe liver disease, being in an anabolic state, and syndromes of inappropriate antidiuretic hormone function.

Renal Failure

Damaged kidneys will not be able to properly conduct all of their functions. If conditions continue to worsen to where kidney function is disrupted to the point they are unable to perform their normal regulatory and excretory functions sufficient to maintain homeostasis the result may be **kidney failure**, which is also called end-stage renal disease (ESRD). In **Fig. 21.21** below is an illustration of five common examples of what can cause renal failure and the appearance of the kidneys as a consequence.

Most often kidney failure is caused by other health problems that cause kidney damage the over a long period of time. Diabetes mellitus is the most common cause of renal failure, while hypertension is the second most common cause. When the kidneys fail, it means they are unable to work well enough without the aid of dialysis or a kidney transplant.

In general, there is acute and chronic renal failure. **Acute** means sudden onset with rapid reduction in urine formation (less than 500ml/day minimum being excreted). **Chronic** mean slow, progressive, insidious loss of renal function. Interestingly, often up to **75%** of renal function can be lost before renal failure is detected. In general, acute renal failure can fall into **3** categories:

1. Prerenal Renal Failure

This category basically means 'before' the kidneys. This type of renal failure can occur from a decrease in effective blood flow to the kidney, which results in a decrease in GFR in both kidneys. If there is low blood volume in the body, or a decrease in cardiac output, this will cause a decrease in volume of blood filtering through the kidneys. There are a number of ways this can result, for example from **dehydration**, **hypovolemia**, **low blood pressure**, **heart failure**, **cirrhosis of the liver**, or **changes in blood flow to the kidneys** that decrease renal perfusion (such as renal artery stenosis). All of these situations will lead to a decrease in GFR. The good news is that typically these conditions are reversible.

2. Intrinsic (Intra-renal) Renal Failure

Intrinsic and intra means 'within', thus this category of renal failure involves direct damage to the kidney itself. It is most commonly due to **ischemic** or **nephrotoxic injury** of the kidney tissue, leading to **nephritis** (inflammation and compromised nephrons). This means that the kidney are either being deprived of O_2 and nutrients, or they are being harmed by harsh toxic chemicals.

Also, most drugs (medications) contain extremely toxic substance to both the **kidney** and **liver** and cause tissue damage to these two organs in particular. For example, the only CDC promoted drug to treat COVID was **remdesivir**, which is well known for causing acute kidney injury, similar to **glomerulonephritis** (tubular necrosis or nephritis), which can lead to complete kidney failure. Other toxic medications like **tacrolimus** used for immunosuppression can also directly damage the tubular cells of the kidney and result in a form of intrinsic kidney failure. Another cause of intrinsic kidney failure is **rhabdomyolysis**, which occurs when damaged muscle tissue releases its proteins and electrolytes into the blood. This leakage into the circulation can severely damage the heart and kidneys.

3. Postrenal Renal Failure

This category refers to acute kidney injury caused by ailments that are *downstream* of the kidney and most often occurs as a consequence of urinary tract obstruction, for example from kidney stones, or some kind of obstruction or dysfunction of the urinary collection system. This kind of renal failure may be caused by kidney stones, bladder stones, or malformation of the bladder, ureters, or prostate (in men). If a urinary catheter is obstructed or if there is an enlarged prostate (again only in men because women do not have a prostate gland) this can also obstruct the flow of urine and harm the kidneys which are upstream from these processes.

Various conditions that can usually lead to Renal Failure

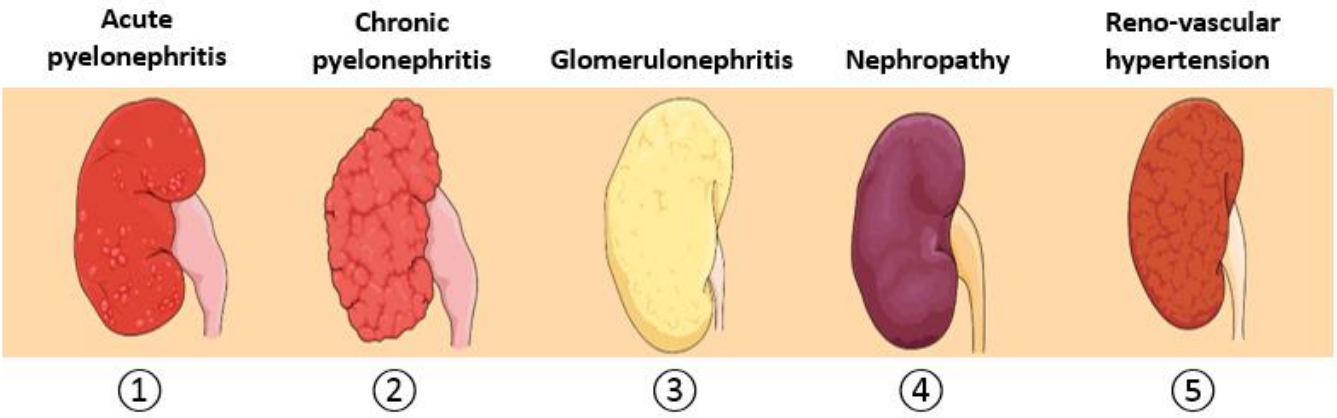


Figure 21.21 Illustrated above are five (5) examples of what can cause renal failure, showing the physical appearance of the kidney and ureter, and other distinguishing features. Details are provided for each state below.

Brief descriptors of the kidney conditions shown above

1. Inflammation (from toxins or poisons) of the renal pelvis (short term).
2. Renal inflammation and fibrosis induced by chronic recurrent or persistent renal infections (long term).
3. Inflammation of glomeruli. May occurs on its own or can be associated with other diseases such as diabetes mellitus.
4. Diabetic nephropathy is the chronic loss of kidney function in those with diabetes mellitus.
5. High blood pressure caused by the narrowing of the renal arteries carrying blood to the kidneys.

Keep in mind that, in general, the term **inflammation** refers to a part of the body that becomes reddened, swollen, hot, and often painful, especially as a reaction to injury. This is caused primarily by an increased blood supply (hence becoming hot, red, and puffy!). In most instances inflammation of the kidneys is an indication of a state of attempted repair of deteriorated renal function. The kidneys, or any organ, can readily recover from periods of acute inflammation as it is a repair mechanism. However, the longer chronic periods of inflammation can be the precursor to **glomerulonephritis**, which is a term for a group of kidney diseases that affect the glomeruli, the tiny filters in the kidneys that remove waste products from the blood are where

Photos of normal and polycystic kidneys are shown below in **Fig. 21.21**.

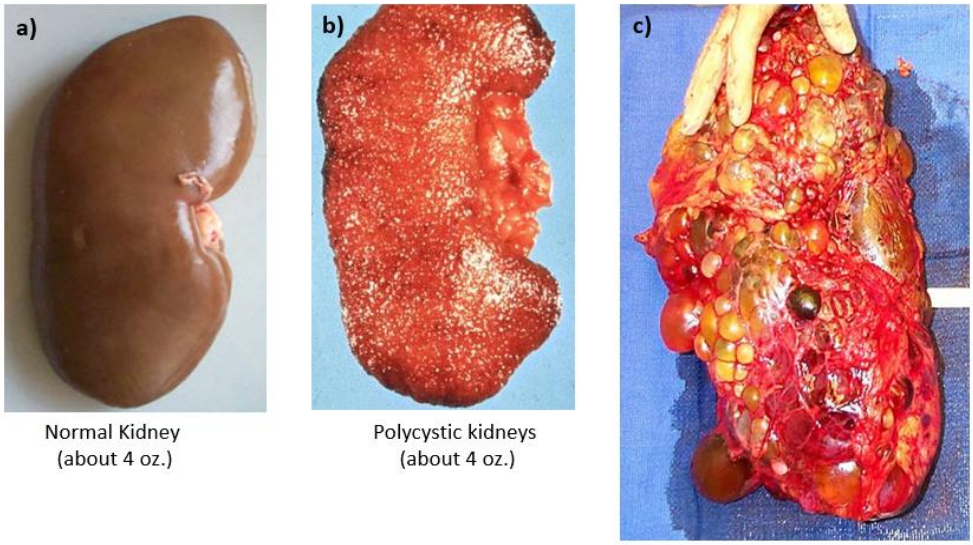


Figure 21.22 Comparison between **a)** a healthy kidney, **b)** a polycystic kidney and **c)** an enormously enlarged polycystic kidney. The cysts are not cancerous but are round sacs on the outer surface of the kidney containing toxic fluid. In people with polycystic kidney disease (PKD), many cysts grow inside of their kidneys, hence making the kidneys much larger than they should be.

Variety of Causes of Renal Failure

We have seen what renal failure is (above) and the categories of renal failure. Regardless of how it looks or the category, there are five broad direct **causes** of renal failure listed below with brief details of each. It may be valuable to view the list below of the 5 basic ways kidneys are harmed as a very important "***things to avoid***" list.

1. Toxic agents in the blood. Anything that is in the blood will come in contact with your kidneys as it filters the blood. Therefore, anything that is toxic (damages living tissue) in the blood has the ability to damage the kidneys. Avoid any type of toxin that's been established to harm your kidneys. Nothing can replace what your kidneys do!

- Ingesting any of the following substances: Most **medications**, **drugs**, **lead**, **arsenic**, **pesticides**, **additives**, preservatives, **artificial flavors** and **colors**, anything like this is tantamount to poison. It damages the nephrons. Please note that many prescribed drugs ('medications') include warnings of 'side effects' that most commonly damaged two internal organs. Can you guess which two organs are most aggressively damaged by many medications? The **kidneys** and the **liver**. These two organs are extremely important and you always want them to be healthy if you want to be happier, as they cleanse and detoxify the body, respectively.

- Long-term exposure to **high aspirin doses**. Isolated *acetylsalicylic acid* (aspirin) in high does over long periods of time can be aggressive and cause tissue damage that can lead to renal failure! Do not pop aspirin like candy, and don't eat candy either, they are both taxing on the kidneys.

2. Infectious organisms. Includes any renal system infections, from kidney, to ureters, bladder and urethra.

- Blood borne microbial toxins: As the kidney filters blood it going to come in contact with whatever is in the blood. Again, the kidneys are susceptible to damage from any toxins in the blood.
- Urinary Tract Infections (UTI's): These can be instigated from outside of the body, gaining access to the urinary tract via the urethra. Females have a greater risk of UTI's due to having a shorter urethra than males.

3. Inflammatory response. This occurs during **allergic reactions**, which are characterized by an exaggerated inflammation response. Often if the body has been primed with an allergen (something the body sees as foreign or toxic), although not necessarily harmful, the re-introduction of it stimulates a full on heightened response. It may be that many some diseases have their roots in pathogenic priming by injections, medications, and substances in food that are not natural and rejected by the body.

- Glomerulonephritis: This state is brought on by inflammation of the glomeruli or blood vessels of the kidney. Acutely it may be caused by infections such as strep throat, or other illnesses, including lupus, nephritic syndrome, acute kidney injury, or chronic kidney disease and polyarteritis nodosa.

- Sepsis: This is the body's extreme response to an infection, and can be life-threatening. Sepsis happens when one infection triggers a chain reaction throughout your body. Infections that lead to sepsis most often start in the lung, urinary tract, skin, or gastrointestinal tract.

4. Obstruction of urine flow. Various temporary or pathological states can block the flow of urine at several points along the urinary tract. *Any* blockage in urine flow can be very damaging to the structures upstream:

- Kidney stones (calcium oxalate, uric acid crystals) and bladder stones.
- Growths or tumors that obstruct and block off urine flow somewhere along the urinary tract.
- Enlarged prostate gland (in men only) that blocks urethra, thus urine flow.

All of these conditions create **back pressure**, which cause a decrease in glomerular filtration rate (GFR). Once there is a significant decrease in GFR, effectively there is no longer sufficient cleansing of the blood, and renal failure is possible.

5. Insufficient renal blood flow. As we know, the kidneys normally receive from **20 to 25%** of cardiac output, which is more blood than the brain receives. It makes sense since the blood needs to be cleansed. Therefore, if there is insufficient blood flow to the kidneys, the blood cannot be properly cleansed.

- As a consequence of heart failure, which exhibits a decrease of blood perfusion to all tissues.
- Hemorrhage or cardiovascular shock, which result in a significant drop in mean arterial pressure (MAP) and again leads to a decrease in perfusion to the kidneys.
- Atherosclerosis of the renal vasculature, decreasing incoming or exiting blood to/from kidneys.

All these conditions can lead to inadequate filtration pressure at the glomerulus, and therefore can prevent adequate filtering and cleansing of the blood.

Potential Ramifications of Renal Failure

Regardless of the cause of renal failure, the **consequences** or **ramifications** can be as follows:

1. **Uremic Toxicity** - This is caused by the retention and buildup of toxins and waste products in blood. The 'ur' in uremia means urine and emia means blood, so it's the state of having urine in your blood. Uremia is a serious condition because it's a sign of severe kidney dysfunction, such as end-stage renal disease. It can cause hormone imbalances, metabolic problems and even death.

2. **Metabolic Acidosis** - This condition is characterized by an increase in plasma **acidity** along with electrolyte disorders, which result in imbalances in the body's **acid-base balance**. Metabolic acidosis develops when too much acid is produced in the body, or when the kidneys cannot remove enough acid from the body. Most often other underlying conditions cause the metabolic acidosis. Symptoms often include rapid breathing, feeling confused or very tired. Severe and lengthy metabolic acidosis is serious and can lead to shock (lack of blood flow) and even death.

3. **Potassium (K^+) Retention** - The inability to secrete K^+ at the kidneys effects RMP. The risk for **hyperkalemia** (abnormally high potassium levels in the blood) is high if the kidneys cannot remove the excess K^+ in the blood. The usual route for excretion of excess K^+ is through urine. If the GFR is significantly low, then so is urine output, which means the extra K^+ will be retained in the blood. Symptoms of hyperkalemia are abdominal pain and diarrhea, heart palpitations or arrhythmia, muscle weakness or numbness in limbs, and nausea and vomiting.

4. **Na^+, Ca^{2+} and PO_4^{3-} (phosphate) Imbalances** - The inability of kidneys to regulate ion reabsorption and secretion leads to many problems. If the kidneys begin to fail they cannot remove the excess Na^+, Ca^{2+} and PO_4^{3-} (phosphate) from the body. Kidney disease also tends to lead to an **increase in parathyroid hormone** release, which leads to a buildup of too much phosphate in the blood (**hyperphosphatemia**) that binds to Ca^{2+}. If GFR declines toward kidney failure levels, there is an inability of the kidneys to excrete the excess PO_4^{3-}. This hyperphosphatemia suppresses the renal hydroxylation of the inactive 25-hydroxy-vitamin D to **calcitriol** (active form of vitamin D). The serum calcitriol levels become low when the GFR is goes below the threshold of 30 mL/min. Thus, if kidneys cannot excrete ions properly, elevated phosphates then leads to lower vitamin D.

5. **Loss of Plasma Proteins** - Low albumin in blood (**hypoalbuminemia**) is common in end-stage renal disease (ESRD) because the damaged kidneys become leaky and allow albumin to get into the filtrate, which will then be lost in the urine (**albuminuria**). The lowered plasma albumin decreases the colloid osmotic pressure of the blood, which greatly upsets body homeostasis.

6. **Anemia** - Renal failure causes the reduction or loss of **erythropoietin** (EPO) release from the kidneys which will lead to anemia, since erythropoietin stimulates the bone marrow to produce more red blood cells. Inadequate production of EPO makes it difficult for the body to cope with increased O_2 demands or to supply O_2 adequately even under normal conditions. Severe anemia can be life threatening.

7. **Depressed immune system** - Increased **toxic waste** and **acidic conditions** across the body suppress many systems, but significantly **suppress immunity** and **repair**. Impairment of the immune system is one of the most critical and serious complications in those with chronic renal failure. Let's all avoid renal failure please.

Possible Treatments for Renal Failure

- Find the cause for renal failure and Stop it. Then begin to alleviate and remove the Cause.
- Dialysis. This involves external devices that filter and cleans the blood for the kidneys.
- Kidney Transplant.

The Renal System is integrated with all other Body Systems

All systems of the body are interrelated. A change in one system will affect all other systems in the body, from mild to devastating effects. A failure of some aspects of renal function may not be too harmful or deleterious, for example, urinary incontinence. It is inconvenient but is not life threatening. However, as discussed above in the **ramifications** of renal failure, the loss of other urinary functions can be very serious and may even prove fatal. A failure to synthesize vitamin D is one such example.

Vitamin D Synthesis

As noted previously, our body makes vitamin D. However, it does require exposure of skin to ultraviolet rays b (UVB). Without this exposure, your body cannot make its own vitamin D. It is also worth mentioning that it is another type of UV light called UVA. This is the type of UV light that can create what is called "photo-damage" to your skin. In terms of UV light, you can think of the A for Aging and the B for Beneficial.

It is very likely that most people have been told and believe that the best time of day to be sure to avoid any sun exposure (in order to stay safe from danger) are the hours between 10am to 2pm, right? It turns out that is the only time that UVB light is at its maximum and therefore it is absolutely the best time frame for healthy sun exposure. Yes, the most beneficial time to get home made vitamin D is between the hours 10am and 2pm. Therefore, the advice to keep out of the sun at those times seems oddly bad, because it means the natural production of your own vitamin D will suffer dramatically if this advice is followed.

Almost as if adding insult to injury, it is often suggested that if you must be outside in the sun at those times, then please for goodness sake use **sunblock** lotions all over your exposed skin. It turns out that most sun block lotions contain many toxic carcinogenic chemicals, such as the common ingredient **oxybenzone**. In addition to its natural toxicity, it also acts to block UVB, not UVA! Wait, what? Therefore, not only is this lotion blocking the 'good' UV rays that make vitamin D, it also introduces a steady stream of synthetic estrogen mimickers into the body. These are not good ideas if you want to be healthy.

If sun exposure is not possible, the next best thing might be to eat foods that naturally contain vitamin D. Taking vitamin D supplements may sound like a good alternative but as mentioned briefly, vitamin D is actually really a **hormone**. This is an important distinction.

Many health scientists have finally suggested that "vitamin" D be referred to as a hormone rather than a vitamin because it actually functions just like a hormone. Change can sometimes take a while. It becomes critical to recognize vitamin D as a hormone because when any hormone is taken as a supplement the consequence is that the natural intrinsic hormone ceases to be made! Put succinctly, if you take Vitamin D, you stop making it, and what you make is far superior to any supplement, so you are much better off making your own.

Deficits in vitamin D may result in problems with tissue proliferation, neuromuscular function, blood clotting, and inflammatory responses. There is also a critical relationship between low (inadequate) vitamin D levels and both depression and impaired healing responses. Individuals with low vitamin D are

more susceptible to many illnesses. Put another way, when vitamin D levels in the body are high, it is very difficult to become ill. Recent research has confirmed that vitamin D receptors are present in most regions and tissues of the body, reflecting the systemic importance of vitamin D.

Activated vitamin D is important for absorption of Ca^{2+} in the digestive tract, its reabsorption in the kidney, and the maintenance of normal serum concentrations of Ca^{2+} and phosphate. Calcium is vitally important in bone health, muscle contraction, hormone secretion, and neurotransmitter release. Inadequate Ca^{2+} leads to disorders like **osteoporosis** (brittle bones) and **osteomalacia** (overly soft bones) in adults and rickets in children.

Healthy Sun Exposure

It turns out that it is relatively **easy** to be out and about in the sun and not get burned and not get toxified. Just properly cover up your body to protect the skin against too much sun exposure. Done. Nice thick natural fiber clothing is very effective. Plus, umbrellas, hats, and scarfs. This way you can enjoy the healing rays of the sun and make your own vitamin D - which is the best possible way for this hormone to have its positive effects on your body.

Perhaps surprising to some, wearing polarizing sunglasses is not a good idea if you want to be in tune with nature. The natural **uncovered eye** allows the retina of the eye to receive pure unfiltered sunlight. The intensity of the sun and other information is detected within the retina, interpreted and shared throughout the body. In this way, the body can then actually prepare for the sunlight conditions appropriately, as it is that perceptive and responsive to the prevailing conditions. If the eyes are covered, the body's response systems (paracrine, nervous and endocrine) are working on erroneous information and their responses become out of sync with the conditions in which the body is surrounded. Therefore, a good suggestion is to avoid sunglasses that filter light and block your eyes from nature, and to not use toxic poisonous lotions on your porous, absorptive skin.

Get into the habit of always thinking of your body as supremely intelligent and that it is always trying to help and protect you. Therefore, it is most beneficial for the body to have the most accurate information available in order to come up with the best solution.

Vitamin K2 is Important

Like vitamin D, vitamin **K2** is very important to health. It is mostly attained through diet and is required to activate two proteins: **1)** Matrix Gla-protein (MGP), and **2)** Osteocalcin. Here is what these do:

The **MGP** (basically = glutamic acid) binds to any excess calcium ions (Ca^{2+}) in arterial walls and prevents it from lining blood vessels. Once removed, then the K2 activated **osteocalcin** transports that calcium into the bone matrix, where it belongs.

Amazingly, there is a relationship between **osteoporosis** (not having enough Ca^{2+} in your bones) and increased incidence of **heart disease**. A South African heart surgeon noted these two conditions go **hand-in-hand**, as vitamin K2 is required to ensure that calcium goes where it's supposed to.

By the way, it was also shown that statin drugs deplete vitamin K2 (Journal of American College of Cardiology and Expert Review of Clinical Pharmacology), and it was suggested it may not be good if to have a vitamin K2-poor diet. Maybe ditch the toxic drugs and eat more natto and other fermented foods, plus gouda and brie cheese, and dark meats for the highest K2 density food sources.

Micturition – Voiding Urine

In the body, urination is termed **micturition** (from Latin micturire, meaning "to desire to urinate") and is defined as the process of eliminating urine from the **urinary bladder** via the **urethra** (see **Fig. 21.23** below). Micturition is also known as the **voiding** phase of bladder control and it is typically a short-lasting event. Urinary flow rate in a full bladder is 20-25ml/s for men and 25-30ml/s for women.

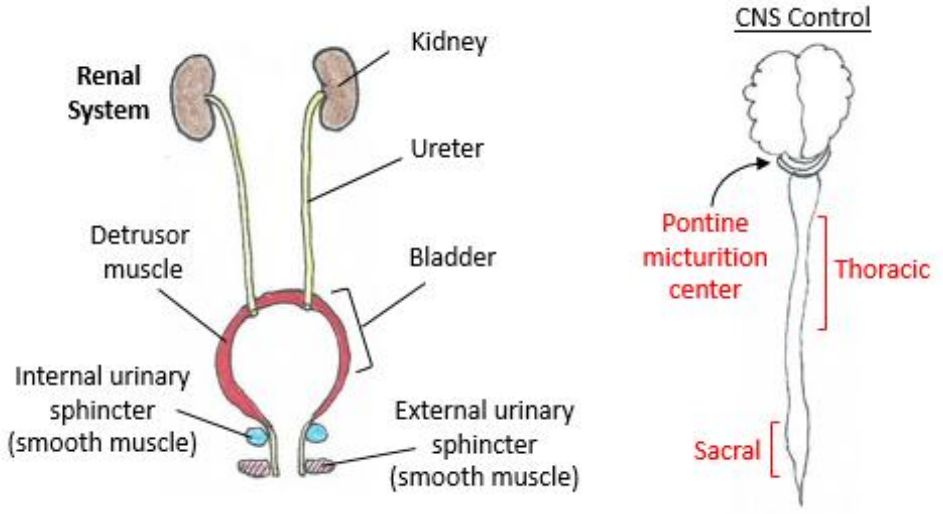


Figure 21.23 Diagram of the renal system showing that the bulk of the bladder wall (at left) is made of detrusor (smooth) muscle, the contents of which are regulated by the internal and external urinary sphincters, composed of smooth and skeletal muscle, respectively. The micturition reflex (voiding of urine) is coordinated by the pons in the central nervous system (CNS) and the thoracic and sacral regions of the spinal cord (at right).

The bladder stores urine which is not modified while in the bladder. The bladder is a muscular container, composed mostly of smooth muscle called **detrusor muscle** (from Latin detrus- 'thrust down') which is arranged in 3 layers: An inner and outer **longitudinal** layer, with a **circular** layer in the middle. T

he volume capacity of the bladder varies from about **300** to **550 ml**. The afferent (incoming) stretch sensitive nerves that have mechanoreceptors embedded in the bladder wall will signal the need to void the bladder after it contains around from **300** to **400** ml of urine. See **Fig. 21.24** below for the arrangement of the regulation of the bladder when it is empty.

The Micturition Reflex

The micturition reflex involves the coordination between the central, autonomic, and somatic nervous systems, each in turn communicating information in sequence to facilitate the elimination of urine.

As mentioned, the brain centers regulating urination include the pontine micturition center in the pons, and the cerebral cortex. In also involves several relays along the thoracic and sacral regions of the spinal cord, which are encumbered within the parasympathetic division of the autonomic nervous system (ANS). Though not entirely, voiding of urine is *predominately* under the control of the **Parasympathetic** division of the ANS.

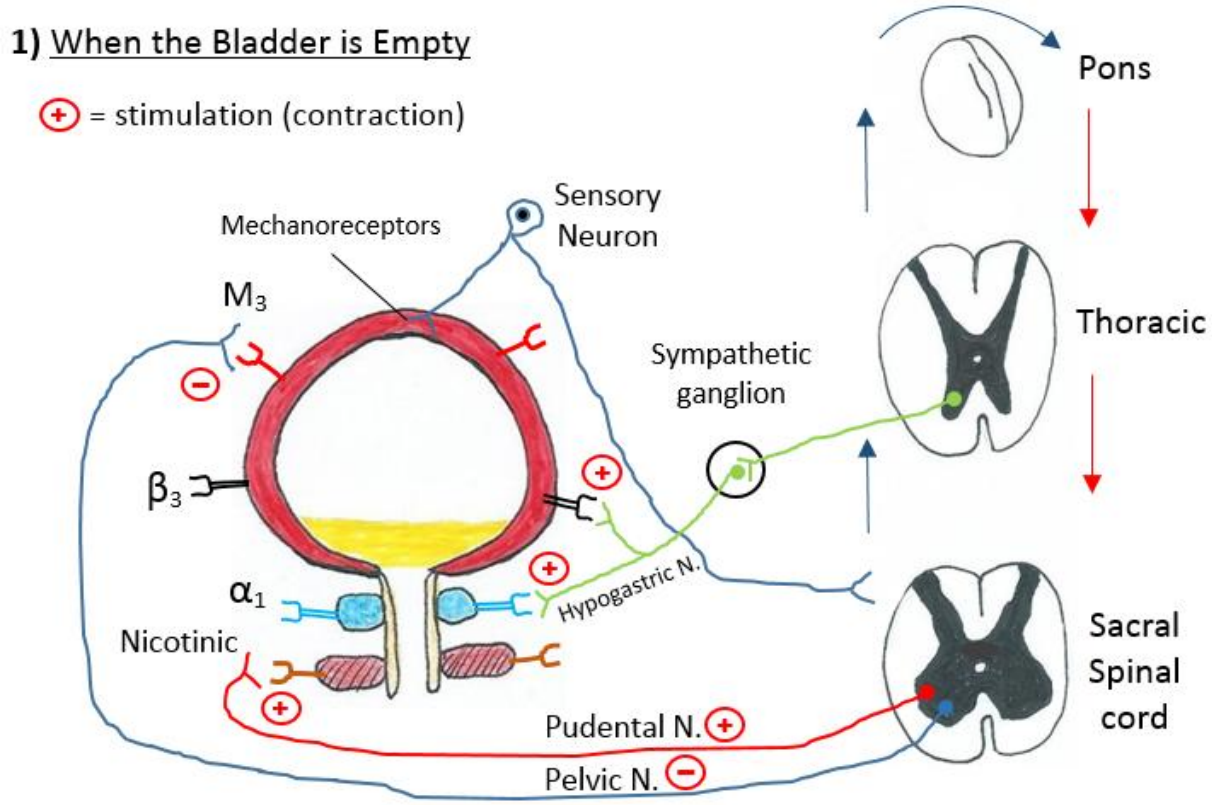


Figure 21.24 Diagram showing the elements involved in maintaining control of the bladder when it is empty or contains low levels of urine. The key component in this state is to ensure that both the internal and external urinary sphincters are closed. When at rest, it is sympathetic innervation via alpha 1 receptors (α_1) that affects the internal urinary sphincter under involuntary control, and it is parasympathetic innervation via nicotinic receptors acting on skeletal muscle of the external urinary sphincter, under voluntary control. In addition, the activation of beta 3 (β_3) receptors inhibits the contractions the bladder. As shown at right, this is all coordinated by the pontine micturition center in the pons of the brain.

Importantly, there are **mechanoreceptors** within the detrusor muscle (see **Fig. 21.24** above) which detect the stretching of the bladder wall as it is filling with urine. They become triggered when a threshold is reached, indicating that the bladder is full and needs to be emptied. Since these receptors are specialized endings of sensory neurons, this sends afferent signals ascending through the spinal cord projecting up into the **pontine micturition center**. These signals then descend back down via motor pathways to innervate various effector tissues of the bladder (see **Fig. 21.25** below).

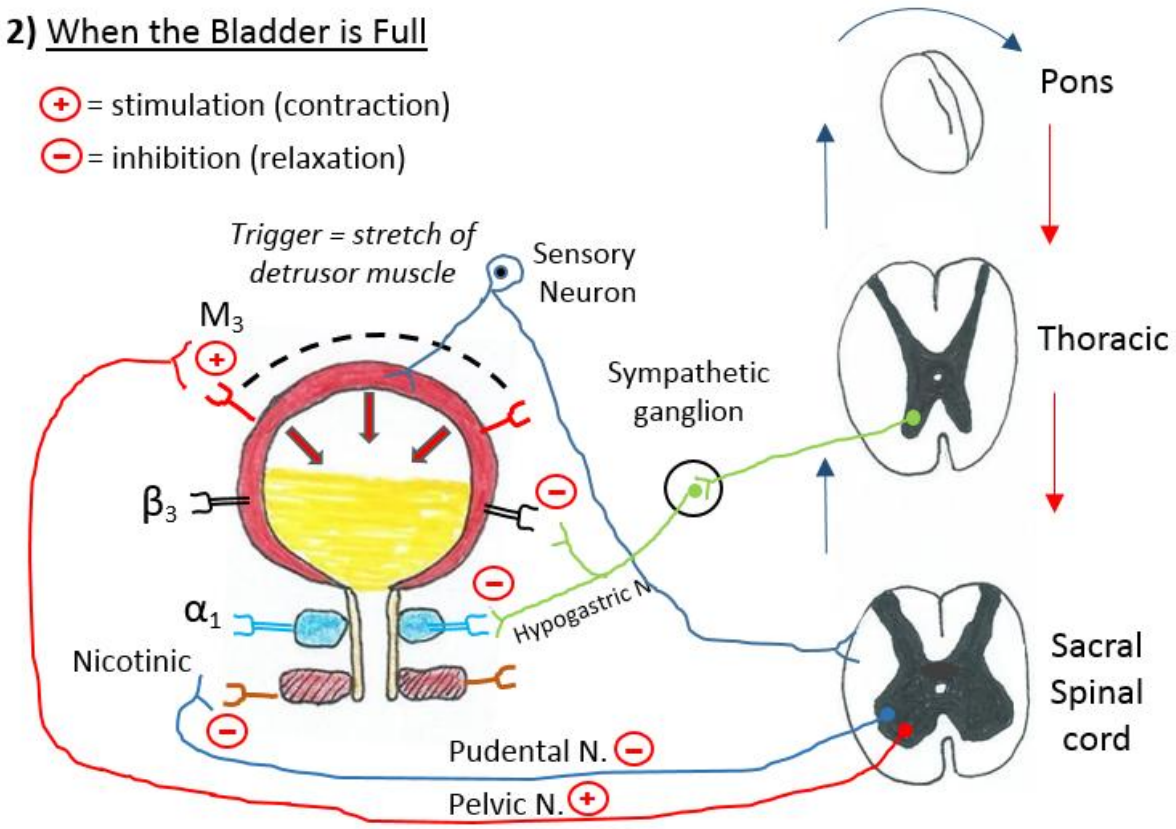


Figure 21.25 Shows a diagram of a full bladder and the mechanisms of the micturition reflex to void stored urine. The first element is the triggering of the mechanoreceptors when the bladder wall is stretched to a critical point from becoming full with urine. The afferent signal ascends the spinal cord to the pons and the descending signal is sent out from the pelvic N. (nerve) which acts on muscarinic 3 (M_3) receptors to contract the detrusor muscle, thereby decreasing the volume of the bladder and forcing urine towards the urethra. The active inhibition of β_3 receptors allows for the contractions the bladder. A central component in this state is to then ensure the inhibition and relaxation of both the internal and external urinary sphincters, allowing them to open. The last process which can prevent urine release is the external urinary sphincter, which most often must be consciously relaxed in order for urine to flow out of the bladder through the urethra and be eliminated out of the body.

After the cerebral integration for the conscious decision to urinate occurs, neurons of the pontine micturition center fire to excite the sacral preganglionic neurons. This activates parasympathetic pelvic nerve (S_{2-4}) causing a release of **ACh**, binding muscarinic 3 (M3) receptors on detrusor muscle **causing the detrusor muscle to contract**, increasing pressure on the urine.

This same micturition center also **inhibits sympathetic stimulation** to the internal urethral sphincter (in males) **causing the internal urethral sphincter to relax and open**. Combined with conscious cerebral control which signals **the external urethral sphincter to relax and open**, this allows the passing of urine out of the bladder via the urethra.

As the bladder fills the **rugae** (internal wrinkles) distend and a constant pressure in the bladder (intra-vesicular pressure) is maintained. This is known as the stress-relaxation phenomenon. The ability to voluntarily control micturition develops from about the age of 2 years as the CNS develops.

Common Bladder Conditions

- Cystitis: Inflammation or infection of the bladder causing acute or chronic pain, discomfort, or urinary frequency or hesitancy.
- Urinary stones: Stones (calculi) may form in the kidney and travel down to the bladder. If kidney stones block urine flow to or from the bladder, they can cause severe pain.
- Urinary incontinence: Uncontrolled urination, which may be chronic. Urinary incontinence can result from many causes.
- Overactive bladder: The bladder muscle (detrusor) squeezes uncontrollably, causing some urine to leak out. Detrusor over activity is a common cause of urinary incontinence.
- Hematuria: Blood in the urine. Hematuria may be harmless, or may be caused by infection or a more serious condition.
- Urinary retention: When urine does not exit the bladder normally due to a blockage or suppressed bladder muscle activity. The bladder may swell to hold more than a quart of urine.
- Cystocele: Weakened pelvic muscles (usually from childbirth) allow the bladder to press on the vagina. Problems with urination can result.
- Bed-wetting (nocturnal enuresis): Bed-wetting is defined as a child age 5 or older who wets the bed at least one or two times a week over at least 3 months.
- Dysuria (painful urination): Pain or discomfort during urination due to irritation, or inflammation of the bladder, urethra, or external genitals.

Urinalysis - Analyzing the Urine

Urine is a waste product made by the **kidneys** as a result of filtering and cleansing the blood. Since the state of urine is a very accurate reflection of the state of the body, a urine test can be conducted to help determine conditions in the body. A **urinalysis** is a thorough test of a urine sample that can be used to detect a wide range of disorders, such as urinary tract infections (UTI's), kidney disease, diabetes, etc. The examination of various components of the urine sample can yield information about a person's health and conditions that may exist. Urine has hundreds of different elements as waste products. What you eat, drink, how much you **exercise**, and how well your **kidneys** work can all affect the composition of your urine. See **Fig. 21.26** below demonstrating various visual representations of urine samples.

A **Urinalysis** of a urine sample most often includes the following tests*:

- **Color:** Many things affect urine color, including fluid balance, **diet**, medicines, and diseases. How dark or light the color indicates water content. Vitamin B **supplements** can turn urine bright yellow. Some medicines, blackberries, beets, rhubarb, or blood in the urine can turn urine red brown.
- **Clarity:** Urine is normally clear. Bacteria, blood, sperm, crystals, or mucus can make urine cloudy.
- **Odor:** Urine does not smell very strong, but has a mild odor. Some diseases cause a change in the odor of urine. For example, an infection with *E. coli* bacteria can cause a foul odor, while **diabetes mellitus** or starvation can cause a sweet, fruity odor.

- **Specific gravity:** This is a measure of the amount of substances in the urine. As water is the standard for specific gravity and how other liquids are assessed, the specific gravity of water is 1.000 (unitless) at 4°C. The higher the specific gravity of urine, the more materials in the urine. After drinking a lot of water, the kidneys make dilute urine, having a higher amount of water and thus a lower specific gravity. When dehydrated, the kidneys make more concentrated urine with less water in it, thus having a higher specific gravity.
- **pH:** The **pH** is of a solution is the measure of H^+ concentration in solution, and urine typically has a pH of about 6, but it can vary from a pH of 4.5 (strongly acidic) to a pH of 8 (alkaline or basic).
- **Glucose:** Glucose is 'blood sugar' and normally there is no glucose found in urine. When blood sugar levels are very high, as in states of uncontrolled **diabetes mellitus**, the hyperglycemia produces high glucose filtrate levels and glucose cannot be reabsorbed because its concentration is too high for the carriers transport maximum, that is, carriers for glucose become saturated. For this reason, not all the glucose is pulled from the filtrate thus it is found in the urine of those with diabetes mellitus. This can also occur when the kidneys are damaged, being taxed or overworked.
- **Protein:** Protein is normally not found in the urine. **Fever**, strenuous **exercise**, **pregnancy**, and some diseases, especially kidney disease, may cause protein to be in urine.
- **Nitrites:** Bacteria associated with **urinary tract infections (UTI's)** make an enzyme that changes urinary nitrates to nitrites. *Nitrites* in urine indicate a UTI might be present.
- **Leukocyte esterase (WBC esterase):** Leukocyte esterase is an enzymes that tests for leukocytes (**white blood cells [WBCs]**) in the urine. WBCs in the urine may indicate a UTI is present.
- **Ketones:** When fat is broken down and used for energy by the body, substances called ketones (or ketone bodies) are produced. These enter the filtrate and are passed into the urine. Large amounts of ketones in the urine may mean a very serious condition of **diabetic ketoacidosis** is present. There are also many other factors. A diet low in sugars and starches (carbohydrates), starvation, or severe **vomiting** may also cause ketones to be in the urine.

*A **Chemstix** is a urine 'dipstick' test used when conducting urinalysis. The test strip is saturated with urine and the test squares change color to indicate the presence or absence of compounds like proteins, ketones, hemoglobin, nitrites and cells, as well as the specific gravity and pH of the urine.

Figure 21.26 The colorations of urine samples can range from the normal light straw yellow color (at left), to slightly dark (dehydration likely), to cloudy (protein or bacteria present), to a very darkly discolored brown urine (likely from blood or protein metabolites in urine due to muscle damage).

Urine Microscopic Analysis

Before considering the examination of urine sediment microscopically, it will be helpful to understand the following concept of the major constituents of **urinary sediment**, as they can be classified into three major groups: **1)** Cells; **2)** Casts; and **3)** Crystals. Below are descriptions of these three groups of sediments.

Cells in urinary sediment can be derived from the lining of the urinary tract or from the blood as a result of normal wear and tear in the body, periods of inflammation, or from various disease processes.

a) Transitional cells: Derived from the transitional epithelium that lines the renal pelvis, ureter, and urinary bladder.

b) Squamous epithelial cells: Derived from the distal portion of the urethra or inflamed areas of the urinary bladder.

c) Red blood cells: These are not normally associated with urine. Their presence in urine (**hematuria**) may be due to temporary strenuous activity or associated with a variety of disorders.

d) White blood cells: More than a few present in the urine may indicate **pyuria** (presence of WBCs or pus) and may be indicative of damage or an infection.

Casts in urine are hardened masses of material formed by the precipitation of proteins and agglutination (clumping) of cells. They often assume the shape of the lumen of a renal tubule in which they form, hence their name, relating to **casting in a mold**. Casts can form as a result of protein in urine passing through renal tubules and changing the consistency, from highly acidic urine, and highly concentrated urine. Casts are named after the cells or substances that compose them, or on the basis of their appearance.

a) Hyaline casts: Consist mostly of a micro-protein derived from renal tubule epithelial cells.

b) Epithelial casts: Consist largely of tubular epithelial cells.

c) Granular casts: Considered one phase in the breakdown of cellular casts. Depending on the degree of breakdown, they may be classified as coarsely granular and finely granular.

d) Waxy casts: Considered the end stage of the breakdown of cellular casts.

e) White blood cell casts: Consist of aggregates of white blood cells.

f) Red blood cell casts: Consist of aggregates of red blood cells.

Crystals

Many **crystals** form in urine, from the end product of tissue metabolism and consumption of excessive amounts of certain foods and drugs. The identification of the crystals is based on their shape.

a) Calcium oxalate: Range in shape from oval to dumbbell to octahedron (8-sided) to dodecahedron (12-sided); latter two shapes appear as "envelopes".

b) Uric acid: Yellow or red-brown rhombic prisms, hexagonal or square plates, or spheres.

c) Triple phosphate: Appear as six to eight sided prisms ("coffin lids") or feathery forms.

Urine Sediment

If a urine specimen is allowed to stand undisturbed for a few hours, many suspended materials will settle at the bottom. This has always been an effective way of collecting casts and crystals that are contained in urine samples. A much faster method to get urine sediments is to **centrifuge** the urine sample. The separation of components within the urine is facilitated by spinning a container with the urine in it at a very high speed in a centrifuge, such as one seen at the left. This very fast rate of spinning separates substances within the fluid based on the density of the objects, as seen in the two tubes at the right. The first tube on the left is unspun and the tube on the right was spun at high speeds with a centrifuge. The higher density material is located at the bottom of the tube and is often called a pellet.

Microscopic Analysis Overview

When you are examining a urine sediment slide, overall, these things may be seen on the slide:

- **Red or white blood cells.** Blood cells are not normally found in urine. Inflammation, disease, or injury to the kidneys, ureters, bladder, or urethra can cause blood in urine. Strenuous exercise, such as running a marathon, can also cause blood in the urine. White blood cells may be a sign of infection or kidney disease.

- **Casts.** Some types of kidney disease can cause these plugs of material (called casts) to form in tiny tubes in the kidneys. The casts then get flushed out in the urine. Casts can be made of red or white blood cells, waxy or fatty substances, or protein. The type of cast in the urine can help show what type of kidney disorder may be present.

- **Crystals.** Healthy people often have only a few crystals in their urine. A large number of crystals, or certain types of crystals, may mean **kidney stones** are present, or there is a problem with how the body is utilizing or metabolizing the food sources provided.

- **Bacteria, yeast cells, or parasites.** There are no bacteria, yeast cells, or **parasites** in urine normally. If these are present, it can mean you have an infection.

- **Squamous cells.** The presence of **squamous cells** may mean that the sample is not as pure as it needs to be. These cells being present does not mean there is a serious problem, but it may require the examination of another urine sample.

Review Questions for Chapter 21: Urinary System

1. Approximately how many times a day is the entire volume of blood in the body filtered by the kidneys?

a) 100 times
b) 5 times
c) 30 times
d) 60 times
e) 20 times

2. Which of the following correctly lists the order of the barriers to filtration at the glomerulus?

a) endothelium of the glomerulus, podocyte, basement membrane of glomerulus.
b) endothelium of the glomerulus, basement membrane of glomerulus, podocyte.
c) basement membrane of glomerulus, endothelium of the glomerulus, podocyte.
d) podocyte, basement membrane of glomerulus, endothelium of the glomerulus.
e) basement membrane of glomerulus, endothelium of the glomerulus, podocyte.

3. Filtrate leaves the distal convoluted tubule through the following structures in which sequence?

a) collecting duct, renal hilus, renal calyces, ureter
b) collecting duct, renal calyces, renal pelvis, ureter
c) renal calyces, collecting duct, renal pelvis, ureter
d) renal calyces, hilum, renal pelvis, ureter
e) collecting duct, renal pelvis, ureter, bladder

4. The osmolarity of the filtrate increases as it flows through the descending loop of Henle because

a) solutes are passively transported into the descending loop
b) solutes are actively transported into the descending loop
c) water moves passively into the descending loop
d) water moves passively out of the descending loop
e) solutes are passively transported out of the descending loop

5. Most, about ____ %, of the glomerular filtrate is reabsorbed in the _____ tubule.

a) 70: renal collecting
b) 70: proximal convoluted
c) 90: loop of Henle
d) 85: proximal convoluted

6. The renal transport of glucose by a carrier down its concentration gradient is an example of

a) facilitated diffusion
b) secondary passive transport
c) primary direct active transport
d) secondary indirect active antiport
e) secondary indirect active symport

7. The osmolarity of filtrate in the PCT is ~_____; and at the bottom of the Loop of Henle its ~_____.
- **a)** isotonic; hypotonic
- **b)** hypertonic; isotonic
- **c)** 300mOsM; 100mOsM
- **d)** hypotonic; hypertonic
- **e)** isotonic; hypertonic

8. In the entire renal system, there are _____ nephrons.
- **a)** over 1 million
- **b)** fewer than 2 million
- **c)** over 2 million
- **d)** over 3 million
- **e)** over 4 million

9. The filtrate that escapes from the glomerular capillaries can be described as which of the following?
- **a)** like plasma, but without plasma proteins.
- **b)** like blood.
- **c)** like plasma, but without large amino acids.
- **d)** a fluid like plasma.
- **e)** like plasma, but without the red blood cells.

10. The osmolarity of urine can range from _____ to _____ mOsM.
- **a)** 295 to 310
- **b)** 100 to 1,200
- **c)** 50 to 1,000
- **d)** 10 to 1,200
- **e)** 50 to 1,200

11. In the nephron, the glomerulus
- **a)** is where secretion occurs.
- **b)** is a sinusoidal capillary.
- **c)** controls protein formation and removal.
- **d)** is where filtration occurs.
- **e)** is where the bulk of reabsorption takes place.

Answers in Appendix B