The organs of the urinary system (**kidneys**, **ureters**, **urinary bladder** and **urethra**) all play a role in **urine** formation, storage, or expulsion. However the function of the urinary system cannot be simply defined as "urine production" or "waste removal."

The primary functions of the urinary system include:

- Regulating blood volume.
- Regulating the chemical make-up of blood.

Secondary functions include:

- Metabolism of **vitamin D**.
- Production of **renin**.
- Production of **EPO**.

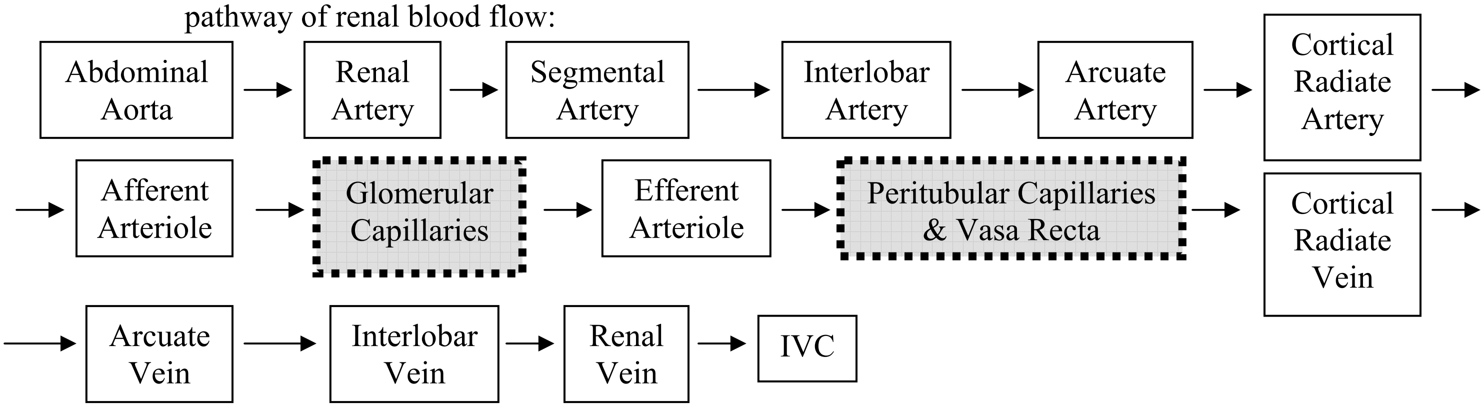
The kidneys lie retroperitoneally in the superior lumbar region. Each kidney is about the size of a large bar of soap. The right kidney lies lower than the left b/c it's crowded by the liver. The kidney's lateral surface is convex and the medial surface is concave. The medial surface has a cleft, the **renal hilum**, which opens into a space, the **renal sinus**. The renal sinus contains the ureter, blood vessels, lymphatics, fat, and nerves. Sitting on top of each kidney is an **adrenal gland** – an endocrine organ that produces epinephrine, norepinephrine, aldosterone, cortisol, and other hormones.

3 layers of supportive tissue surround each kidney. The **fibrous capsule** is a collagenous transparent structure directly adherent to the kidney surface. Next is the **perirenal fat capsule** – a fatty mass that attaches the kidney to the posterior body wall and provides cushioning. The outermost is the **renal fascia** – a layer of dense fibrous CT that anchors the kidney and adrenal gland to surrounding structures.

A frontal section of the kidney reveals 3 distinct regions: **cortex**, **medulla**, and **pelvis**. The most superficial region is the renal cortex. Urine formation occurs there. Deep to the cortex is the renal medulla, which is composed of cone-shaped masses, called **renal pyramids**. The **base** of each pyramid points to the cortex and the **papilla** of each pyramid points internally. The medulla appears striped b/c it is primarily composed of urine-conveying tubes called **collecting ducts**. A single renal pyramid and its associated cortical tissue constitute a **lobe** of the kidney. The cortical tissues that extend btwn and separate the pyramids are the **renal columns**. The renal pelvis is a flat funnel-shaped tube that is continuous with the ureter. Within the kidney, the renal pelvis divides into several **major calyces**. Each major calyx divides into several **minor calyces**. The tip of each minor calyx surrounds a renal papilla.

We can now begin a tracing of urine flow. Urine is formed in the renal cortex → Travels thru collecting ducts in the renal medulla → Continuously drips out of the renal papillae → Into the minor calyces → Flows into major calyces → Flows into the renal pelvis → Flows into the ureter → Flows into and is stored in the urinary bladder → Exits the body via the urethra. The walls of the calyces, pelvises, ureters, bladder, and urethra all contain smooth muscle to propel urine.

Since the kidney's main function is regulating the volume and composition of the blood, it requires an extensive blood supply (≈ 25% of cardiac output). This is the basic pathway of renal blood flow:



The **glomerular capillaries** are the sites of **<u>filtration</u>**, while the **peritubular capillaries** are the sites of **<u>reabsorption</u>** and **<u>secretion</u>**.

The functional unit of the kidney is a set of tubules known as the **nephron**. Each kidney contains 1 million nephrons. Each nephron is intimately associated with a ball of capillaries known as a **glomerulus**. Blood filtration takes place at these glomerular capillaries and is a size-dependent process. The filtered fluid is known as **filtrate** and contains water and solutes smaller than albumin. The filtrate travels through the **renal tubules** of the nephrons and is modified and turned into urine. The renal tubules run alongside the peritubular capillaries, so exchange may take place between the two. Any substance that was filtered but should not be excreted in urine will be reabsorbed – transported from the filtrate within the renal tubules to the blood within the peritubular capillaries. Any substance that was not filtered but should be excreted in urine will be secreted – transported from the blood within the peritubular capillaries to the filtrate within the renal tubules. Whatever remains after filtration, reabsorption and secretion are complete is urine. By regulating how much water is reabsorbed in the nephrons, we can effectively regulate blood volume. By regulating whether or not, and to what degree, certain chemicals are reabsorbed or secreted allows us to regulate the chemical constituency of blood.

Each nephron delivers the urine formed within it to a **collecting duct**. Each kidney contains 1000's of collecting ducts. Each nephron consists of a **glomerulus** – the ball of capillaries where filtration takes place – associated with a renal tubule. The renal tubule begins with the **glomerular capsule**, which is a double-layered structure that almost completely surrounds the glomerulus. The glomerular capsule and the glomerulus are collectively known as the **renal corpuscle**. The glomerular endothelium is fenestrated. This lets lots of solute-rich, protein-free fluid pass from the lumen of the glomerular capillaries to the lumen of the glomerular capsule. The parietal layer of the glomerular capsule is composed of simple squamous epithelium. It plays no role in the formation of filtrate. The visceral layer of the glomerular capsule is composed of branching epithelial cells called **podocytes**. The **foot processes** of the podocytes wrap around the glomerular capillaries and help filter the blood. Only water and small solutes can pass btwn the foot processes (through spaces called **filtration slits**) and move from the lumen of the glomerular capillary to the lumen of the glomerular capsule (i.e. the **capsular space**). Once in the capsular space, the filtrate will pass through a series of tubules. First it enters the **proximal convoluted tubule**. The PCT is composed of simple cuboidal epithelial cells. They have multiple mitochondria (for ATP production) and luminal microvilli (to increase available surface area). Both these structures reflect the large role of the PCT in reabsorption & secretion. Next the filtrate flows into the **loop of Henle**. The loop of Henle has descending and ascending regions. The descending limb is simple squamous epithelium and is freely permeable to water. The ascending limb is simple cuboidal and is impermeable to water. These permeability differences will play a role in the loop's primary function – concentrating urine and maximizing water reabsorption. Next the filtrate passes into the **distal convoluted tubule**. The cells of the DCT are similar to those of the PCT but they have fewer mitochondria and lack microvilli. The DCT is one site where hormones adjust what is reabsorbed and secreted. From the distal convoluted tubule, the filtrate will enter the collecting duct. At this point, the filtrate has been modified and is now urine. Several distal convoluted tubules empty into a single collecting duct. Collecting ducts run thru the medullary pyramids and fuse to form larger and larger ducts that eventually terminate at the renal papillae and continuously drip urine into the minor calyces. The cells of the collecting duct are simple cuboidal and simple columnar.

There are 2 types of nephrons. **Cortical nephrons** are located entirely in the cortex, except for the tips of their loops of Henle. They represent 85% of all nephrons in the kidney and play a big role in regulating urine's chemical constituency. **Juxtamedullary nephrons** are located near the cortex-medulla junction. Their loops of Henle extend deep into the medulla. They represent the other 15% and function primarily in concentrating urine.

The glomerular capillaries receive blood from an afferent arteriole and empty into an efferent arteriole. This makes them unique amongst systemic capillaries. Glomerular capillaries are the sites of blood filtration. A large percentage of blood is able to be filtered b/c the glomerular BP is much higher than the BP of a regular systemic capillary. High glomerular pressure is created b/c the diameter of the afferent arteriole >>> diameter of the efferent arteriole.

The peritubular capillaries receive blood from the efferent arteriole and empty into the cortical radiate vein. They're the sites of reabsorption and secretion. Reabsorption is assisted by the capillaries' low blood pressure and high osmotic pressure. 99% of filtered fluid is reabsorbed at the peritubular capillaries.

In juxtamedullary nephrons the efferent arteriole empties into a set of long straight vessels (the **vasa recta**) that parallel the loop of Henle and help concentrate urine. The vasa recta also empty into the cortical radiate vein.

Every nephron has a region known as the **juxtaglomerular apparatus**. It consists of a distal portion of the ascending loop of Henle and an adjacent portion of the afferent arteriole. This portion of the arteriole contains **juxtaglomerular cells** which release **renin**. The ascending limb of the loop of Henle contains a group of cells called the **macula densa**. The macula densa and juxtaglomerular cells play a role in maintaining systemic BP.

The **filtration membrane** is the structure that separates the lumen of the glomerular capillaries from the capsular space. It consists of:

a. Glomerular endothelium.
b. Visceral layer of glomarular capsule (podocytes).
c. The loose CT btwn the two.

Just about all solutes are filtered except for formed elements and plasma proteins larger than albumin.

Every time blood enters the glomerulus, about 20% of the contained fluid, with solutes, is filtered, enters the nephron and becomes filtrate. (More than 19% of this fluid will be reabsorbed.) The reason for the large volume of filtrate is the high blood pressure within the glomerular capillaries. The actual pressure forcing fluid into the nephron is known as **net filtration pressure** and consists of glomerular BP minus glomerular osmotic pressure minus capsular fluid pressure.

Regulating the rate of filtration, i.e., the **glomerular filtration rate** (**GFR**) is quite important. The kidneys ability to control its own GFR is an example of **autoregulation**. 2 intrinsic mechanisms maintain GFR. The **myogenic mechanism** helps maintain a constant filtration rate and pressure via adjustment of the diameter of the afferent arteriole. If systemic BP drops, the afferent arteriole dilates. This ↑ the volume of blood in the glomerulus and this brings glomerular BP back to normal. If systemic BP rises, the afferent arteriole constricts. This ↓ the volume within the glomerulus and thus brings glomerular BP back to normal.

The **tubuloglomerular feedback mechanism** is a bit more involved. If GFR is too high, filtrate flows quickly thru the nephron and there is little time for sodium reabsorption. Thus, high filtrate [Na^+] indicates a high GFR. The **macula densa cells** sense the high [Na^+] and increase the release of a vasoconstrictor that causes constriction of the afferent arteriole. This reduces GBP and thus GFR. If GFR is too slow, filtrate flows slowly and there is lots of time for sodium reabsorption. Thus, low [Na^+] indicates a low GFR. The macula densa cells will sense the low [Na^+] and thus release less of the vasoconstrictor. This causes the afferent arteriole to dilate, which will increase GBP and GFR.

Extrinsic effects on GFR include the **sympathetic neural mechanism** and the **renin-angiotensin mechanism**.

The sympathetic neural mechanism refers to the effect of the fight-or-flight response on GFR. When sympathetic nervous system activity increases, norepinephrine (from nerve fibers of the renal plexus) and epinephrine (from the adrenal medulla) both act to constrict the afferent arteriole. This reduces GBP and GFR. Reduction of GFR can help maintain BP.

In the **renin-angiotensin mechanism**, the **juxtaglomerular cells** of the afferent arteriole release large amounts of the enzyme **renin** when:

a. BP drops (as measured by the stretch of the afferent arteriole),
b. Stimulated by sympathetic nerve fibers (via NE).

Renin cleaves the plasma protein **angiotensinogen** (made by the liver) into a compound called **angiotensin I**. Angiotensin I is converted to **angiotensin II** by the **Angiotensin-Converting-Enzyme** (**ACE**), which is primarily released by pulmonary capillary endothelial cells. Angiotensin II increases BP b/c:

1. It is a vasoconstrictor that will act to increase peripheral resistance.
2. It directly stimulates renal tubules to reabsorb more sodium and thus more water, which thereby increases blood volume.
3. It stimulates the release of the hormone **aldosterone** from the adrenal cortex. Aldosterone will also increase the renal retention of sodium and water.
4. It prompts the pituitary to release **antidiuretic hormone** (**ADH**), which will also increase the renal retention of water.
5. It activates the hypothalamic thirst center which will eventually cause a rise in blood volume.
6. It causes the efferent arteriole to constrict which lowers the BP of the peritubular capillaries and thus increases water reabsorption.

Assuming that everything is normal, filtrate will be produced at the glomerulus and enter the nephron. This filtrate contains both “good” and “bad” substances and the “good” ones must be reabsorbed. The bulk of reabsorption occurs in the proximal convoluted tubule. A reabsorbed substance must pass thru the luminal membrane of the PCT cell, the basolateral membrane of the PCT cell and then thru the endothelium of the peritubular capillary.

The primary chemical that will drive most reabsorption is **sodium**. Sodium is normally high in concentration in the lumen of the PCT and low in concentration inside the cells lining the PCT lumen. B/c of this concentration gradient, sodium will passively diffuse out of the PCT lumen and into the cytoplasm of the PCT cells. Sodium will then be actively pumped out the other side of the PCT cell and diffuse back into the blood of the peritubular capillaries. This movement of sodium has 3 important effects:

1. It creates an **osmotic gradient** that results in water reabsorption. This is referred to as **obligatory water reabsorption**. Water passes thru the membranes of the PCT cell by way of special water channels known as **aquaporins**.
2. It creates an **electrical gradient** that causes negatively charged ions to “follow along” and be reabsorbed.
3. Diffusion of sodium into the PCT cells releases energy that is harnessed to pump nutrients (glucose, amino acids, etc.) into the PCT cells. This is an example of **secondary active transport**. The nutrients will then diffuse out of the other side of the PCT cells and enter the peritubular capillaries.

There are a finite number of proteins in the PCT that can reabsorb a particular substance. If they're **saturated** then that substance cannot be fully reabsorbed. The maximal rate of reabsorption of a substance in the kidney tubules is known as the **transport maximum**. An example occurs in **diabetes**. In untreated diabetics (who either cannot produce or cannot respond to insulin), blood glucose will rise. When blood glucose rises, filtrate glucose rises. Eventually, when the filtrate [glucose] is greater than the transport maximum of the PCT, it will start to appear in the urine.

By the time filtrate has passed thru the PCT all of the nutrients and the majority of the water and electrolytes have been reabsorbed.

Within the loop of Henle water is reabsorbed in the descending portion and electrolytes are reabsorbed in the ascending loop. This will ultimately assist in the concentration of urine.

Within the DCT the contents of the filtrate are adjusted depending on the body's needs. Reabsorption in the DCT is primarily hormone dependent. Aldosterone increases the reabsorption of sodium (and thus water) in the DCT. Parathyroid hormone increases the reabsorption of calcium in the DCT.

Within the collecting duct water may be reabsorbed from the urine depending on the body's state of hydration. Antidiuretic hormone increases water reabsorption in the collecting duct.

Tubular secretion is the process by which undesirable substances, which were not filtered at the glomerulus, are moved from the peritubular capillaries into the lumen of the PCT. Secretion helps remove foreign substances (e.g., drugs) that are attached to plasma proteins. Secretion helps eliminate excess K^+. Secretion helps control plasma pH by getting rid of excess H^+. Most secretion occurs in the PCT.

Maintaining the concentration of body fluids is integral to homeostasis. Concentration is measured in **osmolality**. A concentrated solution will have a high osmolality and a dilute solution will have a low osmolality. Normal blood osmolality is 300 milliosmoles. If blood osmolality rises, the response will be for water reabsorption to increase and urine volume to decrease. If blood osmolality falls, the response will be for water reabsorption to decrease and urine volume to increase. Blood osmolality is measured by specialized neurons in the **hypothalamus** called **osmoreceptors**. The level of osmolality measured by the osmoreceptors of the hypothalamus will determine how much **antidiuretic hormone** is secreted by the **posterior pituitary gland**. ADH increases water reabsorption in the collecting duct and decreases urine volume. When blood osmolality rises, ADH release increases. When blood osmolality falls, ADH release decreases.

ADH works by increasing the permeability of the CD to water. But, increasing the permeability is not the only thing that must occur. Not only must the CD be permeable to water, but also there must be a concentration gradient btwn the lumen of the CD and the surrounding interstitial fluid. Luckily, the concentration gradient does exist – it's established by the **loop of Henle**.

Let's walk through the response to high osmolality one more time: Increased plasma osmolality → Measured by hypothalamic osmoreceptors → Increased ADH release by the posterior pituitary → Increased water permeability of the collecting duct → Increased reabsorption of water → Decreased plasma osmolality.

The water that exits the collecting duct is picked up by the **vasa recta**. Reabsorption of water that is dependent on plasma ADH levels is referred to as **facultative water reabsorption**.

Aldosterone is produced by the **adrenal medulla** (the insides of the adrenal glands, which sit atop the kidneys). It acts to:

a. Increase sodium reabsorption in the **distal convoluted tubule**. This causes an increase in water reabsorption in the DCT.
b. Increase the secretion of potassium in the DCT.

Its release is stimulated by:

a. Low plasma Na+ levels.
b. High plasma K+ levels.
c. Low blood volume and pressure.

Diuretics are chemicals that enhance urine output. An **osmotic diuretic** is a substance that is filtered but not reabsorbed. Its presence in the nephron will increase the osmolarity of the filtrate and make it more difficult for water to flow out. **Alcohol** is a diuretic b/c it inhibits pituitary ADH release. **Caffeine** is a diuretic b/c it inhibits renal sodium reabsorption.

Urine is a clear to pale yellow fluid (depending on its concentration). Urine volume varies with fluid intake and with fluid output via other routes. Urine pH is usually 6, slightly acidic. Normal range is from 4.5 to 8 and varies with diet. Normal urine contents include:

a. 95% water.
b. 5% solutes, such as: **uric acid** (a metabolite of nucleic acids (DNA, RNA), **creatinine** (metabolite of creatine (a chemical used by skeletal muscle for energy storage), **urea** – an end product of protein metabolism, ions such as Na^+, K^+, Ca^{2+}, Mg^+ and HCO_3^-.

The ureters are slender retroperitoneal tubes that convey urine from the kidneys to the bladder. Their wall consists of 3 layers:

a. Mucosa lined by **transitional epithelium**
b. Smooth muscle muscularis
c. Adventitia

Gravity contributes to urine flow but the primary impetus is provided by peristalsis of ureteric smooth muscle.

The urinary bladder is a collapsible, muscular sac that temporarily stores urine. It sits just posterior to the **pubic symphysis**. 3 openings are found within the bladder – 2 entrances and one exit. Both ureters connect with the posterior bladder via the **ureteric orifices**. The urethra opens inferiorly at the **internal urethral orifice**. In males, it immediately passes through the **prostate gland**. The smooth, triangular region outlined by these openings is referred to as the **trigone**. The **bladder** wall has 3 layers:

a. Mucosa lined by transitional epithelium and exhibiting **rugae**.
b. Thick muscularis composed of smooth muscle and referred to as the **detrusor muscle**.
c. Adventitia (except on the superior surface where it's covered by the parietal peritoneum).

A moderately full bladder will hold approximately 500mL of urine. The maximum capacity of the bladder is 800-1000mL. The bladder allows urine release to be discontinuous even though renal formation of urine is continuous.

The urethra is a thin walled, muscular tube that conveys urine from the bladder to the body exterior. It's lined primarily by pseudostratified columnar epithelium, but contains transitional epithelium near the bladder and stratified squamous epithelium near the external urethral orifice. At the bladder-urethra junction, the detrusor muscle thickens to form the **internal urethral sphincter**. As smooth muscle, it is involuntary. It's unique b/c it contracts to open and relaxes to close. The **external urethral sphincter** surrounds the urethra where it passes through the skeletal muscle layer, known as the **urogenital diaphragm**. The urogenital diaphragm is a small portion of an expanse of skeletal muscle known as the **pelvic diaphragm**. The pelvic diaphragm forms the floor of the pelvic cavity. The female urethra is only 3-4cm long and is tightly bound to the anterior vagina. Its opening is anterior to the external vaginal orifice within the vestibule of the labia minora. The male urethra is 20cm long and is divided into 3 sections:

a. **Prostatic urethra** – proximal portion that runs thru the prostate gland.
b. **Membranous urethra** – middle portion that runs thru the urogenital diaphragm and perineal membrane.
c. **Penile** or **spongy urethra** – distal portion that runs within the **corpus spongiosum** of the penis and ends at the **external urethral orifice**.

Micturition is the process of urination – the act of emptying the bladder. The initial stretch of the bladder activates a reflex that suppresses the act of urination. As 200mL or more of urine accumulates in the bladder, the bladder wall stretches. Stretch receptors sense the stretch and signal the **micturition center** in the **pons**. They also initiate a reflex response in the spinal cord resulting in increased parasympathetic outflow to the bladder. It causes relaxation of the internal urethral sphincter and contraction of the detrusor muscle. At this point, somatic activation of the external urethral sphincter can prevent urination. If the external urethral sphincter is voluntarily contracted, the reflex contractions of the bladder will subside. When volume and stretch become too great, signals from the pons inhibit any motor output to the external urethral sphincter and urination ensues.