KIDNEY (SITE 1)

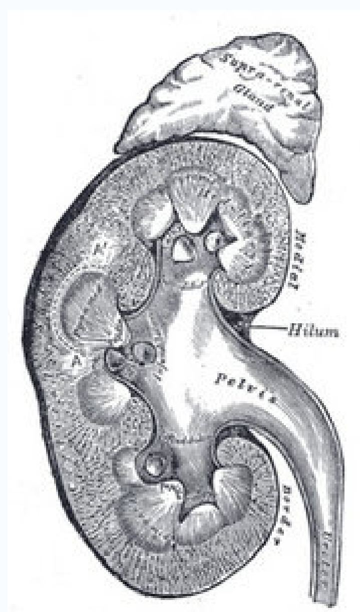
The **kidneys** are bean-shaped excretory organs in vertebrates. Part of the urinary system, the kidneys filter wastes (especially urea) from the blood and excrete them, along with water, as urine. The medical field that studies the kidneys and diseases affecting the kidney is called nephrology, from the Greek name for the kidney; the adjective meaning "kidney-related" is ***renal***, from the Latin

Location

In humans, the kidneys are located in the posterior part of the abdomen. There is one on each side of the spine; the right kidney sits just below the liver, the left below the spleen. Above each kidney is an adrenal gland (also called the *suprarenal gland*).

The kidneys are retroperitoneal, which means they lie behind the peritoneum, the lining of the abdominal cavity. They are approximately at the vertebral level T12 to L3, and the right kidney usually lies slightly lower than the left in order to accommodate the liver.

The upper parts of the kidneys are partially protected by the eleventh and twelfth ribs, and each whole kidney is surrounded by two layers of fat (the perirenal fat and the pararenal fat) which help to cushion it.



Above each human kidney is one of the two adrenal glands.

Structure

Organization

In a normal human adult, each kidney is about 11 cm long and about 5 cm thick, weighing 150 grams. The kidneys are "bean-shaped" organs, and have a concave side facing inwards (medially). On this medial aspect of each kidney is an opening, called the hilum, which admits the renal artery, the renal vein, nerves, and the ureter.

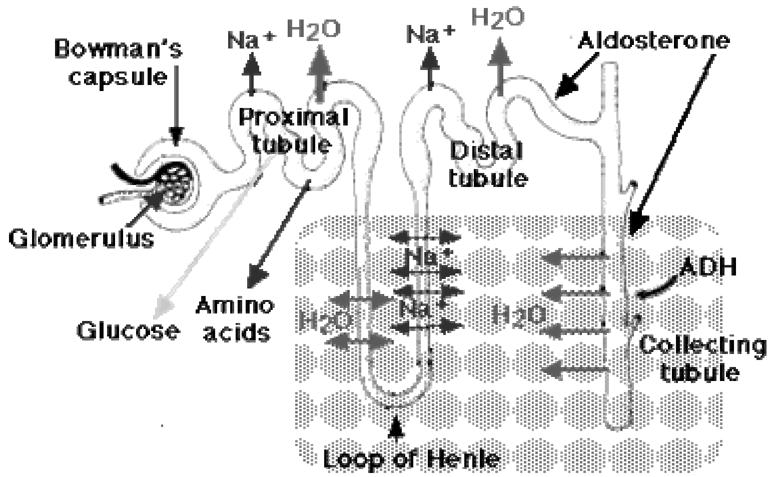
The outermost portion of the kidney is called the renal cortex, which sits directly beneath the kidney's loose connective tissue capsule. Deep to the cortex lies the renal medulla, which is divided into 10-20 renal pyramids in humans. Each pyramid together with the associated overlying cortex forms a renal lobe. The tip of each pyramid (called a *papilla*) empties into a calyx, which empties into the renal pelvis. The pelvis transmits urine to the urinary bladder via the ureter.

Nephron

The basic functional unit of the kidney is the nephron, of which there are more than a million in each normal adult human kidney. Nephrons regulate water and soluble matter (especially electrolytes) in the body by first filtering the blood, then reabsorbing some necessary fluid and molecules while secreting other, unneeded molecules. Reabsorption and secretion are accomplished with both cotransport and countertransport mechanisms established in the nephrons and associated collecting ducts.

Collecting duct system

Fluid flows from the nephron into the collecting duct system. This segment of the nephron is crucial to the process of water conservation by the organism. In the presence of antidiuretic hormone (ADH; also called vasopressin), these ducts become permeable to water and facilitate its reabsorption, thus concentrating the urine and reducing its volume. Failure of the organism to produce ADH (or inability of the collecting ducts to respond to it) may cause excessive urination, called diabetes insipidus. Conversely, when the organism must eliminate excess water, such as after excess fluid drinking, the production of ADH is decreased and the collecting tubule becomes less permeable to water, rendering urine dilute and abundant. Failure of the organism to decrease ADH production appropriately may lead to water retention and dangerous dilution of body fluids, which in turn may cause severe neurological damage. After being processed along the collecting tubules and ducts, the fluid, now called urine, is drained into the bladder via the ureter, to be finally excluded from the organism.



It consists of a:

- **Bowman's capsule**. Located at the closed end, the wall of the nephron is pushed in forming a double-walled chamber.
- **Glomerulus**. A capillary network within the Bowman's capsule. Blood leaving the glomerulus passes into a second capillary network (not shown in the figure) surrounding the
- **Proximal convoluted tubule**. Coiled and lined with cells carpeted with microvilli and stuffed with mitochondria.
- **Loop of Henle**. It makes a hairpin turn and returns to the
- **Distal convoluted tubule**, which is also highly coiled and surrounded by capillaries.
- **Collecting tubule**. It leads to the pelvis of the kidney from where **urine** flows to the bladder and, periodically, on to the outside world.

Functions of the kidney

Filtering wastes from the bloodstream

Wastes are filtered out from the blood in the glomeruli which is enclosed by a Bowman's capsule via the process of ultrafiltration. The glomerulus and the Bowman's Corpuscle together is known as the Malpighian Corpuscle.

The ultrafiltrate is passed through, in turn, the proximal convoluted tubules, the loop of Henle, the distal convoluted tubules and is then collected by the collecting ducts to form urine.

The capillaries in the glomerulus are formed from an afferent arteriole which is a branch of the renal artery. After leaving the Bowman's capsule, the capillaries re-join to form an efferent arteriole.The efferent arteriole then branches into many capillaries which surround the coiled tubules in the cortex and the loop of Henle in the medulla of the kidney again. They eventually join together to form the renal vein.

The renal collecting ducts open into the renal pelvis and drain into the ureters which pass on the urine to the bladder.

Secretion of hormones

- Secretion of *erythropoietin*, which regulates red blood cell production in the bone marrow.
- Secretion of *renin* which leads to the formation of angiotensin II.
- Secretion of the active form of vitamin D - *1,25-dihydroxycholecalciferol* (*calcitriol*) and prostaglandins.

Maintaining body sodium and water balance

There is a stable balance of sodium and water in the body. The major homeostatic control point for maintaining this stable balance is renal excretion.

The kidney is directed to excrete or retain sodium via the action of aldosterone, ADH (anti-diuretic hormone a.k.a. vasopressin), ANP (atrial natriuretic peptide) and other hormones.

Acid-base homeostasis

Metabolic reactions are very sensitive to the pH level (H+ or hydronium ion concentration) of the fluid in which they occur. This is because hydronium ions can influence enzyme function.

The kidneys maintain blood plasma acid-base homeostasis by hydronium regulation. Gain and loss of hydronium must be balanced. Sources of hydrogen-ion gain:

1. Carbon dioxide
2. Production of nonvolatile acids from the metabolism of proteins and other organic molecules.
3. Gain in hydrogen ions due to loss of bicarbonate in diarrhea or other nongastric GI fluids.
4. Gain in hydrogen ions due to loss of bicarbonate in the urine.
5. Hypoventilation

Sources of hydrogen ion loss:

1. Use of hydrogen ions in the metabolism of various organic anions.
2. Loss of hydrogen ions in vomitus.
3. Loss of hydrogen ions in the urine.
4. Hyperventilation.

When hydrogen ion loss exceeds gain, alkalosis occurs. When gain exceeds loss acidosis occurs. There are various renal responses to acidosis and alkalosis:

Responses to acidosis:

1. Bicarbonate is added to the blood plasma by tubular cells.
    - This is caused by sufficient hydrogen ion secretion from the tubular epithelial cells.
    - Extra hydrogen ion secretion will bind to nonbicarbonate urinary buffers and this will lead to more new bicarbonate in the blood plasma.
    - This is also caused by increased glutamine metabolism and ammonia excretion.

Responses to alkalosis:

1. Excretion of bicarbonate in urine.
    - This is caused by lowered rate of hydrogen ion secretion from the tubular epithelial cells.
    - This is also caused by lowered rates of glutamine metabolism and ammonia excretion.

Hydronium ions and carbon dioxide

1. carbon dioxide + water + carbonic anhydrase (catalyst) ↔ carbonic acid ↔ bicarbonate + hydronium ion

Buffering of hydrogen ions

Any substance that can reversible bind hydrogen ions is called a buffer. Hydrogen ions are buffered by extracellular and intracellular buffers.

Homeostatic controls

The kidneys regulate the pH, mineral ion concentration, and water composition of the blood.

By exchanging hydronium ions and hydroxyl ions, the blood plasma is maintained by the kidney at pH 7.4. Urine, on the other hand, becomes either acidic at pH 5 or alkaline at pH 8.

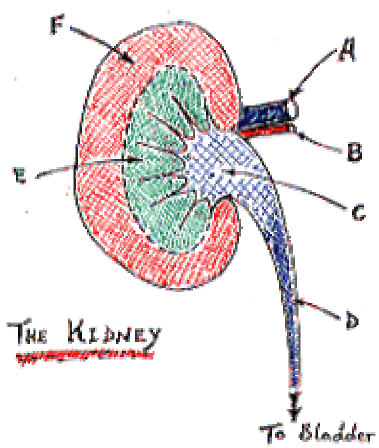
Sodium ions are controlled in a homeostatic process involving aldosterone which increases sodium ion absorption in the distal convoluted tubules.

Any rise or drop in blood osmotic pressure due to a lack or excess of water is detected by the hypothalamus, which notifies the pituitary gland via negative feedback. A lack of water causes the posterior pituitary gland to secrete antidiuretic hormone, which results in water reabsorption and urine concentration. Tissue fluid concentration thus returns to a mean of 98%.

KIDNEYS SIMPLIFIED (SITE 2)

Our kidneys do a grand job removing the toxic waste products of metabolism. This process is called excretion. Our kidneys produce urine which contains urea, excess salts and excess water.

You need to know about the general structure of the kidney and how it works, so let's start with a diagram to show the regions of the kidney. The three main regions are called the cortex, medulla and pelvis. Can you label this diagram. Jot down what you think the parts are called, A to F and then click on each letter in turn to reveal the truth.



You should be able to name all the parts labelled A to F. Click on any one of the letters to find out more about that part.

A. **Renal Vein**

This has a large diameter and a thin wall. It carries blood away from the kidney and back to the right hand side of the heart. Blood in the kidney has had all its urea removed. Urea is produced by your liver to get rid of excess amino-acids.

Blood in the renal vein also has exactly the right amount of water and salts. This is because the kidney gets rid of excess water and salts. The kidney is controlled by the brain. A hormone in our blood called Anti-Diuretic Hormone (ADH for short) is used to control exactly how much water is excreted.

B. **Renal Artery**

This blood vessel supplies blood to the kidney from the left hand side of the heart. This blood must contain glucose and oxygen because the kidney has to work hard producing urine. Blood in the renal artery must have sufficient pressure or the kidney will not be able to filter the blood.

Blood supplied to the kidney contains a toxic product called urea which must be removed from the blood. It may have too much salt and too much water. The kidney removes these excess materials; that is its function.

C. **Pelvis**

This is the region of the kidney where urine collects. If you are very unlucky, you may develop kidney stones. Sometimes the salts in the urine crystallise in the pelvis and form a solid mass which prevents urine from draining out of the medulla of the kidney. You will need treatment: see your doctor.

D. **Ureter**

This one is easy peasy: the ureter carries the urine down to the bladder. It does this 24 hours per day, but fortunately the urine can be stored in a bladder so that it is not necessary to wear a nappy!

E. **Medulla**

The medulla is the inside part of the kidney. It is shown in green in the diagram, but in real life it is a very dark red colour. This is where the amount of salt and water in your urine is controlled. It consists of billions of loops of Henlé. These work very hard pumping sodium ions. ADH makes the loops work harder to pump more sodium ions. The result of this is that very concentrated urine is produced.

The opposite of an anti-diuretic is a "diuretic". Alcohol and tea are diuretics.

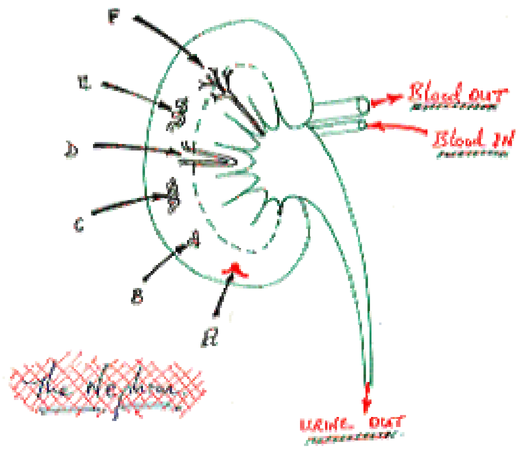
F. Cortex

The cortex is the outer part of the kidney. This is where blood is filtered. We call this process "ultra-filtration" or "high pressure filtration" because it only works if the blood entering the kidney in the renal artery is at high pressure.

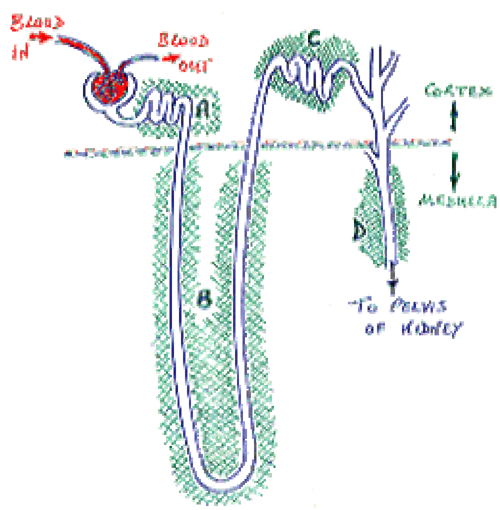
Billions of glomeruli are found in the cortex. A glomerulus is a tiny ball of capillaries. Each glomerulus is surrounded by a "Bowman's Capsule". Glomeruli leak. Things like red blood cells, white blood cells, platelets and fibrinogen stay in the blood vessels. Most of the plasma leaks out into the Bowman's capsules. This is about 160 litres of liquid every 24 hours.

Most of this liquid, which we call "ultra-filtrate" is re-absorbed in the medulla and put back into the blood.

Here is a diagram of the kidney showing a nephron broken up into six parts. Each part has a specific function. You can click on a letter to find out what that part does.



Here is a diagram of a nephron put back together again. You can click on a green or red area to find out what happens there. Ultra-filtration happens in the red area, and re-absorption happens in the green areas.



Glomerulus and Bowman's Capsule

This is where ultra-filtration takes place. Blood from the renal artery is forced into the glomerulus under high pressure. Most of the liquid is forced out of the glomerulus into the Bowman's capsule which surrounds it. This does not work properly in people who have very low blood pressure.

Proximal Convoluted Tubules

Don't worry about remembering the name for your GCSE biology. Jolly good though if you can. Proximal means "near to" and convoluted means "coiled up" so this is the coiled up tube near to the Bowman's capsule.

This is the place where all that useful glucose is re-absorbed from the ultra-filtrate and put back into the blood. If the glucose was not absorbed it would end up in your urine. This happens in people who are suffering from diabetes.

Losing glucose in your urine is bad news; how much did those chips at lunchtime cost you?

Loop of Henlé

This part of the nephron is where water is reabsorbed. Kidney cells in this region spend all their time pumping sodium ions. This makes the medulla very salty; you could say that this is a region of very low water concentration. If you remember the definition of osmosis, you will realise that water will pass from a region of high water concentration (the ultra-filtrate and urine) into a region of low water concentration (the medulla) through cell membranes which are semi-permeable.

Distal Convoluted Tubules

Don't worry too much about the name. Distal means "distant" so it is at the other end of the nephron from the Bowman's capsule. This is where most of the salts in the ultra-filtrate are re-absorbed.

Collecting Duct

Collecting ducts run through the medulla and are surrounded by loops of Henlé. The liquid in the collecting ducts (ultra-filtrate) is turned into urine as water and salts are removed from it. Although our kidneys make about 160 litres of urine every 24 hours, we only produce about ½ litre of urine.

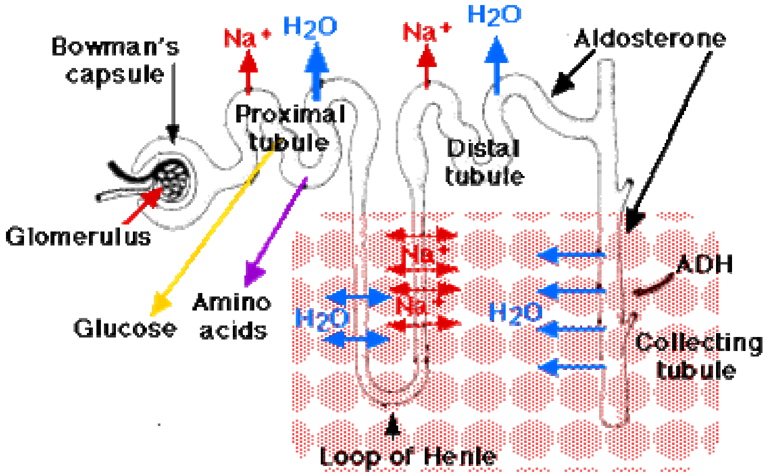
It is called a collecting duct because it collects the liquid produced by lots of nephrons.

So now you know how your kidney works !

The Kidney (SITE 3)

The human kidneys:

- are two bean-shaped organs, one on each side of the backbone.
- Represent about 0.5% of the total weight of the body,
- but receive 20–25% of the total arterial blood pumped by the heart.
- Each contains from one to two million **nephrons**.



The Nephron

The nephron is a tube; closed at one end, open at the other. It consists of a:

- **Bowman's capsule**. Located at the closed end, the wall of the nephron is pushed in forming a double-walled chamber.
- **Glomerulus**. A capillary network within the Bowman's capsule. Blood leaving the glomerulus passes into a second capillary network (not shown in the figure) surrounding the
- **Proximal convoluted tubule**. Coiled and lined with cells carpeted with microvilli and stuffed with mitochondria.
- **Loop of Henle**. It makes a hairpin turn and returns to the
- **Distal convoluted tubule**, which is also highly coiled and surrounded by capillaries.
- **Collecting tubule**. It leads to the pelvis of the kidney from where **urine** flows to the bladder and, periodically, on to the outside world.

Formation of Urine

The nephron makes urine by

- filtering the blood of its small molecules and ions and then
- reclaiming the needed amounts of useful materials.
- Surplus or waste molecules and ions are left to flow out as urine.

In 24 hours the kidneys reclaim

- ~1,300 g of NaCl
- ~400 g $NaHCO_3$
- ~180 g glucose
- almost all of the 180 liters of water that entered the tubules.

The steps:

- Blood enters the glomerulus under pressure.
- This causes water, small molecules (but not macromolecules like proteins) and ions to filter through the capillary walls into the **Bowman's capsule**. This fluid is called **nephric filtrate**. As the table shows, it is simply blood plasma minus almost all of the plasma proteins. Essentially it is no different from interstitial fluid.

Composition of plasma, nephric filtrate, and urine (each in **g/100 ml** of fluid). These are representative values. The values for salts are especially variable, depending on salt and water intake.

Component	Plasma	Nephric Filtrate	Urine	Concentration	% Reclaimed
Urea	0.03	0.03	1.8	60X	50%
Uric acid	0.004	0.004	0.05	12X	91%
Glucose	0.10	0.10	None	-	100%
Amino acids	0.05	0.05	None	-	100%
Total inorganic salts	0.9	0.9	<0.9–3.6	<1–4X	99.5%
Proteins and other macromolecules	8.0	None	None	-	-

- Nephric filtrate collects within the Bowman's capsule and then flows into the **proximal tubule**.
- Here all of the **glucose**, and **amino acids**, >90% of the uric acid, and ~60% of inorganic **salts** are reabsorbed by active transport.

  - The active transport of Na^+ out of the **proximal tubule** is controlled by angiotensin II.
  - The active transport of phosphate (PO_4^{3-}) is regulated (suppressed by) the parathyroid hormone.
- As these solutes are removed from the nephric filtrate, a large volume of the water follows them by osmosis (80–85% of the 180 liters deposited in the Bowman's capsules in 24 hours).
- As the fluid flows into the descending segment of the **loop of Henle**, water continues to leave by osmosis because the interstitial fluid is very hypertonic. This is caused by the active transport of Na^+ out of the tubular fluid as it moves up the ascending segment of the loop of Henle.
- In the **distal tubules**, more sodium is reclaimed by active transport, and still more water follows by osmosis.
- Final adjustment of the sodium and water content of the body occurs in the **collecting tubules**.

Sodium

Although 97% of the sodium has already been removed, it is the last 3% that determines the final balance of sodium — and hence water content and blood pressure — in the body. The reabsorption of sodium in the **distal tubule** and the collecting tubules is closely regulated, chiefly by the action of the hormone **aldosterone**.

Water

- The hypertonic interstitial fluid surrounding the collecting tubules provides a high osmotic pressure for the removal of water.
- Transmembrane channels made of proteins called **aquaporins** are inserted in the plasma membrane greatly increasing its permeability to water. (When open, an aquaporin channel allows 3 billion molecules of water to pass through each second.)
- Insertion of aquaporin-2 channels requires signaling by the **antidiuretic hormone** (**ADH**; also known as **arginine vasopressin** or **AVP**).
  - ADH binds to receptors (called **V2 receptors**) on the basolateral surface of the cells of the collecting tubules.
  - Binding of the hormone triggers a rising level of **cAMP** within the cell.
  - This **"second messenger"** initiates a chain of events culminating in the insertion of **aquaporin-2** channels in the apical surface of the cell.

The release of **ADH** (from the posterior lobe of the pituitary gland) is regulated by the osmotic pressure of the blood.

- Anything that dehydrates the body, such as perspiring heavily,
  - increases the osmotic pressure of the blood;
  - turns on the **ADH** → **V2 receptors** → **aquaporin-2** pathway.

The result:

  - As little as 0.5 liter/day of urine may remain of the original 180 liters/day of nephric filtrate.
  - The concentration of salts in the urine can be as much as four times that of the blood. (But not high enough to enable humans to benefit from drinking sea water, which is saltier still.)
- If the blood should become too dilute (as would occur after drinking a large amount of water),
  - **ADH** secretion is **inhibited**.
  - The aquaporin-2 channels are taken back into the cell by endocytosis.
  - The result: a large volume of watery urine is formed (with a salt concentration as little as one-fourth of that of the blood).

Diabetes insipidus

This disorder is characterized by:

- excretion of large amounts of a watery urine (as much as 30 liters — about 8 gallons — each day!)
- unremitting thirst.

It can have several causes:

- Insufficient secretion of **ADH**.
- Inheritance of two mutant genes for the **ADH receptor** (V2).
- Inheritance of two mutant genes for **aquaporin-2**.

Liddle's Syndrome

The most obvious effect of this rare, inherited disorder is extremely high blood pressure (hypertension). It is caused by a single mutant allele (therefore the syndrome is inherited as a dominant trait) encoding the aldosterone-activated **sodium channel** in the **collecting tubules**. The defective channel is always "on" so too much Na^+ is reabsorbed and too little is excreted. The resulting elevated osmotic pressure of the blood produces hypertension.

Tubular Secretion

Although urine formation occurs primarily by the filtration-reabsorption mechanism described above, an auxiliary mechanism, called tubular secretion, is also involved.

The cells of the tubules remove certain molecules and ions from the blood and deposit these into the fluid within the tubules. Example: Both hydrogen ions (H^+) and potassium ions (K^+) are secreted directly into the fluid within the distal and collecting tubules. In each case the secretion is coupled to the ion-for-ion uptake of sodium ions (Na^+).

Tubular secretion of H^+ is important in maintaining control of the pH of the blood.

- When the pH of the blood starts to drop, more hydrogen ions are secreted.
- If the blood should become too alkaline, secretion of H^+ is reduced.
- In maintaining the pH of the blood within its normal limits of 7.3–7.4, the kidney can produce a urine with a pH as low as 4.5 or as high as 8.5.

The Kidney and Homeostasis

While we think of the kidney as an organ of excretion, it is more than that. It does remove wastes, but it also removes normal components of the blood that are present in greater-than-normal concentrations. When excess water, sodium ions, calcium ions, potassium ions, and so on are present, the excess quickly passes out in the urine. On the other hand, the kidneys step up their reclamation of these same substances when they are present in the blood in less-than-normal amounts. Thus the kidney continuously regulates the chemical composition of the blood within narrow limits. The kidney is one of the major homeostatic devices of the body.

Hormones of the Kidneys

The human kidney is also an endocrine gland secreting two hormones:

- **Erythropoietin** (**EPO**)
- **Calcitriol** (1,25[OH]$_2$ Vitamin D_3), the active form of vitamin D

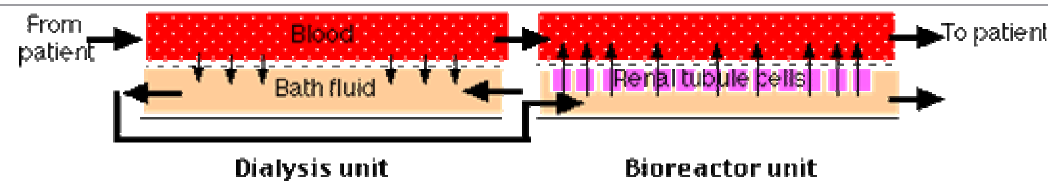
as well as the enzyme **renin**.

The Artificial Kidney

The artificial kidney uses the principle of dialysis to purify the blood of patients whose own kidneys have failed.

The left portion of the figure ("Dialysis unit") shows the mechanism used today in artificial kidneys. Small molecules like urea are removed from the blood because they are free to diffuse between the blood and the bath fluid, whereas large molecules (e.g., plasma proteins) and cells remain confined to the blood. The bath fluid must already have had essential salts added to it to prevent the dangerous loss of these ions from the blood. Note that blood and bath fluid flow in opposite directions across the dialysis membrane. This "counter-current" exchange maintains a diffusion gradient through the entire length

of the system. An anticoagulant is added to the blood so it will not clot while passing through the machine. The anticoagulant is neutralized as the blood is returned to the patient.



Artificial kidneys have proved of great benefit in helping patients of acute kidney malfunction survive the crisis until their own kidneys resume operation. They have also enabled people suffering from chronic kidney failure to remain alive, though at an enormous expense of time (often three sessions of 6 or more hours per week), money, and psychological well-being. Furthermore, although dialysis does a good job at removing wastes, it cannot perform the other functions of the kidney:

- providing precise homeostatic control over the concentration of such vital ingredients as glucose and Na^+
- secreting its hormones

An artificial kidney of the future?

In an attempt to solve these problems, a research team at the University of Michigan is experimenting with adding a "Bioreactor unit" to the dialysis unit. The bioreactor consists of many hollow, porous tubes on the inner wall of which is attached a monolayer of **proximal tubule cells** (derived from pigs). The dialysis bath fluid passes through the lumen of the tubes where molecules and ions can be picked up by the apical surface of the cells. Discharge of essential molecules and ions (as well as hormones) at the basolateral surface of the cells places these materials back in the blood (just as the proximal tubule cells in the nephron normally do). So far, all the testing has been done using dogs, but the results seem promising.

The ideal alternative to long-term dialysis is transplantation of a new kidney. The operation is technically quite easy. The major problems are:

- the shortage of donors suitably matched for histocompatibility molecules
- the problem of graft rejection by the recipient's immune system that — unless the donor and recipient are identical twins — "sees" the kidney as "foreign" even when they share the same major histocompatibility molecules.