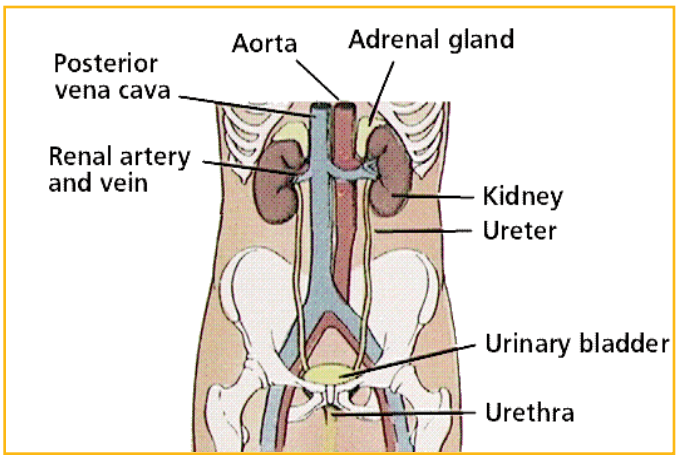
The Kidneys:
Structure, Function, Disorders

by John H. Dirckx, M.D.

Everyone knows that the heart, the lungs, and the brain are vital organs—that is, that their absence or destruction is incompatible with life. But several other bodily structures, including the kidneys, are equally indispensable. Although the kidneys are usually thought of as organs that merely filter water and wastes from the circulation, they actually perform many highly selective excretory functions, reabsorbing most of the water that they filter and many of the substances dissolved in it, but also actively eliminating certain other substances from the blood.



Excretory System

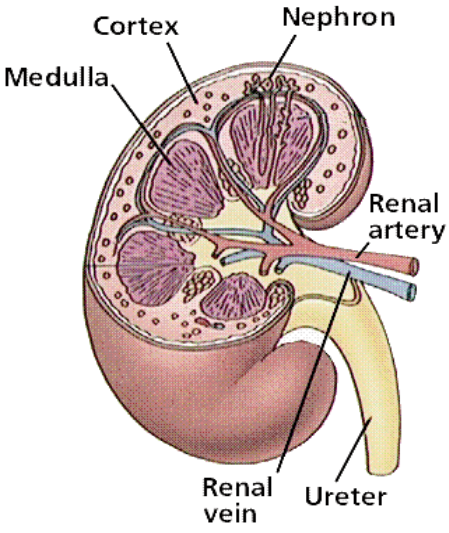
In addition, they act as endocrine glands, secreting hormones that are essential for such diverse processes as blood pressure regulation, red blood cell production, and the optimum calcification of bone. Any disease process or injury that severely impairs the ability of both kidneys to perform these functions can have dire and even lethal consequences.

The kidneys are paired structures whose shape is so familiar that expressions like *kidney beans* and *kidney-shaped swimming pool* are readily understood by all. They lie on either side of the midline just below the posterior attachments of the diaphragm, at the level of the twelfth rib and the first three lumbar vertebrae—much higher than lay persons usually seem to think. The right kidney is slightly lower than the left, probably because of the presence of the liver above it. Each kidney is surrounded by a cushioning envelope of fat and lies deeply imbedded in the posterior abdominal wall. The kidneys are retroperitoneal, that is, they lie behind and outside the peritoneal cavity, which encloses most of the abdominal organs (stomach, small intestine, liver, spleen, and most of the large intestine).

The hilum or notch of each kidney is the point of entry of the renal artery and the point of exit of the renal vein and the ureter. Nerves and lymph vessels also enter and leave at the hilum. The paired renal arteries are the last major branches given off by the abdominal aorta before it bifurcates into the common iliac arteries to supply the pelvic organs and lower limbs. The renal veins have an analogous relation to the inferior vena cava, being the first major tributaries received by it after it is formed by the union of the common iliac veins.

Each kidney is about 12 cm in height, 6 cm in breadth, and 3 cm in thickness, and weighs about 150 g. That's very close indeed to the proportions, size, and weight of a standard computer mouse. The kidney is enclosed by a smooth connective-tissue capsule somewhat like the skin of a sausage. The capsule can easily be peeled away from a normal kidney (although this does tear through a meshwork of fine blood vessels), but not from one that has been scarred by chronic inflammation or infarction.

On being cut open ("on cut section" as pathologists often redundantly express it) the kidney is seen to consist of two zones, a reddish brown outer **cortex** with a granular texture and a lighter-colored inner **medulla** whose fine structure forms a pattern of radiating lines. The medulla surrounds the interior cavity or pelvis of the kidney, into which it sends about a dozen cone-shaped projections, the renal pyramids. Each of these ends



Internal Structure of Kidney

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Two normal kidneys produce about 125 mL of glomerular filtrate each minute. If all that fluid left the body, and if that rate could be sustained for 24 hours, it would amount to 180 L (about 50 gallons) of urine output a day. Obviously most of the glomerular filtrate is reabsorbed, and that is the function of the renal tubules.

in a renal papilla, from which newly formed urine is discharged into the pelvis of the kidney and so to the ureter, by which it is conveyed to the bladder. The pyramids give the renal pelvis a scalloped contour. The recesses of the renal pelvis that extend among the pyramids are called major and minor calyces.

The microscopic structure of the kidney is uniquely complex. The cortex of each kidney contains more than a million renal (malpighian) corpuscles, each about 0.2 mm in diameter, roughly the size of the period at the end of this sentence. A renal corpuscle consists of two major elements: a tuft or tangle of capillaries called the *glomerulus* (Latin, 'little ball of yarn') and a two-layered envelope surrounding it called **Bowman's capsule**. Under the microscope this capsule looks very much like what you would see if you tucked in the tip of a rubber glove finger to form a double-walled, cup-shaped recess.

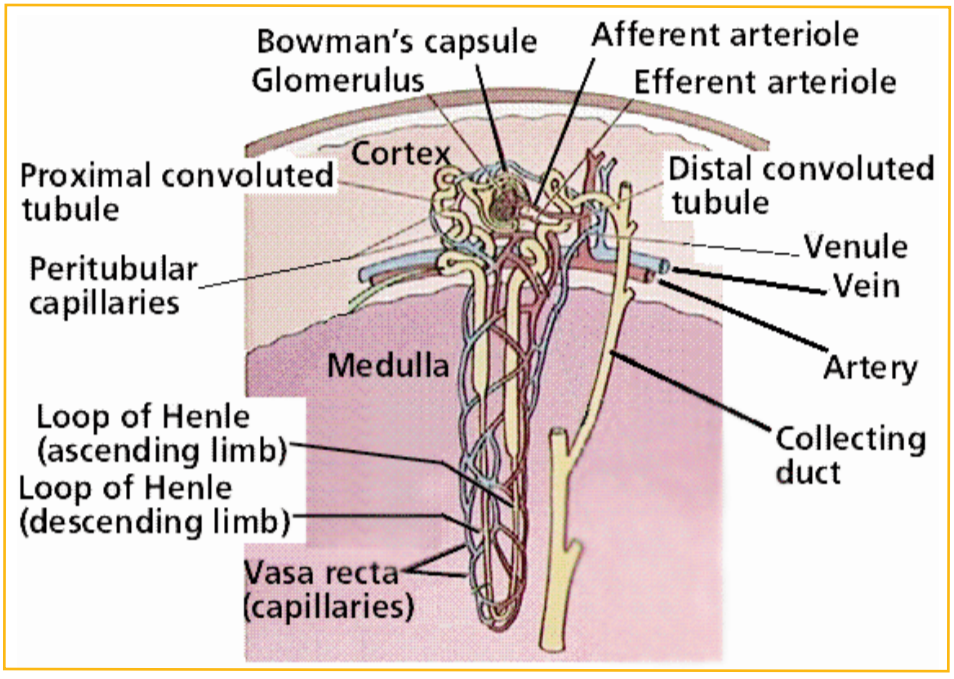
The renal arteries not only deliver blood to the kidneys to be purged of wastes, but also provide oxygen and nutrients to the tissues of the kidney and carry away carbon dioxide to be excreted by the lungs. The blood flow through the kidneys constitutes a very considerable fraction—about one-fourth—of the total cardiac output at rest. As blood passes through the capillaries making up the glomerulus, water and dissolved substances diffuse from it into the space between the two layers of Bowman's capsule.

The normal glomerular membrane is permeable not only to water but also to electrolytes, simple sugars, amino acids, waste products such as urea and creatinine, and indeed nearly all substances carried in the blood except large protein molecules (albumin, globulins, some hormones) and formed elements (red and white blood cells and platelets). The fluid formed in Bowman's capsule thus has essentially the same composition as blood, minus the cells and proteins. The glomerular filtration rate (GFR) depends on systemic blood pressure, the resistance of glomerular capillaries to blood flow, and the integrity of the glomerular basement membrane, which is subject to damage by a variety of inflammatory, degenerative, and toxic factors.

What takes place in the **glomerulus** is indeed purely a matter of filtration, but it is only the beginning of the process of urine formation. Two normal kidneys produce about 125 mL of glomerular filtrate each minute. If all that fluid left the body, and if that rate could be sustained for 24 hours, it would amount to 180 L (about 50 gallons) of urine output a day. Obviously most of the glomerular filtrate is reabsorbed, and that is the function of the renal tubules.

Each Bowman's capsule gives origin to a tubule, which after following a somewhat tortuous course through cortex and medulla discharges its urine from one of the renal papillae into the pelvis of the kidney. The anatomic and functional unit formed by a glomerulus and its renal tubule is called a **nephron**. Formerly considered simply the branches of a collecting and conducting system, the tubules are now recognized as playing an active and crucial role in determining the eventual volume and composition of urine. They do this by simultaneously performing three distinct operations on the glomerular filtrate: passively reabsorbing most of the water and dissolved electrolytes; actively reabsorbing certain substances (sodium, chloride); and actively secreting other substances (potassium, hydrogen ions, urea).

The renal tubule consists of three major anatomic sections, which are called the **proximal convoluted tubule**, the **loop of Henle**, and the **distal convoluted tubule**. Each section performs different reabsorptive and excretory functions, and in fact the loop of Henle can been subdivided into several smaller functional units. Numerous congenital disorders have been identified in which specific excretory or reabsorptive functions of the renal tubules are impaired or lacking. Some of these can cause severe developmental failure, mental retardation, or death.



Microscopic Structure of Kidney

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The rates at which various substances are reabsorbed and excreted depend partly on the concentration of those substances in the glomerular filtrate and partly on a system of feedbacks, neural and hormonal, reflecting the needs of the body for homeostasis, that is, biochemical equilibrium. The ultimate composition of the urine depends on an exceedingly complex interaction of many processes. For example, uric acid passes freely through the glomerular membrane, but most of it is actively reabsorbed in the proximal convuluted tubule, only to be actively pumped back into the urine again by another part of the tubule.

Diuretics (drugs that promote an increased output of urine) are widely used in the treatment of hypertension, congestive heart failure, and other conditions. Because these drugs don't all work on the kidney in the same way, their pharmacologic actions as well as their potential side effects differ. Some act principally on cells in one part of the renal tubule, while others act at different sites. For example, thiazide diuretics (chlorothiazide, hydrochlorothiazide) act at the distal convoluted tubule to block the reabsorption of sodium and potassium. Excessive potassium loss is a possible side effect of these drugs, and so is a rise in uric acid, because they inhibit the excretion of that substance. Although spironolactone also acts at the distal convoluted tubule to promote the excretion of sodium ions, unlike thiazide diuretics it has a potassium sparing effect. Furosemide (Lasix) is called a loop diuretic because its principal site of action is the loop of Henle.

Several organs and tissues besides the kidney, including the lungs, the liver, the intestinal mucosa, and the sweat glands, perform important excretory functions. But the kidneys are the excretory organs par excellence, and their particular province is the disposal of nitrogenous wastes, such as urea and creatinine, that result from the breakdown of protein as a part of normal, day-by-day metabolism. When the kidneys are prevented by severe and extensive disease from excreting nitrogenous wastes, these accumulate in the blood and can exert toxic effects on many tissues, particularly the central nervous system and the cardiovascular system. The buildup of urea and other nitrogenous wastes in the blood as a result of renal failure is called **uremia**.

Besides ridding the body of waste products, the intricate and diversified excretory apparatus of the kidneys also acts to maintain water, electrolyte, and acid-base balance within narrow limits and to stabilize the osmolality of the blood. (Osmolality is a group of physical properties of a solution that depend on the concentrations and molecular weights of all the substances dissolved in it.) By selectively excreting or retaining electrolytes including hydrogen, chloride, bicarbonate, and phosphate ions, the renal tubules work in concert with the lungs to stabilize the pH (hydrogen ion concentration) of the blood.

The concentrations of sodium, potassium, and chloride in the blood depend to a large extent on the renal retention or excretion of these ions. These processes in turn are regulated by aldosterone and related hormones produced by the cortices of the adrenal glands. Aldosterone promotes the renal tubular retention (that is, the reabsorption from glomerular filtrate) of sodium, the principal cation (positively charged ion) of the blood and extracellular fluid, and of chloride, the principal anion (negatively charged ion). It also promotes the tubular excretion of potassium, the principal cation of intracellular fluid. (Aldosterone has similar effects on the retention or excretion of these substances by the sweat glands and the intestinal mucosa.) That is why patients with adrenal failure (Addison disease) lose sodium and water and go into shock, while patients with excessive adrenal activity (or prolonged or excessive steroid treatment) develop Cushing syndrome, with sodium retention and edema (excessive fluid in tissues).

Disease or injury of the pituitary gland that impairs the production of ADH causes diabetes insipidus, in which a large amount of water is lost from the body through the kidneys. In contrast with diabetes mellitus, the urine in this disorder does not contain sugar (glucose)—hence* insipidus *'tasteless'.

The water content of the blood, and hence indirectly that of the body as a whole, is regulated partly by antidiuretic hormone (ADH), also called **vasopressin**. This nonapeptide (substance consisting of 9 amino acids) is released by the posterior pituitary gland when the osmolality of the blood begins to rise, indicating a drop in body water content. The effect of ADH is to open up microscopic channels in the distal convoluted tubules so that water that would otherwise be lost in urine is reabsorbed and restored to the circulation.

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Given the complexities of renal anatomy and physiology, it is no wonder that diseases affecting the kidney can have a broadly diverse range of effects on metabolism and health. The English physician Richard Bright (1789-1858) first drew attention to the close relationship between the kidney and systemic disease when he published his observations on the frequent association, at autopsy, between an enlarged (dilated or hypertrophic) heart and small, contracted or scarred kidneys. The term **Bright's disease**, now outmoded because it is too nonspecific, used to refer to any disease of the kidneys in which albuminuria (the presence of protein, not necessarily albumin, in the urine) is accompanied by edema.

Many cases of Bright's disease represented what would now be called **nephrotic syndrome**—a disorder in which the glomeruli become abnormally permeable to proteins. The body has no way to reabsorb proteins that leak through a diseased glomerular membrane. The loss of these proteins leads to a

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drop in the osmolality of the blood, and as a consequence water leaks from capillaries throughout the body into the tissues, causing edema. Nephrotic syndrome usually occurs as part of a systemic disease such as diabetes mellitus or systemic lupus erythematosus (SLE), but in many cases the cause is unknown. In nephrotic syndrome the concentrations of lipids (cholesterol and triglycerides) in the blood are usually increased, adding another biochemical burden or disadvantage.

More devastating are renal diseases in which excretory function is severely compromised. Acute and chronic renal failure can arise from many causes, including shock, infection, chemical poisons, biological toxins, and obstruction to the outflow of urine from the kidneys. **Acute tubular necrosis** (sometimes referred to as **renal shutdown** or **shock kidney**) is a generalized failure of the renal tubules to perform their excretory functions. This typically results from an interruption of renal blood flow, as in shock, or a metabolic insult to the tubules, as from certain drugs (streptomycin), intravenous contrast media, or hemoglobinuria (excretion of hemoglobin from broken-down red blood cells, as in transfusion reaction, sickle cell anemia, and malaria).

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The distinction between the **nephrotic syndrome** (glomerular leakage of protein, edema, hypercholesterolemia) and **renal failure** (retention of urea, creatinine, potassium, and other substances normally excreted) is largely conceptual. In most severe diseases affecting the kidneys, both elements are combined.

In 1934 the American pathologist Harry Goldblatt, who had observed an association between renal disease and hypertension (high blood pressure), reported a pioneering series of experiments that led eventually to the opening of a whole new chapter in the history of physiology. Goldblatt found that dogs whose renal arteries had been constricted (but not occluded) by a clamp developed hypertension. Further studies revealed that an ischemic kidney (that is, one that is not receiving an adequate flow of blood) produces a substance that raises blood pressure.

We now understand that this occurs because of a derangement in the renin-angiotensin system, which regulates blood pressure and electrolyte balance. Adjacent to each renal glomerulus is a structure called the **juxtaglomerular apparatus**, whose function has been clarified only in recent decades. When the blood flow through the glomerulus falls—for reasons that can range from hemorrhagic shock to arteriosclerosis of the renal artery—the juxtaglomerular apparatus releases a substance called **renin** into the circulation. This touches off a cascade of biochemical reactions whose end result, under ideal conditions, is a restoration of normal blood pressure and renal blood flow.

Here are the key players in the cascade.

- **angiotensinogen**, a globulin (large protein molecule), formed continuously by the liver and circulates in the blood, but is biologically inert.
- **renin**, the enzyme produced by the juxtaglomerular apparatus when glomerular blood flow declines (and also in response to a drop in the sodium chloride concentration of the blood) converts angiotensinogen to
- **angiotensin I**, also biologically inert.
- **angiotensin-converting enzyme** (ACE), a glycoprotein produced mainly in lung tissue, then converts angiotensin I to
- **angiotensin II**, a powerful vasoconstrictor, which raises systemic blood pressure by increasing the resistance to blood flow in capillary beds throughout the body. Angiotensin II also acts as a neurotransmitter, triggering the adrenal cortex to secrete aldosterone, which, as noted above, acts on the kidneys to promote sodium retention and potassium excretion.

Nowadays we recognize that inappropriate activation of this cascade is responsible not only for renal hypertension (the type of high blood pressure resulting directly from compromise of the circulation in at least one kidney) but also for some of the disordered physiology underlying essential hypertension (the much commoner type that runs in families). We also recognize that, while renal ischemia can bring on high blood pressure, the reverse is also true. That is, sustained hypertension from any cause damages arteries, including those of the kidney, and by compromising renal blood flow can create an accelerated or malignant form of hypertension.

In addition, angiotensin II plays a pivotal role in disorders as diverse as congestive heart failure and diabetic nephropathy (the type of kidney damage that occurs in diabetes mellitus). Drugs that block the production of angiotensin II (ACE inhibitors—benazepril, lisinopril, and all the other *prils*) or that prevent some of its actions (angiotensin II receptor blockers—losartan, valsartan, and all the other *sartans*) are useful in these disorders as well as in hypertension.

It has long been recognized that patients with chronic kidney disease often develop severe anemia (reduction in the number of red blood cells in circulating blood), which markedly aggravates the negative impact of the disease on the

cardiovascular system and increases mortality. Renal anemia results from a deficiency of **erythropoietin** (EPO), yet another hormonelike factor produced by the kidney.

EPO normally stimulates the growth and differentiation of primitive cells in bone marrow that are destined to become red blood cells. The synthesis and release of EPO occur in response to hypoxia (a drop in oxygen tension) of the blood passing through the kidney. Although some EPO is produced in the liver, severe renal disease typically leads to a critical deficiency of this agent, with resulting anemia. The standard treatment for renal anemia is administration of synthetic EPO produced by recombinant DNA technology.

Still another complication of chronic kidney disease is a gradual loss of calcium from bone, known as renal osteodystrophy. This again is due to a disturbance in a normal biochemical regulatory mechanism involving the kidney. The absorption of dietary calcium from the digestive tract depends, as we all know, on an adequate intake of vitamin D (calciferol). An essential step in the formation of 1,25-dihydroxy vitamin D_3, the most active form of this vitamin, occurs in the kidney. When renal disease blocks the generation of this form of the vitamin, calcium absorption declines. This results in increased parathyroid hormone production, which tends to preserve the serum level of calcium at the expense of bone. Loss of calcium from bone can lead to varying degrees of osteomalacia (inadequate mineralization of bone) and osteoporosis (reduction of bone volume).

To sum up, the kidney serves many vital functions besides merely disposing of surplus water: removing nitrogenous and other wastes, conserving essential substances, preserving water and electrolyte balance, and supplying chemical mediators necessary for the maintenance of normal blood pressure, red blood cell production, and bone mineralization.

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