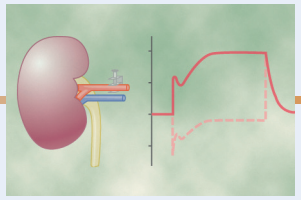

CHAPTER 19

Role of the Kidneys in Long-Term Control of Arterial Pressure and in Hypertension: The Integrated System for Arterial Pressure Regulation

The sympathetic nervous system plays a major role in short-term arterial blood pressure regulation primarily through the effects of the nervous system on total peripheral vascular resistance and capacitance, as well as on cardiac pumping ability, as discussed in Chapter 18.

The body, however, also has powerful mechanisms for regulating arterial pressure week after week and month after month. This long-term control of arterial pressure is closely intertwined with homeostasis of body fluid volume, which is determined by the balance between the fluid intake and output. For long-term survival, fluid intake and output must be precisely balanced, a task that is performed by multiple nervous and hormonal controls and by local control systems within the kidneys that regulate their excretion of salt and water. In this chapter we discuss these renal–body fluid systems that play a major role in long-term blood pressure regulation.

RENAL–BODY FLUID SYSTEM FOR ARTERIAL PRESSURE CONTROL

The renal–body fluid system for arterial pressure control acts slowly but powerfully as follows: If blood volume increases and vascular capacitance is not altered, arterial pressure will also increase. The rising pressure, in turn, causes the kidneys to excrete the excess volume, thus returning the pressure back toward normal.

In the phylogenetic history of animal development, this renal–body fluid system for pressure control is a primitive one. It is fully operative in one of the lowest of vertebrates, the hagfish. This animal has a low arterial pressure, only 8 to 14 mm Hg, and this pressure increases almost directly in proportion to its blood volume. The hagfish continually drinks sea water, which is absorbed into its blood, increasing the blood volume and blood pressure. However, when the pressure rises too high, the kidney simply excretes the excess volume into the urine and relieves the pressure. At low pressure, the kidney excretes less fluid than is ingested. Therefore, because the hagfish continues to drink, extracellular fluid volume, blood volume, and pressure all build up again to the higher levels.

This primitive mechanism of pressure control has survived throughout the ages, almost as it functions in the hagfish; in humans, kidney output of water and salt is just as sensitive—if not more so—to pressure changes as in the hagfish. Indeed, an increase in arterial pressure in the human of only a few mm Hg can double renal output of water, a phenomenon called *pressure diuresis,* as well as double the output of salt, which is called *pressure natriuresis.*

In the human being, just as in the hagfish, the renal–body fluid system for arterial pressure control is a fundamental mechanism for long-term arterial pressure control. However, through the stages of evolution, multiple refinements have been added to make this system much more precise in its control. An especially important refinement, as discussed later, has been the addition of the renin-angiotensin mechanism.

QUANTITATION OF PRESSURE DIURESIS AS A BASIS FOR ARTERIAL PRESSURE CONTROL

Figure 19-1 shows the approximate average effect of different arterial pressure levels on urinary volume output by an isolated kidney, demonstrating markedly increased urine volume output as the pressure rises. This increased urinary output is the phenomenon of *pressure diuresis.* The curve in this figure is called a *renal urinary output curve* or a *renal function curve.* In the human being, at an arterial pressure of 50 mm Hg, the urine output is essentially zero. At 100 mm Hg it is normal, and at 200 mm Hg it is about six to eight times normal. Furthermore, not only does increasing the arterial pressure increase urine volume output, but it also causes an approximately equal increase in sodium output, which is the phenomenon of *pressure natriuresis.*

An Experiment Demonstrating the Renal–Body Fluid System for Arterial Pressure Control. Figure 19-2 shows the results of an experiment in dogs in which all the nervous reflex mechanisms for blood pressure control were first blocked. Then the arterial pressure was suddenly elevated by infusing about 400 ml of blood intravenously. Note the rapid increase in cardiac output to about double normal and the increase in mean arterial pressure to 205 mm Hg, 115 mm Hg above its resting level. Shown

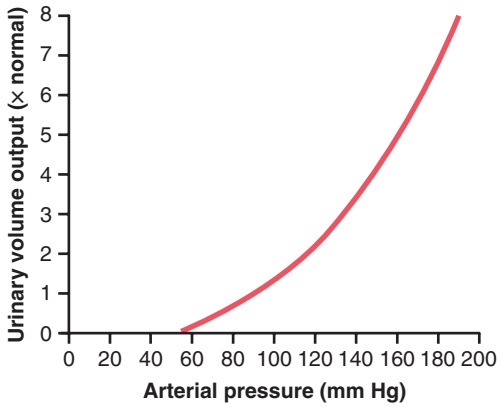

Figure 19-1. A typical renal urinary output curve measured in a perfused isolated kidney, showing pressure diuresis when the arterial pressure rises above normal.

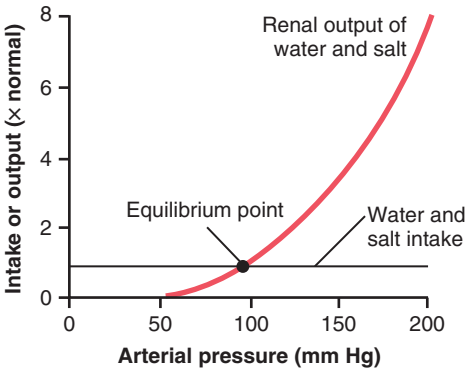

Figure 19-3. Analysis of arterial pressure regulation by equating the renal output curve with the salt and water intake curve. The equilibrium point describes the level to which the arterial pressure will be regulated. (The small portion of the salt and water intake that is lost from the body through nonrenal routes is ignored in this and similar figures in this chapter.)

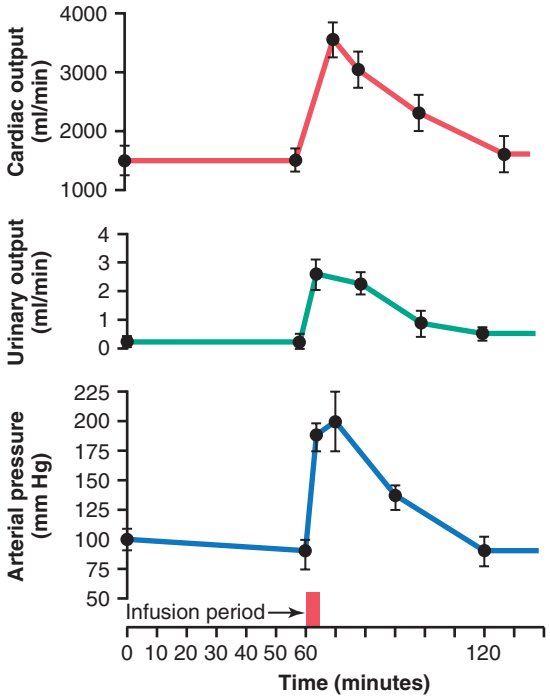

Figure 19-2. Increases in cardiac output, urinary output, and arterial pressure caused by increased blood volume in dogs whose nervous pressure control mechanisms had been blocked. This figure shows return of arterial pressure to normal after about an hour of fluid loss into the urine. *(Courtesy Dr. William Dobbs.)*

by the middle curve is the effect of this increased arterial pressure on urine output, which increased 12-fold. Along with this tremendous loss of fluid in the urine, both the cardiac output and the arterial pressure returned to normal during the subsequent hour. Thus, one sees an extreme capability of the kidneys to eliminate excess fluid volume from the body in response to high arterial pressure and in so doing to return the arterial pressure back to normal.

The Renal–Body Fluid Mechanism Provides Nearly Infinite Feedback Gain for Long-term Arterial Pressure Control. Figure 19-3 shows a graphical method that can be used for analyzing arterial pressure control by the renal–body fluid system. This analysis is based on two separate curves that intersect each other: (1) the renal output curve for water and salt in response to rising arterial pressure, which is the same renal output curve as that shown in Figure 19-1, and (2) the line that represents the net water and salt intake.

Over a long period, the water and salt output must equal the intake. Furthermore, the only place on the graph in Figure 19-3 at which output equals intake is where the two curves intersect, called the *equilibrium point.* Now let us see what happens if the arterial pressure increases above or decreases below the equilibrium point.

First, assume that the arterial pressure rises to 150 mm Hg. At this level, the renal output of water and salt is about three times as great as intake. Therefore, the body loses fluid, the blood volume decreases, and the arterial pressure decreases. Furthermore, this "negative balance" of fluid will not cease until the pressure falls *all the way* back exactly to the equilibrium level. Indeed, even when the arterial pressure is only a few mm Hg greater than the equilibrium level, there still is slightly more loss of water and salt than intake, so the pressure continues to fall that last few mm Hg *until the pressure eventually returns exactly to the equilibrium point.*

If the arterial pressure falls below the equilibrium point, the intake of water and salt is greater than the output. Therefore, body fluid volume increases, blood volume increases, and the arterial pressure rises until once again it returns to the equilibrium point. This return of the arterial pressure *always back to the equilibrium point* is the *near-infinite feedback gain principle* for control of arterial pressure by the renal–body fluid mechanism.

Two Key Determinants of Long-Term Arterial Pressure. In Figure 19-3, one can also see that two basic

long-term factors determine the long-term arterial pressure level.

As long as the two curves representing (1) renal output of salt and water and (2) intake of salt and water remain exactly as they are shown in **Figure 19-3**, the mean arterial pressure level will eventually readjust to 100 mm Hg, which is the pressure level depicted by the equilibrium point of this figure. Furthermore, there are only two ways in which the pressure of this equilibrium point can be changed from the 100 mm Hg level. One way is by shifting the pressure level of the renal output curve for salt and water, and the other is by changing the level of the water and salt intake line. Therefore, expressed simply, the two primary determinants of the long-term arterial pressure level are as follows:

1. The degree of pressure shift of the renal output curve for water and salt
2. The level of the water and salt intake

Operation of these two determinants in the control of arterial pressure is demonstrated in **Figure 19-4**. In **Figure 19-4*A***, some abnormality of the kidneys has caused the renal output curve to shift 50 mm Hg in the high-pressure direction (to the right). Note that the equilibrium point has also shifted to 50 mm Hg higher than normal. Therefore, one can state that if the renal output curve shifts to a new pressure level, the arterial pressure will follow to this new pressure level within a few days.

Figure 19-4*B* shows how a change in the level of salt and water intake also can change the arterial pressure.

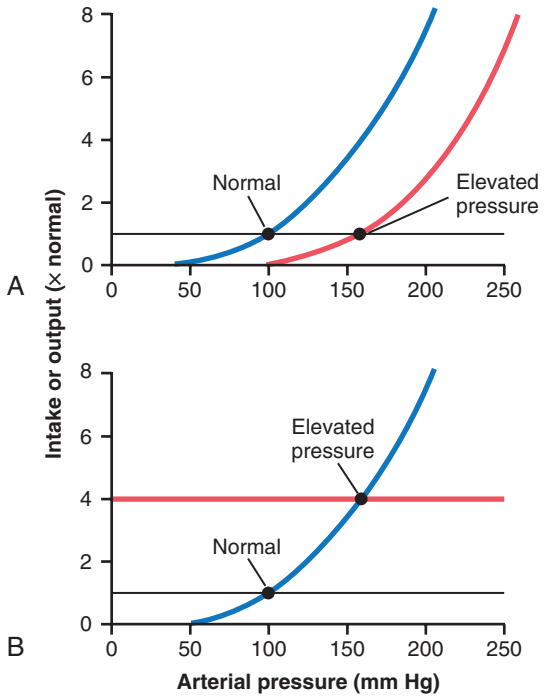

Figure 19-4. Two ways in which the arterial pressure can be increased: **A,** by shifting the renal output curve in the right-hand direction toward a higher pressure level or **B,** by increasing the intake level of salt and water.

In this case, the intake level has increased fourfold and the equilibrium point has shifted to a pressure level of 160 mm Hg, 60 mm Hg above the normal level. Conversely, a decrease in the intake level would reduce the arterial pressure.

Thus, it is *impossible to change the long-term mean arterial pressure level* to a new value without changing one or both of the two basic determinants of long-term arterial pressure—either (1) the level of salt and water intake or (2) the degree of shift of the renal function curve along the pressure axis. However, if either of these is changed, one finds the arterial pressure thereafter to be regulated at a new pressure level, the arterial pressure at which the two new curves intersect.

In most people, however, the renal function curve is much steeper than shown in **Figure 19-4** and changes in salt intake have only a modest effect on arterial pressure, as discussed in the next section.

The Chronic Renal Output Curve Is Much Steeper than the Acute Curve. An important characteristic of pressure natriuresis (and pressure diuresis) is that chronic changes in arterial pressure, lasting for days or months, have much greater effect on renal output of salt and water than observed during acute changes in pressure (**Figure 19-5**). Thus, when the kidneys are functioning normally, the *chronic renal output curve* is much steeper than the acute curve.

The powerful effects of chronic increases in arterial pressure on urine output occur because increased pressure not only has direct hemodynamic effects on the kidney to increase excretion but also indirect effects mediated by nervous and hormonal changes that occur when blood pressure is increased. For example, increased arterial pressure decreases activity of the

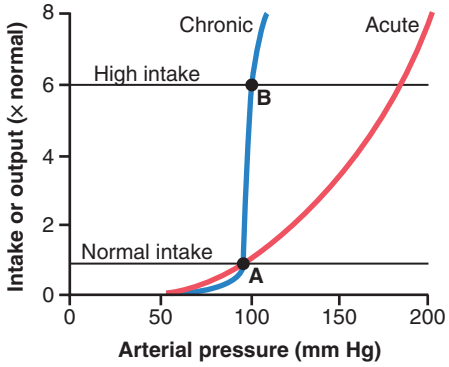

Figure 19-5. Acute and chronic renal output curves. Under steady-state conditions, renal output of salt and water is equal to intake of salt and water. *A* and *B* represent the equilibrium points for long-term regulation of arterial pressure when salt intake is normal or six times normal, respectively. Because of the steepness of the chronic renal output curve, increased salt intake causes only small changes in arterial pressure. In persons with impaired kidney function, the steepness of the renal output curve may be reduced, similar to the acute curve, resulting in increased sensitivity of arterial pressure to changes in salt intake.

sympathetic nervous system and various hormones such as angiotensin II and aldosterone that tend to reduce salt and water excretion by the kidneys. Reduced activity of these *antinatriuretic* systems therefore amplifies the effectiveness of pressure natriuresis and diuresis in raising salt and water excretion during chronic increases in arterial pressure (see Chapters 28 and 30 for further discussion).

Conversely, when blood pressure is reduced, the sympathetic nervous system is activated and formation of antinatriuretic hormones is increased, adding to the direct effects of reduced pressure to decrease renal output of salt and water. This combination of direct effects of pressure on the kidneys and indirect effects of pressure on the sympathetic nervous system and various hormone systems make pressure natriuresis and diuresis extremely powerful for long-term control of arterial pressure and body fluid volumes.

The importance of neural and hormonal influences on pressure natriuresis is especially evident during chronic changes in sodium intake. If the kidneys and the nervous and hormonal mechanisms are functioning normally, chronic increases in intakes of salt and water to as high as six times normal are usually associated with only small increases in arterial pressure. Note that the blood pressure equilibrium point B on the curve is nearly the same as point A, the equilibrium point at normal salt intake. Conversely, decreases in salt and water intake to as low as one-sixth normal typically have little effect on arterial pressure. Thus, many persons are said to be *salt insensitive* because large variations in salt intake do not change blood pressure more than a few mm Hg.

Persons with kidney injury or excessive secretion of antinatriuretic hormones such as angiotensin II or aldosterone, however, may be *salt sensitive,* with an attenuated renal output curve similar to the acute curve shown in **Figure 19-5**. In these cases, even moderate increases in salt intake may cause significant increases in arterial pressure.

Some of the factors that cause blood pressure to be salt sensitive include loss of functional nephrons due to kidney injury and excessive formation of antinatriuretic hormones such as angiotensin II or aldosterone. For example, surgical reduction of kidney mass or injury to the kidney due to hypertension, diabetes, and various kidney diseases all cause blood pressure to be more sensitive to changes in salt intake. In these instances, greater than normal increases in arterial pressure are required to raise renal output sufficiently to maintain a balance between the intake and output of salt and water.

There is evidence that long-term high salt intake, lasting for several years, may actually damage the kidneys and eventually makes blood pressure more salt sensitive. We will discuss salt sensitivity of blood pressure in patients with hypertension later in this chapter.

Failure of Increased Total Peripheral Resistance to Elevate the Long-Term Level of Arterial Pressure if Fluid Intake and Renal Function Do Not Change

Now is the chance for the reader to see whether he or she really understands the renal–body fluid mechanism for arterial pressure control. Recalling the basic equation for arterial pressure—*arterial pressure* equals *cardiac output* times *total peripheral resistance*—it is clear that an increase in total peripheral resistance should elevate the arterial pressure. Indeed, *when the total peripheral resistance is acutely increased,* the arterial pressure does rise immediately. Yet, if the kidneys continue to function normally, the acute rise in arterial pressure usually is not maintained. Instead, the arterial pressure returns all the way to normal within a day or so. Why?

The reason for this phenomenon is that increasing vascular resistance everywhere else in the body *besides in the kidneys* does not change the equilibrium point for blood pressure control as dictated by the kidneys (see again **Figures 19-3** and **19-4**). Instead, the kidneys immediately begin to respond to the high arterial pressure, causing pressure diuresis and pressure natriuresis. Within hours, large amounts of salt and water are lost from the body, and this process continues until the arterial pressure returns to the equilibrium pressure level. At this point blood pressure is normalized and extracellular fluid volume and blood volume are decreased to levels below normal.

As evidence for this principle that changes in total peripheral resistance do not affect the long-term level of arterial pressure if function of the kidneys is still normal, carefully study **Figure 19-6**. This figure shows the approximate cardiac outputs and the arterial pressures in different clinical conditions in which the *long-term total peripheral resistance* is either much less than or much greater than normal, but kidney excretion of salt and water is normal. Note in all these different clinical conditions that the arterial pressure is also normal.

A word of caution is necessary at this point in our discussion. Many times when the total peripheral resistance increases, *this also increases the intrarenal vascular resistance at the same time,* which alters the function of the kidney and can cause hypertension by shifting the renal function curve to a higher pressure level, in the manner shown in **Figure 19-4*A***. We see an example of this mechanism later in this chapter when we discuss hypertension caused by vasoconstrictor mechanisms. However, *it is the increase in renal resistance* that is the culprit, *not the increased total peripheral resistance*—an important distinction.

Increased Fluid Volume Can Elevate Arterial Pressure by Increasing Cardiac Output or Total Peripheral Resistance

The overall mechanism by which increased extracellular fluid volume may elevate arterial pressure, if vascular

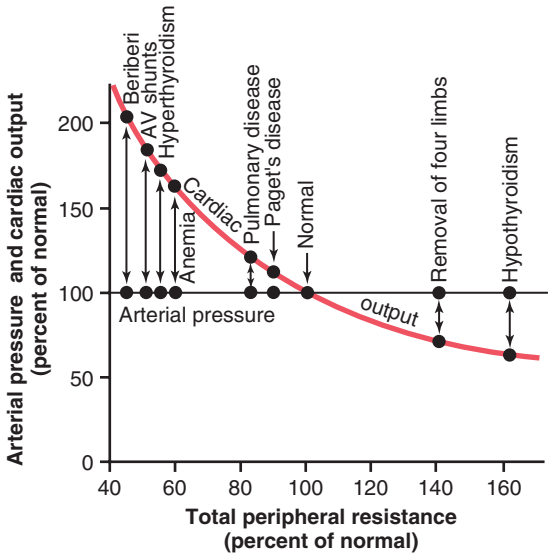

Figure 19-6. Relations of total peripheral resistance to the long-term levels of arterial pressure and cardiac output in different clinical abnormalities. In these conditions, the kidneys were functioning normally. Note that changing the whole-body total peripheral resistance caused equal and opposite changes in cardiac output but in all cases had no effect on arterial pressure. AV, arteriovenous. *(Modified from Guyton AC: Arterial Pressure and Hypertension. Philadelphia: WB Saunders, 1980.)*

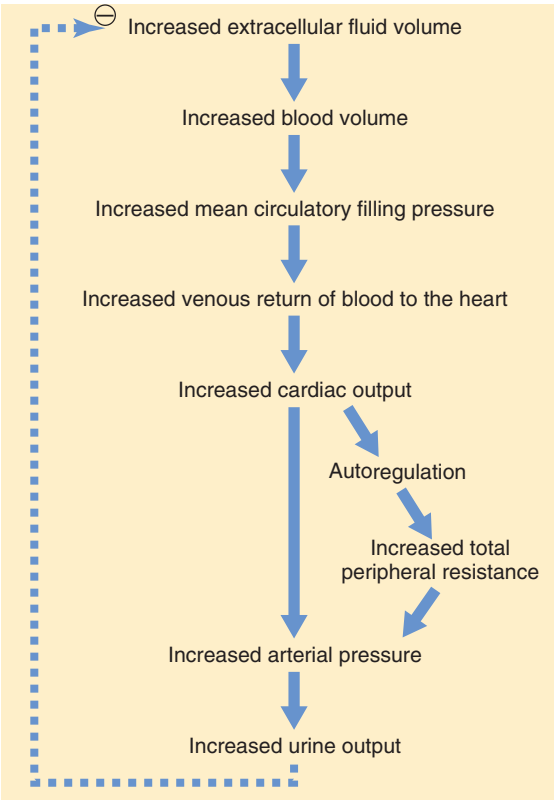

Figure 19-7. Sequential steps by which increased extracellular fluid volume increases the arterial pressure. Note especially that increased cardiac output has both a *direct effect* to increase arterial pressure and an *indirect effect* by first increasing the total peripheral resistance.

capacity is not simultaneously increased, is shown in **Figure 19-7**. The sequential events are (1) increased extracellular fluid volume, which (2) increases the blood volume, which (3) increases the mean circulatory filling pressure, which (4) increases venous return of blood to the heart, which (5) increases cardiac output, which (6) increases arterial pressure. The increased arterial pressure, in turn, increases renal excretion of salt and water and may return extracellular fluid volume to nearly normal if kidney function is normal.

Note especially in this schema the two ways in which an increase in cardiac output can increase the arterial pressure. One of these is the direct effect of increased cardiac output to increase the pressure, and the other is an indirect effect to raise total peripheral vascular resistance through *autoregulation* of blood flow. The second effect can be explained as follows.

Referring to Chapter 17, let us recall that whenever an excess amount of blood flows through a tissue, the local tissue vasculature constricts and decreases the blood flow back toward normal. This phenomenon is called "autoregulation," which means simply regulation of blood flow by the tissue itself. When increased blood volume increases the cardiac output, the blood flow increases in all tissues of the body, so this autoregulation mechanism constricts blood vessels all over the body, which in turn increases the total peripheral resistance.

Finally, because arterial pressure is equal to *cardiac output* times *total peripheral resistance,* the secondary increase in total peripheral resistance that results from the autoregulation mechanism helps greatly in increasing the arterial pressure. For instance, only a 5 to 10 percent increase in cardiac output can increase the arterial pressure from the normal mean arterial pressure of 100 mm Hg up to 150 mm Hg. In fact, the slight increase in cardiac output is often not measurable.

Importance of Salt (NaCl) in the Renal–Body Fluid Schema for Arterial Pressure Regulation

Although the discussions thus far have emphasized the importance of volume in regulation of arterial pressure, experimental studies have shown that an increase in salt intake is far more likely to elevate the arterial pressure than is an increase in water intake. The reason for this finding is that pure water is normally excreted by the kidneys almost as rapidly as it is ingested, but salt is not excreted so easily. As salt accumulates in the body, it also indirectly increases the extracellular fluid volume for two basic reasons:

1. When there is excess salt in the extracellular fluid, the osmolality of the fluid increases, which in turn stimulates the thirst center in the brain, making the person drink extra amounts of water to return the extracellular salt concentration to normal. This increases the extracellular fluid volume.

2. The increase in osmolality caused by the excess salt in the extracellular fluid also stimulates the hypothalamic-posterior pituitary gland secretory mechanism to secrete increased quantities of *antidiuretic hormone*. (This is discussed in Chapter 29.) The antidiuretic hormone then causes the kidneys to reabsorb greatly increased quantities of water from the renal tubular fluid, thereby diminishing the excreted volume of urine but increasing the extracellular fluid volume.

Thus, for these important reasons, the amount of salt that accumulates in the body is the main determinant of the extracellular fluid volume. Because only small increases in extracellular fluid and blood volume can often increase the arterial pressure greatly if the vascular capacity is not simultaneously increased, accumulation of even a small amount of extra salt in the body can lead to considerable elevation of arterial pressure. This is only true, however, if the excess salt accumulation leads to an increase in blood volume and if vascular capacity is not simultaneously increased. As discussed previously, raising salt intake in the absence of impaired kidney function or excessive formation of antinatriuretic hormones usually does not increase arterial pressure much because the kidneys rapidly eliminate the excess salt and blood volume is hardly altered.

CHRONIC HYPERTENSION (HIGH BLOOD PRESSURE) IS CAUSED BY IMPAIRED RENAL FUNCTION

When a person is said to have chronic *hypertension* (or "high blood pressure"), this means that his or her *mean arterial pressure* is greater than the upper range of the accepted normal measure. A *mean* arterial pressure greater than 110 mm Hg (normal is about 90 mm Hg) is considered to be hypertensive. (This level of *mean* pressure occurs when the *diastolic* blood pressure is greater than about 90 mm Hg and the *systolic* pressure is greater than about 135 mm Hg.) In persons with severe hypertension, the *mean* arterial pressure can rise to 150 to 170 mm Hg, with *diastolic* pressure as high as 130 mm Hg and *systolic* pressure occasionally as high as 250 mm Hg.

Even moderate elevation of arterial pressure leads to shortened life expectancy. At severely high pressures—that is, mean arterial pressures 50 percent or more above normal—a person can expect to live no more than a few more years unless appropriately treated. The lethal effects of hypertension are caused mainly in three ways:

1. Excess workload on the heart leads to early heart failure and coronary heart disease, often causing death as a result of a heart attack.
2. The high pressure frequently damages a major blood vessel in the brain, followed by death of major portions of the brain; this occurrence is a *cerebral infarct.* Clinically it is called a "stroke." Depending on which part of the brain is involved, a stroke can be fatal or cause paralysis, dementia, blindness, or multiple other serious brain disorders.
3. High pressure almost always causes injury in the kidneys, producing many areas of renal destruction and, eventually, kidney failure, uremia, and death.

Lessons learned from the type of hypertension called "volume-loading hypertension" have been crucial in understanding the role of the renal–body fluid volume mechanism for arterial pressure regulation. Volume-loading hypertension means hypertension caused by excess accumulation of extracellular fluid in the body, some examples of which follow.

Experimental Volume-Loading Hypertension Caused by Reduced Renal Mass With Simultaneous Increase in Salt Intake. **Figure 19-8** shows a typical experiment demonstrating volume-loading hypertension in a group of dogs with 70 percent of their kidney mass removed. At the first circled point on the curve, the two poles of one of the kidneys were removed, and at the second circled point, the entire opposite kidney was removed, leaving the animals with only 30 percent of normal renal mass. Note that removal of this amount of kidney mass increased the arterial pressure an average of only 6 mm Hg. Then, the dogs were given salt solution to drink instead of water. Because salt solution fails to quench the thirst, the dogs drank two to four times the normal amounts of volume, and within a few days, their average arterial pressure rose to about 40 mm Hg above normal. After 2 weeks, the dogs were given tap water again instead of salt solution; the pressure returned to normal within 2 days. Finally, at the end of the experiment, the dogs were given salt solution again, and this time the pressure rose much more rapidly to a high level, again demonstrating volume-loading hypertension.

If one considers again the basic determinants of long-term arterial pressure regulation, it is apparent why hypertension occurred in the volume-loading experiment illustrated in **Figure 19-8**. First, reduction of the kidney mass to 30 percent of normal greatly reduced the ability of the kidneys to excrete salt and water. Therefore, salt and water accumulated in the body and in a few days raised the arterial pressure high enough to excrete the excess salt and water intake.

Sequential Changes in Circulatory Function During the Development of Volume-Loading Hypertension. It is especially instructive to study the sequential changes in circulatory function during progressive development of volume-loading hypertension. **Figure 19-9** shows these sequential changes. A week or so before the point labeled "0" days, the kidney mass had already been decreased to only 30 percent of normal. Then, at this point, the intake of salt and water was increased to about six times normal and kept at this high intake thereafter. The acute effect was to increase extracellular fluid volume, blood volume, and cardiac output to 20 to 40 percent above normal.

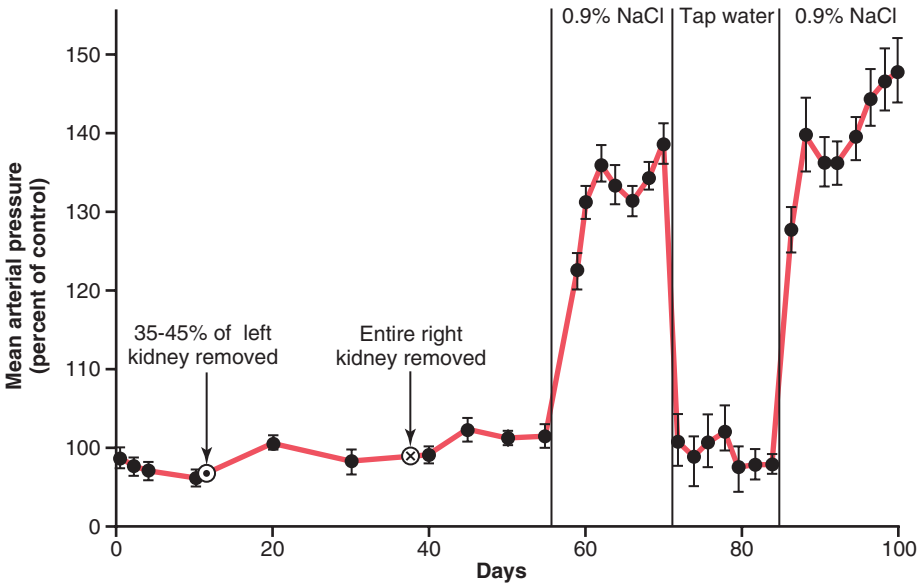

Figure 19-8. The average effect on arterial pressure of drinking 0.9 percent saline solution instead of water in dogs with 70 percent of their renal tissue removed. *(Modified from Langston JB, Guyton AC, Douglas BH, et al: Effect of changes in salt intake on arterial pressure and renal function in partially nephrectomized dogs. Circ Res 12:508, 1963. By permission of the American Heart Association, Inc.)*

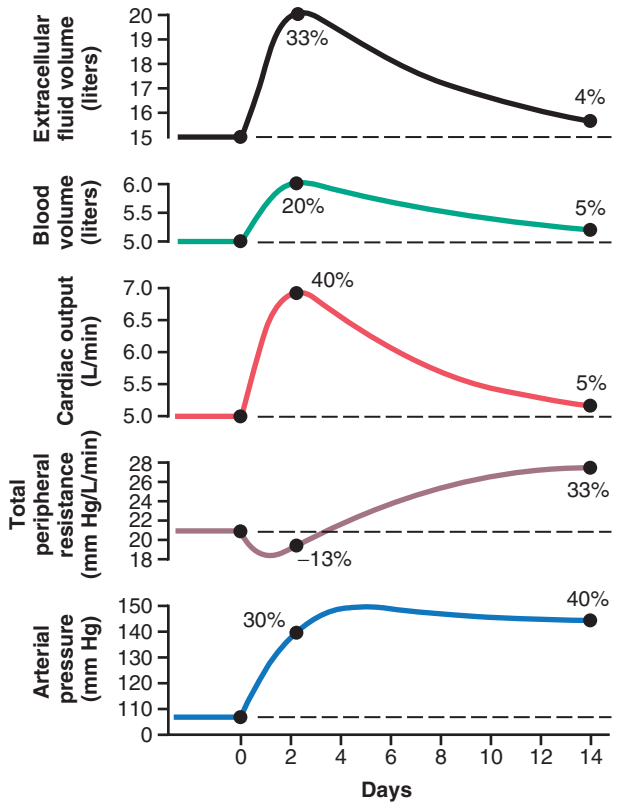

Figure 19-9. Progressive changes in important circulatory system variables during the first few weeks of *volume-loading hypertension.* Note especially the initial increase in cardiac output as the basic cause of the hypertension. Subsequently, the autoregulation mechanism returns the cardiac output almost to normal while simultaneously causing a *secondary increase in total peripheral resistance. (Modified from Guyton AC: Arterial Pressure and Hypertension. Philadelphia: WB Saunders, 1980.)*

Simultaneously, the arterial pressure began to rise but not nearly so much at first as did the fluid volumes and cardiac output. The reason for this slower rise in pressure can be discerned by studying the total peripheral resistance curve, which shows an initial *decrease* in total peripheral resistance. This decrease was caused by the baroreceptor mechanism discussed in Chapter 18, which transiently attenuated the rise in pressure. However, after 2 to 4 days, the baroreceptors adapted (reset) and were no longer able to prevent the rise in pressure. At this time, the arterial pressure had risen almost to its full height because of the increase in cardiac output, even though the total peripheral resistance was still almost at the normal level.

After these early acute changes in the circulatory variables had occurred, more prolonged secondary changes occurred during the next few weeks. Especially important was a *progressive increase in total peripheral resistance,* while at the same time *the cardiac output decreased almost all the way back to normal,* mainly as a result of *the long-term blood flow autoregulation* mechanism that is discussed in detail in Chapter 17 and earlier in this chapter. That is, after the cardiac output had risen to a high level and had initiated the hypertension, the excess blood flow through the tissues then caused progressive constriction of the local arterioles, thus returning the local blood flows in the body tissues and also the cardiac output almost all the way back to normal, while simultaneously causing a *secondary increase in total peripheral resistance.*

Note that the extracellular fluid volume and blood volume also returned almost all the way back to normal along with the decrease in cardiac output. This outcome resulted from two factors: First, the increase in arteriolar resistance decreased the capillary pressure, which allowed

the fluid in the tissue spaces to be absorbed back into the blood. Second, the elevated arterial pressure now caused the kidneys to excrete the excess volume of fluid that had initially accumulated in the body.

Several weeks after the initial onset of volume loading we find the following effects:

1. Hypertension
2. Marked increase in total peripheral resistance
3. Almost complete return of the extracellular fluid volume, blood volume, and cardiac output back to normal

Therefore, we can divide volume-loading hypertension into two sequential stages. The first stage results from increased fluid volume causing increased cardiac output. This increase in cardiac output mediates the hypertension. The second stage in volume-loading hypertension is characterized by high blood pressure and high total peripheral resistance but return of the cardiac output so near to normal that the usual measuring techniques frequently cannot detect an abnormally elevated cardiac output.

Thus, the increased total peripheral resistance in volume-loading hypertension occurs after the hypertension has developed and, therefore, is secondary to the hypertension rather than being the cause of the hypertension.

Volume-Loading Hypertension in Patients Who Have No Kidneys but Are Being Maintained with an Artificial Kidney

When a patient is maintained with an artificial kidney, it is especially important to keep the patient's body fluid volume at a normal level by removing the appropriate amount of water and salt each time the patient undergoes dialysis. If this step is not performed and extracellular fluid volume is allowed to increase, hypertension almost invariably develops in exactly the same way as shown in **Figure 19-9**. That is, the cardiac output increases at first and causes hypertension. Then the autoregulation mechanism returns the cardiac output back toward normal while causing a secondary increase in total peripheral resistance. Therefore, in the end, the hypertension appears to be a high peripheral resistance type of hypertension, although the initial cause is excess volume accumulation.

Hypertension Caused by Excess Aldosterone

Another type of volume-loading hypertension is caused by excess aldosterone in the body or, occasionally, by excesses of other types of steroids. A small tumor in one of the adrenal glands occasionally secretes large quantities of aldosterone, which is the condition called "*primary aldosteronism*." As discussed in Chapters 28 and 30, aldosterone increases the rate of reabsorption of salt and water by the tubules of the kidneys, thereby reducing the loss of these substances in the urine while causing an increase in blood volume and extracellular fluid volume. Consequently, hypertension occurs. If salt intake is increased at the same time, the hypertension becomes even greater. Furthermore, if the condition persists for months or years, the excess arterial pressure often causes pathological changes in the kidneys that make the kidneys retain even more salt and water in addition to that caused directly by the aldosterone. Therefore, the hypertension often finally becomes severe to the point of being lethal.

Here again, in the early stages of this type of hypertension, the cardiac output is increased, but in later stages, the cardiac output generally returns almost to normal while the total peripheral resistance becomes secondarily elevated, as explained earlier in the chapter for primary volume-loading hypertension.

THE RENIN-ANGIOTENSIN SYSTEM: ITS ROLE IN ARTERIAL PRESSURE CONTROL

Aside from the capability of the kidneys to control arterial pressure through changes in extracellular fluid volume, the kidneys also have another powerful mechanism for controlling pressure: the renin-angiotensin system.

Renin is a protein enzyme released by the kidneys when the arterial pressure falls too low. In turn, it raises the arterial pressure in several ways, thus helping to correct the initial fall in pressure.

COMPONENTS OF THE RENIN-ANGIOTENSIN SYSTEM

Figure 19-10 shows the functional steps by which the renin-angiotensin system helps to regulate arterial pressure.

Renin is synthesized and stored in an inactive form called *prorenin* in the *juxtaglomerular cells* (JG cells) of the kidneys. The JG cells are modified smooth muscle cells located mainly *in the walls of the afferent arterioles immediately proximal to the glomeruli*. When the arterial pressure falls, intrinsic reactions in the kidneys cause many of the prorenin molecules in the JG cells to split and release renin. Most of the renin enters the renal blood and then passes out of the kidneys to circulate throughout the entire body. However, small amounts of the renin do remain in the local fluids of the kidney and initiate several intrarenal functions.

Renin itself is an enzyme, not a vasoactive substance. As shown in the schema of **Figure 19-10**, renin acts enzymatically on another plasma protein, a globulin called *renin substrate* (or *angiotensinogen*), to release a 10-amino acid peptide, *angiotensin I*. Angiotensin I has mild vasoconstrictor properties but not enough to cause significant changes in circulatory function. The renin persists in the blood for 30 minutes to 1 hour and continues

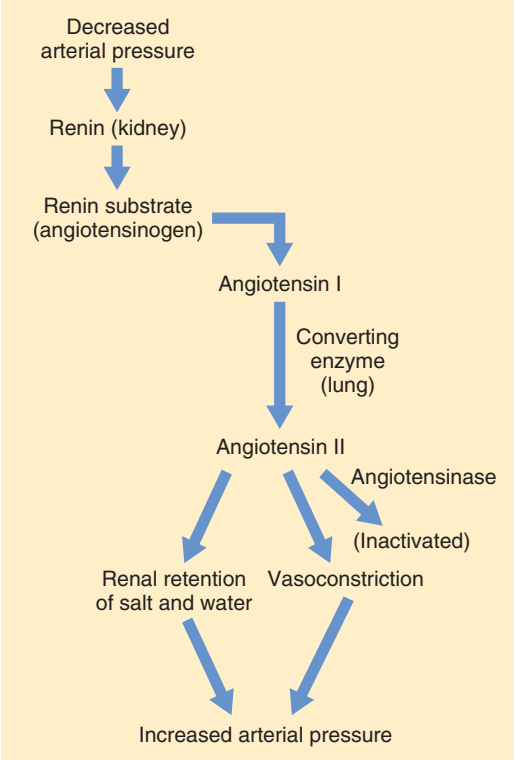

Figure 19-10. The renin-angiotensin vasoconstrictor mechanism for arterial pressure control.

to cause formation of still more angiotensin I during this entire time.

Within a few seconds to minutes after formation of angiotensin I, two additional amino acids are split from the angiotensin I to form the 8-amino acid peptide *angiotensin II*. This conversion occurs to a great extent in the lungs while the blood flows through the small vessels of the lungs, catalyzed by an enzyme called *angiotensin-converting enzyme* that is present in the endothelium of the lung vessels. Other tissues such as the kidneys and blood vessels also contain converting enzyme and therefore form angiotensin II locally.

Angiotensin II is an extremely powerful vasoconstrictor, and it affects circulatory function in other ways as well. However, it persists in the blood only for 1 or 2 minutes because it is rapidly inactivated by multiple blood and tissue enzymes collectively called *angiotensinases*.

Angiotensin II has two principal effects that can elevate arterial pressure. The first of these, *vasoconstriction in many areas of the body,* occurs rapidly. Vasoconstriction occurs intensely in the arterioles and much less so in the veins. Constriction of the arterioles increases the total peripheral resistance, thereby raising the arterial pressure, as demonstrated at the bottom of the schema in **Figure 19-10**. Also, the mild constriction of the veins promotes increased venous return of blood to the heart, thereby helping the heart pump against the increasing pressure.

The second principal means by which angiotensin II increases the arterial pressure is to *decrease excretion of both salt and water* by the kidneys. This action slowly

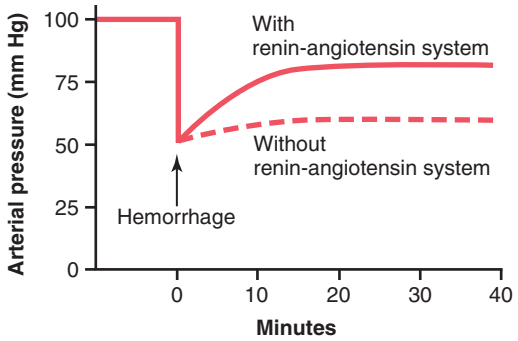

Figure 19-11. The pressure-compensating effect of the renin-angiotensin vasoconstrictor system after severe hemorrhage. *(Drawn from experiments by Dr. Royce Brough.)*

increases the extracellular fluid volume, which then increases the arterial pressure during subsequent hours and days. This long-term effect, acting through the extracellular fluid volume mechanism, is even more powerful than the acute vasoconstrictor mechanism in eventually raising the arterial pressure.

Rapidity and Intensity of the Vasoconstrictor Pressure Response to the Renin-Angiotensin System

Figure 19-11 shows an experiment demonstrating the effect of hemorrhage on the arterial pressure under two separate conditions: (1) with the renin-angiotensin system functioning and (2) without the system functioning (the system was interrupted by a renin-blocking antibody). Note that after hemorrhage—enough to cause acute decrease of the arterial pressure to 50 mm Hg—the arterial pressure rose back to 83 mm Hg when the renin-angiotensin system was functional. Conversely, it rose to only 60 mm Hg when the renin-angiotensin system was blocked. This phenomenon shows that the renin-angiotensin system is powerful enough to return the arterial pressure at least halfway back to normal within a few minutes after severe hemorrhage. Therefore, sometimes it can be of lifesaving service to the body, especially in circulatory shock.

Note also that the renin-angiotensin vasoconstrictor system requires about 20 minutes to become fully active. Therefore, it is somewhat slower to act for blood pressure control than are the nervous reflexes and the sympathetic norepinephrine-epinephrine system.

Angiotensin II Causes Renal Retention of Salt and Water—An Important Means for Long-Term Control of Arterial Pressure

Angiotensin II causes the kidneys to retain both salt and water in two major ways:

1. Angiotensin II acts directly on the kidneys to cause salt and water retention.
2. Angiotensin II causes the adrenal glands to secrete aldosterone, and the aldosterone in turn increases salt and water reabsorption by the kidney tubules.

Thus, whenever excess amounts of angiotensin II circulate in the blood, the entire long-term renal–body fluid mechanism for arterial pressure control automatically becomes set to a higher arterial pressure level than normal.

Mechanisms of the Direct Renal Effects of Angiotensin II to Cause Renal Retention of Salt and Water. Angiotensin has several direct renal effects that make the kidneys retain salt and water. One major effect is to constrict the renal arterioles, thereby diminishing blood flow through the kidneys. The slow flow of blood reduces the pressure in the peritubular capillaries, which causes rapid reabsorption of fluid from the tubules. Angiotensin II also has important direct actions on the tubular cells to increase tubular reabsorption of sodium and water as discussed in Chapter 28. The combined effects of angiotensin II can sometimes decrease urine output to less than one fifth of normal.

Angiotensin II Increases Kidney Salt and Water Retention by Stimulating Aldosterone. Angiotensin II is also one of the most powerful stimulators of aldosterone secretion by the adrenal glands, as we shall discuss in relation to body fluid regulation in Chapter 30 and in relation to adrenal gland function in Chapter 78. Therefore, when the renin-angiotensin system becomes activated, the rate of aldosterone secretion usually also increases, and an important subsequent function of aldosterone is to cause marked increase in sodium reabsorption by the kidney tubules, thus increasing the total body extracellular fluid sodium. This increased sodium then causes water retention, as already explained, increasing the extracellular fluid volume and leading secondarily to still more long-term elevation of the arterial pressure.

Thus both the direct effect of angiotensin on the kidney and its effect acting through aldosterone are important in long-term arterial pressure control. However, research in our laboratory has suggested that the direct effect of angiotensin on the kidneys is perhaps three or more times as potent as the indirect effect acting through aldosterone, even though the indirect effect is the one most widely known.

Quantitative Analysis of Arterial Pressure Changes Caused by Angiotensin II. Figure 19-12 shows a quantitative analysis of the effect of angiotensin in arterial pressure control. This figure shows two renal function curves, as well as a line depicting a normal level of sodium intake. The left-hand renal function curve is that measured in dogs whose renin-angiotensin system had been blocked by an angiotensin-converting enzyme inhibitor drug that blocks the conversion of angiotensin I to angiotensin II. The right-hand curve was measured in dogs infused continuously with angiotensin II at a level about 2.5 times the normal rate of angiotensin formation in the blood. Note the shift of the renal output curve toward higher pressure levels under the influence of angiotensin II. This shift is caused by both the direct effects of angiotensin II on the kidney and the indirect effect acting through aldosterone secretion, as explained earlier.

Finally, note the two equilibrium points, one for zero angiotensin showing an arterial pressure level of 75 mm Hg, and one for elevated angiotensin showing a pressure level of 115 mm Hg. Therefore, the effect of angiotensin to cause renal retention of salt and water can have a powerful effect in promoting chronic elevation of the arterial pressure.

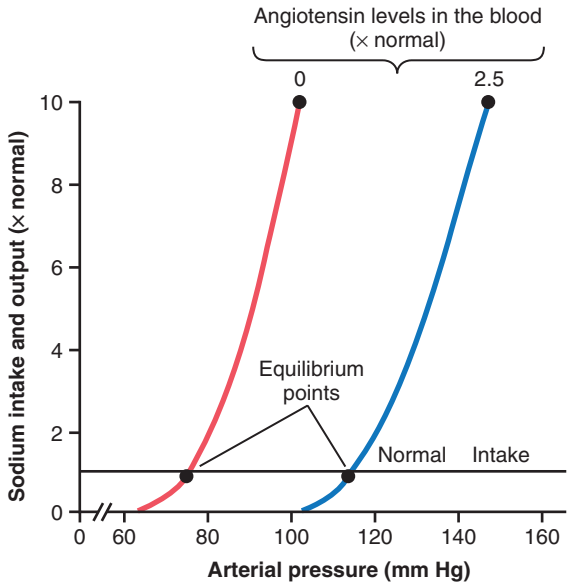

Figure 19-12. The effect of two angiotensin II levels in the blood on the renal output curve, showing regulation of the arterial pressure at an equilibrium point of 75 mm Hg when the angiotensin II level is low and at 115 mm Hg when the angiotensin II level is high.

Role of the Renin-Angiotensin System in Maintaining a Normal Arterial Pressure Despite Large Variations in Salt Intake

One of the most important functions of the renin-angiotensin system is to allow a person to eat either very small or very large amounts of salt without causing great changes in either extracellular fluid volume or arterial pressure. This function is explained by the schema in Figure 19-13, which shows that the initial effect of increased salt intake is to elevate the extracellular fluid volume, in turn elevating the arterial pressure. Then the increased arterial pressure causes increased blood flow through the kidneys, as well as other effects, which reduce the rate of secretion of renin to a much lower level and lead sequentially to decreased renal retention of salt and water, return of the extracellular fluid volume almost to normal, and, finally, return of the arterial pressure almost to normal as well. Thus, the renin-angiotensin system is an automatic feedback mechanism that helps maintain the arterial pressure at or near the normal level even when salt intake is increased. When salt intake is decreased below normal, exactly opposite effects take place.

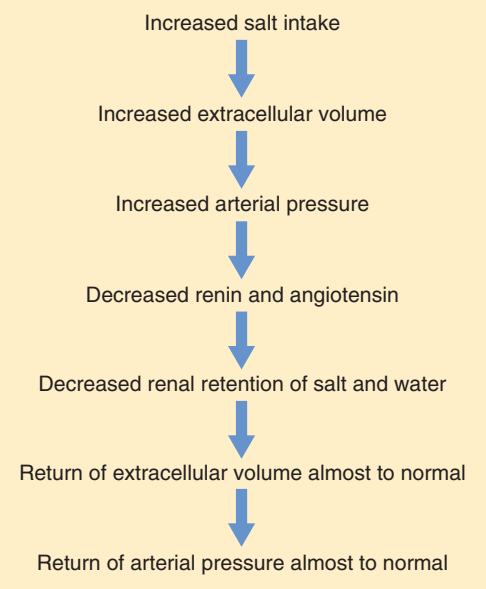

Figure 19-13. Sequential events by which increased salt intake increases the arterial pressure, but feedback decrease in activity of the renin angiotensin system returns the arterial pressure almost to the normal level.

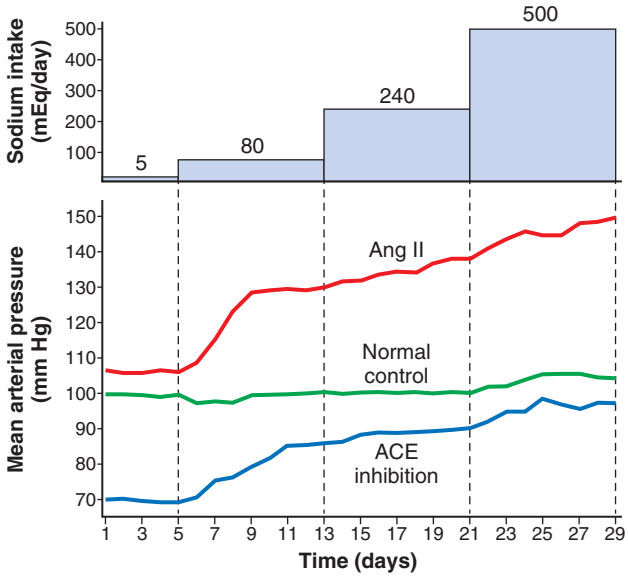

Figure 19-14. Changes in mean arterial pressure during chronic changes in sodium intake in normal control dogs and in dogs treated with an angiotensin-converting enzyme *(ACE)* inhibitor to block angiotensin II *(Ang II)* formation or infused with Ang II to prevent Ang II from being suppressed. Sodium intake was raised in steps from a low level of 5 mmol/day to 80, 240, and 500 mmol/day for 8 days at each level. *(Modified from Hall JE, Guyton AC, Smith MJ Jr, et al: Blood pressure and renal function during chronic changes in sodium intake: role of angiotensin. Am J Physiol 239:F271, 1980.)*

To emphasize the efficacy of the renin-angiotensin system in controlling arterial pressure, when the system functions normally, the pressure rises no more than 4 to 6 mm Hg in response to as much as a 100-fold increase in salt intake (**Figure 19-14**). Conversely, when the renin-angiotensin system is blocked and the usual suppression of angiotensin formation is prevented, the same increase in salt intake sometimes causes the pressure to rise 50 to 60 mm Hg, as much as 10 times the normal increase. When salt intake is reduced to as low as 1/10th normal, arterial pressure barely changes as long as the renin-angiotensin system functions normally. However, when angiotensin II formation is blocked with an angiotensin-converting enzyme inhibitor, blood pressure decreases markedly as salt intake is reduced (**Figure 19-14**). Thus, the renin-angiotensin system is perhaps the body's most powerful system for accommodating wide variations in salt intake with minimal changes in arterial pressure.

TYPES OF HYPERTENSION IN WHICH ANGIOTENSIN IS INVOLVED: HYPERTENSION CAUSED BY A RENIN-SECRETING TUMOR OR BY RENAL ISCHEMIA

Occasionally a tumor of the renin-secreting JG cells occurs and secretes tremendous quantities of renin; in turn, equally large quantities of angiotensin II are formed. In all patients in whom this phenomenon has occurred, severe hypertension has developed. Also, when large amounts of angiotensin II are infused continuously for days or weeks into animals, similar severe long-term hypertension develops.

We have already noted that angiotensin II can increase the arterial pressure in two ways:

1. By constricting the arterioles throughout the entire body, thereby increasing the total peripheral resistance and arterial pressure; this effect occurs within seconds after one begins to infuse angiotensin.
2. By causing the kidneys to retain salt and water; over a period of days, this action, too, causes hypertension and is the principal cause of the long-term continuation of the elevated pressure.

"One-Kidney" Goldblatt Hypertension. When one kidney is removed and a constrictor is placed on the renal artery of the remaining kidney, as shown in **Figure 19-15**, the immediate effect is greatly reduced pressure in the renal artery beyond the constrictor, as demonstrated by the dashed curve in the figure. Then, within seconds or minutes, the systemic arterial pressure begins to rise and continues to rise for several days. The pressure usually rises rapidly for the first hour or so, and this effect is followed by a slower additional rise during the next several days. When the *systemic* arterial pressure reaches its new stable pressure level, the *renal* arterial pressure (the dashed curve in the figure) will have returned almost all the way back to normal. The hypertension produced in this way is called *one-kidney Goldblatt hypertension* in honor of Harry Goldblatt, who first studied the important quantitative features of hypertension caused by renal artery constriction.

The early rise in arterial pressure in Goldblatt hypertension is caused by the renin-angiotensin

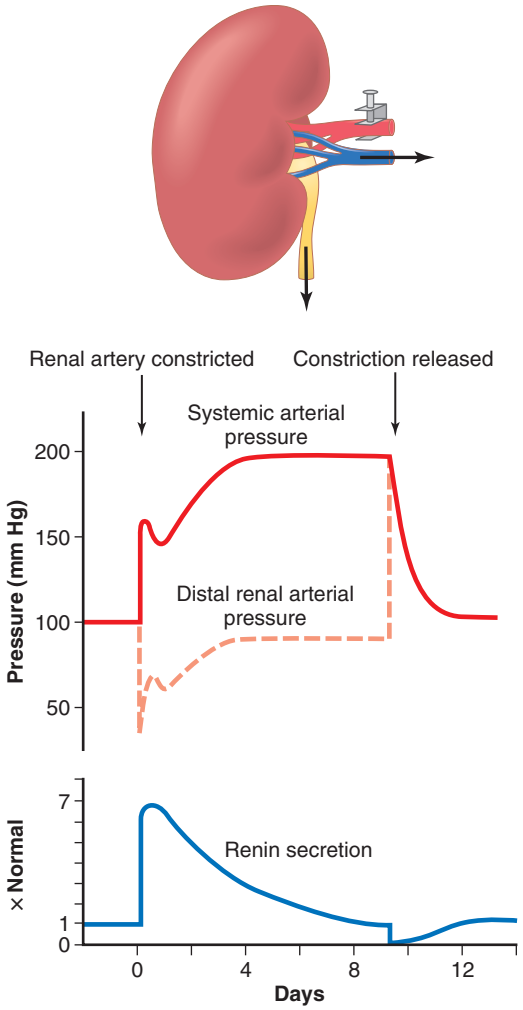

Figure 19-15. The effect of placing a constricting clamp on the renal artery of one kidney after the other kidney has been removed. Note the changes in systemic arterial pressure, renal artery pressure distal to the clamp, and rate of renin secretion. The resulting hypertension is called "one-kidney" Goldblatt hypertension.

vasoconstrictor mechanism. That is, because of poor blood flow through the kidney after acute constriction of the renal artery, large quantities of renin are secreted by the kidney, as demonstrated by the lowermost curve in **Figure 19-15**, and this action increases angiotensin II and aldosterone in the blood. The angiotensin in turn raises the arterial pressure acutely. The secretion of renin rises to a peak in an hour or so but returns nearly to normal in 5 to 7 days because the *renal* arterial pressure by that time has also risen back to normal, so the kidney is no longer ischemic.

The second rise in arterial pressure is caused by retention of salt and water by the constricted kidney (that is also stimulated by angiotensin II and aldosterone). In 5 to 7 days, the body fluid volume increases enough to raise the arterial pressure to its new sustained level. The quantitative value of this sustained pressure level is determined by the degree of constriction of the renal artery. That is, the aortic pressure must rise high enough so that renal arterial pressure distal to the constrictor is enough to cause normal urine output.

A similar scenario occurs in patients with stenosis of the renal artery of a single remaining kidney, as sometimes occurs after a person receives a kidney transplant. Also, functional or pathological increases in resistance of the renal arterioles, due to atherosclerosis or excessive levels of vasoconstrictors, can cause hypertension through the same mechanisms as constriction of the main renal artery.

"Two-Kidney" Goldblatt Hypertension. Hypertension also can result when the artery to only one kidney is constricted while the artery to the other kidney is normal. The constricted kidney secretes renin and also retains salt and water because of decreased renal arterial pressure in this kidney. Then the "normal" opposite kidney retains salt and water because of the renin produced by the ischemic kidney. This renin causes formation of angiotension II and aldosterone, both of which circulate to the opposite kidney and cause it also to retain salt and water. Thus, both kidneys—but for different reasons—become salt and water retainers. Consequently, hypertension develops.

The clinical counterpart of two-kidney Goldblatt hypertension occurs when there is stenosis of a single renal artery, for example, caused by atherosclerosis, in a person who has two kidneys.

Hypertension Caused by Diseased Kidneys That Secrete Renin Chronically. Often, patchy areas of one or both kidneys are diseased and become ischemic because of local vascular constrictions or infarctions, whereas other areas of the kidneys are normal. When this situation occurs, almost identical effects occur as in the two-kidney type of Goldblatt hypertension. That is, the patchy ischemic kidney tissue secretes renin, which, in turn—by acting through the formation of angiotensin II—causes the remaining kidney mass also to retain salt and water. Indeed, one of the most common causes of renal hypertension, especially in older persons, is such patchy ischemic kidney disease.

Other Types of Hypertension Caused by Combinations of Volume Loading and Vasoconstriction

Hypertension in the Upper Part of the Body Caused by Coarctation of the Aorta. One out of every few thousand babies is born with pathological constriction or blockage of the aorta at a point beyond the aortic arterial branches to the head and arms but proximal to the renal arteries, a condition called *coarctation of the aorta*. When this occurs, blood flow to the lower body is carried by multiple, small collateral arteries in the body wall, with much vascular resistance between the upper aorta and the lower aorta. As a consequence, the arterial pressure in the upper part of the body may be 40 to 50 percent higher than that in the lower body.

The mechanism of this upper-body hypertension is almost identical to that of one-kidney Goldblatt hypertension. That is, when a constrictor is placed on the aorta above the renal arteries, the blood pressure in both kidneys at first falls, renin is secreted, angiotensin and aldosterone are formed, and hypertension occurs in the upper body. The arterial pressure in the lower body at the level of the kidneys rises approximately to normal, but high pressure persists in the upper body. The kidneys are no longer ischemic, and thus secretion of renin and formation of angiotensin and aldosterone return to normal. Likewise, in coarctation of the aorta, the arterial pressure in the lower body is usually almost normal, whereas the pressure in the upper body is far higher than normal.

Role of Autoregulation in Hypertension Caused by Aortic Coarctation. A significant feature of hypertension caused by aortic coarctation is that blood flow in the arms, where the pressure may be 40 to 60 percent above normal, is almost exactly normal. Also, blood flow in the legs, where the pressure is not elevated, is almost exactly normal. How could this be, with the pressure in the upper body 40 to 60 percent greater than in the lower body? The answer is not that there are differences in vasoconstrictor substances in the blood of the upper and lower body, because the same blood flows to both areas. Likewise, the nervous system innervates both areas of the circulation similarly, so there is no reason to believe that there is a difference in nervous control of the blood vessels. The main reason is that *long-term autoregulation develops so nearly completely* that the local blood flow control mechanisms have compensated almost 100 percent for the differences in pressure. The result is that, in both the high-pressure area and the low-pressure area, the local blood flow is controlled almost exactly in accord with the needs of the tissue and not in accord with the level of the pressure.

Hypertension in Preeclampsia (Toxemia of Pregnancy). A syndrome called *preeclampsia* (also called *toxemia of pregnancy*) develops in approximately 5 to 10 percent of expectant mothers. One of the manifestations of preeclampsia is hypertension that usually subsides after delivery of the baby. Although the precise causes of preeclampsia are not completely understood, ischemia of the placenta and subsequent release by the placenta of toxic factors are believed to play a role in causing many of the manifestations of this disorder, including hypertension in the mother. Substances released by the ischemic placenta, in turn, cause dysfunction of vascular endothelial cells throughout the body, including the blood vessels of the kidneys. This *endothelial dysfunction decreases release of nitric oxide* and other vasodilator substances, causing vasoconstriction, decreased rate of fluid filtration from the glomeruli into the renal tubules, impaired renal-pressure natriuresis, and the development of hypertension.

Another pathological abnormality that may contribute to hypertension in preeclampsia is thickening of the kidney glomerular membranes (perhaps caused by an autoimmune process), which also reduces the rate of glomerular fluid filtration. For obvious reasons, the arterial pressure level required to cause normal formation of urine becomes elevated, and the long-term level of arterial pressure becomes correspondingly elevated. These patients are especially prone to extra degrees of hypertension when they have excess salt intake.

Neurogenic Hypertension. *Acute neurogenic hypertension* can be caused by strong *stimulation of the sympathetic nervous system.* For instance, when a person becomes excited for any reason or at times during states of anxiety, the sympathetic system becomes excessively stimulated, peripheral vasoconstriction occurs everywhere in the body, and *acute* hypertension ensues.

Another type of *acute* neurogenic hypertension occurs when the nerves leading from the baroreceptors are cut or when the tractus solitarius is destroyed in each side of the medulla oblongata (these are the areas where the nerves from the carotid and aortic baroreceptors connect in the brain stem). The sudden cessation of normal nerve signals from the baroreceptors has the same effect on the nervous pressure control mechanisms as a sudden reduction of the arterial pressure in the aorta and carotid arteries. That is, loss of the normal inhibitory effect on the vasomotor center caused by normal baroreceptor nervous signals allows the vasomotor center suddenly to become extremely active and the mean arterial pressure to increase from 100 mm Hg to as high as 160 mm Hg. The pressure returns to nearly normal within about 2 days because the response of the vasomotor center to the absent baroreceptor signal fades away, which is called central "resetting" of the baroreceptor pressure control mechanism. Therefore, the neurogenic hypertension caused by sectioning the baroreceptor nerves is mainly an acute type of hypertension, not a chronic type.

The sympathetic nervous system also plays an important role in some forms of chronic hypertension, in large part by activation of the renal sympathetic nerves. For example, excess weight gain and obesity often lead to activation of the sympathetic nervous system, which in turn stimulates the renal sympathetic nerves, impairs renal-pressure natriuresis, and causes chronic hypertension. These abnormalities appear to play a major role in a large percentage of patients with *primary (essential) hypertension*, as discussed later.

Genetic Causes of Hypertension. Spontaneous hereditary hypertension has been observed in several strains of animals, including different strains of rats, rabbits, and at least one strain of dogs. In the strain of rats that has been studied to the greatest extent, the Okamoto spontaneously hypertensive rat strain, there is evidence that in early development of the hypertension, the sympathetic nervous system is considerably more active than in normal rats. In the later stages of this type of hypertension, structural changes have been observed in the nephrons of the kidneys: (1) increased preglomerular renal arterial resistance and (2) decreased permeability of the glomerular membranes. These structural changes could also contribute to the long-term continuance of the hypertension. In other strains of hypertensive rats, impaired renal function also has been observed.

In humans, several different gene mutations have been identified that can cause hypertension. These forms of hypertension are called *monogenic hypertension* because they are caused by mutation of a single gene. An interesting feature of these genetic disorders is that they all cause excessive salt and water reabsorption by the renal tubules.

In some cases the increased reabsorption is due to gene mutations that directly increase transport of sodium or chloride in the renal tubular epithelial cells. In other instances, the gene mutations cause increased synthesis or activity of hormones that stimulate renal tubular salt and water reabsorption. Thus, in all monogenic hypertensive disorders discovered thus far, the final common pathway to hypertension appears to be increased salt reabsorption and expansion of extracellular fluid volume. Monogenic hypertension, however, is rare, and all of the known forms together account for less than 1% of human hypertension.

PRIMARY (ESSENTIAL) HYPERTENSION

About 90 to 95 percent of all people who have hypertension are said to have "primary hypertension," also widely known as "essential hypertension" by many clinicians. These terms mean simply that *the hypertension is of unknown origin,* in contrast to the forms of hypertension that are *secondary* to known causes, such as renal artery stenosis or monogenic forms of hypertension.

In most patients, *excess weight gain* and *a sedentary lifestyle* appear to play a major role in causing hypertension. The majority of patients with hypertension are overweight, and studies of different populations suggest that excess weight gain and obesity may account for as much as 65 to 75 percent of the risk for developing primary hypertension. Clinical studies have clearly shown the value of weight loss for reducing blood pressure in most patients with hypertension. In fact, clinical guidelines for treating hypertension recommend increased physical activity and weight loss as a first step in treating most patients with hypertension.

The following characteristics of primary hypertension, among others, are caused by excess weight gain and obesity:

1. *Cardiac output is increased* in part because of the additional blood flow required for the extra adipose tissue. However, blood flow in the heart, kidneys, gastrointestinal tract, and skeletal muscle also increases with weight gain because of increased metabolic rate and growth of the organs and tissues in response to their increased metabolic demands. As the hypertension is sustained for many months and years, total peripheral vascular resistance may be increased.
2. *Sympathetic nerve activity, especially in the kidneys, is increased in overweight patients.* The causes of increased sympathetic activity in obese persons are not fully understood, but recent studies suggest that hormones such as *leptin* that are released from fat cells may directly stimulate multiple regions of the hypothalamus, which in turn have an excitatory influence on the vasomotor centers of the brain medulla. There is also evidence for reduced sensitivity of the arterial baroreceptors in buffering increases in blood pressure in obese subjects.
3. *Angiotensin II and aldosterone levels are increased twofold to threefold in many obese patients.* This increase may be caused partly by increased sympathetic nerve stimulation, which increases renin release by the kidneys and therefore formation of angiotensin II, which in turn stimulates the adrenal gland to secrete aldosterone.
4. *The renal-pressure natriuresis mechanism is impaired, and the kidneys will not excrete adequate amounts of salt and water unless the arterial pressure is high or kidney function is somehow improved.* If mean arterial pressure in the essential hypertensive person is 150 mm Hg, acute reduction of mean arterial pressure to the normal value of 100 mm Hg (but without otherwise altering renal function except for the decreased pressure) will cause almost total anuria; the person will then retain salt and water until the pressure rises back to the elevated value of 150 mm Hg. Chronic reductions in arterial pressure with effective antihypertensive therapies, however, usually do not cause marked salt and water retention by the kidneys because these therapies also improve renal-pressure natriuresis, as discussed later.

Experimental studies in obese animals and obese patients suggest that impaired renal-pressure natriuresis in obesity hypertension is caused mainly by increased renal tubular reabsorption of salt and water due to increased sympathetic nerve activity and increased levels of angiotensin II and aldosterone. However, if hypertension is not effectively treated, there may also be vascular damage in the kidneys that can reduce the glomerular filtration rate and increase the severity of the hypertension. Eventually uncontrolled hypertension associated with obesity can lead to severe vascular injury and complete loss of kidney function.

Graphical Analysis of Arterial Pressure Control in Essential Hypertension. **Figure 19-16** is a graphical analysis of essential hypertension. The curves of this figure are called *sodium-loading renal function curves* because the arterial pressure in each instance is increased very slowly, over many days or weeks, by gradually increasing the level of sodium intake. The sodium-loading type of curve can be determined by increasing the level of sodium intake to a new level every few days, then waiting for the renal output of sodium to come into balance with the intake, and at the same time recording the changes in arterial pressure.

When this procedure is used in patients with essential hypertension, two types of curves, shown to the right in **Figure 19-16**, can be recorded; one is called (1) *salt-insensitive* hypertension and the other (2) *salt-sensitive* hypertension. Note in both instances that the curves are

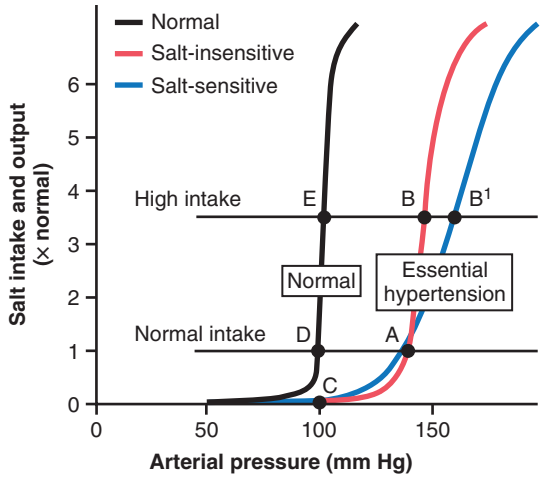

Figure 19-16. Analysis of arterial pressure regulation in (1) salt-insensitive essential hypertension and (2) salt-sensitive essential hypertension. *(Modified from Guyton AC, Coleman TG, Young DB, et al: Salt balance and long-term blood pressure control. Annu Rev Med 31:15, 1980. With permission, from the Annual Review of Medicine, copyright 1980, by Annual Reviews http://www.AnnualReviews.org.)*

shifted to the right, to a higher pressure level than for normal people. In the case of the person with salt-insensitive essential hypertension, the arterial pressure does not increase significantly when changing from normal salt intake to high salt intake. However, in patients who have salt-sensitive essential hypertension, the high salt intake significantly exacerbates the hypertension.

Two additional points should be emphasized. First, salt sensitivity of blood pressure is not an all-or-none characteristic—it is a quantitative characteristic, with some individuals being more salt sensitive than others. Second, salt sensitivity of blood pressure is not a fixed characteristic; instead, blood pressure usually becomes more salt sensitive as a person ages, especially after 50 or 60 years of age.

The reason for the difference between salt-insensitive essential hypertension and salt-sensitive hypertension is presumably related to structural or functional differences in the kidneys of these two types of hypertensive patients. For example, salt-sensitive hypertension may occur with different types of chronic renal disease because of the gradual loss of the functional units of the kidneys (the *nephrons*) or because of normal aging, as discussed in Chapter 32. Abnormal function of the renin-angiotensin system can also cause blood pressure to become salt sensitive, as discussed previously in this chapter.

Treatment of Essential Hypertension. Current guidelines for treating hypertension recommend, as a first step, lifestyle modifications that are aimed at increasing physical activity and weight loss in most patients. Unfortunately, many patients are unable to lose weight, and pharmacological treatment with antihypertensive drugs must be initiated.

Two general classes of drugs are used to treat hypertension: (1) *vasodilator drugs* that increase renal blood flow and glomerular filtration rate, and (2) *natriuretic or diuretic drugs* that decrease tubular reabsorption of salt and water.

Vasodilator drugs usually cause vasodilation in many other tissues of the body, as well as in the kidneys. Different ones act in one of the following ways: (1) by inhibiting sympathetic nervous signals to the kidneys or by blocking the action of the sympathetic transmitter substance on the renal vasculature and renal tubules, (2) by directly relaxing the smooth muscle of the renal vasculature, or (3) by blocking the action of the renin-angiotensin-aldosterone system on the renal vasculature or renal tubules.

Drugs that reduce reabsorption of salt and water by the renal tubules include, in particular, drugs that block active transport of sodium through the tubular wall; this blockage in turn also prevents the reabsorption of water, as explained earlier in the chapter. These natriuretic or diuretic drugs are discussed in greater detail in Chapter 32.

SUMMARY OF THE INTEGRATED, MULTIFACETED SYSTEM FOR ARTERIAL PRESSURE REGULATION

By now, it is clear that arterial pressure is regulated not by a single pressure controlling system but instead by several interrelated systems, each of which performs a specific function. For instance, when a person bleeds severely so that the pressure falls suddenly, two problems confront the pressure control system. The first is survival; the arterial pressure must be rapidly returned to a high enough level that the person can live through the acute episode. The second is to return the blood volume and arterial pressure eventually to their normal levels so that the circulatory system can reestablish full normality, not merely back to the levels required for survival.

In Chapter 18, we saw that the first line of defense against acute changes in arterial pressure is the nervous control system. In this chapter, we have emphasized a second line of defense achieved mainly by kidney mechanisms for long-term control of arterial pressure. However, there are other pieces to the puzzle. **Figure 19-17** helps put these pieces together.

Figure 19-17 shows the approximate immediate (seconds and minutes) and long-term (hours and days) control responses, expressed as feedback gain, of eight arterial pressure control mechanisms. These mechanisms can be divided into three groups: (1) those that react rapidly, within seconds or minutes; (2) those that respond over an intermediate time period, that is, minutes or hours; and (3) those that provide long-term arterial pressure regulation for days, months, and years.

Rapidly Acting Pressure Control Mechanisms That Act Within Seconds or Minutes. The rapidly acting

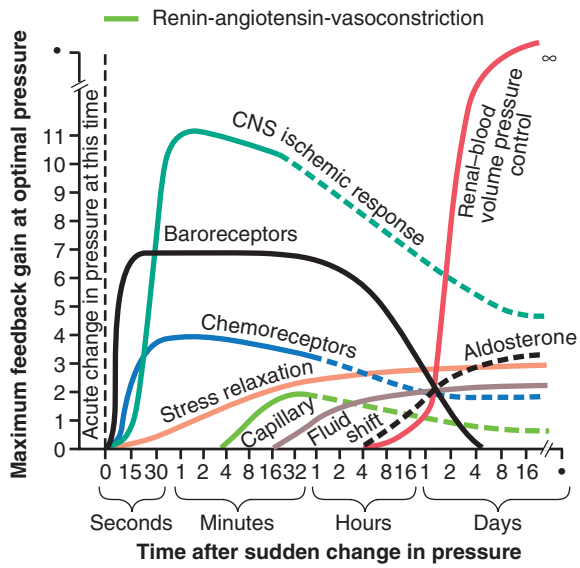

Figure 19-17. Approximate potency of various arterial pressure control mechanisms at different time intervals after the onset of a disturbance to the arterial pressure. Note especially the infinite gain (∞) of the renal body fluid pressure control mechanism that occurs after a few weeks' time. CNS, central nervous system. *(Modified from Guyton AC: Arterial Pressure and Hypertension. Philadelphia: WB Saunders, 1980.)*

pressure control mechanisms are almost entirely acute nervous reflexes or other nervous responses. Note in **Figure 19-17** the three mechanisms that show responses within seconds. They are (1) the baroreceptor feedback mechanism, (2) the central nervous system ischemic mechanism, and (3) the chemoreceptor mechanism. Not only do these mechanisms begin to react within seconds, but they are also powerful. After any acute fall in pressure, as might be caused by severe hemorrhage, the nervous mechanisms combine to cause (1) constriction of the veins and transfer of blood into the heart, (2) increased heart rate and contractility of the heart to provide greater pumping capacity by the heart, and (3) constriction of most peripheral arterioles to impede flow of blood out of the arteries. All these effects occur almost instantly to raise the arterial pressure back into a survival range.

When the pressure suddenly rises too high, as might occur in response to rapid transfusion of excess blood, the same control mechanisms operate in the reverse direction, again returning the pressure back toward normal.

Pressure Control Mechanisms That Act After Many Minutes. Several pressure control mechanisms exhibit significant responses only after a few minutes following acute arterial pressure change. Three of these mechanisms, shown in **Figure 19-17**, are (1) the renin-angiotensin vasoconstrictor mechanism, (2) stress-relaxation of the vasculature, and (3) shift of fluid through the tissue capillary walls in and out of the circulation to readjust the blood volume as needed.

We have already described at length the role of the renin-angiotensin vasoconstrictor system to provide a semi-acute means for increasing the arterial pressure when this is necessary. The *stress-relaxation mechanism* is demonstrated by the following example: When the pressure in the blood vessels becomes too high, they become stretched and keep on stretching more and more for minutes or hours; as a result, the pressure in the vessels falls toward normal. This continuing stretch of the vessels, called *stress-relaxation,* can serve as an intermediate-term pressure "buffer."

The *capillary fluid shift mechanism* means simply that any time capillary pressure falls too low, fluid is absorbed from the tissues through the capillary membranes and into the circulation, thus building up the blood volume and increasing the pressure in the circulation. Conversely, when the capillary pressure rises too high, fluid is lost out of the circulation into the tissues, thus reducing the blood volume, as well as virtually all the pressures throughout the circulation.

These three intermediate mechanisms become mostly activated within 30 minutes to several hours. During this time, the nervous mechanisms usually become less and less effective, which explains the importance of these non-nervous, intermediate time pressure control measures.

Long-Term Mechanisms for Arterial Pressure Regulation. The goal of this chapter has been to explain the role of the kidneys in long-term control of arterial pressure. To the far right in **Figure 19-17** is shown the renal–blood volume pressure control mechanism (which is the same as the renal–body fluid pressure control mechanism), demonstrating that it takes a few hours to begin showing significant response. Yet, it eventually develops a feedback gain for control of arterial pressure nearly equal to infinity. This means that this mechanism can eventually return the arterial pressure nearly *all the way* back, not merely partway back, to the pressure level that provides normal output of salt and water by the kidneys. By now, the reader should be familiar with this concept, which has been the major point of this chapter.

Many factors can affect the pressure-regulating level of the renal–body fluid mechanism. One of these, shown in **Figure 19-17**, is aldosterone. A decrease in arterial pressure leads within minutes to an increase in aldosterone secretion, and over the next hour or days, this effect plays an important role in modifying the pressure control characteristics of the renal–body fluid mechanism.

Especially important is interaction of the renin-angiotensin system with the aldosterone and renal fluid mechanisms. For instance, a person's salt intake varies tremendously from one day to another. We have seen in this chapter that salt intake can decrease to as little as one-tenth normal or can increase to 10 to 15 times normal and yet the regulated level of the mean arterial pressure will change only a few mm Hg if the renin-angiotensin-aldosterone system is fully operative. However, without a

functional renin-angiotensin-aldosterone system, blood pressure becomes very sensitive to changes in salt intake.

Thus, arterial pressure control begins with the life-saving measures of the nervous pressure controls, then continues with the sustaining characteristics of the intermediate pressure controls, and, finally, is stabilized at the long-term pressure level by the renal–body fluid mechanism. This long-term mechanism, in turn, has multiple interactions with the renin-angiotensin-aldosterone system, the nervous system, and several other factors that provide special blood pressure control capabilities for special purposes.

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