Despite extensive animal and clinical experimentation, the mechanisms responsible for the normal regulation of arterial pressure and development of essential or primary hypertension remain unclear. One basic concept was championed by Guyton and other authors [1–4]: the long-term regulation of arterial pressure is intimately linked to the ability of the kidneys to excrete sufficient sodium chloride to maintain normal sodium balance, extracellular fluid volume, and blood volume at normotensive arterial pressures. Therefore, it is not surprising that renal disease is the most common cause of secondary hypertension. Furthermore, derangements in renal function from subtle to overt are probably involved in the pathogenesis of most if not all cases of essential hypertension [5]. Evidence of generalized microvascular disease may be causative of both hypertension and progressive renal insufficiency [5,6]. The interactions are complex because the kidneys are a major target for the detrimental consequences of uncontrolled hypertension. When hypertension is left untreated, positive feedback interactions may occur that lead progressively to greater hypertension and additional renal injury. These interactions culminate in malignant hypertension, stroke, other sequelae, and death [7].

In normal persons, an increased intake of sodium chloride leads to appropriate adjustments in the activity of various humoral, neural, and paracrine mechanisms. These mechanisms alter systemic and renal hemodynamics and increase sodium excretion without increasing arterial pressure [3,8]. Regardless of the initiating factor, decreases in sodium excretory capability in the face of normal or increased sodium intake lead to chronic increases in extracellular fluid volume and blood volume. These increases can result in hypertension. When the derangements also include increased levels of humoral or neural factors that directly cause vascular smooth muscle constriction, these effects increase peripheral vascular resistance or decrease vascular capacitance. Under these conditions the effects of subtle increases in blood volume are compounded because of increases in the blood volume relative to...
the capacitance, often referred to as the effective blood volume. Through the mechanism of pressure natriuresis, however, the increases in arterial pressure increase renal sodium excretion, allowing restoration of sodium balance but at the expense of persistent elevations in arterial pressure [9]. In support of this overall concept, various studies have demonstrated strong relationships between kidney disease and the incidence of hypertension. In addition, transplantation studies have shown that normotensive recipients from genetically hypertensive donors have a higher likelihood of developing hypertension after transplantation [10].

This unifying concept has helped delineate the cardinal role of the kidneys in the normal regulation of arterial pressure as well as in the pathophysiology of hypertension. Any different extrinsic influences and intrarenal derangements can lead to reduced sodium excretory capability. Many factors also exist that alter cardiac output, total peripheral resistance, and cardiovascular capacitance. Accordingly, hypertension is a multifactorial dysfunctional process that can be caused by a myriad of different conditions. These conditions range from stimulatory influences that inappropriately enhance tubular sodium reabsorption to overt renal pathology, involving severe reductions in filtering capacity by the renal glomeruli and associated marked reductions in sodium excretory capability. An understanding of the normal mechanisms regulating sodium balance and how derangements lead to altered sodium homeostasis and hypertension provides the basis for a rational approach to the treatment of hypertension.

**FIGURE 1-1**
Aortic distensibility. The cyclical pumping nature of the heart places a heavy demand on the distensible characteristics of the aortic tree. A. During systole, the aortic tree is rapidly filled in a fraction of a second, distending it and increasing the hydraulic pressure. B. The distensibility characteristics of the arterial tree determine the pulse pressure (PP) in response to a specific stroke volume. The normal relationship is shown in curve A, and arrows designate the PP. A highly distensible arterial tree, as depicted in curve B, can accommodate the stroke volume with a smaller PP. Pathophysiologic processes and aging lead to decreases in aortic distensibility. These decreases lead to marked increases in PP and overall mean arterial pressure for any given arterial volume, as shown in curve C. Decreased distensibility is partly responsible for the isolated systolic hypertension often found in elderly persons. Recordings of actual aortic pressure and flow profiles in persons with normotension and systolic hypertension are shown in panel A [11,12]. (Panel B Adapted from Vari and Naver [4] and Panel A from Nichols et al. [12].)

**HEMODYNAMIC DETERMINANTS**

*For any vascular bed:*
\[
\text{Blood flow} = \frac{\text{Arterial pressure gradient}}{\text{Vascular resistance}}
\]

*For total circulation averaged over time:*
\[
\text{Blood flow} = \text{cardiac output}
\]

Therefore,
\[
\text{Cardiac output} = \frac{\text{Arterial pressure - right atrial pressure}}{\text{Total peripheral resistance}}
\]

and:
\[
\text{Mean arterial pressure} = \frac{\text{Cardiac output} \times \text{total peripheral resistance}}{1100}
\]

**FIGURE 1-2**
Hemodynamic determinants of arterial pressure. During the diastolic phase of the cardiac cycle, the elastic recoil characteristics of the arterial tree provide the kinetic energy that allows a continuous delivery of blood flow to the tissues. Blood flow is dependent on the arterial pressure gradient and total peripheral resistance. Under normal conditions the right atrial pressure is near zero, and thus the arterial pressure is the pressure gradient. These relationships apply for any instant in time and to time-integrated averages when the mean pressure is used. The time-integrated average blood flow is the cardiac output that is normally 5 to 6 L/min for an adult of average weight (70 to 75 kg).
The Kidney in Blood Pressure Regulation

FIGURE 1-3
Volume determinants of arterial pressure. The two major determinants of arterial pressure, cardiac output and total peripheral resistance, are regulated by a combination of short- and long-term mechanisms. Rapidly adjusting mechanisms regulate peripheral vascular resistance, cardiovascular capacitance, and cardiac performance. These mechanisms include the neural and humoral mechanisms listed. On a long-term basis, cardiac output is determined by venous return, which is regulated primarily by the mean circulatory pressure. The mean circulatory pressure depends on blood volume and overall cardiovascular capacitance. Blood volume is closely linked to extracellular fluid (ECF) volume and sodium balance, which are dependent on the integration of net intake and net losses [13]. (Adapted from Navar [3].)

FIGURE 1-4
A, Relationship between net sodium balance and extracellular fluid (ECF) volume. Sodium balance is intimately linked to volume balance because of powerful mechanisms that tightly regulate plasma and ECF osmolality. Sodium and its accompanying anions constitute the major contributors to ECF osmolality. The integration of sodium intake and losses establishes the net amount of sodium in the body, which is compartmentalized primarily in the ECF volume. The quotient of these two parameters (sodium and volume) determines the sodium concentration and, thus, the osmolality. Osmolality is subject to very tight regulation by vasopressin and other mechanisms. In particular, vasopressin is a very powerful regulator of plasma osmolality; however, it achieves this regulation primarily by regulating the relative solute-free water retention or excretion by the kidney [13–15]. The important point is that the osmolality is rapidly regulated by adjusting the ECF volume to the total solute present. Corrections of excesses in extracellular fluid volume involve more complex interactions that regulate the sodium excretion rate.

B, Relationship between the ECF volume and blood volume. Under normal conditions a consistent relationship exists between the total ECF volume and blood volume. This relationship is consistent as long as the plasma protein concentration and, thus, the colloid osmotic pressure are regulated appropriately and the microvasculature maintains its integrity in limiting protein leak into the interstitial compartment. The shaded area represents the normal operating range [13]. A chronic increase in the total quantity of sodium chloride in the body leads to a chronic increase in ECF volume, part of which is proportionately distributed to the blood volume compartment. When accumulation is excessive, disproportionate distribution to the interstitium may lead to edema. Chronic increases in blood volume increase mean circulatory pressure (see Fig. 1-3) and lead to an increase in arterial pressure. Therefore, the mechanisms regulating sodium balance are primarily responsible for the chronic regulation of arterial pressure. (Panel B adapted from Guyton and Hall [13].)