■ Renin, a major regulator of blood pressure, is secreted by the kidneys in response to decreased blood pressure in afferent arterioles. In turn, renin cleaves angiotensinogen to angiotensin I; subsequent peripheral catabolism produces angiotensin II, which regulates blood pressure by increasing vascular smooth muscle cell tone and by increasing adrenal aldosterone secretion and thereby renal sodium resorption.

Pathogenesis of Hypertension

Hypertension is a disorder with multiple genetic and environmental contributions. As already noted, **the vast majority (90% to 95%) of hypertension is idiopathic**. Even without knowing the specific lesions, it is reasonable to suppose that multiple small changes in renal sodium homeostasis and/or vessel wall tone or structure act in combination to cause essential hypertension (Fig. 11-5). Most other causes fall under the general rubric of renal disease, including renovascular hypertension (due to renal artery occlusion). Infrequently, hypertension has an underlying endocrine basis.

Pathogenesis of Secondary Hypertension. In many secondary forms of hypertension, the underlying pathways are reasonably well understood:

- In *renovascular hypertension*, renal artery stenosis causes decreased glomerular flow and pressure in the afferent arteriole of the glomerulus. This induces renin secretion, which, as already discussed, increases vascular tone and blood volume via the angiotensin-aldosterone pathway (Fig. 11-5).
- *Single-gene disorders* cause severe but rare forms of hypertension:
  - *Gene defects affecting enzymes involved in aldosterone metabolism (e.g., aldosterone synthase, 11β-hydroxylase, 17α-hydroxylase).* These lead to an increase in secretion of aldosterone, increased salt and water resorption, plasma volume expansion and, ultimately, hypertension. *Primary hyperaldosteronism* is one of the most common causes of secondary hypertension (Chapter 24).
  - *Mutations affecting proteins that influence sodium reabsorption.* For example, the moderately severe form of salt-sensitive hypertension, called *Liddle syndrome*, is caused by gain-of-function mutations in an epithelial Na^+ channel protein that increase distal tubular reabsorption of sodium in response to aldosterone.

Mechanisms of Essential Hypertension

- *Genetic factors* influence blood pressure regulation, as shown by comparisons of monozygotic and dizygotic twins, and genetically related versus adopted children. Moreover, as noted earlier, several single-gene disorders cause relatively rare forms of hypertension (and hypotension) by altering net sodium reabsorption in the kidney. It is also suspected (but not yet proven) that variations in blood pressure may result from the cumulative effects of polymorphisms in several genes that affect blood pressure; for example, sequence variants in both the angiotensinogen and the angiotensin receptor genes have been associated with hypertension in some studies.
- *Reduced renal sodium excretion* in the presence of normal arterial pressure may be a key initiating event in essential hypertension and, indeed, a final common pathway for the pathogenesis of hypertension. Decreased sodium excretion may lead sequentially to an increase in fluid volume, increased cardiac output, and peripheral vasoconstriction, thereby elevating blood pressure. At the higher blood pressure, enough additional sodium is excreted by the kidneys to equal intake and prevent further fluid retention. Thus, a new steady state of sodium balance is achieved ("resetting of pressure natriuresis"), but at the expense of an increase in blood pressure.
- *Vasoconstrictive influences*, such as factors that induce vasoconstriction or stimuli that cause structural changes in the vessel wall, can lead to an increase in peripheral resistance and may also play a role in essential hypertension.
- *Environmental factors*, such as stress, obesity, smoking, physical inactivity, and heavy salt consumption are all implicated in hypertension. Indeed, the evidence linking dietary sodium intake with the prevalence of hypertension in different populations is particularly impressive.

Vascular Pathology in Hypertension

Hypertension not only accelerates atherogenesis (see later) but also causes degenerative changes in the walls of large and medium arteries that can lead to both aortic dissection and cerebrovascular hemorrhage. Hypertension is also associated with two forms of small blood vessel disease: hyaline arteriolosclerosis and hyperplastic arteriolosclerosis (Fig. 11-6).

MORPHOLOGY

Hyaline arteriolosclerosis. Arterioles show homogeneous, pink hyaline thickening with associated luminal narrowing (Fig. 11-6*A*). These changes reflect both plasma protein leakage across injured endothelial cells, as well as increased smooth muscle cell matrix synthesis in response to the chronic hemodynamic stresses of hypertension. Although the vessels of older patients (either normotensive or hypertensive) also frequently exhibit hyaline arteriosclerosis, it is more generalized and severe in patients with hypertension. The same lesions are also a common feature of diabetic microangiography; in that case, the underlying etiology is hyperglycemia-induced endothelial cell dysfunction (Chapter 24). In **nephrosclerosis** due to chronic hypertension, the arteriolar narrowing of hyaline arteriosclerosis causes diffuse impairment of renal blood supply and glomerular scarring (Chapter 20).

Hyperplastic Arteriolosclerosis. This lesion occurs in severe hypertension; vessels exhibit concentric, **laminated ("onion-skin")** thickening of the walls with luminal narrowing (Fig. 11-6*B*). The laminations consist of smooth muscle cells with thickened, reduplicated basement membrane; in malignant hypertension, they are accompanied by fibrinoid deposits and vessel wall necrosis **(necrotizing arteriolitis)**, particularly in the kidney (Chapter 20).