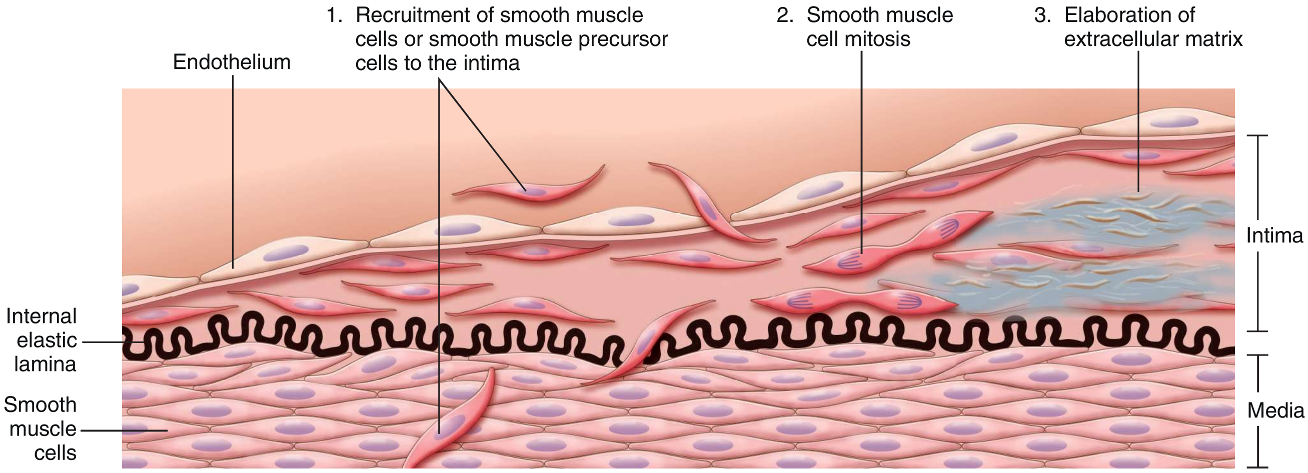

Figure 11.3 Stereotypical response to vascular injury. Schematic diagram of intimal thickening, emphasizing intimal smooth muscle cell migration and proliferation associated with extracellular matrix synthesis. Intimal smooth muscle cells can derive from the underlying media or can be recruited from circulating precursors; the intimal cells are shown in a darker shade to emphasize that they have a proliferative, synthetic, and noncontractile phenotype distinct from medial smooth muscle cells.

circulating precursors. Medial SMCs or circulating smooth muscle precursor cells also migrate into the intima, proliferate, and synthesize ECM in much the same way that fibroblasts fill in a wound (Fig. 11.3). The resulting neointima is typically completely covered by ECs. This neointimal response occurs with any form of vascular damage or dysfunction, regardless of cause. Thus intimal thickening is the stereotypical response of the vessel wall to any insult.

Neointimal SMCs have a phenotype that is distinct from that of medial SMCs. Specifically, neointimal SMCs are more proliferative, with increased biosynthetic capabilities and reduced contractile function. This neointimal SMC behavior is regulated by cytokines and growth factors derived from platelets, ECs, and macrophages, as well as thrombin and activated complement factors. With time and restoration and/or normalization of the EC layer, the neointimal SMCs can return to a nonproliferative state.

KEY CONCEPTS

RESPONSE OF VASCULAR WALL CELLS TO INJURY

- All vessels are lined by endothelium; although all ECs share certain homeostatic properties, ECs in specific vascular beds have special features that allow for tissue-specific functions (e.g., fenestrated ECs in renal glomeruli).
- EC function is tightly regulated in both the basal and activated states. Various physiologic and pathophysiologic stimuli induce endothelial activation and dysfunction that alter the EC phenotype (e.g., procoagulative vs. anticoagulative, proinflammatory vs. antiinflammatory, and nonadhesive vs. adhesive).
- Injury (of almost any type) to the vessel wall results in a stereotyped healing response involving SMC proliferation, ECM deposition, and intimal expansion.
- The recruitment and activation of the SMCs involves signals from cells (e.g., ECs, platelets, and macrophages) as well as mediators derived from coagulation and complement cascades.
- Excessive thickening of the intima can result in luminal stenosis and vascular obstruction.

HYPERTENSIVE VASCULAR DISEASE

Systemic and local tissue blood pressures must be maintained within a narrow range to prevent untoward consequences. Low pressures (hypotension) result in inadequate organ perfusion and can lead to dysfunction or tissue death. Conversely, high pressure (hypertension) can cause end-organ damage and is one of the major risk factors for atherosclerosis (see later).

Like height and weight, blood pressure is a continuously distributed variable. Detrimental effects of blood pressure increase continuously as the pressure rises—no rigidly defined threshold level of blood pressure identifies those who have an increased risk for cardiovascular disease. Both the systolic and the diastolic blood pressure are important in determining risk; specifically, according to the newest guidelines, individuals with diastolic pressures above 80 mm Hg or systolic pressures above 120 mm Hg are considered to have clinically significant hypertension. Approximately 46% of individuals in the general population are therefore hypertensive based on these newer criteria. However, such cutoffs do not reliably assess risk in all patients; for example, when other risk factors such as diabetes are present, lower thresholds are applicable.

Table 11.2 lists the major causes of hypertension. Although the molecular pathways that regulate normal blood pressure are reasonably well understood, the causes of hypertension in most individuals remain largely unknown. A small number of patients (approximately 10%) are said to have *secondary hypertension* resulting from an underlying renal or adrenal disease (e.g., primary aldosteronism, Cushing syndrome, or pheochromocytoma), renal artery stenosis, or other identifiable cause. However, approximately 90% of hypertension is idiopathic—so-called essential hypertension. It seems likely that hypertension is a multifactorial disorder resulting from the cumulative effects of multiple genetic polymorphisms and interacting environmental factors.

The prevalence and vulnerability to complications of hypertension increase with age and are higher among African

Table 11.2 Types and Causes of Hypertension (Systolic and Diastolic)

Essential Hypertension
Accounts for 90%–95% of all cases
Secondary Hypertension
Renal
Acute glomerulonephritis
Chronic renal disease
Polycystic disease
Renal artery stenosis
Renal vasculitis
Renin-producing tumors
Endocrine
Adrenocortical hyperfunction (Cushing syndrome, primary aldosteronism, congenital adrenal hyperplasia, licorice ingestion)
Exogenous hormones (glucocorticoids, estrogen [including pregnancy-induced and oral contraceptives], sympathomimetics and tyramine-containing foods, monoamine oxidase inhibitors)
Pheochromocytoma
Acromegaly
Hyperthyroidism (thyrotoxicosis)
Pregnancy-induced (preeclampsia)
Cardiovascular
Coarctation of the aorta
Polyarteritis nodosa
Increased intravascular volume
Increased cardiac output
Rigidity of the aorta
Neurologic
Psychogenic
Increased intracranial pressure
Sleep apnea
Acute stress, including surgery

Americans. Besides increasing risk of atherosclerosis, hypertension can cause cardiac hypertrophy and heart failure *(hypertensive heart disease)* (Chapter 12), multi-infarct dementia (Chapter 28), aortic dissection (discussed later in this chapter), and renal failure (Chapter 20). Unfortunately, hypertension typically remains asymptomatic until late in its course, and even severely elevated pressures can be clinically silent for years. Left untreated, roughly half of hypertensive patients die of ischemic heart disease or congestive heart failure, and another third die of stroke. Treatment with blood pressure–lowering drugs dramatically reduces the incidence and death rates attributable to all forms of hypertension-related pathology.

A small percentage of hypertensive persons (as much as 5%) show a rapidly rising blood pressure that, if untreated, leads to death within 1 to 2 years. This form of hypertension, called *malignant hypertension,* is characterized by severe pressure elevations (i.e., systolic pressure more than 200 mm Hg, diastolic pressure more than 120 mm Hg), renal failure, and retinal hemorrhages and exudates, with or without papilledema (swelling of the optic nerve that reflects increased intracranial pressures). It can develop in previously normotensive persons but more often is superimposed on preexisting "benign" hypertension.

In this section, we will first briefly outline normal blood pressure homeostasis, followed by a discussion of pathogenic mechanisms that underlie hypertension and a description of hypertension-associated pathologic changes in vessels.

Blood Pressure Regulation

Blood pressure is a function of cardiac output and peripheral vascular resistance, both of which are influenced by multiple genetic and environmental factors (Fig. 11.4). The integration of the various inputs ensures adequate systemic perfusion, despite regional demand differences.

- *Cardiac output* is a function of stroke volume and heart rate. The most important determinant of stroke volume is the filling pressure, which is regulated through sodium homeostasis and its effect on blood volume. Heart rate and myocardial contractility (a second factor affecting stroke volume) are both regulated by the α- and β-adrenergic systems, which also have important effects on vascular tone.
- *Peripheral resistance* is regulated predominantly at the level of the arterioles by neural and hormonal inputs.

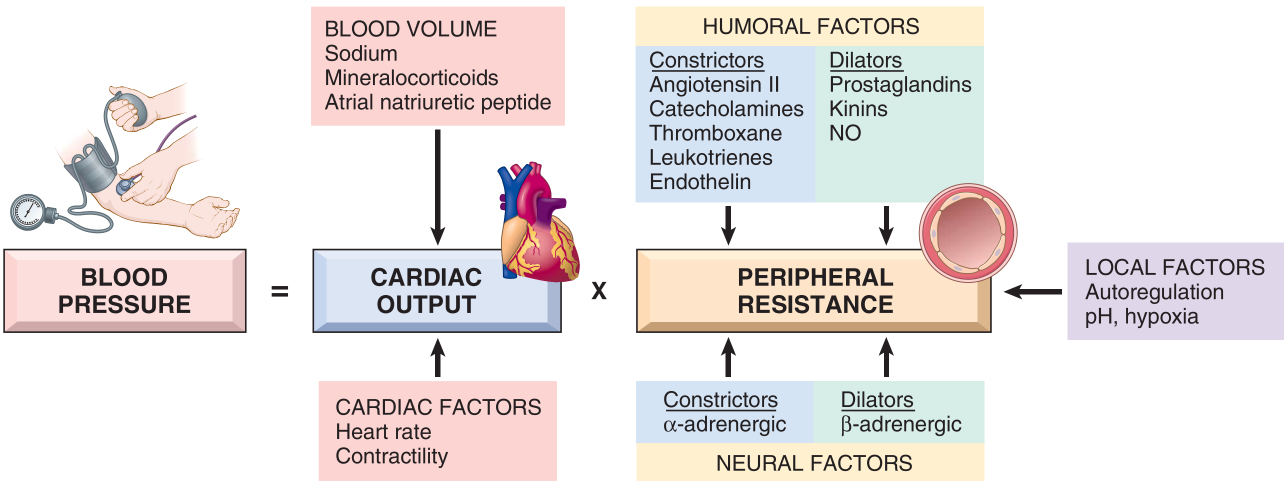

Figure 11.4 Blood pressure regulation. Diverse influences on cardiac output (e.g., blood volume and myocardial contractility) and peripheral resistance (neural, humoral, and local effectors) impact the output blood pressure.

Vascular tone reflects a balance between vasoconstrictors (including angiotensin II, catecholamines, and endothelin) and vasodilators (including kinins, prostaglandins, and NO). Resistance vessels also exhibit autoregulation, whereby increased blood flow induces vasoconstriction to protect tissues against hyperperfusion. Finally, blood pressure is fine-tuned by tissue pH and hypoxia to accommodate local metabolic demands.

Factors released from the kidneys, adrenals, and myocardium interact to influence vascular tone and to regulate blood volume by adjusting sodium balance (Fig. 11.5). The kidneys filter 170 liters of plasma containing 23 moles of salt daily. Thus with a typical diet containing 100 mEq of sodium, 99.5% of the filtered salt must be reabsorbed to maintain total body sodium levels. About 98% of the filtered sodium is reabsorbed by several constitutively active transporters. The small amount of remaining sodium is subject to resorption by the epithelial sodium channel (EnaC), which is tightly regulated by the renin-angiotensin-aldosterone system; it is this pathway that determines net sodium balance.

The kidneys and heart contain cells that sense changes in blood pressure or volume. In response, these cells release circulating effectors that act in concert to maintain normal blood pressure. Kidneys influence peripheral resistance and sodium excretion/retention primarily through the renin-angiotensin-aldosterone system.

- *Renin* is a proteolytic enzyme produced by renal juxtaglomerular cells, which are myoepithelial cells adjacent to the glomerular afferent arterioles. Renin is released in response to low blood pressure in afferent arterioles, elevated levels of circulating catecholamines, or low sodium levels in the distal convoluted renal tubules. The latter occurs when the glomerular filtration rate falls (e.g., when the cardiac output is low), leading to increased sodium resorption by the proximal tubules.
- *Renin cleaves plasma angiotensinogen to angiotensin I, which in turn is converted to angiotensin II by angiotensin-converting enzyme (ACE),* mainly a product of vascular endothelium. Angiotensin II raises blood pressure by (1) inducing vascular contraction, (2) stimulating aldosterone secretion by the adrenal gland, and (3) increasing tubular sodium resorption. Adrenal aldosterone increases blood pressure by its effect on blood volume; aldosterone increases sodium resorption (and thus water) in the distal convoluted tubules, which increases blood volume.
- *The kidney also produces a variety of vascular relaxing substances* (including prostaglandins and NO) that can counterbalance the vasopressor effects of angiotensin.

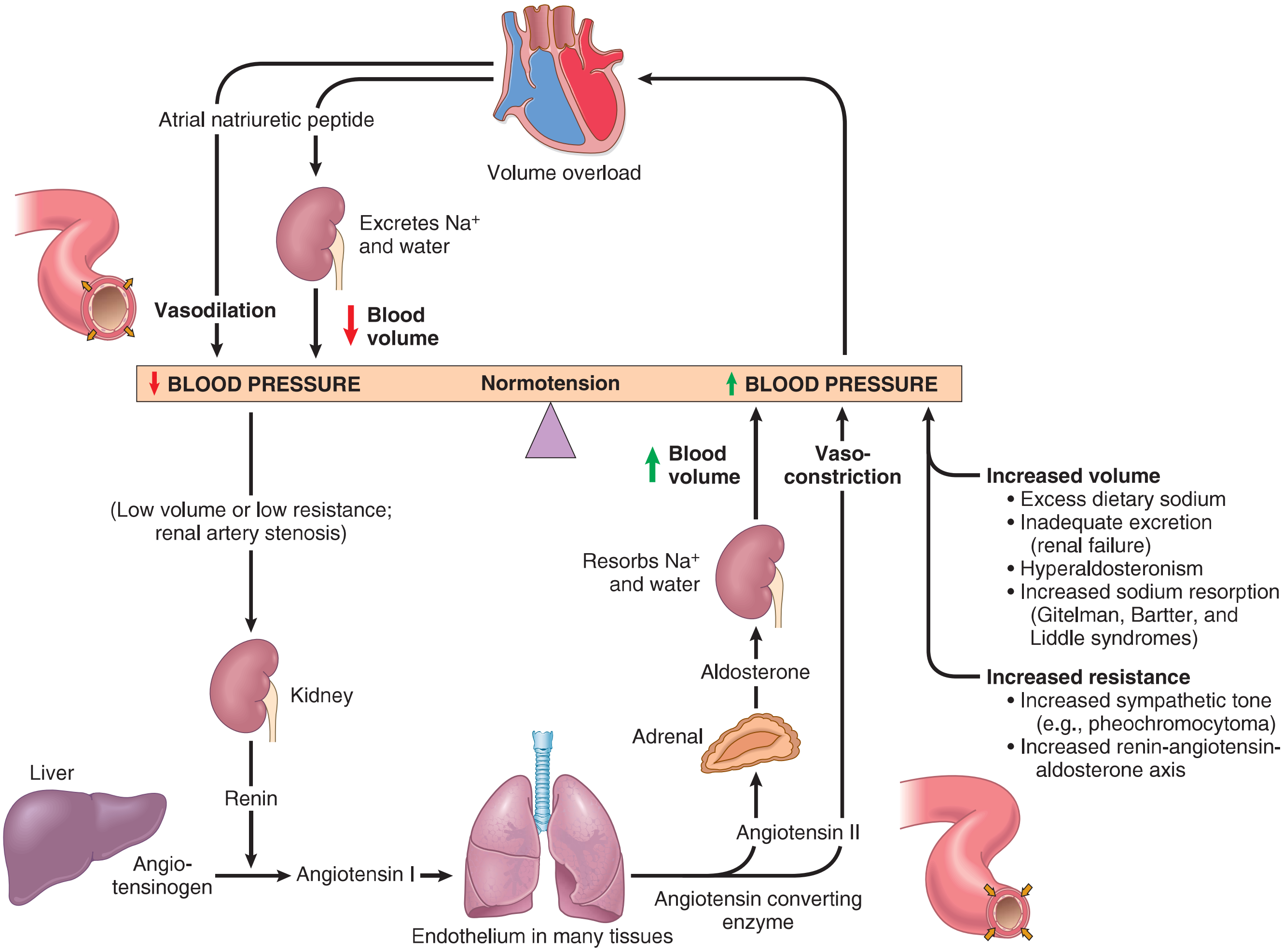

Figure 11.5 Interplay of renin-angiotensin-aldosterone and atrial natriuretic peptide in maintaining blood pressure homeostasis.

Myocardial natriuretic peptides are released from atrial (dominant contributor) and ventricular (minor contributor) myocardium in response to volume expansion; these inhibit sodium resorption in the distal renal tubules, thus leading to sodium excretion and diuresis. They also induce systemic vasodilation.

KEY CONCEPTS

BLOOD PRESSURE REGULATION

- Blood pressure is determined by vascular resistance and cardiac output.
- Vascular resistance is regulated at the level of the arterioles, influenced by neural and hormonal inputs.
- Cardiac output is determined by heart rate and stroke volume, which is strongly influenced by blood volume. Blood volume in turn is regulated mainly by renal sodium excretion or resorption.
- 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 endothelial catabolism produces angiotensin II, which regulates blood pressure by increasing vascular SMC tone and by increasing adrenal aldosterone secretion, thereby increasing renal sodium resorption.

Pathogenesis of Hypertension

The vast majority (90% to 95%) of hypertension is idiopathic, the result of interacting genetic and environmental factors. Even without knowing the specific lesions, it is reasonable to suppose that small changes in renal sodium homeostasis and/or vessel wall tone or structure act in combination to cause essential hypertension (see 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.

Mechanisms of Secondary Hypertension. For many of the 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. As already discussed, this induces renin secretion leading to increased blood volume and vascular tone via angiotensin and aldosterone pathways (see Fig. 11.5).
- *Primary hyperaldosteronism* is one of the most common causes of secondary hypertension (Chapter 24). It may be idiopathic or less commonly caused by aldosterone-secreting adrenal adenomas.
- *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)* can lead to increased aldosterone secretion with downstream increases in salt and water resorption, plasma volume expansion, and, ultimately, hypertension.
  - *Mutations affecting proteins that influence sodium reabsorption.* For example, the moderately severe form of salt-sensitive hypertension, called Liddle syndrome, is caused by mutations in an epithelial Na^+ channel protein that increase distal tubular reabsorption of sodium in response to aldosterone.

Mechanisms of Essential Hypertension. As mentioned earlier, in the vast majority of cases hypertension results from complex interactions between multiple genetic and environmental influences.

- *Genetic factors* definitely contribute to 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. Large genome-wide association studies point to more than 60 genetic loci in which variants individually contribute minimally to blood pressure levels but in sum have larger effects.
- *Insufficient 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. Insufficient 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 all are 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. Three forms of small vessel disease are hypertension-related (Fig. 11.6).

MORPHOLOGY

Hyaline arteriolosclerosis. Arterioles show homogeneous, pink hyaline thickening with associated luminal narrowing (Fig. 11.6A). These changes reflect both plasma protein leakage across injured ECs and increased SMC matrix synthesis in response to the chronic hemodynamic pressures 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 and diabetes (Chapter 24). In **nephrosclerosis** due to chronic hypertension, the arteriolar

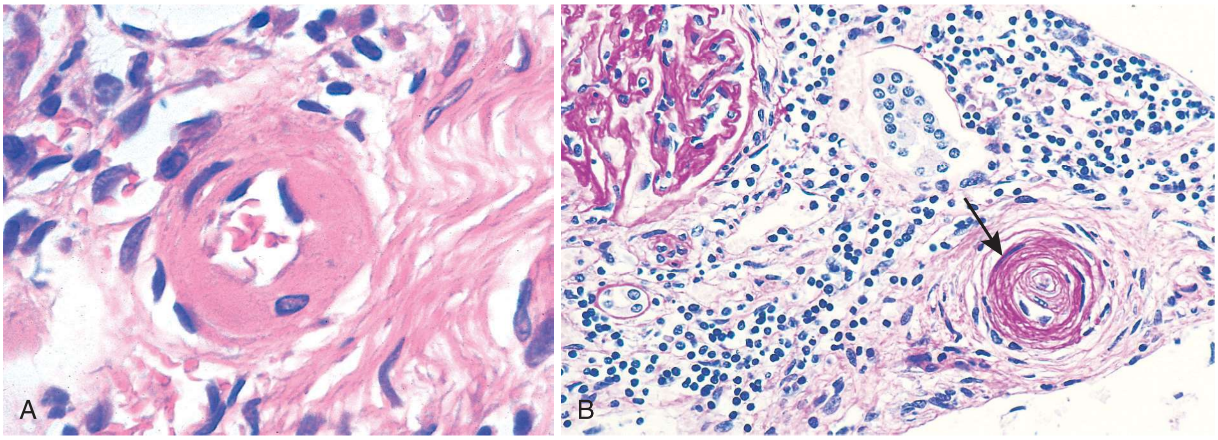

Figure 11.6 Vascular pathology in hypertension. (A) Hyaline arteriolosclerosis. The arteriolar wall is thickened with increased protein deposition (hyalinized), and the lumen is markedly narrowed. (B) Hyperplastic arteriolosclerosis (onion-skinning) causing luminal obliteration *(arrow)* (periodic acid-Schiff stain). (B, Courtesy Helmut Rennke, MD, Brigham and Women's Hospital, Boston, Mass.)

narrowing 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. 11.6B). The laminations consist of SMCs 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).

Pulmonary hypertension can be caused by several entities including left heart failure, congenital heart disease, valve disorders, obstructive or interstitial lung disease, and recurrent thromboemboli. The arterioles in such affected lungs typically show histologic changes ranging from fibrotic intimal thickening to medial hyperplasia. These are described in greater detail in Chapter 15.

KEY CONCEPTS

HYPERTENSION

- Hypertension is a common disorder affecting roughly half of adults in the United States; it is a major risk factor for atherosclerosis, congestive heart failure, and renal failure.
- Essential hypertension represents 90% to 95% of cases and is a complex, multifactorial disorder involving both environmental influences and genetic polymorphisms that influence sodium resorption, aldosterone pathways, and the renin-angiotensin-aldosterone system.
- Hypertension is occasionally caused by single-gene disorders or is secondary to diseases of the kidney, adrenal, or other endocrine organs.
- Sustained hypertension requires participation of the kidney, which normally responds to hypertension by eliminating salt and water. In established hypertension, both increased blood volume and increased peripheral resistance contribute to the increased pressure.
- Histologically, hypertension is associated with thickening of arterial walls caused by hyaline deposits and, in severe cases, by proliferation of ECs or SMCs and replication of the basement membrane.

ARTERIOSCLEROSIS

Arteriosclerosis literally means "hardening of the arteries"; it is a generic term for arterial wall thickening and loss of elasticity. There are four general patterns, with different clinical and pathologic consequences.

- *Arteriolosclerosis* affects small arteries and arterioles and may cause downstream ischemic injury. The two anatomic variants, hyaline and hyperplastic, were discussed earlier in relation to hypertension.
- *Mönckeberg medial sclerosis* is characterized by calcifications of the medial walls of muscular arteries, typically starting along the internal elastic membrane. Adults older than age 50 are most commonly affected. The calcifications do not encroach on the vessel lumen and are usually not clinically significant.
- *Fibromuscular intimal hyperplasia* occurs in muscular arteries larger than arterioles. It is driven by inflammation (as in a healed arteritis or transplant-associated arteriopathy; see Chapter 12) or by mechanical injury (e.g., associated with stents or balloon angioplasty; see later) and can be considered as a healing response. The affected vessels can become quite stenotic; indeed, such intimal hyperplasia underlies in-stent restenosis and is the major long-term limitation of solid-organ transplants.
- *Atherosclerosis,* from Greek root words for "gruel" and "hardening," is the most frequent and clinically important pattern and is discussed here.

ATHEROSCLEROSIS

Atherosclerosis underlies the pathogenesis of coronary, cerebral, and peripheral vascular disease and causes more morbidity and mortality (roughly half of all deaths) in the Western world than any other disorder. Because coronary artery disease is an important manifestation of the disease, epidemiologic data related to atherosclerosis mortality typically reflect deaths caused by ischemic heart disease (Chapter 12); indeed, myocardial infarction is responsible for almost a quarter of all deaths in the United