fenestrated (they have *holes,* presumably to facilitate filtration), while central nervous system endothelial cells (along with the associated perivascular cells) create an impermeable blood-brain barrier.

Endothelial cells are versatile multifunctional cells with a wealth of synthetic and metabolic properties. In the normal state they have several constitutive activities that are critical for vessel homeostasis and circulatory function. Endothelial cells have a nonthrombogenic surface that maintains blood in a fluid state (Chapter 4). They also modulate medial smooth muscle cell tone (thereby influencing vascular resistance), metabolize hormones such as angiotensin, regulate inflammation, and affect the growth of other cell types, particularly smooth muscle cells. Although interendothelial junctions are largely impermeable in normal vessels, vasoactive agents (e.g., histamine) allow the rapid egress of fluids, electrolytes and protein; in inflammation, even leukocytes can slip between adjacent endothelial cells (Chapter 3).

Endothelial cells can respond to various stimuli by adjusting their steady-state (constitutive) functions and by expressing newly acquired (inducible) properties—a process termed *endothelial activation* (Fig. 11-2). Inducers of endothelial activation include cytokines and bacterial products, which elicit inflammation and, in severe cases, septic shock (Chapter 4); hemodynamic stresses and lipid products, critical to the pathogenesis of atherosclerosis (see later); advanced glycation end-products (important in the pathologic sequelae of diabetes, Chapter 24); as well as viruses, complement components, and hypoxia. Activated endothelial cells, in turn, express adhesion molecules (Chapter 3) and produce cytokines and chemokines, growth factors, vasoactive molecules that result either in vasoconstriction or in vasodilation, major histocompatibility complex molecules, procoagulant and anticoagulant factors, and a variety of other biologically active products.

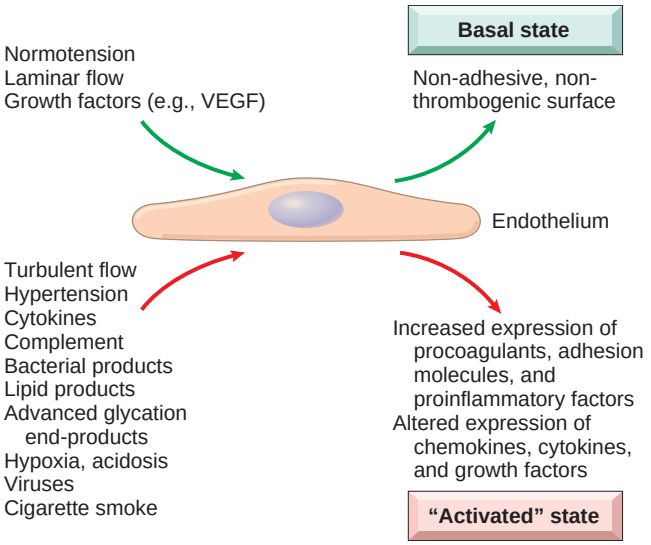

Figure 11-2 Basal and activated endothelial cell states. Normal blood pressure, laminar flow, and low growth factor levels promote a basal endothelial cell state that maintains a nonthrombotic, nonadhesive surface with appropriate vascular wall smooth muscle tone. Injury or exposure to certain mediators results in endothelial activation, a state where endothelial cells develop a procoagulant surface that can be adhesive for inflammatory cells, and also express factors that cause smooth muscle contraction and/or proliferation and matrix synthesis. VEGF, vascular endothelial growth factor.

Endothelial cells influence the vasoreactivity of the underlying smooth muscle cells through the production of both relaxing factors (e.g., nitric oxide [NO]) and contracting factors (e.g., endothelin). Normal endothelial cell function is characterized by a balance of these responses.

Endothelial dysfunction refers to an alteration in endothelial phenotype seen in many different conditions that is often both proinflammatory and prothrombogenic. It is responsible, at least in part, for the initiation of thrombus formation, atherosclerosis, and the vascular lesions of hypertension and other disorders. Certain forms of endothelial dysfunction are rapid in onset (within minutes), reversible, and independent of new protein synthesis (e.g., endothelial cell contraction induced by histamine and other vasoactive mediators that causes gaps in venular endothelium, Chapter 3). Other changes such as upregulation of adhesion molecules involve alterations in gene expression and protein synthesis and may require hours or even days to develop.

Vascular smooth muscle cells are the predominant cellular element of the vascular media, playing important roles in normal vascular repair and pathologic processes such as atherosclerosis. Smooth muscle cells have the capacity to proliferate when appropriately stimulated; they can also synthesize collagen, elastin, and proteoglycans and elaborate growth factors and cytokines. Smooth muscle cells are also responsible for the vasoconstriction or dilation that occurs in response to physiologic or pharmacologic stimuli.

Intimal Thickening: A Stereotyped Response to Vascular Injury

Vascular injury—associated with endothelial cell dysfunction or loss—stimulates smooth muscle cell recruitment and proliferation and associated matrix synthesis; the result is intimal thickening. Healing of injured vessels is analogous to the healing process that occurs in other damaged tissues (Chapter 3). Endothelial cells involved in repair may migrate from adjacent uninjured areas into denuded areas or may also be derived from circulating precursors. Medial smooth muscle cells or smooth muscle precursor cells also migrate into the intima, proliferate, and synthesize extracellular matrix in much the same way that fibroblasts fill in a wound (Fig. 11-3). The resulting neointima is typically completely covered by endothelial cells. 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 smooth muscle cells have a phenotype that is distinct from that of medial smooth muscle cells. Specifically, rather than primarily functioning as contractile cells, neointimal smooth muscle cells are motile, undergo cell division, and acquire new biosynthetic capabilities. The function of neointimal smooth muscle cells is regulated by cytokines and growth factors derived from platelets, endothelial cells, and macrophages, as well as thrombin and activated complement factors. With time and restoration and/or normalization of the endothelial layer, intimal smooth muscle cells can return to a nonproliferative state. However, the healing response results in intimal thickening that may impede vascular flow.