by synthesizing, degrading, and repairing damage to their extracellular matrix constituents. Aneurysms can occur when the structure or function of the connective tissue within the vascular wall is compromised. Although we cite here examples of inherited defects in connective tissues, weakening of vessel walls is important in the more common, sporadic forms of aneurysms as well.

- *The intrinsic quality of the vascular wall connective tissue is poor.* In *Marfan syndrome*, for example (Chapter 5), defective synthesis of the scaffolding protein *fibrillin* leads to aberrant TGF-β activity and weakening of elastic tissue; in the aorta, this may result in progressive dilation. *Loeys-Dietz syndrome* is another cause of aneurysms; in this disorder, mutations in TGF-β receptors lead to defective synthesis of elastin and collagens I and III. Aneurysms in such individuals can rupture fairly easily (even at small size) and are thus considered to follow an "aggressive" course. Weak vessel walls due to defective type III collagen synthesis are also a hallmark of the vascular forms of *Ehlers-Danlos syndrome* (Chapter 5), and altered collagen cross-linking associated with vitamin C deficiency (scurvy) is an example of a nutritional basis for aneurysm formation, that is thankfully rare these days.
- *The balance of collagen degradation and synthesis is altered by inflammation and associated proteases.* In particular, increased matrix metalloprotease (MMP) expression, especially by macrophages in atherosclerotic plaque or in vasculitis, likely contributes to aneurysm development; these enzymes have the capacity to degrade virtually all components of the extracellular matrix in the arterial wall (collagens, elastin, proteoglycans, laminin, fibronectin). Decreased expression of tissue inhibitors of metalloproteases (TIMPs) can also contribute to the extracellular matrix degradation. The risk of aneurysm formation in the setting of inflammatory lesions (e.g., atherosclerosis) may be associated with MMP and/or TIMP polymorphisms, or altered by the nature of the local inflammatory response. For example, abdominal aortic aneurysms (AAA; see later) are associated with local production of cytokines (such as IL-4 and IL-10) that stimulate release of elastolytic MMP from macrophages.
- *The vascular wall is weakened through loss of smooth muscle cells or the synthesis of noncollagenous or nonelastic extracellular matrix.* Ischemia of the inner media occurs when there is atherosclerotic thickening of the intima, which increases the distance that oxygen and nutrients must diffuse. Systemic hypertension can also cause significant narrowing of arterioles of the vasa vasorum (e.g., in the aorta), which causes outer medial ischemia. Medial ischemia may lead to "degenerative changes" of the aorta, whereby smooth muscle cell loss—or change in synthetic phenotype—leads to scarring (and loss of elastic fibers), inadequate extracellular matrix synthesis, and production of increasing amounts of amorphous ground substance (glycosaminoglycan). Histologically, these changes are collectively recognized as *cystic medial degeneration* (Fig. 11-19), which can be seen in a variety of settings, including Marfan syndrome and scurvy.

  Tertiary syphilis is another rare cause of aortic aneurysms. The obliterative endarteritis characteristic of late-stage syphilis shows a predilection for small vessels, including those of the vasa vasorum of the thoracic aorta. This leads to ischemic injury of the aortic media and aneurysmal dilation, which sometimes involves the aortic valve annulus.

Figure 11-19 Cystic medial degeneration. **A,** Cross-section of aortic media from a patient with Marfan syndrome, showing elastin fragmentation and areas devoid of elastin that resemble cystic spaces but are actually filled with proteoglycans *(asterisks).* **B,** Normal media for comparison, showing the regular layered pattern of elastic tissue. In both **A** and **B**, elastin is stained black.

The two most important causes of aortic aneurysms are atherosclerosis and hypertension; atherosclerosis is a greater factor in AAAs, while hypertension is the most common etiology associated with ascending aortic aneurysms. Other factors that weaken vessel walls and lead to aneurysms include trauma, vasculitis (see later), congenital defects (e.g., fibromuscular dysplasia and *berry aneurysms* typically in the circle of Willis; Chapter 28), and infections *(mycotic aneurysms).* Mycotic aneurysms can originate (1) from embolization of a septic embolus, usually as a complication of infective endocarditis; (2) as an extension of an adjacent suppurative process; or (3) by circulating organisms directly infecting the arterial wall.

Abdominal Aortic Aneurysm (AAA)

Aneurysms occurring as a consequence of atherosclerosis form most commonly in the abdominal aorta and common iliac arteries. A variety of factors discussed earlier collaborate to weaken the media and predispose to aneurysm formation.