FIVE

Pathology of the Pulmonary Circulation

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Pulmonary Hypertension Caused by Chronic Left Heart Failure, Obstruction of Pulmonary Venous Return, and Parenchymal Lung Disease

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Hemodynamically, pulmonary arterial hypertension is defined as a systolic pressure in excess of 30 mm Hg or a mean pulmonary pressure greater than 20 mm Hg; severe pulmonary hypertension is present if the pulmonary systolic pressure exceeds 75% of the systemic arterial systolic pressure.[1] There are numerous etiologies of pulmonary hypertension (Display 20-1); in this chapter, we will discuss the pathophysiology and pathology of pulmonary hypertension associated with obstruction to pulmonary venous drainage, which usually occurs as a result of structural or functional abnormalities of the left side of the heart. Less frequently, the obstruction is caused by lesions of the pulmonary veins themselves. Pulmonary hypertension secondary to underlying parenchymal lung diseases will also be examined.

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PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION CAUSED BY IMPEDANCE OF PULMONARY VENOUS DRAINAGE

The normal pulmonary artery systolic pressure at sea level is 18 to 25 mm Hg, the end-diastolic pulmonary artery and mean pulmonary venous pressures are 6 to 10 mm Hg, and the mean pulmonary artery pressure is 12 to 16 mm Hg.[1,2] Thus, the normal arteriovenous pressure difference or gradient, which drives blood flow across the pulmonary capillary bed, is 2 to 10 mm Hg. Pulmonary vascular resistance is dependent on the interaction of multiple variables, including lung tissue mass being perfused, proximal pulmonary artery obstruction (*e.g.*, pulmonary coarctation, pulmonary embolism), intraparenchymal vascular compression (*e.g.*, interstitial edema), blood viscosity, and the cross-sectional area of arteries, arterioles, veins, and venules.[2]

In response to an acute increase in pulmonary artery pressure,

DISPLAY 20-1. ETIOLOGIES OF PULMONARY HYPERTENSION

Impedance of Pulmonary Venous Drainage
- Left atrial hypertension
  - Mitral stenosis or regurgitation
  - Cor triatriatum
  - Left atrial myxoma
- Elevated left ventricular diastolic pressure
- Left ventricular systolic dysfunction
  - Myocardial ischemia or infarction
  - Dilated cardiomyopathy
- Left ventricular diastolic dysfunction
  - Myocardial ischemia or infarction
  - Hypertrophic cardiomyopathy
  - Restrictive cardiomyopathy
  - Aortic valvular stenosis or regurgitation
  - Constrictive pericarditis
- Pulmonary venous obstruction
  - Congenital pulmonary vein stenosis
  - Anomalous pulmonary venous connections with obstruction
  - Pulmonary venoocclusive disease
  - Fibrosing mediastinitis

Impedance to Blood Flow Across the Pulmonary Vascular Bed
- Parenchymal disease
  - Chronic obstructive lung disease
  - Granulomatous diseases
  - Connective tissue diseases
  - Pulmonary fibrosis
  - Amyloidosis
  - Malignant neoplasms
- Pulmonary arterial vascular disorders
  - Congenital heart disease with left-to-right shunts
  - Thromboembolic pulmonary disease
  - Primary pulmonary hypertension
  - Neoplasms
  - Persistent fetal circulation in the newborn
  - High-altitude pulmonary hypertension
  - Pulmonary hypoplasia or agenesis

Adapted from Grossman WB, Braunwald E. Pulmonary hypertension in heart disease. In: Braunwald E, ed. Heart disease. Philadelphia: WB Saunders, 1992:790.

the normal right ventricle can generate a systolic pulmonary pressure of 45 to 50 mm Hg. The production of such sustained pressure eventually determines right ventricular hypertrophy. The normal left atrial pressure is approximately 6 to 10 mm Hg; as left atrial pressure rises to 25 mm Hg, the pulmonary artery pressure increases in equal proportion so that pulmonary vascular resistance is unchanged at a constant pulmonary blood flow. However, when left atrial pressure increases above 25 mm Hg, there is a disproportionate increase in pulmonary artery pressure resulting in an increased arteriovenous pressure gradient and vascular resistance. This augmented hypertensive response of the pulmonary arterial bed is the result of vasoconstriction.[2]

There is substantial interindividual variability of vasoconstriction in response to chronically elevated pulmonary venous pressure; marked pulmonary hypertension occurs in fewer than one third of patients with severe mitral stenosis.[2] Neural factors, hypoxia-induced arterial vasoconstriction, and airway compression by engorged pulmonary veins, or compression of pulmonary arteries by interstitial edema, are probably important factors.[2] In contrast to pulmonary venous hypertension, individuals with primary pulmonary hypertension (PPH) with plexiform lesions have normal pulmonary capillary and venous pressures (see Chap. 23). A comparison among representative intravascular pressures in the cardiopulmonary circulation in normal controls, those with significant mitral stenosis with and without pulmonary arterial vasoconstriction, and those with PPH is depicted in Figure 20-1.

Fluid balance within the pulmonary vasculature, interstitium, and alveoli is controlled by Starling-law forces, consisting of intravascular and extravascular hydrostatic pressure and intravascular and extravascular colloid osmotic pressure.[3–5] In cases of obstruction of pulmonary venous return or chronic left heart failure, there is an increase in intravascular hydrostatic pressure. As pressure rises, fluid and small molecules gain access to the alveolar interstitium; mild increases in interstitial volume are accommodated by an increase in lymphatic outflow so that no net interstitial fluid accumulation occurs. However, when lymphatic drainage is no longer able to maintain fluid balance, interstitial edema results. The accumulation of macromolecules within the interstitium increases extravascular colloid osmotic pressure, further promoting the efflux of intravascular fluid into the interstitial space. The resulting increases in interstitial volume and pressure compress lymphatics and limit lymphatic drainage. Eventually, when the interstitial pressure overcomes the alveolar epithelial cell tight junctions, extravasation of fluid and macromolecules into alveolar spaces occurs (*i.e.,* edema).

As pulmonary venous pressure increases, the elevated pressure is transmitted retrograde to the pulmonary arterial system and is augmented by pulmonary arterial vasoconstriction. The resultant pulmonary arterial hypertension and increased vascular resistance protect the pulmonary capillary bed and prevent pulmonary edema by way of reduced flow. However, sustained, severe pulmonary hypertension inevitably results in right ventricular hypertrophy and dilatation with eventual right heart failure.

The main causes of pulmonary hypertension due to obstruction of pulmonary venous return and chronic left heart failure are presented in Display 20-1. In general, the most common etiologies involve left heart dysfunction or abnormalities of the mitral valve (*i.e.*, stenosis or incompetence), with regurgitation or mixed stenotic-regurgitant mitral lesions producing relatively more pulmonary arterial pathology than stenotic lesions alone (Figs. 20-2 and 20-3).[2,5–7] Specific disorders of the mitral valve include rheumatic mitral stenosis and mitral regurgitation due to mitral valve prolapse or endocarditis.

In severe mitral stenosis, in addition to elevated pulmonary venous pressure, reactive arterial and arteriolar vasoconstriction has been well described.[7–9] In these patients, signs and symptoms of right heart failure and low cardiac output (*e.g.*, fatigue, jugular venous distention, hepatomegaly, ascites, peripheral edema) predominate over left heart findings (*e.g.*, dyspnea, pulmonary venous congestion).[2] The combination of severe pulmonary arterial hypertension, right heart failure, and low cardiac output may protect the pulmonary vascular bed from overt pulmonary edema, but it carries a very poor prognosis.

The most common cause of left ventricular systolic dysfunction is ischemic heart disease with myocardial scarring secondary to infarction (Fig. 20-4). Less common causes of left systolic failure include cardiomyopathy (*e.g.*, idiopathic dilated cardiomyopathy) and aortic valve disease. Pulmonary hypertension is produced by way of increased left ventricular end-diastolic pressure and volume associated with passive increases in left atrial, pulmonary venous, and pulmonary arterial pressures. In most cases of left ventricular systolic dysfunction, pulmonary hypertension is not severe unless increased pulmonary vascular resistance develops.[2]

Left ventricular diastolic dysfunction (*i.e.*, reduced ventricu-

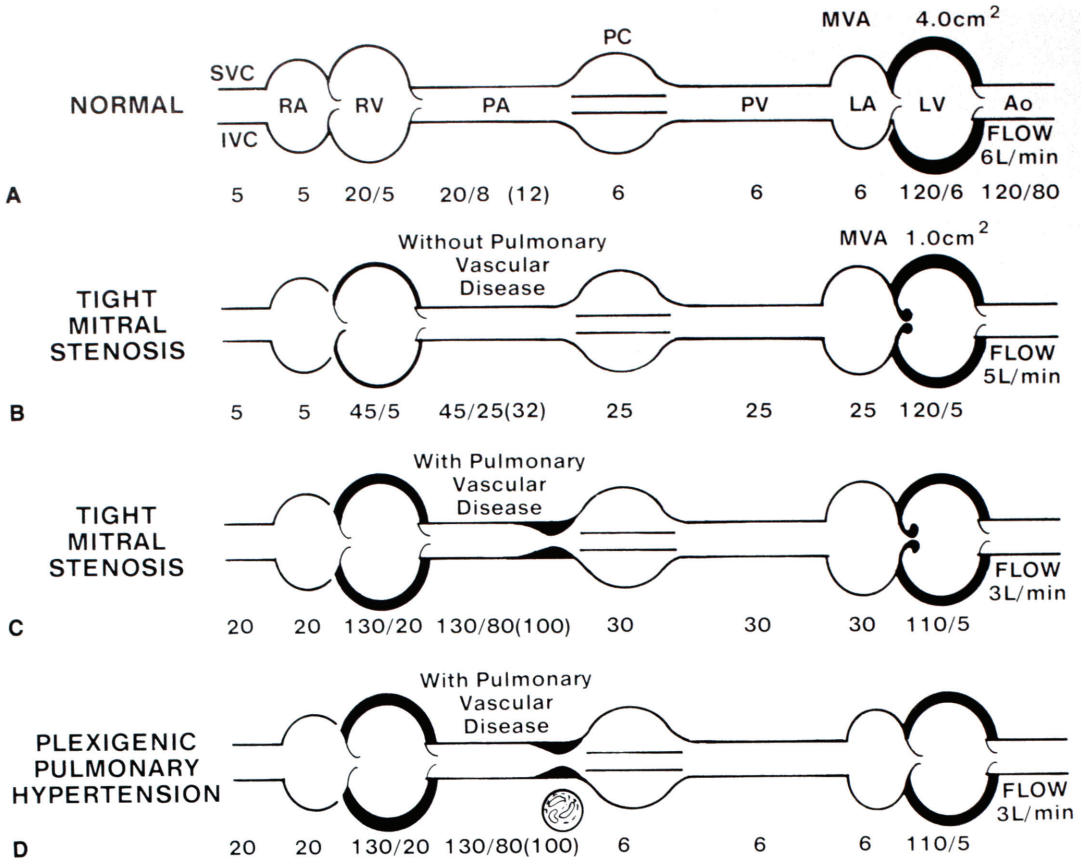

FIGURE 20-1. (**A**) Pressures and flows in the cardiopulmonary circuit under normal conditions. (**B**) Pressures and flows in a patient with severe mitral stenosis without pulmonary arterial disease. (**C**) Pressures and flows in a patient with severe mitral stenosis with pulmonary arterial disease. (**D**) Pressures and flows in a patient with primary pulmonary hypertension with plexogenic lesions. Pressures are expressed in mm Hg for the aorta (Ao), left atrium (LA), left ventricle (LV), pulmonary arteries (PA), pulmonary capillaries (PC), pulmonary veins (PV), right atrium (RA), right ventricle (RV), and superior and inferior vena cavae (SVC; IVC). Severe pulmonary hypertension and right ventricular failure follow the development of pulmonary arterial disease (**C, D**). (Adapted from Grossman WB, Braunwald E. Pulmonary hypertension in heart disease. In: Braunwald E, ed. Heart disease. Philadelphia: WB Saunders, 1992:790.)

lar compliance as a result of ischemic disease, hypertrophic cardiomyopathy, or restrictive cardiomyopathy) may be associated with increased pulmonary venous pressures, but severe pulmonary hypertension is uncommon.[2] Congenital heart lesions, such as cor triatriatum, congenital mitral stenosis or atresia, and total anomalous venous return are unusual causes of chronic pulmonary venous hypertension. Rarely, a left atrial myxoma may increase pulmonary venous pressure by obstructing left atrial emptying. Obstruction of pulmonary veins in their intramediastinal course by inflammatory and sclerosing processes (*i.e.*, fibrosing mediastinitis) is another uncommon cause of pulmonary hypertension. Whatever the cause of the pulmonary venous hypertension, the venous and arterial lesions are not specific for any one entity.

PATHOLOGY OF ACUTE AND CHRONIC VENOUS HYPERTENSION OF THE LUNG

Parenchymal Pathology

In acute pulmonary edema due to left cardiac dysfunction, the lung weight is markedly increased (>1000 g combined weight), and on cut section, the parenchyma exudes pink, frothy fluid. Microscopically, the vessels are congested and the interstitium is distended. Exudation of fluid and macromolecules into alveolar spaces appears as homogeneous or grainy pink material on hematoxylin and eosin staining (see Fig. 20-4*A*). Scattered intraalveolar erythrocytes may be present (see Fig. 20-4*B*). Morphologic changes in pulmonary arteries and veins are not apparent in the acute state (see Chap. 13).

In chronic venous hypertension of left cardiac etiology, the gross lung is rusty brown to orange as a result of congestion, especially in centriacinar-centrilobular areas, resulting in a leopard-spot appearance.[3] Lung weight is normal unless an acute exacerbation of pulmonary congestion has complicated a chronic process. Typically, the lung surface is dry, and perivascular fibrosis may be seen grossly.[6] Microscopically, there is interstitial thickening consisting of fine fibrosis and distended capillaries. There is basement membrane disruption with capillary rupture resulting in extravasation of erythrocytes into alveolar spaces. Focal or diffuse hemosiderin-laden macrophages (*i.e.*, heart failure cells) are often abundant in intraalveolar spaces (see Fig. 20-4*C*), and extracellular iron pigment may be seen in pulmonary septa, in pleura, and in the walls of blood vessels and bronchi. Pulmonary hemosiderosis can be found in other forms of pulmonary hypertension; therefore, it is not specific for venous hypertension.

In cases of severe, persistent pulmonary venous hypertension,

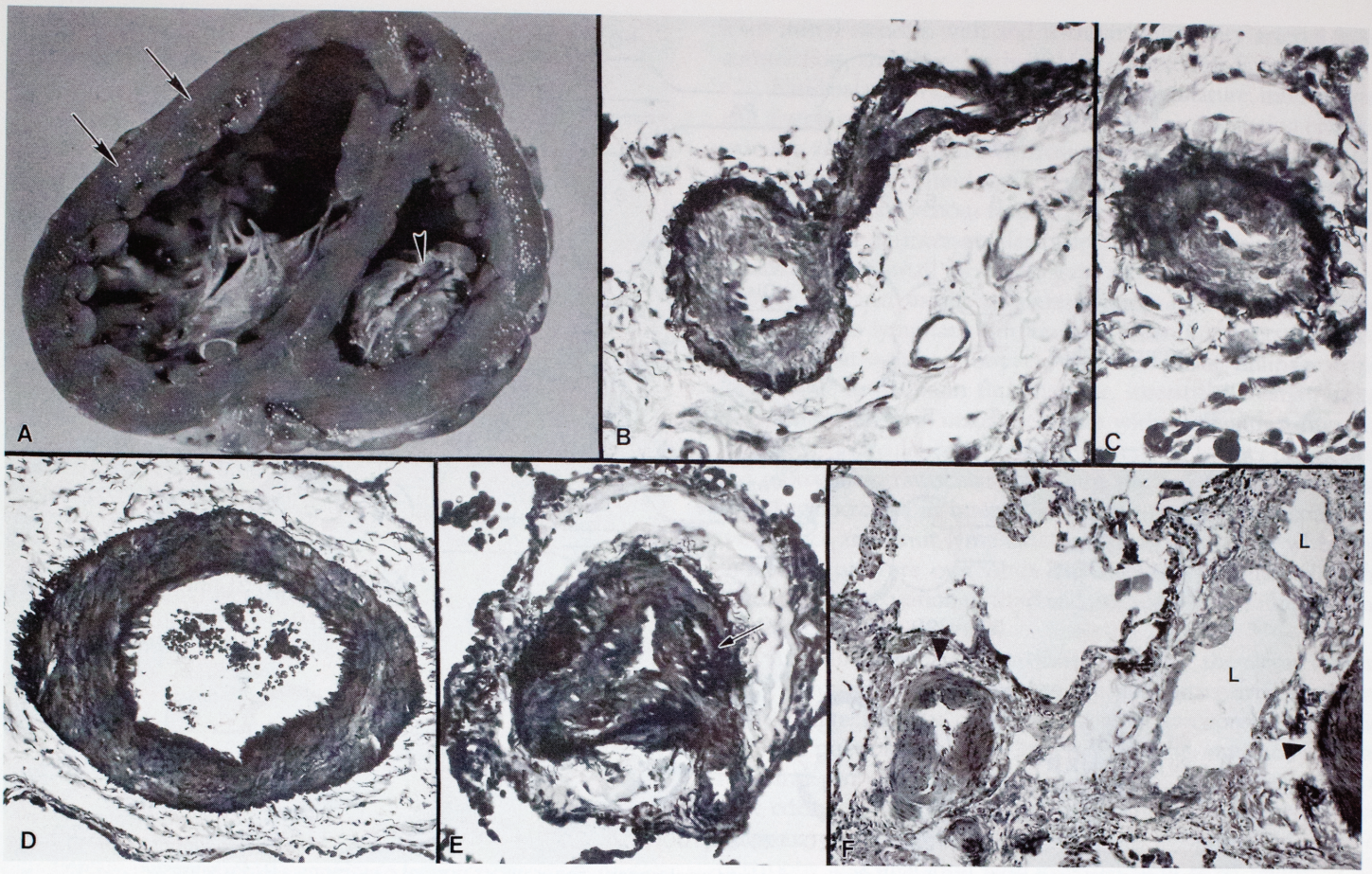

FIGURE 20-2. Cardiac and pulmonary vascular pathology in a patient with mitral stenosis with pulmonary venous hypertension. (**A**) At autopsy, the heart had a stenotic mitral valve (*arrowhead*) and a dilated, hypertrophied right ventricle (*arrows*). (**B, C**) Small pulmonary veins show reduplication of the internal elastic lamina with an attempt to form a medial layer and marked intimal fibrosis with luminal narrowing. (**D**) The muscular pulmonary artery demonstrates medial hypertrophy but no intimal proliferation. (**E**) The small pulmonary artery has marked fibrous intimal proliferation, muscularization, and reduplication of the internal elastic lamina (*arrow*). (**B–E:** Movat elastic tissue stain; intermediate magnification.) (**F**) Dilated lymphatic channels (L) are adjacent to pulmonary arteries (*arrowheads*). (H & E stain, low magnification.)

diffuse subpleural interstitial fibrosis is common.[6] Alveoli may be lined by cuboidal epithelial cells containing large nuclei (*i.e.*, metaplasia). Ultrastructural studies have shown that the thickened, fibrotic interstitium consists of swollen endothelial cells, thickened and split basement membranes, and increased collagen and elastic fibers.[10] Medial and intimal lesions of muscular arteries, arterioles, and veins are striking in their severity (Fig. 20-5; see Fig. 20-4*D–F*). Although not specific for pulmonary venous hypertension, both intraalveolar microlithiasis and ossification are seen more often than they are in other forms of pulmonary hypertension.[6,10] Microliths, also called calcospherites, range in size from 100 to 600 μm in diameter, consist of calcium phosphate, and have a uniform, laminated appearance (see Fig. 20-3*A*). They are typically sparsely scattered throughout the lung fields and rarely are so numerous as to be recognized on chest x-ray films. Bony nodules have a knobby character and vary in size from 0.5 mm to several millimeters (see Fig. 20-5*F*). Organization of intraalveolar fibrinous exudates may be involved in the etiology of these ossifications, but this is speculative.

Pulmonary Vein Pathology

Thickening of venous walls characterized by medial hypertrophy, fibrosis, and elastosis is the pathologic hallmark of long-standing venous hypertension.[6,11] The normally irregularly arranged elastic fibers in pulmonary veins become organized into an internal and external elastic lamina (see Fig. 20-4*D, E*).[11] These arterialized veins are typically associated with medial hypertrophy, and care must be exercised in identifying these vessels as veins and not arteries. It helps to remember that muscular pulmonary arteries are always associated with airways, whereas veins can be best recognized at the periphery of the secondary lobule and interlobular septae. Hyaline intimal fibrosis of pulmonary veins (see Figs. 20-3*A* and 20-4*D*) is commonly seen in older individuals but is probably more severe and more frequently identifiable in chronic venous hypertension.[6,11] Within the intimal fibrosis, smooth muscle cells occasionally may be seen. The walls of larger pulmonary veins are thicker than normal in chronic venous hypertension, and pulmonary venous varices have been described.[6,12] Venous intimal fibrosis secondary to chronic venous hypertension rarely progresses to occlusion of the vessel.[11] Intimal fibrosis and medial hypertrophy are typically accompanied by adventitial thickening and fibrosis.[11] Medial hypertrophy is commonly found in the lower lung fields, whereas intimal fibrosis is relatively more severe in the upper lung fields.[6]

The venous changes described above must be distinguished from pulmonary venoocclusive disease (see Chap. 23). Histologically, the venous involvement in the latter tends to be focal, and it is characterized by intimal fibrosis resembling organized thrombi. Fibrous septa within veins vary from fine to thickened

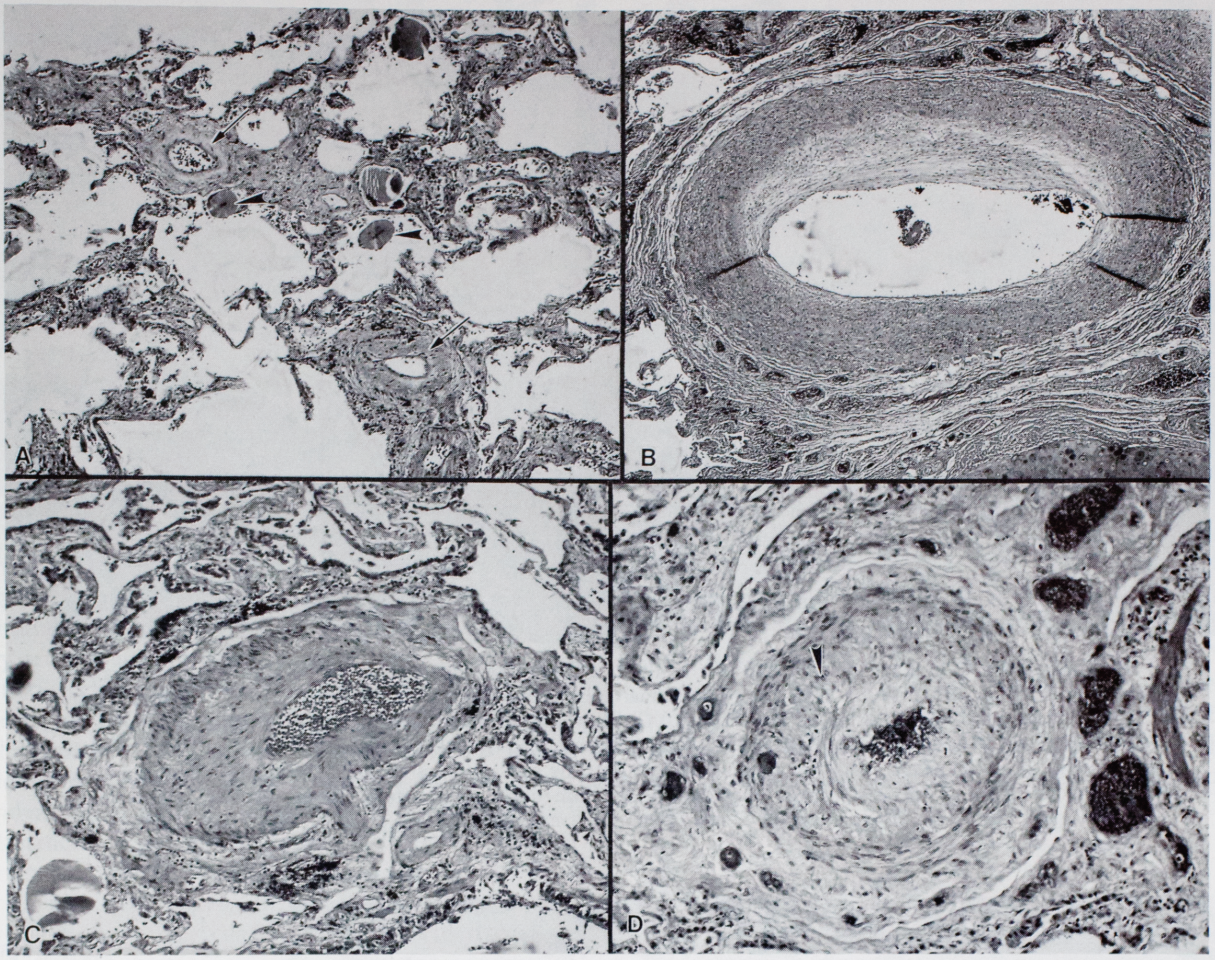

FIGURE 20-3. Pulmonary vasculature in a 70-year-old man with mitral stenosis and insufficiency, atrial fibrillation, and congestive heart failure. (**A**) A low-power view of the lung demonstrates prominent pulmonary veins with intimal proliferation and fibrosis (*arrows*); microliths are present within alveolar spaces (*arrowheads*). (**B**) The large elastic pulmonary artery shows intimal thickening. (**A, B:** H & E stain; low magnification.) (**C, D**) The muscular pulmonary arteries have medial hypertrophy and prominent intimal proliferation that is eccentric in **C** and concentric in **D**. Longitudinally oriented smooth muscle cells are seen in **D** (*arrowheads*). (**C, D:** H & E stain; intermediate magnification.)

collagenous strands containing large endothelialized vascular channels.

Pulmonary Artery Pathology

The pulmonary trunk and main pulmonary arteries are thickened and dilated in chronic venous hypertension. Microscopically, these vessels contain increased medial mucopolysaccharides and normally aligned medial elastic lamellae. Atherosclerosis of these vessels is common, occasionally accompanied by calcification.[6] Rarely, main pulmonary artery aneurysms and, in fatal cases, rupture of a main pulmonary artery have been described.

Medial hypertrophy of muscular pulmonary arteries and arterioles is perhaps the earliest detectable indication of pulmonary venous hypertension (see Figs. 20-2*D* and 20-4*F*). Normal medial thickness, as a percent of the arterial external elastic lamina diameter, is 7%.[6,13] In a study of 20 autopsy patients with pulmonary venous hypertension secondary to mitral valve diseases, the average medial thickness was greater than normal in 17, averaging 9.2%.[6,13] An additional important aspect in the development of medial hypertrophy in pulmonary venous hypertension is the muscularization of small arterioles that normally are devoid of a well-defined medium.[13,14] In chronic venous hypertension, a well-demarcated medium may be seen in arterioles 30 to 50 μm in diameter and occasionally in those as small as 20 μm in diameter (see Fig. 20-4*F*). Medial hypertrophy may take the form of longitudinally oriented smooth muscle cell layers in the intima (see Fig. 20-3*D*) and adventitia between reduplicated internal elastic laminae.[6]

Within the muscular arterial and arteriolar intima, fibrosis is commonly seen and is far in excess of the normal, age-related change.[6] The intimal fibrosis consists of connective tissue with few smooth muscle cells and varying amounts of collagen and elastic fibers. In a few cases, elastosis is pronounced and is associated with deposits of acid mucopolysaccharides.[6] Occasionally, there is intimal iron deposition and calcification of the internal elastic lamina. Intimal fibrosis may be eccentric or concentric and rarely demonstrates an onion-skin arrangement like that seen in congenital left-to-right cardiac shunts[6] or PPH. The intimal fibrosis must also be differentiated from that seen in thromboembolic disease in which endothelial-lined recanalized vascular channels are typically present. Serial sections demonstrate that the length of the vessel involved by intimal proliferation is far greater in cases of chronic venous hypertension than it is in thromboembolic disease.

Fibrinoid necrosis and inflammatory vasculitis in muscular

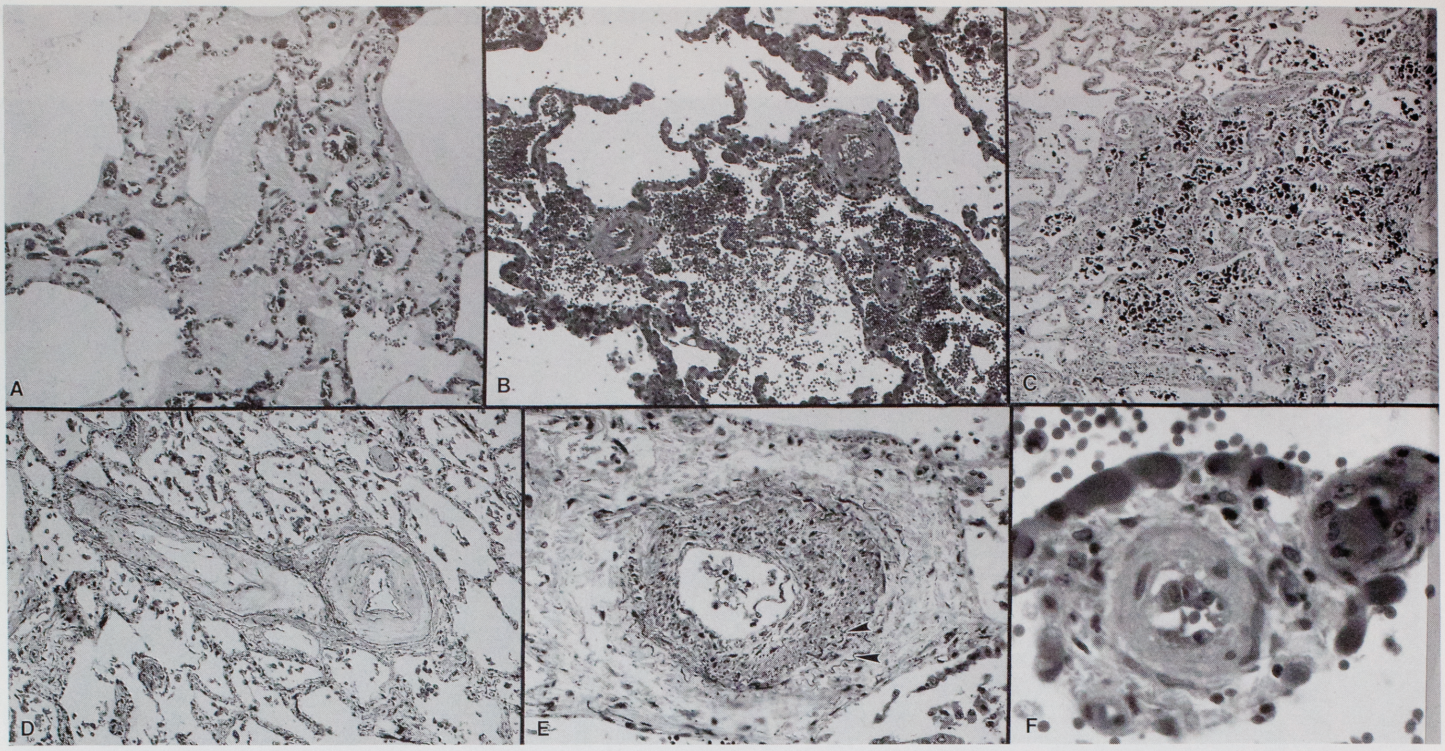

FIGURE 20-4. Pulmonary pathology in congestive heart failure secondary to dilated or ischemic cardiomyopathy. (**A**) A low-power view shows homogeneous intraalveolar pulmonary edema. (**B**) There is marked congestion of alveolar capillaries with intraalveolar hemorrhage. (**C**) Hemosiderin-laden macrophages are present in the alveolar spaces. (**A–C:** H & E stain; low magnification.) (**D**) The pulmonary vein is hyalinized and thickened with luminal narrowing. (Elastic tissue stain; low magnification.) (**E**) The small pulmonary vein shows reduplication of the internal elastic lamina (*arrowheads*) and marked intimal smooth muscle proliferation. (Elastic tissue stain; intermediate magnification.) (**F**) Muscularization of small pulmonary arteriole has taken place. (H & E stain; intermediate magnification.)

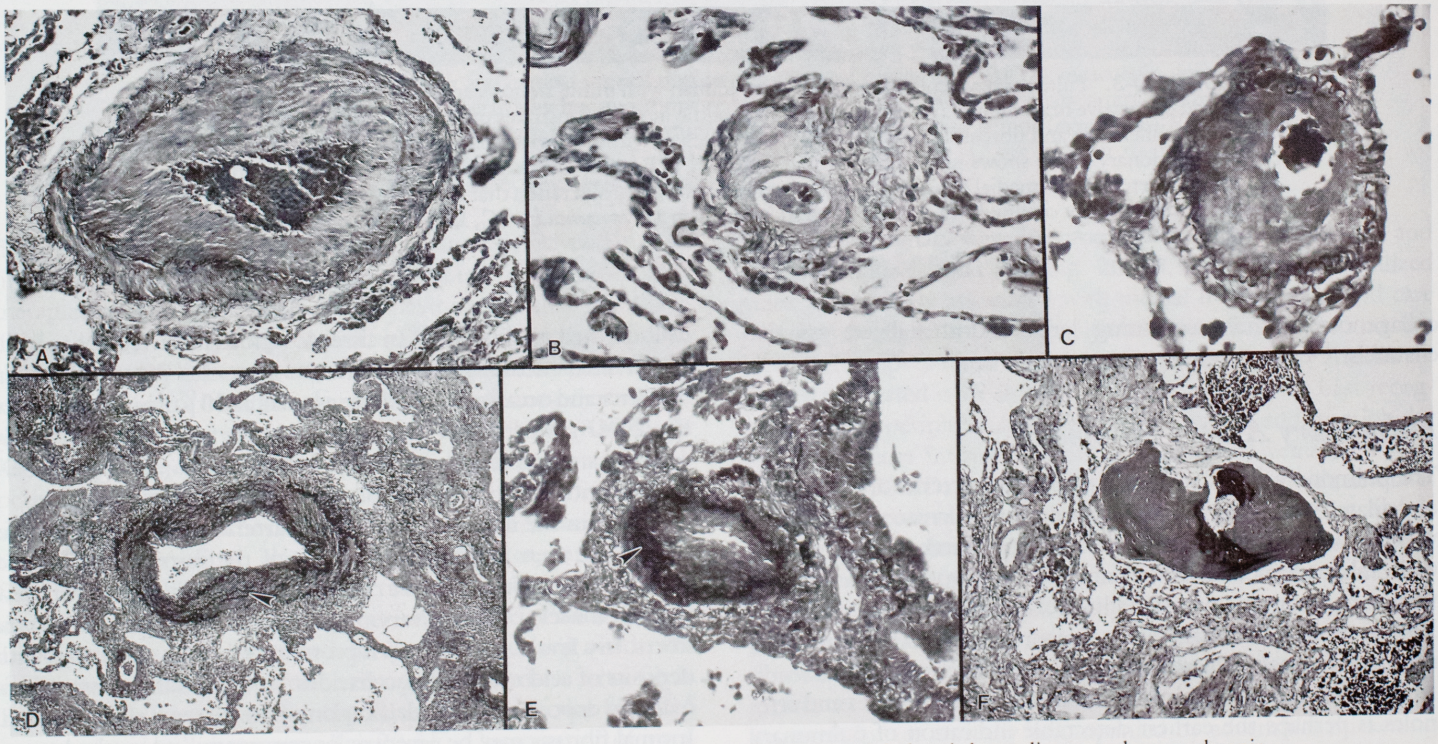

FIGURE 20-5. (**A–C**) Pulmonary vessels from a 76-year-old man with ischemic heart disease and severe chronic obstructive pulmonary diseases and (**D–F**) from a 90-year-old man with emphysema and pulmonary fibrosis. (**A**) The muscular pulmonary artery shows medial and intimal thickening. (Movat elastic tissue stain; low magnification.) (**B, C**) Small pulmonary arterioles demonstrate intimal thickening and marked hyalinization in (**C**). (Movat elastic tissue stain; intermediate magnification.) (**D**) The muscular pulmonary artery shows medial hypertrophy and reduplicated internal elastic lamina (*arrowhead*). (Movat elastic tissue stain; low magnification.) (**E**) The small pulmonary artery shows medial thickening, reduplicated internal elastic lamina (*arrowhead*), and intimal proliferation. (Movat elastic tissue stain; intermediate magnification.) (**F**) An osseous nodule shows interstitial fibrosis. (Movat elastic tissue stain; low magnification.)

pulmonary arteries and arterioles, consisting of infiltration by polymorphonuclear leukocytes and lymphocytes, have been reported in atypical cases of pulmonary venous hypertension.[6] At The Armed Forces Institute of Pathology, we have never observed vasculitis in chronic venous hypertension. In contrast to intracardiac shunt or PPH, dilatation and plexiform lesions are not seen in cases of chronic pulmonary venous hypertension.[6,15] The absence of dilatation or plexiform lesions in chronic venous hypertension is not easily explained, but it may be related to adventitial thickening, which prevents the occurrence of arterial dilatation. The arterial adventitia is thickened by increased collagen deposition and averages more than twice the normal thickness.[6,16] Tandon and Kasturi have reported dilatation lesions in patients with mitral stenosis, but their illustrations are not convincing.[17]

There are conflicting data in attempting to correlate the severity of pathologic changes in pulmonary arterial and venous segments with increases in pulmonary artery pressures. Some researchers have reported a close relationship between the severity of pulmonary arterial medial thickening and intimal fibrosis with pulmonary pressures and chest x-ray vascular findings.[18–21] In a study of mitral stenosis, medial hypertrophy of small muscular pulmonary arteries and muscularization of arterioles were seen only at pulmonary vascular resistances greater than 260 dynes-sec-cm^{-5}; normal is 67 ± 23 dynes-sec-cm^{-5}.[22] However, in other reports, clinicopathologic correlations are quite tenuous, and no linear relationship between the degree of pulmonary artery hypertension and medial hypertrophy was found.[22–25] The consensus is that, unlike studies of pulmonary arteries in congenital heart disease, pulmonary artery hypertensive findings in acquired left heart disease are neither sensitive nor specific for identifying patients with severe pulmonary hypertension and cannot be used to predict clinical responses to therapy (*e.g.*, mitral valve replacement).

Bronchial Vessel Pathology

Morphologic changes in bronchial arteries and veins are also present in chronic pulmonary venous hypertension. In bronchial arteries, there is an increase in longitudinally oriented medial smooth muscle cells, and bronchopulmonary arterial anastomoses are increased.[6] In severe cases of venous hypertension, massive dilatation of bronchial veins may occur in the form of peribronchiolar varices, which may rupture, leading to hemoptysis.[6] Bronchopulmonary venous anastomoses are also increased.[26]

Lymphatic Channel Pathology

As a consequence of increased flow in chronic venous hypertension, pulmonary lymphatics are dilated and increased in number and demonstrate increased wall thickness.[27,28] Kerly B lines, seen on chest x-ray films, especially in the lower lung fields, represent dilated lymphatic channels and interstitial edema.

PULMONARY HYPERTENSION IN PARENCHYMAL LUNG DISEASES

Chronic Bronchitis and Emphysema

Although pulmonary hypertension is not uncommon in chronic bronchitis and emphysema,[29] severe hypertension is unusual, and there is no strong correlation between the extent of destruction of the alveolar bed and the severity of hypertension. The relative infrequency of severe pulmonary hypertension in chronic bronchitis and emphysema is probably a result of the lung's large vascular reserve.[6] In most cases of obstructive pulmonary disease, the major stimulus of pulmonary hypertension is probably hypoxia-induced vasoconstriction.[30–32] However, in patients with very severe airway obstruction and pulmonary hypertension at rest, there are some data that suggest that vascular narrowing by medial hypertrophy and intimal fibrosis plays a greater role than dynamic hypoxic vasoconstriction.[33] The degree of arteriolar muscularization may be correlated with the severity of right ventricular hypertrophy.[34] Right ventricular hypertrophy is more common in centrilobular than in panacinar emphysema, probably as a consequence of the relatively worse gas exchange in the former (see Chaps. 26 and 27).[2]

In chronic bronchitis and emphysema associated with pulmonary hypertension, the elastic pulmonary arteries (*i.e.*, main pulmonary trunk and its major branches) may demonstrate dilatation, medial hypertrophy, and atherosclerotic plaques. Muscular pulmonary arteries show medial hypertrophy (see Fig. 20-5*A*, *D*), and there is muscularization of small arterioles, which normally would not have a well-defined layer of muscular media.[6,35] Intimal longitudinally arranged smooth muscle fibers associated with reduplicated elastic fibers may be seen (see Fig. 20-5*D*, *E*).[34,36] Intimal fibrosis is uncommon in chronic bronchitis in the absence of superimposed previous pneumonia, pulmonary fibrosis, or left heart failure.[36]

Granulomatous Diseases

These entities may cause pulmonary hypertension by way of the development of interstitial fibrosis or by direct granulomatous narrowing and obstruction of the pulmonary vasculature. In pulmonary tuberculosis, arteries, arterioles, venules, and veins may demonstrate luminal obliteration in areas close to pulmonary caseation. In nonobliterated vessels, there may be intimal fibrosis and mild medial hypertrophy in areas of scarring. Granulomatous arteritis can also occur (see Chap. 41).

Pulmonary hypertension occurs in approximately 1% to 4% of patients with sarcoidosis and is usually associated with interstitial pulmonary fibrosis with accompanying destruction of the vascular bed or, less common, granulomatous vasculitis (Fig. 20-6).[37–39] Pulmonary hypertension due to medial hypertrophy and intimal proliferation in the absence of vasculitis or interstitial fibrosis has also been reported (see Chap. 66).[40] Although pulmonary involvement is common in Takayasu arteritis,[41] pulmonary hypertension secondary to granulomatous arteritis is unusual (see Chap. 70).[42]

Connective Tissue Diseases

Of the connective tissue diseases, scleroderma is most closely associated with pulmonary hypertension. Of 30 autopsy cases of scleroderma reported by Young and Mark,[43] 14 had moderate or marked abnormalities of the pulmonary arteries. In 9 of these 14 patients, respiratory symptoms were the predominant manifestation, with 3 patients having rapidly fatal pulmonary failure. Individuals with the CREST syndrome variant of scleroderma (*i.e.*, calcinosis, Raynaud phenomenon, esophageal dysmotility, sclero-

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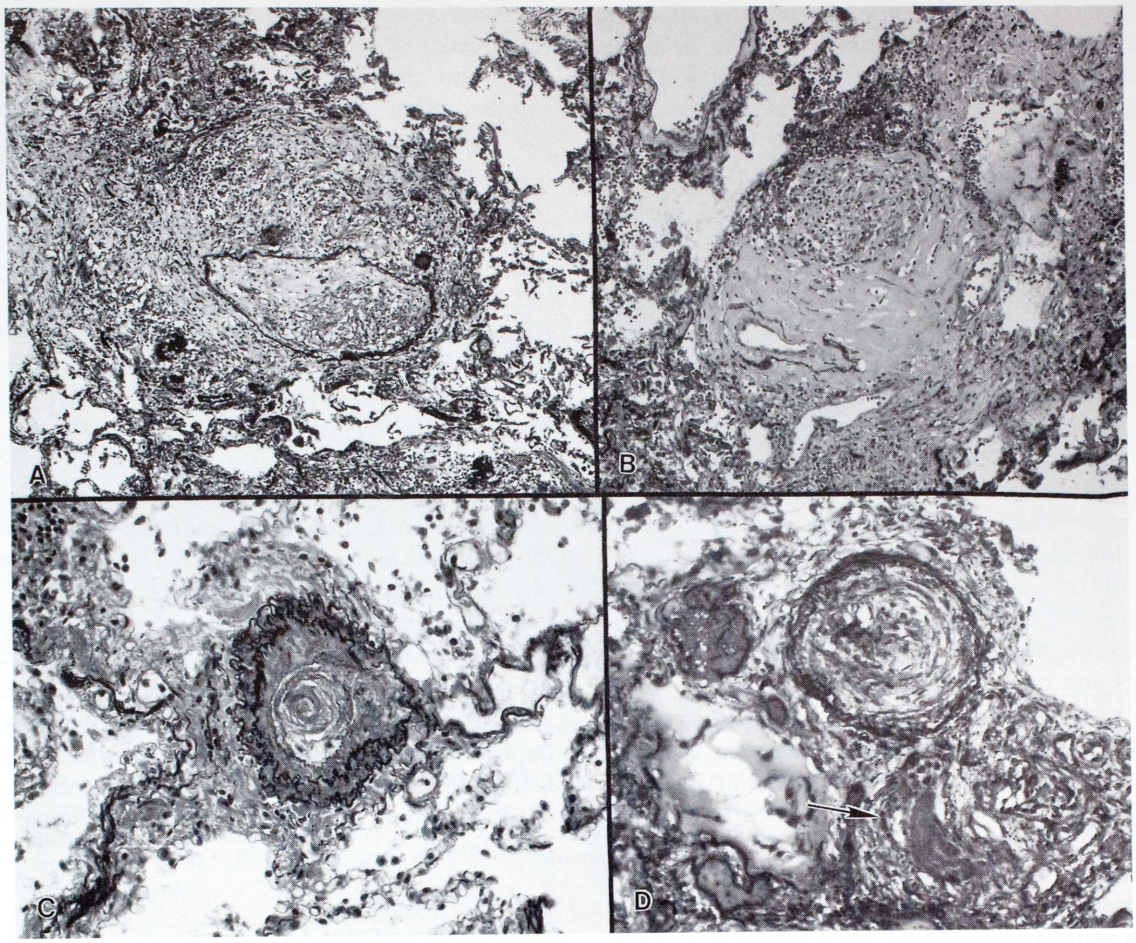

FIGURE 20-6. Pulmonary vascular pathology in sarcoidosis with pulmonary hypertension. (**A**) Lung from a 45-year-old woman with pulmonary sarcoidosis and pulmonary hypertension (*i.e.*, pulmonary artery pressures 120/45 mm Hg; mean, 52 mm Hg) was seen at autopsy. Noncaseating granulomas surround the vessel. Note the intimal proliferation and obliteration of the lumen. (Movat elastic tissue stain; low magnification.) (**B**) Fibrosis and narrowing of a vein occurs next to a hyalinizing granuloma. (Movat elastic tissue stain; low magnification.) (**C**) The muscular pulmonary artery demonstrates medial thickening and marked concentric intimal proliferation not associated with granuloma. (**D**) Concentric intimal proliferation and luminal obstruction are adjacent to a noncaseating granuloma (*arrow*). (Movat elastic tissue stain; low magnification.)

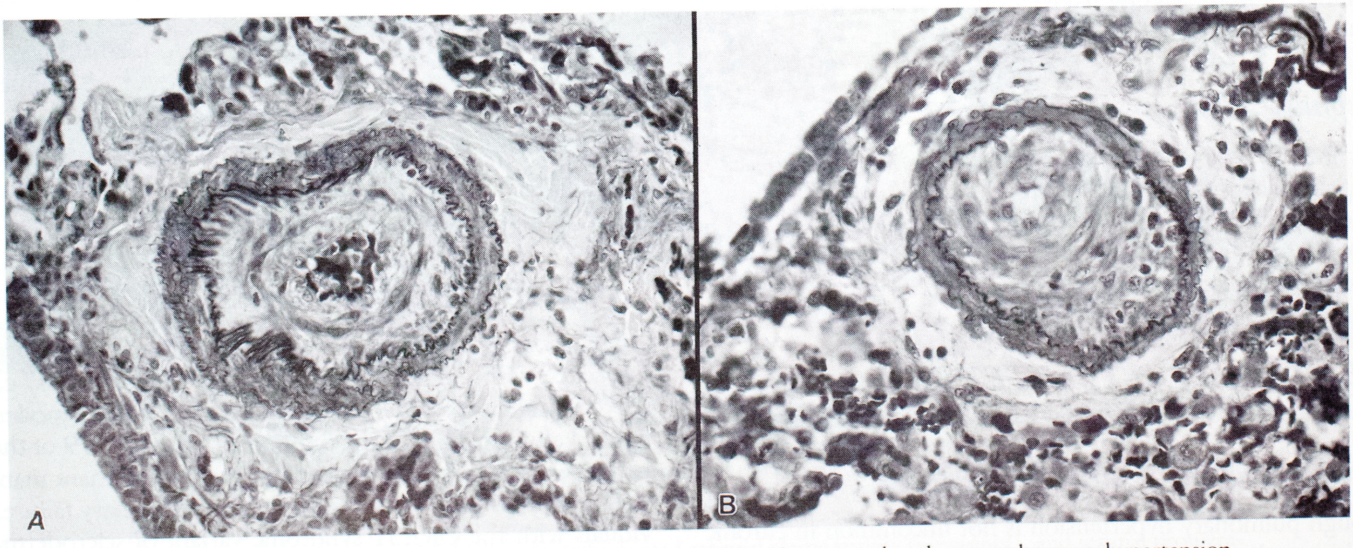

FIGURE 20-7. Pulmonary arterial pathology in a young girl with severe scleroderma, pulmonary hypertension, and biventricular heart failure, with marked luminal narrowing by (**A**) concentric and (**B**) eccentric proliferation of smooth muscle and fibrous tissue in small muscular arteries. (Movat elastic tissue stain; intermediate magnification.)

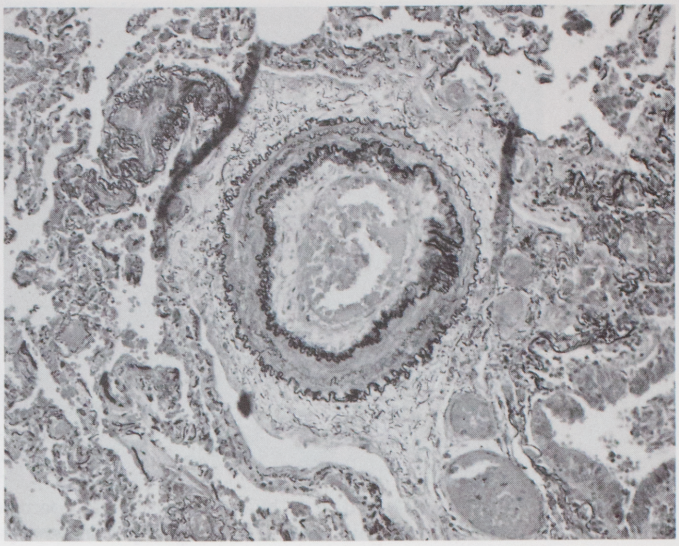

FIGURE 20-8. Pulmonary vascular pathology in rheumatoid arthritis. Medial thickening and mild concentric intimal proliferation occurred in a medium-sized pulmonary artery from a 54-year-old man with rheumatoid arthritis, pulmonary hypertension, and cor pulmonale. (Movat elastic tissue stain; low magnification.)

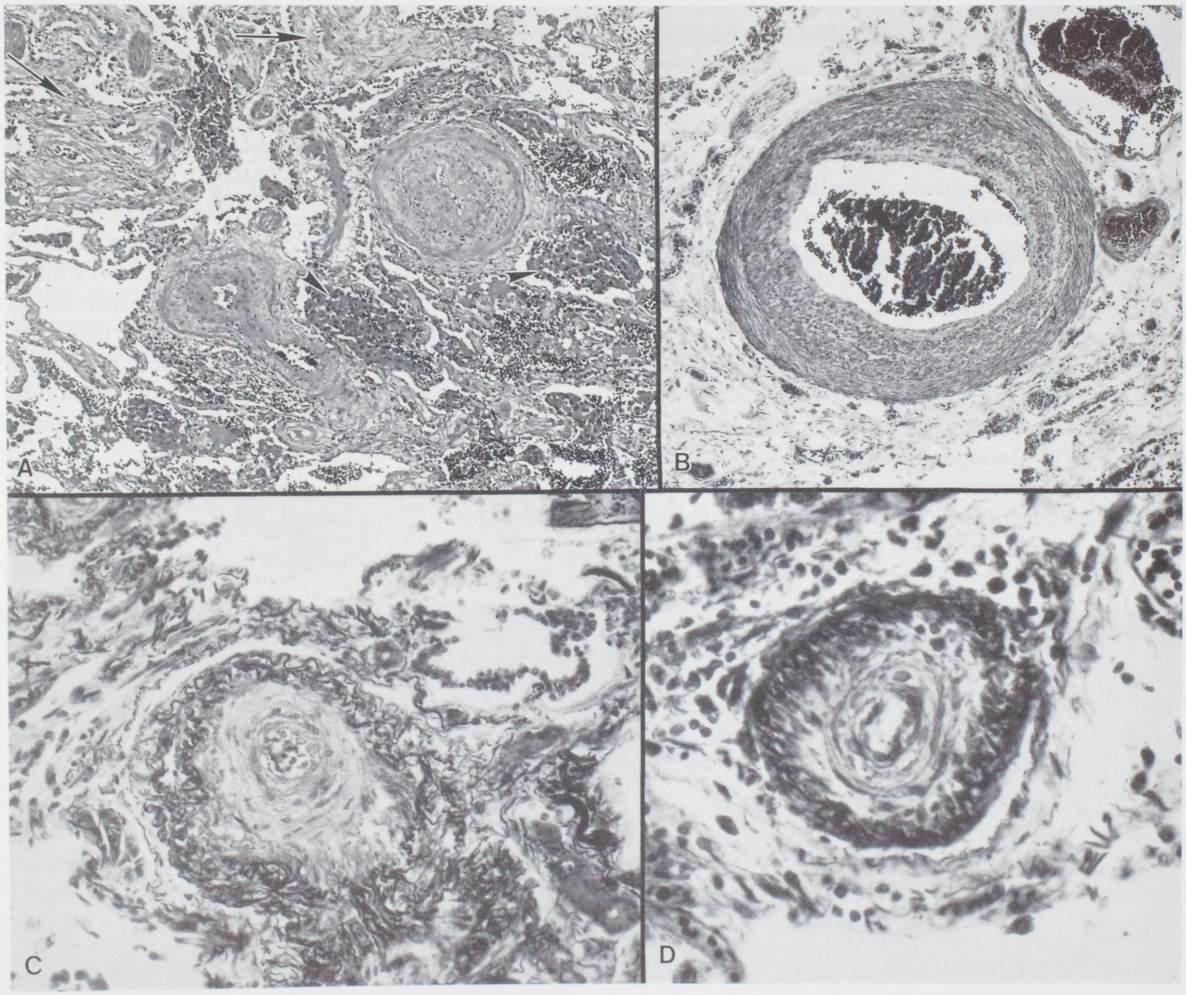

FIGURE 20-9. Pulmonary vascular pathology in interstitial fibrosis. (**A**) A low-power view demonstrates interstitial fibrosis (*arrows*) and numerous intraalveolar macrophages (*arrowheads*). There is marked medial and intimal thickening of two muscular pulmonary arteries with severe fibromuscular hyperplasia of the intima and narrowing of the lumen. (H & E stain; low magnification.) (**B**) Large muscular pulmonary artery with thickened intima and media; note prominent smooth muscle cells within the intima. (H & E stain; low magnification.) (**C, D**) Small veins within intralobar septa demonstrating reduplication of the elastic lamina with severe concentric intimal proliferation and small central lumina. (Movat elastic tissue stain; intermediate magnification.)

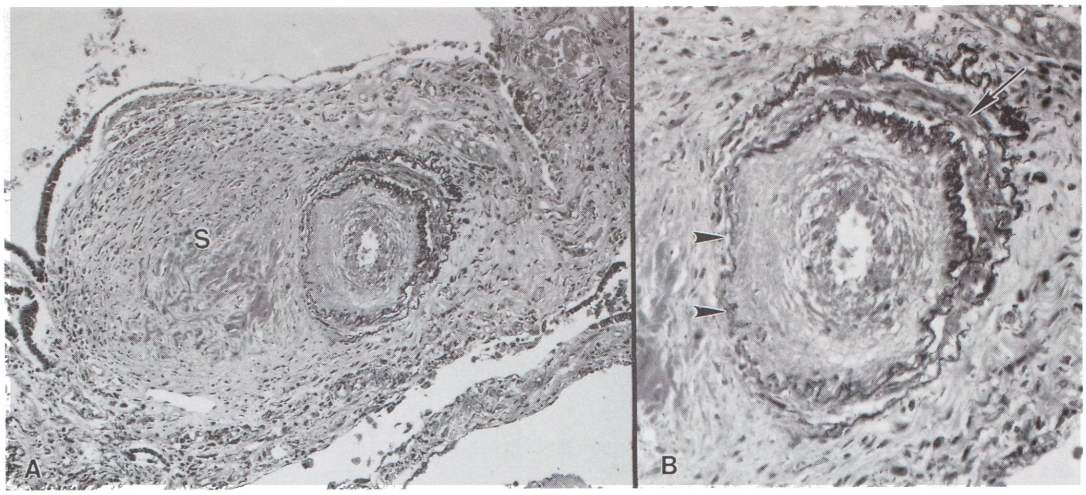

FIGURE 20-10. (**A**) Nodule of silicosis (S) occurred in a 54-year-old, male sandblaster. (Movat elastic tissue stain; low magnification.) (**B**) A higher power shows partial destruction of the media (*arrowheads*) and focal medial thickening (*arrow*). The concentric intimal proliferation has resulted in a small central lumen. (Movat elastic tissue stain; intermediate magnification.)

dactyly, and telangiectasia) appear to be particularly susceptible to the development of severe pulmonary hypertension.[44,45] There are two forms of pulmonary involvement in scleroderma: interstitial inflammation and fibrosis, and primary vascular disease. Pulmonary vascular morphology in scleroderma, especially in patients with the CREST syndrome, consists of medial hypertrophy and intimal fibrosis with concentric intimal proliferation; obliteration of the arterial lumen is not uncommon (Fig. 20-7). A double muscular layer just subjacent to the endothelium may be present,[6] but medial thickening is not pronounced. Intimal fibrosis of veins and acute vasculitis are rarely seen.

Pulmonary hypertension is an uncommon complication of systemic lupus erythematosus, and, when present, histology demonstrates intimal fibrosis and necrotizing vasculitis of muscular pulmonary arteries.[46–50] Immunoglobulin and complement deposits in the walls of pulmonary vessels have been described.[51] Patients usually have widespread organ involvement, including renal disease and Raynaud phenomenon. In rheumatoid arthritis, the most common cause of pulmonary hypertension is interstitial fibrosis with medial thickening and intimal proliferation (Fig. 20-8)[52–54]; vasculitis of small and medium-sized pulmonary arteries as the etiology of pulmonary hypertension has been proposed.[53–55] Pulmonary hypertension occurs frequently in mixed connective tissue disease, or overlap syndrome, with features of systemic lupus erythematosus, scleroderma, and polymyositis.[56] Interstitial fibrosis, medial hypertrophy and intimal fibrosis of medium-sized arteries, fibrin thrombi in small vessels, necrotizing vasculitis, and plexiform lesions have been described.[56–58] Vessel wall immunofluorescence staining for immunoglobulin and complement components has been reported.[57] Rare cases of pulmonary hypertension secondary to obliterative fibrointimal proliferation of small pulmonary arteries in patients with polymyositis[59] and dermatomyositis[60] have been described (see Chaps. 31 and 67).

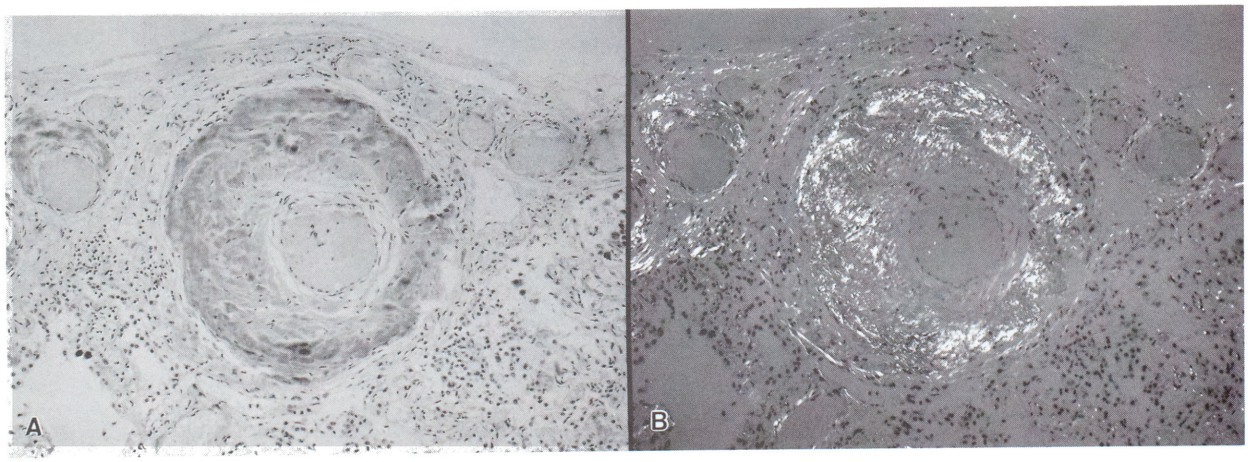

FIGURE 20-11. Primary pulmonary amyloidosis in a 40-year-old man with dyspnea and biventricular heart failure. At autopsy, in addition to amyloidosis of the lungs, there was primary amyloidosis involving the heart, kidneys, and liver. (**A**) A muscular pulmonary artery has amyloid deposits in the media and intima (H & E stain; low magnification.) (**B**) Polarization of (**A**) reveals birefringence characteristic of amyloid (Congo red stain; low magnification.)

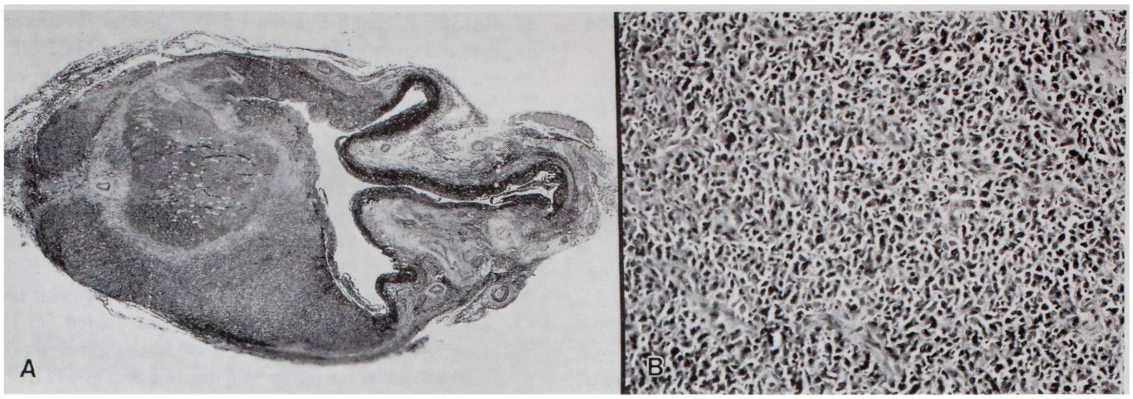

FIGURE 20-12. Primary sarcoma of the pulmonary artery with pulmonary hypertension. A 21-year-old man with right heart failure had a mass in the pulmonary trunk that extended into the right pulmonary artery. (**A**) A whole-mount section of the pulmonary trunk demonstrates a tumor occupying approximately one half of the lumen. (Movat elastic tissue stain; panoramic view.) (**B**) A closer view of the tumor reveals a poorly differentiated sarcoma. (H & E stain; low magnification.)

Pulmonary Fibrosis

Interstitial pulmonary fibrosis is often idiopathic but may be the end-stage manifestation of a variety of disorders, including pneumoconiosis, granulomatous disease, connective tissue disease, or infectious pneumonitis. Pulmonary hypertension is primarily caused by hypoxia-induced vasoconstriction rather than direct loss of pulmonary vasculature. Pulmonary hypertension is common in pulmonary fibrosis in which there is destruction of the alveolar capillary bed by the fibrotic process.[6,15] Muscular pulmonary arteries demonstrate medial hypertrophy and intimal fibrosis, and there may be arterialization and fibrosis of pulmonary veins (Fig. 20-9). In spared areas of the pulmonary parenchyma, vessels are normal, but capillaries are distended and bronchial arteries are enlarged. Pulmonary hypertension is an unusual sequela of silicosis in which vessels within or close to silicotic nodules demonstrate luminal narrowing secondary to medial thickening and intimal fibrosis (Fig. 20-10; see Chap. 31).

Amyloidosis

In the lungs, amyloid deposits may be seen in the tracheobronchial tree, in solitary or multiple nodules, or as diffuse vascular and parenchymal involvement.[61] When clinically present, pulmonary hypertension is typically caused by cardiac amyloidosis resulting in increased left-sided pressures and restrictive cardiomyopathy. Rarely, pulmonary hypertension may be caused by diffuse pulmonary amyloidosis, in the absence of extensive cardiac involvement,[62] and is typically associated with multiple myeloma.[63] A case of pulmonary hypertension from diffuse pulmonary amyloidosis in the setting of familial Mediterranean fever has be reported.[64] Amyloid deposits may be seen in small and medium-sized pulmonary vessels, resulting in luminal compromise (Fig. 20-11), and in the alveolar interstitium (see Chap. 32).[63]

Malignant Neoplasms

Malignant tumors invading or, less frequently, arising in the pulmonary vascular compartment may occasionally produce pulmonary hypertension. Bronchogenic carcinoma compressing main pulmonary arteries,[65] lymphangitic spread of primary and metastatic neoplasms,[66] or metastatic spread along the pulmonary endothelium[67] may lead to obstruction of large and small pulmonary arteries. Sarcomas arising in the main pulmonary arteries may obstruct right ventricular outflow and result in right ventricular failure (Fig. 20-12; see Chaps. 56 and 60).[68] Histologically, fibrosarcoma, fibromyxosarcoma, and leiomyosarcoma have been described.

Miscellaneous Causes of Pulmonary Hypertension

There are various other miscellaneous conditions that may be associated with pulmonary hypertension, including fibrosing mediastinitis,[69,70] which may produce narrowing and obstruction of large pulmonary veins within the inflammatory process mediastinum; a common cause is histoplasmosis with necrotizing granulomas and local scarring, but other cases are idiopathic (see Chap. 74).[69,70] Other rare conditions that can lead to pulmonary hypertension include toxic oil syndrome,[71] oral contraceptive use,[72] sickle cell disease,[73] and human immunodeficiency virus infection (see Chap. 45).[74]

REFERENCES

1. Kloner RA. Pulmonary hypertension and cor pulmonale. Cardiovasc Rev Rep 1991;12:27.
2. Grossman WB, Braunwald E. Pulmonary hypertension in heart disease. In: Braunwald E, ed. Heart disease. Philadelphia: WB Saunders, 1992:790.
3. Lammers RJ, Bloor CM. Edema, emboli and vascular anomalies. In: Dail DH, Hammar SP, eds. Pulmonary pathology. New York: Springer-Verlag, 1988:671.
4. Staub NC. Pulmonary edema. Physiol Rev 1974;54:678.
5. West JB. Pulmonary pathophysiology—the essentials. Baltimore: Williams & Wilkins, 1990:45.
6. Wagenvoort CA, Wagenvoort N. Pathology of pulmonary hypertension. New York: John Wiley & Sons, 1977:177.
7. Grossman W. Profiles in valvular heart disease. In: Grossman W, Bain DS, eds. Cardiac catheterization, angiography and intervention. Philadelphia: Lea & Febiger, 1991:557.

8. Dexter L. Physiologic changes in mitral stenosis. N Engl J Med 1956;829:254.
9. Schlant RC. Altered cardiovascular function of rheumatic heart disease and other acquired valvular disease. In: Hurst JL, Logue RB, eds. The heart. New York: McGraw-Hill, 1978:971.
10. Kay JM, Edwards FR. Ultrastructure of the alveolar-capillary wall in mitral stenosis. J Pathol 1973;111:239.
11. Wagenvoort CA. Morphologic changes in intrapulmonary veins. Hum Pathol 1970;1:205.
12. Kelvin FM, Boone JA, Peretz D. Pulmonary varix. J Can Assoc Radiol 1972;23:227.
13. Wagenvoort CA. Pathology of congestive pulmonary hypertension. Progress in Respiration Research 1975;9:195.
14. Heath D, Edwards JE. Histological changes in the lung in diseases associated with pulmonary venous hypertension. Br J Dis Chest 1959;53:8.
15. Edwards WD. Pathology of pulmonary hypertension. Cardiovasc Clin 1988;18:321.
16. Olsen EGJ. Perivascular fibrosis in lungs in mitral valve disease. Br J Dis Chest 1966;60:129.
17. Tandon HD, Kasturi J. Pulmonary vascular changes associated with isolated mitral stenosis in India. Br Heart J 1975;37:26.
18. Heath D, Whitaker W. The pulmonary vessels in mitral stenosis. J Pathol Bacteriol 1955;70:291.
19. Evans W, Short DS. Pulmonary hypertension in mitral stenosis. Br Heart J 1957;457:19.
20. Davies LG, Goodwin JF, Steiner RE, Van Leuven BD. The clinical and radiological assessment of the pulmonary artery pressure in mitral stenosis. Br Heart J 1953;15:393.
21. Aber CP, Campbell JA, Meecham J. Arterial patterns in mitral stenosis. Br Heart J 1963;25:109.
22. Jordan SC, Hicken P, Watson DA, Heath D, Whitaker W. Pathology of the lungs in mitral stenosis in relation to respiratory function and hemodynamics. Br Heart J 1966;28:101.
23. Henry EW. The small pulmonary vessels in mitral stenosis. Br Heart J 1952;14:406.
24. Goodale F, Sanchez G, Friedlich AL, Scannel JG, Myers GS. Correlation of pulmonary arteriolar resistance with pulmonary vascular changes in patients with mitral stenosis before and after valvulotomy. N Engl J Med 1955;252:979.
25. Thomas WA, Kyo TL, Rabin ER, O'Neal RM. Mitral stenosis and pulmonary arteriosclerosis: correlation of pulmonary arteriosclerosis, right ventricular hypertrophy and thrombo-embolism in autopsied patients who died with mitral stenosis. Arch Pathol 1956;62:257.
26. Wagenvoort CA, Wagenvoort N, Becker AE. The effect of obstructed pulmonary venous blood flow on the development of alternative pathways in the lung. J Pathol 1972;107:21.
27. Uhley HN, Leeds SE, Sampson JJ, Friedman M. Role of pulmonary lymphatics in chronic edema. Circ Res 1962;11:966.
28. Fichera G, Haagerstrand I. Studies on vascular changes in chronic lung congestion. Acta Pathol Microbial Scand 1962;56:377.
29. Burrow B, Kettel LJ, Niden AH, et al. Patterns of cardiovascular dysfunction in chronic obstructive lung disease. N Engl J Med 1972; 286:912.
30. Harvey RM, Ferrer MI, Richards DW, Cournand A. Influence of chronic pulmonary disease on the heart and circulation. Am J Med 1951;10:719.
31. Abraham AS, Cole RB, Bishop JM. Reversal of pulmonary hypertension by prolonged oxygen administration to patients with chronic bronchitis. Circ Res 1968;23:147.
32. Abraham AS, Cole RB, Green ID, et al. Factors contributing to the reversible pulmonary hypertension of patients with acute respiratory failure studied by serial observations during recovery. Circ Res 1969; 24:51.
33. Magee F, Wright JL, Wiggs BR, Pare PD, Hogg JC. Pulmonary vascular structure and function in chronic obstructive pulmonary disease. Thorax 1988;43:183.
34. Hicken P, Heath D, Brewer DB, Whitaker W. The small pulmonary arteries in emphysema. J Pathol Bacteriol 1965;90:107.
35. James WRL, Thomas AJ. Right ventricular hypertrophy and the small pulmonary arteries in chronic lung disease. Br Heart J 1963; 25:583.
36. Wagenvoort CA, Wagenvoort N. Hypoxic pulmonary vascular lesions in man at high altitude and in patients with chronic respiratory disease. Pathol Microbiol 1973;39:276.
37. Mitchell DN, Scadding JG. Sarcoidosis. Am Rev Respir Dis 1974; 110:774.
38. Smith LJ, Lawrence JB, Katzenstein AL. Vascular sarcoidosis: a rare cause of pulmonary hypertension. Am J Med Sci 1983;285:38.
39. Levine BW, Saldana M, Hutter AM. Pulmonary hypertension in sarcoidosis: a case report of a rare but potentially treatable cause. Am Rev Respir Dis 1971;103:413.
40. Barst RJ, Ratner SJ. Sarcoidosis and reactive pulmonary hypertension. Arch Intern Med 1985;145:2112.
41. Lupe HE, Sánchez TG, Marcushamer J, et al. Takayasu's arteritis: clinical study of 107 cases. Am Heart J 1977;93:94.
42. Haas A, Stiehm ER. Takayasu's arteritis presenting as pulmonary hypertension. Am J Dis Child 1986;140:372.
43. Young RH, Mark GJ. Pulmonary vascular changes in scleroderma. Am J Med 1978;64:998.
44. Salerni R, Rodnan GP, Leon DF, Shaver JA. Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). Ann Intern Med 1977;86:394.
45. Yousem SA. The pulmonary pathologic manifestations of the CREST syndrome. Hum Pathol 1990;21:467.
46. Cummings P. Primary pulmonary hypertension and SLE. N Engl J Med 1973;288:1078.
47. Kanemoto N, Sato M, Moriuchi U, et al. An autopsied case of systemic lupus erythematosus with pulmonary hypertension—a case report. Angiology 1988;39:187.
48. Fayemi AO. Pulmonary vascular disease in systemic lupus erythematosus. Am J Clin Pathol 1976;65:284.
49. Nair SS, Askari AD, Popelka CG, Kleinerman JF. Pulmonary hypertension and systemic lupus erythematosus. Arch Intern Med 1980; 140:109.
50. Schwartzberg M, Lieberman DH, Getzoff B, Ehrlich GE. Systemic lupus erythematosus and pulmonary vascular hypertension. Arch Intern Med 1984;144:605.
51. Quismorio FP, Shama O, Koss M, et al. Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. Semin Arthritis Rheum 1984;13:349.
52. Key JM, Banik S. Unexplained pulmonary hypertension with pulmonary arteritis in rheumatoid disease. Br J Dis Chest 1977;71:53.
53. Morikawa J, Kitamura K, Habuchi Y, et al. Pulmonary hypertension in a patient with rheumatoid arthritis. Chest 1988;93:876.
54. Helmers R, Galvin J, Hunninghake GW. Pulmonary manifestations associated with rheumatoid arthritis. Chest 1991;100:235.
55. Young ID, Ford SE, Ford PM. The association of pulmonary hypertension with rheumatoid arthritis. J Rheumatol 1989;16:1266.
56. Alpert MA, Goldberg SH, Singsen BH, et al. Cardiovascular manifestation of mixed connective tissue disease in adults. Circulation 1983;68:1182.
57. Wiener-Kronish JP, Solinger AM, Warnock ML, et al. Severe pulmonary involvement in mixed connective tissue disease. Am Rev Respir Dis 1981;124:499.
58. Ueda N, Mimura K, Maeda H, et al. Mixed connective tissue disease with fatal pulmonary hypertension and a review of the literature. Virchows Arch [A] 1984;404:335.
59. Bunch TW, Tancredi RG, Lie JT. Pulmonary hypertension in polymyositis. Chest 1981;79:105.
60. Caldwell IW, Aitchison JD. Pulmonary hypertension in dermatomyositis. Br Heart J 1956;18:273.
61. Rubinow A, Celli BR, Cohen AS, et al. Localized amyloidosis of the lower respiratory tract. Am Rev Respir Dis 1978;118:603.

62. Shiue ST, McNally DP. Pulmonary hypertension from prominent vascular involvement in diffuse amyloidosis. Arch Intern Med 1988; 148:687.
63. Smith RRL, Hutchins GM, Moore GW, et al. Type and distribution of pulmonary parenchymal and vascular amyloid: correlation with cardiac amyloidosis. Am J Med 1979;60:96.
64. Johnson WJ, Lie JT. Pulmonary hypertension and familial Mediterranean fever: a previously unrecognized association. Mayo Clin Proc 1991;66:919.
65. Gopal AS, Austin JH, Homma S. Reversible pulmonary artery obstruction in a patient with bronchogenic carcinoma. Chest 1992; 101:570.
66. Aiello VD, Mansur AJ, Lopes EA, Bellotti G, Pillegi F. Severe pulmonary hypertension due to carcinomatous lymphangitis of the lungs associated with unsuspected gastric cancer. Am Heart J 1988; 116:197.
67. Wagenvoort C, Morrow GW, Ten Cate HW. Squamous cell carcinoma of the renal pelvis with muco-epidermoid metastasis. J Urol 1961;85:717.
68. Cook DJ, Tanser PH, Dobranowski J, Tuttle RJ. Primary pulmonary artery sarcoma mimicking pulmonary thromboembolism. Can J Cardiol 1988;4:393.
69. Arnett EN, Bacos JM, Macher AM, et al. Fibrosing mediastinitis causing pulmonary arterial hypertension without pulmonary venous hypertension: clinical and necropsy observations. Am J Med 1977;63:634.
70. Berry DF, Buccigrossi D, Peabody J, Peterson KL, Moser KM. Pulmonary vascular occlusion and fibrosing mediastinitis. Chest 1986;89:296.
71. Gomez-Sanchez MA, Saenz de la Calzada C, Gomez-Pajuelo C, et al. Clinical and pathologic manifestations of pulmonary vascular disease in the toxic oil syndrome. J Am Coll Cardiol 1991;18:1539.
72. Kleiger RE, Boxer M, Ingham RE, Harrison DC. Pulmonary hypertension in patients using oral contraceptives: a report of 6 cases. Chest 1976;96:227.
73. Hammond TG, Mosesson MS. Fatal small-bowel necrosis and pulmonary hypertension in sickle cell disease. Arch Intern Med 1989; 149:447.
74. Polos PG, Wolfe D, Harley RA, Strange C, Sahn SA. Pulmonary hypertension and immunodeficiency virus infection: two reports and a review of the literature. Chest 1992;101:474.