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Primary Pulmonary Hypertension and Venoocclusive Disease

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Two forms of pulmonary hypertension are discussed in this chapter: primary pulmonary hypertension (PPH) and pulmonary venoocclusive disease (PVOD). Pathologically, PPH refers to an obstruction of the pulmonary circulation at a precapillary level without underlying cardiac disease, pulmonary parenchymal disease, or an extrapulmonary source of emboli.[1] Although the histologic hallmark of PPH is the plexiform lesion, it should be stressed that the pathology of this condition is variable (Display 23-1).

PVOD, on the other hand, scars and occludes pulmonary veins, resulting in pulmonary outflow obstruction and pulmonary hypertension (see Display 23-1).[2] Although sometimes PVOD has been considered a subcategory of PPH, in this chapter the two entities will be dealt with separately. The distinction between the two is based on important epidemiologic, clinical, and pathologic differences.

A pathologic diagnosis of PPH or PVOD should be confirmed by hemodynamic data whenever feasible, and in either case other causes of pulmonary hypertension should be strictly ruled out (Display 23-2). The cause of both diseases is unknown; they are incurable and eventually fatal.

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PRIMARY PULMONARY HYPERTENSION

Definitions

As is the case with any disease of unknown etiology and nonspecific histopathologic features, the definition of PPH is not straightforward. "Primary" implies idiopathic *arterial* hypertension and should exclude patients with cirrhosis and collagen-vascular disease, two entities that predispose to a clinical and pathologic syndrome identical to PPH. Most patients with PPH are young women, and there is often a family history.[3]

Etiology

It has been proposed that the initiating event in PPH is an endothelial injury of unknown cause that precipitates vasoconstriction, progressing to medial thickening, cellular intimal proliferation, concentric luminal fibroelastosis, fibrinoid necrosis, and, finally, plexiform and dilatation lesions.[4]

Exogenous agents have been implicated in the pathogenesis of PPH, such as patients who have ingested aminorex fumarate,[5] a small percentage of patients with toxic oil syndrome,[6,7] and animals ingesting seeds or extracts from *Crotalaria spectabilis*.[8,9] It seems likely, therefore, that a diverse group of chemical compounds can cause the initial endothelial injury in PPH.

DISPLAY 23-1. A COMPARISON OF THE HISTOLOGIC FEATURES OF PRIMARY PULMONARY HYPERTENSION AND PULMONARY VENOOCCLUSIVE DISEASE

Primary Pulmonary Hypertension

Plexiform type
Plexiform lesions always present; other arterial changes variably present

Primary medial or intimal type
Medial or intimal thickening present; other arterial changes absent

Thrombotic type
Thrombotic lesions present; plexiform or dilatation lesions and arteritis absent

Other rare forms
Isolated arteritis, normal arteries, medial dysplasia of pulmonary arteries

Pulmonary Venoocclusive Disease

Veins obliterated by venous intimal thickening and thrombosis; plexiform or dilatation lesions absent; other arterial changes variably seen

Capillary proliferation into veins or interlobular septa (*i.e.*, capillary hemangiomatosis)

Adapted from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:269.

DISPLAY 23-2. SECONDARY PULMONARY HYPERTENSION, UNDERLYING CONDITIONS

Histologically Identical to Primary Pulmonary Hypertension, Plexogenic Type

Congenital cardiac left-to-right shunts
Collagen-vascular disease or portal hypertension*

Histologically Resembles Primary Pulmonary Hypertension in Primary Medial or Intimal Thickening

Pulmonary parenchymal disease

Histologically Similar to Primary Pulmonary Hypertension, Thrombotic Type

Thromboembolic disease
Collagen-vascular disease or portal hypertension*

Histologically Resembles Venoocclusive Disease but Lacks Venous Recanalization and Obstruction

Mitral stenosis
Mediastinal fibrosis

Specific Histologic Entities that Cause Secondary Pulmonary Hypertension

Precapillary
Embolic carcinoma
Takayasu disease
Amyloidosis
Schistosomiasis
Foreign-body granulomas (*e.g.*, as in drug addicts)

Postcapillary
Sarcoidosis involving veins
Granulomatous venulitis

** Pulmonary hypertension in patients with collagen-vascular disease and portal hypertension has been variably considered primary or secondary.*

From Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:269.

Lack of hepatic detoxification in patients with portosystemic shunts with or without liver disease causes an increased risk of pulmonary arterial hypertension with plexogenic as well as thrombotic lesions.[10–12] Pulmonary arteriolar spasm may also result from the increased blood volume commonly seen in cirrhotics with portal hypertension.[13]

An immunologic role in the endothelial injury in PPH is also supported by the observation of patients with collagen-vascular disease without evidence of pulmonary fibrosis, who develop pulmonary arterial hypertension with or without plexiform lesions.[14–20] Up to 30% of patients with PPH have antinuclear antibodies in their serum,[3,11] and patients with some forms of autoimmune disease, especially CREST (*i.e.*, calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia) syndrome and mixed connective tissue disease, are likely to develop pulmonary hypertension.[4,15,16]

The role of *in situ* thrombosis in the pathogenesis of PPH is unclear; however, thrombi are frequently seen in familial PPH in which there is no suspicion of secondary thromboembolism.[4]

Clinical Features

There is a female predominance of at least 2 : 1 in adults[3]; however, no gender predilection is seen in children.[21,22] Dyspnea is usually the most common presenting symptom, followed by fatigue and syncope, chest pain, and, rarely, hemoptysis.[3] Chest radiographs are usually normal, but right ventricular hypertrophy, dilated pulmonary trunk, and decreased peripheral vascular markings may be present. The diagnosis is confirmed by right heart catheterization and measurement of pulmonary artery pressures.

The mean survival in PPH is somewhere between 3 and 5 years after diagnosis,[4] and various forms of treatment, including oxygen, vasodilators, and anticoagulants, have been tried with limited success.[23,24] A subset of patients with PPH die suddenly of cardiac arrhythmias, presumably of a nature similar to that of arrhythmias causing syncopal attacks. In a series of 56 patients with PPH, 2 deaths occurred without any previous history of pulmonary or cardiovascular disease.[4] It is difficult to estimate the percentage of cases that are familial; the mode of inheritance is either autosomal recessive or dominant.[25]

There are three categories of patients with collagen-vascular diseases and elevated pulmonary artery pressures. One group is composed of patients with typical PPH but no clinical stigmata of specific collagen-vascular diseases, with the possible exception of Raynaud phenomenon and positive antinuclear antibodies; up to 30% of cases of PPH fit this category.[3] The second category is a group of patients with known collagen-vascular disease, usually scleroderma or mixed connective tissue disorder, who subsequently develop the syndrome of PPH without pulmonary interstitial fibrosis radiologically, clinically, or pathologically.[15,16] A third group of patients develops severe pulmonary scarring as a result of collagen-vascular disease; in the absence of typical plexiform lesions,[14,20] pulmonary hypertension is best considered secondary to destruction of the pulmonary vascular bed.

In addition to scleroderma and mixed connective tissue disor-

der, pulmonary hypertension has been documented in patients with systemic lupus erythematosus,[17] rheumatoid arthritis,[18] and polymyositis.[19]

The presence of a portacaval shunt predisposes to pulmonary hypertension. A review of cases at The Armed Forces Institute of Pathology revealed that 12 of 56 cases with PPH had preexisting portal hypertension, usually as a result of cirrhosis.[4] In addition, other types of portal shunts have been noted, including surgical LeVeen shunts, nodular regenerative hyperplasia, and idiopathic portal vein thrombosis.[4,10] The age and gender of these patients differ from those of typical patients with PPH and reflect the underlying liver condition that, in the case of cirrhosis, is often seen in elderly males. The clinical symptoms and pathologic features are identical to those of PPH, however, but tend to occur years after the diagnosis of cirrhosis is made.

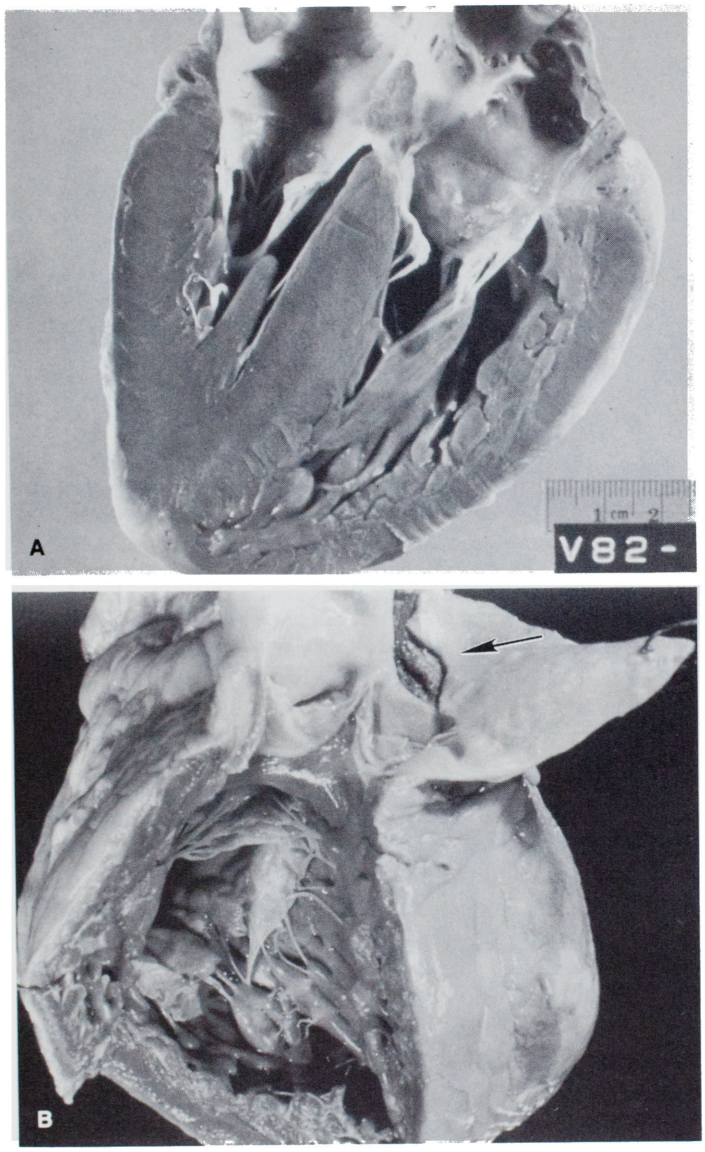

FIGURE 23-1. Gross heart changes in cases of primary pulmonary hypertension (PPH). (**A**) Note the marked thickening of the right ventricular wall of the heart of a young women who died of PPH, plexogenic type. (**B**) A 58-year-old man had right-sided cardiac failure and severe PPH; soon after catheterization, he died suddenly because of rupture and dissection of the pulmonary artery (*arrow*). Note atherosclerosis of the pulmonary trunk, which is indicative of severe pulmonary hypertension.

Pathologic Features

The gross pathology of PPH is limited to the pulmonary arteries and right heart.[26,27] Typically, there is right ventricular hypertrophy (Fig. 23-1), and the pulmonary trunk and main pulmonary arteries may be dilated and atherosclerotic. Occasionally, the pulmonary artery can rupture (see Fig. 23-1*B*) and is a rare cause of sudden death.[28]

Although the pathologic features of PPH are variable (see Display 23-1), the hallmark is the plexiform lesion, which typically occurs at branch points of medium-sized pulmonary arteries (Figs. 23-2 and 23-3). Pathologically, there is medial destruction of the artery, granulationlike endothelial proliferation in the lumen extending into the adventitia (*i.e.*, glomeruloid or angiomatoid lesions; see Fig. 23-3*A*), and often small areas of necrosis of the vessel wall. The latter two features are especially important in differentiating plexiform lesions from organized thrombi, and serial sections may be required to demonstrate the diagnostic features. The diagnosis of all forms of pulmonary hypertension is greatly facilitated by the use of elastic stains, which outline the elastic laminae that are invariably destroyed in areas of plexiform change.

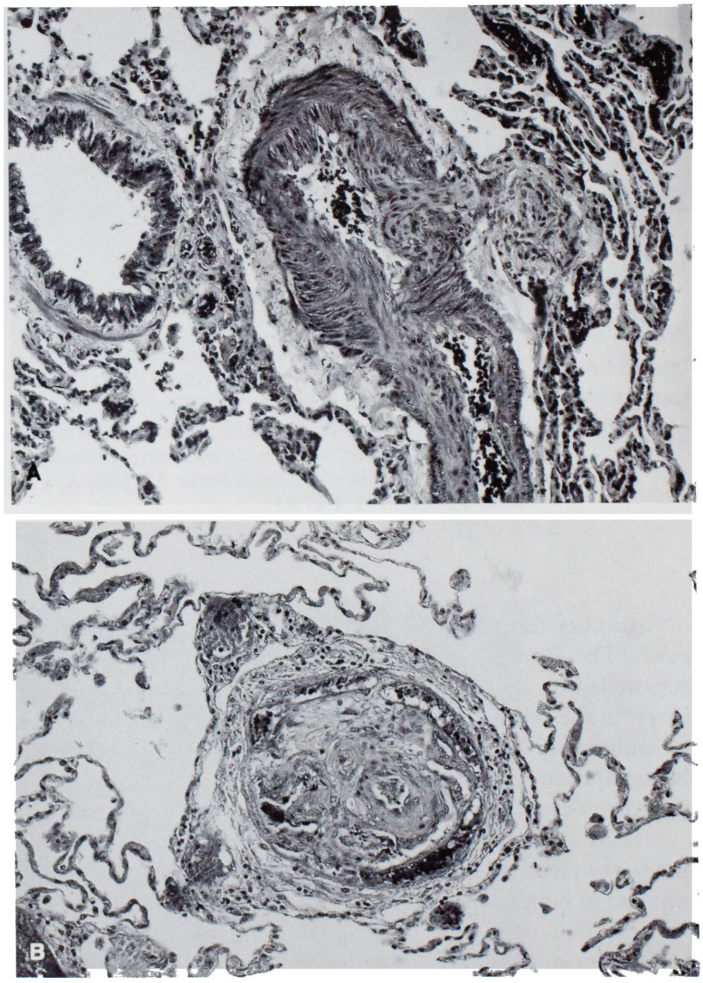

FIGURE 23-2. (**A**) A plexiform lesion at a branching point causes destruction of the arterial media with extension of the vascular proliferation into the adjacent lung parenchyma. (**B**) Occasionally, plexiform lesions superficially resemble an organized thrombus; however, there is no vessel wall. Deeper sections revealed that the lesion was attached to a pulmonary artery. (H & E stain; low magnifications.)

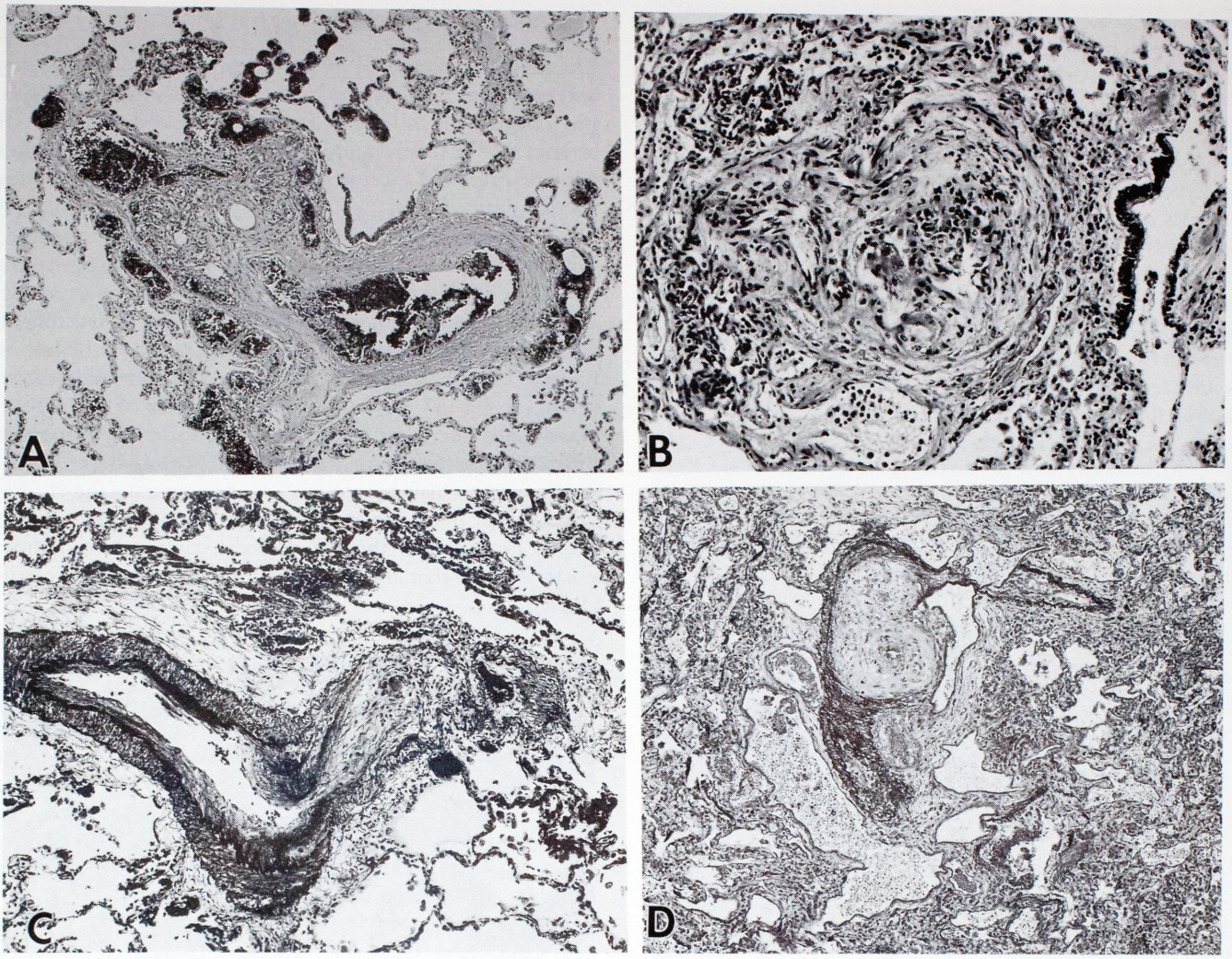

FIGURE 23-3. Plexiform-dilatation lesions. (**A**) A typical plexiform structure is surrounded by a dilatation lesion consisting of enlarged, engorged, thin-walled vessels. (H & E stain; low magnification.) (**B**) A higher-power view of a plexiform lesion. (H & E stain; intermediate magnification.) (**C**) Elastic stain demonstrates obvious medial destruction at the site of a plexiform lesion. (Movat elastic tissue stain; low magnification.) (**D**) A dilatation lesion surrounds an artery with severe concentric fibrosis; deeper sections revealed plexiform lesion. (Mavat elastic tissue stain; low magnification; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:273.)

Another feature of the plexiform structure is the dilatation lesion. The latter is an area of widening and engorgement of thin-walled vessels surrounding the plexiform lesion proper (Fig. 23-4). In the original grading system that was applied to secondary pulmonary hypertension in patients with congenital heart disease and cardiac shunts, both plexiform and dilatation lesions were considered an advanced stage of pulmonary hypertension.[29]

There are two other major pathologic changes that, in addition to the plexiform-dilatation lesion, represent the morphologic response of pulmonary arteries to severe elevated pulmonary arterial pressures: concentric intimal fibroelastosis (*i.e.,* onion-skin configuration) of muscular arteries and arteritis. Together, these four histologic changes are considered irreversible in the evolution of PPH as well as in secondary pulmonary hypertension, particularly in pediatric patients with congenital heart malformations.[30] Additionally, they are usually *not* present in secondary causes of pulmonary arterial hypertension, such as pulmonary parenchymal disease and mitral valve stenosis. In general, intimal fibroelastosis and the plexiform lesion are found concomitantly in lungs with PPH; significant degrees of arteritis are unusual.

Concentric laminar fibroelastosis represents splitting and reduplication of elastic laminae within the intima of pulmonary arteries and is best seen with elastic stains (Fig. 23-5*A*, *B*). Intimal thickening without elastic deposition is not considered as specific and is often present in organized thromboemboli. Arteritis was originally considered an end stage of severe pulmonary hypertension;[29] however, small areas of medial necrosis and arteritis often accompany plexiform lesions, and arteritis is now considered a precursor of the plexiform change (Fig. 23-6*A–D*).[27] Rarely, arteritis can be the only histologic finding in patients with PPH.[31]

There are several nonspecific changes in pulmonary arteries that often accompany plexiform lesions and occasionally are the only morphologic manifestations of the disease (see Display 23-1). These include medial hypertrophy (Fig. 23-7*A–C*) and intimal thickening (Fig. 23-8*A–C*) of muscular pulmonary arteries and arterioles. The normal medial thickness of pulmonary arteries is

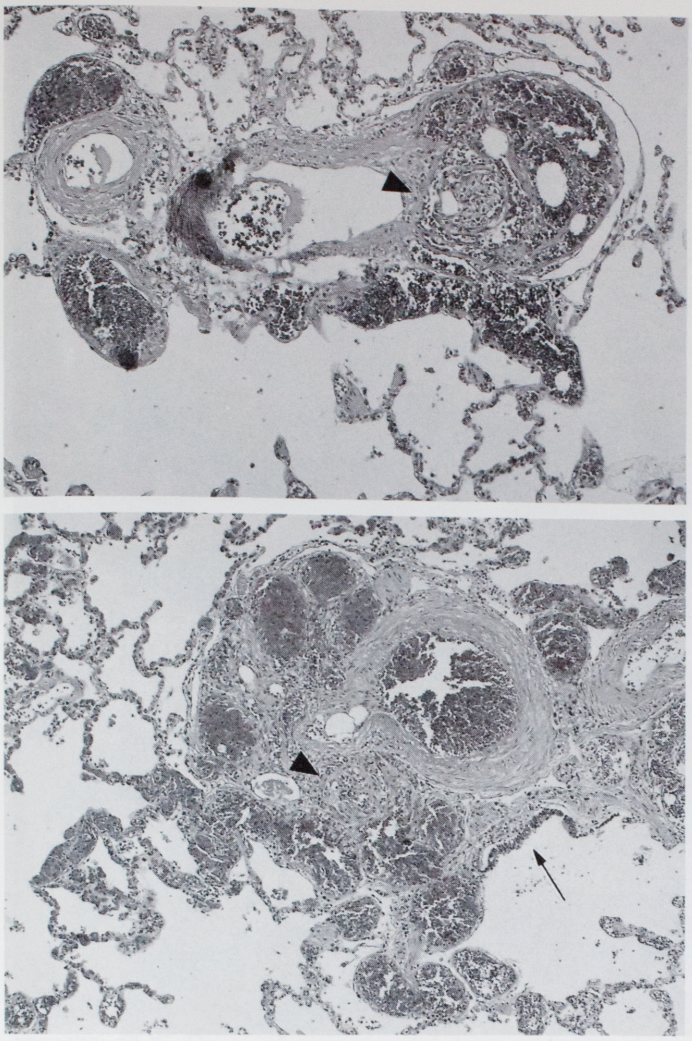

FIGURE 23-4. Dilatation lesions often surround and obscure plexiform lesions (*arrowheads*). In these examples, the most striking finding is vascular dilatation around the affected pulmonary artery. A portion of the adjacent airway is visible (*arrow*). (H & E stain; low magnification.)

less than 10% of the vessel diameter; greater than 15% is clearly abnormal. Intimal thickening can be predominantly cellular in early stages, or acellular and hyaline in later stages. The etiology of some intimal lesions is most likely luminal thrombosis, especially when eccentric.

Some degree of luminal thrombosis in varying stages of organization is not uncommon in PPH (see Display 23-1).[4] Some cases of clinical PPH will demonstrate luminal thrombosis and few other pathologic changes.[4,5] Such cases probably represent the thrombotic form of PPH rather than occult thromboembolism of the pulmonary circulation. Finally, rare cases of clinical PPH may show normal pulmonary vessels altogether.

Differential Diagnosis and Other Morphologic Findings

Plexiform lesions and concentric fibroelastosis are best seen in PPH or congenital heart disease with shunts. Reports of plexiform lesions in secondary pulmonary hypertension due to schistosomiasis have been questioned (see Chap. 22). Other changes, such as medial hypertrophy, intimal thickening, and thromboses, can be seen in chronic heart failure and pulmonary parenchymal diseases causing secondary pulmonary hypertension. Acellular intimal thickening of arteries and veins is a common finding in the elderly and should not be considered diagnostic of pulmonary hypertension (see Fig. 23-8*A–C*). In addition, intimal arterial thickening can be seen in cases of pulmonary parenchymal disease without pulmonary hypertension.

Several pathologic processes cause pulmonary hypertension that clinically mimics PPH. They include medial dysplasia of pulmonary arteries,[32] amyloidosis of pulmonary vessels,[33] and carcinomatous emboli.[34]

Ultrastructure and Immunohistochemistry

Ultrastructural and immunohistochemical studies have contributed to the understanding of the pathogenesis of PPH. Alterations in the cellular cytoskeleton and migration of medial smooth muscle cells have been described; increments in endothelial endo-

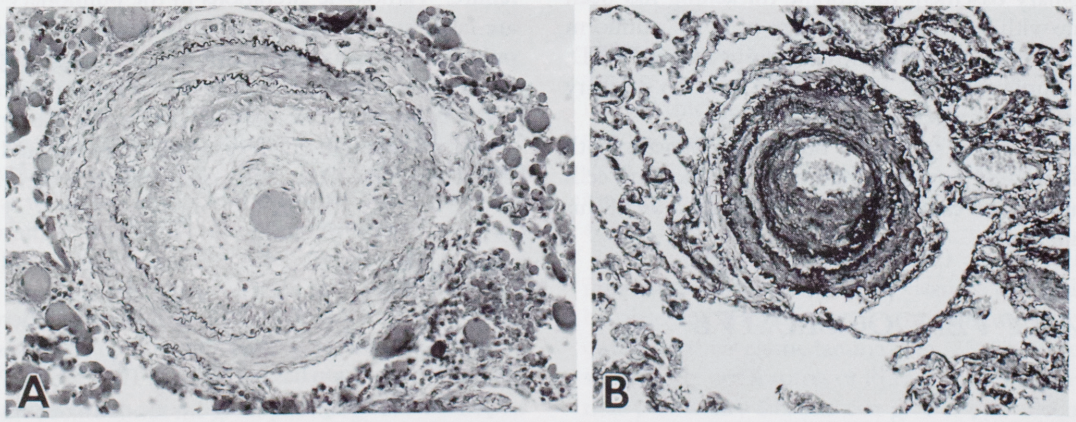

FIGURE 23-5. Concentric fibroelastosis is a relatively specific marker of pulmonary arterial hypertension in either primary or congenital cardiac left-to-right shunts. (**A**) Acellular concentric intimal fibrosis. (**B**) Note duplication of the internal elastic lamina, or fibroelastosis (*i.e.*, onion skinning). (Elastic van Gieson stain; low magnification; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:272.)

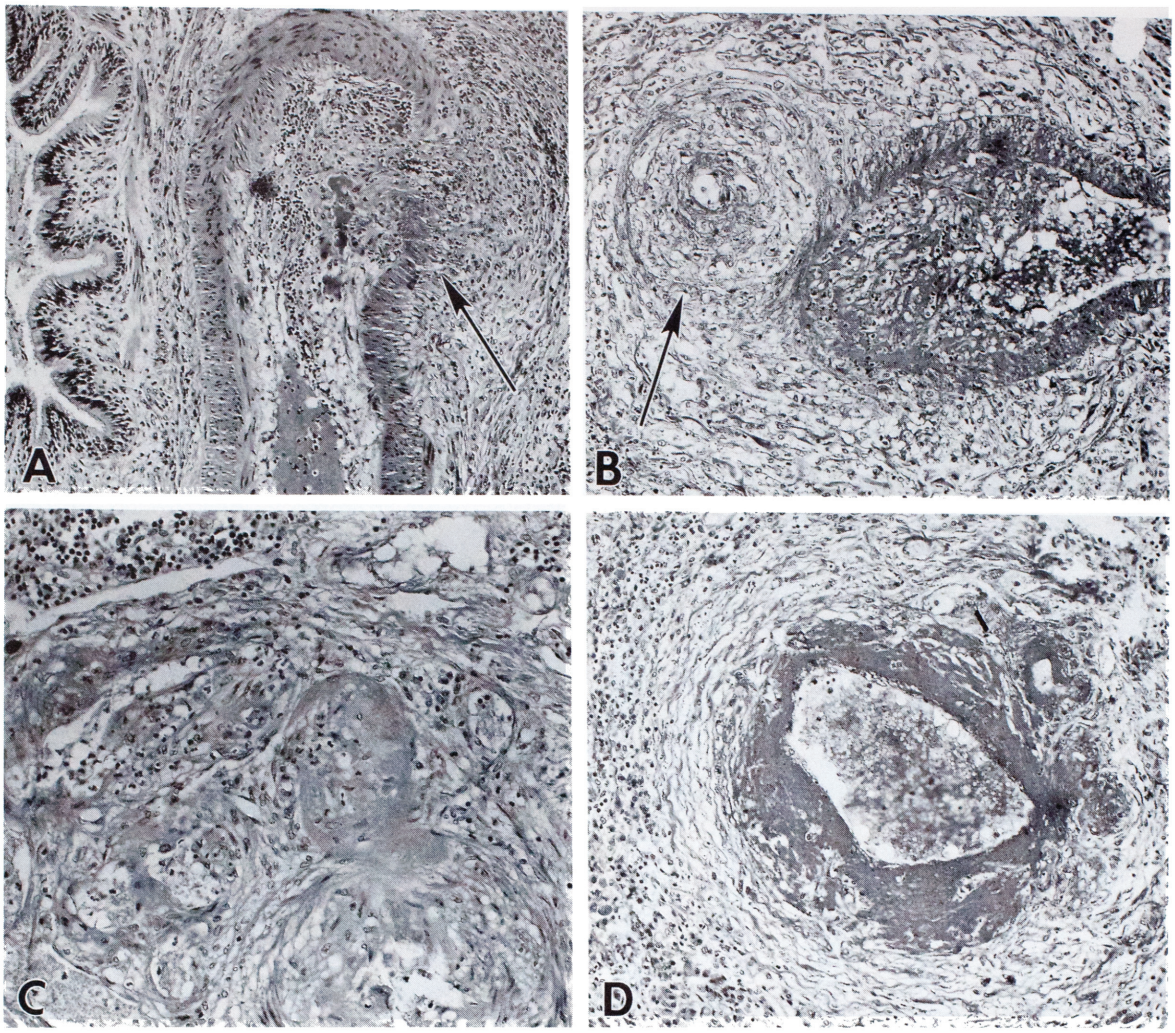

FIGURE 23-6. Stages of arteritis with the formation of plexiform lesions. (**A**) Medial destruction with early intimal proliferation and neovascularization (*arrow*). (**B**) Arteritis with an adjoining plexiformlike lesion (*arrow*). (**C**) A well-formed plexiform lesion showing fibrinoid necrosis, angiomatoid lesions, and intimal proliferation. (**D**) Necrotizing fibrinoid arteritis may occasionally occur without plexiform lesions; in this case, plexiform lesions were present in other areas. (H & E stain; low magnifications; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:273.)

plasmic reticulum and surface microvilli have also been noted.[35–38] The type of capillary basement membrane thickening has been found to correlate with the histologic subtype of PPH[39]; uniform thickening of the capillary basement membrane was seen in PVOD, thickening with duplication was seen in PPH, and no capillary changes were detected in thromboembolic disease.

Immunohistochemical studies of bronchi in patients with PPH have demonstrated increased numbers of endocrine cells containing bombesin and calcitonin.[40,41] The significance of this change is still unknown.

PULMONARY VENOOCCLUSIVE DISEASE

Definitions

PVOD is a primary sclerosing disease of pulmonary veins that causes symptoms of pulmonary venous hypertension. The diagnosis excludes secondary causes of venous hypertension, such as sclerosing mediastinitis, mitral valve disease, or severe left heart failure.[2] Pathologic alterations in the pulmonary veins of PVOD are fairly specific and are usually absent in secondary causes of pulmonary venous hypertension. The veins in PVOD show thickening of the adventitial wall, occlusive intimal lesions, thrombosis, and recanalization, sometimes producing the image of a vessel within a vessel. The changes in secondary venous hypertension are less severe, and recanalized lesions are not seen.

Etiology

The pathogenesis of PVOD is unknown. There is no familial component, and no association with collagen-vascular disease or portal hypertension has been noted. Two cases of PVOD have been reported following renal[42] and bone marrow transplantation.[43] A viral etiology has also been suggested.[44] The association of PVOD with chemotherapeutic agents administered for cancer has been recognized in a subset of older patients, a subject discussed and illustrated in Chapter 16.

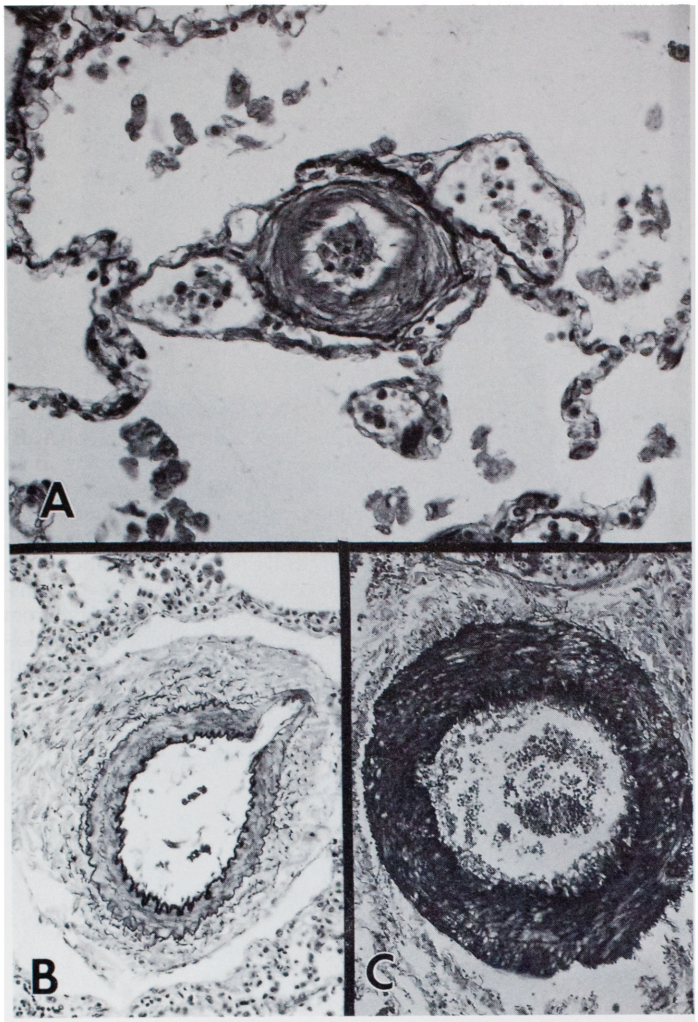

FIGURE 23-7. Nonspecific arterial medial changes. (**A**) Muscularization of intraacinar arteriole in a patient with primary pulmonary hypertension (PPH), plexiform type. (Movat elastic tissue stain; intermediate magnification.) (**B**) Mild medial hypertrophy in a patient with an unusual case of PPH in which this was the only histologic finding. (**C**) Severe medial hypertrophy in a patient with PPH, plexiform type. Any of these changes can also be seen in cardiac or pulmonary parenchymal disease. (Movat elastic tissue stain; low magnifications; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991; 4:270.)

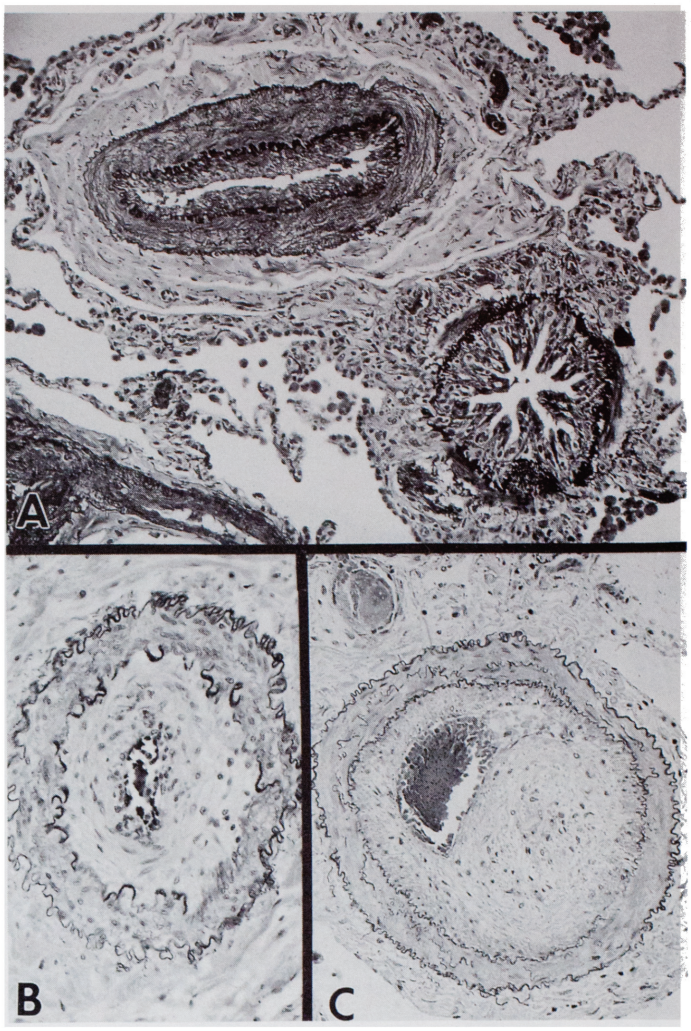

FIGURE 23-8. Spectrum of intimal arterial changes. (**A**) Mild intimal and medial thickening in a patient with venoocclusive disease. The artery has a diameter similar to that of the accompanying airway. (**B**) Concentric intimal thickening in a patient with venoocclusive disease. (**C**) Eccentric cellular intimal thickening, probably post-thrombotic, in a patient with primary pulmonary hypertension. (Movat elastic tissue stain; low magnifications; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:272.

Clinical Features

In contrast to PPH, there is a male-to-female predominance of nearly 2:1.[2] The mean age at presentation is approximately 25 years, slightly younger than that for PPH. The clinical symptoms are quite similar to those of PPH, although hemoptysis is somewhat more common in PVOD. Nodular infiltrates have been described on chest radiographs,[45] but they are generally not seen in PPH. Only one case has been reported as a sudden death.[46]

Pathologic Features

There is nothing specific about the gross pathology of PVOD. The histologic features are venous sclerosis[2,47–49] with thickening of the adventitial wall, occlusive luminal organization, thrombosis, and recanalization (Fig. 23-9). The recognition of these features depends on the ability to identify pulmonary veins, which can be obscured by septal fibrosis (Fig. 23-10). In addition, pulmonary arteries in PVOD may show marked medial hypertrophy as well as intimal thickening. The pathologist may overlook the diagnostic venous changes because of their focality, and a misdiagnosis of PPH without plexiform structures may then be rendered. Plexiform lesions, arteritis, and concentric laminar fibroelastosis are absent in PVOD (Fig. 23-11).

The diagnosis of both PVOD and PPH is difficult, if not impossible, without the use of elastic stains. Pulmonary veins can be obscured within scarred septa and are made visible only by outlining their elastic lamina (Fig. 23-12). Interstitial and septal scarring are not features of PPH, and it is important to remember that pulmonary fibrosis can give rise to secondary intimal and medial thickening in pulmonary arteries. In PVOD, however, septal scarring can simulate the appearance of pulmonary fibrosis. In these cases, diagnostic features of venous recanalization must be sought on elastic stains before the diagnosis can be established.

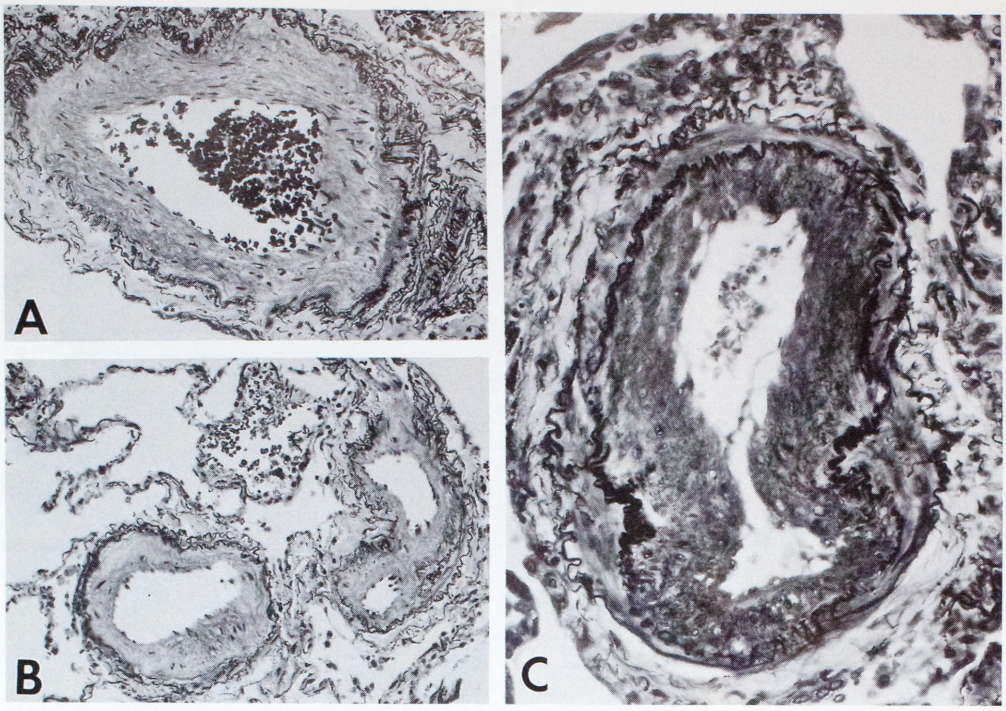

FIGURE 23-9. Nonspecific intimal changes in both veins and arteries. (**A, B**) Acellular venous intimal thickening in an 84-year-old man without significant cardiopulmonary disease. (Movat elastic tissue stain; low magnifications.) (**C**) Moderate arterial intimal thickening in a patient with congestive heart failure. (Movat elastic tissue stain; intermediate magnification; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:272.)

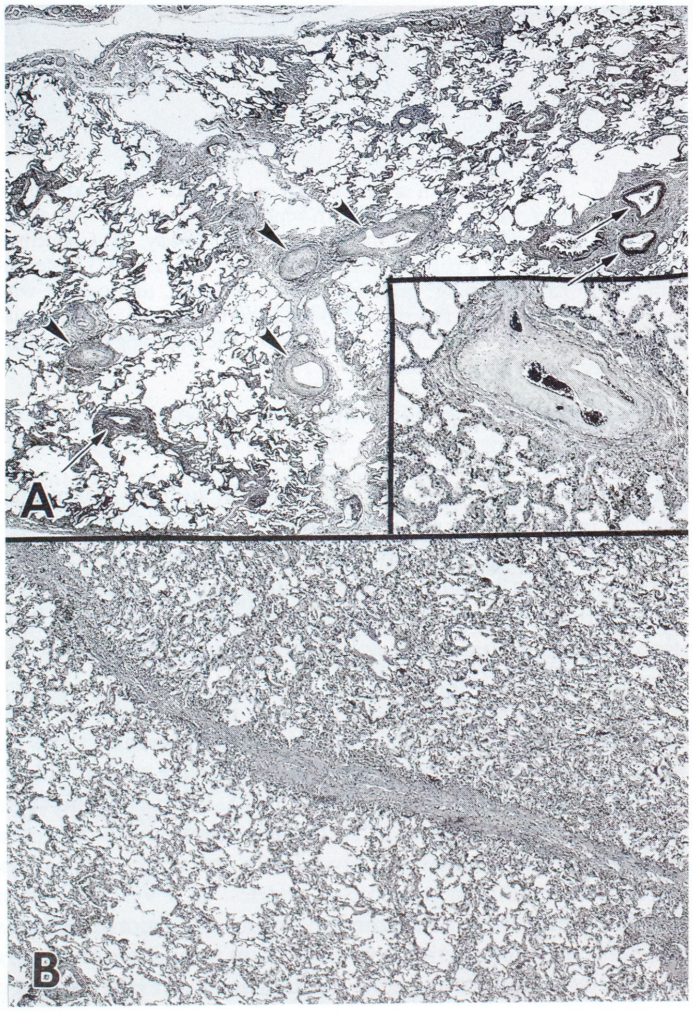

FIGURE 23-10. In veno-occlusive disease, examination of low-power specimens is especially important. (**A**) The veins (*arrowheads*), which are variably fibrotic, course in the edematous interlobular septa. Recanalization of the vein (*insert*) is pathognomonic of venoocclusive disease. Arteries (*arrows*) can also be thickened, but usually, as in this case, changes are mild. (Movat elastic tissue stain; low magnification.) (**B**) Septal fibrosis can be prominent in venoocclusive disease and may obscure veins and lymphatics. (H & E stain; low magnification; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:274.)

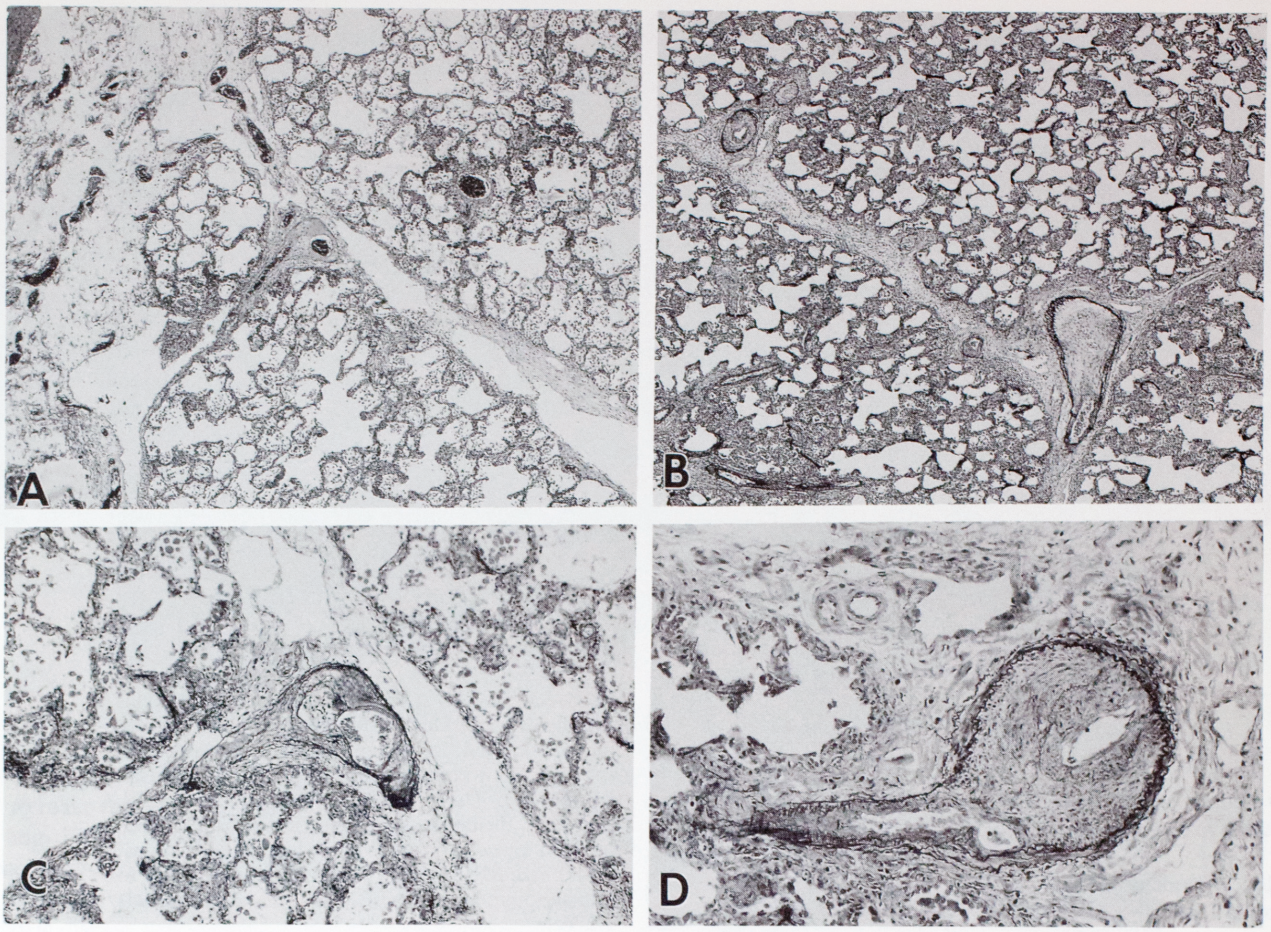

FIGURE 23-11. The degree and extent of venous sclerosis in veno-occlusive disease can vary. (**A**) Septal edema, lymphatic dilatation, and focal venous obliteration. (H & E stain; low magnification.) (**B**) Septal fibrosis with pronounced venous obliteration. (Movat elastic tissue stain; low magnification.) (**C**) A higher magnification of (**A**). (Movat elastic tissue stain; intermediate magnification.) (**D**) Pulmonary vein showing fibrous obliteration of lumen with luminal channels. This extent of venous obstruction is not seen in secondary venous outflow obstruction. Prominent elastic lamina simulates an artery, but the location is wrong for the latter. (Movat elastic tissue stain; intermediate magnification; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:275.)

Nonspecific changes of secondary pulmonary venous hypertension are present in cases of PVOD as well. These are similar to the histologic appearance of the lungs in cases of mitral stenosis. There is marked hemosiderosis, pulmonary congestion, nonspecific arterial thickening, and, occasionally, osseous metaplasia (Fig. 23-13). Previously, the term "pulmonary venous hypertension" was applied to cases of idiopathic pulmonary congestion in the absence of primary venous obstruction. Some, if not all, of these cases most likely represent PVOD in which the diagnostic features were not appreciated or sampled. We have seen cases of occult mitral stenosis in which pulmonary biopsy was performed to evaluate pulmonary interstitial disease. The diagnosis of mitral stenosis was made by echocardiography and angiography after the pathologist suggested the diagnosis of pulmonary venous obstruction. Such cases emphasize the need for the clinical history and the hemodynamic evaluation in the diagnosis of pulmonary vascular disease.

Capillary Hemangiomatosis

Other changes common in venoocclusive disease include the pseudoangiomatous features: vascular proliferation in interlobular septa, and capillary engorgement and proliferation. In some cases, the term "capillary hemangiomatosis"[50–55] is applied when these changes predominate. Features of capillary hemangiomatosis include the presence of double capillaries on both sides of alveolar walls, back-to-back capillaries, capillary invasion of vessels and airways, and abrupt transition from abnormal to normal capillaries (Fig. 23-14).

It has been argued that coexistent venous changes of PVOD in cases of capillary hemangiomatosis are secondary to ingrowth of capillaries; however, only 7 of 25 cases of PVOD seen at The Armed Forces Institute of Pathology had capillary hemangiomatosis with capillary ingrowth into larger vessels. Also, it should be noted that the term "capillary hemangiomatosis" was originally used to describe a neoplastic proliferation of atypical capillary channels causing pulmonary hypertension.[54]

What is the role of the pathologist in the diagnosis of pulmonary hypertension due to PPH or PVOD?

> There are some benefits in establishing a specific histopathologic diagnosis. In heart-lung transplant recipients, establishing the recurrence of PPH and PVOD is essential. Because of its known familiar nature, it is also important

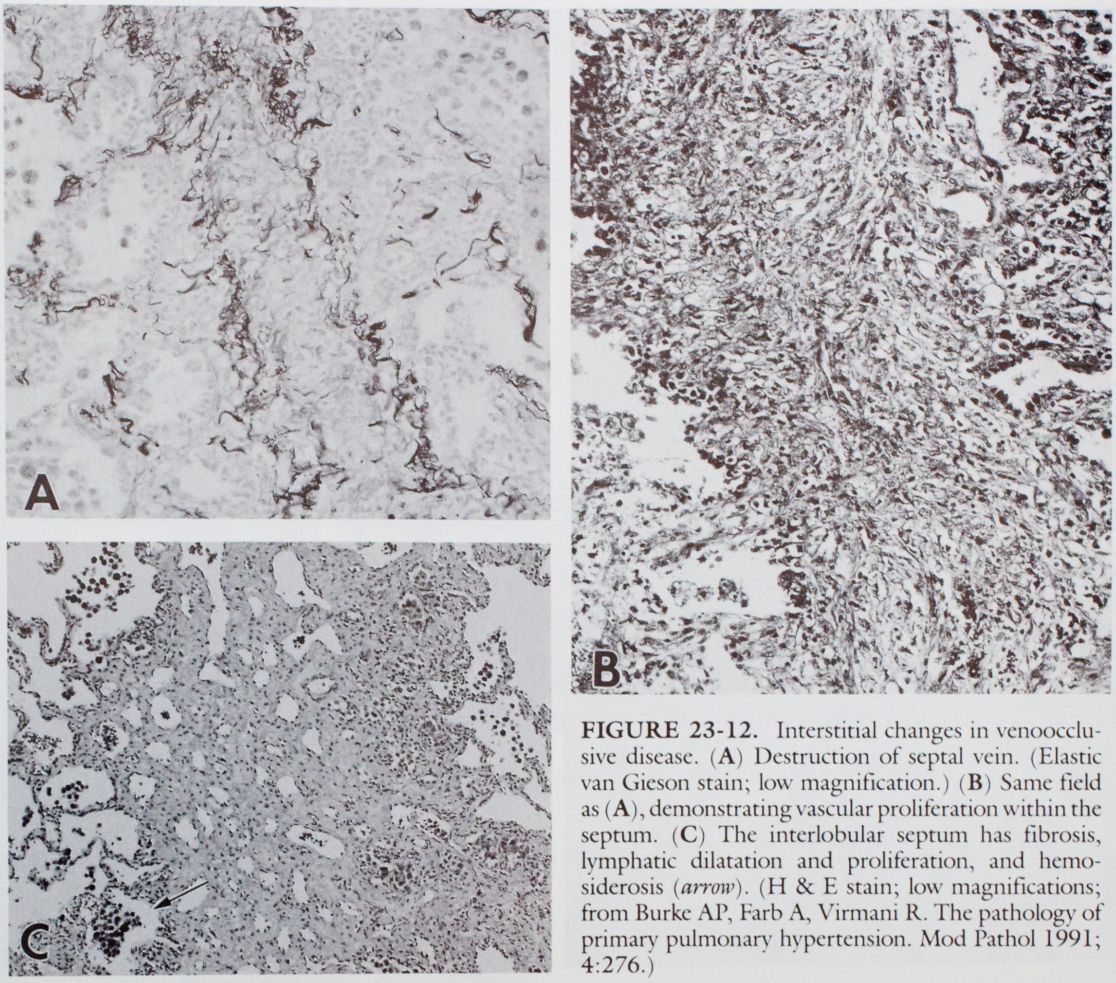

FIGURE 23-12. Interstitial changes in venoocclusive disease. (**A**) Destruction of septal vein. (Elastic van Gieson stain; low magnification.) (**B**) Same field as (**A**), demonstrating vascular proliferation within the septum. (**C**) The interlobular septum has fibrosis, lymphatic dilatation and proliferation, and hemosiderosis (*arrow*). (H & E stain; low magnifications; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991; 4:276.)

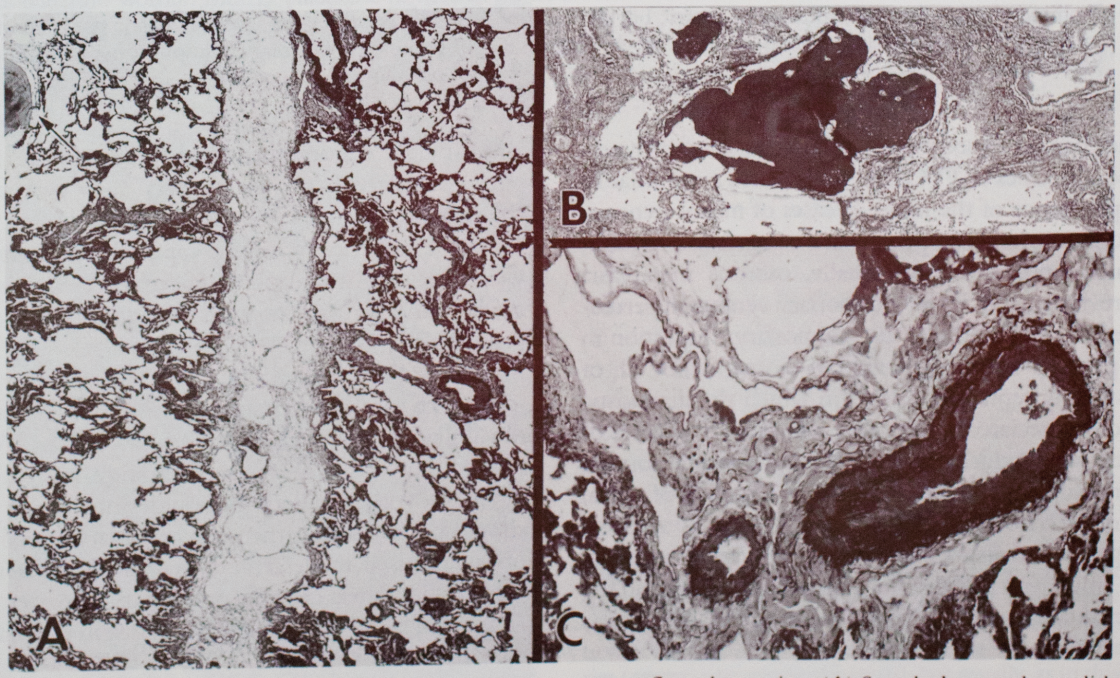

FIGURE 23-13. Nonspecific changes in venous pulmonary outflow obstruction. (**A**) Septal edema and osteolith (*arrow*) occur in a patient with mitral stenosis. (Movat elastic tissue stain; low magnification.) (**B**) An osteolith from a patient with venoocclusive disease. (H & E stain; low magnification.) (**C**) Venous arterialization and sclerosis occur in a patient with mitral stenosis; note the adjacent dilated lymphatics. (Movat elastic tissue stain; low magnification; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:275.)

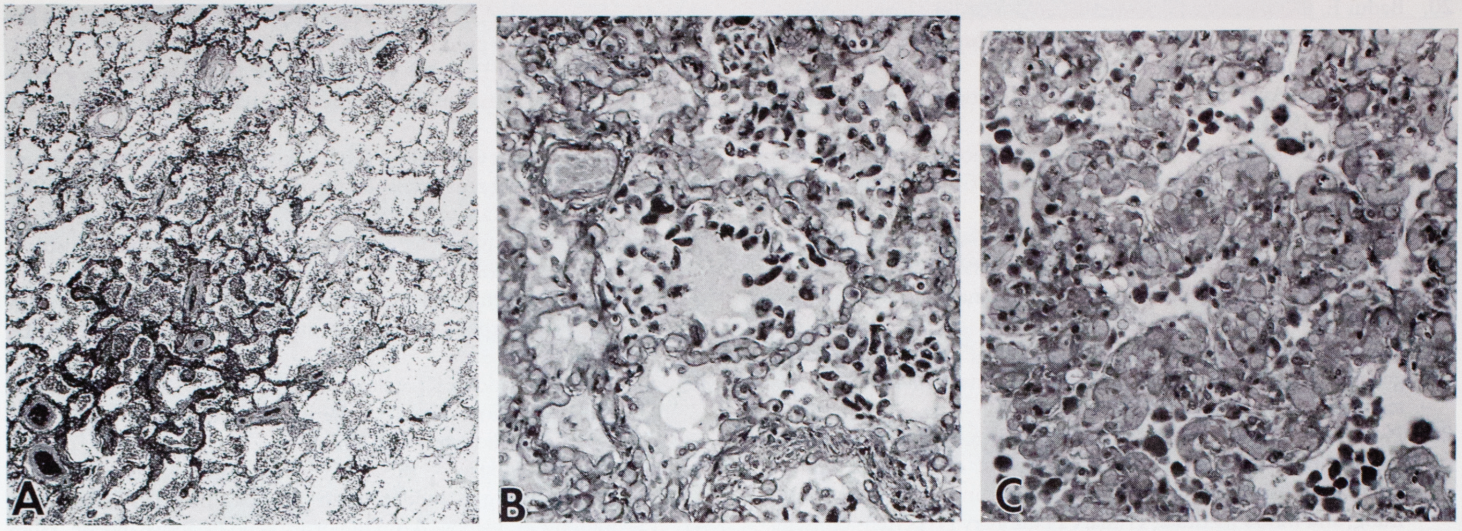

FIGURE 23-14. Capillary hemangiomatosis in venoocclusive disease. (**A**) One feature of capillary hemangiomatosis is focality. (H & E stain; low magnification.) (**B**) Capillary engorgement is common in venoocclusive disease and secondary venous obstruction and is not diagnostic of capillary hemangiomatosis. (H & E stain; intermediate magnification.) (**C**) Capillary proliferation on both sides of alveolar walls is diagnostic for capillary hemangiomatosis; this finding has been seen in otherwise typical venoocclusive disease. (H & E stain; intermediate magnification; from Burke AP, Farb A, Virmani R. The pathology of primary pulmonary hypertension. Mod Pathol 1991;4:277.)

to make the specific diagnosis of PPH for family counseling. PVOD has no familial component.

Secondary causes of pulmonary hypertension, such as chronic obstructive lung disease, interstitial lung disease, and cardiac disease, can usually be excluded clinically without the need for biopsy. However, there are less common causes of secondary pulmonary hypertension, such as thromboemboli,[56] amyloidosis,[33] talc granulomas,[57] sarcoidosis,[58] tumor emboli,[34] and granulomatous venulitis,[59] that can be diagnosed on biopsy material. In addition, in some cases, the clinical presentation of PVOD can resemble interstitial lung disease, and only the biopsy will help in elucidating this problem.

PPH[60] and, less commonly, PVOD can cause sudden death[46] with or without a previous history of syncope. Only the pathologist or forensic pathologist is able to establish the presence of pulmonary hypertension and the cause of death.

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