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# 22

# Thromboembolic Pulmonary Hypertension, Intravenous Drug Addiction, and Rare Forms of Pulmonary Embolization

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Pulmonary thromboembolism is responsible for 300,000 hospitalizations and 50,000 deaths, per year, in the United States.[1–3] The pathology of the acute fatal episode has already been discussed in Chapter 18. Clinical trials evaluating the management of acute pulmonary thromboembolism have demonstrated pulmonary hypertension in 70% to 80% of these patients.[3] The pulmonary hypertension is usually modest, and the pulmonary pressures typically return to normal within 3 weeks, except in patients with underlying cardiopulmonary disorders. In about 2% of patients with recurrent episodes of pulmonary thromboemboli, chronic pulmonary hypertension will develop.[4–6]

This chapter is a review of the pathology of the pulmonary circulation in patients with prior or recurrent episodes of pulmonary thromboembolism, whether or not there is demonstrable pulmonary hypertension. The pulmonary pathology of particular subsets of patients in whom pulmonary hypertension and other complications can occur, namely, intravenous drug abusers, those with schistosomiasis, and those with neoplastic emboli, are discussed. The phenomenon of tissue emboli to the lungs will also be briefly examined (Display 22-1).

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army or the Department of Defense.

## *PATHOLOGY OF THE PULMONARY CIRCULATION IN OLD AND RECURRENT THROMBOEMBOLIC DISEASE*

### *Elastic Arteries*

Old organized thromboemboli may become transformed into intraluminal fibrous strands in the pulmonary arteries.[7–9] These "bands" and "webs" were first described by Zahn in 1889, who interpreted them as arterial malformations.[9] Dunhill in 1968 showed that the fibrous strands represented organized thromboemboli by reproducing them in animals.[10]

Microscopically, most organized thromboemboli show marked fibrosis with or without recanalization (Fig. 22-1). An occlusive

**DISPLAY 22-1. THROMBOEMBOLIC PULMONARY HYPERTENSION AND NON-THROMBOTIC EMBOLIZATION TO THE LUNGS**

**Pathology of Thromboembolic Pulmonary Hypertension**

Elastic arteries

Muscular pulmonary arteries and arterioles

Thromboembolic pulmonary hypertension *versus* primary pulmonary hypertension

Pulmonary capillaries, veins, and bronchial arterial collaterals

**Nonthrombotic Emboli to the Lungs**

Intravenous drug abuse and foreign-body emboli

Pulmonary schistosomiasis

Tumor emboli

Tissue embolism (*e.g.*, fat, bone marrow, brain, liver, bone, skin)

thrombus, especially in the right or left main pulmonary artery, may be fully organized and recanalized; however, more often it becomes an eccentric fibrous plaque that narrows the arterial lumen to varying degrees (Fig. 22-2). A fatal pulmonary embolus in the right or left main pulmonary artery is usually preceded by smaller pulmonary thromboemboli in the muscular arteries that have become organized, leading to some degree of pulmonary hypertension.[9] The presence of underlying pulmonary hypertension explains why thromboembolic occlusion of a single main pulmonary artery can be fatal, whereas unilateral pulmonary artery ligation during pneumonectomy is well tolerated (see Chap. 19).

## *Muscular Pulmonary Arteries and Arterioles*

Thromboemboli usually lodge in muscular arteries and rarely in arterioles.[9] It is estimated that more than 16,000 thromboemboli in arteries varying in size from 0.3 mm to 1 mm in diameter must

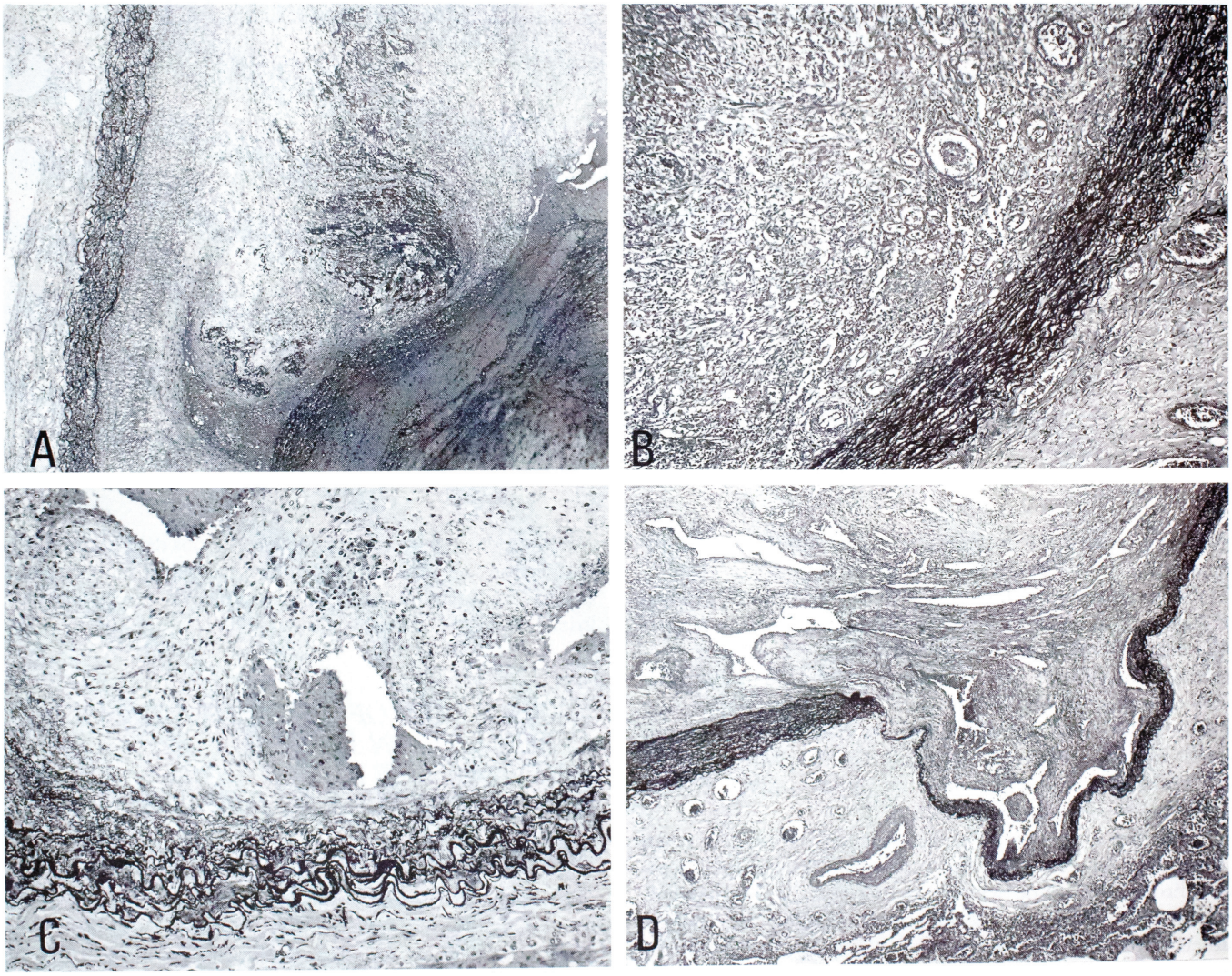


**FIGURE 22-1.** Intrapulmonary elastic arteries showing various stages of organization of thromboemboli. (**A**) Early organization of a large fibrin thromboembolus. (**B**) Advanced stage of organization of a thromboembolus with extensive neovascularization. (**C**) Almost total organization with recanalization of a thromboembolus with few hemosiderin-laden macrophages within the fibrointima. (**D**) Fully healed recanalized thromboembolus. (Movat elastic tissue stain; panoramic views.)

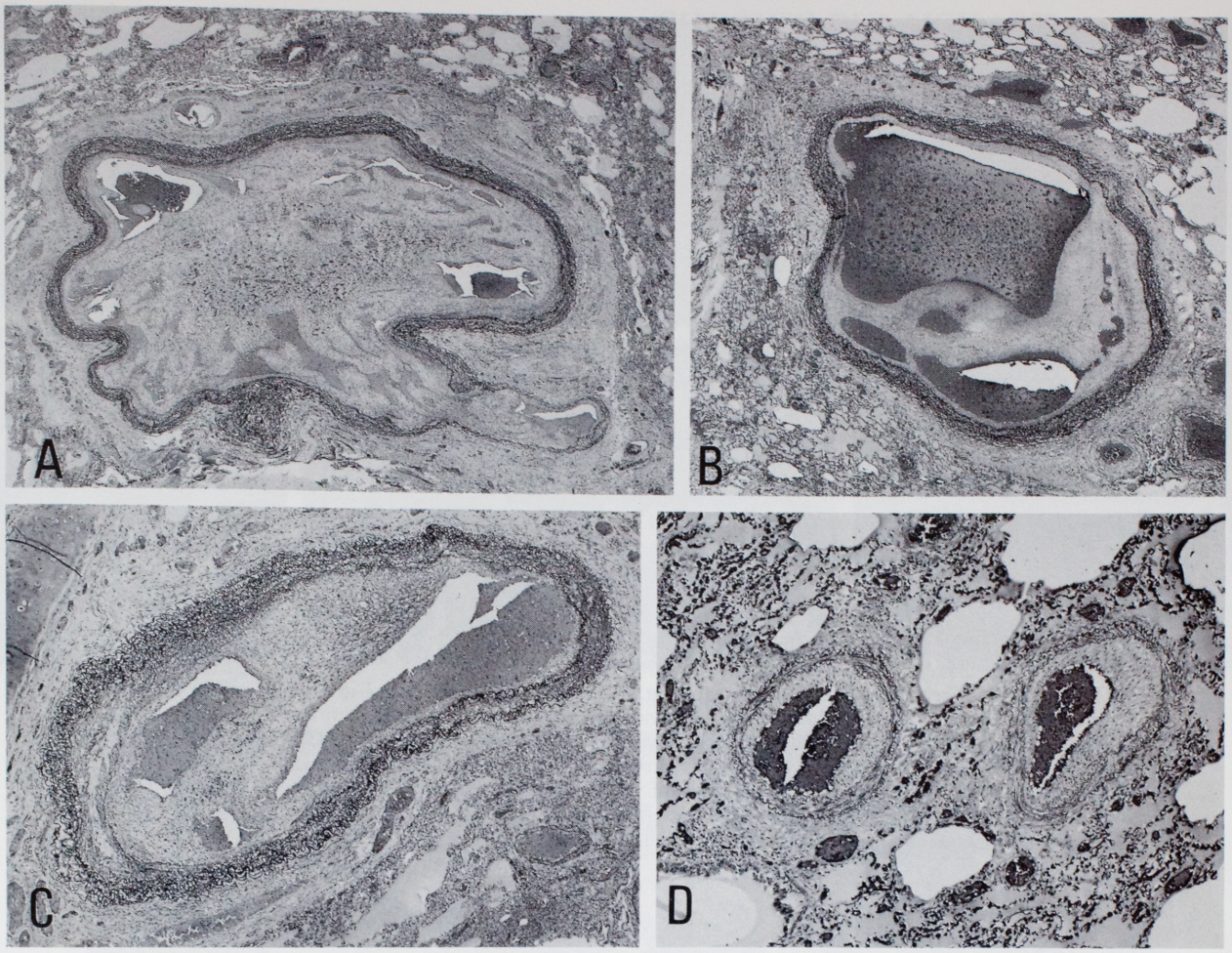


**FIGURE 22-2.** Intrapulmonary elastic arteries showing organization of thromboemboli with multiluminal channels. (**A**) An organized occlusive thromboembolus. (**B, C**) Eccentric recanalized thromboemboli. (**D**) Two muscular arteries with medial thickening and eccentric fibrointimal proliferation. (Movat elastic tissue stain; low magnifications.)

be present before chronic pulmonary hypertension will result.[4] Therefore, it is not surprising that chronic pulmonary hypertension as a result of thromboembolic disease is rare.

All thromboemboli may be recent, but more often thromboemboli in various stages of organization are found (Fig. 22-3). A thromboembolus may be adherent or nonadherent to the vessel wall, and occlusive or nonocclusive; however, both types are usually present simultaneously.[9,11–13] Depending upon the age of the thromboembolus, it may be composed solely of fibrin or intermixed with erythrocytes and leukocytes. An endothelial lining may also be present.[9]

As organization proceeds, there is polymorphonuclear leukocytic infiltration followed by neovascularization and mononuclear cell penetration. Fibroblastic ingrowth starts later, ultimately resulting in complete organization with fibrosis. The hallmark of an occlusive organized thromboembolus is the presence of multiple recanalized endothelialized channels separated by fibrous septa of varying thicknesses, from thin, latticelike strands to coarse fibrous bands.[9,11–13] An organized, nonocclusive thromboembolus is characterized by an eccentric intimal proliferation composed of fibroblasts and fibrous tissue and with scant elastic fibers. Hemosiderin may be seen early during organization, but fully organized thromboemboli seldom demonstrate hemosiderin.[6,7]

Rarely, concentric intimal fibrosis results from organized thromboemboli, but the lesions usually lack the associated elastic lamellar proliferation (*i.e.*, onion-skin formation), which is a hallmark of primary pulmonary hypertension (PPH) of the thrombotic type (see Chap. 23). Plexiform lesions, angiomatoid lesions, and vasculitis have never been seen in thromboembolic disease, yet plexiform lesions must be distinguished from organized recanalized thromboemboli. The former occur at branch points originating in smaller muscular arteries as aneurysmal lesions with definite breaks in the muscular arterial walls. In contrast, organized thromboemboli involve arteries of all sizes irrespective of branch points, and there is usually thinning but no discontinuity of the muscular arterial wall.[14]

## *Thromboembolic Pulmonary Hypertension* versus *Primary Pulmonary Hypertension*

The relationship between thromboembolic pulmonary hypertension (TPH) and PPH has been a matter of much debate (see Chap. 23).[15] The most common symptoms of PPH include fatigue and dyspnea on exertion, whereas chest pain, syncope, hemoptysis, and cyanosis are less frequent and are more often associated with

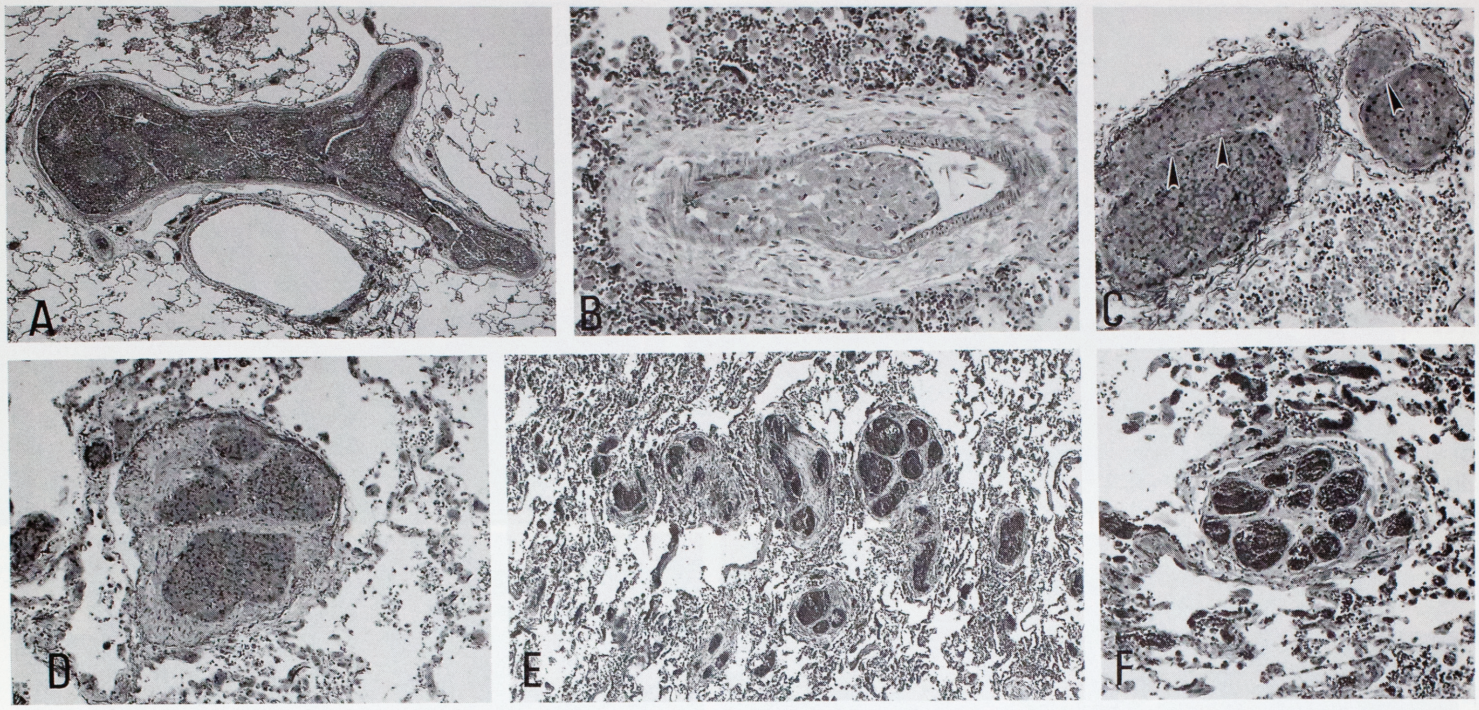


**FIGURE 22-3.** Varying stages of recent, organizing, and organized thromboemboli in small muscular pulmonary arteries. (**A**) A recent, occlusive thromboembolus without organization. (H & E stain; low magnification.) (**B**) A nonocclusive thromboembolus showing early organization with endothelialization. (**C**) Organized thrombus showing thin, fibrous strands (*arrowheads*). (**D**) Coarse, fibrous strands in an organized thromboembolus within a dilated muscular pulmonary artery. (**E**) A group of vessels, cut at various angles, showing fully organized and recanalized thromboemboli. (**F**) Close-up view of an organized recanalized thromboembolus. (Movat elastic tissue stain; low magnifications.)

**TABLE 22-1**
Primary Pulmonary Hypertension *versus* Recurrent Pulmonary Emboli

| Differences | Primary Pulmonary Hypertension | Recurrent Pulmonary Emboli |
|---|---|---|
| **CLINICAL** | | |
| Age | 20 to 40 y | >50 y |
| Male-to-female ratio | 1 : 2 | 1 : 1 |
| Clinical course | Rapidly downhill | Downhill with periodic stabilizations |
| Pulmonary artery systolic pressure | >60 mm Hg | <60 mm Hg |
| Pulmonary artery arteriogram | Pruning (thrombi may occur) | Intraluminal filling defects (pruning may be seen) |
| Lung scan | No segmental perfusion defects | Segmental or large perfusion defects |
| **PATHOLOGY** | | |
| Plexiform lesions | Common | Absent |
| Medial hypertrophy | Severe | Absent, but may be present late in disease |
| Intimal proliferation | Concentric, onion-skin type | Fresh, organizing, and recanalized thrombi with multiluminal channels; eccentric internal proliferation |

*Adapted from Goldhaber SZ. Pulmonary embolism death rates. Am Heart J 1988;115:1342.*

TPH. The clinical course of PPH includes progressive right heart failure with elevated right heart pressures and a normal pulmonary capillary wedge pressure. In TPH, lung scans show segmental perfusion defects and ventilation-perfusion mismatches. Pulmonary angiograms may show intraluminal filling defects in TPH, but angiographic pruning of the arterial tree may be seen in both PPH and TPH. Although PPH (see Chap. 23) and TPH have similarities, there are differences that help separate these two entities (Table 22-1).

### *Pulmonary Capillaries, Veins, and Bronchial Artery Collaterals*

The pulmonary capillaries and veins are generally free of any pathologic process in TPH. However, depending upon the age of the patient, the veins may show age-related changes consisting of acellular intimal thickening. The bronchial arteries in the vicinity of the obstructed pulmonary artery undergo dilation, medial hypertrophy, and intimal thickening.[16,17] There are anastomoses of systemic arteries from the mediastinum, thoracic cage, and diaphragm to pulmonary arteries.[16]

## *CHRONIC PULMONARY HYPERTENSION CAUSED BY NONTHROMBOTIC EMBOLI*

### *Intravenous Drug Abuse and Foreign-Body Emboli*

Chronic intravenous drug abuse is associated with many medical complications, including septicemia, bacterial endocarditis, hepatitis, HIV infection, and tetanus. Pulmonary hypertension is mainly due to talc granulomas lodged predominantly within the pulmonary arteries.[18–22] The formation of granulomas is a well-recognized sequela of intravenous injection of a drug intended for oral use that contains a variety of filler materials, including lactose, sucrose, polyethyleneglycol, tragacanth, magnesium stearate, and magnesium trisilicate (*i.e.*, talc).[18] Other materials that have been identified are cotton fibers and cornstarch.[23] The two compounds that can initiate a granulomatous reaction are talc and cornstarch; reactions due to cornstarch alone are infrequent, innocuous, and transient.[19,24]

The reaction to talc in the lungs is variable; in some individuals, there is an interstitial granulomatous reaction with few granulomas in the pulmonary arteries (Fig. 22-4). In others, there is a

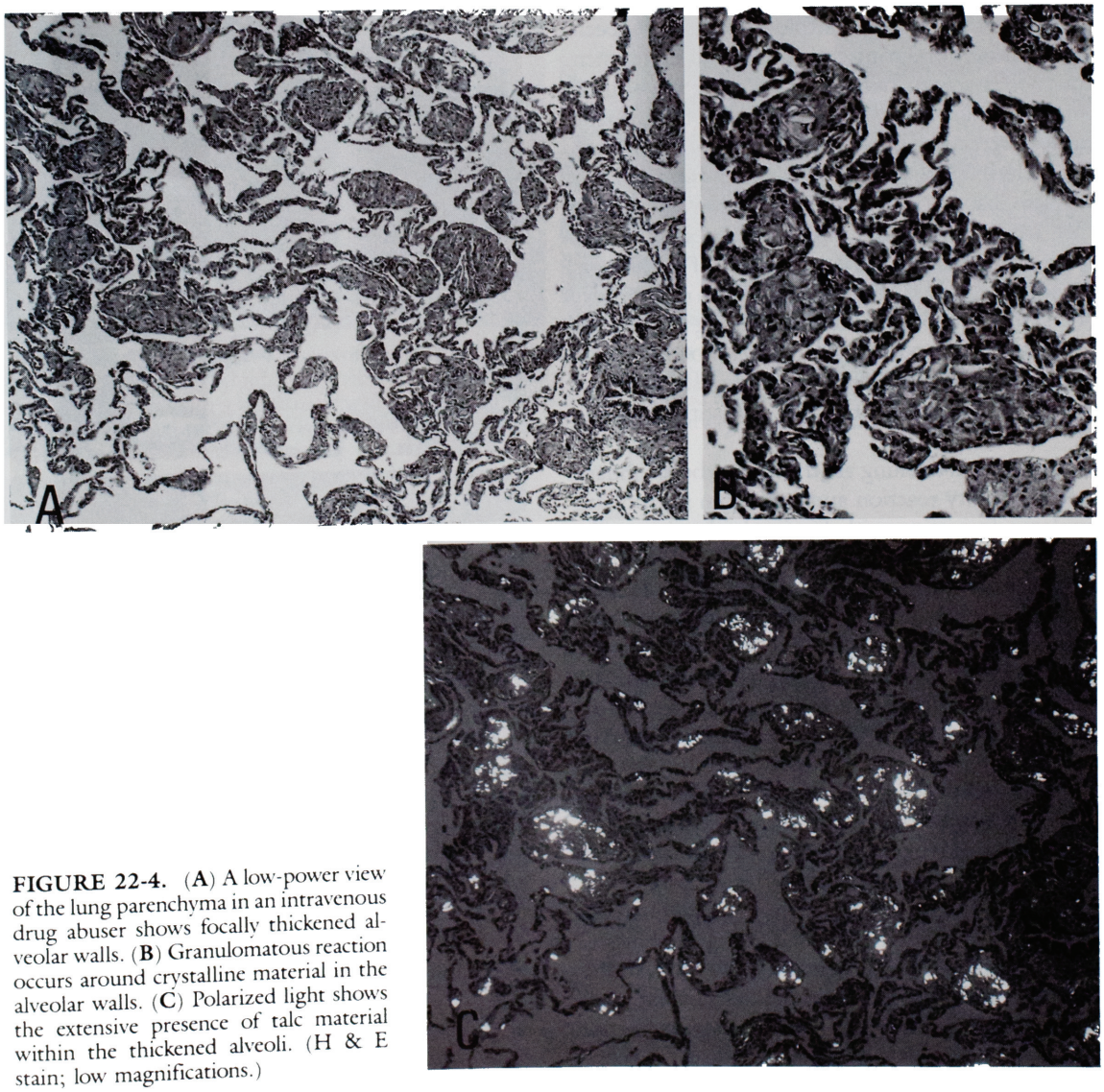


**FIGURE 22-4.** (**A**) A low-power view of the lung parenchyma in an intravenous drug abuser shows focally thickened alveolar walls. (**B**) Granulomatous reaction occurs around crystalline material in the alveolar walls. (**C**) Polarized light shows the extensive presence of talc material within the thickened alveoli. (H & E stain; low magnifications.)

predominant granulomatous reaction within the lumina of small pulmonary arteries with relative sparing of the interstitium (Fig. 22-5). In the former, interstitial pulmonary fibrosis may develop, whereas in the latter, pulmonary hypertension occurs.[20] Often, the granulomatous reaction is mild, and the patient may have no symptoms. When the reaction is extensive, the pulmonary lesions may be a factor in the death of the patient. The vascular lesions show intravascular and perivascular granulomas consisting of macrophages, lymphocytes, and foreign-body giant cells containing birefringent crystalline material typical of talc. The fibrosis may vary from moderate to severe. The vascular lumina may be severely compromised and sometimes totally occluded by an overlying thrombus. Some arteries demonstrate medial hypertrophy with or without intimal proliferation; rarely, plexiform lesions may be seen. Although the majority of patients who abuse intravenous drugs have minimal hypertensive changes, there are few reported cases of severe pulmonary hypertension.[20,23,25] The subject of HIV-related pulmonary hypertension among intravenous drug abusers is discussed in Chapter 45.

## *Pulmonary Schistosomiasis*

Parasitic infections, especially the helminthic parasites, have been known to occur accidentally or during their normal life cycle when they enter the pulmonary circulation. Their presence in the lung may or may not produce clinical symptoms; however, they usually incite a granulomatous reaction. Some of the parasites reported to occur in the lung include *Schistosoma*, *Ascaridia*, *Filaria*, and *Echinococcus* species (see Chap. 44).[9] By far the best known of these is *Schistosoma*, which has been reported to cause pulmonary hypertension.[26,27] There is controversy as to the type of pathologic change seen with schistosomiasis. The *Schistosoma* ova may embolize to the lung, becoming trapped in arterioles varying in size from 50 to 100 μm in diameter.[28] The ova may evoke a reaction within the arterial wall, penetrate the wall, and produce a response in the surrounding parenchyma that may lead to interstitial fibrosis (Fig. 22-6).[26–28]

The lesions produced in the lung are thought to be secondary to a delayed hypersensitivity reaction and vary from necrotizing arteritis to granuloma formation with foreign-body giant cells, histiocytes, lymphocytes, and eosinophils. The ova are usually calcified and no longer identifiable.[9,28] Concurrently, the muscular arteries and arterioles may show medial hypertrophy and intimal hyperplasia with or without plexiform lesions.[9,27,28] Whether the latter are true plexiform lesions or represent pseudoplexiform lesions is debatable. Naeye believes that true plexiform lesions do not contain ova,[26] whereas others have reported their presence in plexiform lesions.[29]

Most cases with schistosomal pulmonary hypertension have hepatosplenic schistosomiasis, cirrhosis of the liver, portal hypertension, and portosystemic anastomosis.[30] The eggs are shunted from the mesenteric veins to the lungs by way of the portosystemic collateral veins. It has been proposed that the plexiform lesions seen in schistosomiasis are due to portal hypertension complicated by pulmonary hypertension.[9,31] Naeye has speculated that the pulmonary hypertension in schistosomiasis is secondary to thromboemboli,[26] but true plexiform lesions do not develop in TPH.

## *Tumor Emboli*

Pulmonary hypertension from vascular tumor emboli to the lung is a rare complication, but there are several reported cases.[32–38] The most frequent malignancies giving rise to pulmonary vascular

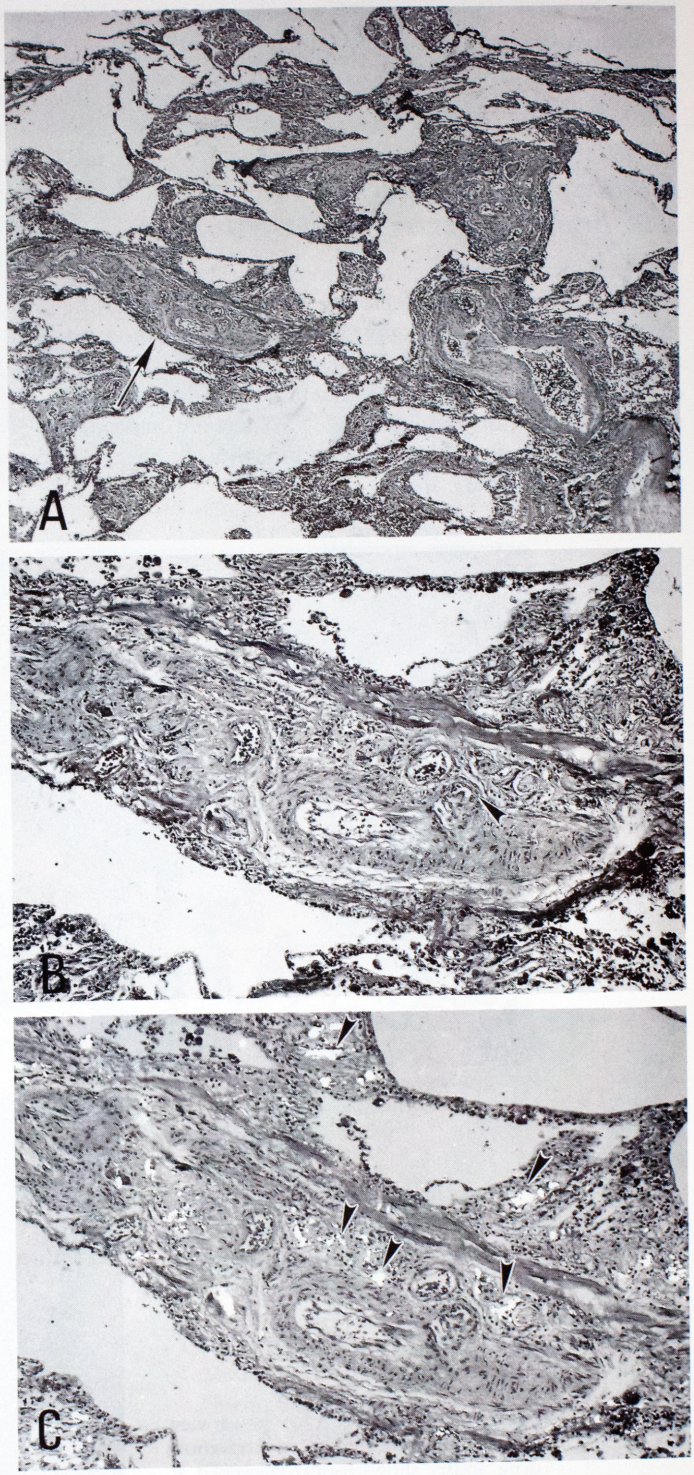


**FIGURE 22-5.** Intravenous drug abuser's lung. (**A**) A low-power view of the lung shows prominent thickened arteries. (**B**) Higher magnification of the artery seen in (**A,** *arrow*) shows medial and intimal thickening with recanalization (*arrowhead*). (**C**) Polarized light shows areas of talc (*bright material, arrowheads*) in the granulomas. (H & E stain; low magnifications.)

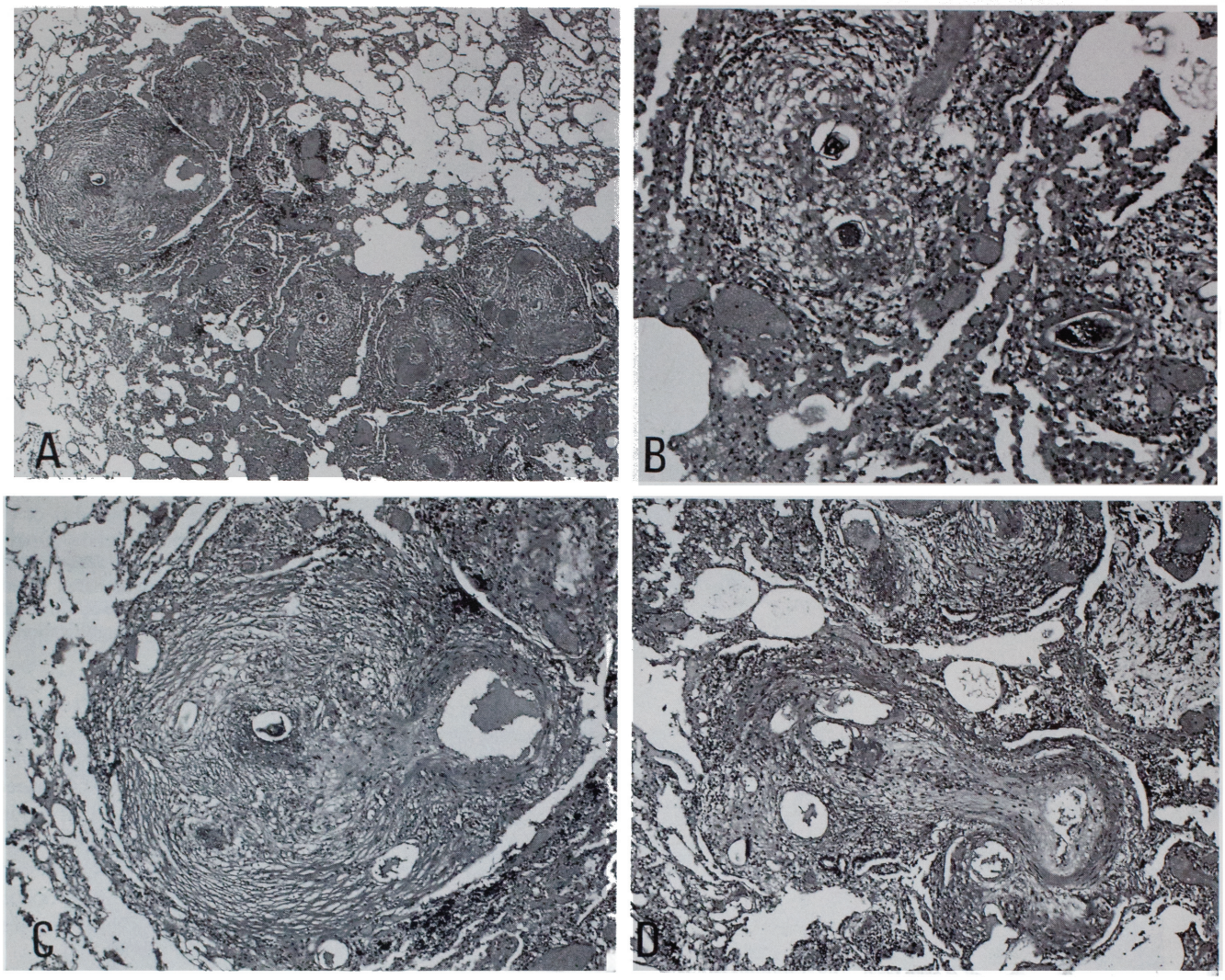


**FIGURE 22-6.** Schistosomiasis of the lung. (**A**) *Schistosoma* granulomas are present within arteries with markedly thickened walls. (**B**) A high-power view of the ova with surrounding lymphohistiocytic infiltrate and fibrosis. (**C**) A muscular artery with a break in its wall and formation of a fibrotic globoid mass containing ova; a granulomatous reaction and neovascularization are also apparent. (**D**) Another muscular artery shows a plexiform lesion but no ova. (H & E stain; low magnifications.)

tumor emboli include adenocarcinomas of the breast, prostate (Fig. 22-7), kidney, lung (Fig. 22-8), liver, stomach, and choriocarcinoma. The overall incidence of microscopic tumor emboli is 2.4% in autopsy cases of solid malignant neoplasms.[33] Tumor vascular microemboli are probably the underlying cause of unexplained dyspnea and death in nearly one half of these cases. In patients with pulmonary metastasis, Winterbauer found evidence of microscopic tumor emboli in 60 of 69 patients.[32] The majority of the tumor emboli were classified as incidental findings at autopsy; however, in 15% of cases, the vascular involvement was considered contributory to the patient's symptoms.

In hepatoma, renal cell carcinoma, and choriocarcinoma, venous drainage is directly into the inferior vena cava; therefore, it is not surprising that pulmonary vascular emboli are a frequent occurrence. A significant number of pulmonary arteries must be occluded by tumor emboli for pulmonary hypertension to occur.[36] Also, the rate of embolization is important—the more frequent the pulmonary embolic showers, the greater the likelihood of life-threatening pulmonary hypertension.[38] The histologic appearance may vary from vessels completely occluded by tumor cells to vessels with few tumor cells and varying amounts of fibrin, platelets, and hematopoietic cells (see Fig. 22-8). Intimal proliferation may or may not be present. Large tumor thromboemboli are often necrotic with varying degrees of myxoid change. Small muscular arteries may show medial hypertrophy and intimal proliferation that may be concentric.[39]

## *TISSUE EMBOLI*

### *Bone Marrow Emboli*

Massive fat embolism has already been discussed (see Chap. 18). Bone marrow emboli are a frequent incidental finding at autopsy and may occur in three different settings: accidental fractures, seizures, cardiopulmonary resuscitation, and electroconvulsive

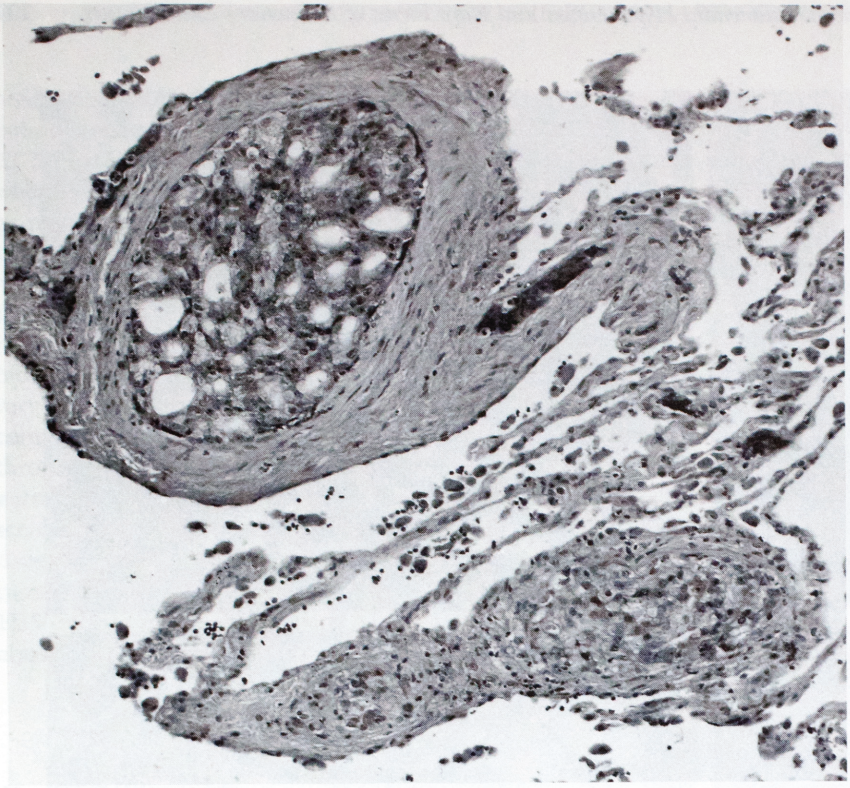

**FIGURE 22-7.** Metastatic adenocarcinoma from the prostate with vascular embolization. The appearance of the tumor varies from that of a well-differentiated glandular lesion to a poorly differentiated carcinoma seen in the lower right-hand corner. (H & E stain; low magnification.)

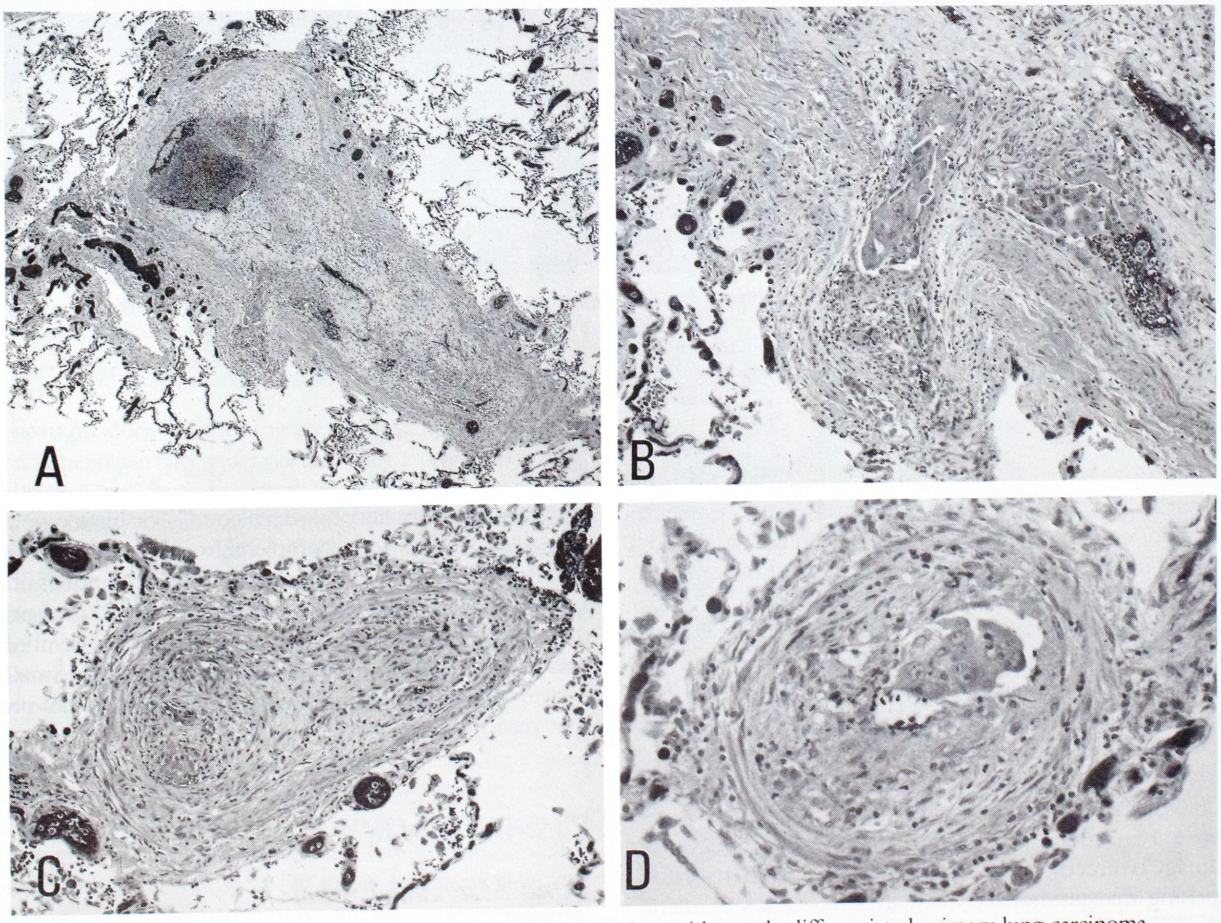


**FIGURE 22-8.** Photomicrographs of the lung of a patient with poorly differentiated primary lung carcinoma show extensive tumor embolization of the muscular arteries, with varying stages of organization. (**A**) A muscular artery shows an organizing occlusive thrombus containing tumor cells. (**B**) A closer view of the branch in (**A**) reveals the presence of tumor within the embolus. (**C, D**) Other arteries show extensive organization around tumor emboli. (H & E stain; low magnifications.)

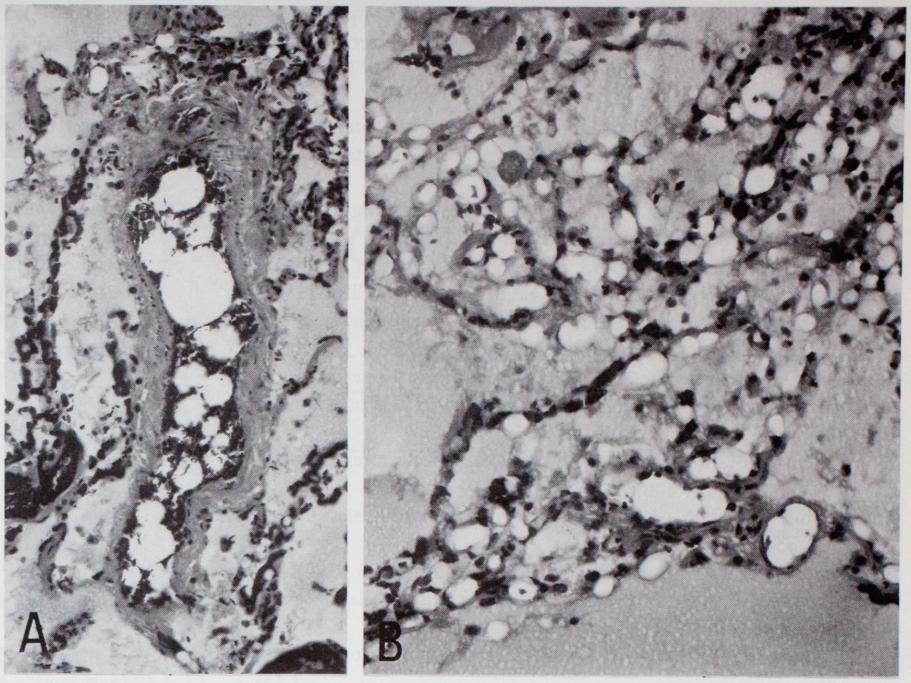


**FIGURE 22-9.** Photomicrographs of the lung of a patient with sickle cell disease and bone infarcts. (**A**) Fat globules and a large number of red cells are present in a longitudinally cut arteriole. (**B**) Alveolar capillaries are distended by fat globules. (H & E stain; low magnifications.)

therapy; pathologic fractures, osteoporosis, and arthritis; and bone marrow infarcts, especially in sickle cell anemia (Fig. 22-9).[40] The histologic diagnosis of bone marrow emboli requires the presence of hematopoietic and fat elements (*i.e.*, bone marrow) within arteries and arterioles (Fig. 22-10).[41] Pulmonary bone marrow emboli in the dog have been shown to cause elevation in pulmonary artery pressure, increased pulmonary resistance, and a reduction in systemic arterial oxygen tension, and these changes have been attributed to an increase in 6-keto-prostaglandin $F_{1\alpha}$[42].

## *Emboli of Other Tissues*

*Brain* emboli are rare but may occur with accidental, self-inflicted, or surgical head trauma; they rarely occur in newborns with central nervous system malformations or severe head trauma during delivery.[43,44] Brain emboli are of little clinical significance because by themselves they do not cause death. Rarely, *liver* emboli may be seen, and these are also associated with trauma or massive hepatic necrosis. Other tissues that have been reported to embolize to the lungs include *bone* fragments in patients undergoing bone marrow transplantation,[45] and *skin*.[46]

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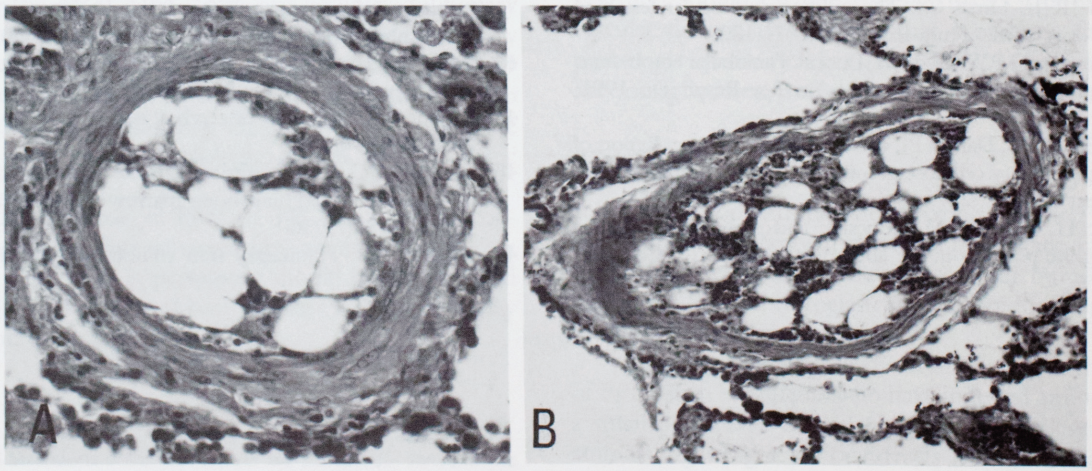


**FIGURE 22-10.** (**A, B**) Bone marrow emboli in muscular pulmonary arteries. (H & E stain; intermediate magnifications.)

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