Diagnosis of Diseases of the Chest

VOLUME III

THIRD EDITION

VOLUME III

Diagnosis of Diseases of the Chest

THIRD EDITION

Robert G. Fraser, M.D.
Professor Emeritus
Department of Radiology
University of Alabama at Birmingham
Birmingham, Alabama

J.A. Peter Paré, M.D.
Professor Emeritus
Department of Medicine
McGill University
Montreal, Quebec

P.D. Paré, M.D.
Professor of Medicine
University of British Columbia
Head, Respiratory Division
University of British Columbia and
St. Paul's Hospital
Vancouver, British Columbia

Richard S. Fraser, M.D.
Associate Professor of Pathology
McGill University
Pathologist, Montreal General Hospital
Head, Department of Pathology
Montreal Chest Hospital Institute
Montreal, Quebec

George P. Genereux, M.D.
Professor of Radiology
University of Saskatchewan, Saskatoon
Radiologist, University of Saskatchewan Hospital
Saskatoon, Saskatchewan

1990
W.B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
Philadelphia London Toronto Montreal Sydney Tokyo

W. B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
The Curtis Center
Independence Square West
Philadelphia, PA 19106

Library of Congress Cataloging-in-Publication Data
(Revised for vol. 3)

Diagnosis of diseases of the chest.

Rev. ed. of: Diagnosis of diseases of the chest /
Robert G. Fraser, J. A. Peter Paré. 2nd ed. 1977–
Includes bibliographies and indexes.

1. Chest—Diseases—Diagnosis—Collected works.
2. Thoracic Diseases—diagnosis. 3. Thoracic Radiology.
I. Fraser, Robert G., 1921–

RC941.D52 1990 87–4678

ISBN 0–7216–3879–1 (set)

ISBN 0–7216–3870–8 (v. 1)

ISBN 0–7216–3871–6 (v. 2)

ISBN 0–7216–3872–4 (v. 3)

Listed here are the latest translated editions of this book together with the language of the translation and the publisher.

Italian (2nd Edition)—Editrice Ambrosiana, Milan, Italy
Spanish (2nd Edition)—Salvat Editores S.A., Barcelona, Spain
Portuguese (2nd Edition)—Editora Manole Ltda., Sao Paulo, Brazil
German (2nd Edition, Vol. IV)—F. K. Schattauer Verlag, Stuttgart, West Germany

Editor: Lisette Bralow
Designer: W. B. Saunders Staff
Production Manager: Carolyn Naylor
Manuscript Editor: Carol Robins
Illustration Coordinator: Walt Verbitski
Indexer: Julie Schwager/Kathy Garcia

Volume I ISBN 0-7216-3870-8
Volume II ISBN 0-7216-3871-6
Volume III ISBN 0-7216-3872-4
Set ISBN 0-7216-3879-1

Diagnosis of Diseases of the Chest

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2

DEDICATION

This volume is dedicated to the memory of Dr. George Genereux, whose untimely death ended the distinguished career of a dear friend and co-author.

9

Embolic and Thrombotic Diseases of the Lungs

PULMONARY THROMBOSIS

Although embolization is undoubtedly the most frequent mechanism involved to explain the presence of intrapulmonary thrombus, *in situ* thrombosis of pulmonary vessels is probably more common than is generally appreciated. However, because of the difficulty in distinguishing thromboembolus from *in situ* thrombus both radiologically and pathologically, and because the predisposing conditions for pulmonary thrombosis are frequently the same as those for systemic venous thrombosis, it can be difficult to state with certainty which of the two processes is operative. The pathogenesis and effects of pulmonary vascular thrombosis are related to some extent to the site and can be conveniently discussed under three categories: (1) arteries, (2) arterioles and capillaries, and (3) veins.

Pulmonary Arteries

It is in the pulmonary arteries that the distinction between *in situ* thrombosis and embolism can be particularly difficult; in fact, in some cases, differentiation is not possible. Probably the most common underlying cause of *in situ* arterial thrombosis is *infectious pneumonia*, in which vascular damage occurs in relation to abscesses and foci of active granulomatous inflammation. Thrombosis related to primary or metastatic neoplasm is also relatively common; it can result from either invasion of the vessel by the neoplasm or vascular compression by expanding tumor. Less common causes include immune-mediated vasculitis,[1] trauma,[2] aneurysms,[3] indwelling catheters,[4] congenital heart anomalies associated with decreased pulmonary blood flow such as tetralogy of Fallot,[5] and sickle-cell trait or disease;[6–8] in the last named condition, thrombosis is sometimes associated with sudden death.[9] Other pulmonary and cardiac diseases, such as emphysema,[10] pneumoconiosis, mitral stenosis, and primary pulmonary hypertension,[11] have also been associated; however, pulmonary thromboemboli occur with such frequency in these conditions that it is difficult, if not impossible, to estimate with any degree of accuracy the true incidence of thrombosis.

Pathologically, *in situ* arterial thrombosis should be suspected grossly if there is adjacent parenchymal disease or if there is extensive and continuous thrombus in multiple vessels; the formation of a cast of the arterial tree would not be possible with the multiple fragments of thrombus characteristic of emboli. In one literature review of 100 cases considered to represent *in situ* thrombosis, the site of thrombus formation was the right lung in 49 per cent, the left in 6 per cent, and both lungs in 45 per cent;[11] the author suggested that the longer course of the right pulmonary artery and its association with other mediastinal structures were responsible for the higher incidence in this lung. Histologically, *in situ* thrombosis should be considered when there is associated vasculitis or if the thrombus is eccentrically located on the side of the vessel wall adjacent to a focus of parenchymal inflammation (Fig. 9–1). The genesis of isolated thrombi unassociated with pneumonia or other active inflammatory pulmonary disease cannot be determined histologically in most instances; although such *in situ* thrombi undoubtedly occur, they are usually considered thromboemboli.

Thrombosis is found most often in small elastic or muscular arteries supplying lung that is already the site of disease; as a result, the effects of the thrombus are often difficult to evaluate in determining roentgenographic or clinical manifestations. An exception is the necrosis and cavitation that occur in some cases of pneumonia (lung "gangrene") or vasculitis, the pathogenesis being related at least in part to the thrombosis and resulting ischemia. In addition, thrombus can occasionally extend proximally from a focus of active parenchymal inflammation, especially in tuberculosis;[11] such extension can sometimes occur as far as the pulmonary trunk and opposite main pulmonary artery, resulting in severe obstruction of pulmonary blood flow and cor pulmonale.

Pulmonary Arterioles and Capillaries

Thrombosis of small pulmonary vessels occurs in immunologically mediated leukocytoclastic vasculitis (*see* page 1264); in these cases, it is usually associated with other evidence of vascular damage, particularly parenchymal hemorrhage. Fibrin thrombi, believed to be the product of an acute hypercoagulability state, are also found in the lungs of animals and humans who have died of "shock"[12] and disseminated intravascular coagulation[13] related to such conditions as septicemia and amniotic fluid

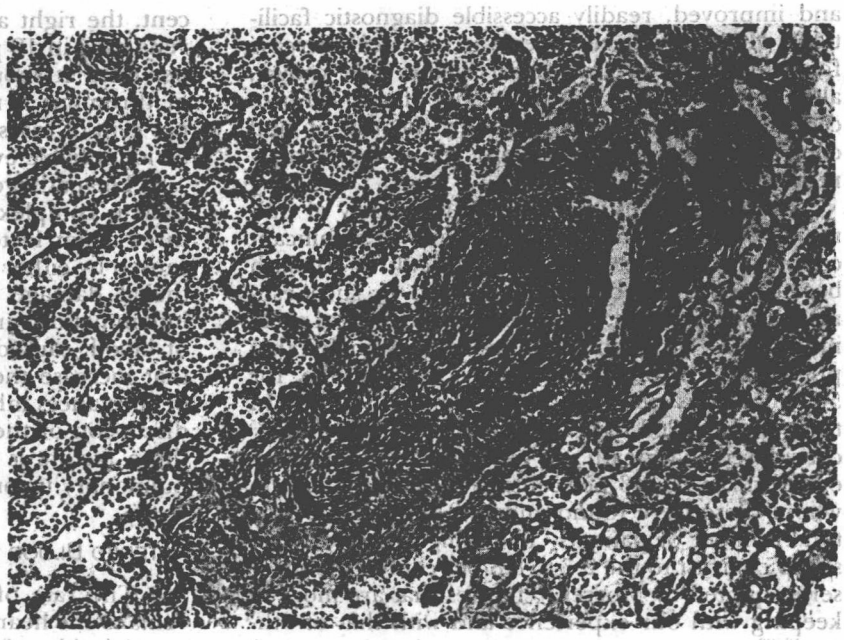

Figure 9–1. Pulmonary Artery Thrombosis *In Situ*. The left portion of the figure shows alveolar airspaces full of polymorphonuclear leukocytes, representing an acute bacterial pneumonia. A pulmonary artery at the junction of affected and unaffected lung reveals eccentric thrombosis in relation to the pneumonia (× 80).

embolism. *In situ* thrombosis of small as well as large pulmonary vessels can occur in sickle cell disease.[6]

Pulmonary Veins

As in the arterial circulation, pulmonary venous thrombosis commonly develops secondary to an infectious process or neoplasm. Other related conditions include those in which there is decreased blood flow, such as tetralogy of Fallot,[5] sclerosing mediastinitis,[14, 15, 718] and veno-occlusive disease; in fact, venous thrombosis has been considered by some to be intimately involved in the pathogenesis of the last-named disorder.

PULMONARY THROMBOEMBOLISM

INCIDENCE

Estimates of the incidence of pulmonary thromboembolism vary considerably in different series, largely as a result of differences in the character of the population under study and the techniques and criteria used in diagnosis. In general, thromboemboli are an infrequent cause of hospital admission, ranging in incidence from 0.49 to 2.5 per cent of medical patients and 0.09 to 0.6 per cent of surgical patients in three series.[16] As a *diagnosed* complication of hospitalization, they are also relatively uncommon; in one retrospective study of patients discharged from the hospital over a 10-year period, the incidence was only 0.21 per cent.[16] The incidence of fatal pulmonary embolism after routine surgery is also very low, estimated at only two to three per 1,000 procedures.[17] Despite these figures, however, it is well recognized that the true incidence of thromboembolism is much higher, a belief that is based on three observations:

1. Signs and symptoms are lacking in many patients; it has been estimated that about 80 per cent of pulmonary thromboembolic episodes are unrecognized as a result of the absence of clinical findings.[18, 19]

2. A definitive diagnosis is difficult to make during life, even when symptoms and signs are present.[20]

3. Thromboemboli are frequently identified at autopsy; in retrospective necropsy studies, the incidence in most series ranges from 5 to 20 per cent.[16, 22, 23] If lung specimens are examined in detail prospectively, the incidence is even higher: in one series of 61 consecutive necropsies, 64 per cent were found to contain organized or recent thromboemboli.[24] In another investigation of 263 right lungs,[25] emboli were found in 51.7 per cent, and, as the authors admitted, the true incidence must have been even higher, since only one lung was examined. Even when the pulmonary embolism is of major degree, the correct diagnosis is often not made before death: of 54 autopsies performed at the Peter Bent Brigham Hospital on patients with this finding, the correct diagnosis was made ante mortem in only 16 (30 per cent); misdiagnosis was most frequent in the elderly and in patients with established pneumonia.[26] Misdiagnosis is not invariably related to underdiagnosis; in one study, 61.9 per cent of all clinical diagnoses of pulmonary embolism were false positives.[21]

Although the precise incidence of pulmonary thromboembolism is not known, it appears to be increasing,[27] particularly in previously healthy young adults.[28, 29] Some of this increase can be attributed to a higher index of clinical suspicion

and improved, readily accessible diagnostic facilities.[27] However, there appears to be a real increase for which not all the causal factors are known, although the increasing complexity of surgical procedures and the vast increase in the use of oral contraceptives (*see* further on) are at least partly responsible.

An accurate estimate of the frequency of pulmonary thromboembolism as a major or significant contributory cause of death is difficult to establish because of the subjectivity involved in such estimates. Nevertheless, the condition is clearly of great importance; for example, it has been estimated that pulmonary thromboembolism is responsible for 50,000 deaths per year in the United States.[30] In their study of 263 right lungs, Morrell and Dunnill[25] considered that death was attributable to thromboembolism in 56 (43 per cent) of the 136 patients in whom these were found and in 21 per cent of the total number of patients. These high figures are in sharp contrast to the 2.7 to 8.8 per cent in the three series quoted by Morrell,[16] figures that are more in keeping with our experience and with that of others.[16, 23]

ETIOLOGY AND PATHOGENESIS

The pathogenesis of pulmonary thromboembolism can be conveniently considered under (1) the development of venous and cardiac thrombosis and (2) the effects on the lungs of the thromboemboli themselves.

Venous and Cardiac Thrombosis

Since by definition pulmonary thromboembolism is characterized by the transport to and impaction within the lung of a fragment of thrombus, the process must be preceded by the development of thrombus elsewhere in the circulatory system. In the great majority of cases, this occurs in the veins of the legs, particularly the thighs. Other relatively common sites are the pelvic veins (including the periprostatic veins in men), the inferior vena cava, and the right atrium. The right ventricle[31] (rarely in association with a right ventricular myxoma),[32, 33] right-sided heart valves, superior vena cava,[34] and the veins of the neck and arms are infrequent sources. The incidence of deep venous thrombosis in the arms[35] is estimated to be less than 2 per cent of all cases;[36] however, complicating pulmonary embolism is not proportionately rare, being reported in three of 25 patients in one series[37] and in five of 16 in another.[38] Foci of peripheral thrombosis are sometimes multiple, making detection of the precise source of an embolus difficult; for example, in one necropsy study of 78 patients known to have had pulmonary embolism,[39] peripheral thrombi were found in 62, at multiple sites in more than a third; the leg veins were involved in 46 per cent, the right atrium in 23 per cent, the inferior vena cava in 19 per cent, and the pelvic veins in 16 per cent. It should be emphasized that the source of thrombus is not found during life in up to 50 per cent of cases of fatal embolism[40, 41] and may not be identifiable even at autopsy.[40]

The pathogenesis of cardiac and venous thrombosis is complex and is related to one or more of three major factors: (1) an alteration in blood flow, caused by either stasis or local turbulence; (2) endothelial damage, usually the result of trauma or inflammation; and (3) a change in the coagulability of blood, caused by either substances or processes that increase the clotting tendency or a deficiency of substances inhibiting clot formation. A thorough discussion of the pathogenesis and effects of these three factors is essential for an understanding of pulmonary thromboembolism.

Altered Blood Flow

The rate of blood flow through the systemic veins to the heart depends upon the input from the arterial side of the circulation, the resistance to venous flow, the milking action of the local musculature, and, in those veins in which they are present, intraluminal valves. An alteration in any of these can lead to a decrease in blood flow that may predispose to thrombus formation. Many of the clinical conditions associated with venous thrombosis, particularly in the legs, are in turn associated with an abnormality of one or more of these factors. Such conditions include left-sided heart failure and shock (decreased arterial input),[27, 42] obesity, pregnancy, intra-abdominal tumors, right-sided heart failure, external pressure from leg casts or bandages (increased resistance to flow),[43] strokes[42, 44] and the postsurgical or paraplegic state (immobility with loss or decrease of muscle activity), and varicose veins.[17, 27, 42, 45, 46] Slowing of blood flow that is caused by intrinsic abnormality of the blood itself, such as in multiple myeloma[47, 48] and sickle-cell anemia,[49] also predisposes to thrombosis.

Because of their distance from the heart and the effects of gravity and immobility, the legs are the most vulnerable site for an alteration in venous blood flow, and the frequency of pulmonary thromboembolism directly parallels thrombosis in this site. In high-risk patients, deep venous thrombosis in the legs is common, being found in 27 to 60 per cent of patients in large autopsy series.[23, 50, 51] When detected by phlebography and scanning techniques, thrombosis associated with immobility or surgery is equally frequent; in their study of 160 patients undergoing total hip replacement, Stamatakis and colleagues[52] found evidence of deep venous thrombosis in the legs in 81 (50 per cent). In another series of 132 consecutive patients undergoing elective surgery (not on the legs), 40 (30 per cent) showed evidence of thrombosis by ^{125}I fibrinogen test and phlebography;[53] only 20 of these had clin-

ical signs, only four had detectable pulmonary emboli, and in 14 there was evidence of lysis of the thrombus within 72 hours. Isotopic scanning techniques and radiographic phlebography have shown deep venous thrombosis (DVT) in up to 60 per cent of patients with strokes,[44] and in 34 to 37 per cent of patients with myocardial infarction:[54, 55] in the latter group, the incidence of DVT appears to be closely associated with the severity of myocardial damage and does not occur in the majority of cases of uncomplicated myocardial infarction.[56]

In the legs, most thrombi appear to be initiated by local fibrin–platelet–red blood cell aggregates, often in the region of a valve pocket.[51, 57, 719] Although many initially form in the calf, it is clear from postmortem anatomic studies[50, 51, 57] and *in vivo* phlebographic investigations[52, 58] that a substantial proportion arise in the veins of the thigh. It is widely believed that it is from this site rather than the calf where the majority of clinically significant pulmonary thromboemboli arise,[23, 59–61] although occasional well-documented cases have been described in which the calf was the site of origin.[62]

Localized areas of blood turbulence are probably responsible, at least in part, for the thrombus related to foreign objects, such as indwelling Swan-Ganz arterial catheters,[63, 64] pacing catheters,[65] and cerebrospinal fluid shunt[66] or inferior vena cava plication[67] devices.

Endothelial Injury

The role of endothelial injury in the genesis of deep venous thrombosis is currently believed to be of little importance in most situations.[51, 68, 719] In his study of 50 small thrombi in the pockets of femoral vein valves, Sevitt[57] generally identified no evidence of antecedent intimal damage; however, he did find within apparently normal valves microscopic foci of fibrin thrombi, which he speculated were the precursors of future macroscopic thrombi. In addition, although experimental venous trauma is associated with limited platelet adherence to exposed subendothelial tissue, it has been found to be a weak promoter of fibrin thrombus formation.[719] Thus, venous thrombosis secondary to injury or inflammation of the vessel wall (thrombophlebitis) is probably uncommon compared to the typical bland thrombosis unassociated with these events. Despite these observations, endothelial injury can be a significant factor in some situations in which there is localized venous trauma, such as total hip replacement.[52] It may also be important in the thrombosis associated with bacterial endocarditis and immunologically mediated vasculitis.

Paradoxically, the contrast medium used to detect venous thrombosis can itself initiate thrombosis, presumably as a result of endothelial damage;[69, 70] it has been estimated that this complication occurs in 3 to 5 per cent of patients undergoing this procedure.[70] A follow-up study of a group of patients 5 to 10 years after proven venous thrombosis in a lower limb revealed a surprising incidence of filling defects, presumably representing organized thrombi in vessels initially found to be patent; the authors suggested that the diagnostic venography might have been responsible.[71]

Coagulation Abnormalities

Most instances of venous thrombosis and pulmonary thromboembolism, particularly those that are acute and massive, are associated with medical, surgical, or obstetric conditions with well-defined risk factors.[72] However, some patients in whom peripheral venous thrombosis develops, with or without associated embolization, are otherwise healthy. In many such cases, questioning will reveal other potential pathogenetic factors for the thrombosis, such as sitting for long periods in a cramped position while traveling (as has been reported in active duty servicemen[73, 74]) or standing for long periods at work in occupations such as nursing.[75, 76] In such circumstances and in those in which no other pathogenetic factors are evident, the possibility of a hypercoagulable state should be considered. Although the existence of such a condition has long been suspected and there is abundant indirect evidence for its presence, its precise nature has been documented only rarely. Thus, a familial deficiency of antithrombin III, an alpha-2-globulin capable of inactivating thrombin and factor Xa, is associated with a substantially increased incidence of deep venous thrombosis and occasionally pulmonary emboli,[77] usually in association with a second risk factor, such as pregnancy or surgery, but in one instance following venography.[69] Similarly, deficiencies of either of the coagulation inhibition proteins C or S may be associated with recurrent venous thrombosis and pulmonary thromboembolism.[720, 721]

Patients with myeloproliferative disorders manifesting thrombocytosis (such as polycythemia vera and essential thrombocythemia)[78] are prone to thrombotic and hemorrhagic complications, whereas those with reactive thrombocytosis tend not to be.[79] Platelet aggregate formation has been proposed as a factor in the pathogenesis of recurring venous thrombosis, and in such patients treatment with dipyridamole and aspirin has been shown to increase platelet survival time[80, 81] and prevent venous thrombosis.[81] Physical conditioning, pedalling devices, and such physical methods as elastic or pneumatic compression and electrical stimulation of the muscles of the extremities have been shown to prevent thrombosis, possibly by increasing fibrinolytic activity[82–84] in addition to increasing flow. In addition, some disease entities, including hypertension and hyperlipidemia,[85] predispose to thrombosis because of an apparent alteration in the noncellular elements of the coagulation system. As in other conditions which have been associated with a tendency to increased coagulation, such as the post-

operative and posttraumatic states, the precise alteration in blood components leading to this has not been clearly defined and is likely multifactorial and complex.

Two other factors that predispose to thrombus formation—neoplasms and oral contraceptives—deserve more detailed discussion. Patients with certain neoplasms, particularly those of the lung, gastrointestinal tract, and genitourinary tract,[86] show a propensity for the development of venous thrombosis, and affected patients have an increased incidence (approximately four-fold) of pulmonary thromboembolism. In some cases, the thrombus has been associated with intravascular mucus, suggesting that this might be the initiator of thrombosis; in others, alteration in the normal level of coagulation factors such as fibrinogen, antithrombin, and thromboplastin has been identified.[722]

Since the late 1960s, it has become evident that there is an increased risk of venous thrombosis and pulmonary thromboembolism in women taking oral contraceptives.[87–92] The risk is dose-related[90] and is believed to be especially serious in patients with congenital left-to-right intracardiac shunts.[93] The culpable ingredient in the hormone pill is thought to be estrogen,[94] which both augments clotting and impairs fibrinolysis;[95] lowering the estrogen content of such medication has resulted in a decrease in morbidity but not mortality caused by venous thromboembolic disease.[96]

Several epidemologic studies support the association. The incidence of postoperative thromboembolism is increased three to four times in women taking oral contraceptives,[97] and it has been estimated that healthy women between the ages of 20 and 34 taking oral contraceptives run a risk of death from pulmonary or cerebral embolism that is seven to eight times that in nonusers.[88] Stated another way, one of every 2,000 women taking oral contraceptives in one study required inpatient treatment for venous thrombosis in contrast to only one of 20,000 not taking these drugs.[89] Since thromboembolism is an uncommon cause of death in healthy women in this age group, these figures are statistically equivalent to eight deaths per half-million users of the contraceptive pill compared to one death per half-million nonusers. However, the risk of thromboembolism due to pregnancy itself should be balanced against these figures when contraceptive therapy is being considered.

Miscellaneous Factors

A number of other conditions that are associated with venous thrombosis and pulmonary thromboembolism are characterized by a pathogenesis that is even less well understood:

1. It has been shown in many studies that the incidence of thromboembolism increases with age.[16, 25] It is not known to what extent this is a feature of the aging process itself or simply a reflection of the increased incidence of the other known risk factors in this group.

2. Blood group O has been shown to be the least likely to be associated with venous thrombosis, particularly in postoperative and pregnant or puerperal women.[98, 99]

3. Cigarette smoking has been claimed to increase the risk of venous thromboembolism,[100] although evidence for this association is not at all convincing.[92] For example, two studies of patients with recent myocardial infarction[101, 102] found a significantly greater incidence of deep venous thrombosis in nonsmokers than in smokers; isotopic scanning revealed deep venous thrombosis in 42 of 74 (56 per cent) nonsmokers but in only 24 of 126 (19 per cent) smokers (whose smoking had been stopped on hospital admission).

4. Strangely, thromboembolism appears to be an infrequent cause of mortality in patients with chronic renal failure. In a series of 2,255 autopsies on adults, the overall incidence of pulmonary embolism was 32.3 per cent (18.4 per cent microscopic, 4.4 per cent macroscopic, and 9.9 per cent both); by contrast, in the 95 patients with chronic renal failure (serum creatinine level over 5.0 mg/dl), the incidence was only 9.47 per cent (all microscopic).[103]

This brief discussion of the pathogenesis of venous and cardiac thrombosis has separated predisposing factors into three groups. However, it is important to realize that in many clinical conditions two and sometimes all three of these are involved in the increased risk and that assessment of the relative importance of each can be exceedingly difficult.[104, 105] The multifactorial pathogenesis of thromboembolism is well illustrated by pregnancy, in which the incidence is clearly increased; in addition to increased venous pressure in the legs and the risk of varicosities in the pelvic and leg veins, there is an increase in the concentration of several components of the clotting mechanism.[108] An additional hazard in pregnancy is thrombophlebitis of the ovarian veins, especially in the presence of sepsis.[108, 109] Most studies indicate that thromboembolic disease is not common ante partum;[108] for example, in one study, measurement of the uptake of ^{125}I-labeled fibrinogen[104] revealed puerperal deep vein thrombosis in only one of 100 women considered to be at high risk. Instead, embolism tends to occur during the postpartum period, most often after difficult or traumatic delivery and especially if there has been hemorrhage.[110] However, others have shown an increased incidence of thrombosis and pulmonary embolism in pregnancy, even during the first trimester;[109, 111] for example, in one investigation of women over the age of 35 who required assisted delivery and were taking estrogen therapy to inhibit lactation, the incidence of peripheral thrombosis was increased tenfold.[105]

Because of the risk and expense of administering prophylactic low-dose heparin to all patients considered to be susceptible to thromboembolic

disease, attempts have been made to identify those patients who should receive such medication based on a predictive index calculated from euglobulin lysis time, concentration of fibrin-related antigen, percentage overweight for height, and presence or absence of varicose veins.[106, 107]

Thromboembolism

A fragment of embolized thrombus lodged within a pulmonary artery has two immediate consequences—an increase in pressure proximal to the thrombus and a decrease or cessation of flow distal to it. The effects of thromboemboli are largely a result of these two consequences, the final clinical, roentgenographic, and pathologic manifestations being modified by a number of factors, including the size of the embolus, the presence of bacteria within the thrombus (septic embolism), the presence and extent of underlying lung abnormality (including previous thromboemboli), and the presence of extrapulmonary disease, particularly of the cardiovascular system. These manifestations can be discussed under four headings: (1) hemorrhage and infarction, (2) atelectasis, (3) hypertension, and (4) edema.

Hemorrhage and Infarction

Parenchymal consolidation secondary to sudden occlusion of a pulmonary artery is due to one or more of three processes: (1) hemorrhage alone, (2) hemorrhage with necrosis of lung parenchyma (infarction), or (3) pneumonia. The last-named occurs in association with septic thromboemboli (*see* later) or with infection superimposed on infarcted lung. The first two are a direct consequence of a deficiency of pulmonary arterial blood flow and may represent in part different manifestations of the severity of the vascular occlusion. It should be noted that because clinical and roentgenographic findings seldom permit reliable differentiation between hemorrhage and infarction, at least in their early stages, the two are usually referred to under the single term infarction; in addition, pure pulmonary hemorrhage has sometimes been referred to as "incipient" or "incomplete" infarction.[112] Although it is likely that some of these latter cases do in fact represent true tissue necrosis as well as hemorrhage at a stage before pathologic or roentgenographic identification is possible, it is clear that others are simply a reflection of reversible ischemic damage to the alveolocapillary membrane.

Despite this fundamental pathogenetic distinction, we feel it proper to use the word "infarct" roentgenographically *in all situations in which a pulmonary opacity develops within one or more bronchopulmonary segments or subsegments distal to an occluded pulmonary artery.* Should follow-up examinations show rapid clearing, it would be reasonable to consider the lesion to be caused by hemorrhage alone. Should the opacity clear more slowly, over several weeks, the reasonable inference can be made that the vascular insult resulted in tissue death. On the other hand, from a pathologic point of view, a precise distinction between hemorrhage and infarction is usually possible, and in the following pathologic descriptions these terms are used according to their specific connotation.

Although the precise pathogenesis of pulmonary hemorrhage following thromboembolism has not been clearly established, the probable mechanism is ischemic damage to endothelial and alveolar epithelial cells, permitting the passage of red blood cells and edema into the airspaces. The hemorrhage has been considered to be derived from the bronchial arteries via bronchopulmonary anastomoses[116] but theoretically can also come from the pulmonary artery itself when the vessel is only partly occluded or after clot retraction or fibrinolysis has partly reopened the vessel.

It is not known precisely what proportion of emboli result in infarction, although some necropsy reviews have suggested that the incidence is as low as 10 to 15 per cent.[24, 113] From both clinical and experimental findings, however, it is well known that pulmonary vascular occlusion, particularly of one of the main pulmonary arteries, usually results in no permanent tissue damage unless other factors coexist.[114] The most common underlying condition predisposing to infarction is congestive heart failure,[112] an association believed to be explained by increased pulmonary venous pressure and resulting decreased bronchial artery blood flow.

Experimentally, ligation of the pulmonary veins in the presence of thromboembolism has been shown to cause pulmonary infarction, supporting this hypothesis.[114] Shock, possibly by decreasing blood flow through the bronchial arteries, is also frequently accompanied by infarction.[22] Other conditions associated with an increased incidence of infarction include malignancy (especially of the lung in one series),[115] multiple emboli, the number of lobes containing emboli, the presence of peripheral as opposed to central emboli,[22, 116] and, experimentally, chest wall compression and pleural effusion.[114] In one recent study in which the factors associated with pulmonary infarction were examined, the major determinants were the functional status of the patient, the number of lobes containing emboli, the presence of left ventricular failure, and the coexistence of lung cancer.[115] Using discriminant analysis on a group of 21 patients, the combination of these four variables predicted the presence of infarction with 70 per cent accuracy; the size of the infarct was correlated most strongly with the use of vasodilators and the embolic burden.[115]

Atelectasis

Pathophysiologic consequences of sudden occlusion of a pulmonary vessel include local decrease

in compliance and in ventilation, caused at least partly by bronchoconstriction resulting from decreased P_{CO_2} within the bronchus supplying the occluded segment.[117–119] Loss of lung volume follows and is attributable at least in part to surfactant depletion;[120–123] this manifestation of pulmonary embolism is a common roentgenographic finding and is usually more striking when accompanied by infarction.[124]

After induction of pulmonary embolism in dogs,[125] airway resistance increased but bronchography showed no change in caliber of the large bronchi. If this takes place in humans, the airway obstruction must occur in small bronchi, bronchioles, or alveolar ducts.[126] In fact, experiments in dogs have implicated airways of 0.5 to 3.5 mm in diameter as being responsible for this response;[127] roentgenographic opacification with powdered tantalum of airways as small as 0.5 mm in diameter showed that all outlined intrapulmonary airways constricted equally after either ipsilateral or contralateral vascular occlusion by embolus. Airways whose initial caliber was 0.5 to 3.0 mm were the site of maximal narrowing, which occurred 80 to 120 seconds after embolization; the caliber became normal again in 4 to 40 minutes. Subsequently, it was shown[128] that autologous thrombi injected into the pulmonary artery of the left diaphragmatic lobe of dogs resulted in narrowing of right-sided airways of 0.4 to 15 mm in inner diameter, indicating reflex bronchoconstriction. Prior section of the left cervical vagus nerve significantly reduced contralateral bronchoconstriction, indicating that the parasympathetic nervous system partially controls airway narrowing after acute pulmonary thromboembolism. Using a similar technique plus bronchial pressure measurements, another group[129] injected aged, fresh, and inert (agarose) clots as emboli, to assess mechanical and humoral factors in the pathogenesis of bronchoconstriction. Bronchoconstriction of airways 0.3 to 3.0 mm in diameter occurred in all three groups. Since humoral effects derived from the thrombus could be discounted or minimized in the inert agarose and aged clots, it was concluded that mechanical factors were the common denominator. Bronchoconstriction was usually transient, the airways returning to normal dimensions within 5 minutes; the time of bronchoconstriction correlated with a drop in pulmonary compliance and an increase in airway resistance. This transient bronchoconstriction in response to pulmonary embolism in dogs has been demonstrated by radionuclide imaging,[130] unilateral pulmonary artery occlusion resulting in immediate diminution in ventilation of the ischemic lung and return to normal in 4 to 6 hours. Inhalation of 8 per cent CO_2 improved ventilation in some dogs.

Humoral effects of thrombi may be involved in the pathogenesis of bronchoconstriction. Experiments with animals showed that thrombi passing through the bloodstream to the lungs collect platelets which, when exposed to fresh thrombin, release serotonin and histamine, giving rise to bronchoconstriction.[131] In animals[131] and in humans,[132] this response can be prevented with heparin. In animals, postembolic bronchoconstriction is evidenced functionally by decreased lung compliance and increased resistance.[133]

Clinical and physiologic studies in humans also have indicated that pulmonary emboli induce the release of vasoactive and bronchoconstrictive substances such as serotonin, prostaglandins, and histamine, leading to bronchoconstriction, vasoconstriction, and perhaps altered pulmonary microcirculatory permeability.[134] Physiologic evidence of bronchoconstriction was found in 61 of 72 patients with pulmonary emboli, and only some had rhonchi.[135] In another study,[136] only 12 of 250 patients with acute pulmonary embolism (proved by angiography) had sufficient wheezing to justify a diagnosis of bronchial asthma; six of the 12 had an allergic diathesis, bronchial asthma having been diagnosed several years before embolism developed.

Hypertension

The effects of pulmonary embolism on the pulmonary vasculature are somewhat similar to its effects on the airways. Small pulmonary emboli increase pulmonary arterial pressure and arterial hypoxemia, the pressure rise depending on both mechanical blockage and vasoconstriction.[137] Angiography after induction of pulmonary air embolism in dogs[138, 139] showed that air injected into the main pulmonary artery resulted in a 140 per cent increase in pulmonary arterial pressure, no change in pulmonary wedge or left atrial pressures, and a 28 per cent decrease in cardiac output; all these changes disappeared within 13 minutes. Proximal branches of the pulmonary artery became wide and tortuous, and peripheral branches tapered rapidly with both unilateral and bilateral embolization. With the former, peripheral vasoconstriction occurred in the nonembolized lung, indicating a reflex origin. The angiograms also revealed faster passage of contrast material from pulmonary arteries to pulmonary veins, indicating that the increased pressure had opened arteriovenous anastomoses, creating a right-to-left shunt and explaining at least partly the arterial hypoxemia. Additional evidence for vasoconstriction in humans with thromboembolic disease lies in the partial reversibility of chronic pulmonary hypertension following the administration of vasodilating agents.[141]

Multiple small pulmonary emboli rarely cause sudden death and do so only when there is severe underlying lung disease. These patients may have no symptoms indicative of an embolic episode, but occlusion of the major portion of the pulmonary vascular tree almost inevitably results in acute pulmonary hypertension, cor pulmonale, and right-sided heart failure (a small atrial or ventricular

septal defect may be sufficient to relieve the right-sided hypertension and is the rare exception to this general rule). Even if there are multiple pulmonary emboli, pulmonary hypertension is not sustained until at least 50 per cent (probably closer to 70 per cent) of the pulmonary vascular tree is occluded.[142–147] However, transient pulmonary hypertension may result from vasoconstriction, particularly when smaller vessels are occluded;[142, 148–152] this may depend on a reflex or humoral mechanism.[145, 153]

When an increase in pulmonary artery pressure is discovered in patients with recent pulmonary embolism, it is usually necessary to exclude previous embolic occlusions or underlying disease, such as chronic obstructive pulmonary disease (COPD), as being responsible for the pulmonary hypertension. In such patients, the ratio of the mean pulmonary arterial pressure to the severity of vascular occlusion observed angiographically may effectively distinguish those patients in whom recent pulmonary embolism is the primary determinant of the postembolic hemodynamic abnormality from those in whom the pre-embolic hemodynamic abnormalities play the dominant role.[154] The presence of pulmonary hypertension in patients with COPD is an indication of advanced disease; a simple measurement of the FEV_1 as an indicator of the severity of disease may be useful in distinguishing underlying disease from embolic disease as the cause of the rise in pulmonary artery pressure.[155]

Pulmonary Edema

Diffuse pulmonary edema sometimes develops after pulmonary embolism.[140] Many patients are in heart failure at the time of the embolic episode,[159, 160] in which case the edema is readily explained on this basis alone. In experiments on animals, however, embolization of only one lung sometimes resulted in bilateral pulmonary edema, suggesting the possibility of a neurogenic mechanism.[161, 162] Another possible pathogenetic mechanism of pulmonary edema, applicable only in patients suffering massive embolism, is the pulmonary arterial hypertension that accompanies obstruction of a large cross section of the pulmonary vascular bed. Since right ventricular output must pass through a markedly reduced vascular bed, the pulmonary hypertension that inevitably ensues can conceivably cause high capillary hydrostatic pressures with resultant edema, analogous to that which occurs in some individuals at high altitudes; as might be expected, this is particularly true of patients with congenital absence of the right or left pulmonary artery.[163] Pulmonary edema localized to the left upper lobe has been well documented in a patient with massive embolism affecting the vasculature of the left lower lobe and right lung.[164] Sparing of the nonperfused areas of lung in both acute and chronic pulmonary embolization has been reported in patients who develop noncardiogenic pulmonary edema.[165, 166]

PATHOLOGIC CHARACTERISTICS

Lung Parenchyma

In the majority of instances, lung parenchyma distal to a pulmonary thromboembolus is either normal or shows only mild atelectasis and minimal intra-alveolar hemorrhage or edema. When changes are more marked, they consist of either hemorrhage alone or a combination of hemorrhage and necrosis. In the early stages, the two may be difficult to distinguish grossly, possessing a typical appearance of a more or less wedge-shaped area of deep red consolidation whose base abuts the pleura.

In the absence of tissue death, parenchymal hemorrhage usually disappears fairly rapidly and its residue may not be grossly detectable if the lung is examined a week or more after the embolic episode. Occasionally, deposition of hemoglobin-derived pigment on parenchymal and vascular interstitial tissue imparts a distinct yellow appearance to the previously affected lung for weeks after the initial event. In the early stages, histologic examination shows only intra-alveolar hemorrhage and

Figure 9–2. Recent Pulmonary Infarct. A wedge-shaped focus of hemorrhagic lung parenchyma is present adjacent to the pleura (*small arrows*). The lobule at the left is somewhat more hemorrhagic, although the entire area is necrotic. The lung architecture is easily identified in the necrotic regions. Note the thrombus in the feeding pulmonary artery (*large arrow*) and the fibrinous pleuritis (P).

Figure 9–3. Thromboembolism with Multiple Pulmonary Infarcts. A slice of right lung shows multiple recent pleural-based infarcts in the middle and lower lobes (*arrows*).

edema, with intact alveolar walls. Later on, hemosiderin-laden macrophages usually are the only evidence of prior damage.

Within 1 or 2 days of the thromboembolic event, an infarct becomes more easily recognizable as a firm, more or less wedge-shaped area of hemorrhagic consolidation typically abutting the pleura (Fig. 9–2). Although it is usually well demarcated, patchy areas of parenchymal hemorrhage may be present adjacent to it; it is this zone that can cause the poor definition of infarcts roentgenographically. Overlying fibrinous pleuritis is often present at this stage (Fig. 9–2). Multiple foci of infarction are not infrequent (Fig. 9–3). With time, the necrotic parenchyma becomes clearly demarcated from adjacent lung by a zone of organization tissue that may be red in appearance (reflecting the vascularity of the organization tissue) or distinctly white as a result of the influx of a large number of polymorphonuclear leukocytes (Fig. 9–4). Eventually, the infarcted parenchyma is completely replaced by fibrous tissue, resulting in a contracted, somewhat elongated scar associated with pleural puckering. Cavitation within the infarct usually but not invariably[167, 168] indicates the presence of superimposed infection, although it may be difficult to distinguish this from primary pneumonia with secondary vascular thrombosis. Whatever the etiology, cavitation is typically associated with a prominent leukocytic infiltrate, the enzymes from the latter presumably causing liquefaction of necrotic tissue as a precursor to drainage

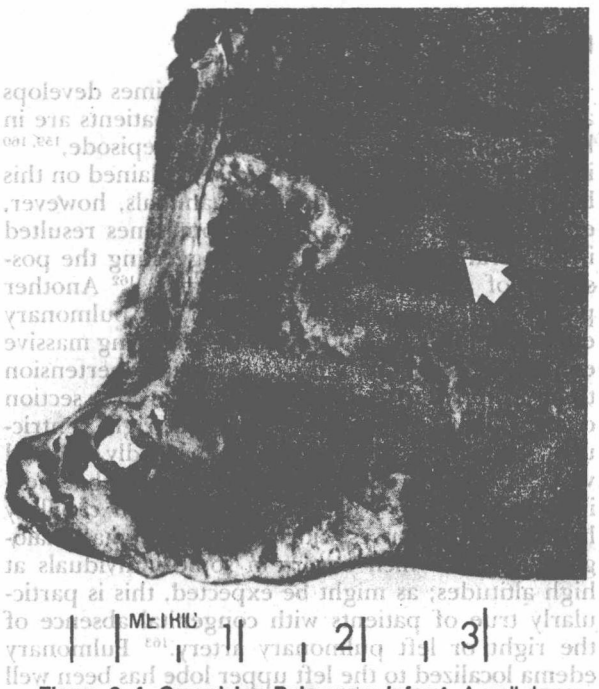

Figure 9–4. Organizing Pulmonary Infarct. A well-demarcated infarct is present in the basal aspect of the lower lobe. At the junction of necrotic and viable parenchyma, there is a distinct zone of white tissue representing a prominent polymorphonuclear leukocytic reaction. In relation to this, there is focal liquefaction and cavitation. Note that the underlying lung architecture in the necrotic zone is preserved; note also the pulmonary artery thrombus (*arrow*) and the residual pleuritis.

and cavity formation. Occasionally, the hemorrhagic appearance of a partly organized infarct is lacking, the affected parenchyma appearing white and granular; such a lesion can be mistaken grossly for neoplasm.

Histologically, infarcted lung parenchyma shows coagulative necrosis, which in the early stages may be somewhat obscured by alveolar hemorrhage and edema. Organization by granulation tissue is identifiable at the periphery after several days (Fig. 9–5). Reactive epithelial changes, particularly of type 2 pneumocytes, are often present at the margin of the infarct; when expectorated, these cells occasionally give rise to a false-positive cytologic diagnosis of malignancy.[169] Long-standing infarcts show dense parenchymal fibrosis in which the underlying lung architecture often can still be recognized. Airways within the fibrotic region may remain patent and viable, reflecting the preservation of the bronchial circulation; recanalized thrombus may be identifiable in pulmonary arteries (Fig. 9–6). The pleura in the vicinity of the infarct typically shows a prominent increase in vascularity as well as fibrosis and retraction into the lung itself (Fig. 9–6).

Experimental investigations in dogs and observations on humans with protracted pulmonary artery occlusion reveal a gradual increase in the bronchial circulation, which anastomoses freely with pulmonary vessels until the normal pulmonary arterial blood flow is equaled.[170, 171] Systemic-pulmo-

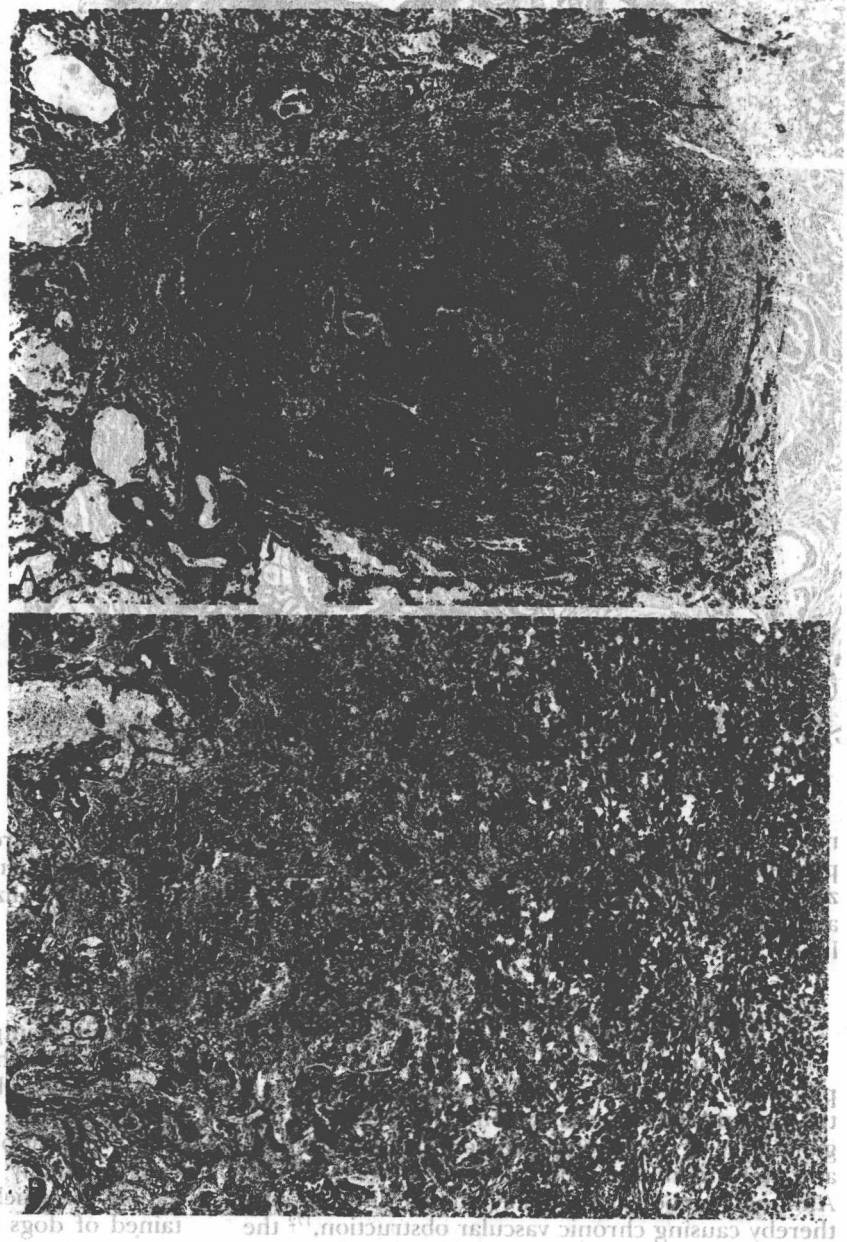

Figure 9–5. Organizing Pulmonary Infarct. A histologic section at low power (*A*) reveals a fairly well demarcated focus of necrotic lung parenchyma surrounded by a zone of organization tissue. Note the prominent vascularity in the adjacent pleura. A magnified view (*B*) shows coagulative necrosis of lung tissue on the left and granulation tissue on the right. (*A*, × 25; *B*, × 100.)

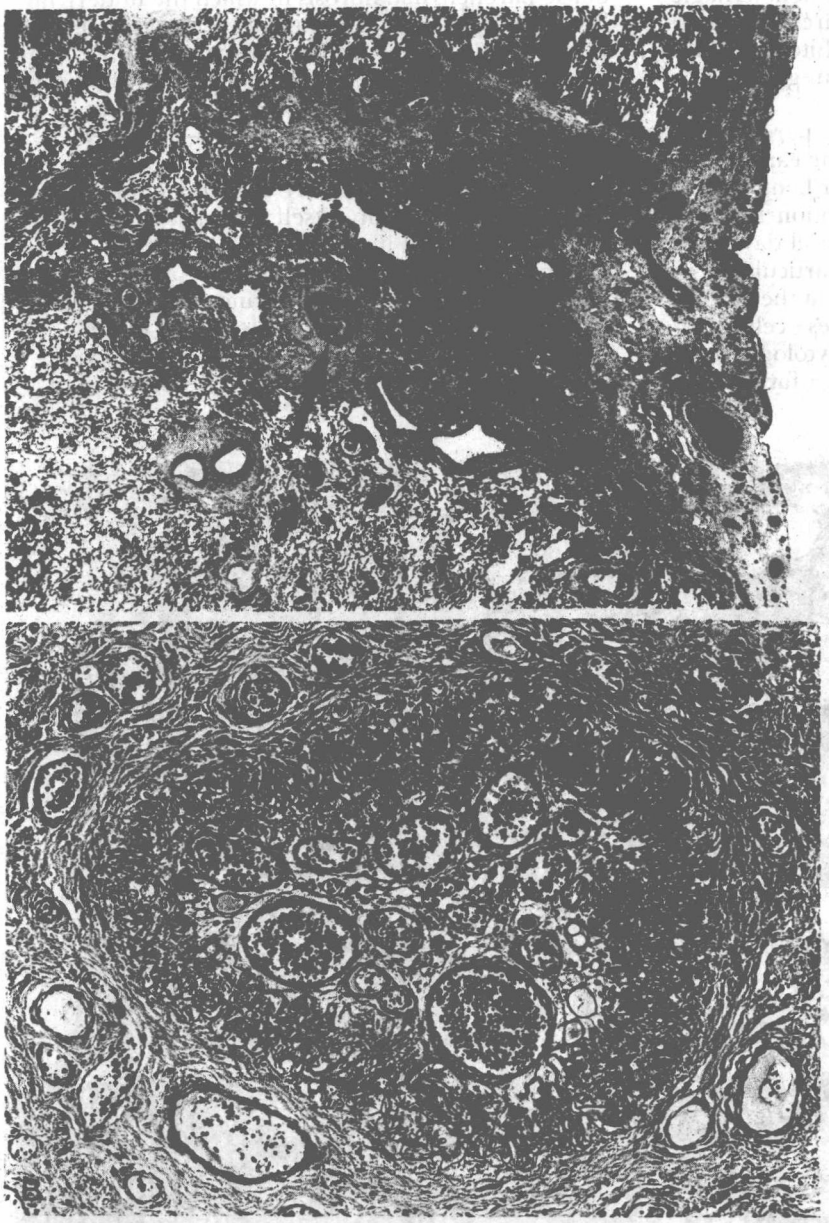

Figure 9–6. Remote Pulmonary Infarct. A histologic section (*A*) reveals a well-demarcated area of parenchymal fibrosis that abuts the pleura; the pleura itself is fibrotic and retracted into the lung (*short arrows* denote the pleura-lung interface). Note the histologically viable bronchi within the infarct and the partly occluded pulmonary artery (*large arrow*) containing recanalized thrombus. A magnified view (*B*) shows the pulmonary artery to better advantage. (*A*, × 10; *B*, × 120.)

nary arterial anastomoses are usually inapparent on postmortem aortography 3 to 7 days after embolization, but are well formed by 3 to 4 weeks; these anastomoses presumably play a major role in the lung's response to later emboli.[39]

Thromboembolus and Pulmonary Vessels

The fate of pulmonary thromboemboli depends on multiple factors, including the status of the patient's fibrinolytic system, the degree of organization of the thrombus before its embolization, and the amount of new thrombus added *in situ*. Although emboli occasionally change little in size, thereby causing chronic vascular obstruction,[172] the vast majority are largely degraded by one or more of three mechanisms—lysis, fragmentation and peripheral embolization, and organization and recanalization.

Lysis

Both roentgenographic[173] and perfusion scanning[174] studies have established that, in many cases, flow through obstructed arteries returns relatively rapidly in the first few days after embolization. These clinical observations have been substantiated experimentally by several workers. In one investigation in which serial roentgenograms were obtained of dogs following administration of throm-

boemboli labeled with powdered tantalum, Austin and his coworkers[175] found a gradual decrease in the breadth of the radiopaque labels in the individual clots, particularly during the first 2 to 4 days after embolization. In another study of fresh clot emboli in dogs,[176] the volume of the embolized clot was seen to diminish by 50 per cent in 3 hours. Such rapid and extensive dissolution suggests the effect of fibrinolysis. This subject is discussed in greater detail on page 1773.

Fragmentation and Peripheral Embolization

In the study by Austin and colleagues,[175] the clots were observed to fragment into multiple small pieces which embolized further towards the periphery of the lung; this change was observed somewhat later than lysis and was most prominent after the first week following embolization. The pathogenesis of this fragmentation may be related to splitting of the thrombus into smaller and smaller pieces as a result of ingrowth of endothelial cells and macrophages from the vessel wall.[177]

Organization and Recanalization

Ingrowth of fibroblasts, capillaries, and endothelial cells from the vessel wall into the peripheral portion of a thrombus can also result in its organization and eventual incorporation into the wall as a fibrous plaque, typically in an eccentric location (Fig. 9–7). Alternatively, some thrombi undergo lysis and

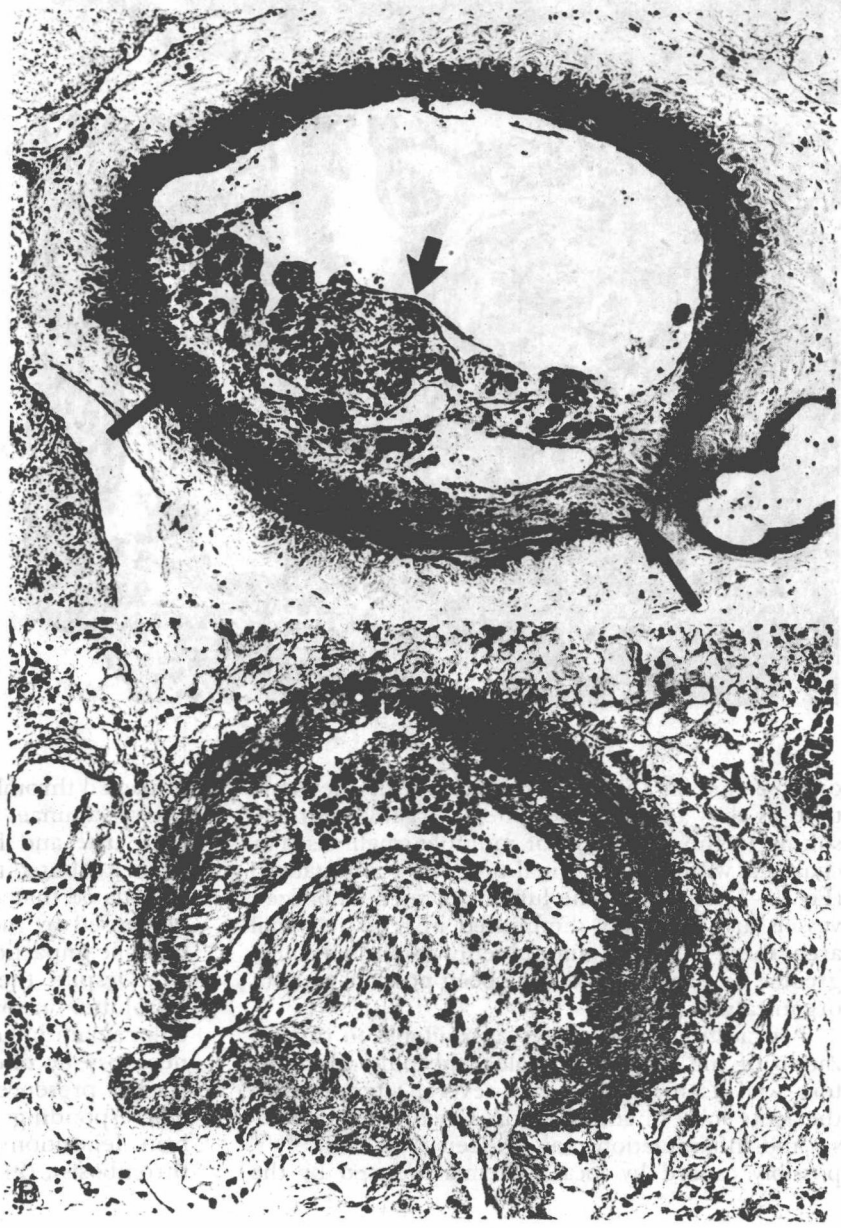

Figure 9–7. Organizing Thromboembolus. A histologic section of a muscular artery of medium size (*A*) shows a small amount of thrombus (*short arrow*) in the lower aspect. Its luminal surface is smooth and covered by endothelial cells; the thrombus was originally in direct contact with the vessel wall but has been partly replaced by fibrous tissue (*long arrows*). A section of another vessel (*B*) shows a more advanced stage of organization, the thrombus being completely replaced by fibrous tissue. Such eccentric intimal thickening is highly suggestive of remote thromboembolism.

Illustration continued on following page