Pathology of the Lung

H. Spencer

Fourth edition

Volume 2

PATHOLOGY OF THE LUNG

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(IN TWO VOLUMES)

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Preface to the Fourth Edition

"At first glance the lungs may seem uncomplicated, but many wise men have gone astray in their labyrinths." These words were written by the late Dr A. A. Liebow in his original foreword to the first edition of this book and they remain as true today. The author would like to pay tribute to the memory of Dr Liebow whose many original contributions to lung pathology will serve as his memorial. Also the author owed much to Dr Liebow for his help and encouragement over many years.

Pathology, in common with all branches of science, is for ever changing as new concepts of disease and new techniques are developed and applied. From being largely concerned with descriptions of morphological changes in diseased organs, it is becoming increasingly concerned with trying to understand how such changes occur. The development of immunology, molecular biology, enzyme chemistry and the application of newer physical methods of examination such as electron microscopy and dust particle analysis are rapidly changing some of the older concepts of disease. Nevertheless, the value of careful and thoughtful macroscopic and microscopic examination still remain the basic techniques in pathology. Some of the results of the application of the newer techniques are included in this text.

In this fourth edition the subject matter in every chapter has been re-examined, altered, elaborated or deleted, and several newly recognized diseases have been included. Pathology, the study of disease, should not be limited to a narrow description of structural changes, but should of necessity include consideration of all relevant matter concerned with the condition. Although the main emphasis is still placed upon the structural changes, many such changes result from disordered physiology and the physiology of the lungs need ever to be considered.

In earlier editions pulmonary tuberculosis was not included, as its pathology had been so thoroughly and well described in earlier years when it was still a major scourge in developed nations. The recession of its former importance in such countries, however, has tended to obscure the fact that it still remains one of the foremost diseases when the world is considered as a whole. For this reason an outline of the pathology of pulmonary tuberculosis has now been included. The bacterial pneumonias now include pneumonias caused by the *Legionella* group of micro-organisms.

The realization of the importance of immunology as a factor in many pulmonary diseases such as interstitial alveolar fibrosis and the angeitic disorders is better realized. Also the relationship of lymphomatous conditions to disordered immunological states is still but dimly appreciated. The importance of natural or induced immunodepression as a cause of opportunist fungal, parasitic and viral diseases has led to a great increase in such diseases. Neoplastic disorders such as Kaposi sarcoma spreading to the lungs, which formerly was only seen in African children, is now seen in immunodepressant states in adults.

About sixty new illustrations have been added to illustrate both new diseases and to improve upon earlier pictures.

The author would again like to acknowledge the continuing help with both material and illustrations that he has received from many pathologists and friends throughout the world without which this book

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Volume 1

CHAPTER 15

Pulmonary Thrombosis, Fibrin Thrombosis, Pulmonary Embolism and Infarction

Pulmonary Thrombosis

The importance and frequency of pulmonary embolism have caused it to over-shadow pulmonary thrombosis which in the past was regarded as of little importance in lung pathology.

Because the conditions under which thrombosis is likely to occur are also likely to favour embolism, it is often impossible to be certain whether intravascular thrombi are autochthonous or embolic in origin. The problem has been extensively reinvestigated during recent years, particularly in connection with certain forms of congenital heart disease, but the findings apply equally to all conditions in which the pulmonary blood-flow is reduced, including mitral stenosis and primary pulmonary hypertension.

The introduction of more exact methods of measuring intracardiac pressure and determining cardiac output, together with the introduction of surgical procedures to mitigate the effects of congenital heart disease and to repair certain of the abnormalities, has resulted in a careful reappraisal of the circulatory states in these various conditions and of the causes of surgical failure.

Thrombosis of arteries will occur when (a) the flow through the vessel is reduced below a certain critical level, (b) when the state of the circulating blood renders it more liable to clot and (c) when the vessel walls are damaged. Aschoff (1909) also regarded turbulence of the blood-stream as a predisposing cause of thrombus formation.

Thrombosis of the *major pulmonary arteries* can result from traumatic injuries of the chest, showing no external evidence of any injury or wound (Dimond and Jones, 1954). This condition is of forensic interest and importance. An elastic stain of the thrombosed pulmonary arterial wall shows a break in the media underlying the thrombus. More severe injury of the pulmonary artery may result in the formation of a false aneurysm. The very rare but true aneurysms of the pulmonary artery, as well as very severe pulmonary artery atheroma or syphilitic pulmonary arteritis, can both cause thrombosis. It may occasionally result from such primary lung diseases as pulmonary tuberculosis, emphysema, pneumoconioses and conditions of chronic cardiac failure. Spreading pulmonary artery thrombosis may also follow pneumonectomy, the thrombotic process originating in the stump of the ligated branch of the pulmonary artery. Clinically, the picture is one of increasing dyspnoea, syncopal attacks, fatigue and evidence of rapidly increasing right heart failure, and closely resembles that seen in any patient with chronic pulmonary hypertension. Owing to the failure of lung perfusion in the presence of continuing adequate ventilation, the end tidal (i.e. alveolar) CO_2 tension falls below the arterial pCO_2. Angiocardiographic studies enables the obstruction to be visualized in the pulmonary arteries. Also a hilar shadow may be seen in an antero-posterior chest radiograph.

At post-mortem, the pulmonary arteries on one or both sides are partly filled with a smooth polypoid mass of laminated ante-mortem

thrombus which projects into the main divisions (Fig. 15.1), and is attached within the intrapulmonary part of the arteries to the endothelial surface. The thrombus is not coiled upon itself.

Thrombosis of the *smaller pulmonary muscular arteries and veins* occurs when the pulmonary blood-flow is greatly reduced by such congenital abnormalities as Fallot's tetralogy, uncomplicated pulmonary stenosis, congenital stenosis of the tricuspid valve, and may also occur in association with neonatal sepsis and sickle-celled anaemia (Haemoglobin-S disease). Heath and Thompson (1969) described a case of sudden death in a young Negro man with Haemoglobin-S disease in whom many of the elastic branches of the pulmonary arteries were occluded by recent and recanalized thrombi. Newly formed capillary channels traversed the walls of the affected pulmonary arteries and joined branches of the bronchial arteries. The muscular arteries distal to the anastomoses, however, showed no hypertensive changes. Previously Wintrobe (1961) had noticed that arterial blood was frequently unsaturated with oxygen in haemoglobin-S disease and had suggested this might be caused by shunting of pulmonary arterial blood in the lung.

Heath *et al.* (1959a) found that pulmonary thrombosis occurred in congenital heart disease when the pulmonary index fell below 2·5 litres (the pulmonary index = pulmonary blood-flow in litres per minute per square metre of body surface, the normal figure being 2·5–4·4 litres per minute).

Rich (1948) reported that thrombosis occurred in about 90 per cent of untreated cases of Fallot's tetralogy, but Ferencz (1960a) found that it was present in only about 73 per cent of such cases. Thrombosis may extend to the major branches of the pulmonary arteries and is often accompanied by thrombosis of the pulmonary veins and dilatation of the bronchial arteries. Ferencz found that little correlation existed between the

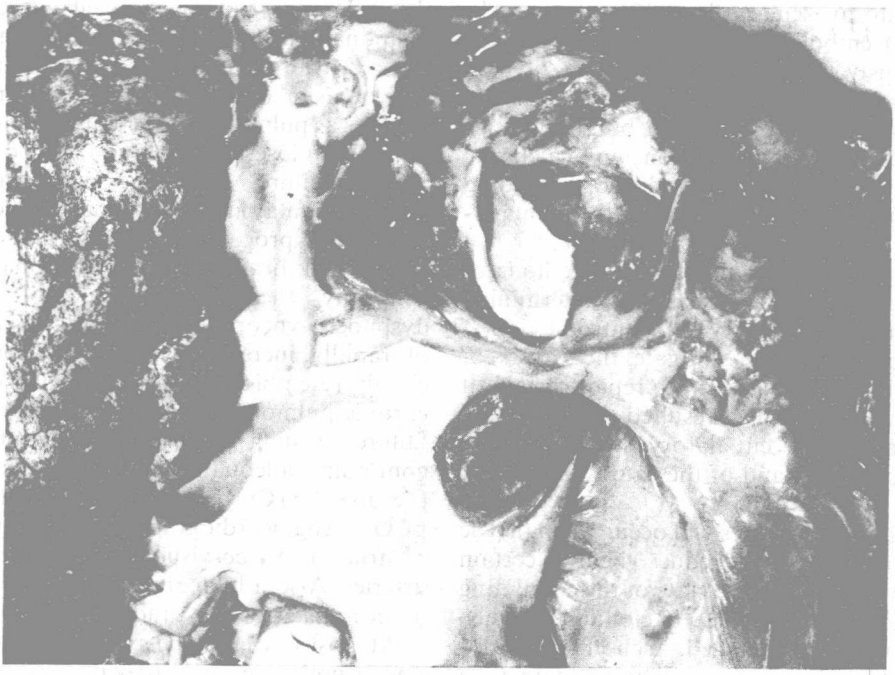

FIG. 15.1. Pulmonary artery thrombosis showing a smooth polypoid mass of thrombus projecting centrally from the left pulmonary artery. The right pulmonary artery is free of thrombus. Approx. three-quarters natural size.

degree of polycythaemia and the incidence of arterial thrombosis, but Heath *et al.* (1958a) stated that when the haemoglobin content exceeded 20 g/100 ml pulmonary thrombosis was likely to occur especially in older patients. The thrombosis may occur in the small pulmonary arteries during cyanotic attacks because Hamilton *et al.* (1950) found that during such attacks the pulmonary blood-flow, as judged by oxygen uptake, fell to very low levels. Ferencz (1960b) described the post-operative vascular changes following anastomoses of systemic to pulmonary arteries (Blalock operation) and found that in those cases with an inadequate anastomosis, thrombosis tended to occur in the pulmonary circulation, but thrombus formation was discouraged by the establishment of an adequate circulation. In the later stages of Fallot's tetralogy, pulmonary stenosis, and especially congenital tricuspid stenosis, by-pass operations may no longer afford relief as so many of the smaller intrapulmonary arteries become permanently obliterated by organized intravascular thrombi.

Pulmonary arterial thrombosis due to decreased pulmonary blood-flow may be accompanied, as already stated, by pulmonary venous thrombosis. It has been suggested that the latter change is largely responsible for causing lung infarction in pulmonary embolism. Embolization of infected pulmonary venous thrombus can be responsible for the development of metastatic abscesses in the brain in those forms of congenital heart disease with a decreased pulmonary index. Campbell (1957), however, believed that the cerebral abscesses, which are usually caused by microaerophilic streptococci, resulted from cerebral thrombosis or embolism followed by bacteriaemia and localization of the infection in the devitalized brain tissue.

Pulmonary arteriolar thrombosis may occur as a complication of generalized infections in the

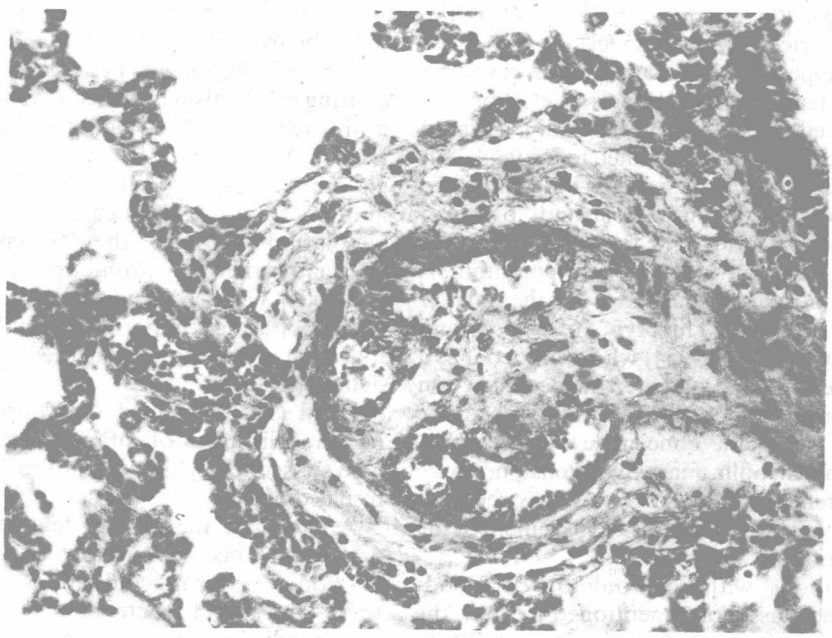

FIG. 15.2. Organizing thrombus in a pulmonary artery from a case of congenital pulmonary stenosis. × 280 H and E.

neonate (Groniowski, 1963), and both pulmonary thrombosis and embolism occur as terminal complications in patients dying from chronic emphysema (Ryan, 1963). Thrombosis of the small pulmonary muscular arteries may occur in heterozygous sickle-cell anaemia although the majority of the complications in this disease, including haemolytic anaemia, are more commonly found in homozygous cases. The first cases of pulmonary thrombosis in sickle-cell anaemia were described by Yates and Hansmann (1936). The sickle-cell trait is of special importance in patients who also suffer from asthma, in whom heterozygous sickle-cell anaemia may prove fatal.

An increased tendency for the red blood-cells to agglutinate (sludge) in the pulmonary capillaries and for thrombosis to occur is found in conditions of profound circulatory collapse such as occurs in severe burns, in haemolytic anaemias and in leukaemia. The capillary changes are usually restricted to the subpleural region and macroscopically the affected region of the lung is haemorrhagic and oedematous (see Chapter 13).

Microscopically, the organized thrombi in the muscular arteries may result in lesions with more than one type of appearance. The resulting fibroelastic tissue which replaces the thrombus may grow either as an eccentrically situated plaque or polypoid mass attached to the wall, or it may organize, leaving the lumen divided into two or more channels by narrow strands of fibroelastic tissue that bridge the lumen (Fig. 15.2).

Another change, which is less common, is concentric intimal fibroelastosis in the smaller pulmonary arteries. This type of lesion was described by Barnard (1954) who regarded it as a sequel to periodic or sustained vasoconstriction with diminished blood-flow through the artery concerned. The same concentric intimal fibroelastosis is met in pulmonary hypertension, where vasoconstrictive impulses are known to occur and initially play a large part in the development of the arterial changes.

In conditions with low pulmonary blood-pressure such as those mentioned above, the media of the elastic and muscular arteries is hypoplastic and reduced in thickness.

Fibrin Thrombosis of Pulmonary Vessels

This rare condition may follow as a delayed complication of amniotic fluid embolism (Ratnoff and Vosburgh, 1952; Tuller, 1957), and it has also been reported by Schneider (1951) in a pregnant woman who died after developing abruptio placentae; in the latter fibrin blocked many of the pulmonary arterioles. A similar case was also recorded by Johnstone and McCallum (1956). The condition has also been reported in patients suffering from carcinoma of the prostate, carcinoma of the pancreas, leukaemia, and following pneumonectomy.

Fibrin thrombi also form in the lung and other capillaries in septicaemic states, and often result in a consumption coagulopathy. Fibrin thrombi are a prominent feature in many cases of the disseminated intravascular coagulation syndrome following endotoxaemia.

In some cases, fibrinolysins develop and dissolve the intravascular fibrin thrombi. In such cases afibrinogenaemia may be present but was likely to remain undetected as signs and symptoms of disease due to the presence of thrombi are completely absent.

Various components necessary for the normal clotting mechanism have been found to be absent in this rare condition, including blood platelets, Factor V, Factor VII and anti-haemophilic globulin. Placenta, decidua, and presumably the amniotic fluid which gains entrance to the circulation through the placental site are unusually rich in thromboplastic substances. Schneider (1952) discussed the routes whereby thromboplastic materials could reach the maternal circulation from the site of placental detachment.

Boyd (1958) claimed that fibrin thrombosis occurred in lungs of infants borne by mothers who subsequently showed an abnormal tendency to bleeding.

Apart from the general tendency for haemorrhages to occur in various sites and the production of sticky mucoid blood-stained sputum, there are no characteristic changes whereby the condition may be recognized clinically or naked-eye at post-mortem. Microscopically,

FIG. 15.3. A fibrin "thrombus" in a branch of the pulmonary artery. × 100 approx. P.T.A.H. stain.

numerous intravascular fibrin thrombi are found filling the alveolar capillaries and they stain dark blue with phosphotungstic-haematoxylin (Fig. 15.3).

Fibrin thrombi have been produced experimentally in animals with pyrrolizidine alkaloids and the principal ultramicroscopic changes noted have been widening of the alveolar capillary endothelial gaps.

The thrombi in small arteries display a laminated appearance suggesting their formation and deposition from a fast-moving bloodstream.

Boyd (1960) claimed to have shown the presence of fibrin thrombo-embolism in the vessels of stillborn children and others dying within 3 days of birth and considered that it was responsible for death. In such cases laminated fibrin thrombi were found in the pulmonary vessels together with similar vegetations on the heart valves. Children surviving for a few days developed haemorrhages. The route by which the coagulating factor entered the circulation remained uncertain.

In a most unusual case seen by the author the pulmonary veins throughout the lungs were filled and occluded with a fibrin network which was absent in other organs (Fig. 15.3). The appearances were quite unlike post-mortem blood clot and the cause was unknown.

Pulmonary Embolism

The term pulmonary embolism has by common use come to mean impaction of thrombus which has been transported in systemic veins to the pulmonary arteries. Pulmonary embolism in the strict pathological sense may be produced by any substance which is capable of being transported in the blood to the pulmonary arteries. There is, however, one fundamental difference between embolism caused by thrombus and the other forms of embolism to be considered in this section: thrombotic emboli are formed initially within the vascular system, whereas the other kinds of emboli all originate outside vessels

and subsequently, owing to extravascular tissue pressure changes or growth of cells, are sucked, spread or are injected into vessels and subsequently transported to the lungs in the usual way.

THROMBOTIC EMBOLISM (PULMONARY EMBOLISM)

The dramatic clinical picture of a patient dying suddenly from a massive pulmonary embolus a few days after an operation has been recognized since the early days of major surgery and was well known to the early pathologists. The frequency with which symptomless emboli occur in both adult medical and surgical patients is not, however, so generally appreciated. Several series of post-mortem statistics on the true incidence of pulmonary emboli have been published and in Table 15.1 figures from some of the larger series have been included. The quoted figures vary widely depending upon the nature of the cases examined and the ages of the patients. Very high incidence rates occur among persons over the age of 45 who survive major lower limb fractures for a week or longer (Sevitt and Gallagher, 1959).

The incidence of proved pulmonary emboli varies directly with the amount of care that is taken in the examination of the lungs at autopsy.

TABLE 15.1

	Total post-mortems	Percentage with pulmonary emboli
Belt (1934a)	567	10
McCartney (1934) (injury cases)	1604	3·8
McCartney (1936) (post-operative cases)	2058	5·1
Hunter *et al.* (1941)	350	14·5
Hampton and Castleman (1943)	3500	9
Spain and Moses (1946)	1000	10·9
Raeburn (1951)	130	15·3
Morrell and Dunnill (1968)	263	51·7
MacIntyre and Ruckley (1974)	2291	13·2

All observers, however, are agreed that the incidence in children and young adults is very much lower than the figures quoted in Table 15.1 which largely reflects the post-mortem findings in middle-aged and elderly persons. Haber and Bennington (1962), however, found that in Chicago 1·25 per cent of fatal pulmonary emboli occurred in children less than 10 years old. The incidence of pulmonary embolism fell during the two World Wars only to rise again to higher levels than previously during the subsequent peace-time (Zeitlhofer and Reiffenstuhl, 1952).

The rising incidence of pulmonary thromboembolism is reflected in the Registrar-General's statistics for England and Wales where despite inaccuracies due to under-reporting and changes in the method of classification introduced in 1967, the death rate per million of the population has shown a continuing rise since 1945 and a rapid rise since 1953. Freiman *et al.* (1965) found the overall incidence of pulmonary thromboembolism in 2319 adult autopsies at the Beth Israel Hospital in Boston amounted to 33 per cent and in a specially examined series of sixty-one consecutive post-mortems to 64 per cent (39 cases). A similar post-mortem study by Morrell and Dunnill in which they examined only the right lung showed emboli present in 51·7 per cent. The usual frequency, however, is considered to be between 11 and 25 per cent. The continuous rise in incidence since the end of the Second World War has not been affected by the introduction of anticoagulant therapy as was shown by Barritt and Jordan (1961) who described seventy-two cases of pulmonary embolism in patients receiving such therapy. The introduction of subcutaneous low dosage heparin and dextran-70 regimens may hopefully reduce post-operative and puerperal thrombotic risks in the future. Furthermore, the introduction of the ^{125}I-fibrinogen test, radionucleotide venography, conventional venography, and Doppler ultrasound while helping to confirm the presence of venothromboses in the legs re-emphasizes the great frequency of peripheral vein thrombosis in adult surgical, medical and obstetric patients and enables those at risk of developing pulmonary emboli to be more readily detected and treated.