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THE NATURE AND SIGNIFICANCE OF THE STRUCTURAL CHANGES IN THE LUNGS IN MITRAL STENOSIS *

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INTRODUCTION

The lesions in cardiac disease are usually located in the left side of the heart, and it is the dysfunction of this side that is responsible for the majority of instances of circulatory failure. Ever since Corvisart's and Hope's contributions, morphologists have advocated a somewhat simplified mechanical "back pressure" concept of congestive failure. From time to time other explanations of circulatory failure have been offered, but the "back pressure" theory has received adequate support through the more recent physiological and chemical investigations. These studies have revealed that it is the disturbance of the pulmonary circulation that is the center of the problem of congestive failure.[1, 2] It is to the physiological and morphological changes within this circuit that the majority of the clinical manifestations are referable. While the study of the human pulmonary circulation during life has only recently become feasible, the effect of persistent passive congestion on the structure of the lungs has long been recognized and known under the term "brown induration." Furthermore, the pathological changes in the larger pulmonary arteries are familiar and are routinely looked for at autopsy, particularly in cases of mitral stenosis.

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Nevertheless, studies of the minute histological changes in the smaller blood vessels and alveolar capillaries have not been numerous. A detailed analysis of the relation of the morphological changes in the minute pulmonary vessels to structural alterations in the alveolar wall is also lacking. Thus it seems to us timely to analyze the physiological significance of the morphological alterations within the lungs in the presence of heart disease.

In a recent article zu Jeddeloh [3] has presented a review of the past studies of pulmonary congestion and in addition has reported his own observations on changes in the alveolar walls in chronic passive congestion. He did not include a study of the vascular changes apart from those of the capillaries. Brenner [4] has reviewed the literature on the pathology of pulmonary vessels; hence the presentation of such data is superfluous.

Our interest in this subject was aroused by the rather unusual clinical behavior and striking postmortem findings in a case of mitral stenosis, which is reported below. The study was later extended to a large group of cases presenting various types of pulmonary parenchymatous and vascular disturbances.

Material and Methods

In addition to the case reported in detail below, we have studied 9 cases of mitral stenosis. We have also examined the lungs in cases of rheumatic heart disease of varied pathology, of arterial hypertension, congenital heart disease, cardiac asthma, bacterial endocarditis, and in 1 case of marked kyphosis with right-sided hypertrophy and heart failure.

In the material under study during the past 2 years sections were taken from the upper and lower parts of each lobe and were run through separately. The tissues were fixed in Zenker's fluid and were routinely stained with phloxine-methylene blue and the Lee-Brown modification of Mallory's aniline blue connective tissue stain. In certain instances elastic tissue and reticulum stains were also employed.

Measurements of the structural components of the alveolus were done with the aid of a micrometer. In order to correct the error due to shrinkage of tissues, the instrument was calibrated in relation to the size of the red cells contained within the lung tissue. The average

diameter of 10 to 20 red cells was accepted as indicating 7.5 microns. The number of capillaries visible in normal and in congested lungs was counted.

Results

I. Structure of Normal Alveolar Wall

Before proceeding to a description of the pathological changes in the minute vessels and corresponding alveolar wall, it would seem

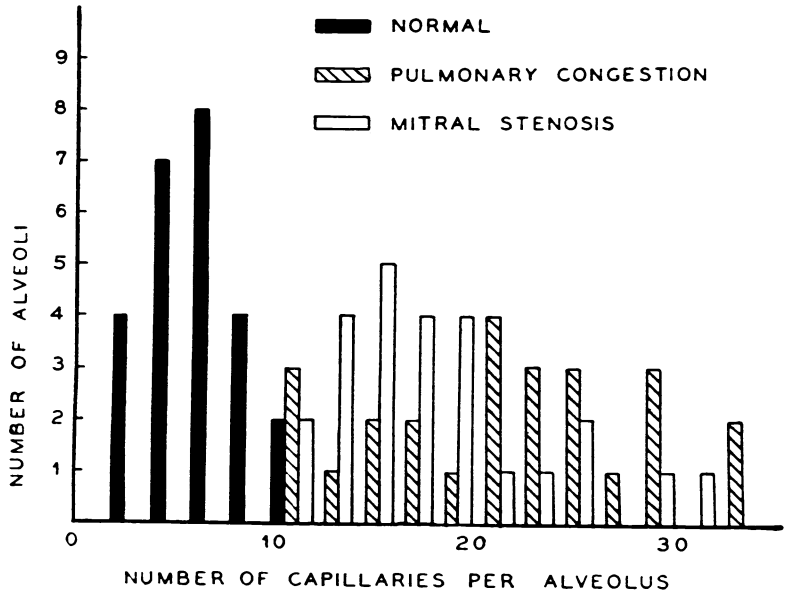

CHART 1

Comparative distribution of the number of visible ("open") capillary lumens per cross-section of a single alveolus in the normal lung, in the lung with simple congestion, and in advanced mitral stenosis

wise to review briefly the normal structure and dimensions of the alveolar wall.

The alveolar wall is covered by a layer of what, in our opinion, are flattened epithelial cells. Beneath these cells is a delicate band of collagen, the so-called alveolar basement membrane. This appears as a homogeneous structure, staining light blue with the Lee-Brown stain. Often placed somewhat eccentrically in the wall and close to the alveolar surface is a capillary whose lumen is sufficiently

wide to admit with ease the passage of a single red cell. In the normal lung the average diameter of the capillary lumen is between 9 and 10 microns. In the absence of congestion one sees relatively few capillaries with a diameter of over 14 microns. Surrounding these capillaries is a layer of collagen, the capillary basement membrane. The thickness of the tissues between the alveolar space and the capillary lumen is between 1 and 2 microns, while that of

TABLE I

Comparison of Diameters of Capillaries and of the Corresponding Alveolar Wall of the Normal Lung and the Lung in Advanced Mitral Stenosis

NORMAL		MITRAL STENOSIS	
Capillary (μ)	Alveolus (μ)	Capillary (μ)	Alveolus (μ)
9	16	20	54
14	17	25	67
9	15	16	45
10	14	10	68
12	16	26	26
9	12	28	55
9	12	20	72
9	14	30	68
10	15	12	70
8	12	7	41

the opposite side of the capillary is between 2 and 3 microns. Ordinarily the alveolar and capillary basement membranes are so close together that they appear as one layer, whereas they are quite separate. This is demonstrated, as will be shown, in instances where there is edema of the wall or an infiltration of cells between the two membranes. In addition to the above components, there are elastic fibers, an occasional delicate bundle of collagen, and a rare fibroblast or histiocyte.

Within the transverse diameter of the alveolar wall there is but 1 capillary. Along the circumference of a cross-sectional surface of the alveolar wall we have counted from 2 to 10 capillary cross-sections, with an average of about 5. Whether these visible cross-sections represent separate capillaries or whether some are parts of the same capillary cannot be stated.

The structure of the normal alveolar wall may be diagrammatically represented, as in Figure 3. Sample measurements of the normal capillary lumen and the alveolar wall, the ratio of the diameter of the capillary to the thickness of the alveolar wall and the relation of these findings to similar measurements obtained in the case of

mitral stenosis are presented in Table I. Chart 1 shows the number of capillaries visible ("open") per cross-section of a single alveolus in a normal lung, as compared with the number visible in congested ones. The difference, which was a consistent finding in counting the capillaries of numerous alveoli, indicates that in the normal lung as compared with the diseased, as observed postmortem, a considerable proportion of the capillaries are collapsed.

II. Structure of Minute Vessels and of Alveolar Wall in Cases with Cardiac and Pulmonary Pathology

Report of a Case

Clinical History: On Dec. 29, 1933, a 33 year old Irish-American female candy worker was admitted to the Boston City Hospital with the history of "heart trouble" of $2\frac{1}{2}$ years duration.

At the age of 10 years the patient was out of school for 6 months with a "nervous condition," probably chorea. At the age of 15 she suffered from generalized joint pain, with tenderness, swelling and redness. This condition lasted but 1 or 2 weeks. Six years before admission to the hospital she developed dyspnea on exertion, and suffered from coughing spells 5 to 6 times a year. About $2\frac{1}{2}$ years ago a heavy tray was dropped on the patient's head. Within a few hours she developed severe cyanosis, precordial pain and orthopnea. The pain radiated to the left side of the back and was accompanied by a sensation of heat down the left arm. Ever since this episode the patient had been an invalid, confined to bed during the greater part of the day. On several occasions she had been troubled by attacks of severe dyspnea, orthopnea, palpitation and precordial pain. During the past year, on 5 occasions she experienced severe attacks of a choking sensation with obligatory orthopnea, followed by rather profuse hemoptysis. On each occasion the sudden hemorrhage was followed by the raising of dark clots and streaked sputum for 3 or 4 days. During the week before she entered the hospital the patient became intensely dyspneic and felt chilly.

The family, social and past histories contained no additional pertinent facts. There was no history of nocturia or of edema. The patient had lost some 12 kg. during her illness, weighing 42 kg. at entrance to the hospital. Her height was 157 cm.

Physical Examination: On admission she appeared rather poorly nourished, and had to be propped up in bed. She was quite dyspneic, the lips were intensely cyanotic and her condition seemed alarming. The head and neck were normal without evidence of venous congestion. The chest showed symmetrical and somewhat limited excursion. The lungs were resonant with the exception of the right base, which was somewhat dull. Anteriorly over the subclavicular area, moist râles, and over the axillae and posteriorly toward the base, crackling râles were heard.

The apex impulse of the heart was in the fifth space, where the maximal left border was 11 cm. A systolic thrill was felt in the fourth space on the left side of the sternum. The first cardiac sound was marked by a presystolic murmur

over the apex. There was also a diastolic murmur and a snapping second sound. A gallop type of rhythm with a third heart sound and with a markedly accentuated second sound was heard. The pulmonary second sound was also accentuated and coincidentally a "shock" was felt over the pulmonary conus. The pulses were small. The arterial pressure was 60/30 mm. Hg. on admission; later the average level was 110/60 mm.

The liver edge was felt two fingers below the costal margin. There was no subcutaneous edema. The results of the rest of the examination were irrelevant.

Course of Illness: During almost 3 months stay in the hospital the patient suffered from numerous attacks characterized by intense dyspnea, orthopnea and accentuated cyanosis. On such occasions the lungs filled up with bubbling moist râles and she expectorated frothy, blood-tinged fluid. The patient became livid blue and later ashy gray. On each occasion she went into circulatory collapse. The attacks were relieved with oxygen and caffein. Between attacks she remained propped up in bed. During the first half of her last illness in the hospital the lungs cleared up fairly well between the attacks of dyspnea and pulmonary edema, but during the last 6 weeks of life coarse bubbling râles were present throughout the lung fields, particularly through the *upper part of the lungs*. Signs of fluid appeared in the right pleural cavity about 6 weeks before death, and on four occasions thereafter 1300 to 1500 cc. of amber colored fluid were removed, with temporary relief. Slight edema of the ankles appeared during the last 2 weeks. The patient expired on March 17, 1934, following an attack of dyspnea.

The temperature was essentially normal during the first 4 weeks; thereafter it rose to 101° F. at irregular intervals. The heart rate fluctuated between 80 and 120 per minute, and the respirations from 20 to 30.

Laboratory Data: X-ray examination of the chest (Dec. 29, 1933) revealed rheumatic deformity of the heart with congestive changes in both lungs. On Jan. 18, 1934, the diameter of the great vessels was 5 cm., the maximal transverse diameter of the heart 13.8 cm., and of the thorax 24 cm. Evidence of a small amount of fluid was present over the right base. On Jan. 24, 1934, in addition to the previous findings, localized shadows over the left axilla suggested small infarctions or pneumonia.

On Dec. 29, 1933, and on Jan. 25, 1934, the electrocardiogram revealed normal sinus rhythm. The P-R interval was 0.16 second, the Q-R-S 0.08 second. T_1 was flat, T_2 and T_3 inverted. The axis indicated right ventricular preponderance. On March 6, 1934, the electrocardiogram revealed auricular fibrillation.

Numerous analyses of the urine failed to reveal abnormal findings. The result of the concentration and dilution test of the urine was normal. The non-protein nitrogen of the blood was 41, 37 and 35 mg. per 100 cc. on different occasions. The Kahn test of the blood was negative. The red blood cell count varied between 4,000,000 and 5,200,000 per cubic millimeter, and the hemoglobin ranged from 69 to 84 per cent. The hematocrit reading was 42 per cent, mean corpuscular hemoglobin concentration 31.4 per cent, mean corpuscular hemoglobin 25.3 micrograms, mean corpuscular volume 80 cubic microns. The platelets were essentially normal and there was slight achromia. There was a continuous slight leukocytosis, 10,800 to 15,700 white blood cells per cubic millimeter, which on two occasions rose to 28,700 and 22,000. The polymorphonuclears varied from 63 to 86, lymphocytes 10 to 24, monocytes 4 to 10, eosinophils 1, basophils 2 per cent. Blood cultures were sterile. The chest fluid showed a specific gravity of from 1.006 to 1.012, red blood cells 2500 to 9000, white blood

cells 160 to 2200 per cubic millimeter; polymorphonuclear leukocytes predominated. The non-protein nitrogen content of the pleural fluid was 20 to 29 mg. per 100 cc.; protein 1.1 to 1.5 gm. per 100 cc.

Clinical Diagnoses: Rheumatic heart disease with advanced mitral stenosis; paroxysmal dyspnea (cardiac asthma) with attacks of acute pulmonary edema; chronic passive congestion and chronic edema of the lungs; right hydrothorax and congestive failure of the circulation; pulmonary infarcts.

Autopsy Report

Gross Findings: The examination was performed 5 hours postmortem. There was intense cyanosis of the lips and face, and marked lividity of the dependent parts. Slight pitting edema was present up to the knees. The *peritoneal cavity* contained 1000 cc. of clear amber fluid. The liver edge was 17 cm. below the xiphoid base, and 8 cm. below the costal margin on the right. The right *pleural cavity* contained 800 cc. of clear fluid; the left was obliterated by firm fibrous adhesions. The *pericardial cavity* contained 200 cc. of fluid.

The *heart* weighed 380 gm. The trabeculae of the right ventricle were moderately thickened. The endocardium of the left auricle was white and opaque and the auricular myocardium presented trabeculation. The mitral valve was rigid and sclerotic. The opening was represented by a narrow slit, 2 cm. long and 2 mm. wide (Fig. 1). The edges of the leaflets were slightly overlapping, and there was evidence of fusion of the leaflets at both edges of the fissure. The chordae tendineae were greatly thickened, shortened and calcified. The trabeculae of the left ventricle were markedly thinned. The aortic cusps showed questionable slight fusion at the commissures. The other valves were normal. The coronary arteries were also normal.

The cardiac measurements were as follows: tricuspid circumference 11 cm.; pulmonary opening 6.5 cm.; mitral slit 2 cm. long and 0.2 cm. wide; aortic opening 6 cm. The thickness of the left ventricle was 0.8 to 1.4 cm., and that of the right 0.2 to 0.5 cm. The aorta was delicate and elastic. There were traces of yellow atheromatous streaking in the lumbar region. The circumference measured 6 cm. at the ring, 3.5 cm. at the upper dorsal level, 3.4 cm. at the first lumbar vertebra, and 2.5 cm. at the bifurcation.

The *lungs* weighed 1350 gm.; the right 700 gm. and the left 650 gm. The pleural surface on the right was glistening, and on the left

contained fibrous tags. The cut section presented a rather unusual picture. The lower halves of both lungs were gray and somewhat firm and dense, though crepitant; they contained little blood. The upper halves were red and intensely engorged (Fig. 2). Over the upper half and middle portion of the right lung there were several small infarcts, one of which was located at the tip of the apex. The trachea and bronchi were dull brownish red. The pulmonary artery was somewhat dilated and was of normal elasticity, but the intima revealed numerous, rather soft, yellow atheromatous patches.

The *liver* weighed 1460 gm. The surface was slightly granular. The vascular markings were intensified.

The rest of the postmortem examination, except for evidence of passive congestion, was irrelevant.

Anatomical Diagnoses: Rheumatic heart disease with an unusually high degree of stenosis and calcification of the mitral valve; pulmonary congestion and edema of the upper half, and induration of the lower half of the lungs; small pulmonary infarcts; right hydrothorax; obliterative healed left pleuritis; ascites; passive congestion of the liver; edema of the gall bladder; chronic cystitis and vaginitis.

Microscopic Description

In describing the pathological changes in the *lungs*, their various component parts will be taken up separately:

1. *Alveolar Walls:* The severity of the lesions varied with the different lobes and portions of the lobes. In general, the lower lobes showed the most marked changes, particularly the lower parts of these lobes. Also, the lower portions of all the lobes were involved more markedly than the upper.

The least severe change noted was a marked dilatation of the capillaries, the diameters of their lumens being five or six times that of a red cell. In regions where the lesions were more advanced, not only were the capillaries dilated but they also appeared increased in number. This apparent increase may well have been due in part to increased length or to tortuosity. Often such capillaries presented an aneurysmal dilatation and bulged out into the alveolar space (Fig. 5). Accompanying this stage, the capillary basement membrane frequently showed slight thickening, but the alveolar basement membrane was normal.

A greater degree of change consisted in an increase in thickness of the capillary basement membrane and also of the interstitial collagen; the alveolar basement membrance even at this stage was normal. The capillaries here were dilated but showed less herniation into the alveolar spaces (Fig. 6).

Where the process had advanced further there was a definite increase in the interstitial connective tissue, and the capillary basement membrane was markedly thickened while the alveolar basement membrane remained normal. At this stage the capillaries were usually separated by the interstitial collagen from the alveolar space, which tended to be lined with cuboidal cells (Fig. 7). These cells often contained fat vacuoles. Thus the capillaries were separated from the alveolar space by structures of considerable thickness. Finally, the capillaries in such thickened walls became small, and in some none could be made out. Even in these advanced stages the alveolar basement membrane was never thickened, in contrast to the capillary basement membrane. These advanced structural changes were common findings in the lower third of the lungs.

Edema of the interstitial tissue of the wall was not uncommon. This was evidenced by separation of the component parts by fluid, with resulting thickening of the wall. The alveolar basement membrane was ballooned outward and it was in this condition that this membrane could best be recognized (Figs. 8 and 9). Such interstitial edema was by no means always accompanied by edema of the alveolar spaces.

The elastic tissue showed no definite changes.

There was often an infiltration of lymphocytes and macrophages in the thickened walls, and diapedesis of red blood cells into the walls was frequently seen. The alveolar spaces contained varying numbers of pigmented macrophages, and also edema fluid. In some areas emphysema was present. This led to narrowing of the alveolar wall with resultant diminution in the capillary lumens, often of such a high degree that a single red cell could barely pass through. In some such walls there was thickening of the collagen, indicating that congestion had existed here before the emphysema developed (Fig. 10).

A section through an infarct showed a picture, the significance of which will be discussed later. The parenchyma adjacent to the

infarct exhibited the most marked changes described above; *i.e.* great thickening of the alveolar walls with the air spaces lined by cuboidal epithelium. The alveolar walls in the infarcted area, on the other hand, showed slight if any increase in collagen and were

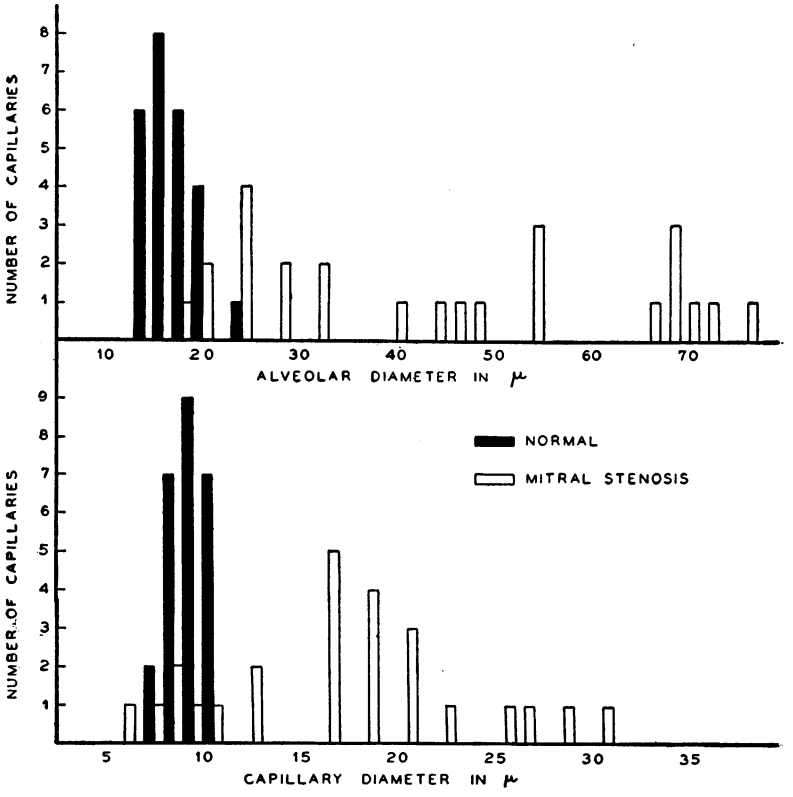

CHART 2

Sample of comparative measurements of the diameters of 25 alveolar walls and of corresponding capillary lumens of the normal lung and of the lung in advanced mitral stenosis

essentially normal as far as the connective tissue content of their walls was concerned. The condition of the smaller arteries and arterioles in the infarcted area could not be determined, since all cellular elements were, of course, completely necrotic.

The diameters of several hundreds of capillary lumens and of alveolar walls have been measured. Table I shows examples of such

measurements. There was usually a striking increase in both of these measurements, but the changes within the same alveolus did not parallel each other. Over the basal portion of the lungs, capillaries of normal diameter (7 to 9 microns) were often embedded centrally or eccentrically in alveolar walls of 40 to 60 microns in thickness, containing collagen staining intensely blue with the aniline blue stain. Chart 2 presents comparative measurements of the diameters of the alveolar walls and of the corresponding capillary lumens.

An attempt was made also to count the number of capillary lumens visible along the cross-section of an average sized alveolus. Chart 1 presents sample data of such counts in a normal lung, in a case of simple pulmonary basal congestion without heart disease, and in the case with mitral stenosis. As indicated, three to four times as many capillaries were visible in the presence of pulmonary congestion. It is of interest that the increase in the simple pulmonary congestion was of the same order of magnitude as in the case with mitral stenosis with intense active and passive congestion. Obviously, the number of capillary lumens visible along the cross-section of the alveolus does not correspond with the number of capillaries within the alveolus. If a capillary is tortuous the section may contain several cross-sections of the same capillary. Such counts as are presented in Chart 1 indicate, nevertheless, that in the normal lung (postmortem) the majority of the capillaries are not filled with blood unless there is active or passive congestion. Judging from the histological appearance of the capillaries and from the capillary counts, in the case of mitral stenosis not only were all the available pulmonary capillaries filled with blood, but they were stretched to their maximal capacity.

2. *Arteries:* (*A*) *Large Arteries:* These vessels showed marked thickening of the intima as a result of proliferation of connective tissue, which in its deeper portions often contained large, lipoid-filled macrophages. Reduplication and splitting of the internal elastic laminas were present. Thrombi undergoing various stages of organization were common.

(*B*) *Medium Sized Arteries:* These presented an unusual picture. The early lesion apparently consisted of a subendothelial deposition of fibrin with an associated proliferation of the lining endothelial cells (Fig. 11). Accompanying this stage was an increase in the

intimal connective tissue, in which appeared a number of capillaries. In the late stage the lumen was represented by narrow endothelial-lined spaces and the intima by vascular connective tissue (Fig. 12).

(*C*) *Small Arteries:* Marked intimal thickening due to increase in connective tissue and also some medial hypertrophy characterized the changes in this group. The alterations of the intima were the more striking, and resulted in a disproportion between the thickness of this layer as compared with that of the media.

(*D*) *Arterioles:* The walls of these vessels showed a high degree of thickening with apparent diminution in the diameters of their lumens. This thickening was due to a concentric proliferation of the cells making up their walls (Figs. 13 and 14). Between these cells lay delicate bands of collagen. In addition, a rare vessel undergoing necrotizing arteriolitis could be found (Fig. 15). Such arterioles showed blurring of the outlines of their walls with karyorrhexis of the nuclei and diapedesis of red cells. This type of lesion was also noted at the periphery of an infarct of some age. Hyalinization of the arterioles was not seen.

3. Veins: The only change of note was a thickening and hyalinization of the surrounding collagen.

4. Interstitial Connective Tissue: Edema of the septa was present in a marked degree without an associated edema of the alveolar spaces (Fig. 16). There were several foci of myelocytes and nucleated red cells in the perivascular and pleural connective tissue. The pleura showed marked increase in connective tissue.

Heart: There was some fibrous thickening of the epicardium with an infiltration of lymphocytes. In the myocardial connective tissue a rare Aschoff body and a few lymphocytes were noted. There was a minimal amount of scarring. Branches of the coronary arteries were thickened.

Liver: Hemorrhagic central necrosis, both old and recent, was present.

The other organs revealed nothing remarkable on postmortem examination.

Summary

The main features of this case may be summarized as follows:

1. An unusually advanced degree of mitral stenosis was associated with attacks of dyspnea, orthopnea and pulmonary edema.

During the last 4 weeks of life the patient exhibited a constant state of pulmonary edema and congestion. Clinical evidence of failure of the peripheral circulation appeared only as a terminal manifestation.

2. Because of the intense basal pulmonary congestion and edema and probable secondary infection, a severe degree of induration of the lower half of the lungs developed. This induration consisted mainly in a marked degree of thickening of the alveolar walls due to increased connective tissue and to a change of the flat epithelial layer into a cuboidal one. As a result of these changes the pulmonary capillaries became compressed; many of them were displaced into the middle portion of the alveolar wall and became surrounded by thick layers of collagen. Several of the alveoli contained no capillaries.

3. As a result of the above changes over the lower half of the lungs the congestion over the upper part of the lungs became intensified. Here, including even the apical area, the capillaries became widely dilated, many of them showing aneurysmal dilatation and bulging into the alveolar spaces. The capillary basement membrane showed various degrees of thickening, in contrast to the unchanged alveolar basement membrane. Separation of the two basement membranes by pericapillary edema was frequently observed.

4. There was atherosclerosis of the larger pulmonary arteries, healing and healed rheumatic arteritis of the medium sized arteries, and hyperplastic arteriolosclerosis and rarely necrotizing arteriolitis of the arterioles. It was particularly significant that both the frequency and the degree of the arteriolar changes increased from the apex towards the base.

5. The main changes in the veins consisted in increased connective tissue surrounding them.

6. Edema of the interlobular septa occurred independently of alveolar transudation.

Findings in Other Cases

In order to ascertain the significance of the pulmonary and vascular lesions observed in the case described, we have studied in a similar detailed manner 9 additional cases with mitral stenosis of rheumatic origin. Four cases in this group showed alveolar and vascular changes similar to those found in the first case but without rheu-

matic arteritis. In the remaining 5 cases the lesions were much slighter, consisting mainly of some thickening of the alveolar walls with a moderate degree of increase in the collagen and with distended capillaries over the lower portion of the lungs; there were no changes in the small arteries and the arterioles.

A comparison of the clinical and gross morphological characteristics of the 5 cases with advanced pulmonary vascular and parenchymatous lesions with those of the 5 cases with mainly intense pulmonary passive congestion revealed the following features: Four of the 5 subjects with marked pulmonary and vascular changes were young, the ages varying between 26 and 36 years. The age of the 5th subject was 58 years. The first rheumatic infection and the discovery of heart disease in each case dated back to childhood, but in all cases manifestations of a pronounced degree of cardiac failure appeared within 1 to 3 years of death. The circulatory failure was characterized mainly by intense cyanosis, complete physical disability associated with progressive and continuous severe dyspnea and orthopnea, precordial oppression and pain, with or without radiation, and later superimposed attacks of paroxysmal dyspnea and hydrothorax. The patients complained of periodic attacks of severe cough, "bronchitis" and hemoptysis. All these symptoms were present at first without evidence of peripheral congestive failure, such as venous engorgement, ascites, enlargement of the liver, jaundice, and edema of the lower extremities. Such manifestations developed relatively late. Once advancing cardiac failure appeared, the patients responded poorly to treatment. The cardiac rhythm was regular or auricular fibrillation. The first cardiac sound was loud and the pulmonary second sound accentuated and reduplicated. Other cardiac manifestations of mitral stenosis were also present. The electrocardiograms in three instances revealed high P waves. The contour of the X-ray picture revealed mitral bulging and varying degrees of increased pulmonary conus. The clinical features of these patients corresponded in several aspects to those described by Held, Goldbloom and Lieberson,[5] but the degree of cyanosis and respiratory difficulties were more intense.

Postmortem examination revealed a slit shaped, narrow mitral orifice in 4 cases. In the 5th case there was stenosis admitting the tip of the little finger. In all 5 cases the narrowed and distorted mitral leaflets were sclerosed and calcified and the chordae tendineae

were shortened and thickened. Acute rheumatic verrucous endocarditis was not present. The other valves were normal except in 2 cases in which the edges of the aortic cusps were "rolled" and slightly thickened. The weight of the heart was slightly or moderately increased. The left ventricle was of normal size and thickness, but the other chambers of the heart showed pronounced dilatation as well as thickening. In each of the 5 cases mural auricular thrombi were present. One or both of the pleural cavities contained from 1 to 2 liters of fluid. The peritoneal cavity was either filled with fluid or normal. The large pulmonary arteries showed a slight degree of sclerosis. The bases of both lungs in each of the 5 cases were gray, the consistence was increased and firm, and they contained a decreased amount of air. The upper portions of the lungs were red and congested and contained one or more small red infarcts. The severity and extensiveness of the basal induration and congestion of the upper portions varied, but in none of the 4 cases was the degree as severe as in Case 1.

The ages in the other group of 5 cases were more advanced. The onset of the rheumatic infection dated back to youth, and the duration of heart disease was longer. The onset and the progress of the symptoms of advancing cardiac failure were gradual, and there was a lesser degree of dyspnea, orthopnea and suffering in general than in the group previously described. These patients did not suffer from paroxysmal dyspnea. Cyanosis was either slight or absent. The clinical manifestations of pulmonary and peripheral congestion appeared simultaneously.

Postmortem examination showed a healed, scarred and calcified mitral valve admitting the tip of one finger. The chordae tendineae were shortened and thickened. In addition to the mitral stenosis, 1 case showed slight aortic stenosis, 1 a moderate degree of tricuspid stenosis and 1 aortic insufficiency. The degree of cardiac hypertrophy was greater and the auricular dilatation less than in the previous group.

The pleural cavities contained no fluid or only moderate amounts; the peritoneal cavity was either partially or completely filled with fluid. The large pulmonary arteries showed a moderate degree of sclerosis. The lungs exhibited basal congestion.

In addition to the detailed study of these 10 cases, the routine histological sections of 13 cases with mitral stenosis of varying de-

gree associated with other types of rheumatic cardiac involvement were examined, but sections of only 2 of these cases exhibited diffuse sclerosis of the small arteries and of the arterioles. A certain degree of thickening of the alveolar wall was frequently observed.

Control Cases

It is of interest that sections of the lungs from 5 cases of congenital cardiac septal defect, 12 cases of congestive circulatory failure of luetic and hypertensive origin, 15 cases showing pulmonary emphysema, 1 case of marked kyphosis and sclerosis of the larger pulmonary arteries, 20 cases of thrombosis or embolism of the pulmonary arteries, 19 cases showing chronic interstitial pneumonitis, and 3 cases of pulmonary fibrosis of non-cardiac origin failed to reveal pulmonary vascular and parenchymatous changes similar to those in the 5 cases that showed advanced mitral stenosis.

Through the courtesy of Dr. Tracy B. Mallory we have also examined the slides from a case diagnosed as Ayerza's disease (No. 6248). In this case, however, the small vessels were not involved and the alveolar structure was normal. Intimal proliferation and occlusion of several of the larger vessels were the main findings.

Discussion of Pathological Findings

The changes in the alveolar walls described above are in essential agreement with those reported by zu Jeddeloh.[3] Such changes are presumably the result of long continued hypertension, stagnation and edema. As a result of the increased intravascular pressure there occurs first a dilatation and apparent elongation of the capillaries. Following this there is a thickening of the capillary basement membrane, and this finally is followed by an increase in the interstitial collagen of the alveolar wall. This latter change we consider the result of interstitial edema.

As a result of the increased connective tissue and the consequent separation of the capillaries from the alveolar spaces, the involved alveoli are no longer capable of functioning. This is indicated by the cuboidal type of cells lining the air sacs. Function is also interfered with by the interstitial edema which fills and increases the space between the capillaries and air sacs. Furthermore, at various areas emphysema results in a marked diminution in the caliber of the cap-

illary bed, due to stretching with resulting narrowing of the alveolar walls. The diameter of the capillaries in such thin alveolar walls is frequently less than normal, and this narrowed capillary bed provides an increased resistance to the blood flow. It is of interest to note that emphysema occurred in some regions where apparently chronic congestion had existed previously, as indicated by the increased amount of collagen in the alveolar walls.

The vascular changes varied with the size of the blood vessels in question. The larger arteries showed proliferative changes in the intima with, in addition, the occurrence of lipoid-filled macrophages. The intimal proliferative changes consisted of increased connective tissue with splitting and reduplication of the internal elastic laminas. Such changes have for many years been ascribed to the effect of hypertension, and in our opinion are rightly so interpreted, since analogous lesions are seen in the kidney in cases of hypertension.

The changes in the medium sized arteries described in our first case are to be regarded as probably of rheumatic origin, in view of the studies of VonGlahn and Pappenheimer.[6] We observed such lesions in none of our other cases. In them, the medium sized and smaller arteries showed marked fibrous thickening of the intima of such a degree that often the intima was thicker than the media. There was also some hypertrophy of the media.

The arterioles presented the picture of hyperplastic arteriolosclerosis (productive endarteritis), *i.e.* thickening of the walls due to concentric cellular proliferation, giving an onion-like layer of cells in the walls. This vascular change especially aroused our interest because of its similarity to the arteriolar changes in the kidney in malignant hypertension. This similarity was further emphasized by the occurrence — rare, it is true — of necrotizing arteriolitis. This lesion, in addition to being present in scattered areas in the lung, was found also in the vicinity of an infarct, a fact the significance of which for renal infarcts has been discussed by Klemperer and Otani[7] and more recently by Kimmelstiel and Wilson.[8] No hyaline degeneration of the arterioles such as is seen in the kidney, pancreas and adrenals in benign hypertension was noted in the lungs in our series.

In reviewing the vascular changes in the lung described above, one is struck by their similarity to the changes observed in the kidney in malignant hypertension. In both organs the larger arteries

show proliferative changes in the intima. The arterioles show hyperplastic arteriolosclerosis and in addition necrotizing arteriolitis In view of this, it seemed of interest to determine approximately the dimensions of the vessels showing these various changes in the two organs under discussion. For this purpose, the external diameters of the vessels were measured. In both organs it was found that the great majority of vessels showing hyperplastic arteriolosclerosis and arteriolonecrosis measured less than 100 microns, while those showing intimal proliferative changes measured more than 150 microns.

The vascular changes in both organs lead to serious interference with their functional units, *i.e.* the glomerulus and the alveolar wall. These two structures have in common certain anatomical and physiological functions. Both are made up of capillaries, surrounded by a basement membrane which is covered by epithelium. As a result of vascular alterations, both units undergo changes which eventually result in the complete loss of function. In the kidney the glomerulus becomes a hyalined scar; in the lung the alveolar wall a broad band of rather avascular connective tissue.

Finally, we feel that the histological picture found in the infarct in Case 1 is important from the point of view of the length of time necessary to produce the pulmonary changes we have described. As pointed out in the microscopic description, the alveolar walls in the infarct showed no increase in connective tissue, while the adjacent walls exhibited a marked degree of thickening and the alveolar epithelium was cuboidal in type. There are apparently two explanations of the above picture: (1) the infarct involved normal tissue, and (2) the infarct occurred before the parenchymatous changes had taken place. Against the first suggestion is the fact that all the surrounding parenchyma is pathologically altered and it seems improbable that there should be a directly contiguous area of normal tissue, since the process in any one given area tends to be uniform and diffuse. If the second explanation, which seems the more probable, is correct, then we have definite evidence that the changes in the alveolar walls can occur in a comparatively short period of time, for the infarct shows but little signs of healing. In our estimation the duration was weeks rather than months.

Clinical and Physiological Significance of Structural Alterations in the Lungs

The clinical manifestations of failure of the pulmonary circulation are believed to depend on a dynamic alteration of the blood flow secondary to the back pressure effect of cardiac lesions or dysfunction in the left side of the heart. The physiological changes manifest themselves primarily in retardation and stagnation of the flow, which is more marked over the lower than over the upper portions of the lungs.[2, 9, 10, 11] The observations here presented, however, demonstrate that the circulatory engorgement can induce permanent structural alteration of various tissue components of the lung, which, in turn, can then be the source of disturbed functions, as well as of clinical symptoms and signs. *The nature of these structural changes is such that they interfere with the vital pulmonary function of gaseous exchange.* Over the lower half of the lungs the capillary basement membrane becomes thickened and deposition of a considerable amount of collagen separates the capillary lumen from the alveolar space. Not infrequently the flat, thin epithelial cells become thickened and cuboidal. The normal thickness of 1 to 3 μ of the alveolar tissue, through which oxygen and carbon dioxide have to diffuse, can change to a thickness of 30–50 μ. Over such pulmonary areas the blood flow is shunted without any appreciable degree of alteration of its gaseous contents. In advanced cases of "tight mitral stenosis," thickening of the alveolar wall with markedly dilated capillaries may be present not only in the lower but also, as has been shown, in the upper portion up to the apex. In spite of the fact that even in these high non-dependent areas the pericapillary collagen can be somewhat increased, both oxygen and carbon dioxide obviously must diffuse freely through these alveolar structures. Nevertheless, the fact that the diameters of the *distended capillaries* permit the simultaneous passage of from five to twenty or more red cells, instead of one or two, must be a significant contributory factor to the maintenance of arterial anoxemia. It is, however, of interest that study of the arterial blood in patients with circulatory failure often indicates no increase in the carbon dioxide content, even in the presence of a severe degree of anoxemia.[12] This difference in oxygen and carbon dioxide content must be explained by the greater diffusion coefficient of carbon dioxide. Liljestrand and

Sahlstedt [13] have found that carbon dioxide diffuses about forty times more rapidly than oxygen through the alveolar wall of the lung of the frog.

Patients with chronic heart disease, particularly with mitral stenosis, at times exhibit intense cyanosis regardless of subsequent myocardial improvement, as indicated by studies of hemodynamics. The structural alterations in the pulmonary architecture observed in this study suggest that if, as a result of long existing pulmonary engorgement, the structural alterations are permitted to develop, certain symptoms such as cyanosis and even dyspnea may persist regardless of the myocardial improvement established thereafter. The change in size and in the elastic properties of the lung tissue in these cases must represent, for the development of dyspnea and tachypnea, a stimulus to the nerve endings located in the lungs and in the pleura similar to that present in chronic emphysema or interstitial pneumonitis. The finding of thickened alveoli exhibiting increased amounts of collagen and other changes demonstrates that in the presence of chronic failure of the circulation not only physiological but also structural alterations contribute to the *stiffening of the lungs* ("Lungenstarre" of von Basch[14]).

Some of the patients whose lungs were studied exhibited rather profuse transient pulmonary hemorrhages. The rupture of the large bulging capillaries observed is an obvious source of such hemorrhages. Whether diseased arterioles rupture at times, we do not know.

We have been impressed in the past by the frequent lack of correlation between acute or chronic dyspnea and orthopnea, on the one hand, and such clinical signs as pulmonary râles, on the other hand. On postmortem examination one observes heavy lungs with only a moderate degree of hyperemia and no appreciable amount of edema within the air passages. The demonstration of the existence of *pericapillary edema* without intra-alveolar edema offers adequate explanation for such a situation, and the findings presented demonstrate also that a considerable amount of tissue fluid may accumulate around the capillary bed. Such a state of affairs must contribute to the patient's distress, and this type of edema, in contrast to other structural changes, should be amenable to therapeutic procedures. We have also observed not uncommonly the opposite situation, namely, the existence of *intra-alveolar edema* without capillary en-

gorgement and without alteration in the structure of the alveoli. In this type of pulmonary edema a primary alteration of the permeability must be the determining factor. Finally, pericapillary and intra-alveolar edema often coexist.

When both primary pulmonary *emphysema and heart disease* were present, the capillary bed usually was not dilated. In these cases, although the alveolar wall shows no thickening or only a slight degree of thickening, an increase in the collagen content of the alveolar wall has been demonstrated. Hence, here, too, the circulatory engorgement contributes through structural alterations to the further rigidity of the alveoli. The fact that in an emphysematous lung the already diminished capillary bed cannot dilate, represents loss of an important vascular reserve function of the lung, which is essential under certain types of stress. Loss of such reserve function must facilitate the development of pulmonary hypertension.

In attempting to throw light on the etiology of pulmonary arteriolosclerosis, it seemed significant that the advanced vascular lesions were situated in the lower portions of the lungs, while in the upper portions sclerosis was not present or was but slight. This striking difference in the distribution of the vascular lesions must bear pertinently on the origin of the type of sclerosis described. The main differential characteristics of the functional state of the lower portions of the lungs as contrasted with those of the upper portions in the cases studied were: (1) higher capillary and arteriolar pressure; (2) slower blood flow and stagnation; and (3) pericapillary and intra-alveolar edema. It is therefore rational to conclude that the vascular changes observed are dependent on these three factors, or on chemical or morphological alterations which are secondary to these factors. It is of significance, also, that in malignant nephrosclerosis, high pressure, as well as stagnation, is present within the arterioles exhibiting sclerosis, as is indicated by injection methods.[15]

That combination of these three factors seems to be essential is shown by the fact that in pathological conditions where only one of the factors is present, arteriolar sclerosis, and particularly necrotizing arteriolitis are not observed. Thus the clinical and histological examinations of the upper portion of the lung in Case 1 have indicated markedly increased vascular pressure, but vascular sclerosis was not present. In the control group of pulmonary emphysema and congenital heart disease with hypertrophied right ventricle, sclerosis

was also absent, in spite of the fact that the pulmonary blood pressure was presumably high. Similarly, in a group of cases with long persisting chronic passive congestion and edema of cardiac origin, or with chronic pneumonitis and fibrosis, the vascular lesions were not present. On the other hand, it has been shown recently that long persisting pulmonary edema induced in the rat by the prolonged administration of oxygen under high barometric pressure can induce a type of pulmonary arteriolosclerosis consisting of a thickening and hyalinization of the walls with ultimate thrombosis of many.[16] It is of interest that in addition to engorgement and edema, the lungs of these animals also exhibited increased arterial pressure.[17] These studies are of particular interest because they rule out anoxemia as an etiological factor.

It would be of significance to be able to estimate the time element essential for the development of the arteriolar lesions described. It is therefore pertinent that when the patient in Case 1 entered the hospital the lung fields were essentially of normal density, as indicated by X-ray examinations, and the marked degree of density of the lower half of the lungs developed during a period of $2\frac{1}{2}$ months. It was also of significance that the red infarcted areas contained no thickened alveoli, while the non-infarcted areas at a corresponding level exhibited all grades of parenchymatous changes. As these infarctions were not older than 1 or 2 months, the advanced pulmonary lesions must have developed within the same period of time. That in malignant nephrosclerosis similar types of lesions can develop in the kidney within a period of the same order has been actually demonstrated by us in a comparative study of the two kidneys of the same case obtained at an interval of 67 days.[18] Finally, it has been shown that pulmonary arteriolosclerosis and an increase in the interstitial collagen can be induced experimentally within 30 to 40 days.[16]

Advanced ("tight," "non-regurgitant," "buttonhole") mitral stenosis is but one type of lesion that can lead at times to the combined presence of the three pulmonary factors mentioned. In cases with chronic pulmonary emphysema or congenitally increased pulmonary vascular resistance in which repeated attacks of pneumonitis or other types of change associated with edema develop, the three responsible factors are particularly apt to coexist and hence pulmonary arterial and arteriolar sclerosis are expected to occur.

Such may indeed be the etiological mechanism in instances described as primary pulmonary sclerosis of "Ayerza syndrome."

The 5 cases of hyperplastic and necrotizing arteriolitis exhibited intense dyspnea, orthopnea, tachypnea, cyanosis and precordial oppression and pain. Superimposed on these difficulties were attacks of severe cough, hemoptysis and cardiac asthma with transient intra-alveolar edema. The pulmonary second sound was loud and reduplicated. These manifestations are indicative of unusually high pulmonary pressure. The postmortem examination likewise suggested high pressure throughout the pulmonary circuit.

It has also been shown in this study that these cases of advanced mitral stenosis exhibited vascular changes quite similar to those found in the arterioles of the larger circuit, particularly in the kidneys of patients with malignant arterial hypertension. It has also been stressed earlier that a number of similarities exist between the function and structure of the glomerulus and alveolus. While in the presence of advanced mitral stenosis the pulmonary vascular system is involved and the arteriolar system of the larger circuit is normal, in cases of uncomplicated malignant hypertension of the larger circuit the situation is reversed, and the vascular system of the pulmonary circuit is normal. These clinical and physiological considerations, together with the morphological findings here presented, indicate a close similarity existing in the pulmonary circuit in the group of cases of mitral stenosis, and in the larger circuit in the group designated as malignant hypertension with malignant nephrosclerosis.[18] Hence these advanced cases of mitral stenosis can be considered as exhibiting the clinicopathological syndrome of *pulmonary hypertension with malignant sclerosis*. This designation does not imply that the syndrome is always clear-cut, or that clinically it can always be sharply differentiated from the syndrome of pulmonary hypertension without advanced or malignant sclerosis. In this respect, too, the problem of the malignant sclerosis of the two vascular circuits is identical.

Because the mechanical and circulatory factors active in this type of mitral stenosis leading to malignant pulmonary sclerosis are known to a large extent, further studies on the origin of these pulmonary vascular lesions may well throw light on the etiology of vascular changes in malignant hypertension and malignant nephrosclerosis.

Summary and Conclusions

1. The changes in the blood vessels and alveolar walls in the lungs in cases showing an advanced degree of rigid mitral stenosis associated with intense failure of the pulmonary circulation are presented, and the structural alterations found are compared with those observed in other types of mitral stenosis and in a control group with varied types of cardiac and pulmonary disease.

2. The lesions in the pulmonary vessels consisted of (*a*) intimal thickening of the arteries, and (*b*) hyperplastic arteriolar sclerosis and arteriolar necrosis.

3. The changes in the alveolar walls consisted of (*a*) marked dilatation of the capillaries, (*b*) increase in the thickness of the capillary basement membrane, (*c*) increase in the interstitial tissue (collagen), (*d*) interstitial pericapillary edema, and (*e*) a tendency of the flat epithelial cells to become cuboidal in shape.

4. The normal thickness of 1 to 3 μ of alveolar tissue through which oxygen and carbon dioxide have to diffuse can increase up to a thickness of 30–50 μ.

5. Even in the presence of an advanced degree of thickening of the alveolar wall and of the capillary basement membrane, the alveolar basement membrane remains normal.

6. With progressive pulmonary engorgement, first the visible capillaries increase in number, and only later do they dilate. Often the capillaries become displaced and are separated from the alveolar surface by a considerable degree of edema or by thick layers of collagen.

7. Pericapillary and intra-alveolar edema frequently develop independently.

8. Permanent structural alterations in the lungs caused by circulatory failure interfere with the gaseous exchange, partly through altered permeability of the alveolar wall, and partly as a result of the simultaneous passage through the individual capillaries of numerous columns of red cells, instead of a single red cell.

9. In the causation of the pulmonary arterial and arteriolar lesions, an important rôle is played by the prolonged combined presence of (*a*) high intravascular pressure, (*b*) stagnation of blood flow, and (*c*) edema.

10. Evidence is presented that advanced vascular lesions in the

pulmonary, as well as in the larger circulation, can develop within about 2 months.

11. The clinicopathological syndrome of pulmonary hypertension with "malignant" sclerosis is described and the similarity between this condition and arterial hypertension with malignant nephrosclerosis is discussed.

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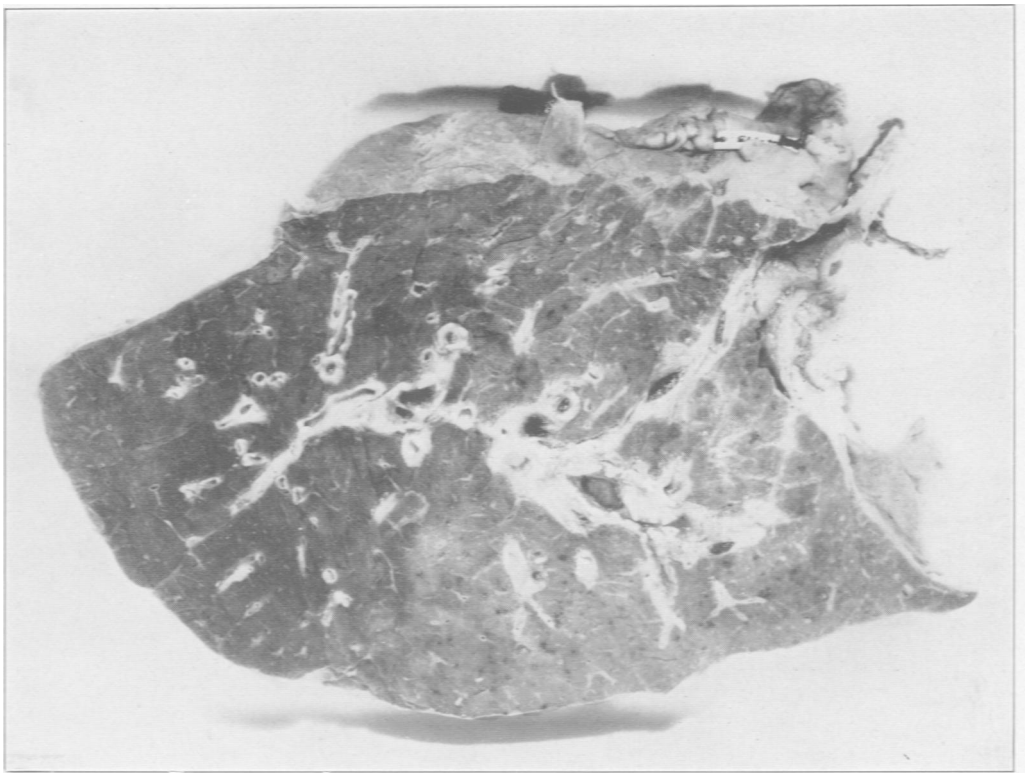
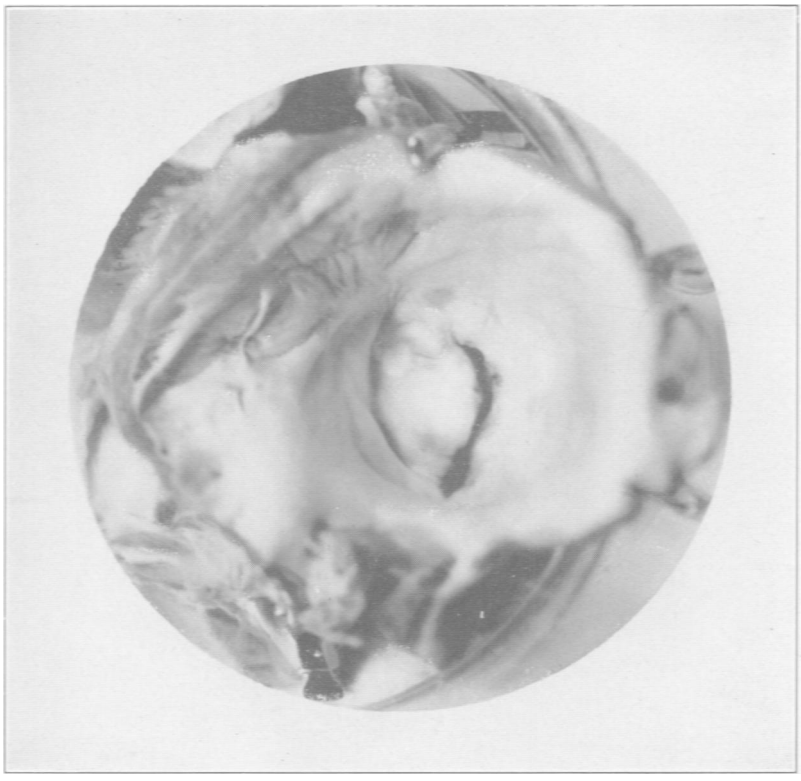
DESCRIPTION OF PLATES

PLATE 106

FIG. 1. Mitral valve from Case 1, viewed from above. Note narrow, slit-like, rigid orifice.

FIG. 2. Lung from Case 1. Upper half red and congested, lower half gray and indurated.





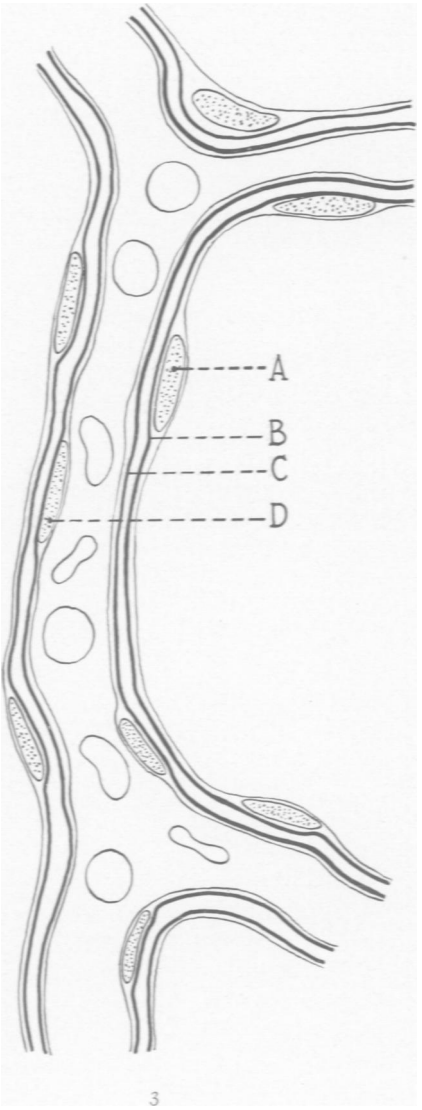
Parker and Weiss Structural Changes in Lungs in Mitral Stenosis

PLATE 107

FIG. 3. Diagrammatic drawing of structure of alveolar wall, emphasizing the location and relations of the basement membranes.

A = epithelial cell lining alveolus
B = alveolar basement membrane
C = capillary basement membrane
D = endothelial cell lining capillary

FIG. 4. Normal alveolar wall. Capillary sufficiently wide to admit passage of a single red cell. Alveolar and capillary basement membranes appear as a single thin line. Aniline blue stain. × 670.



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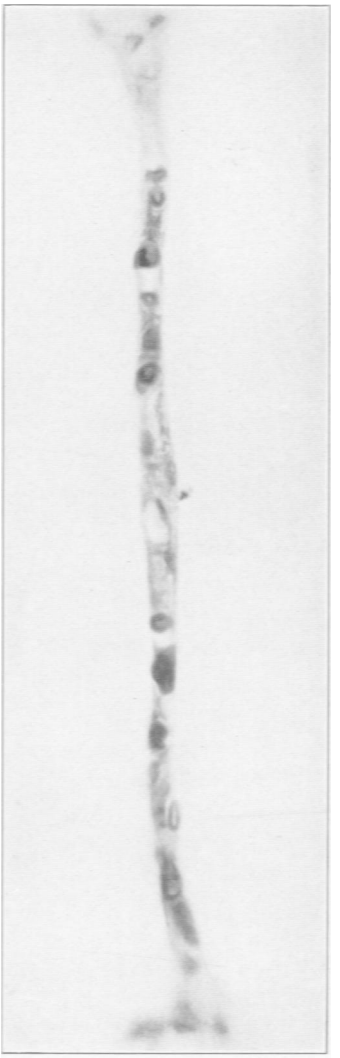

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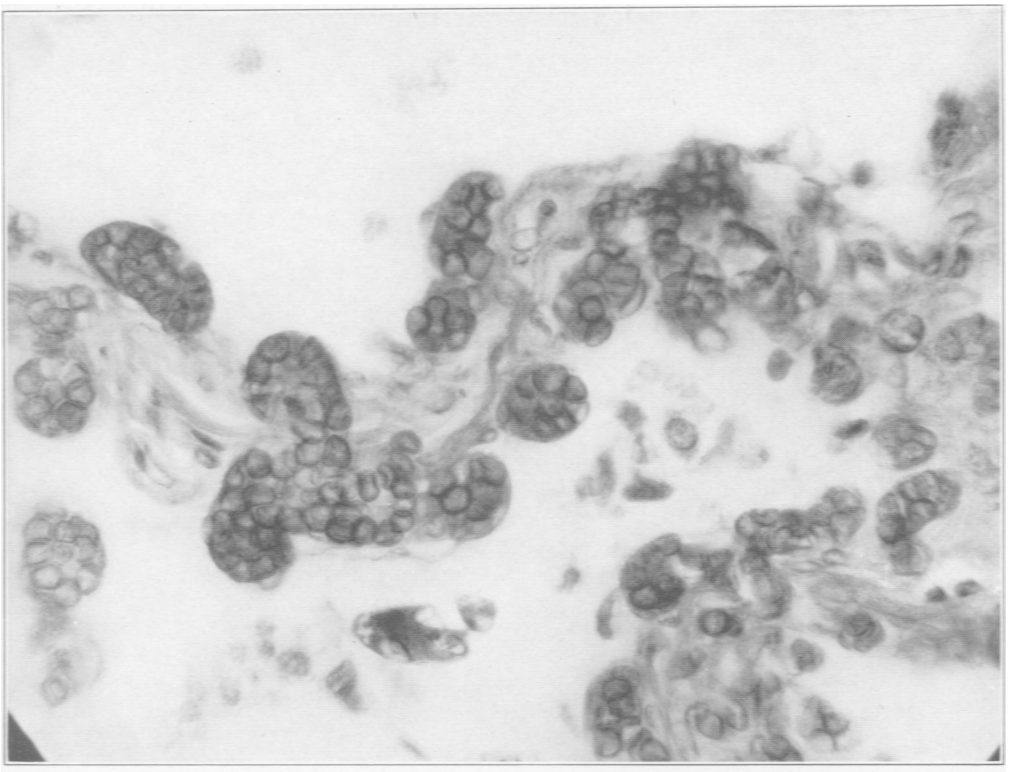
PLATE 108

FIG. 5. Section from tip of apex from Case 1. Congestion and increase in number of visible capillaries, and dilatation of same with herniation into alveolar spaces. Each capillary is sufficiently wide to admit the simultaneous passage of several red cells. Aniline blue stain. × 670.

FIG. 6. A somewhat more advanced stage than that shown in Fig. 5. In addition to the dilatation and increased number of visible capillaries, there is thickening of the capillary basement membrane. Aniline blue stain. × 600.



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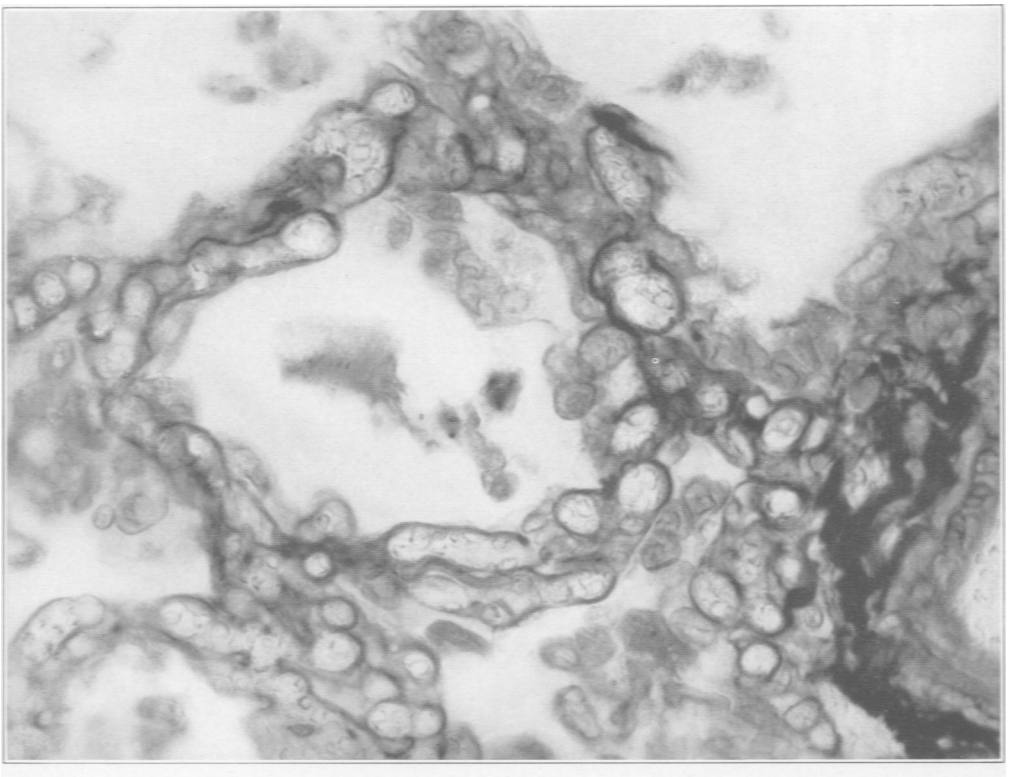

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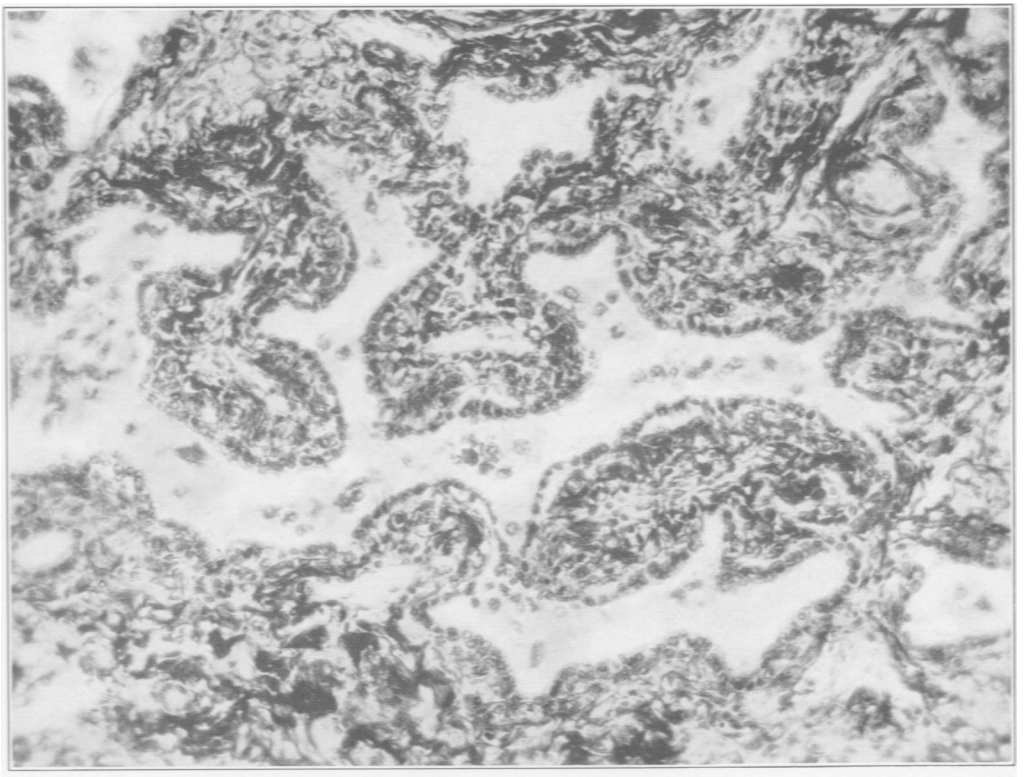
PLATE 109

FIG. 7. Late stage. Alveolar walls thickened and covered with cuboidal cells. Capillaries small and displaced from the alveolar spaces. Aniline blue stain. × 210.

FIG. 8. Pericapillary edema. The thin, unchanged alveolar basement membrane is ballooned out by the fluid. Aniline blue stain. × 670.



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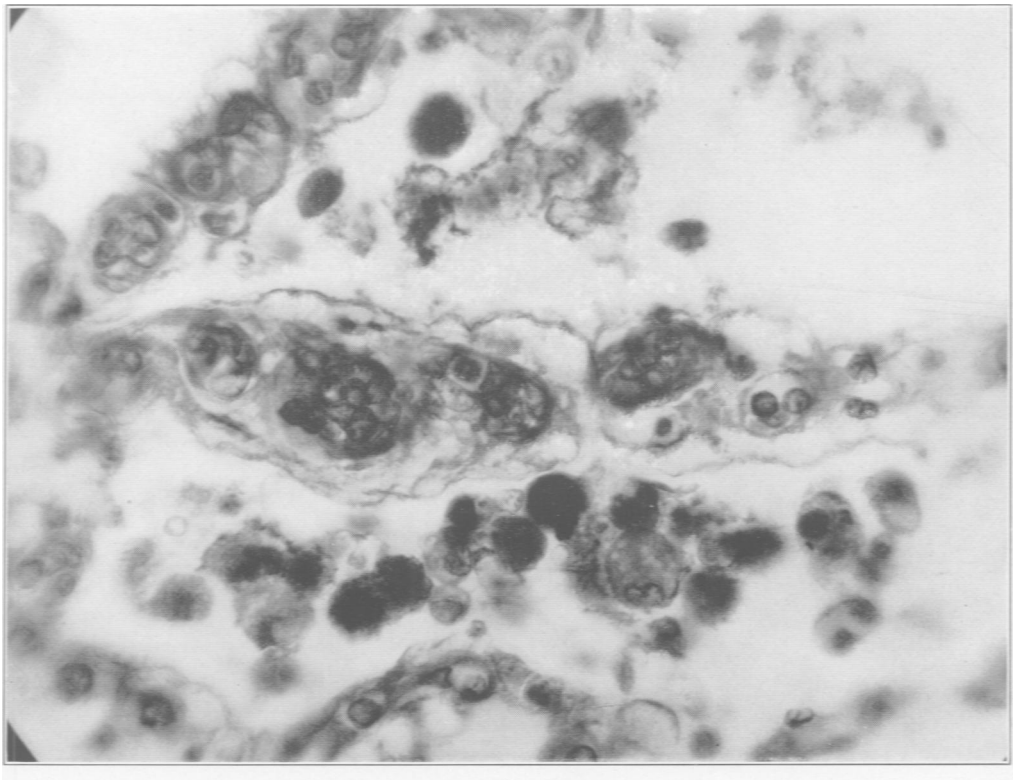

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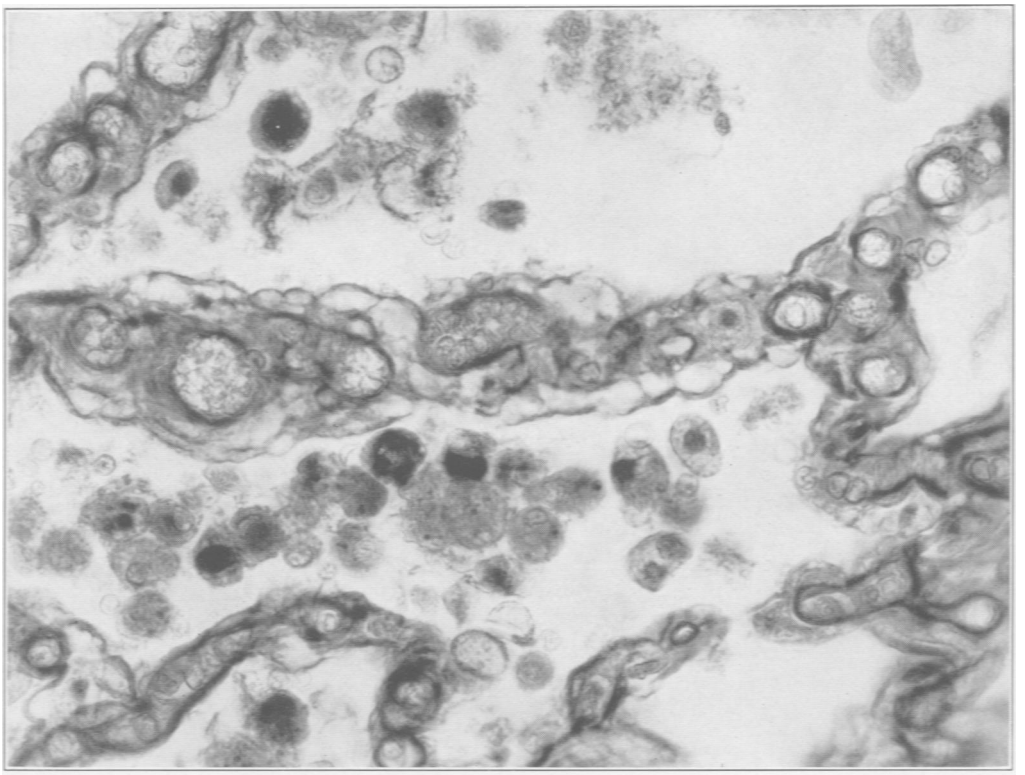
PLATE 110

FIG. 9. Pericapillary edema. Alveolar basement membrane as in Fig. 8. In addition, thickening of capillary basement membrane. Aniline blue stain. × 600.

FIG. 10. Emphysema of a previously congested alveolus as indicated by increased collagen in the wall. Capillary lumens less than normal in diameter. Aniline blue stain. × 285.



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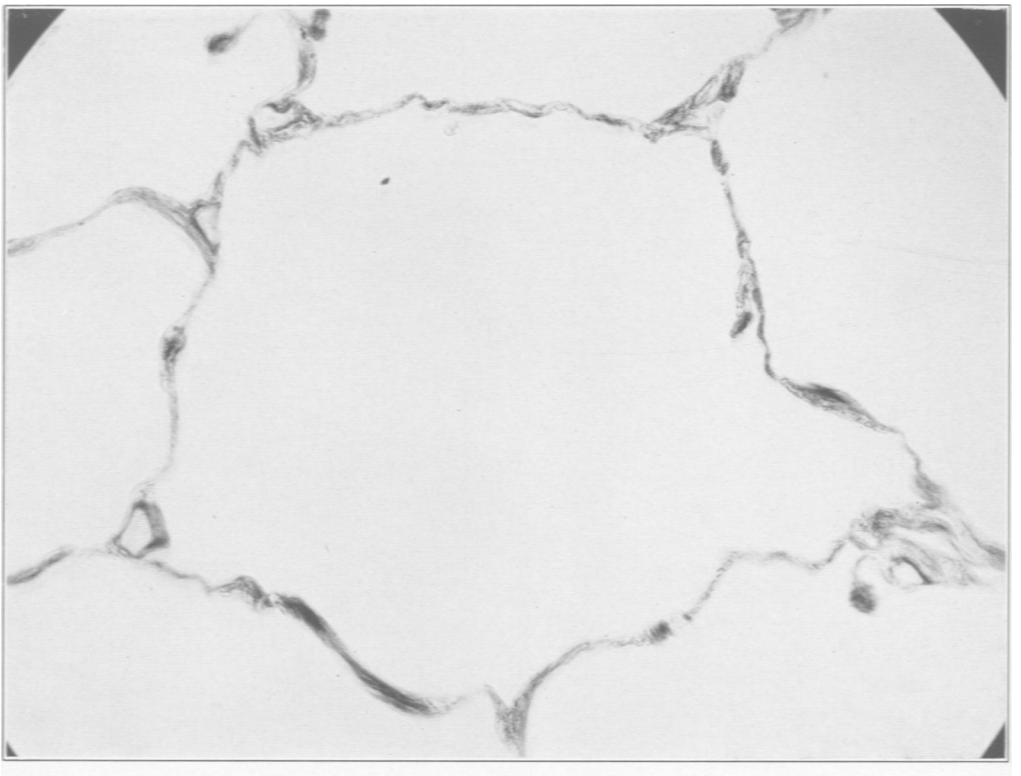

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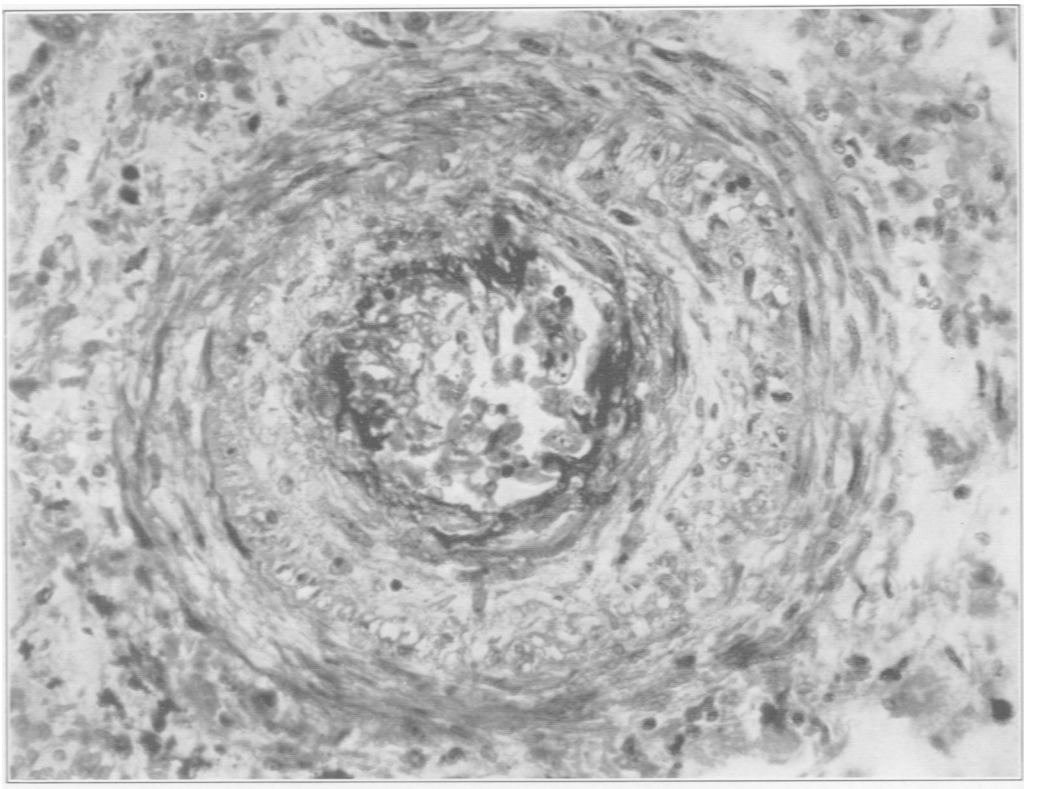
Plate III

Fig. 11. Case 1. Rheumatic arteritis, early stage. Subendothelial deposition of fibrin with proliferation of endothelial cells. Phloxine-methylene blue stain. × 360.

Fig. 12. Case 1. Rheumatic arteritis, late stage. Lumen represented by endothelial lined spaces. Intima consists of vascular connective tissue. Phloxine-methylene blue stain. × 360.



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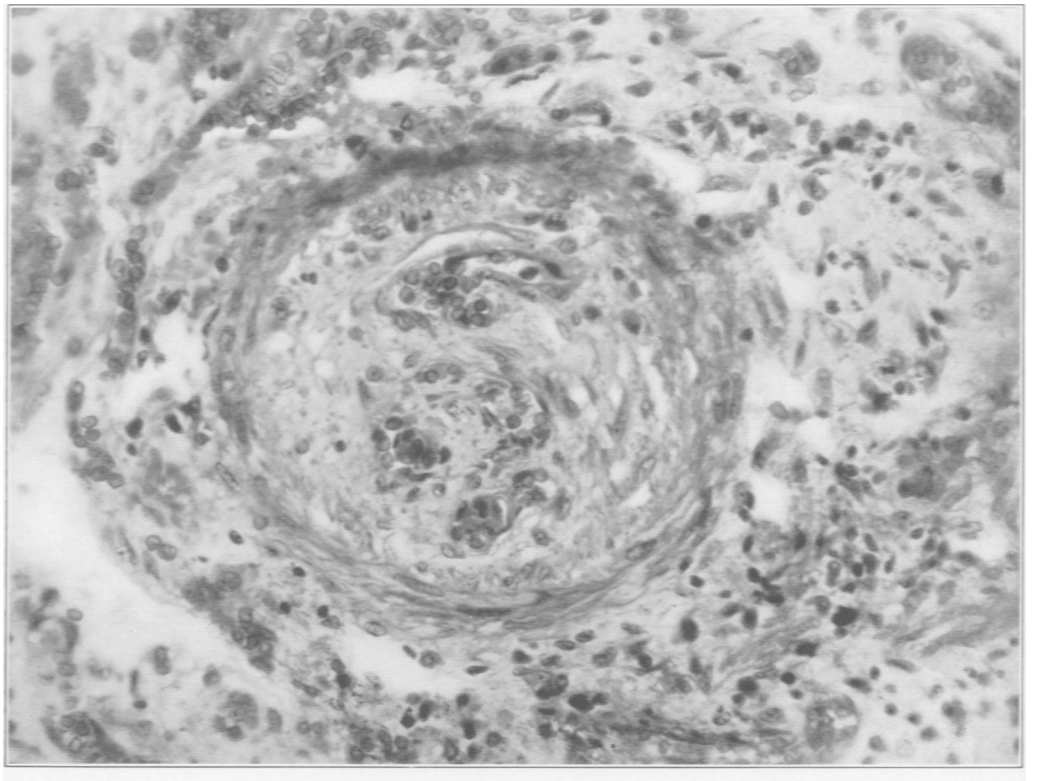

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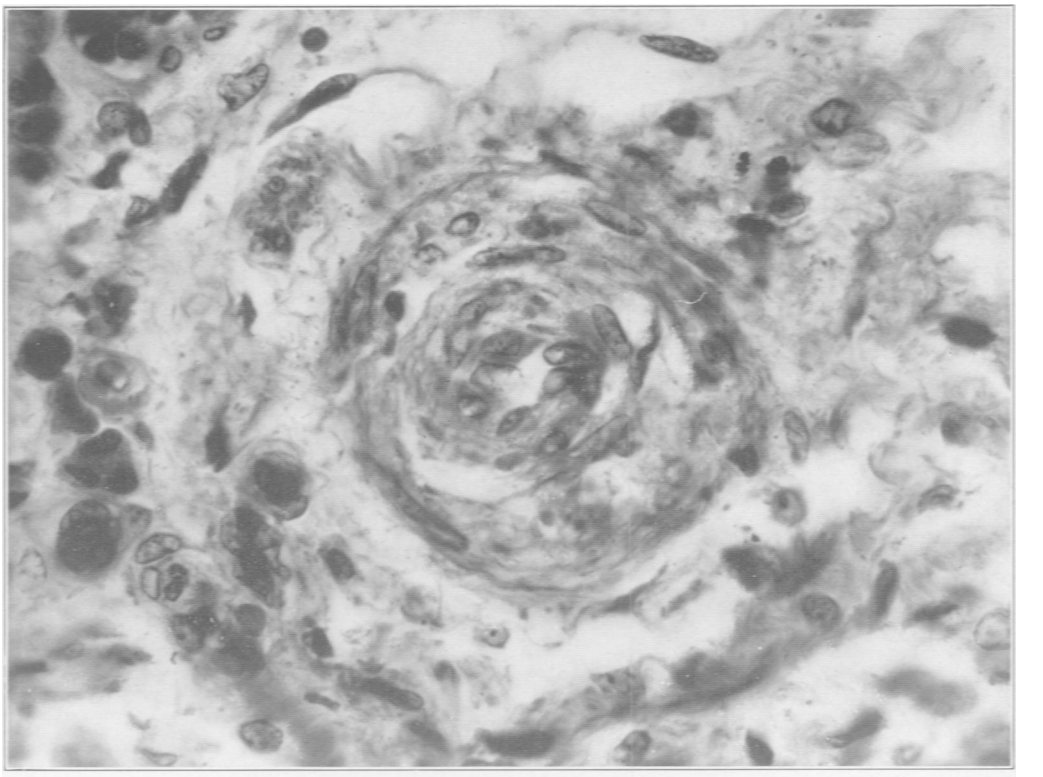
PLATE 112

FIG. 13. Hyperplastic arteriolosclerosis. Phloxine-methylene blue stain. × 800.

FIG. 14. Hyperplastic arteriolosclerosis. Phloxine-methylene blue stain. × 800.



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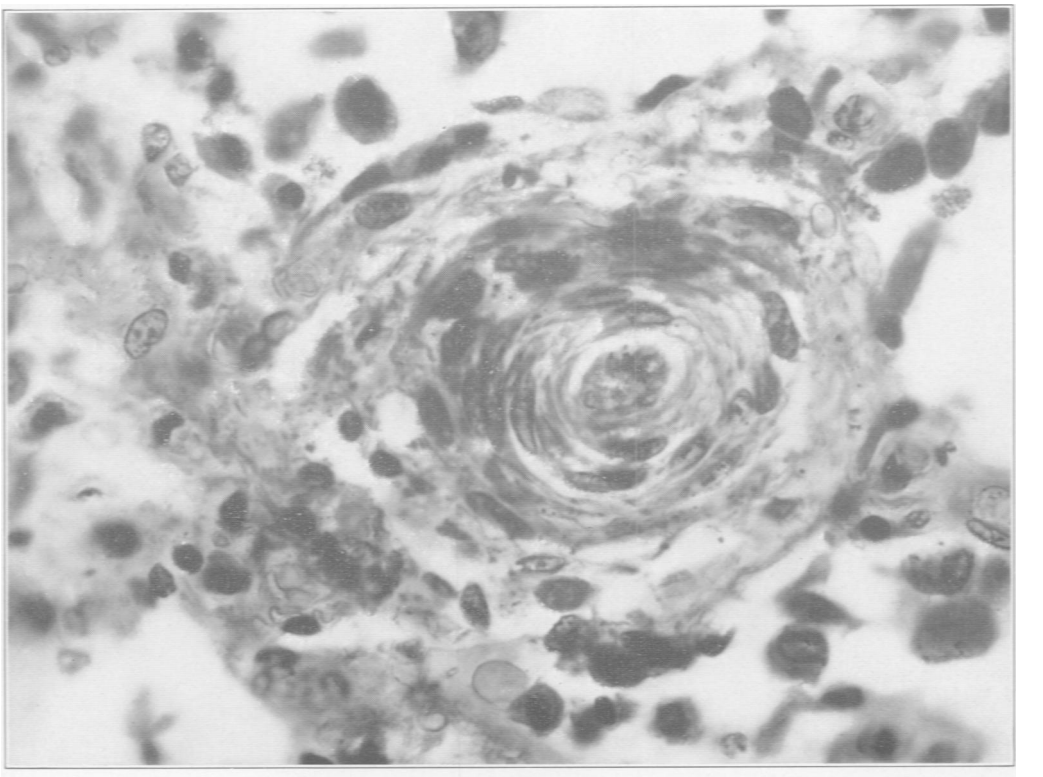

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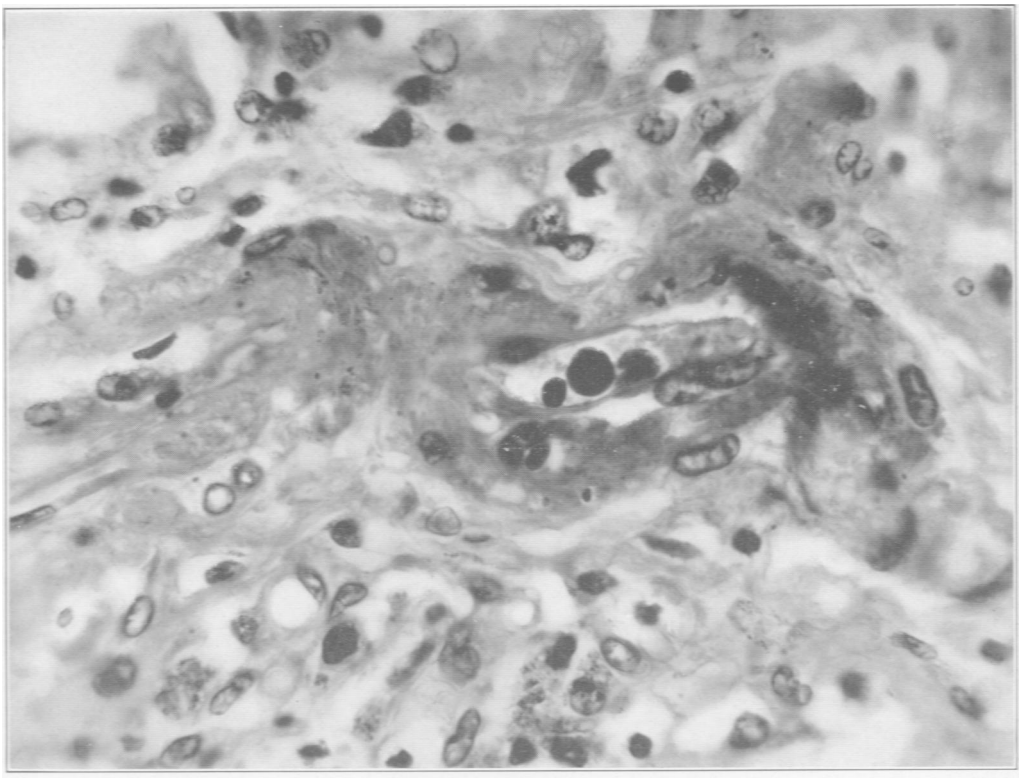
PLATE 113

FIG. 15. Necrotizing arteriolitis. Phloxine-methylene blue stain. × 800.

FIG. 16. Edema of septum with no edema of adjacent alveoli. Aniline blue stain. × 80.



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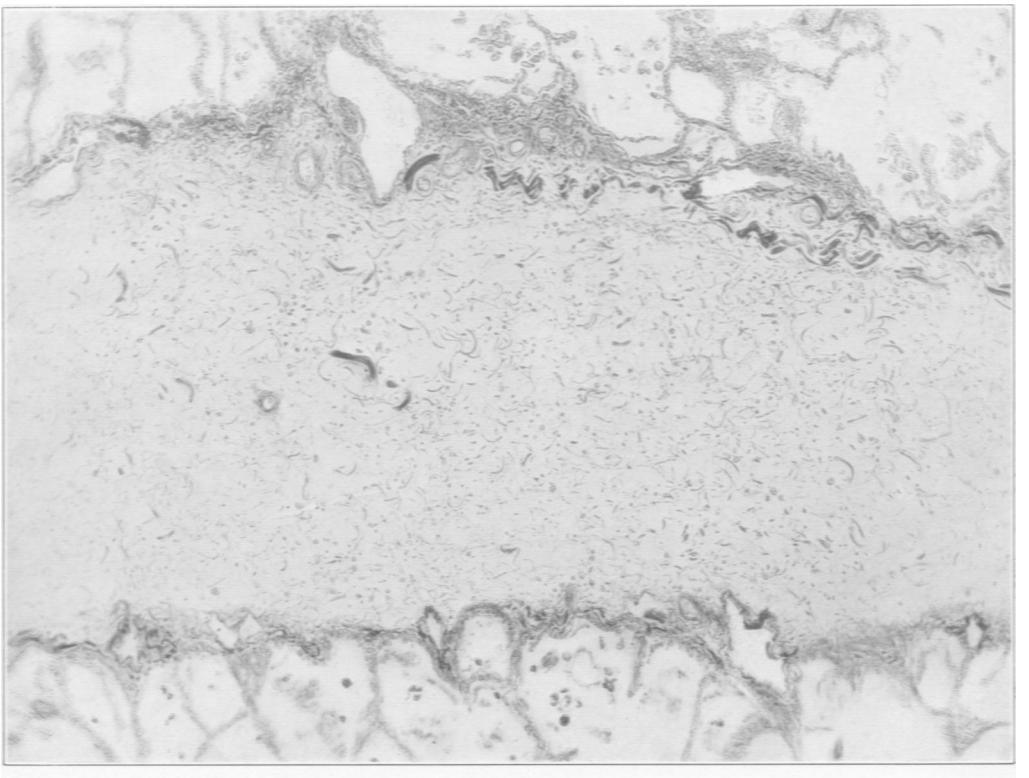

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