

## PULMONARY FIBROSIS SECONDARY TO PNEUMONIA \*

STEWART H. AUERBACH, M.D., OSCAR M. MDMS, M.D., and ERNEST W. GOODPASTURE, M.D.  
(From the Laboratory and Medical Services, Thayer Veterans Administration Hospital, and the Department of Pathology, Vanderbilt University School of Medicine, Nashville, Tenn.)

In the microscopic examination of sections of lung from necropsies performed at Thayer Hospital during the past 4 years, the occurrence of organization in pulmonary exudates seemed more common than anticipated on the basis of experience in general hospitals in the past. Casual survey of some of the material confirmed this impression, and a more thorough examination of all material was undertaken. Simple statistical analysis of the results showed a much higher incidence than was expected. When we attempted to compare this experience with those of others we were disappointed to find only rare statistical studies, although detailed descriptions of the pathogenesis and pathologic aspects were numerous. With respect to incidence, Symmers and Hoffman,<sup>1</sup> in a survey of 125 necropsies of lobar pneumonia prior to 1923, found organization in 3.2 per cent. Of 210 necropsies of lobar or "croupous" pneumonia, Lord<sup>2</sup> reported an incidence of 7.6 per cent of "organizing or indurative pneumonia," and Lauche<sup>3</sup> stated that with lobar pneumonia organization occurred in from 1 to 6 per cent and in a slightly higher percentage with patchy pneumonia. In a clinical study, Musser and Norris<sup>4</sup> reported "delayed resolution" in 105 of 2,548 cases of pneumonia, but in a more recent clinical study Gleichman, Leder, and Zahn<sup>5</sup> observed delayed resolution (failure of resolution to occur within 30 days) in 52 of 198 cases. Our series is not comparable to any of these, since the material studied by us consisted of consecutive necropsies regardless of causes of death and was not confined to cases showing pneumonia.

### MATERIAL

Sections from 307 complete necropsies (group I) collected over a 4-year period from mid-1946 to mid-1950 were available for study. A variable number of representative sections of lung were included in all cases. All individuals were adult and, with one exception, were male. The primary causes of death differed widely, but there was an unusually large proportion of malignant neoplastic diseases.

The sections of lung were examined microscopically for evidence of

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fibrosis. It was quickly apparent that pulmonary fibrosis of some type and degree was very common and that restriction of the study to organization of "pneumonic" exudate would be advantageous. Therefore, a number of common types of pulmonary fibrosis were arbitrarily excluded. For instance, cases of tuberculosis and other granulomatous diseases in which fibrosis is a natural sequel were not included. For the same reason chronic suppurative pulmonary diseases were omitted. Also excluded were numerous cases of primary or metastatic neoplasms of the lung and all examples of bronchogenic carcinoma and other thoracic tumors showing fibrosis attributable to radiation treatment. As nearly as possible the cases of fibrosis secondary to vascular disturbances (chronic passive congestion and infarction) were likewise omitted, but, among these, there were some showing lesions which were interpreted as additional organization of exudates. In brief, we attempted to confine our observations to instances of pulmonary fibrosis secondary to pneumonia, presumptively caused by exogenous infectious agents, in which resolution would be the usual expected outcome. As an exception to this generality, 7 cases of proliferative reaction of unknown cause occurring in the lungs of patients dying in renal failure were included.

In order to obtain a comparable series and with the idea that the increased use of antibiotics might have affected the incidence of organization, the files of the Department of Pathology of Vanderbilt University were consulted. One hundred necropsies from each of the years 1940 (group II) and 1930 (group III) were reviewed using the criteria and exceptions mentioned.

#### GROSS INCIDENCE

Organization in this restricted sense was encountered in 38 of the 307 necropsies in group I, or somewhat more than 12 per cent. Of the 100 cases in group II there were 7 instances of organization, and of the 100 cases in group III there were 5.

These relatively small groups do not permit of generalization or of deduction that organization is increasing, but the suggestion is made to stimulate similar comparisons.

#### ANATOMICAL LESIONS

The lesions of group I varied in size from lobar or greater to small microscopic areas. Only the extensive areas of carnification following lobar pneumonia were recognized as such in the gross; there were 3 such cases. Of the remaining 35, none was diagnosed until the microscopic sections were examined. Review of the gross descriptions

contributed no constant or peculiar findings, and small areas of organization were often hopelessly intermixed with fresh pneumonic exudates. Some few areas of gross size were set apart by circumscription and by firmness, suggesting metastatic tumor; and small patches of atelectasis were associated with underlying organization in several instances.

The microscopic characteristics varied also, but two fairly distinctive patterns were recognized: one in which intra-alveolar organization was predominant and one in which interstitial fibrosis was predominant. Although all cases fell into one of these patterns because of the major type of lesion, in many instances there was overlapping, and characteristics of both patterns could be seen in the same lung.

*Primary intra-alveolar organization* occurred in 16 cases in group I, one in group II (1940), and 3 in group III (1930). Fibroblastic invasion of the exudate with ultimate formation of strands of fibrous tissue in the alveoli and bronchioles was characteristic. Anatomically, these lesions frequently were found in a peribronchial or subpleural position, but, if large, resulted in a fleshy, elastic, carnified lung. The following cases illustrate this pattern:

#### *Case 1*

J. J. was a Negro male, 48 years old, who was admitted to Thayer Hospital on May 19 and died on June 22, 1947. Nine days prior to admission he had sudden onset of right pleuritic pain accompanied by cough, dyspnea, and fever. Several days before admission he was given sulfa tablets and penicillin by his local physician without improvement. The initial diagnosis was lobar pneumonia and empyema due to pneumococcus type I. Purulent pericarditis was recognized 4 days later. He received penicillin from May 19 through June 22, sulfadiazine from May 30 to June 8, and had repeated chest and pericardial taps. His course was gradually downward.

The major anatomical diagnoses were chronic suppurative pericarditis, organizing pneumonia of the right lower lobe with localized empyema, and early left lower lobar pneumonia. The right lower lobe was densely adherent to the chest wall, was solid and heavy, and cut with the consistency of liver.

Microscopically, the alveolar sacs containing young connective tissue were not more than one-third of the total. They appeared in the majority at first glance because of partial collapse of the intervening sacs. The connective tissue bands and plugs anastomosed freely with neighboring masses, apparently through pre-existing defects (Fig. 1). The outer surface of the plugs often was covered partly or continuously with a layer of cells like those lining the alveolar membranes. The peripheral connective tissue of the plugs was dense while the central part was less compactly fibrous and contained many pigment-filled

macrophages and small round cells. These looser central portions also contained blood-filled capillaries and occasionally it was possible to see that these were derived from points of contiguity with alveolar walls. The air-containing alveoli were partially collapsed and contained numerous macrophages filled with hemosiderin. The walls were thickened but slightly or not at all, except as due to partial collapse. Polymorphonuclear leukocytes were numerous only in several bronchioles and immediately adjacent alveoli. There was early lobar consolidation in the left lung.

*Comment.* During this patient's 6-weeks illness, carnification of the right lower lobe and other complications occurred while he was receiving penicillin and sulfonamide therapy. Delayed and initially inadequate treatment probably contributed materially to the onset of the complications.

#### *Case 2*

E. R., a white male, 28 years old, was admitted on April 1 and died on May 8, 1947. Three hours prior to admission he suffered a self-inflicted gunshot wound of the head. The patient underwent operation immediately and had a very stormy post-operative course. He received penicillin intramuscularly, sulfadiazine intravenously and orally, and penicillin intrathecally from April 1 to 11. A clinical diagnosis of pneumonia was not made. During the next month the patient improved slowly from the effects of the wound but he died suddenly and unexpectedly.

The major anatomical diagnosis was gunshot wound of the head with penetration of the cerebral hemispheres, the right lateral ventricle, and corpus callosum. The lungs were generally air-bearing and essentially normal. There were several patches of subpleural atelectasis.

Microscopically, a number of terminal bronchioles and alveolar ducts contained solid fibrous plugs in which only a few centrally located macrophages persisted (Fig. 2). Cuboidal epithelium or low columnar epithelium covered some of the surface of the bronchiolar plugs. There was moderate infiltration of monocytes and lymphocytes in the surrounding bronchiolar and alveolar tissues.

*Comment.* Although a clinical diagnosis of pneumonia was never made, it is probable that this patient developed the infection during the critical postoperative period while on "prophylactic" penicillin and sulfonamide treatment. This minimal or abortive pneumonitis probably was of bacterial etiology. There was failure of resolution or incomplete resolution under intensive anti-bacterial therapy. The resulting organization of exudate was fully finished in 5 weeks.

#### *Case 3*

J. K., a white male, 54 years of age, was admitted on March 11 and expired on March 22, 1950. He had had pneumonia five times during the preceding 23 years

and "flu" 1 year before. He had frequent colds and was said to have had asthma for 10 years, although no treatment was necessary. About 2 weeks before entry he contracted a cold which was followed by "flu" and was characterized by fever, chills, diarrhea, and a cough which produced tenacious blood-streaked sputum. His local physician administered penicillin and sulfadiazine for "double pneumonia." After 3 days of medication the patient developed anuria and a measles-like eruption. The anuria lasted 2 days. All medication was discontinued 2 days before entry.

On admission there was evidence of extensive infiltration of the right lung, which later spread to the left. Breathing was deep and rapid but there was cyanosis of the hands and feet. Blood pressure was consistently low. The daily urine volume was 1,500 to 2,000 cc. but the specific gravity was about 1.013. There was retention of sodium without detectable edema, and the non-protein nitrogen levels were markedly elevated. Carbon dioxide combining power of the plasma was moderately lowered throughout the course. Repeated sputum cultures yielded only *Proteus*. The patient received streptomycin, aureomycin, penicillin, and chloromycetin singly and in combination without appreciable benefit.

The major anatomical diagnoses were confluent bronchopneumonia, unresolved; early portal cirrhosis; and nephrosis. There was epithelial regeneration in the damaged renal tubules, which was interpreted as a healing sulfonamide nephrosis.

The right lung weighed 1,470 gm. and the left, 1,060 gm. The right upper and lower lobes were firmly solid and other lobes showed patchy consolidation. The gross section was moist, deeply congested, and exuded frothy fluid. The smaller bronchi of both lungs contained yellow pus. There were poorly defined, soft, yellowish areas of necrosis in the right upper lobe.

Microscopic sections from the solid lobes presented a confused picture of septal thickening blended with intra-alveolar fibroplasia, and residual exudation of serum, fibrin, and leukocytes. The septa were thickened by edema, hyperemia, and infiltration of numbers of monocytes and small round cells (Fig. 3). In many areas there was active fibrosis in the septa, this being most notable at points of confluence and around the small vessels. Many alveoli were filled with loose, proliferating, fibrous tissue, often intermixed with fibrin containing monocytes, which fused with neighboring septa to obliterate normal structure in many small areas (Fig. 4). The majority of alveolar sacs were reduced in size and were commonly lined by a nearly continuous layer of small cells. The lumina contained serofibrinous material which was rich in monocytes and small round cells. Polymorphonuclear cells were very infrequent except in the scattered pus-filled bronchioles and adjacent alveoli. There were small irregular areas of acute necrosis in some of the sections, usually in relation to bronchioles.

Other areas of the lungs showed thin alveolar walls and alveolar sacs of normal size filled with seropurulent exudate. In one such area a lobule was acutely necrotic and contained masses of fungi identified as

Monilia. There was virtually no reaction to the presence of these organisms.

*Comment.* The lesions in this case illustrate intra-alveolar organization combined with interstitial fibrosis. It appears that the exudate being organized was a product of the initial infection which began about 25 days before death and which was excited by an organism sensitive to penicillin or sulfadiazine. The purulent, occasionally necrotizing, bronchiolitis and bronchopneumonia were attributed to superimposed infection by a strain of *Proteus* resistant to antibiotics. Infection by *Monilia* was considered to be terminal, but the background of therapy probably played an important part in its onset.

*Interstitial fibrosis* was the major lesion in 22 cases in group I, 6 cases in group II (1940), and 2 cases in group III (1930). In the stages studied, the lesions were fundamentally productive. While actual conversion of fibrinous exudate into fibrous tissue was a lesser feature, it did contribute to septal thickening, and the whole was therefore regarded as a "failure of resolution." Fibroplastic widening of the alveolar walls was an outstanding feature. The attendant alveolar exudate was composed of fibrin and was very dense, frequently taking the form of "hyaline membranes." Fibroblastic invasion of this material usually was apparent. The end result of the process was the formation of scars of varying size, usually subpleural or peribronchial. The following cases illustrate this pattern:

#### Case 4

M. W., a white male, 52 years old, was admitted on March 9 and died on March 17, 1948. The patient noted the onset of mild, cramping, abdominal pain 2½ days prior to admission and, 4 hours before, developed severe right lower quadrant pain. Emergency laparotomy revealed a perforated appendix and generalized peritonitis. His postoperative course was very stormy, and he received penicillin and sulfadiazine throughout his hospital stay. On the day before death a clinical diagnosis of pneumonia and pleural effusion was made.

The major anatomical diagnoses were peritonitis, due to *Escherichia coli*, with secondary pelvic abscess, and lobular pneumonia of both lungs.

On microscopic examination some areas were relatively normal. In all sections, however, there were rather large and poorly defined areas of alveolar fibrosis which were usually in relation to bronchioles. The fibrosis varied from slight to marked and the alveolar sacs were correspondingly reduced in size (Fig. 5). Fibroplasia was active, so that the alveolar walls appeared cellular and there were moderate numbers of infiltrating monocytes and lymphocytes. The appearance of cellularity was exaggerated further by proliferation of alveolar lining cells

which often formed a nearly continuous membrane around the constricted sacs. In all the diseased areas there were many membranous deposits of dense fibrin lining alveolar ducts and sacs. Monocytes in small numbers were present in and about this material. Invasion of the fibrin by fibroblasts derived from alveolar walls was evident in some areas.

In several patches there was acute purulent exudation superimposed on the older disease. The fibrin deposits appeared less abundant and somewhat less dense in these patches, as if there were partial solution.

*Comment.* This patient was in good health until the onset of appendicitis and peritonitis. Assuming that pneumonia developed during the immediate postoperative period, it was of not more than 8 days' duration. His pulmonary complications developed in spite of intensive anti-bacterial therapy. The microscopic picture is quite different from that seen in cases 1 to 3 and more nearly resembles that described for viral pneumonia.

#### *Case 5*

J. B. was a white male, 41 years old, who was admitted on February 5 and expired on February 12, 1948. The patient had had malaise and intermittent low grade fever since 1945 and swelling of the abdomen, jaundice, and enlarged lymph nodes, since October, 1947. The past history was of interest in that the patient had pneumonia on three occasions from 1941 to 1945 while in the Navy. Details of these attacks were unknown. The clinical impression on admission to this hospital was Hodgkin's disease, which was confirmed by cervical node biopsy. He was given small doses of roentgen therapy over the abdomen and inguinal regions and supportive treatment but went rapidly downward. Penicillin was administered only during the last 2 days of life.

The major anatomical diagnosis was Hodgkin's disease of the abdominal and thoracic lymph nodes, the liver, spleen, and sternal bone marrow. The pulmonary parenchyma was not involved. Gross examination of the lungs showed only congestion of the lower lobes.

Microscopically, there were moderate numbers of "dust cells" and erythrocytes in many alveoli. Scattered bronchioles were loosely filled with fibrinopurulent exudate. Approaching the pleura, there was rather prominent peribronchial fibrosis, and the tissue was infiltrated with leukocytes of all kinds including moderate numbers of polymorphonuclear cells. The subpleural portion of several sections presented zones of varying width in which the alveolar walls were markedly thickened with fibrous tissue (Fig. 6). Some walls were ruptured, creating large, irregular air spaces. Other spaces of alveolar size were surrounded or constricted by wide fibrous walls. Scattered monocytes and lymphocytes were present, and the air spaces contained many macrophages. In one small area the air sacs contained a dense deposit of fibrin and

there was early organization of this material. Polymorphonuclear leukocytes were rarely seen in this area.

In another section a wider zone of loose, subpleural scarring was present (Fig. 7). Remnants of ducts incorporated in this scar retained their epithelial lining and there were many dilated non-muscular blood vessels. Slight fibroblastic activity was observed around an entering bronchiole and in some of the bordering alveolar walls.

*Comment.* The pulmonary lesions in this case seemed to be unrelated to the Hodgkin's disease. The peribronchial and subpleural scarring appeared to be a logical sequel to such a process as described in case 4. This patient gave a history of three bouts of pneumonia from 1941 to 1945, the details of which are not known, but these illnesses might well account for the remote pulmonary fibrosis discovered at necropsy.

Seven of the 22 cases of interstitial fibrosis differed somewhat from those described and deserve special comment because of common clinical and pathologic findings. All of them occurred in cases of *intrinsic disease of the kidneys terminating in uremia*. Pathologic features common to all were engorgement, edema, and leukocytic infiltrations of the alveolar walls combined with endothelial swelling and cellular proliferation. The alveoli usually contained exudate composed of serous fluid, blood, or compact fibrin, this sometimes taking the form of hyaline membranes. In addition, there were small foci of active organization, usually intraluminal but sometimes interstitial. The following cases illustrate these changes:

#### Case 6

C. C., a white male, 25 years of age, was admitted on December 23, 1947, and expired on February 6, 1948. In November, 1947, the patient had "flu," followed in 2 weeks by edema of the feet, legs, and face, and "smoky" urine. He remained under the care of his local physician until referred to this hospital. A clinical diagnosis of acute glomerulonephritis was made. The patient was described as being in uremia at the time of admission, and his blood non-protein nitrogen rose to 146 mg. per 100 cc. His course was progressively downward despite dietary and supportive therapy. On several occasions he developed pulmonary edema and congestive failure. Penicillin was administered during the first week of hospitalization and again during the last 2 days of his life.

The major anatomical diagnosis was progressive glomerulonephritis. There were also fibrinous pericarditis and myocardial hypertrophy. Grossly, the lungs showed splotchy bright red or dark red discoloration in the hilar areas shading to faint pink near the pleural surface.

Microscopically, congestive changes were severe but not uniform. Patchy or lobular distribution of the graver lesions usually was apparent. Alveolar walls were thickened by hyperemia, edema, and



endothelial swelling. Some capillaries were thrombosed. Leukocytes, predominantly polymorphonuclear, infiltrated the walls in some lobules and in these there was intra-alveolar hemorrhage. Intra-alveolar edema was not a feature.

In addition to these more acute lesions, there were changes which seemed older. Scattered throughout in random fashion were small groups of alveoli filled with compact fibrin containing only a few monocytes. Some such deposits appeared inert, perhaps by reason of shorter duration, whereas others were being organized *in situ* or incorporated in the alveolar wall (Fig. 8). The product of the former was a striking focus of endothelial and fibroblastic proliferation partially filling an alveolus, and, of the latter, a similar cellular focus expanding a septum. The over-all picture of cellularity of the diseased areas was enhanced by proliferation of alveolar lining cells.

#### Case 7

B. F., a white male, 56 years old, was admitted for the fourth time on October 28 and died on November 9, 1949. He was known to have had severe hypertension for more than 2 years and had experienced anginal pain, dyspnea, and headaches for about 2 years. For 8 days prior to admission he had symptoms of left ventricular failure. In this hospital he improved temporarily on digitalis, penicillin, and supportive therapy but then developed intractable pulmonary edema and expired. The non-protein nitrogen was elevated throughout his hospital stay and several days before death was 108 mg. per 100 cc.

The major anatomical diagnoses were arteriolar nephrosclerosis, cardiac hypertrophy, and generalized arteriosclerosis. Grossly, the left lung was largely atelectatic. The right was wet and boggy. The lower lobe was firmer and darker.

Microscopically, the lesions were congestive, exudative, and proliferative, combined in varying degrees. No particular distribution of lesions was apparent. Some areas were air-containing and only mildly hyperemic. Others were more congested and showed numerous thin, fibrinous membranes lining alveolar ducts and sacs. Several sections, of which one contained a portion of a medium bronchus and was thus identified as being from the hilar region, presented large areas of very compact solidarity. The air spaces were packed with fibrinous or serofibrinous exudate, often mixed with blood. Monocytes dominated the cellular response in most areas but there were many polymorphonuclear leukocytes in the serous exudate. There was acute purulent bronchiolitis in one section and polymorphonuclear cells were predominant in the exudate of neighboring alveoli.

In the solid area the alveolar walls were markedly thickened by congestion, edema, endothelial swelling, and infiltration of leukocytes.

The appearance of widening and cellularity of the septa was accentuated by proliferation of alveolar lining cells (Fig. 9). Scattered throughout were many small areas of organization, some almost confined to alveolar spaces and others, usually smaller, expanding alveolar walls. The actively organizing luminal plugs often were capped with hyperplastic alveolar lining cells.

#### DISCUSSION

The volume of material studied in this series does not warrant a conclusion that pulmonary fibrosis secondary to pneumonia is increasing. But comparison with the similarly unselected cases from the years 1930 and 1940 seems to make the suggestion valid. Of possible factors contributing to such an increase, two are foremost: one pertaining to etiology, and one to antibacterial therapy.

There is a considerable body of opinion that the clinical picture of pneumonia has become altered during the past decade, primarily by an increase in atypical or viral pneumonia.<sup>6-9</sup> It has even been suggested that viral pneumonia might represent the underlying disease in most bacterial pneumonias (Francis<sup>8</sup>), including the pneumococcal type (Israel *et al.*<sup>6</sup>). The pulmonary lesions of primary atypical pneumonia are described as purulent bronchiolitis, mononuclear cell infiltration of bronchial and alveolar walls, and the formation of hyaline alveolar membranes (Golden<sup>10</sup>), a descriptive picture which is very similar to that of 1918 influenza (Goodpasture<sup>11</sup>). It is stated that organization of the intra-alveolar fibrinous membranes is "not infrequent" (Golden<sup>10</sup>) or as occurring in "the majority of cases" but not extensively (Parker, Jolliffe, and Finland<sup>12</sup>). The lesions in 15 of 22 cases of interstitial fibrosis in this series conformed in major respects to those of primary atypical pneumonia. Additionally, there are several showing active alveolar fibroplasia which closely resembled, except in extent, the acute diffuse fibrosis of Hamman and Rich,<sup>13</sup> a disease presumed by them to be of viral etiology. Also encountered were a number of more or less subpleural scars similar in structure to the non-specific apical caps studied by MacMillan<sup>14</sup> and thought to be due to mild or chronic disease, possibly viral. In none of our 15 cases in group I was a clinical diagnosis of viral pneumonia entertained. Cultural examinations were performed on a minority of the 15 and all yielded a mixture of organisms, predominantly of types not ordinarily expected to be pulmonary pathogens. Acute purulent bronchiolitis was superimposed on the older disease in some of these.

Intra-alveolar organization, which was the principal lesion in 16 of the 38 cases in group I, was presumed to be secondary to bacterial

pneumonia, although cultural evidence was seldom conclusive. Mixed flora were obtained from the sputum and throat cultures performed, including those from one case of classical lobar pneumonia. Prior antibacterial therapy had been administered in nearly every instance. The cultural data were generally disregarded because they conflicted with the clinical findings; but there is evidence to indicate that alteration of the flora by antibacterial treatment may have adversely affected natural resolution of pneumonic exudates due to pneumococci. Experimental pneumococcal pneumonia seldom organizes (Sale and Wood,<sup>15</sup> Gunn<sup>16</sup>), but organization is a prominent feature of experimental pneumonia due to Friedlander's bacillus. Pneumonia induced in dogs by a mixture of staphylococci and pneumococci was more prone to organize than pneumonia due to pneumococci alone (Wadsworth<sup>17</sup>).

Also, and perhaps more importantly, antibacterial agents, especially antibiotics, may alter the natural host response through the effect on the causative organism. Solution of fibrin has long been held to be a function of enzymes derived from polymorphonuclear leukocytes. Exudates which are rich in fibrin and poor in these leukocytes are more apt to organize. In our material there was notable paucity of polymorphonuclear cells in the involved areas of most cases, and the predominant cell was the monocyte. However, organization was in an advanced stage in some of these, so that there was little persistent cellular response of any kind. Experimental confirmation of this possibility is lacking, although Wood *et al.*<sup>18-21</sup> observed that macrophages were more important in the phagocytosis of pneumococci in experimentally infected animals treated with sulfapyridine than in those treated with antiserum.

An attempt to correlate the factor of time with respect to duration of disease and period of antibiotic therapy was not satisfactory. The date of onset of pneumonia could seldom be determined with reasonable certainty and many of the patients were on "prophylactic" penicillin treatment. However, it could be established from three of the records that organization was active within 7, 8, and 9 days after the onset of pneumonia. This is a distinctly shorter interval than the usually accepted 2-week period.<sup>3,22</sup>

The significance of uremia as a cause of "pneumonia" accompanied by fibroplasia is unknown. "Uremic edema" or "uremic pneumonia" has been referred to as an entity principally because of its peculiar central or hilar distribution as seen in the radiologic shadow. The few pathologic descriptions of the pulmonary disease<sup>23,24</sup> emphasize capillary congestion, thickening of the alveolar wall, and deposition of dense fibrin in alveoli and bronchioles. Organization of the fibrin gives rise

to the "bronchiolitis obliterans" of Ehrich and McIntosh.<sup>25</sup> The 7 cases of "uremic pneumonia" in this series conformed in most respects to the previous descriptions. We were impressed with the similarity of the microscopic lesion to those of the so-called rheumatic pneumonia.<sup>26</sup> The foci of organization were indistinguishable from the "Masson body."<sup>27</sup> All of the patients in our series had experienced one or more episodes of left ventricular failure, and it seems likely that this was the principal common feature.

#### SUMMARY

Pulmonary fibrosis secondary to pneumonia was found in 38 (12 per cent) of 307 necropsies performed between 1946 and 1950. Comparable series of 100 cases from each of the years 1940 and 1930 showed 7 and 5 per cent, respectively. The evidence suggests that the use of antibacterial agents contributes to a rising incidence of organization of pulmonary exudates, and that small areas of fibrosis may be the consequence of viral pneumonia.

#### REFERENCES

1. Symmers, D., and Hoffman, A. M. The increased incidence of organizing pneumonia. *J. A. M. A.*, 1923, **81**, 297-298.
2. Lord, F. T. Diseases of the Bronchi, Lungs, and Pleura. Lea & Febiger, Philadelphia, 1925, p. 304.
3. Lauche, A. Die Organisation pneumonischen Exsudates. In: Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie. Julius Springer, Berlin, 1928, **3**, Pt. 1, 822-832.
4. Musser, J. H., and Norris, G. W. The Symptoms, Diagnosis and Prognosis of Lobar Pneumonia. In: Osler, W. Modern Medicine. Lea Brothers & Co., Philadelphia, 1907, **2**, p. 590. (Cited by Lord, F. T. Diseases of the Bronchi, Lungs, and Pleura. Lea & Febiger, Philadelphia, 1925, p. 321.)
5. Gleichman, T. K., Leder, M. M., and Zahn, D. W. Major etiological factors producing delayed resolution in pneumonia. *Am. J. M. Sc.*, 1949, **218**, 369-373.
6. Israel, H. L., Mitterling, R. C., and Flippin, H. F. Pneumonia at the Philadelphia General Hospital, 1936-1946. *New England J. Med.*, 1948, **238**, 205-212.
7. Commission on Acute Respiratory Diseases. Primary atypical pneumonia. *Am. J. Pub. Health*, 1944, **34**, 347-357.
8. Francis, T., Jr. Virus pneumonia. *Canad. Pub. Health J.*, 1944, **35**, 49-54.
9. Dingle, J. H. Common virus infections of the respiratory tract; diagnosis and etiology. *J. A. M. A.*, 1948, **136**, 1084-1088.
10. Golden, A. Pathologic anatomy of "atypical pneumonia, etiology undetermined": acute interstitial pneumonitis. *Arch. Path.*, 1944, **38**, 187-202.
11. Goodpasture, E. W. The significance of certain pulmonary lesions in relation to the etiology of influenza. *Am. J. M. Sc.*, 1919, **158**, 863-870.
12. Parker, F., Jr., Jolliffe, L. S., and Finland, M. Primary atypical pneumonia. Report of eight cases with autopsies. *Arch. Path.*, 1947, **44**, 581-608.
13. Hamman, L., and Rich, A. R. Acute diffuse interstitial fibrosis of the lungs. *Bull. Johns Hopkins Hosp.*, 1944, **74**, 177-212.

14. MacMillan, H. A. Apical pneumonic scars. *Arch. Path.*, 1949, **48**, 377-381.
15. Sale, L., Jr., and Wood, W. B., Jr. Studies on the mechanism of recovery in pneumonia due to Friedländer's bacillus. I. The pathogenesis of experimental Friedländer's bacillus pneumonia. *J. Exper. Med.*, 1947, **86**, 239-248.
16. Gunn, F. D. The Lung. In: Anderson, W. A. D. Pathology. C. V. Mosby Co., St. Louis, 1948, p. 735.
17. Wadsworth, A. B. A study of experimental organizing pneumonia. *J. M. Research*, 1918-19, **39**, 147-151.
18. Wood, W. B., Jr., and Irons, E. N. Studies on the mechanism of recovery in pneumococcal pneumonia. II. The effect of sulfonamide therapy upon the pulmonary lesion of experimental pneumonia. *J. Exper. Med.*, 1946, **84**, 365-376.
19. Wood, W. B., Jr., McLeod, C., and Irons, E. N. Studies on the mechanism of recovery in pneumococcal pneumonia. III. Factors influencing the phagocytosis of pneumococci in the lung during sulfonamide therapy. *J. Exper. Med.*, 1946, **84**, 377-386.
20. Wood, W. B., Jr., Smith, M. R., and Watson, B. Studies on the mechanism of recovery in pneumococcal pneumonia. IV. The mechanism of phagocytosis in the absence of antibody. *J. Exper. Med.*, 1946, **84**, 387-402.
21. Wood, W. B., Jr., and Smith, M. R. Host-parasite relationships in experimental pneumonia due to pneumococcus type III. *J. Exper. Med.*, 1950, **92**, 85-100.
22. Floyd, R. Organization of pneumonic exudates. *Am. J. M. Sc.*, 1922, **163**, 527-548.
23. Bass, H. E., and Singer, E. Pulmonary changes in uremia. *J. A. M. A.*, 1950, **144**, 819-823.
24. Clinico-pathologic conference: renal insufficiency. *Am. J. Med.*, 1950, **9**, 247-258.
25. Ehrich, W., and McIntosh, J. F. The pathogenesis of bronchiolitis obliterans; observations in cases of Bright's disease. *Arch. Path.*, 1932, **13**, 69-79.
26. Masson, P., Riopelle, J. L., and Martin, P. Poumon rhumatismal. *Ann. d'anat. path.*, 1937, **14**, 359-382.
27. Neuburger, K. T., Geever, E. F., and Rutledge, E. K. Rheumatic pneumonia. *Arch. Path.*, 1944, **37**, 1-15.

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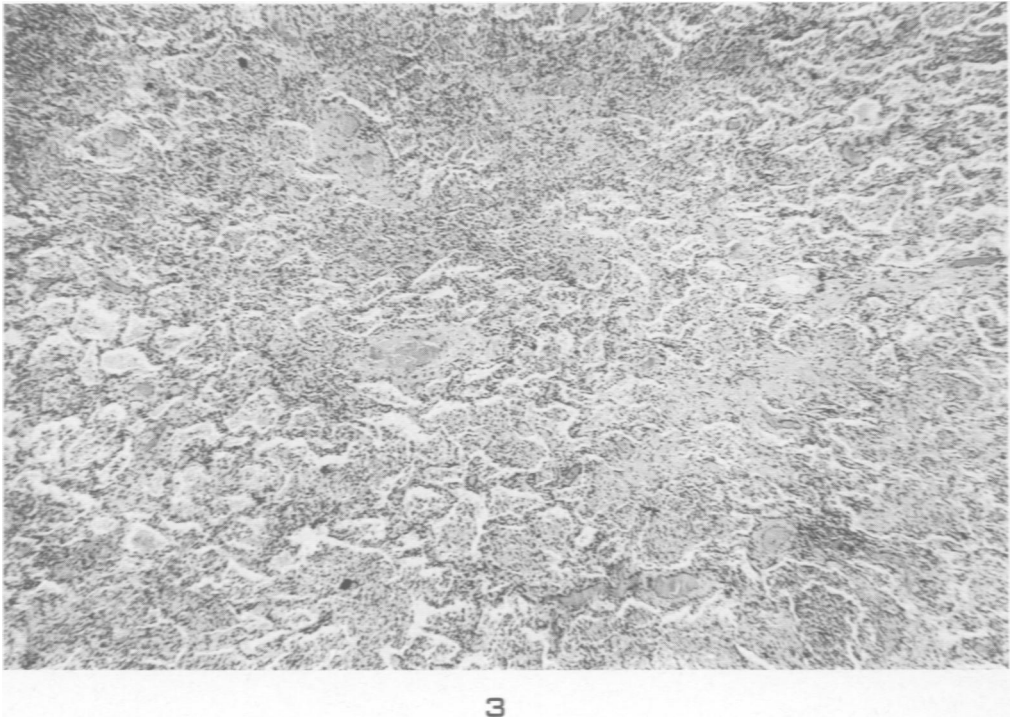
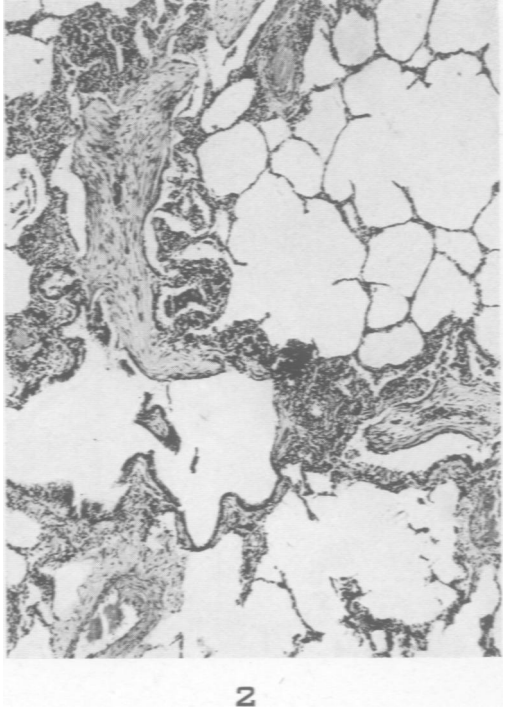
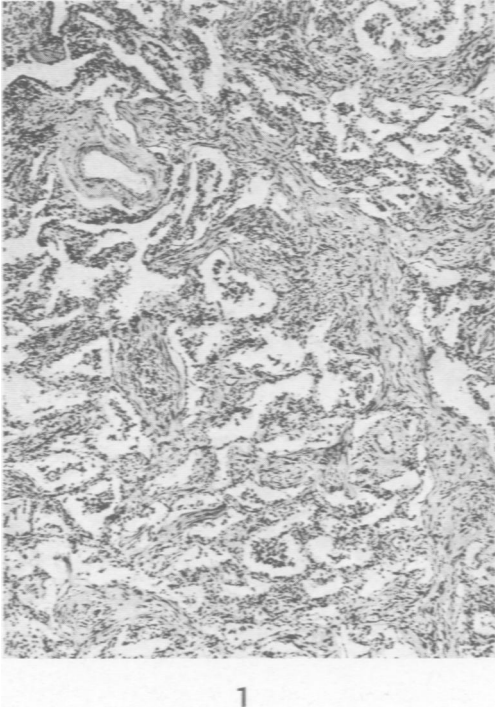
[ Illustrations follow ]

## DESCRIPTION OF PLATES

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### PLATE 9

- FIG. 1. Case 1. Intraluminal organization secondary to pneumococcal lobar pneumonia. Anastomosing fibrous bands fill many alveoli.  $\times 60$ .
- FIG. 2. Case 2. Intraluminal organization in a terminal bronchiole about 5 weeks following pneumonia. The large fibrous plug is partially covered with cuboidal epithelium.  $\times 60$ .
- FIG. 3. Case 3. Combined intraluminal and interstitial organization about 25 days after the onset of pneumonia.  $\times 40$ .



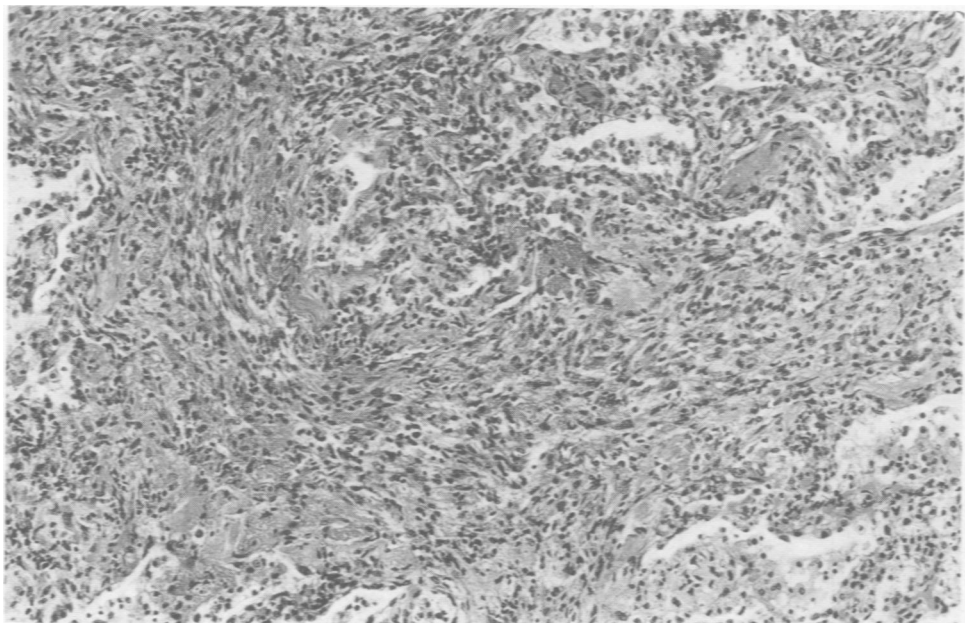
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Pulmonary Fibrosis Secondary to Pneumonia

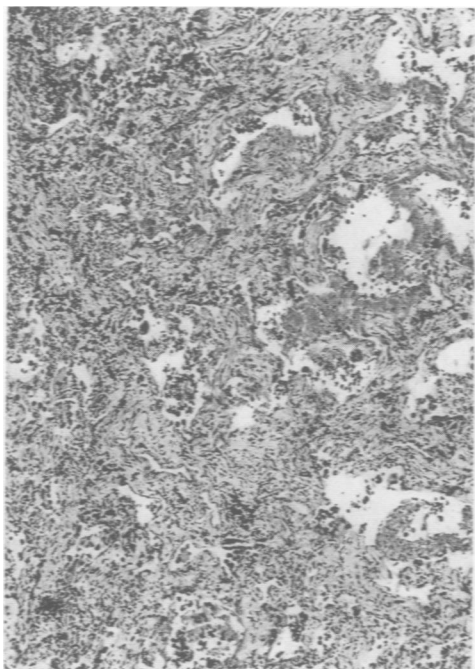
PLATE 10

- FIG. 4. Case 3. Higher magnification of Figure 3, illustrating active fibrosis obliterating small groups of alveoli. The residual exudate is mononuclear.  $\times 120$ .
- FIG. 5. Case 4. Interstitial fibrosis, probably secondary to viral pneumonia. Membranous deposits of dense fibrin appear darker and are partly incorporated in the septal walls.  $\times 60$ .
- FIG. 6. Case 5. Interstitial fibrosis, possibly secondary to viral pneumonia. Intraluminal deposits of fibrin are more distinct. Mononuclear cells predominate in the reaction.  $\times 60$ .

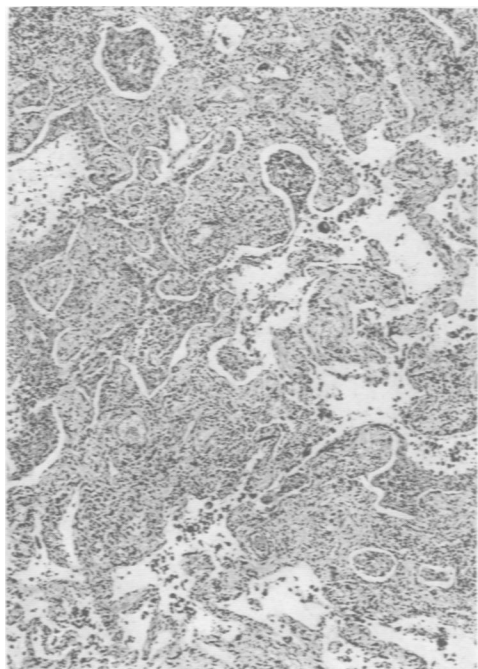




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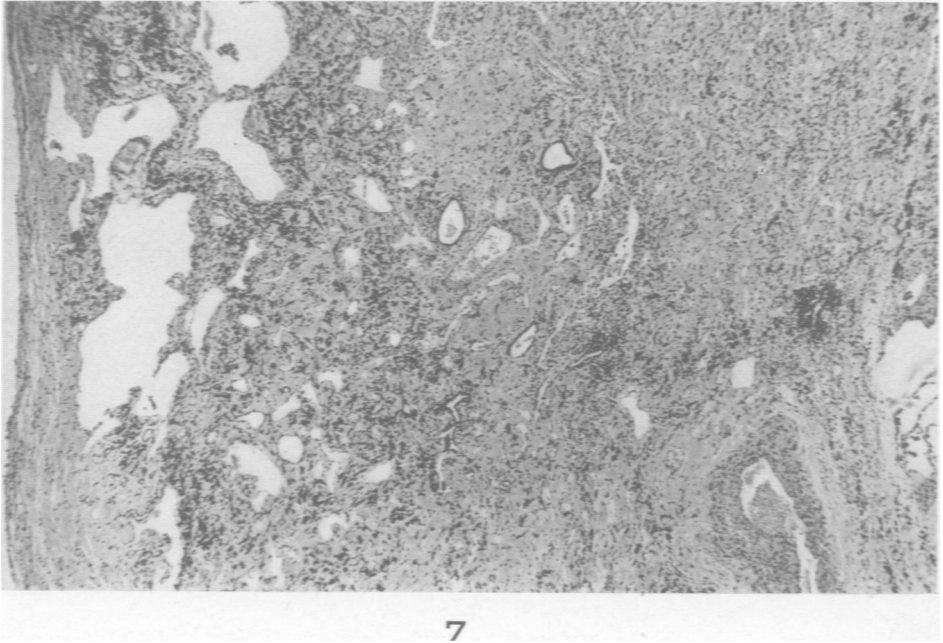
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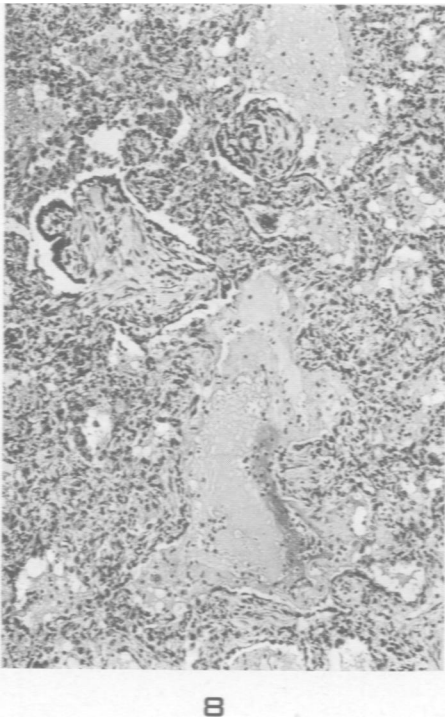
Pulmonary Fibrosis Secondary to Pneumonia

PLATE II

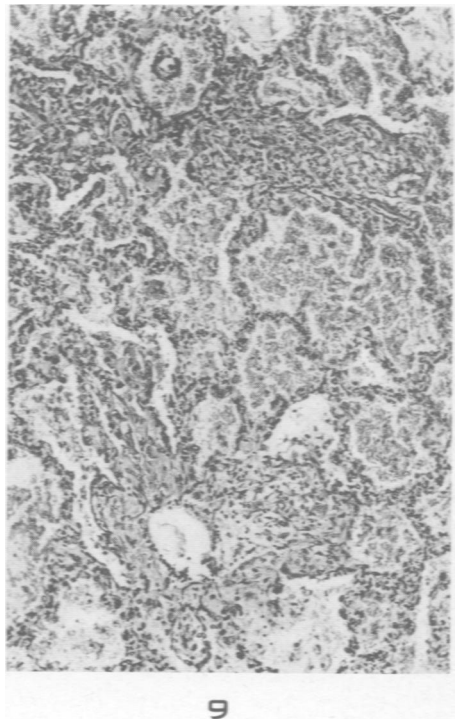
- FIG. 7. Case 5. Subpleural scar, possibly secondary to viral pneumonia. Persistent ducts lined by cuboidal epithelium are scattered through the mid-portion of the area.  $\times 30$ .
- FIG. 8. Case 6. Septal thickening and intra-alveolar organization in uremia. The large intraluminal plug is covered with cuboidal cells. Dense edema fluid in other sacs.  $\times 100$ .
- FIG. 9. Case 7. Septal fibrosis in uremia. Intraluminal plugs were present in other areas.  $\times 100$ .



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