UREMIC PNEUMONITIS *

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Systemic manifestations of uremia are classified ordinarily under headings indicating involvement of the central nervous, gastrointestinal, respiratory, and cardiovascular apparatus. Necrotizing and inflammatory reactions have been described in the gastrointestinal tract, heart, pericardium, pleura, peritoneum, spleen, skin, and synovia, and have been related to the signs and symptoms of uremia. Many of the necrotizing and inflammatory lesions which characterize uremia have been described in detail, especially those of the heart, pericardium, gastrointestinal tract, and skin. Various pathologic changes in the respiratory system have been reported. Fishberg[1] mentioned bronchitis and, more recently, Allen[2] has described an interstitial pneumonitis. Doniach[3] and Bass and Singer[4] have summarized the clinical, roentgenographic, and pathologic pulmonary findings in several cases of uremia. However, few descriptions of characteristic pulmonary lesions have appeared in the literature.

Approximately 12 years ago we became aware of pulmonary changes associated with uremia and, since that time, we have studied the lungs of 107 individuals who died with uremia, and have made comparable studies in a control group of 429 individuals who did not have uremia at the time of death. From this we have concluded that morphologic changes in the lungs of many persons with uremia (62 per cent in this series) are sufficiently distinctive to warrant application of the term *uremic pneumonitis.*

Gross Characteristics

Gross characteristics of the lungs in uncomplicated uremic pneumonitis include moderate increase in weight and diffuse rubbery induration. Often these lungs did not collapse to the usual extent when the thoracic cavity was opened. Cut surfaces were pale red and usually drier than anticipated from the increased weight and diffuse induration. In a few cases the limitation of the process to the more central areas of the lungs was appreciated and described. Hyperemia and edema were variable, probably related to congestive failure as a ter-

* Presented at the Fifty-first Annual Meeting of the American Association of Pathologists and Bacteriologists, Philadelphia, April 8, 1954.
Received for publication, June 28, 1954.

minal complication. Fibrinous pleuritis was frequent, being present in approximately 20 per cent of cases. Of the 66 cases of uremic pneumonitis studied, 25, or approximately one third, were uncomplicated by bacterial pneumonia, infarction, or chronic passive congestion. The average weight of the lungs (together) in this group was 1,008 gm.

Microscopic Characteristics

Microscopically, lungs with uremic pneumonitis exhibited slight to moderate edema, usually rich in protein and with amorphous or granular protein precipitate evident. More striking was the considerable amount of fibrin present in the alveoli. This was arranged as a fine network (Figs. 1 and 2), occasionally in dense hyaline masses or bands (Figs. 3 and 4), and sometimes adherent to the alveolar wall in the form of an asphyxial membrane (Figs. 5 and 6). Frequently there were small numbers of erythrocytes present in this fibrin-rich edema fluid, apparently representing hemorrhage *per diapedesin.* Granulocytes were absent in cases uncomplicated by bronchopneumonia or other septic process. Cellular "exudate" usually was evident, however, made up principally of macrophages.

In uncomplicated cases there was no evidence of necrosis of alveolar septa or of thrombosis. Acute passive congestion, when present, involved principally arteries and veins, tending to spare alveolar capillaries. Interstitial pneumonitis was observed only occasionally. Bronchiolitis, obliterative or otherwise, was not a prominent feature. Necrotizing arteritis, suggested as a possible factor in pathogenesis of these lesions by Bass and Singer,[4] was not observed in our series. All sections studied were embedded by the celloidin technique. The routine staining procedure employed hematoxylin and eosin. Special staining procedures used in selected cases included van Gieson's, Gram-Weigert's, azocarmine, phosphotungstic acid hematoxylin, and periodic acid-Schiff's stains, and silver impregnation for reticulin.

Incidence

Correlation with Extrapulmonic Manifestations of Uremia. One hundred and seven cases of uremia, with material adequate for this study, were collected from the University of Chicago necropsy files covering a period of 40 years (1902–1942). From microscopic examination of the lungs a diagnosis of uremic pneumonitis was made in 66 cases, an incidence of 62 per cent. Of the 107 cases of uremia, 60 (56 per cent) had uremic pericarditis and 26 (24 per cent) had either gross or microscopic evidence of uremic colitis.

Of the 66 cases with uremic pneumonitis, 33 (50 per cent) had pericarditis also and 13 (20 per cent) had uremic colitis also. In only 8 (7 per cent) of the 107 cases of uremia studied, did uremic pneumonitis, pericarditis, and colitis occur together.

The diagnosis, uremic pneumonitis, was graded on the basis of severity and extent as 1 plus to 4 plus. Nine of the 66 cases were diagnosed 4 plus (14 per cent); 20 cases, 3 plus (30 per cent); 19 cases, 2 plus (29 per cent); and 18 cases, 1 plus (27 per cent).

Correlation with Other Changes in the Lung. Of the 66 cases of uremic pneumonitis, 38 exhibited evidence of coexisting bronchopneumonia either grossly or microscopically, while 28 (42 per cent) were not associated with bacterial pneumonia. In 4 cases there was chronic passive congestion; in 3 there were infarcts and/or thrombi. In 3 cases purulent bronchitis was present without significant bronchopneumonia. Atelectasis was present in nearly half of the cases, but usually was marginal or limited to small foci elsewhere.

Evaluation of Unknowns

To test the validity of our concept and to evaluate the histopathologic criteria of uremic pneumonitis just set forth, sections of the lungs from 461 consecutive necropsies (1049 sections) were reviewed. These were evaluated as unknowns and any diagnosis of uremic pneumonitis was made without knowledge of clinical data or gross necropsy findings and entirely upon the microscopic appearance of the lungs. In 44 cases, uremic pneumonitis was diagnosed on this basis. Of these, the diagnosis of uremia had been established in 27 cases (61 per cent). In 8 additional cases (18 per cent) there was at least moderately severe renal disease or clinical data which made the presence of uremia likely. In 9 cases (21 per cent), histologically diagnosed as uremic pneumonitis, there was no evidence of uremia clinically or from necropsy findings. Further study of these 9 cases revealed the following pertinent diagnoses: resolving lobar pneumonia (2 cases); organizing pneumonia; asthma with arteriosclerotic heart disease; carcinoma of lung with organizing and resolving pneumonia (2 cases); carcinoma of hypopharynx with atypical pulmonary congestion and edema; carcinoma of stomach with necrotic pulmonary metastases; carcinoma of pancreas and pernicious anemia.

Pathogenesis

Pathogenesis of the uremic syndrome is not clear. There is abundant evidence that retention of nitrogenous products such as urea, creati-

nine, and uric acid are not responsible for signs, symptoms, and pathologic changes. Retention of phenols, guanidine, indol, or unknown toxic substances has been considered by some to be most important. Volhard[5] has pointed out that the xanthoproteic reaction most closely parallels uremia and that this measures aromatic substances in general, including phenols (mostly conjugated), dihydroxy phenols, and oxy- acids. Bradley,[6] in his review of the pathologic physiology of uremia, stated: "The derangement of total chemical structure of the plasma, convincingly shown to be present in every case, seems to provide an adequate explanation for the impressive array of symptoms."

Explanation has been offered for the development of various inflammatory and necrotizing lesions which occur in relation to uremia, but in no case is the explanation entirely acceptable. For instance, it has been suggested that uremic colitis, often ulcerative or membranous, is the result of bacterial conversion of increased amounts of urea to ammonia. Some of the dermatologic manifestations of uremia (uremides) have been attributed to very high local concentrations of urea. It has been suggested that focal myocardial necrosis is an effect of hypocalcemia. No satisfactory pathogenesis has been offered for the pericarditis, which is one of the more common inflammatory reactions resulting from uremia.

Clinical Pathologic Correlation

As a basis for considering the pathogenesis of uremic pneumonitis, the 107 cases of uremia studied were evaluated from the standpoint of age and sex of the patient, etiology of the uremia, duration of uremia, blood chemical changes, including blood urea nitrogen, nonprotein nitrogen, serum chlorides, serum pH and CO_2-combining power, blood pressure, and whether oxygen therapy had been used. Table I summarizes this data.

From this evaluation it appears that age and sex do not vary significantly in patients with uremic pneumonitis as compared with the total group, nor is there apparent difference dependent upon the type of renal disease underlying the uremia. Concerning the duration of uremia, the data are not very reliable in that group in which signs or symptoms were evident for less than 1 month before death, since many of these patients were unable to give a reliable account of their "present illness." With this consideration, there appears to be no significant correlation between duration of uremia and occurrence of uremic pneumonitis. It is evident that uremic pneumonitis may develop

quickly (several days) after onset of uremia and that it may be present in patients who have had uremia for longer than 6 months.

Regarding chemical changes of the blood, uremic pneumonitis did

TABLE I

Data Pertaining to the Pathogenesis of Uremic Pneumonitis

Attribute and number of cases			With uremic pneumonitis	Without uremic pneumonitis
Sex	Male 77		44 (57%)	33
	Female 30		22 (73%)	8
Age	Average 45.2 years		43.6 years (average)	48.1 years (average)
Etiology	Glomerulonephritis	35	23 (66%)	12
	Pyelonephritis	25	12 (48%)	13
	Arteriolonephrosclerosis	20	14 (70%)	6
	Hydronephrosis	10	6 (60%)	4
	Amyloidosis	6	4	2
	Polycystic kidneys	4	2	2
	Cholemic nephrosis	3	2	1
Duration (of uremia)	Less than 1 week	19	16 (84%)	3
	1 week to 1 month	31	20 (65%)	11
	1 month to 6 months	32	18 (56%)	14
	More than 6 months	4	4	0
	B.U.N. or N.P.N. (mg. per cent)			
Azotemia (highest terminal value)	15–30 30–60	5	0	5
	30–60 60–120	14	4 (28%)	10
	60–120 120–240	39	31 (79%)	8
	120–240 240–480	18	15 (83%)	3
Serum Cl, mEq/l (lowest, terminally)	80–100	12	8	4
	100–110	5	4	1
	110–120	4	3	1
Serum CO_2 comb. p., mEq/l (lowest, terminally)	5–10	8	8	0
	10–15	9	7	2
	15–20	10	8	2
	20+	5	3	2
Blood pressure, systolic (highest value)	120–160 (mm. of Hg)	36	26 (72%)	10
	160–200	27	15 (55%)	12
	200+	28	22 (79%)	6
Blood pressure, diastolic	80–90 (mm. of Hg)	31	22 (71%)	9
	91–100	11	6	5
	101–110	7	4	3
	110+	41	30 (73%)	11
Oxygen therapy	Yes	8	6 (75%)	2
	No	25	17 (68%)	8

not occur in patients with blood urea nitrogen below 30 mg. per cent (or non-protein nitrogen below 60 mg. per cent). A high incidence of uremic pneumonitis did not occur until blood urea nitrogen values were over 60 mg. per cent (non-protein nitrogen over 120 mg. per

cent). Serum chloride levels were not related to the incidence of uremic pneumonitis.

Most significant was the fact that of 8 patients with serum CO_2-combining power below 10 mEq/l, all had uremic pneumonitis, and of 26 patients who had a CO_2-combining power below 20 mEq/l, 24 (92 per cent) had uremic pneumonitis.

Comment

Morphologic changes which characterize uremic pneumonitis have undoubtedly been observed by many pathologists. The relatively few recorded descriptions of this process in the lungs of uremic patients may be due to the fact that each of the component changes are, in themselves, quite non-specific. The process may be confused with resolving and organizing pneumonia, as is indicated by Doniach[3] and as is seen from the summary of missed diagnoses in our "unknown" cases in which 6 of 9 cases represented resolving or organizing pneumonitis of bacterial origin or reaction peripheral to neoplasm. Characteristic changes of uremic pneumonitis may be dismissed as protein-rich edema fluid or perhaps considered as a non-representative section taken near a focus of bacterial pneumonia. The diffuse nature and homogeneous appearance of uremic pneumonitis are best recognized in uncomplicated cases in which several sections of each lung are studied.

The diffuse pulmonary lesion which most closely resembles uremic pneumonitis is rheumatic pneumonitis. In our experience rheumatic pneumonitis usually is accompanied by more hemorrhage and by necrosis of alveolar septa.

That this uremic pulmonary lesion deserves wider recognition by pathologists is suggested by the number of papers in the literature of Roentgenology describing the characteristic pulmonary lesions. Furthermore, the condition sometimes is important in differential diagnosis. One of us recently performed a necropsy on a patient with malignant hypertension in whom uremic pneumonitis probably was responsible for the presenting symptoms, which led to difficulty in diagnosis since he was considered to have bacterial pneumonia.

Several observers have suggested that left heart failure is important in the pathogenesis of uremic pneumonitis and that elevation of pulmonary venous pressure plus an increase in capillary permeability, due to toxic products associated with azotemia, are responsible for the outpouring of fibrin into the alveolar spaces. Our studies indicate that the lesions may occur with little or no clinical or pathologic evidence

of left heart failure. Furthermore, it seems that the degree of acidosis, as judged by the depression in blood CO_2-combining power, is more readily correlated with the development of the lesions. The fact that uremic pneumonitis appears to occur less often in recent cases of uremia may reflect more effective control of acid-base balance in modern therapy of uremia.

SUMMARY

The gross and microscopic characteristics of uremic pneumonitis are described and correlated with other inflammatory and necrotizing manifestations of uremia.

The etiology and pathogenesis of uremic pneumonitis are discussed.

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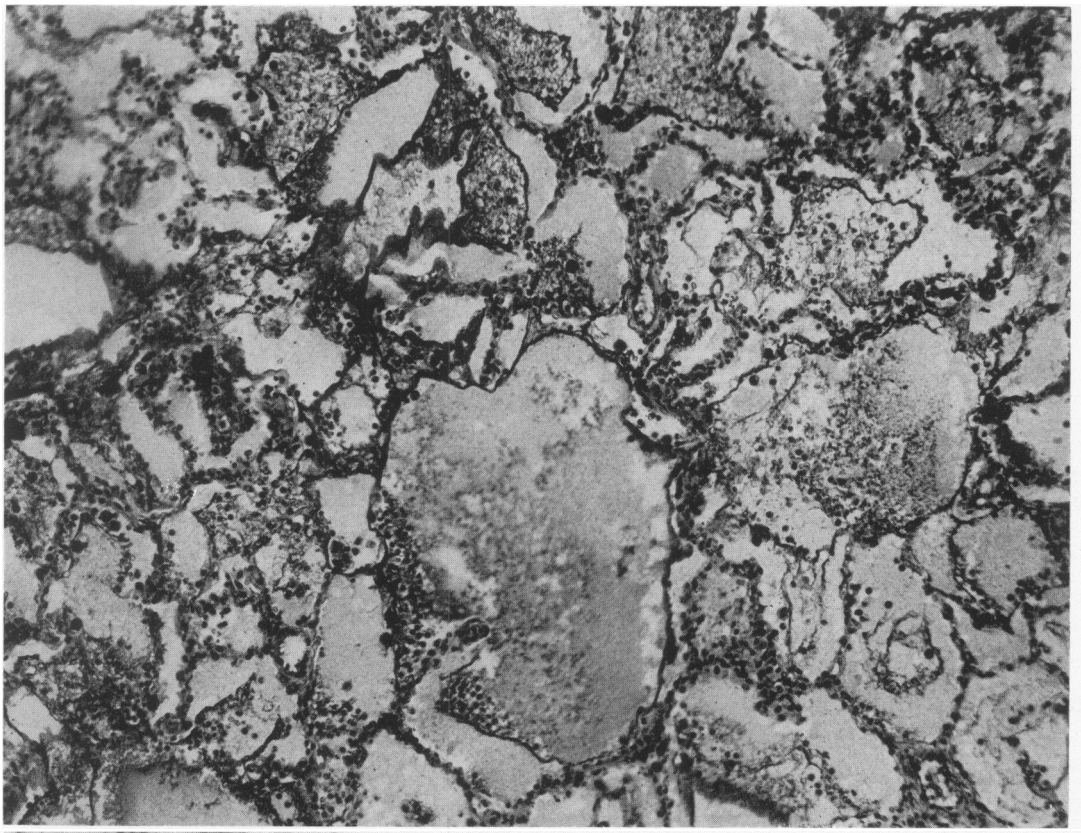
[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. A-3728. The protein-rich edema fluid contains a small amount of fibrin. Intra-alveolar cells are principally macrophages. Hematoxylin and eosin stain, celloidin embedded. × 125.

FIG. 2. A-3512. Fibrin is a prominent constituent of the edema fluid. Hematoxylin and eosin stain, celloidin embedded. × 165.



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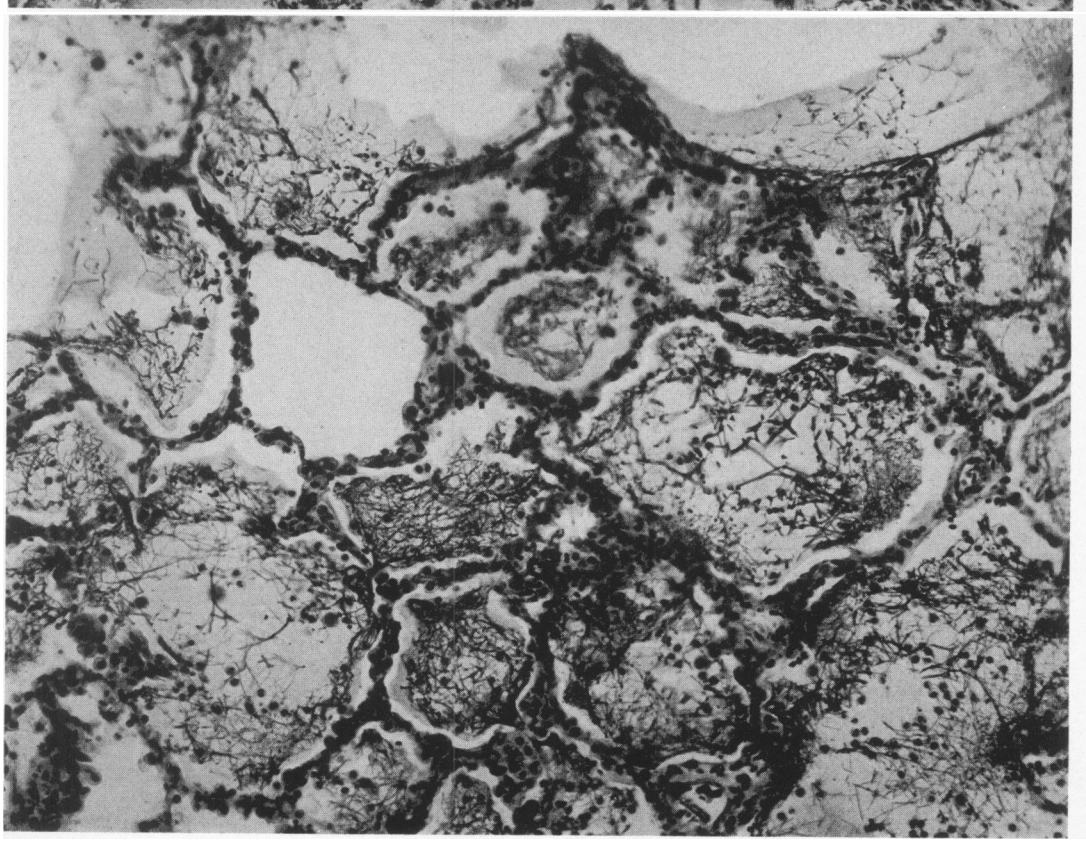

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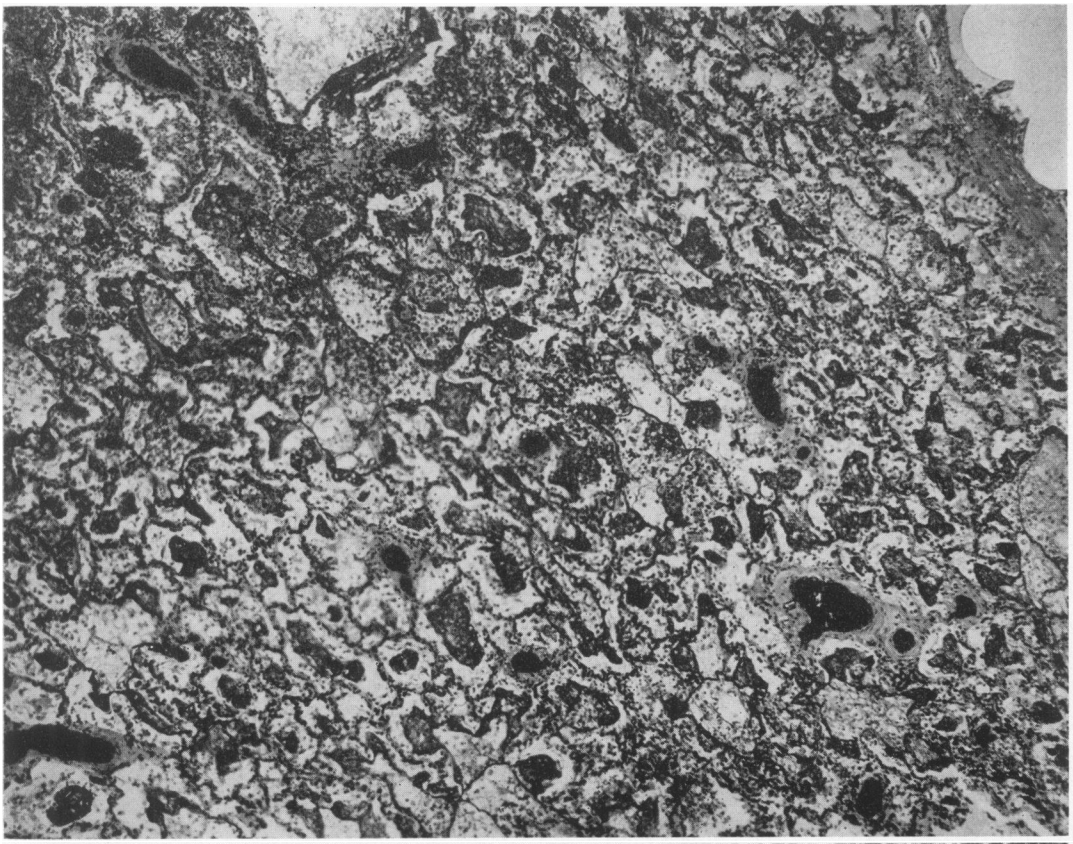
FIG. 3. A-4317. Fibrin is quite abundant and is massed in dense clumps. Cellular exudate is composed principally of macrophages. Hematoxylin and eosin stain, celloidin embedded. × 65.

FIG. 4. A-4317. Fibrin is quite abundant and is massed in dense clumps. Cellular exudate is composed principally of macrophages. Hematoxylin and eosin stain, celloidin embedded. × 165.



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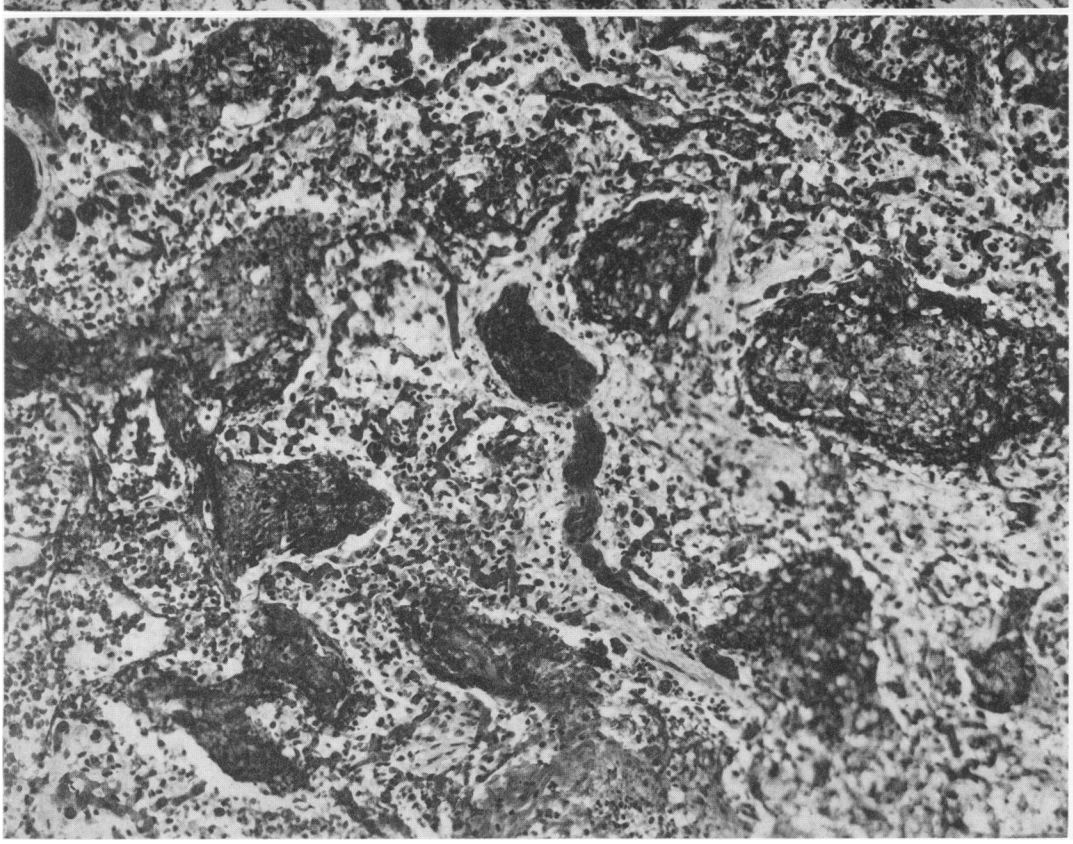

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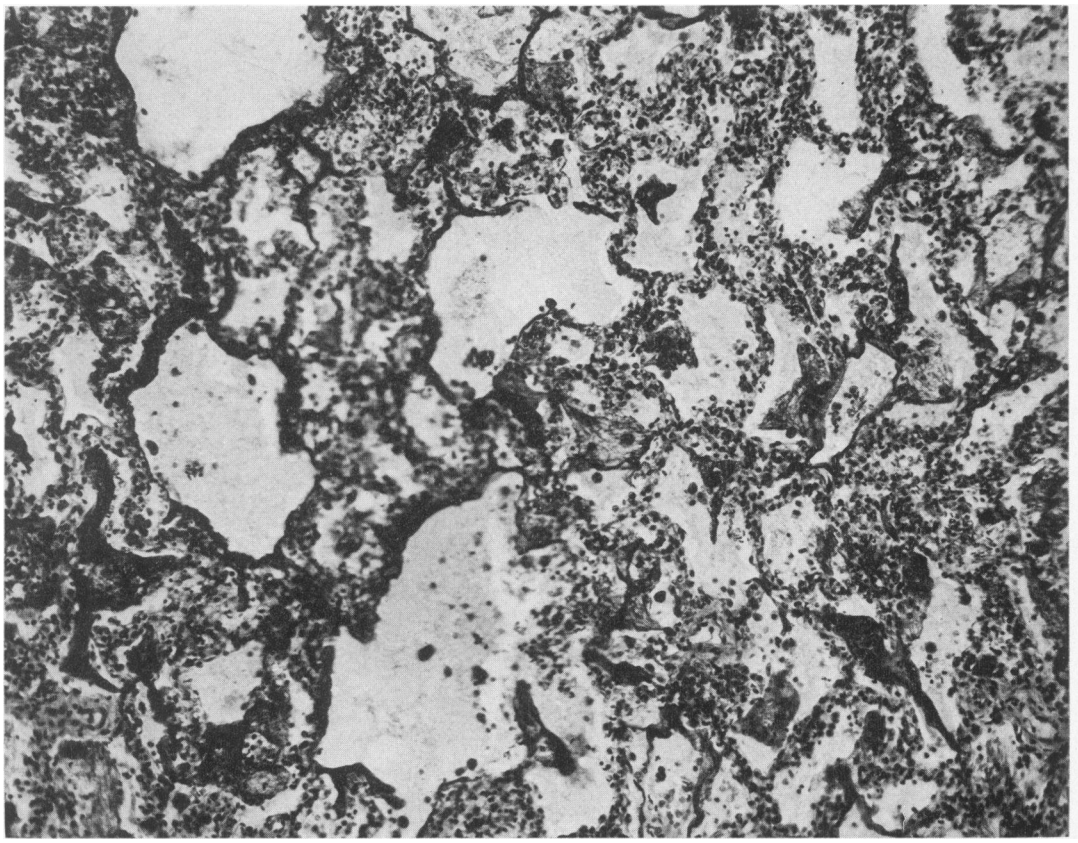
FIG. 5. A-4129. Fibrin is arranged in the form of an asphyxial membrane. Hematoxylin and eosin stain, celloidin embedded. × 125.

FIG. 6. A-3885. In addition to protein-rich edema fluid and fibrin in membranous form, there is focal atelectasis and emphysema. Hematoxylin and eosin stain. celloidin embedded. × 125.



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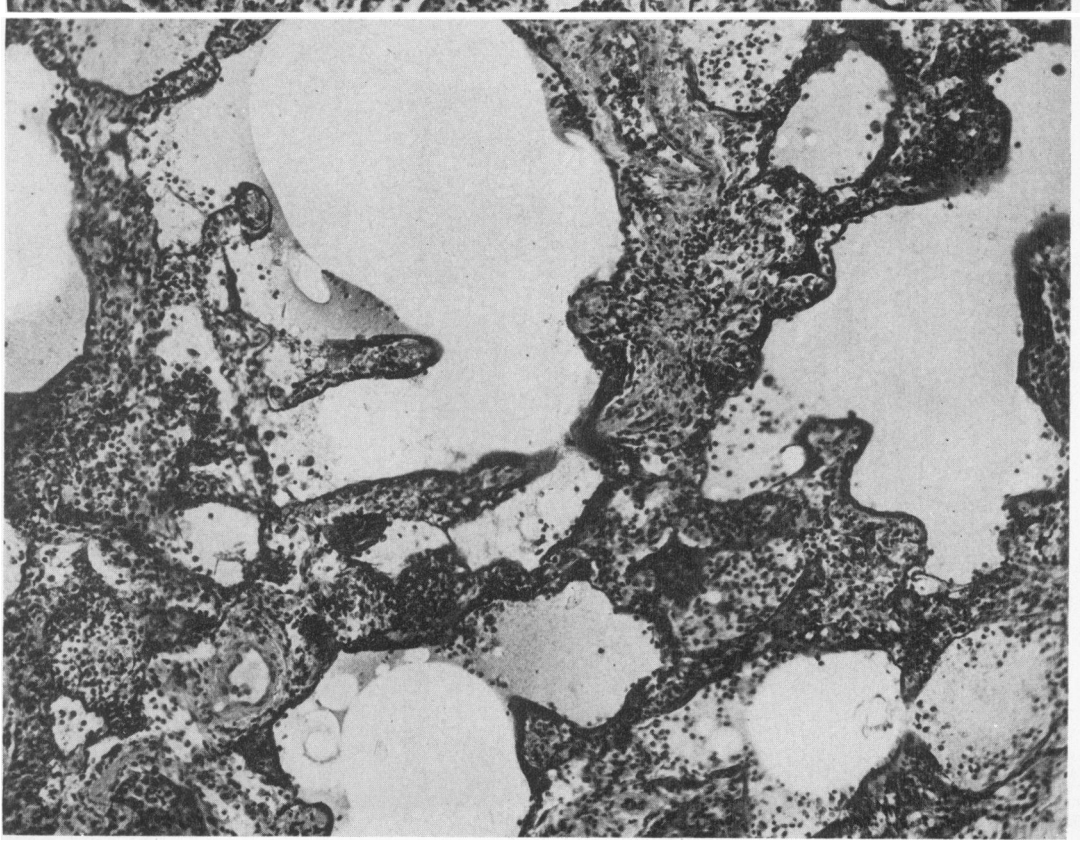

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