PATHOLOGIC FEATURES OF ALTITUDE SICKNESS

N. C. Nayak, M.D.; S. Roy, M.D., and T. K. Narayanan, D.C.P.*

From the Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

An altitude sickness characterized by pulmonary edema is known to develop suddenly in certain apparently healthy individuals who make a rapid ascent to heights above 9,000 feet. This condition occurs most frequently in children and young adults who have earlier been acclimatized to high altitude and return to heights after a short stay at sea level. On the other hand, it has been observed only rarely in indiviuals who go up to high altitude for the first time. The nature of this peculiar malady is obscure. Some recent reports have described in detail the clinical, radiologic, electrocardiographic and cardiac catheter studies in cases of pulmonary edema occurring among mountaineers, skiers, and in the Peruvian Andes.[1-8] These patients present with acute pulmonary distress, mild fever and sometimes cyanosis. They respond quickly to bed rest and oxygen therapy while antibiotic agents have no effect.[2,5,6] With proper and immediate treatment the pulmonary lesion usually clears away within 24 to 48 hours. Thus the vast majority of patients recover promptly, and reports on necropsy studies are extremely few.[1,2,9] In some of these cases only gross examination of the lung has been reported.[1] Recently we had the opportunity of studying in detail the gross and microscopic features of necropsy material from 13 individuals dying of "pulmonary distress" at high altitude. The changes in the lung were quite striking. As the cases occurred in outlying areas where adequate hospital facilities were not available, detailed clinical studies were not possible. The present communication deals essentially with the anatomic changes in the lung and other organs in this condition.

Material and Methods

Necropsy examinations were carried out in outlying stations in 13 men who had developed acute respiratory distress at altitudes above 8,000 feet and had died shortly afterwards. Formalin-fixed organs and tissues along with clinical findings and notes on the gross appearance of the organs in the fresh state at the time of necropsy were made available to us. Because of the lack of facilities, radiologic, microbiologic or cardiac catheter studies were not possible in any of the cases. Careful gross evaluation of the formalin-fixed organs was made by us, and detailed microscopic examination was carried out with particular attention to the lungs. Several blocks were taken from

Accepted for publication, April 10, 1964.

* Col. Narayanan is Chief of the Command Laboratory, Military Hospital, Lucknow.

each lung and only representative sections from other organs. After usual processing, paraffin sections were cut at 5 μ and all sections were stained with hematoxylin and eosin and Mallory's phosphotungstic acid hematoxylin (PTAH). Selected sections were stained by the periodic acid-Schiff (PAS) method, Gram's stain and Perls's method for hemosiderin.

RESULTS

Clinical Features

All patients in this series were men between 21 and 42 years of age, the majority (9 cases) being between 25 and 35 years. The altitude at which the symptoms developed varied between 8,400 to 14,000 feet. All were healthy prior to onset of symptoms. Several of the men had come to high altitude for the first time and had stayed for a few days before the symptoms developed. In most cases there was a history of exercise in the nature of marching over long distances or climbing mountains. Presenting symptoms at the time of admission were dyspnea, mild fever (99 to 100° F.), cough, cyanosis, pain in the chest, frothy sputum, edema of the hands and feet, headache, nausea, vomiting and unconsciousness, in that order of frequency. In 2 cases the sputum was blood-stained. Examination revealed signs of pulmonary edema in most of the cases. They were treated with antibiotic agents, including the broad spectrum group, but apparently without any effect. Oxygen, administered only in 2 cases in the terminal stage, failed to improve the condition. The time from onset of symptoms to death varied from 12 hours to 12 days; 8 died within 48 hours, 3 within 4 days, 1 on the twelfth day and in 1 case, the exact interval could not be ascertained.

Anatomic Findings

Necropsies were performed within 24 to 48 hours of death. The lungs universally presented striking features both on gross and microscopic examination. They were much heavier than normal, often weighing more than 1,200 gm. together, and were markedly congested in all cases. Tracheal and bronchial mucosa was also congested, and the lumens frequently contained frothy, mucoid or blood-stained fluid. The cut surface of the lungs exuded blood-stained edema fluid and in several cases showed patchy areas of hemorrhage and noncrepitant solid areas simulating pneumonia. In the formalin-fixed material it was difficult to appreciate edema, but patchy areas of hemorrhage and consolidation with intervening crepitant lung parenchyma were quite evident. The extent of these lesions varied from case to case, and in one the areas of hemorrhage were very massive, involving almost the entire lung parenchyma. The pleura was thin and transparent except in one case where small scattered patchy opacities were seen over both lungs. There was no evidence of

emphysema, and the branches of the pulmonary artery showed a smooth intima in all cases.

The significant findings on microscopic examination are shown in Table I. Striking and constant histologic features were congestion of alveolar capillaries and pulmonary edema (Fig. 1). Congestion, when

TABLE I

PULMONARY ABNORMALITY IN 13 CASES OF ALTITUDE SICKNESS

	Grading*				
	—	±	+	++	+++
Alveolar congestion	0	0	1	6	6
Edema	1	0	3	5	4
Intra-alveolar fibrin	1	4	4	2	2
Hyaline membrane	6	2	2	3	0
Capillary thrombi	7	0	0	5	1
Intra-alveolar hemorrhage	1	3	3	0	2
Bronchiolitis and bronchopneumonia	3	4	4	2	2
Atelectasis	6	4	4	2	0

* —, absent; ±, minimal; +, mild; ++, moderate; +++, severe.

marked, caused widening of the alveolar septums due to markedly dilated capillaries; no septal thickening was noted. The congestion was severe in 6, moderate in 6 and mild only in 1 case. Edema was severe in 4 cases, being widespread in distribution, and in many places the alveoli were greatly distended by edema fluid. It was present with moderate degree of severity in 5, mild and focal in 3 and absent in 1 case. In the lung where edema was absent, there was very marked congestion of the capillaries and significant atelectasis.

Some interesting features observed in the lungs were deposition of intra-alveolar fibrin and hemorrhage (Fig. 2). Fibrin and red cells appeared either alone or together in varying proportions. The fibrin strands were mostly present as thin, delicate, interwoven filaments, sometimes concentrated in the central portion of alveoli and occasionally forming hyaline clumps. They were deep blue with the Mallory PTAH stain and were unaccompanied by any significant inflammatory cell exudate. In some areas the fibrin strands aggregated to form thicker bands or hyaline-like membranes often forming a lining of the alveoli, alveolar sacs and ducts (Fig. 3). Morphologically these were identical to the hyaline membranes described in infants and in adults with various types of pulmonary lesions. In a few cases fibrin was found to be retracted from the alveolar walls undergoing a process of organization (Fig. 4). Fibrin was present in 12 cases, being severe in 2, moderate in 2 and only mild and focal in 4 cases. Its presence was considered minimal in 4 cases and in 1 case there was no fibrin. Hyaline membranes were present in 7 cases; moderate in 3; mild in 2, and minimal in 2. A significant finding in lungs

from 6 of the cases was the presence of hyaline fibrin thrombi in the alveolar capillaries (Figs. 2 and 5) and in some of the branches of the pulmonary artery (Fig. 6). When present they could be seen to plug the dilated capillaries, mostly in the form of homogeneous masses, but sometimes they had an indistinct laminated appearance, always giving a strongly positive reaction with the PTAH stain (Fig. 7). According to our morphologic grading, 1 case was quite severe and 5 moderately severe. Intra-alveolar hemorrhage was present in 9 cases. It was mostly fresh and mild (7 cases), involving scattered focal areas of lung parenchyma. In 2 cases, however, the hemorrhage was severe, involving most of the parenchyma, greatly distending the alveoli (Fig. 8), and in many places breaking the alveolar septums. Hemorrhage was minimal in 3 cases and absent in 1.

Bronchiolitis and bronchopneumonia were present in 6 cases; it was severe in 2, moderately severe in 2 and mild in 2 cases. In all these cases, significant edema was present, often far removed from the areas of inflammation. In one lung with severe bronchopneumonia, a large amount of aspirated vegetable matter was present in the bronchioles and parenchyma, and the inflammatory process was most marked surrounding those foreign bodies (Fig. 9). In the other severe case the inflammatory picture was that of lobar pneumonia; this patient had lived for 12 days after the onset of symptoms. Besides these changes, focal areas of atelectasis could be observed in 3 cases; atelectasis was minimal in 4 others. In 2 cases scattered multinucleated cells resembling megakaryocytes were seen.

Other Organs

Gross examination revealed no significant abnormality in other organs. Particular attention was paid to the heart, which was within normal range of size and weight in all 13 cases. There was no hypertrophy or dilatation of the right ventricle, and the pulmonary trunk and ring were normal. Microscopic examination showed small focal areas of myocardiolysis in 2 cases. The liver often showed evidence of mild to moderate centrilobular congestion (10 cases). In addition, 8 cases showed mild fatty change. The spleen showed well-marked congestion of the red pulp. In 1 case, multiple fibrin thrombi were observed in the kidney, plugging the glomerular and several peritubular capillaries (Figs. 10 and 11). These thrombi were of the type seen in blood vessels of the lung and were intensely stained by PTAH. Similar thrombi and small plugs of fibrin strands were also present in the sinusoids of the liver in this case (Fig. 12). There were small areas of focal liver cell necrosis. This finding of fibrin thrombi in the systemic circulation, although quite striking by itself, was not seen in the other cases of this series.

No significant microscopic change was observed in the brain and other organs.

Discussion

Interest in a detailed study of high altitude pulmonary edema is relatively recent, and during the last few years several reports giving detailed clinical and laboratory data in this condition have appeared in the literature. Mosso,[10] in 1898, may have been the first to describe this disease which has since long been known in the Peruvian Andes as "Soroche" or "mountain sickness." It was, however, Hurtado[11] who characterized the clinical picture and suggested that it was essentially an acute pulmonary edema. Hultgren, Spickard, Hellriegel and Houston,[1] as late as 1961, introduced the term "high altitude pulmonary edema" apparently for its simplicity. The disease appears with characteristic clinical and radiologic manifestations, with diffuse or patchy mottling seen in both lung fields on x-ray. The symptoms quickly disappear on proper treatment though the radiologic changes may sometimes persist for longer periods.[3,4] Admittedly, in the cases reported in the present series, the clinical data were far from complete. However, the presenting features and clinical signs on physical examination were typical of this syndrome in all cases and all of them proved fatal.

Necropsy studies are rare, and in only 4 cases are the anatomic findings well documented.[2,9] Hultgren and co-workers[1] reported 5 deaths among 13 mountaineers who developed the syndrome. In 2 (cases 3 and 4) of their series where necropsy was possible, a diagnosis of bilateral fulminating pneumonia was made on gross examination. The same group of workers[2] have recently reported 8 additional cases of altitude edema. Two of these proved fatal and necropsy showed edema, congestion and red cells in the alveoli. In 1 case, there were, in addition, intra-alveolar fibrin, neutrophils and histiocytes, together with thrombi in the capillaries and small arteries. Many megakaryocytes were present in the lungs in both cases. More recently 2 fatal cases have been reported from Peru.[9] At necropsy the lungs showed edema alternating with emphysema, congestion, hyaline membranes and vascular thrombi although no mention was made of intra-alveolar fibrin and red cells.

It is evident that these findings in the literature are similar to the anatomic features observed in the lungs in our cases. In our material, although alveolar edema and congestion were universal changes apparently characteristic of this syndrome, the presence of intra-alveolar hemorrhage and fibrin and vascular thrombi in a significant number was a striking feature. These changes appear to be also integral parts of the basic pulmonary lesion. The hyaline membranes have almost certainly evolved out of the fibrin in the alveoli as seen by their topographic rela-

tions and staining characters. We observed fibrin in 12 of 13 cases, and hyaline membranes in 7. Pulmonary edema by itself is not an uncommon finding in various types of acute and chronic cardiac and pulmonary disorders, but in such cases hyaline membranes are extremely rare. Swann,[12] who described the morphologic features of pulmonary edema in cases of sudden asphyxial death from various causes, made no reference to hyaline membranes. We are inclined to believe that the membranes found in association with pulmonary edema in this syndrome originated from fibrin-rich intra-alveolar edema fluid. Even though no mention of fibrin was made in the report by Arias-Stella and Kruger,[9] their Figure 5 shows suggestions of fibrin threads inside some of the alveoli. The exact relationship of fibrin thrombi in the alveolar capillaries and intra-alveolar fibrin is not clear. Extravasation of red cells into the alveolar lumens was a significant feature and explains the blood-stained sputum that several of the patients produced. Even hemoptysis has been reported in some cases.[1] Two patients in our series showed massive hemorrhage into the air spaces (Fig. 8). In one other case, atelectasis was the predominant feature; in others, small foci of atelectasis were observed.

The basic nature and genesis of these pulmonary changes are matters for speculation, but certain factors can reasonably be excluded on the basis of clinical, functional and morphologic observations. The fact that a failure of the left heart is not responsible for the acute pulmonary episode is accepted by all workers in the field. No organic disease of the heart is found in these cases, and myocarditis observed in one of the 2 necropsies reported by Hultgren, Spickard and Lopez[2] was interpreted by the authors as incidental, without in any way contributing to the development of pulmonary lesions. The role of infection is unacceptable because of a uniform lack of response to antibiotic therapy and of some features in the clinical picture as stressed by various observers.[2,5] The scanty inflammatory reaction in the lung is probably a secondary phenomenon. In none of our cases was a microbiologic study possible, but the foci of bronchopneumonia observed in some cases appeared to us to be too insignificant to be primary. Quite often such foci could be related to aspirated material.

There can be little doubt that hypoxia is in some way responsible for the lung changes. Prompt administration of oxygen or rapid descent to low altitudes dramatically reverses the condition. Necropsy studies in persons exposed to high altitude in aircraft accidents[13] or to simulated altitudes in decompression chambers[14] have shown severe edema and congestion in the lung. In an experimental study on dogs, Mosso[15] observed mild pulmonary edema on exposing the animals to low barometric pressures.

The exact manner in which hypoxia initiates the lung lesion is, however, obscure. It is possible that a post-capillary vasoconstriction in the pulmonary bed, resulting from hypoxia, may lead to pulmonary hypertension [9,16-19] and edema.[3,20] This, however, would not explain the presence of alveolar fibrin and hemorrhage seen so prominently in our cases, and severe injury to the capillaries would be necessary for these events to occur. The question of a coagulation disorder resulting in *in vivo* precipitation of fibrin also needs elucidation. It is difficult to speculate the genesis of pulmonary changes observed in this syndrome, on the basis of anatomic findings. However, capillary damage due to a factor or factors operating at high altitude combined with excessive physical exercise may very well be the primary mechanism. Obviously, more elaborate physiologic and experimental observations are necessary before reasonable conclusions can be drawn.

Summary

Pathologic study of necropsy material from 13 men dying of respiratory distress at altitudes above 8,000 feet has been reported. All individuals were healthy prior to the onset of symptoms. The clinical picture was characteristic of high altitude pulmonary edema described by other workers.

Striking changes were observed in the lung. In addition to edema and congestion which were universally present, a significant number showed intra-alveolar fibrin, hemorrhage, hyaline membranes and thrombi in alveolar capillaries. In a few cases one or more of the latter were predominant microscopic findings. In one case vascular thrombi were also observed in the kidneys and liver.

The nature and pathogenesis of the lung lesions are discussed in the light of available clinical, pathologic and experimental data.

References

1. Hultgren, H. N.; Spickard, W. B.; Hellriegel, K., and Houston, C. S. High altitude pulmonary edema. *Medicine,* 1961, **40,** 298–313.
2. Hultgren, H.; Spickard, W., and Lopez, C. Further studies of high altitude pulmonary oedema. *Brit. Heart J.,* 1962, **24,** 95–102.
3. Fred, H. L.; Schmidt, A. M.; Bates, T., and Hecht, H. H. Acute pulmonary edema of altitude. Clinical and physiologic observations. *Circulation,* 1962, **25,** 929–937.
4. Alzamora-Castro, V.; Garrido-Lecca, G., and Battilana, G. Pulmonary edema of high altitude. *Am. J. Cardiol.,* 1961, **7,** 769–778.
5. Houston, C. S. Acute pulmonary edema of high altitude. *New England J. Med.,* 1960, **263,** 478–480.
6. Stewart, L. R. Acute pulmonary oedema of high altitude. *New Zealand Med. J.,* 1961, **60,** 79–80.

7. MARTICORENA, E.; TOPIA, F. A.; DYER, J.; SEVERINO, J.; BANCHERO, N.; GAMBOA, R.; KRUGER, H., and PENATOZA, D. Pulmonary edema by ascending to high altitudes. *Dis. Chest.*, to be published. (Quoted by Arias-Stella.[9])
8. RAEZ, E. Primer caso de edema pulmonar agudo por soroche grave estudiado en Huancayo. *Rev. Viernes. Med.*, 1960, **9**, 114.
9. ARIAS-STELLA, J., and KRUGER, H. Pathology of high altitude pulmonary edema. *Arch. Path.*, 1963, **76**, 147–157.
10. Mosso, A. Life of Man in the High Alps. T. F. Unwin, Publishers, London, 1898.
11. HURTADO, A. Aspectos fisiópatológicos y patológicos de la vida en la altura. Imprenta Editora Rimac S. A., Lima, 1937, p. 30.
12. SWANN, H. E. Occurrence of pulmonary edema in sudden asphyxial deaths. *Arch. Path.*, 1960, **69**, 557–570.
13. ROBIE, R. R.; LOVELL, F. W., and TOWNSEND, F. M. Pathological findings in three cases of decompression sickness. *Aerospace. Med.*, 1960, **31**, 885–896.
14. HAYMAKER, W., and DAVISON, C. Fatalities resulting from exposure to simulated high altitudes in decompression chambers; a clinicopathologic study of 5 cases. *J. Neuropath. & Exper. Neurol.*, 1950, **9**, 29–59.
15. Mosso, A. L'uomo sulle alpi. Fratelli Treves, Milano, 1909.
16. ARIAS-STELLA, J., and RECAVARREN, S. Right ventricular hypertrophy in native children living at high altitude. *Am. J. Path.*, 1962, **41**, 55–64.
17. MONGE-CASSINELLY, C.; CAZORLA, A.; WHITTEMBURY, G.; SAKATA, Y., and RIZO-PATRÓN, C. Descripcion de la dinámica circulatoria en al corazón y pulmones de habitantes del nivel del mar y de las grandes alturas por medio de la técnica de dilución del colorante. *An. Fac. med., Lima*, 1956, **39**, 498–511.
18. KUIDA, H.; TSAGARIS, T. J., and HECHT, H. H. Evidence for pulmonary venoconstriction in brisket disease. *Circulation Res.*, 1963, **12**, 182–189.
19. HULTGREN, H. N. Pulmonary edema at high altitude. Discussion in: Normal and Abnormal Pulmonary Circulation. Fifth annual conference on research in emphysema, Aspen, Colo., 1962, June 13–16.
20. GORDON, I. B., and KATZ, L. N. Hypoxia and pulmonary vasculature. *Perspect. Biol. & Med.*, 1962, **5**, 275–292.

LEGENDS FOR FIGURES

Except where indicated, photomicrographs were made of sections stained by hematoxylin and eosin.

FIG. 1. The lung exhibits pronounced edema and alveolar capillary congestion. × 180.

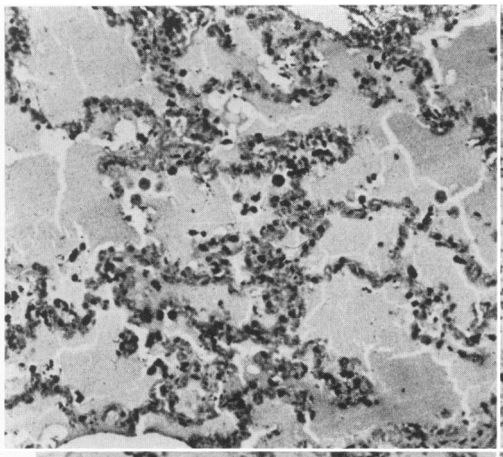
FIG. 2. Fibrin and red cells appear in the alveolar lumens. Fibrin plugs are also evident in the alveolar capillaries (arrow). × 180.

FIG. 3. Hyaline membranes line portions of the alveolar wall. Threads of fibrin can also be seen in the alveoli. × 180.

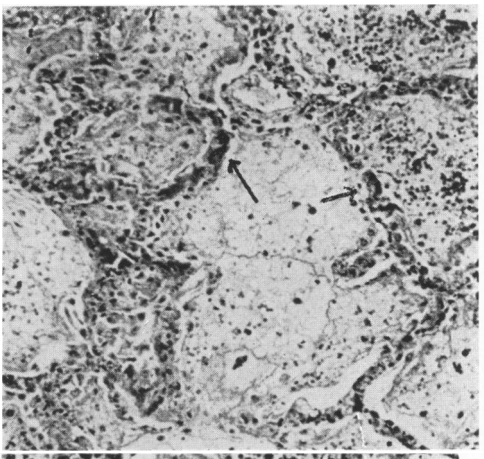
FIG. 4. Retraction of the fibrin exudate from the alveolar walls has occurred, and there is early organization. × 180.

FIG. 5. An alveolar capillary contains a hyaline fibrin thrombus in its lumen (arrow). × 600.

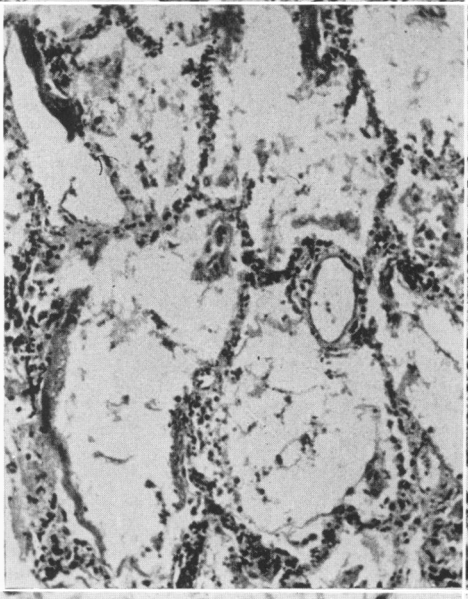
FIG. 6. A small pulmonary arteriole exhibits a thrombus. × 180.



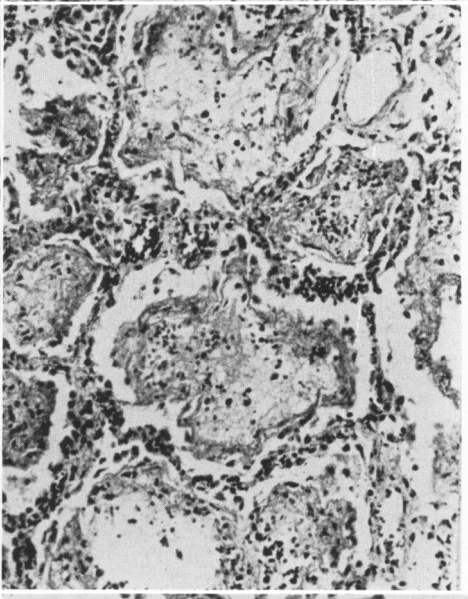
1



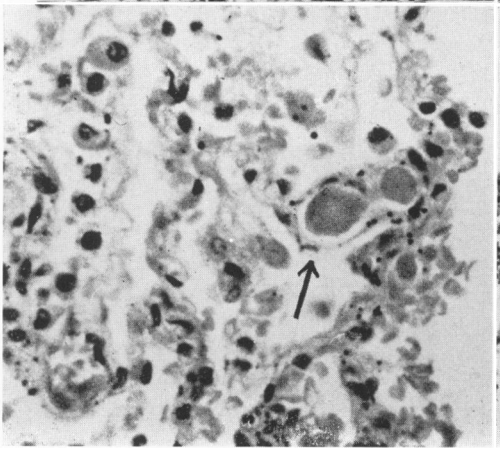
2



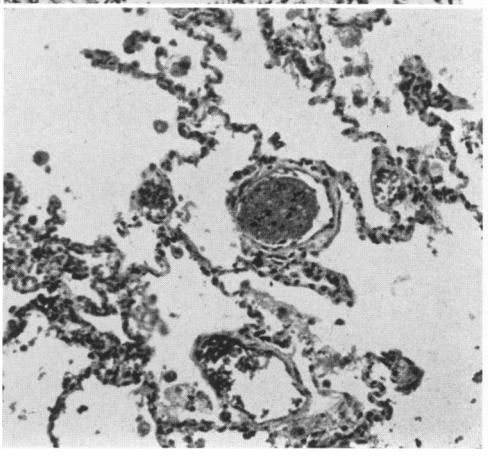
3



4



5



6

FIG. 7. Intra-alveolar fibrin and thrombi inside the alveolar capillaries take a strongly positive stain with PTAH. × 180.

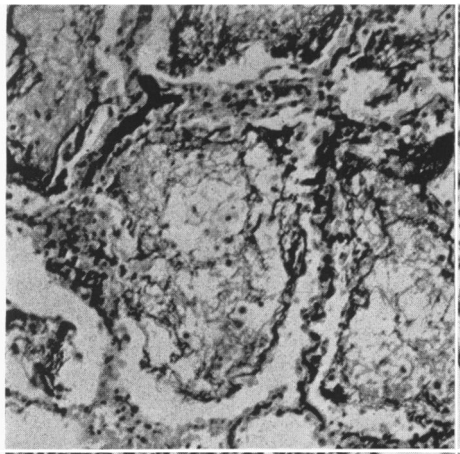
FIG. 8. Massive intra-alveolar hemorrhage. × 180.

FIG. 9. An area of bronchopneumonia surrounds aspirated vegetable matter. The neighboring lung parenchyma is edematous. × 180.

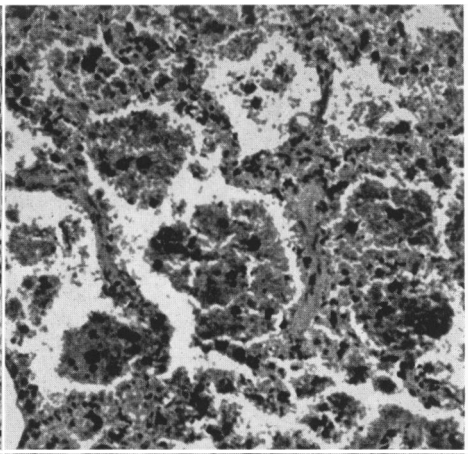
FIG. 10. Multiple fibrin thrombi are manifest in the glomerular capillaries. A few peritubular capillaries also contain fibrin plugs (arrow). PTAH stain. × 180.

FIG. 11. A glomerulus contains thrombi in most of its capillaries. × 600.

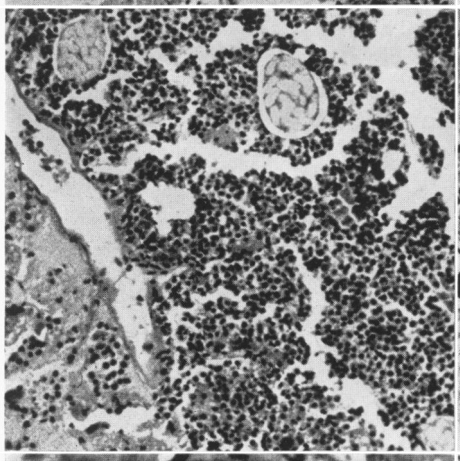
FIG. 12. Liver. Clumps of fibrin threads appear in the sinusoids (arrows). PTAH stain. × 600.



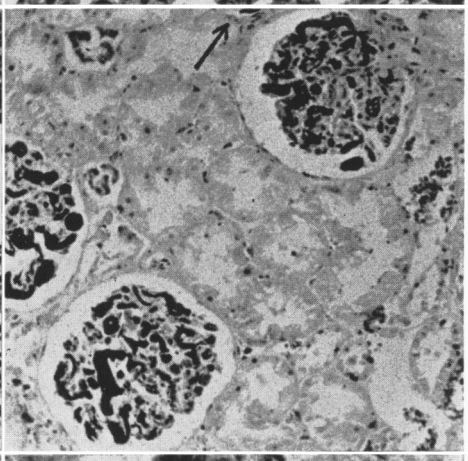
7



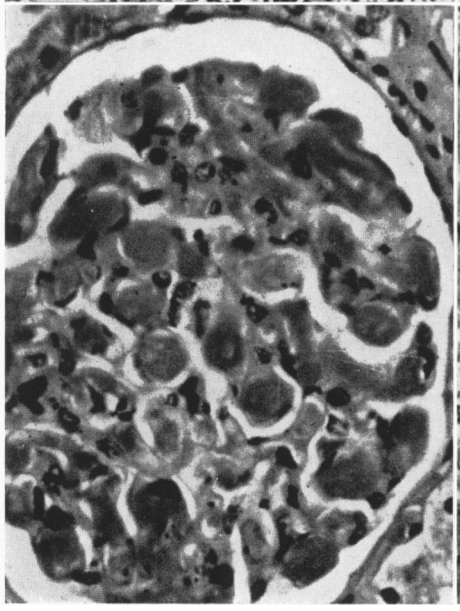
8



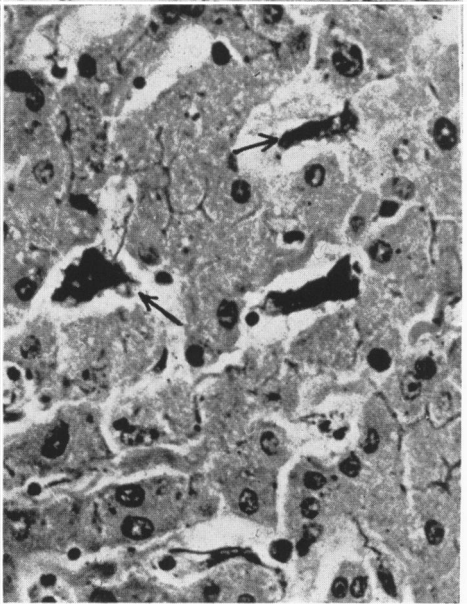
9



10



11



12