PULMONARY CAPILLARY PROLIFERATION INDUCED BY OXYGEN INHALATION *

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Pulmonary physiologists have long known that a progressive alteration in pulmonary function occurs during prolonged exposure to inhalation of atmospheres containing high concentrations of oxygen. Not only is there a progressive loss of vital capacity over a period of several days' exposure, but recovery of the original vital capacity is slow and may require several days.[1,2] Examination of pulmonary tissue from animals sacrificed after days or weeks of exposure to increased oxygen has revealed such features as "hyperemia,"[1,3,4] "engorgement and hemorrhage,"[5] "fibrinous pneumonia and congestion,"[6,7] and "damage to capillary walls."[2]

On several occasions the author has had opportunity to examine pulmonary tissue from persons who had died following prolonged progressive pulmonary disease, and who had had oxygen therapy for considerable periods before death. A peculiar similarity in the appearance of several such lungs, even though the causes of the pulmonary insufficiency were different, gave rise to the suspicion that oxygen might be contributing to the terminal structural abnormality. In essence, the lesion appeared to be an overgrowth of capillaries in the alveolar septums. Since a search of the literature revealed scattered descriptions of this type of reaction but none in which it was attributed to oxygen inhalation, a number of necropsy cases were reviewed with specific attention to the possible influence of oxygen upon pulmonary tissue.

MATERIAL AND METHODS

Two groups of cases were chosen for study. Group I was selected by examination of a series of clinical records from the University Hospital, Columbus, Ohio. A consecutive series of 10 necropsied patients was selected on the basis of their having received oxygen therapy during the hospital stay. The microscopic sections of pulmonary tissue were re-examined in order to determine the presence or absence of capillary proliferation. In this laboratory it is customary to prepare at least 3 sections from different lobes of the lungs, and often a section from each lobe is available. All slides in each case were reviewed and were similar to each other in appearance except in those instances

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where one or two lobes were the seat of pneumonia or carcinoma. Stains for elastic tissue and reticulum were made on new sections prepared from the original tissue blocks.

Group II consisted of a consecutive series of 22 necropsy cases culled from the records of the University Hospital Pathology Department. The microscopic sections of pulmonary tissue were simply removed from the file, examined, and an opinion was formed as to whether or not capillary proliferation was present. The clinical records were then checked. In addition to this material, a few specimens of surgically resected pulmonary tissue and others showing pulmonary edema and atelectasis were studied in order to substantiate the belief that the lesions ascribed to oxygen exposure were specific for this condition.

Results

The clinical and histologic data in group I are arranged in order of the duration of oxygen inhalation. The observations in group II are summarized in Table I.

Group I

Case 1. Male, 57 years. Old and recent cerebrovascular accidents. There were no preceding respiratory complaints, but nasal catheter oxygen was begun on admission because of Cheyne-Stokes respiration. Oxygen administration was continued for 19 days at 7 liters per minute, ending 5 days before death. Progressive respiratory impairment was noted and was considered the probable cause of death. The total lung weight at necropsy was 870 gm.; grossly the lung tissue was "congested."

Five sections of lung tissue were available for study. All showed generalized slight to moderate alveolar septal thickening with increased numbers of congested capillaries (Fig. 1). In many small foci, alveolar structure was obscured, and in these areas fibrocytes and distinct delicate collagen fibers were noted (Fig. 2). A few foci of purulent lobular pneumonia were readily distinguished.

Case 2. Male, 77 years. Old and recent cerebrovascular accidents. There were no preceding respiratory complaints, but nasal catheter oxygen was begun on admission because of "moderate respiratory distress." It was continued for 16 days, until death, at the rate of 4 to 5 liters per minute. Progressive respiratory impairment was the probable cause of death. The total lung weight at necropsy was 990 gm.; the lungs were dark red, firm, and a "small amount of red fluid" could be expressed.

Three sections of lung tissue were available for study. All showed almost complete obliteration of alveolar spaces, with marked thickening of the remaining recognizable septums (Fig. 3A). In many regions only "sheets" of closely packed capillaries could be seen. In those areas where alveoli could still be discerned, capillary tufts were observed to project into the alveolar lumens (Figs. 4 and 6). A distinct scarring obscured the pulmonary structure in scattered areas (Fig. 5). Most of the smaller bronchi contained mucoid material in which neu-

trophils were suspended, but no evidence of leukocytic reaction was seen elsewhere.

Case 3. Male, 79 years. Generalized arteriosclerosis with cerebral thrombosis. There were no preceding respiratory complaints, but nasal catheter oxygen was given because of "moderate dyspnea." It was continued for 8 days at 6 liters per minute. Death resulted from a massive cerebral hemorrhage. The lungs weighed 780 gm. and were purplish-blue in color.

Three sections of lung tissue were available for study, and two of these showed partial consolidation by purulent bronchopneumonia. In nonpneumonic areas capillary congestion and irregular thickening of alveolar septums were seen (Fig. 8). A few intra-alveolar tufts could be found, but in general the changes were relatively inconspicuous.

Case 4. Male, 79 years. Pulmonary emphysema with cor pulmonale and congestive heart failure. Because of dyspnea, oxygen was administered by nasal catheter at 6 liters per minute for 6 days. Treatment was discontinued 4 days prior to death, which was attributed to edema. The lungs weighed 1,390 gm. and showed congestion. On section there were red patches from which oozed foamy material.

Five sections of lung tissue were available for study, and all showed evidence of pulmonary edema. In addition there was a generalized thickening of alveolar septums with an increased prominence of capillaries. Occasional intra-alveolar tufts were present. Inflammatory cells were absent except in relation to bronchioles. Here, there was usually lymphocytic infiltration which was interpreted as an indication of chronic bronchitis related to the emphysema. Even the affected bronchioles showed numerous prominent capillaries in their walls and subepithelial regions (Fig. 9), and in many respiratory bronchioles, capillaries appeared in the lumens (Fig. 10). The latter lesion was not prominent in any other cases in group I but was seen in some of those in group II.

Case 5. Female, 40 years. Subarachnoid hemorrhage. Nasal catheter oxygen was given because of unexplained hyperpnea. The rate was 7 liters per minute for 6 days, and this was terminated 6 days before death. The lungs weighed 430 gm.

Two sections of lung tissue were available. In each the alveolar septums were uniformly thin and the spaces empty. The capillary lesion noted in the other cases was not apparent, but it is possible that it may have regressed subsequent to interruption of oxygen exposure. The clinical record was not sufficiently detailed to permit a conclusion on this point.

Case 6. Female, 80 years. Arteriosclerotic cardiovascular disease with congestive failure. Because of dyspnea, cyanosis, and pleural effusion, nasal catheter oxygen was given for 3 days at 4 liters per minute, until death. Death was attributed to congestive failure. The lungs weighed 610 gm. and were dark red, congested and atelectatic.

Three sections of lung tissue were available. All showed generalized capillary congestion and proliferation; in many regions the septal tissue occupied more area than the air spaces. There were no definite

examples of intra-alveolar capillary tuft projection. There were occasional foci of fresh hemorrhage which may have been either ante or post mortem.

Case 7. Male, 66 years. Myocardial infarction. Because of marked dyspnea, nasal catheter oxygen was given at 6 liters per minute for about 24 hours, ending 2 days before death. The latter was the result of pulmonary embolism. The lungs weighed 630 gm. and showed generalized congestion with patchy dark red areas measuring 3 to 4 cm. in diameter.

Three sections of lung tissue were available. All showed generalized evidence of capillary congestion and dilatation, but there was no significant degree of septal thickening or capillary tuft formation (Fig. 11).

Cases 8, 9 and 10. Each received oxygen for less than 24 hours and showed only minimal capillary congestion, or none at all. The lungs weighed 720, 630, and 650 gms., respectively.

Group II

Examination of Table I which lists the patients in group II reveals a high frequency of oxygen administration to terminally ill patients; 15 of the 22 consecutive cases reviewed had been so treated. It is apparent that each of the 6 cases considered to have a slight degree (+) of capillary proliferation had had prolonged oxygen therapy, the briefest period being 36 hours (case 8345). On the other hand there were 3 cases (8338, 8342 and 8344) in which oxygen had been administered for 2 to 4 days, but no capillary proliferation was manifest.

Summary of Pathologic Observations

In this study, the gross appearance of the lungs was determined only by review of the necropsy protocols. In all instances the descriptions indicated a generally uniform appearance of the two lungs and the various lobes. When the changes were described as "patchy," the patches were noted in all lobes and appeared similar everywhere. The lungs were never described as collapsed or small, and the terms "excessively red" and "congested" appeared in most of the protocols. It is significant that all of the lungs showing capillary proliferation were unusually heavy. Those patients having the longest oxygen exposure had the heaviest lungs except in instances where pulmonary edema was also present because of congestive failure (cases 4 and 6).

Microscopically, the rate of development of the capillary alterations appeared to be variable in different persons. Thus in some instances proliferation was as prominent after only 2 to 3 days of exposure (cases 8337 and 8345) as after 7 days (case 8350). On the other hand, a few cases showed only capillary congestion after as much as 4 days' exposure (cases 5, 8338 and 8344).

Despite these variations, the sequence of events in the development of the lesion can be reconstructed. The first change presumably consists of congestion and dilatation of the alveolar septal capillaries (Fig. 11). The dilatation becomes progressively more pronounced and the septal walls thicker until the stromal tissue, rather than air spaces,

TABLE I

Group II. Correlation of Capillary Proliferation and Oxygen Therapy

Case no.	Age	Clinical diagnosis	Alveolar septums*	Duration of oxygen therapy
8330	68	Miliary tuberculosis	±	1 hour
8331	19	Granulomatous infection	o	o
8332	74	Bronchopneumonia	o	24 hours
8333	63	Thrombocytopenic purpura	o	o
8334	27	Carcinoma of colon with metastases	o	1 hour
8335	70	Bronchogenic carcinoma	+++	7 days
8336	2	Pneumonia; enteritis	o	o
8337	42	Lobar pneumonia	++	3 days
8338	35	Intestinal obstruction; septicemia	±	4 days
8339	78	Carcinoma of breast with metastases	+	2 days
8340	73	Bronchogenic carcinoma	o	12 hours
8341	47	Nutritional cirrhosis; massive hemorrhage	o	o
8342	77	Pyelonephritis	o	3 days
8343	70	Coronary occlusion	o	15 hours
8344	48	Acute pancreatitis	±	2 days
8345	60	Traumatic injuries (automobile)	++	36 hours
8346	6	Monocytic leukemia	±	8 hours
8347	64	Carcinoma of prostate	o	o
8348	—	Stillborn	o	o
8349	64	Carcinoma of uterus	±	o
8350	74	Subdural hemorrhage	++	7 days
8351	64	Hodgkin's disease	o	o
8352	68	Emphysema and cor pulmonale	++	4 days

* Key
o = thin septums; inconspicuous capillaries.
± = thin septums; capillaries congested; no proliferation.
+ = thin septums; capillaries congested; slight proliferation.
++ = thickened septums; capillaries congested; moderate proliferation.
+++ = thickened septums; capillaries congested; marked proliferation; early fibrosis.

occupies the major portion of each microscopic field. In such instances any given field has the appearance of collapsed lung, but the generalized character of the lesion in a lung of normal size and increased

weight is not consistent with mere atelectasis. A further distinction may be made by the fact that in atelectasis it is possible to make out the individual thin alveolar septums apposed to each other (Fig. 7). In the lesion induced by oxygen exposure one would be forced to postulate an actual fusion of adjacent septums to explain the appearance on the basis of collapse alone (Fig. 6). It seems clear that when the degree of change is such that the amount of stroma equals or exceeds the volume of air space, there has been capillary proliferation in addition to the opening of all existing vessels. Additional features provide unmistakable evidence of capillary proliferation in the form of papillary tufts projecting into the lumens of alveolar spaces (Figs. 1 and 4) and bronchioles (Fig. 10).

In early lesions, examples of this condition are difficult to detect. After 4 or more days of exposure, however, many intra-alveolar capillary tufts are present. There is also increase in the number of capillaries in the submucosa and walls of bronchioles (Fig. 8). Finally, after one to two weeks or more of continuous exposure to oxygen, fibrocytes appear among the proliferated capillaries and a diffusely distributed deposition of delicate collagen fibers occurs (Figs. 2 and 5).

Evidence of inflammatory reaction in these lungs is quite inconspicuous. The dark staining cells seen in the septums in most of the illustrations suggest a lymphocytic infiltration, but close inspection reveals that most of them are erythrocytes. Often the erythrocytes in the septums are arranged in rows; this is taken to indicate that they lie in longitudinally cut capillaries even if the vessel walls are not clearly visible in every instance. Nuclei of endothelial cells are numerous and usually rather large. The persisting alveolar spaces are generally empty except for a small number of phagocytes. Occasionally moderate numbers of extravasated erythrocytes are seen, and these presumably represent capillary hemorrhage, although extravasation during sectioning of the lung may also occur. There is, in some instances, slight edema of the alveolar septums.

Intra-alveolar fibrin, neutrophils, and edema fluid are absent except in the few cases having pneumonic consolidation or congestive failure (cases 1, 3, 4, 8337, 8352). In case 8337 (lobar pneumonia) capillary proliferation was present only in the nonpneumonic lobes.

Discussion

The observations are considered to indicate that oxygen causes not only pulmonary alveolar capillary congestion, but a marked proliferation of the capillaries as well. This is accompanied by thickening of alveolar septums and even papillary projections of capillary tufts into

the alveolar spaces. The lesions are occasionally accompanied by capillary hemorrhage or slight pulmonary edema. They are present in all lobes but are often patchy in distribution. A few apparently uninvolved septums are almost invariably found near those showing capillary proliferation. It is important to note also that the affected lungs are generally exceedingly heavy and are often described as being excessively red in color.

The observations in an unselected series of consecutive necropsied patients (group II) reveal a surprisingly high frequency of oxygen administration during terminal illnesses. The related alterations in pulmonary septal capillaries are thus probably so common as to have escaped specific comment heretofore. Many of the specimens reviewed had been described as showing "patchy atelectasis" with or without "pulmonary edema and hemorrhage."

There are various reasons for the failure of certain patients to develop capillary changes even though exposed to oxygen inhalation. Among these is the chance that for technical reasons or because of shallow respirations, administration of the gas may not actually have appreciably raised the pulmonary oxygen concentration. For example, some of these patients were placed in an oxygen tent, an inefficient method of administration. Another possible explanation is the fact that oxygen has been found to have a more pronounced effect when administered to the normal individual than to the patient with a pathologic state accompanied by hypoxemia.[2]

The lesions described seem entirely compatible with the observation that there is progressive loss of pulmonary function when oxygen exposure is continuous over a period of days. This has been attributed to the "irritant" effect of oxygen[2,6,8] which was considered to result in edema and hemorrhage. It is difficult to see why such responses, if they are indeed inflammatory, should be so slow in developing, since oxygen should be just as irritating on the first as on the fifth day. Similarly, it seems logical that simple inflammation should resolve promptly on discontinuation of oxygen administration; yet physiologists have shown that recovery of normal function may be delayed for two weeks after cessation of oxygen exposure. In view of these discrepancies and, in addition, the absence of fibrin deposit and neutrophil infiltration, and the paucity of edema, it is believed that oxygen specifically provokes capillary proliferation and does not excite inflammation as in the case of an ordinary irritant. The mechanism of this action remains to be investigated although the first step is probably already known since physiologists have shown that capillary dilatation occurs within minutes after inception of oxygen exposure.[8]

If one examines the illustrations in papers describing the results of exposure of normal animals to oxygen, one finds several examples of the same type of capillary lesions in the alveolar septums of these animals (Fig. 3, ref. 4; Figs. 5 and 6, ref. 5).

It might be suggested that oxygen does not itself cause capillary proliferation, but merely prolongs life so that another factor has time to produce the lesion. On the other hand, many patients with similar diseases, though untreated with oxygen, have lived as long and did not show the capillary alteration.

In certain respects the lesions are reminiscent of interstitial pneumonitis or of diffuse interstitial fibrosis. It was for this reason that two consecutive groups of cases were reviewed. Since both of these conditions are rather infrequent, it is scarcely possible they would occur with the observed frequency by chance in these randomly selected consecutive groups of patients receiving oxygen therapy for a wide variety of conditions.

The appearance of diffuse pulmonary fibrosis in some of the patients with the most prolonged exposure to oxygen is of importance in that this may well indicate the possibility of irreversible alteration. There is reason to believe that capillary proliferation alone may be reversible since various reports[2,6,8] state that human volunteers who show changes in pulmonary function after several days' exposure in oxygen chambers regain original functional capacity within a week or so after returning to normal atmosphere. However, this matter requires further study; it would be desirable to make actual observations of the regression of the lesion. Moreover, patients receiving oxygen should be followed during life, with subsequent correlation of necropsy lesions and clinical manifestations. The same procedure should be used to clarify the significance of pulmonary fibrosis. Since cases of this nature will obviously be rare, investigations with experimental animals should be planned.

The observations reported are not necessarily presented to emphasize the hazards of oxygen administration. These are becoming generally appreciated and are less frequent as increasing care is exercised in the administration of this gas. The morphologic expression of toxicity may serve as an explanation for the development of "dependence" upon oxygen administered to persons with respiratory impairment. The thickened alveolar septums would interfere with oxygen diffusion into blood. Thus, on return to normal atmospheric oxygen concentration the patient would be expected to have greater difficulty than before oxygen therapy was begun. The need for "weaning" the patient from oxygen is also clarified.

Mention should be made of the possibility that the pulmonary lesions described may have a more general systemic significance. The effects of high concentrations of oxygen upon retinal capillary development, especially in premature infants are well documented.[7,9] It is also now recognized that cutaneous angiomas are more common in premature infants than in normal children, and that the incidence has decreased as oxygen administration in early infancy has been curtailed.[10]

Finally, attention is directed to the fact that the pulmonary changes induced by oxygen often have been erroneously considered to be manifestations of certain obscure pulmonary diseases. Thus capillary proliferation is mentioned in the original article[11] and in numerous subsequent publications concerning the Hamman-Rich syndrome.[12,13] Similar lesions have also been described in other chronic progressive pulmonary disorders characterized by respiratory insufficiency.[14,15] Since most patients with these conditions receive oxygen therapy during the final stages of their ailments, the likelihood that septal capillary proliferation may be a reflection of oxygen inhalation requires consideration. So-called "plasma cell pneumonia of premature infants"[16] is said to be characterized by generalized septal thickening without clinical or morphologic evidences of infection, but with progressive pulmonary insufficiency. This may also be a manifestation of oxygen toxicity.

SUMMARY

Evidence has been presented to show that with oxygen inhalation for as little as two days, pulmonary alterations consisting of capillary congestion and proliferation may be observed. After continuous inhalation for approximately two weeks, diffuse fibrosis has been encountered. Alveolar concentrations of oxygen obtained during administration by nasal catheter are believed to be sufficient to cause these alterations.

The capillary lesions are thought to be responsible for the development of "oxygen dependence" and for the variations in pulmonary function which occur during and after inhalation of high concentrations of oxygen. They are presumably reversible at least until the time fibrosis supervenes.

Failure of previous recognition of the effect of oxygen upon pulmonary tissue is attributed to the high frequency of its administration. The lesion has thus been so commoplace as to be considered a normal variation in pulmonary structure.

The importance of appreciating the potential effect of oxygen on pulmonary parenchyma and of differentiating the lesions induced from those of various obscure pulmonary diseases is emphasized.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Case 1. Oxygen, 19 days. Some pulmonary aveolar septums are thin; others, especially one in the lower left, are thickened. Capillaries are prominent everywhere and a capillary tuft occupies the lumen of the alveolar space in the center of the field. Several capillaries can be traced from the septum into the alveolar lumen. Hematoxylin and eosin stain. × 400.

FIG. 2. Case 1. Septal thickening and increased numbers of thin-walled capillaries are seen. In addition, fibrocytes and a few strands of collagen are present. Hematoxylin and eosin stain. × 400.

FIG. 3. Distribution and pattern of the pulmonary lesions in patients exposed to oxygen. Hematoxylin and eosin stain. × 4.

A. Case 2. Oxygen exposure, 16 days. The alveolar spaces are almost completely obscured by septal thickening. For detail see Figure 4.

B. Case 3. Oxygen exposure, 8 days. This illustrates the effect of squeezing on the pattern produced by the septal thickening.

C. Case 8335. Oxygen exposure, 7 days. Some alveolar spaces are obscured by septal thickening. Those which remain show minor variability in size. This pattern is often interpreted as patchy atelectasis or as the result of rough handling of tissue at necropsy.

D. Case 4. Oxygen exposure, 3 days. The pattern is entirely similar to that in Figure 3C.

E. Lobar atelectasis in a patient not receiving oxygen. For detail see Figure 7.

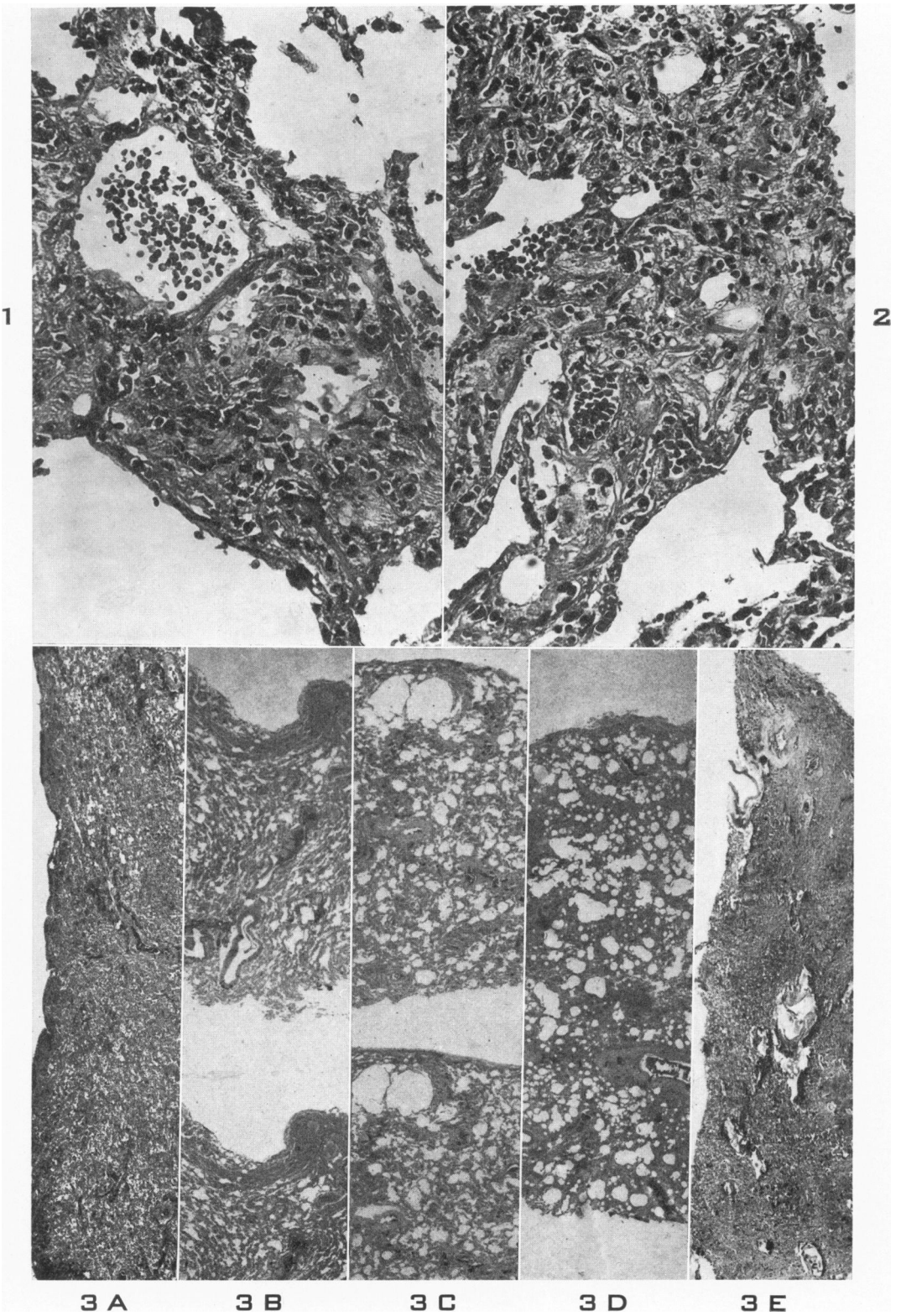
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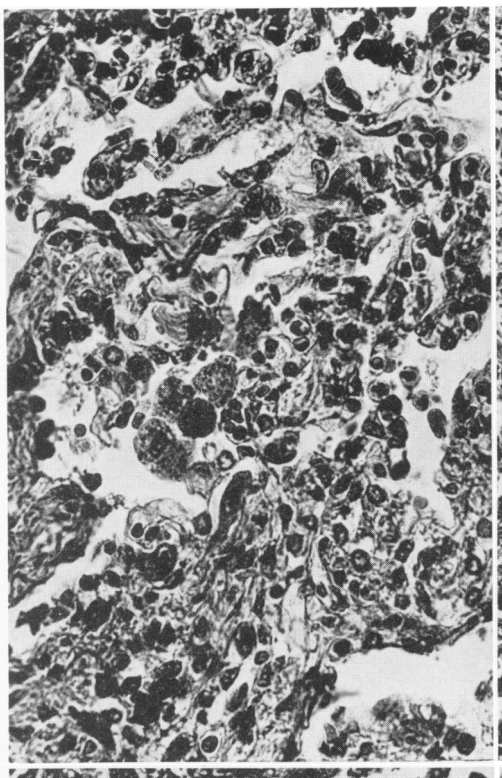
FIG. 4. Case 2. Oxygen. 16 days. There is thickening of all alveolar septums, producing a pattern superficially resembling atelectasis. Close inspection will reveal many thin-walled capillaries, with lumens often packed with erythrocytes. There is a tuft of capillaries in the lumen of the alveolus at the center. Hematoxylin and eosin stain. × 400.

FIG. 5. Case 2. Photograph illustrates the widespread character of the lesion present in Figure 4. Note also the scattered strands of collagen. Hematoxylin and eosin stain. × 100.

FIG. 6. Case 2. The pattern of reticulum in the walls of the proliferated capillaries is shown. Note tufts projecting into alveolar spaces. Compare with Figure 7. Foot's modification of the Bielschowsky stain for reticulum. × 400.

FIG. 7. Reticulum stain of atelectatic lung tissue for comparison with Figure 6. Although apposed, individual septums are uniformly thin and readily distinguishable. Foot's modification of the Bielschowsky stain for reticulum. × 400.



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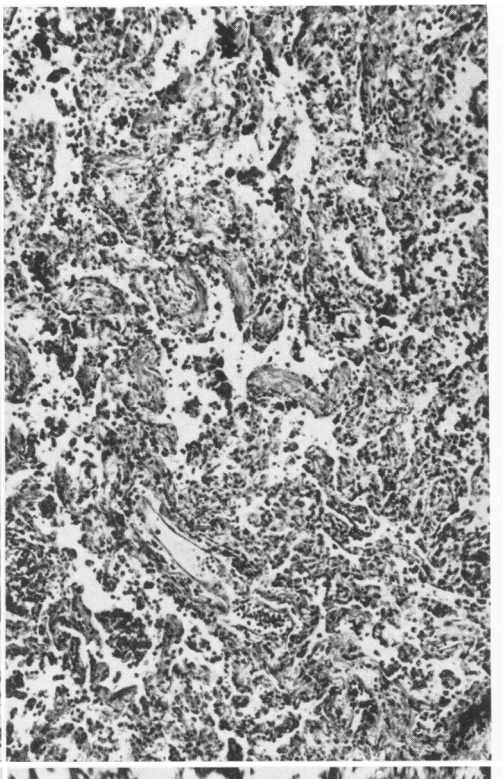

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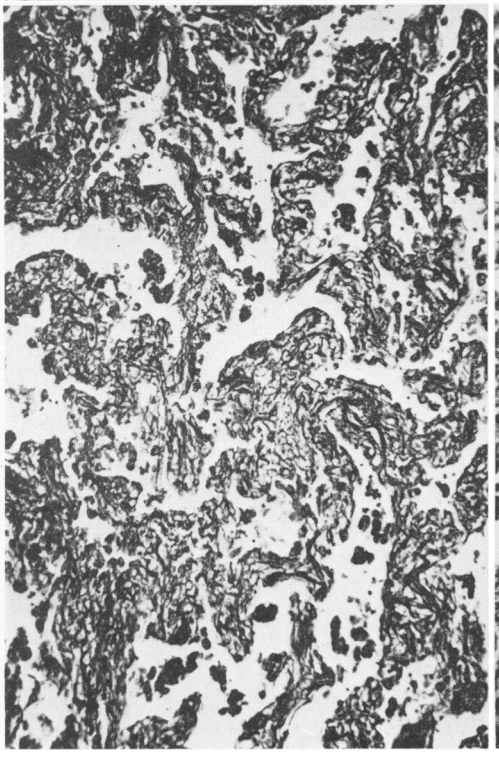

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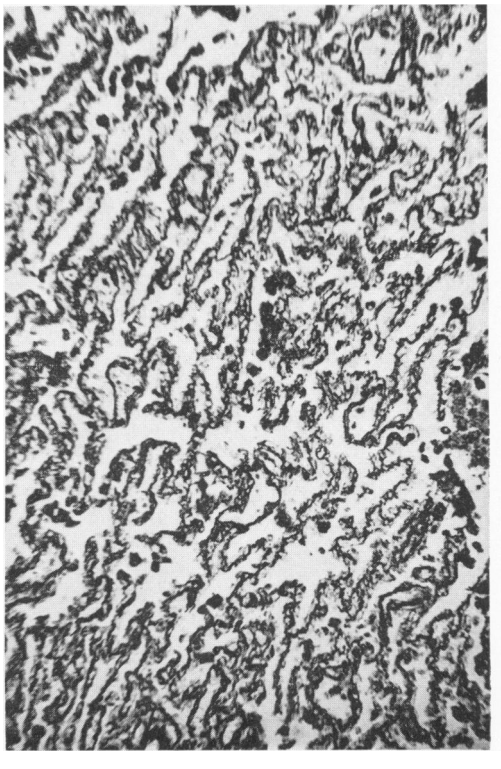

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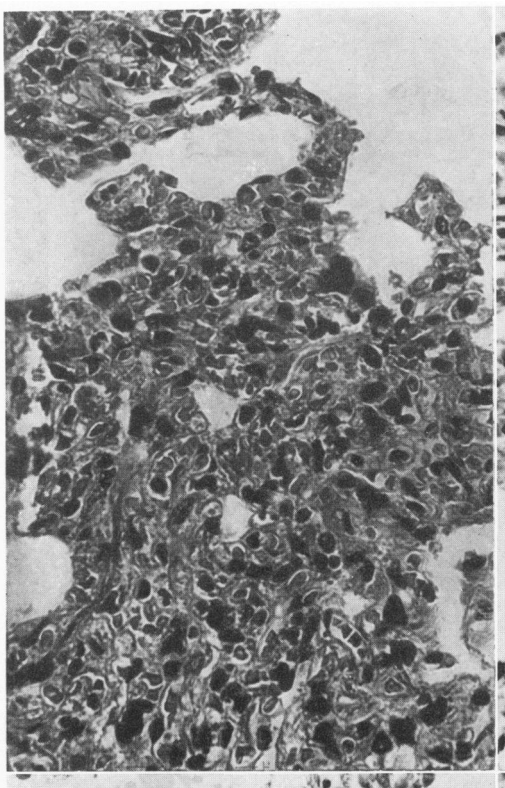
FIG. 8. Case 3. Oxygen, 8 days. Alveolar septal thickening, with congested and numerous capillaries. Most of the dark-staining cells are erythrocytes, and they can often be seen in rows. Hematoxylin and eosin stain. × 400.

FIG. 9. Case 4. Oxygen, 6 days. The epithelium of a respiratory bronchiole is shown at the bottom. The lumen of the bronchiole is distended by capillaries. Hematoxylin and eosin stain. × 400.

FIG. 10. Case 4. The wall of a small bronchus contains increased numbers of capillaries in the submucosa. These are also evident outside the muscular layer. Note the numerous capillaries in the adjacent pulmonary tissue, at the bottom. Hematoxylin and eosin stain. × 400.

FIG. 11. Case 7. Oxygen, 1 day. The capillaries are prominent and rather congested, but there is no evidence of proliferation. These changes are nonspecific and this field may be considered as a normal control for comparison with other illustrations. Hematoxylin and eosin stain. × 400.



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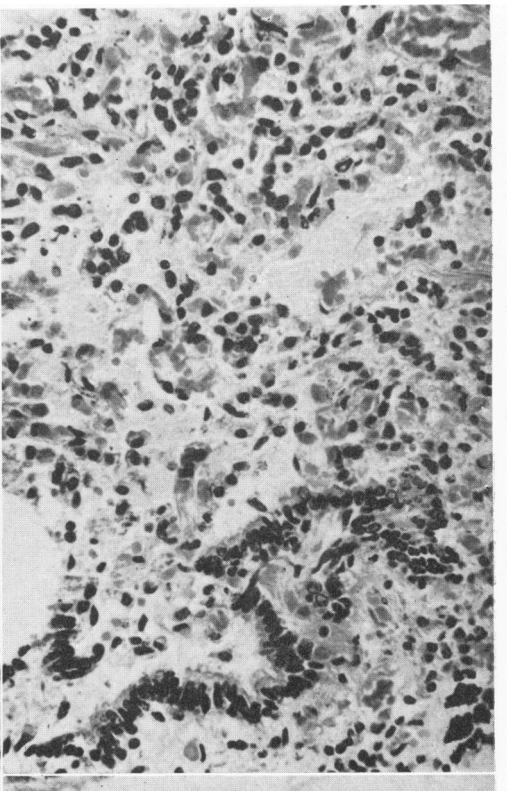

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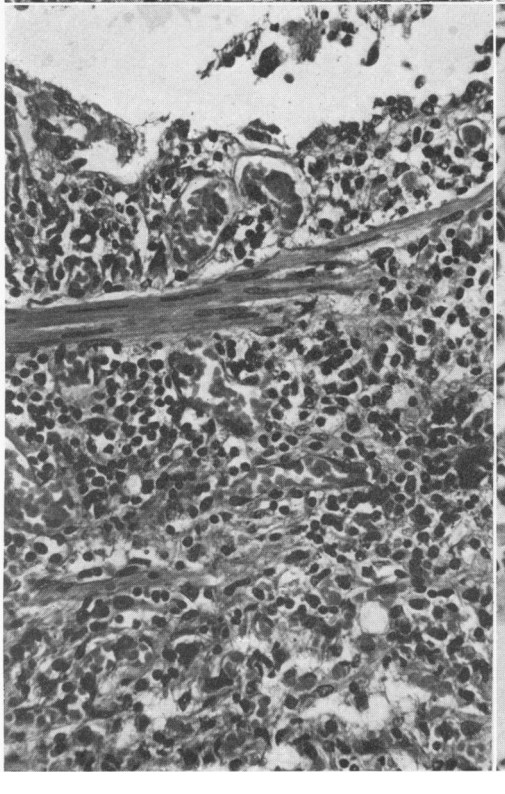

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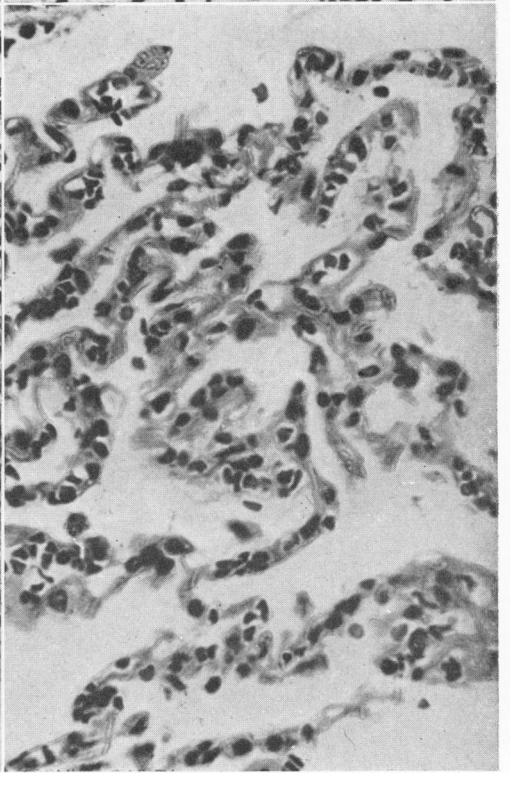

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