REVIEW ARTICLE

DIFFUSE ALVEOLAR DAMAGE—THE ROLE OF OXYGEN, SHOCK, AND RELATED FACTORS

Diffuse Alveolar Damage—The Role of Oxygen, Shock, and Related Factors

A Review

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EVIDENCE HAS ACCUMULATED that diffuse alveolar damage (DAD) can be produced in association with shock, by exposure of the lungs to oxygen at sufficiently high tension for a sufficient length of time, and during hypoperfusion as in pulmonary bypass, or by some combination of these factors. In fact, they can potentiate each other. Diffuse alveolar damage is manifested by injury to alveolar lining and endothelial cells, pulmonary edema, hyaline membrane formation, and later by proliferative changes involving alveolar and bronchiolar lining cells, and interstitial cells.[1,2] Such damage, while it may differ from case to case in intimate detail of pathogenesis and morphology, represents a *type* of response of the lung to injury. It can be produced not only under the several circumstances mentioned but also by a multitude of other agents and mechanisms. There can be varying degrees of damage, and it is quite clear that many patients with DAD recover, and that the changes can resolve. In those with the more severe degrees of damage there can be progress to pulmonary fibrosis of a predominantly interstitial type, but occasionally also intraalveolar type. In fact, such DAD is an excellent model of the classic or "usual" interstitial pneumonia (UIP) with changes indistinguishable from those described by Hamman and Rich.[3]

It is the aim of this review to consider factors in the pathogenesis of DAD and to enlarge upon concepts both of the complexity and nonspecificity of the lesion. We will concentrate primarily upon the pulmonary lesions of oxygen toxicity, shock, and related factors which, because they have been so thoroughly studied, may be considered excellent models for the pathogenesis of DAD due to many other causes. The various pathologic stages in the evolution of oxygen-induced DAD will be described in detail using case material from our own consultation file. Finally, other factors which are unrelated but which produce similar pulmonary lesions will be briefly reviewed.

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Oxygen, Shock, and Related Factors

Of the many factors that can cause DAD, oxygen, because of its widespread therapeutic usage, is probably the one of greatest clinical importance. Although the adverse effects of prolonged oxygen breathing have been known for many years,[4,5] it was only recently that the complications of the therapeutic administration of oxygen became apparent.[6] Subsequently, there have been extensive investigations into the problem of pulmonary oxygen toxicity. We will review both the clinical and experimental studies which examine the role of oxygen in the development of DAD. The contribution to pulmonary injury of related factors such as shock and nonthoracic trauma, which themselves may have precipitated the need for oxygen, will also be reviewed.

Pratt [6] was the first to relate changes in the pulmonary parenchyma to therapeutic oxygen administration. He noted identical pulmonary lesions in patients dying from a variety of causes, all of whom had received oxygen. The earliest change was alveolar capillary congestion, which was followed by capillary proliferation and occasionally by interstitial fibrosis.[6,7] Cederberg *et al.*[8] described hyaline membranes at autopsy in 11 patients who had received oxygen at a concentration greater than 40%. Similar changes were noted in a patient who had been treated with hyperbaric oxygen for an anaerobic infection.[9] Although it has been emphasized that hyaline membranes are by no means pathognomonic of oxygen toxicity, they have nevertheless been considered to be a characteristic early finding.[10-17]

Nash *et al.*[18] provided the first detailed pathologic description of the evolution of pulmonary changes related both to concentration of inspired oxygen and to duration of therapy. The earliest changes were exudative, consisting of capillary congestion, intraalveolar edema and hemorrhage, and hyaline membranes. With prolonged oxygen therapy these lesions progressed to proliferative changes characterized by alveolar lining cell hyperplasia and interstitial fibrosis. Similar findings have been inferred from morphometric studies on the lungs of patients exposed to oxygen.[19]

Ultrastructural studies have confirmed the presence of early exudative and later proliferative phases.[20] Alveolar lesions were seen after only 14 hours of 70% oxygen. The earliest changes were swelling of membranous pneumocytes and endothelial cells, with cytoplasmic blebs in the former and myelin figures in the latter. This damage progressed with continued oxygen exposure, and by 2 to 6 days there was extensive sloughing of membranous pneumocytes and endothelial cells. Only minor cytoplasmic changes were seen during this time in the granular pneumocytes. The basement membrane which was thus denuded was gradually covered by

granular and fibrillar debris. Septal edema, due to loss of integrity of capillary endothelium, became prominent. Fibrin thrombi were frequently seen within alveolar capillaries. Hyperplasia of granular pneumocytes became prominent after 6 days, and by 10 days these cells had almost totally replaced the membranous pneumocytes. Septal fibrosis was also seen after 6 days and became more extensive with continued oxygen exposure.

The injurious effects of oxygen in the lung are not confined to adults. Similar changes, termed *bronchopulmonary dysplasia*, have been described in neonates exposed to high concentrations of oxygen for treatment of severe hyaline membrane disease.[21,22] Pulmonary lesions have been seen after only 50 hours' exposure and at concentrations as low as 40%.[23,24] Ultrastructurally, damage to alveolar epithelial and endothelial cells was the earliest lesion.[25] As in adults, a proliferative phase with alveolar lining cell hyperplasia and interstitial fibrosis subsequently developed. In addition, intraalveolar fibrosis with focal scarring was noted, and an obliterative bronchiolitis was not uncommon.[25]

The studies cited above provide ample evidence that patients who are treated with high concentrations of oxygen for prolonged periods of time develop characteristic pulmonary changes. These changes which result from initial injury to alveolar epithelial and endothelial cells may descriptively be termed *diffuse alveolar damage*. Whether DAD is the direct effect of oxygen toxicity, per se, whether it is related to the underlying condition which precipitated the need for oxygen, or whether the contribution of several factors produced it are questions which need to be considered.

Pulmonary changes similar to the early lesion of oxygen-induced DAD have been described following hemorrhagic shock,[26-28] severe trauma,[29-32] multiple fractures,[33] head injury,[34,35] drug coma,[36] sepsis,[37-39] complicated major intraabdominal surgery,[40] and cardiopulmonary bypass.[41] The earliest findings in those patients dying very soon after the major systemic insult are capillary congestion, atelectasis, intraalveolar hemorrhage, and pulmonary edema,[30,32] hence the eponyms *traumatic wet lung*[42] and *congestive atelectasis*.[43] In those patients surviving for more than 72 hours, hyaline membranes, alveolar epithelial cell hyperplasia, and interstitial edema and fibrosis appear.[30,33,39] The difficulty of differentiating the latter changes from those described in pulmonary oxygen toxicity has been emphasized.[26] In fact, many of the reported patients have been treated by a respirator with high oxygen concentration following the initial systemic insult,[26,29,32,33,39,40] and a multifactorial etiology of the pulmonary lesions has thus been proposed.[32,40]

There are approximately 90 reported cases of pulmonary oxygen toxicity in adults in which adequate historical data regarding the initial reason for oxygen therapy has been provided. In 80 of these 90 cases, the use of oxygen followed one or more of the systemic insults which, as noted above, may themselves lead to pulmonary changes.[6,8-14,16,17,20,44,45] These included severe trauma, sepsis, hemorrhage, cardiogenic shock, complicated intraabdominal surgery, head injury, stroke, or drug coma. Five of the remaining 10 cases had underlying pulmonary disorders including emphysema, pneumonia, and cardiogenic pulmonary edema, and 2 had inhaled smoke. Therefore, in only 3 of 90 cases could oxygen alone be implicated in etiology. These three included cases of Guillain-Barré syndrome, tetanus, and portal vein thrombosis. The situation is even more complicated in newborns, most of whom have hyaline membrane disease. The early changes in the latter may be very difficult to separate from oxygen induced DAD.

Although pulmonary functional changes have been described in normal volunteers breathing pure oxygen, the pathology of these changes has, of course, not been studied.[46,47] There have, however, been a few prospective clinical studies which examine the toxic effects of oxygen uncomplicated by other factors. Barber *et al.*[48] treated 10 patients with irreversible brain damage with 100% oxygen for periods of 31 to 72 hours. Significant functional abnormalities were noted after 40 hours, although there were no gross or histologic differences between the study group and a control group. However, ultrastructural changes were not examined. Singer *et al.*[49] compared two groups of patients recovering from cardiac surgery. One group was ventilated with 100% oxygen, and the other group received the minimal oxygen needed to maintain adequate arterial oxygen tension (inspired oxygen in all cases was less than 42%). Although no functional or clinical differences between the two groups could be identified, maximum oxygen exposure was only 48 hours. Two other patients were described, however, who received 100% oxygen for longer periods of time. One recovered after 5 days of therapy. One who died following 7 days of 100% oxygen showed focal areas of DAD with hyaline membranes and interstitial fibrosis. Hyde and Rawson [50] described 5 patients with respiratory insufficiency who were treated with over 80% oxygen for 10 to 32 days. These patients all suffered from muscular weakness, 4 secondary to myasthenia gravis and 1 related to intracranial surgery. After 4 to 10 days of exposure, all patients developed pulmonary infiltrates which, in 4 patients, gradually resolved after the inspired oxygen concentrations were decreased. The lungs of 1 patient who died after 32 days of 100% oxygen showed the proliferative phase of DAD. It is of some interest that this

patient had had previous brain surgery, a factor which itself may have predisposed to DAD. The effect of prolonged ambulatory oxygen therapy in patients with chronic obstructive pulmonary disease was studied by Petty *et al.*[51] They attributed histologic changes to oxygen toxicity in 6 of 12 autopsied patients. Clinically, however, these patients (who had received oxygen for an average of 26.7 months) showed no adverse effects.

The most compelling evidence for the pulmonary toxicity of oxygen comes from experimental studies. The effect of breathing 90 to 100% oxygen has been extensively investigated in various animal species including adult mice,[52-55] rats,[56-62] squirrels,[63] oppossums,[64] goats,[65] dogs,[66,67] and monkeys.[68-72] Generally, the smaller animals such as mice and rats are more sensitive to oxygen than the larger animals such as dogs and monkeys.[73] There is also moderate interspecies variation in the relative oxygen susceptibility of the various alveolar cells. For example, in mice and rats, the initial injury is to the endothelial cells, which leads to interstitial edema.[52,53,56,57] Subsequently, degenerative changes are seen in membranous pneumocytes, although these cells are especially resistant in rats.[62] In dogs, on the other hand, the primary injury is to the membranous pneumocytes, with endothelial cells being affected only later.[66] Of the various species, nonhuman primates (especially baboons) show the greatest similarities to humans in their susceptibility to oxygen.[70,72] Respiratory distress develops in monkeys after 2 days of oxygen breathing. Ultrastructurally, swelling of endothelial cells and interstitial edema can be seen at this time. Damage to membranous pneumocytes follows and by 4 days most are destroyed.[68] Intraalveolar edema, hemorrhage, and hyaline membranes develop as in humans. After 5 to 7 days, the proliferative changes of interstitial fibrosis and granular pneumocyte hyperplasia are seen.[69,71] Cytodynamic studies in mice have shown that it is these granular pneumocytes which, in the healing phase of oxygen toxicity, can transform into membranous pneumocytes to restore the normal alveolar architecture.[74] Moreover, there is evidence that this granular pneumocyte proliferation may protect against further oxidant damage, perhaps because these cells are rich in enzymes which mediate antioxidant mechanisms.[75-77]

There have been similar experimental studies in various newborn animals including newborn rabbits,[73] mice,[78,79] guinea pigs,[80] and lambs.[81] Although newborn animals are generally less susceptible to oxygen toxicity than mature animals,[73] they do show evidence of alveolar damage which resembles that in adults.[78,80] The changes are not affected by the use of artificial ventilation.[81] Moreover, oxygen increases the severity of respiratory distress due to bilateral cervical vagotomy in newborn rabbits,[73] a

situation which seems analogous to that in newborn infants with hyaline membrane disease who are treated with oxygen.

Pathology of Diffuse Alveolar Damage

From 1965 to 1975, 420 cases of DAD due to a variety of causes were seen in consultation. Thirty-five cases were attributed to oxygen toxicity, and in 16 of these cases, precise details were available regarding concentration of oxygen and duration of exposure. These form the basis for the following review of the pathologic changes in DAD. The patients ranged in age from 9 to 69 (average age 33) and 10 were less than 30 years old. None had underlying pulmonary disease and most had been in previously good health. All had suffered acute insults which necessitated the need for oxygen. These included hemorrhagic shock, sepsis, severe trauma, complicated intraabdominal and thoracic surgery, narcotic overdose, and cardiac arrest following minor surgery. All were treated with 80 to 100% oxygen via respirator for periods ranging from 22 hours to 32 days.

The earliest lesions which were seen in all cases exposed to oxygen for less than 3 days were capillary congestion and focal intraalveolar edema. Fibrin thrombi were present within capillaries and small arteries in a few cases. Hyaline membranes lined the alveolar septa in all cases exposed for 7 days or less and persisted focally in some cases up to 2 weeks, (Figure 1). Suprisingly, well-formed membranes were seen in 1 patient who died after only 22 hours of oxygen. In some cases, the formation of hyaline membranes was focal, with adjacent regions of lung showing an intraalveolar fibrinous exudate and cellular debris (Figure 2). Interstitial edema was seen after 3 days and was prominent in both the interalveolar and larger interacinar septa. A striking mononuclear cell infiltrate was also seen within the septa, and was most evident in patients dying in less than a week. The infiltrating cells consisted of lymphocytes, plasma cells, and often atypical cells which were difficult to classify. Alveolar lining cell hyperplasia became marked in all cases after 1 week, although focal proliferation was seen as early as 3 days in some cases (Figure 2C and D). These lining cells were larger than normal, cuboidal to columnar, and tended to line up in sheets along either the luminal or septal side of the hyaline membranes (Figure 3). In some cases the cells were very atypical and contained bizarre nuclei with fine chromatin and large prominent nucleoli. After 8 days, interstitial fibrosis was extensively present in all cases, although occasionally small foci of fibroblastic proliferation were evident after only 3 days. By 2 weeks the process had a suprisingly chronic appearance, and the etiology at this time could only be inferred from the clinical history (Figure 4).

These observations are in agreement with those of other investigators to whom reference has already been made. They support the evidence for the progression of an early exudative lesion to a later proliferative lesion in the evolution of pulmonary oxygen toxicity. There are, however, two features which have not received much attention in the literature. One is the prominence of the interstitial mononuclear infiltrate, a finding which is usually considered more characteristic of the interstitial pneumonias. The second is the great rapidity with which extensive interstitial fibrosis may occur and yet appear very chronic.

Discussion

Diffuse alveolar damage is a nonspecific reaction of the lung to a multitude of injurious agents. The common denominator in all cases is endothelial and alveolar lining cell injury which leads to fluid and cellular exudation and in some cases progresses to extensive interstitial fibrosis. Adult respiratory distress syndrome,[29,82] respiratory insufficiency syndrome,[83] shock lung,[84] traumatic wet lung,[42] congestive atelectasis,[43] and progressive pulmonary consolidation [40] are some of the terms that have variously been applied to this process. Clinically there is severe tachypnea, increasing hypoxemia, and decreasing pulmonary compliance.[85] Radiographically, bilateral alveolar infiltrates resembling pulmonary edema are seen initially.[14] Later, linear to coarse nodular infiltrates develop.[13] Although there is abundant evidence that oxygen, shock, and other factors can by themselves produce this syndrome, in most cases a combination of many factors is implicated.

Pulmonary oxygen toxicity is a useful model for all types of DAD since the evolution of this lesion can be studied over a definite time period. Using this model, the pathogenesis of other types of DAD can be inferred. For example, changes similar to the exudative form of oxygen toxicity are seen in patients with severe cutaneous burns [86] and following smoke inhalation.[87] Hyaline membranes and edema are well-known features of acute viral pneumonias.[88,89] The similarity of pulmonary changes in influenza pneumonia to those following inhalation of chlorine or phosgene gas was noted many years ago.[89] Exposure to mercury vapor and carbon dioxide at high tensions results in similar lesions.[90] Noncardiogenic pulmonary edema may be seen following acute pancreatitis,[91] after near-drowning,[92,93] and after heroin overdose.[94,95] Thoracic irradiation produces both hyaline membranes and alveolar lining cell hyperplasia.[96] Diffuse alveolar damage may follow ingestion of certain chemicals, most notably kerosene and paraquat.[90,97,98] There is some evidence that the Group B β-hemolytic streptococcus induces DAD in neonates.[99] Numerous drugs

have been implicated including busulfan,[100,101] bleomycin,[102,103] Cytoxan,[104] melphalan,[105] hexamethonium,[106] nitrofurantoin,[107-109] and methysergide,[110] and others which have been reviewed elsewhere.[111] In many of these cases, interstitial fibrosis with varying degrees of alveolar lining cell hyperplasia is seen, rather than edema and hyaline membranes. Thus, the evolution of the lesion at this stage from the early exudative phase can only be inferred from knowledge of the natural history of DAD and from the clinical history. The same is true for classic or usual interstitial pneumonia which is often seen only at a very chronic stage.[1] While usual interstitial pneumonia may be the end result of an acute viral pneumonia, or any one of the other factors listed above, many cases remain idiopathic. Sophisticated analytic methods may be of help in uncovering the etiologic agent in some cases.[112] This is not to imply, however, that all cases of interstitial fibrosis evolve from DAD. On the contrary, many and diverse pulmonary lesions may progress to interstitial fibrosis, including sarcoid and other interstitial microgranulomatous reactions, eosinophilic granuloma, and desquamative interstitial pneumonia. It is important, however, to recognize DAD in the evolution of some pulmonary lesions since the changes may be reversible upon removal of the inciting agent.

The above observations should serve to emphasize that DAD is not a diagnosis; it is a concept which is useful in understanding the pathogenesis of a group of similar pulmonary lesions which result from numerous and dissimilar agents. It implies nothing about etiology. Neither pathologist nor clinician should feel complacent if a pulmonary biopsy shows features of DAD. Rather, the recognition of DAD should stimulate a thorough search for and subsequent eradication of the underlying cause.

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[*Illustrations follow*]

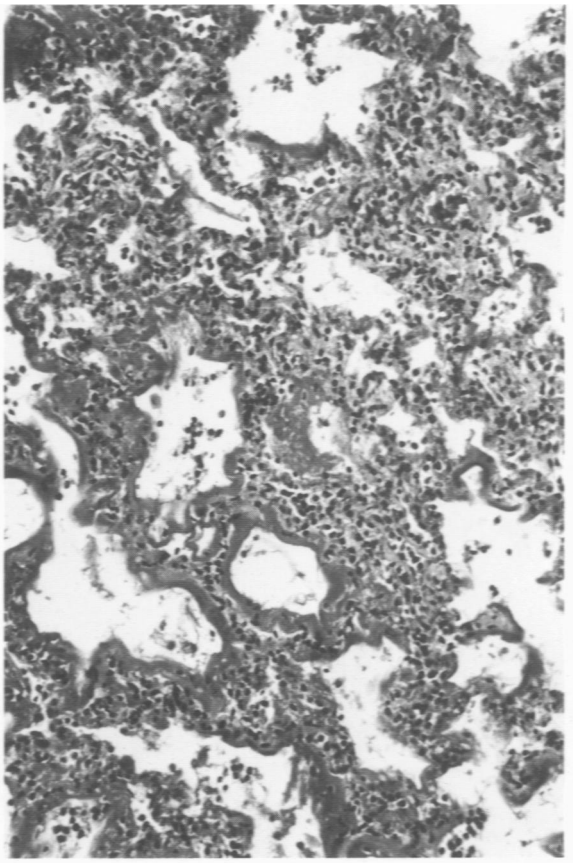
Legends for Figures

Figure 1—Early exudative phase of diffuse alveolar damage. **A and B**—Sections from a 9-year-old boy who suffered a cardiac arrest during minor surgery. He was resuscitated and died after receiving 100% oxygen via a mechanical respirator for only 22 hours. **A**—Low magnification showing well-formed hyaline membranes and marked interstitial infiltrate (H&E, × 125). **B**—Higher magnification to show the interstitial mononuclear infiltrate and capillary congestion. Note the nuclear debris within the membranes. (H&E, × 400) **C and D**—Lung sections from a 24-year-old woman who died 3 days after taking a barbiturate overdose. She received 80 to 100% oxygen via respirator during this time. **C**—Low magnification showing the marked interstitial edema, especially within the large interacinar septa. Fibrinous edema is present also within the alveolar spaces. (H&E, × 100) **D**—Higher magnification to show the interstitial edema with infiltrate of mononuclear cells, many of which are atypical (H&E, × 400).

Figure 2—Early proliferative changes in diffuse alveolar damage. This patient had two complicated abdominal operations for a bleeding gastric ulcer. Respiratory distress developed following the second operation and 80 to 100% oxygen was administered via respirator for 3 days. **A**—One focus showing marked capillary congestion and fibrinous intraalveolar exudate (H&E, × 100). **B**—Another region from same lung showing prominent interstitial edema and well-formed hyaline membrane (H&E, × 100). **C**—Focal interstitial fibrosis, even at this early stage (H&E, × 400). **D**—Focal hyperplasia of alveolar lining cells (H&E, × 400).

Figure 3—Alveolar lining cell hyperplasia in diffuse alveolar damage. This 27-year-old man suffered severe injury with multiple fractures in an automobile accident. Eighty to one hundred percent oxygen and mechanical ventilation was administered for 8 days until death. **A**—Lung section showing striking alveolar lining cell hyperplasia and a few persisting hyaline membranes (H&E, × 100). **B**—Section showing lining cells growing in sheets along the alveolar septa and along the septal side of the hyaline membranes (H&E, × 250). **C**—Higher magnification of alveolar lining cells, showing quite atypical appearance in some (H&E, × 400).

Figure 4—"Chronic" stage of diffuse alveolar damage. Note marked interstitial fibrosis, focal intraalveolar fibrosis, and lining cell hyperplasia in all. **A**—Section from a 34-year-old woman dying after 14 days of oxygen therapy via respirator (H&E, × 125). **B**—Section from a 55-year-old man who died after thoracic surgery. He had received oxygen via respirator for 16 days. (H&E, × 125) **C and D**—Sections from a 28-year-old woman who developed respiratory failure following surgery for a ruptured ectopic pregnancy. She died after 32 days of oxygen therapy. (H&E, **C**, × 100; **D**, × 250)



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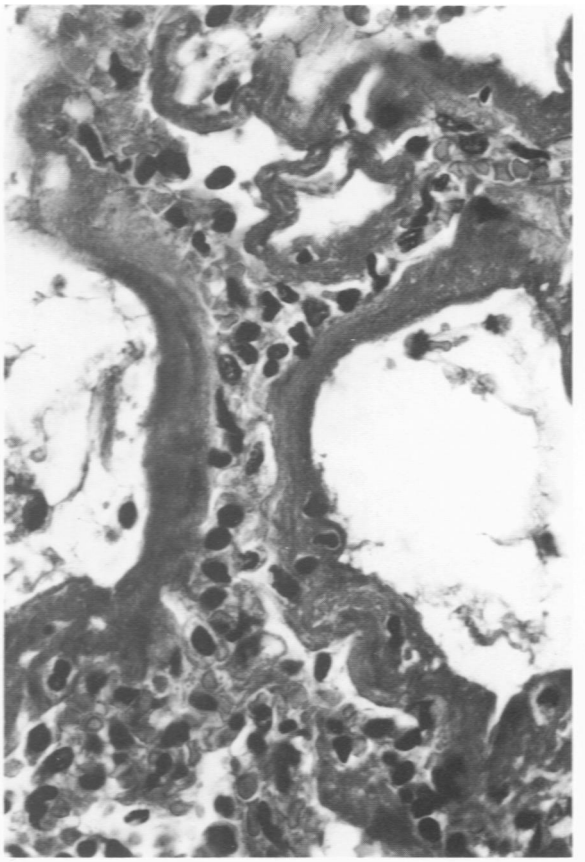

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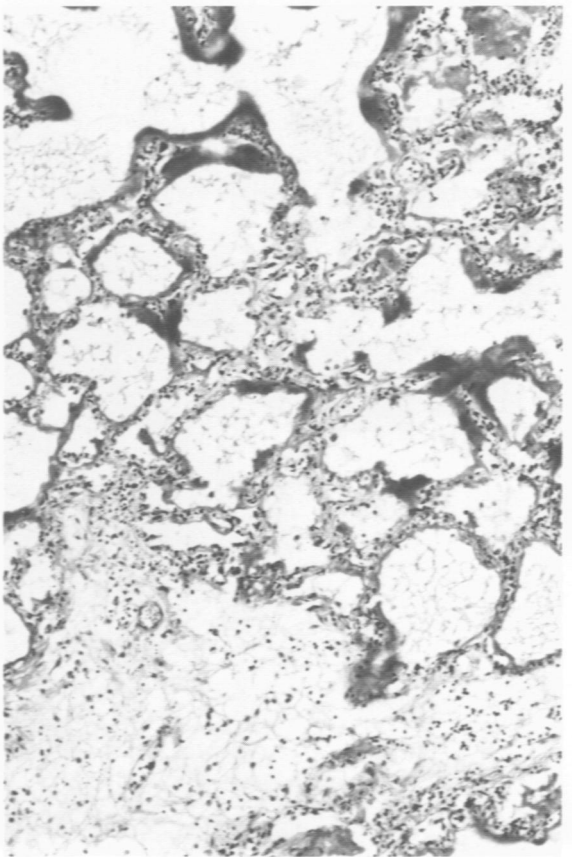

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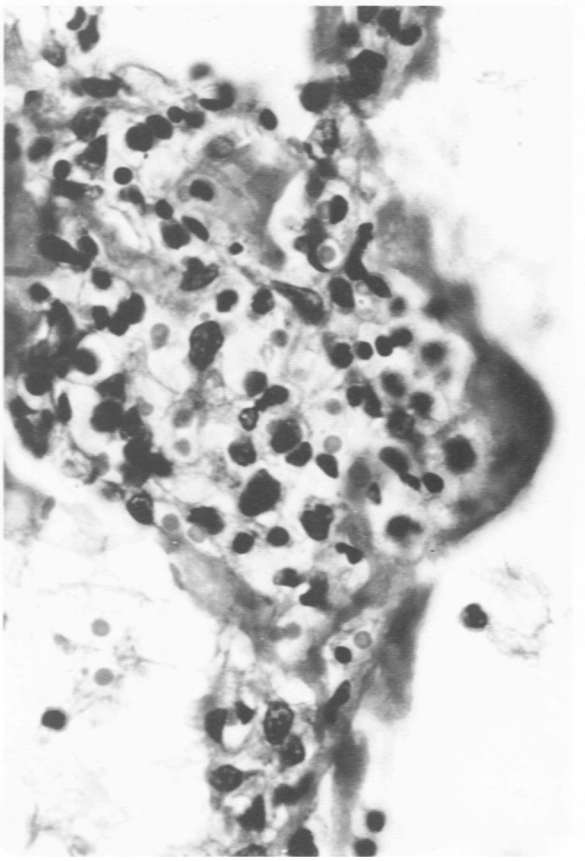

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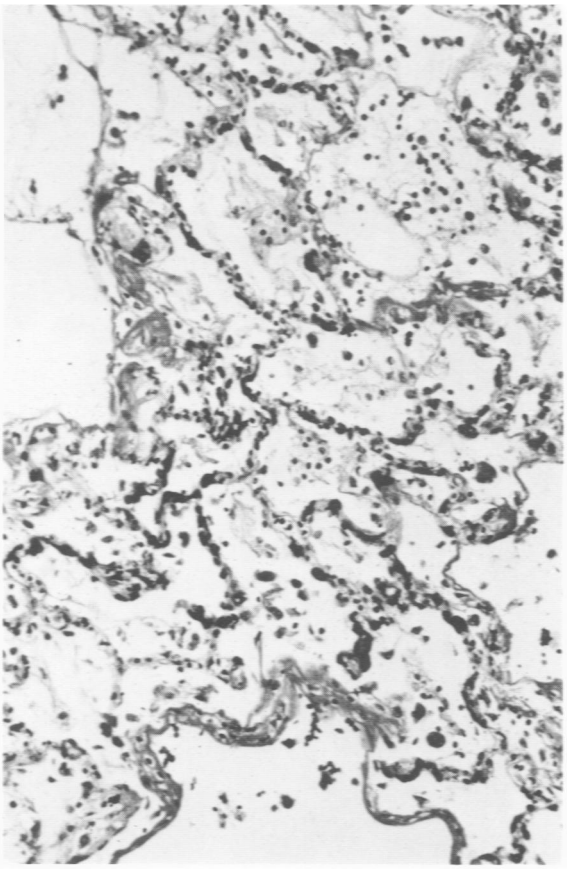

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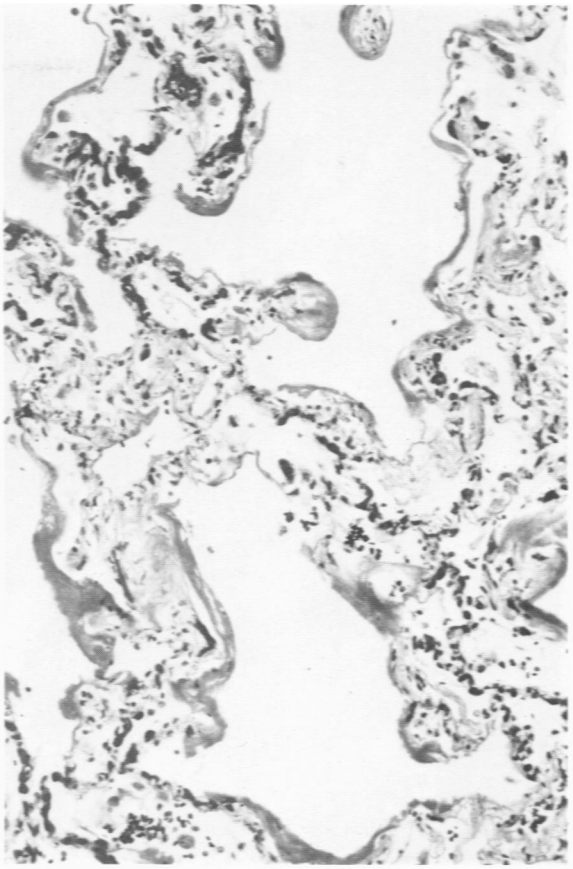

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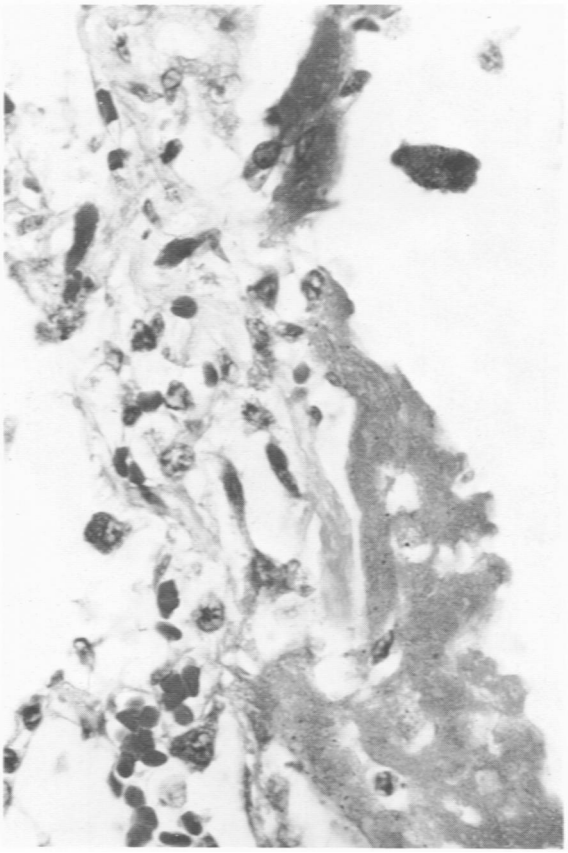

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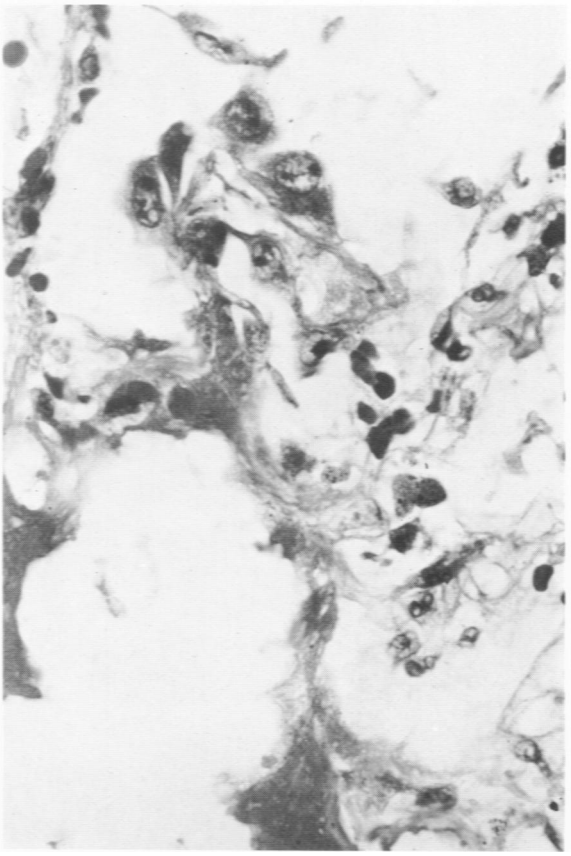

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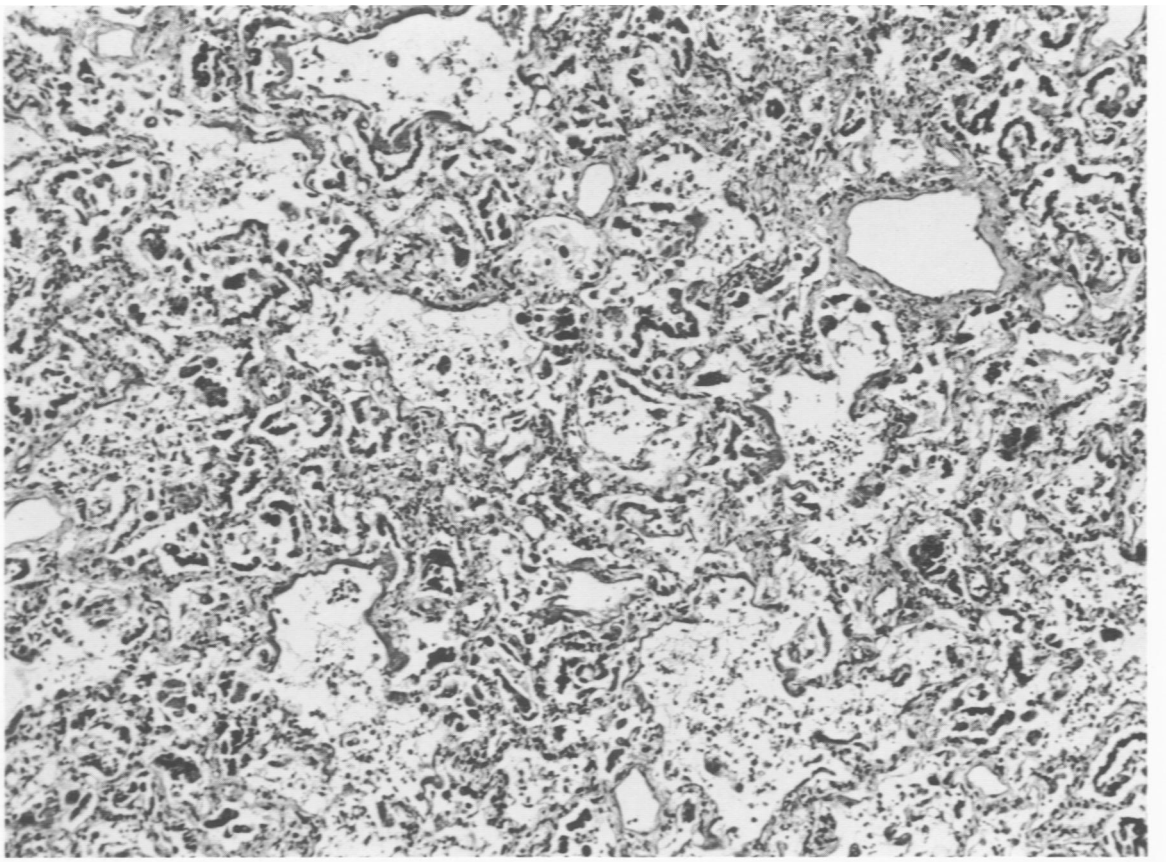

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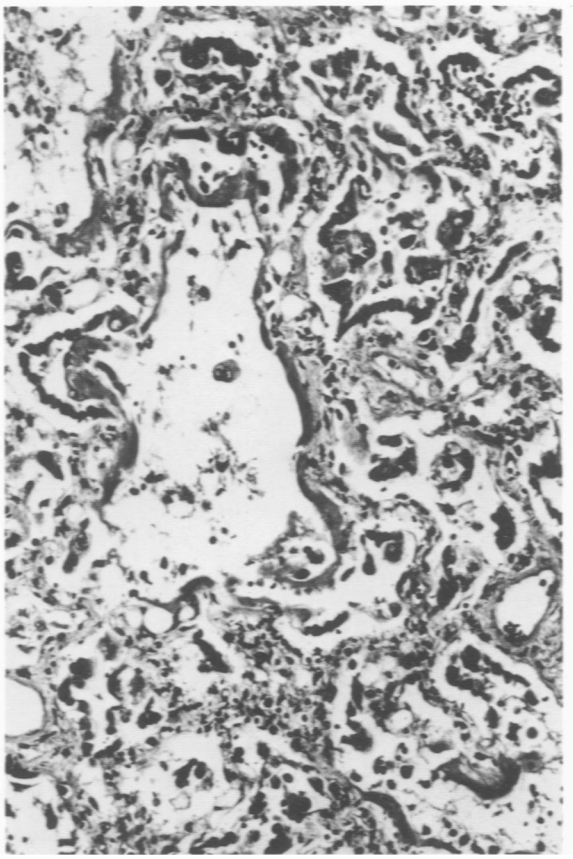

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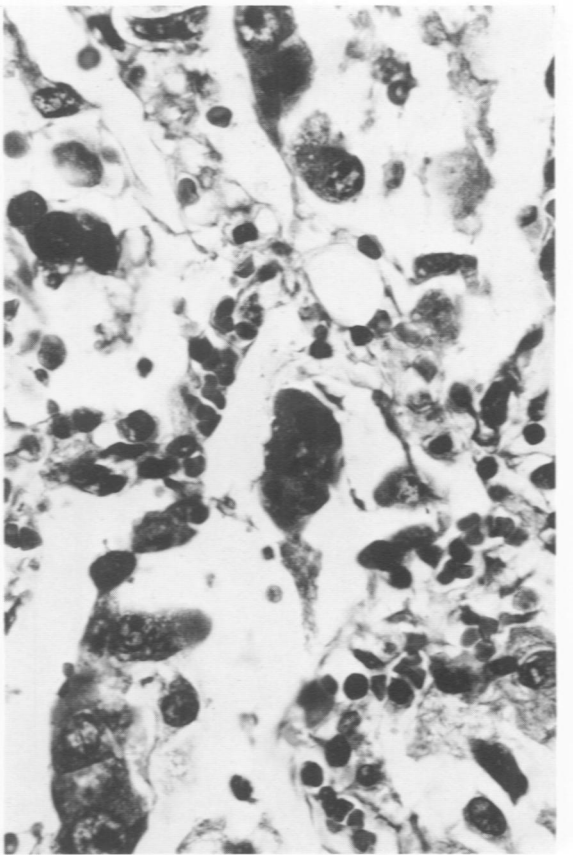

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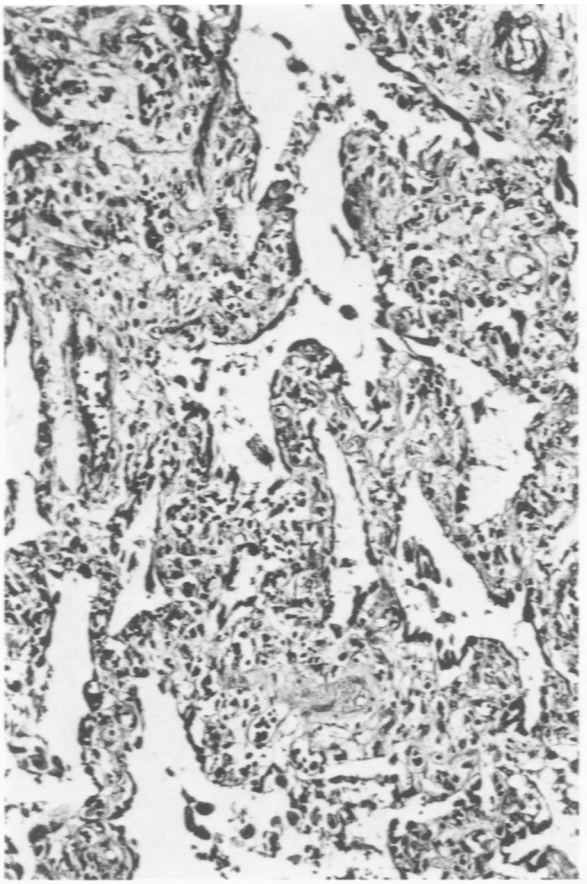

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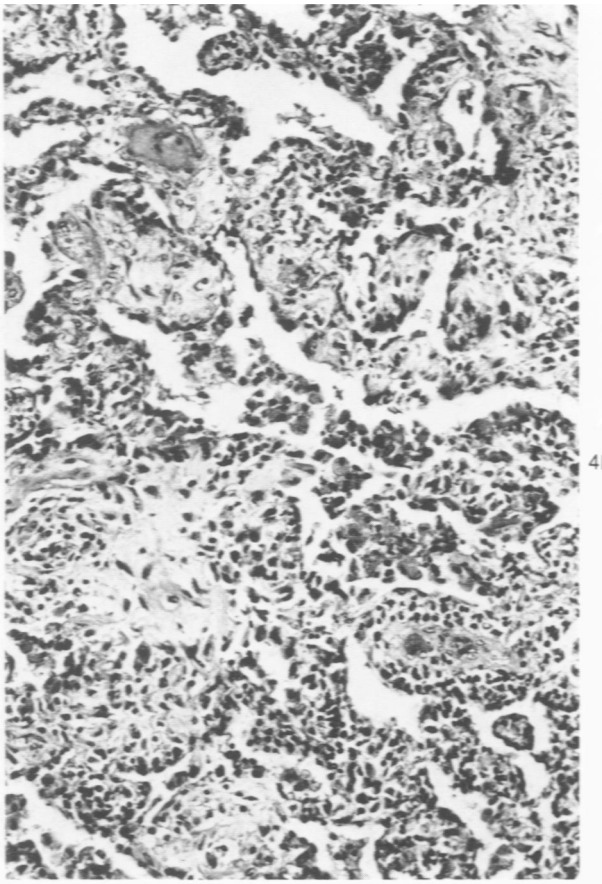

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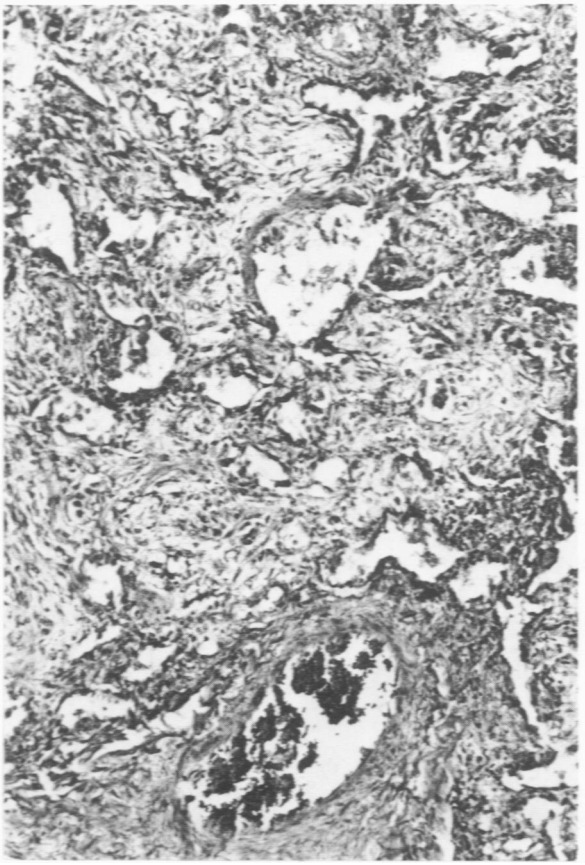

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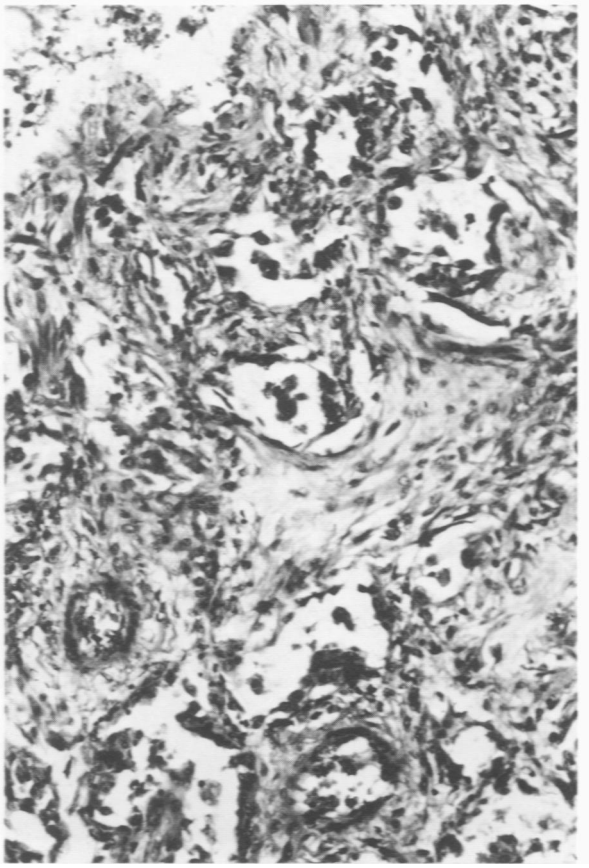

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