Pulmonary Morphology in a Multihospital Collaborative Extracorporeal Membrane Oxygenation Project

I. Light Microscopy

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This report presents the light microscopic morphology found at autopsy in 59 patients who participated in an organized controlled trial of extracorporeal oxygenation as therapy for acute respiratory failure. Observations were recorded as objectively as possible and were analyzed by computer. The experimental therapy produced no specific alteration in the observed pulmonary lesions. Many of the lesions tabulated had significant correlation coefficients with time, all of which were higher when correlated with the duration of respiratory failure than with the duration of the entire acute illness. The rapid progression of the lesions to fibrosis is emphasized as is the predilection of both early and late lesions to involve alveolar ducts to a far greater degree than the distal alveolar spaces. A unifying mechanistic hypothesis consistent with these observations, as well as others, is that the lesions may result as much from oxygen damage as from the original acute illness. (Am J Pathol 95:191–214, 1979)

MOST REPORTS dealing with human pulmonary morphology associated with acute respiratory failure [1-7] present observations derived from relatively few cases and often do not reveal the number involved in the study.[5,6] The patients involved usually had a variety of conditions initiating the clinical syndrome, developed respiratory distress after varying latent periods, and progressed at varying rates to the eventual autopsy. Thus, interpretations as to sequences of events tend to be based on individual illustrative cases which appear to support an author's particular concept. Such sequences are then the basis for elaborate derivations of mechanisms and therapeutic implications.

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The opportunity to see pathologic material from a sizable number of exceptionally well-studied cases of adult respiratory distress syndrome derived from a multihospital randomized clinical trial was therefore felt by the authors to be of great potential value. It was clear that numbers would be sufficient to permit statistical analysis of tabulated data and to evaluate the validity of apparent sequential changes and other phenomena. The evaluation of the effects on pathologic findings of extracorporeal oxygenation compared with conventional therapy, although an essential component of the project, was only one aspect of the studies carried out at the Pathology Center.

Materials and Methods

The clinical methods and criteria for admitting patients to this study and for randomizing these patients between extracorporal oxygenation or conventional therapy have been described in detail elsewhere.[8] Key criteria were that the candidates should not have had any chronic pulmonary disease preceding the onset of acute respiratory insufficiency and that the arterial oxygen tension should be 45 mmHg or less while breathing 100% oxygen. Patients meeting these criteria were randomized to one of the two treatment groups by a central office. All patients received any indicated available modality of conventional therapy such as oxygen, blood transfusions, antibiotics, ventilatory assistance, positive end-expiratory pressure; the only difference between groups was in the use or non-use of an extracorporeal oxygenator. Permission for autopsy was requested at the earliest possible time after any patient was declared dead, and autopsies were performed as promptly as possible.

The Pathology Center distributed an autopsy manual to each Clinical Center so that procedures would be as uniform as possible. This manual included many details such as transthoracic glutaraldehyde injection,[9] collection of frozen tissue for chemical studies, and preparation of postmortem chest radiographs. These methods will not be described in detail here since they are not pertinent to this report.

Collection of tissue for light microscopy was kept purposely simple. Refinements such as inflation-fixation were avoided because it was felt that such procedures might increase variability between centers and make interpretation and data handling more complicated. The only instructions were that the prosector should obtain at least one "representative" tissue block from each lobe of each lung, to be individually identified and fixed in 10% formalin. If specific gross lesions were present, additional selected identified blocks could be submitted. Forms for recording gross observations and diagrams for indicating the sites of origin of tissue blocks were provided. Identified tissue blocks were to be submitted from the trachea, both main bronchi, and at least one segmental bronchus of each lung.

Following receipt at the Pathology Center, blocks were trimmed to suitable size for paraffin embedding and sectioning. Five consecutive sections were prepared from each block and were stained with hematoxylin and eosin, Masson's trichrome, reticulin, elastic tissue, and bacterial [10] and periodic acid–Schiff methods.[11]

All slides were examined by a single observer (PCP). In every instance the slides were examined without knowledge of the clinical center of origin, the original disease, the duration of respiratory therapy, or the use of extracorporeal oxygenation. In other words, the observations were made in as objective a manner as could be achieved. A form was prepared for use in recording the observations and was designed so that the recorded observations could readily be transcribed to data cards for computer analysis.

A completed observation form is illustrated in Table 1. Case identification and separate columns labeled for individual lobes are at the top. Along the left side is the list of lesions

evaluated for every available slide. The first three items are estimates of the percentage of the respiratory area of each slide consisting of stroma, fluid (edema, exudate, or free blood), or air space. Air space included not only open alveoli but also collapsed alveoli if the lumen was empty and the septums thin so that the spaces appeared potentially expandable. The next 11 items constitute observations pertinent specifically to the pulmonary parenchyma, ie, alveolar ducts and alveoli. The next five items related to bronchioles and the last two to intrapulmonary vessels. Observations in major bronchi were recorded separately and will not be discussed in this report. Each lesion type is characterized briefly in the *Appendix*.

Two numbers ranging from 0 to 3 were recorded in each space opposite each item in the left column if a slide was available from that lobe. A "0" indicated that the structure in question was normal or that the lesion in question was absent. The first number referred to the extent (in proportional area to the whole parenchyma) of the involvement of the particular structure or lesion. A "1" meant involvement of less than ⅓ of the whole structure; "2" between ⅓ and ⅔; and "3" more than ⅔ of the whole. For example, if ⅓ of all alveolar ducts in a right upper lobe showed hyaline membranes, a "1" would be placed

Table 1—ECMO Light Microscopic Observations (EC-75-2)

		RUL	RML	RLL	LUL	LLL
	Estimated percent tissue	65	75	65	65	90
	Estimated percent edema-exudate	5	5	5	5	5
	Estimated air	30	20	30	30	5
Parenchyma	Septal thickening	2-2*	2-2	2-2	2-2	3-3
	Hyaline membrane	2-3	2-3	2-3	2-3	2-2
	Edema	1-1	1-1	1-1	1-1	1-1
	Capillaries	2-2	2-2	2-2	2-2	2-2
	Fibroblasts	2-2	2-2	2-2	2-2	2-2
	Fibrosis	2-2	2-2	2-2	2-2	2-2
	Cuboidal epithelium	1-1	1-1	1-1	1-1	1-1
	Macrophages (Nor-0:0)	0-0	0-0	0-0	0-0	0-0
	Blood in alveoli	2-2	2-2	2-2	2-2	2-2
	Active acute pneumonia	1-1	1-1	1-1	1-1	1-1
	Organized pneumonia	0-0	0-0	0-0	0-0	0-0
Bronchioles	Goblet cells	2-2	2-2	2-2	2-2	2-2
	Epithelial extension	2-2	2-2	1-2	1-2	1-1
	Ciliated	1-1	1-1	1-1	1-1	1-1
	Squamous	2-2	2-2	1-2	1-2	2-2
	Blood in lumen	2-2	2-2	2-2	2-2	2-2
Vessels	Recent emboli	0-0	0-0	0-0	0-0	0-0
	Organizing emboli	0-0	0-0	0-0	0-0	1-1

Completed microscopic observation form for a 15-year-old patient treated for respiratory failure for 12 days. The record shows that the various lung lobes were generally similar in appearance. Percentage of tissue was markedly increased and air was decreased. There was a small amount of exudate, consisting of acute pneumonia. Hyaline membranes were prominent, and there was moderate fibrosis in the distribution of alveolar ducts, not as organized pneumonia.

* The first number refers to extent of the lesion and the second to severity. Extent: 1 = <1/3; 2 = 1/3–2/3; 3 = > 2/3. Severity: 1 = slight; 2 = moderate; 3 = severe.

RUL = right upper lobe; RML = right middle lobe; RLL = right lower lobe; LUL = left upper lobe; LLL = left lower lobe.

See *Appendix*.

in the column labeled "RUL" opposite hyaline membrane. The second number in each space indicated the severity of the lesion in question, with "0" again meaning normal structure or absence of lesion. Numbers 1, 2, and 3 represented the total range of severity, with 1 being slight and 3 the most severe. For hyaline membranes the numbers would reflect relative thickness of the membrane.

The procedure in recording data was to evaluate the slide from the right upper lobe completely. The slide from the middle lobe was then examined. If it were essentially similar to the first lobe, the numbers in the first column would simply be repeated in the second column. If a lesion were appreciably more or less prominent in the middle lobe, the numbers recorded for that lesion would be changed appropriately. This procedure was repeated for each lobe, comparing each with the right upper lobe.

For purposes of computer handling, the data, recorded as in Table 1, were entered on computer cards, one card for each lobe. The computer was programmed to multiply the two numbers recorded for each parameter and each lobe and to calculate the mean value of this product for all lobes of each case. This mean value for each lesion type was the value used to make comparisons of means between the various cases and treatment groups.

Following evaluation of the slides, but at a different time, the available information from the clinical center was reviewed for the purpose of tabulating a number of pertinent clinical facts to be correlated later with the morphologic data. This was intentionally done without knowledge of the morphology for purposes of objectivity.

Information recorded as precisely as possible for each case was as follows: a) the diagnosis of the original illness and the duration from its onset to the patient's death; b) the onset of respiratory distress and of respiratory therapy and the duration from these points to death; and c) the date of entry into the study (ie, of "randomization") and the assignment of the patient to extracorporeal oxygenation or to conventional therapy.

Following completion of the morphology table and the clinical table, each case was then reviewed *in toto* to arrive at a final evaluation as to the major factors responsible for the patient's death. These were found to include mainly respiratory failure, hemorrhage, sepsis, and "brain death." In patients dying from respiratory failure, a judgment was made as to whether this had resulted from pulmonary consolidation by hemorrhage, edema, or infection or from pulmonary fibrosis. Pathologic processes in organs other than the lung were accepted as recorded by the pathology departments at the individual clinical centers.

The initiating disease process was also recorded; these were subsequently grouped into seven classes. (See Table 6.)

Results

Qualitative Morphology

Numerous acceptable descriptions of the gross and light microscopic morphology of respiratory distress syndrome have been published [1-7]; therefore, no complete presentation is necessary here. However, several phenomena of special interest were noted during the slide interpretation. The marked predilection for hyaline membranes to involve alveolar ducts has been noted by most authors but deserves re-emphasis since later lesions also emphasize these structures.[1] Figures 1 through 4 illustrate this sequence in an unusual way; all are from a single case. Figures 1 and 2 show an area of infarcted lung in which the pattern of hyaline membrane deposition along alveolar ducts is still well seen. Figures 3 and 4 are from viable tissue in the same patient, who died after 12 days of treatment for

respiratory insufficiency. The interstitial fibrosis clearly follows a pattern comparable to that in Figure 1. The intervening alveoli are much less involved but are small, with slight septal thickening and prominent cuboidal epithelialization. This pattern of fibrosis was present in virtually all lungs of this series if the patient survived for 10 or more days after onset of respiratory insufficiency. Often the duct lumen was completely filled by fibrosis (Figure 3), but in many cases fibrosis was present as a layer at the periphery of the duct with a central persisting lumen (Figures 5 and 6). Since this pattern of fibrosis is characteristic of the lesions in the patients who died after prolonged respiratory distress, the authors propose that it deserves a specific name: "alveolar duct fibrosis."

In patients with acute infection as a terminal event, cross sections of such alveolar ducts could easily be misinterpreted as microabscesses (Figures 7 and 8). Similarly, if pulmonary hemorrhage occurred terminally, the ducts, with fibrotic walls and fresh blood in the lumen, would suggest abnormal pulmonary vessels (Figures 9 and 10).

A final observation of importance was the presence in several cases of clusters of rounded cyst-like spaces without recognizable lining or anatomic orientation (Figures 11 and 12). These varied up to 1 or 2 mm in diameter. These lesions were eventually interpreted as foci of interstitial emphysema, probably resulting from the high inflation pressures used to ventilate such patients after the lung has become extensively fibrosed. These cystic areas were often associated with fresh hemorrhage.

Quantitative Morphology

The total number of patients entered into the clinical study from all centers was 90 and the total number of survivors was 8, equally divided between patients on extracorporeal oxygenation and those on conventional therapy. Of the 82 patients who died, the Pathology Center received adequate tissue and clinical information for complete evaluation on 59 cases. In 10 cases, either no autopsy was done or medicolegal considerations prevented release of material. In the remaining 13 cases, either the tissue submitted or the clinical summary did not permit adequate completion of the data tabulations.

The available 59 cases have been sorted by the computer into various groupings, and the mean value for each lesion type has been calculated and tested for statistical significance of differences between groups using the Student t test.[12] In addition, the coefficient of correlation [12] has been determined between the value for each lesion type in each individual case and the duration of the total illness, the duration of respiratory symptoms, and the duration of active therapy for respiratory insufficiency. Active

therapy was considered to have begun with oxygen therapy, assisted ventilation, or positive end expiratory pressure, whichever was used first. Usually all were begun at approximately the same time.

The results of the statistical analyses are presented in Tables 2 through 5. Table 2 shows the coefficient of correlation (r) between the calculated score for each lesion parameter and either the overall length of the patient's illness or the duration of therapy for respiratory insufficiency. The statistical significance of the various correlations is also shown. It is apparent in Table 2 that many of the lesions did show trends to change with time, some increasing (positive coefficients) and others decreasing (negative coefficients). In almost every instance, and in all statistically significant ones, the coefficient is higher between score and "therapy duration" than between score and "length of illness." Ten lesions were significantly correlated with therapy and only 7 with duration of illness.

Table 3 shows the mean score for each lesion in the patients receiving extracorporeal oxygenation and those receiving conventional therapy. Only three scores were significantly different; all others had probability levels higher than 0.05.

Table 4 shows the lesion types which were found to be significantly associated with the underlying or initiating disease process. This test was carried out by calculating the mean score for all cases within one disease class and comparing it with the mean score for all other cases together.

Table 2—Coefficients of Correlation Between Lesion Scores and Time

Lesion	Duration	
	Total illness (r)	Respiratory treatment (r)
Percent tissue	0.41*	0.48*
Percent fluid	−0.35*	−0.42*
Percent air	−0.12	−0.12
Septal thickening	0.48*	0.51*
Hyaline membranes	−0.13	−0.32*
Septal edema	−0.22	−0.24
Septal capillaries	0.32*	0.34*
Septal fibroblasts	0.29*	0.43*
Septal fibrosis	0.38*	0.58*
Cuboidal epithelium	0.31*	0.51*
Macrophages	0.11	0.38*
Alveolar blood	0.10	−0.02
Acute pneumonia	−0.24	−0.38*
Organizing pneumonia	−0.02	0.03
Goblet cells	0.17	0.11
Epithelial extension	0.14	0.06

* Probability less than 0.05; all others greater than 0.05

Table 3—Comparison of Average Lesion Scores in Conventional Treatment and Oxygenator Treatment Groups

Lesion	Mean score		
	Conventional (27)		Oxygenator (32)
Percent tissue	38.4		44.9
Percent fluid	38.4		33.8
Percent air	23.1		21.4
Septal thickening	2.9		3.3
Hyaline membranes	1.3		1.3
Septal edema	1.2	*	0.9
Capillary congestion	1.0		1.0
Septal fibroblasts	2.3		3.2
Septal fibrosis	2.1	*	3.5
Cuboidal epithelium	2.1		2.8
Alveolar macrophages	0.8		1.1
Alveolar blood	0.8	*	1.2
Acute pneumonia	2.9		2.0
Organizing pneumonia	0.1		0.2
Goblet cells	0.5		0.2
Epithelial extension	0.5		0.2

* Probability of difference less than 0.05; all others greater than 0.05

Table 4 reveals that, of all the values compared (16 lesions × 7 disease classes = 112), only five lesion types showed statistically significant association with underlying disease. These included extension of columnar epithelium to line alveoli adjacent to bronchioles in the 21 cases beginning with viral pneumonitis; alveolar septal edema and organizing pneumonia in the 4 postsurgery cases; and alveolar filling (percent fluid) and alveolar blood in the 2 cases with Goodpasture's syndrome.

Table 5 shows lesion types which were significantly associated with treatment centers. This comparison was carried out similarly to the above test of underlying diseases. The case from Center 2 had significantly more blood in alveoli than did all other cases; the 6 cases from Center 3 had a greater mean percentage of air; the 9 cases from Center 4 had a higher

Table 4—Lesions Significantly Associated With Underlying Disease

Disease class	Number	Lesion	Score in disease class	Score in all other diseases	$P <$
Viral pneumonia	21	Epithelial extension	0.52	0.22	0.03
Viral pneumonia	21	Ciliated	0.84	0.22	0.005
Postsurgery	4	Septal edema	0.76	1.1	0.04
Postsurgery	4	Organizing pneumonia	0.53	0.12	0.04
Goodpasture syndrome	2	Percent fluid	71.8	35.2	0.02
Goodpasture syndrome	2	Alveolar blood	1.8	0.92	0.05

Table 5—Lesions Significantly Associated With Treatment Center

Center	Number	Lesion	Score for center	Score for all other centers	$P <$
2	1	Alveolar blood	2.49	0.93	0.02
3	6	Percent air	38.5	20.5	0.004
4	9	Epithelial extension	0.65	0.25	0.05
6	4	Percent tissue	68.8	39.2	0.006
6	4	Septal thickening	4.7	2.9	0.04
6	4	Septal fibroblasts	6.2	2.4	0.002
6	4	Septal fibrosis	7.0	2.4	0.001
6	4	Cuboidal epithelial	5.0	2.3	0.002
6	4	Alveolar blood	0.22	1.01	0.02

mean score for bronchiolar epithelial extension; and, finally, the 4 cases from Center 6 had a significant excess of five lesion types and a lesser amount of one type.

Table 6 shows the results of the overall evaluation of the cases as to immediate cause of death. The cases are divided into seven disease classes and are separated into first-week, second-week, and third-or-greater-week deaths. Death was considered to have resulted from respiratory failure when pulmonary involvement appeared severe enough to produce failure and when there was no clinical or pathologic evidence in the record to indicate the likelihood of another mechanism. When other mechanisms were present, eg, "brain death" or massive hemorrhage, the case was not counted as a death from respiratory failure. Table 6 also indicates the

Table 6—Evolution of Lesions and Major Cause of Death With Time

	Duration of therapy prior to death									
	< 1 week			1-2 weeks			> 2 weeks			
Underlying disease	A	B	C	A	B	C	A	B	C	Totals
Viral infection	5	0	0	2	1	3	0	1	8	20
Trauma	3	0	0	0	0	0	0	3	4	10
Diabetes	1	0	0	0	0	0	0	1	3	5
Postsurgery	1	0	0	0	1	1	0	0	1	4
Parturition	0	1	0	0	1	1	0	0	2	5
Goodpasture's syndrome	2	0	0	0	0	0	0	0	0	2
Other	3	1	0	1	3	1	0	0	2	11
Group totals	15	2	0	3	6	6	0	5	20	57*
Totals	17			15			25			

A = Number of cases with hyaline membranes but no alveolar duct fibrosis (ADF).
B = Number of cases with ADF present but not the major cause of death.
C = Number of cases with ADF as the major cause of death.
* Two of the 59 cases involved neither hyaline membranes nor fibrosis. One began with viral infection and the other with trauma.

major pathologic process in the lung. Examination of Table 6 will show that all of the 17 patients who died during the first week had identifiable mechanisms other than respiratory failure and most had hyaline membranes; two already showed alveolar duct fibrosis. In no case in the study did it appear that hyaline membranes were a major cause of death. Among the 15 patients who died during the second week, 6 were considered to have died of respiratory failure caused by alveolar duct fibrosis. All of the 25 patients who died after more than 2 weeks of therapy for respiratory insufficiency had alveolar duct fibrosis, and 20 of these died of respiratory failure related to it. It can also be seen in Table 6 that the morphologic findings are consistently distributed among the various initiating disease processes. None occur earlier or later in one disease class compared with the others. The total of cases represented in Table 6 is 57 rather than 59. Two patients died with neither hyaline membranes nor fibrosis.

Discussion

The findings in this study confirm numerous concepts previously published concerning the morphologic events in lungs during the evolution of the adult respiratory distress syndrome. Several workers have described the early phases as exudative (congestion, edema, and hyaline membranes) followed in several days by cell proliferation (Type II cells, interstitial cells, macrophages, and fibroblasts) and, after only a week or two, by interstitial fibrosis.[1-7]

This sequence of events was demonstrated in a statistically valid way in this study. The reader is reminded that the slides of each case were interpreted without knowledge of the background facts such as original illness or duration of respiratory failure. Yet, when the lesions recorded were subsequently correlated with duration of respiratory failure, many statistically significant correlations were found, as shown in Table 2. Thus, percentage of free fluid and hyaline membranes decreased with time while percentage of tissue, alveolar septal thickening, capillaries, fibroblasts, fibrosis, and cuboidal epithelium all increased.

It should be noted also that these correlation coefficients are higher between lesions and duration of respiratory failure than between lesions and duration of original disease. This observation raises a question as to the mechanisms responsible for the lesions. The current concept is that any of the many initiating disease processes may produce diffuse alveolar damage that subsequently evolves to hyaline membrane and the final stage of fibrosis.[1,4,5,7] If this process began with the initial disease, it would seem more likely that the lesions would correlate better with this duration.

This is one of several points to be described in this paper which suggest to the authors that the lesions may be related more to the respiratory failure itself, or the therapy for it, than to the original disease.

The comparison of lesion scores between patients treated with extracorporeal oxygenation and those with conventional therapy (Table 3) showed few statistically significant differences. Those lesions which did differ significantly can be readily understood. The lesser amount of alveolar septal edema probably resulted from the decreased volume of blood perfused through the lung tissue because of diversion of venous blood to the oxygenator. The greater amount of fibrosis can be related to the fact that the mean survival time for patients on the oxygenator was several days longer than that of the patients undergoing conventional therapy; since fibrosis increased with time, the longer survivors should have more fibrosis. The greater amount of blood in alveoli can be attributed to the fact that all patients on the oxygenator had to be heparinized. Thus, when lung tissue was damaged, eg, by development of interstitial emphysema, the oxygenator patients would be expected to have more hemorrhage than the controls. Other lesions which might have been expected to have higher scores in the oxygenator patients (percentage of tissue, septal fibroblasts, and others) were higher, although they did not reach statistical significance.

The implication of the above findings is that the use of extracorporeal oxygenation exerted no specific effect on the pulmonary morphology of these patients. This observation could be interpreted as supporting the concept that the pathologic sequence, once initiated by the original disease, is inexorably progressive. However, the concept that lesions may be largely the result of therapeutic efforts is still tenable since patients on extracorporeal oxygenation also continued to receive ventilatory assistance and oxygen therapy, with their mean inhaled oxygen concentration being 55% compared with the mean concentration of 77% used with conventional therapy patients (data from Summary Statistics distributed to participants in the Collaborative Study).

The test for association between lesions and underlying disease (Table 4) showed few such associations. One difference did appear to be clear: the association of viral pneumonia with the finding of extension of columnar bronchial epithelium outward to line peribronchiolar alveoli. This phenomenon is well-described in the literature [13,14] and its detection in this study tends to enhance the validity of other observations. The diagnosis of viral pneumonia in these cases had been made at the various clinical centers. In some instances influenza virus had been cultured; in others, rising antibody titers were demonstrated; and in some, the diagnosis was

based on clinical manifestations and the concurrent existence of an epidemic. Postsurgical cases had significantly less septal edema and significantly more organized pneumonia than did those of other disease classes. No logical inference from this association has occurred to the authors. Recalling that over 100 comparisons were made in developing this table, it appears that these two statistical associations can be attributed to chance. Finally, in Table 4, it is shown that the 2 patients with Goodpasture's syndrome had significantly more alveolar consolidation and alveolar blood than did those in the other disease classes; absence of this finding would have been a disappointment.

When association between treatment center and lesions was examined (Table 5), two centers showed single lesion differences, again best attributed to chance. Center 4 had a significantly greater degree of bronchiolar epithelial extension than the other centers. Since 6 of the 9 patients treated at that center had viral pneumonitis as the initiating illness, this association is valid.

The 4 cases from Center 6 differed from all others in 6 lesions (Table 5). Those multiple differences and the low probability level of most of these suggest that a real distinction must exist between that center and the others. All but one of the lesions were processes showing positive correlations with duration of respiratory failure; this might suggest that patients survived longer at Center 6 than at other centers. However, this was not the case since the mean duration at all centers was 17.8 days, with standard deviation of 5.9, and the mean at Center 6 was 20 days (data from Summary Statistics distributed to participants in the Collaborative Study). Examination of other possible factors such as age, sex, underlying illness, mechanical ventilation, inspiratory and end expiratory pressures, and inhaled oxygen concentration revealed no clear-cut difference between this center and the others. Oxygen concentration was suspected by the authors to be a likely mechanism, but available data do not adequately support this concept: although this center was among those with higher mean oxygen concentrations, two other centers were above this one, with comparable duration of the course. The striking difference in results at Center 6 remains unexplained.

One of the most significant observations arising from this study is that the lesions of ARDS were most accentuated in the alveolar duct region and that these progressed to fibrosis of the alveolar ducts in patients who survived more than 10 days.

Numerous authors, in describing the morphology associated with adult respiratory distress syndrome, have noted the accentuation of hyaline membranes along alveolar ducts. Only one has reported that the inter-

stitial fibrosis is also centered on alveolar ducts.[1] None has attempted to develop a mechanistic rationale to account for this characteristic location.

In the present authors' opinion, at least two mechanisms might explain the predilection of the lesions of ARDS to involve alveolar ducts. The first is that this is the primary site of injury caused by the initiating lung insult. Since the mechanism of the primary insult which causes ARDS is poorly understood, this alternative cannot be fully evaluated. However, the earliest observable lesion in ARDS is thought to be an alveolar capillary membrane injury and leakage of fluid into the lung interstitium. This suggests a diffuse alveolar site of injury rather than one localized to the alveolar ducts. In addition, a wide variety of injuries can result in ARDS and some arise from primary trauma to a distant organ, which suggest that lung injury is mediated by some product carried intravascularly. This concept of the origin of ARDS does not readily explain the predilection for the injury to involve the alveolar duct region.

The second hypothesis is that the increased damage to the alveolar duct region occurs as a product of therapy given to these patients. All the patients received inspired oxygen concentrations in the range of 40 to 100%. It is now well-established that oxygen is toxic for cells and that the range of concentration causing toxicity is within that attained during therapeutic use.[3,15] The lesion of oxygen toxicity in animals usually involves both the alveolar duct and the alveolar region. An explanation of how oxygen toxicity would cause alveolar duct fibrosis in ARDS patients has not been established. However, several other toxic oxidant gases such as ozone,[16] nitrogen dioxide,[17,18] and phosgene [19] produce their major lesion in the region of respiratory bronchioles and alveolar ducts. A likely reason for a selective effect with these gases is that this is the location where gas-exchange surfaces are exposed to the highest concentration of the inhaled toxic gas. Ventilatory volume and tracheobronchial volume changes during inhalation are such that the interface between newly inhaled air and the remaining air from the previous breath travels into the alveolar ducts.[20] Distribution beyond this level is by diffusion. Therefore, the inhaled concentration of a toxic gas will reach the alveolar ducts, but more distal alveoli will receive a lesser concentration.

Although this is true for gases like NO_2 and O_3, it is not commonly believed that stratified inhomogeneity exists for oxygen in the normal lung for more than brief portions of the respiratory cycle. Equilibrium of oxygen concentrations between the alveolar ducts and the alveoli by diffusion is estimated to take less than 0.5 seconds following each inspiration.[21] It is possible, however, that these characteristics of oxygen transport are not valid for the lung injured by ARDS. In portions of the

injured lung, the diffusion distances may be greatly increased and a significant oxygen gradient between the alveolar ducts and the alveoli could occur. Possible contributing factors to this include contraction of the muscle bundles in the alveolar ducts, which could be a response to increased oxygen concentrations. Once hyaline membranes have begun to form, they can produce narrowing of the lumen and thereby decrease gas transport between the alveolar ducts and the alveoli. Other explanations would be that the alveolar duct region may be unusually sensitive to oxygen toxicity in humans or that the alveolar duct fibrosis may be the result of combined injury. The toxic effects of viral pneumonia and oxygen therapy have been shown to be additive in mice.[22] It is reasonable to postulate that the initial insult of ARDS when combined with subsequent therapy with even 50% oxygen results in significant progressive lung injury.

Other modalities of therapy for respiratory failure include mechanical assistance of ventilation, positive end expiratory pressure, high peak inspiratory pressures, and tracheotomy. Several published studies indicate that mechanical ventilation with room air does not produce pulmonary damage [23,24]; positive end expiratory pressure (10 cm H_2O, breathing room air) has also been shown not to produce pulmonary lesions in lambs after 1 week.[25] High peak pressures may produce damage to lungs, but this appears to affect primarily bronchi and bronchioles, with epithelial hyperplasia and subepithelial fibrosis, rather than alveolar ducts and alveoli.[26] Careful evaluation of the clinical evolution of bronchopulmonary dysplasia in infants, a condition reminiscent of the fibrotic stage of ARDS, has led to the suggestion that prolonged exposure to oxygen above 40% is probably of more etiologic importance than intubation or mechanical ventilation.[27]

On the basis of the above concepts, the authors postulate the following pathogenic sequence for adult respiratory distress syndrome. The initial illness (shock, virus, trauma, burn) produces a pulmonary lesion (microthrombi, interstitial edema, "alveolar damage") which causes hypoxemia. Some of these lesions are probably self-limiting and reversible; in experimental models involving hemorrhage, trauma, or burns, animals generally either die early or completely recover.[28] However, if the hypoxemia is severe enough to require oxygen therapy, its effects may be added to those of the original process. The additional cell damage, interstitial edema, and hyaline membranes which result undoubtedly interfere further with gas exchange and thus force prolongation of the therapy with even higher concentrations of oxygen. Thus, the process can become a vicious cycle, with progression of the extent of cell damage and thickness of membranes.

There is evidence to suggest that fibrin, which is present in hyaline membranes, may be a stimulant for proliferation and collagen deposition by fibroblasts.[29] Thus, fibrosis involving alveolar ducts would be expected to follow the extended duration of the hyaline membranes.

It is widely believed that a large variety of disease processes, eg, shock, trauma, burn, viral pneumonitis, radiation, uremia, can produce hyaline membranes and that these are therefore nonspecific. When papers describing these in human material are carefully reviewed, it is almost always clear that the patients did have oxygen therapy, although the authors usually think it too brief or too dilute to be significant.[4,7] In contrast, several patients with diseases such as burns or massive hemorrhage, who for various reasons did not receive oxygen prior to death, did not have any membranes.[30] It has been reported that an increased frequency of hyaline membranes in burn patients in recent years could be attributed to increased use of oxygen rather than to prolonged survival of the patients.[31] Thus, it is probable that hyaline membranes, and especially their persistence beyond 1 or 2 days, are much more closely related to oxygen exposure than is usually assumed.

The question of a "safe" concentration of oxygen is often raised. It is doubtful that one can identify a specific safe level, because in all probability there is a wide spectrum of susceptibility among individuals. Some will develop cell damage at levels which are innocuous for others and it is also possible that disease processes may alter susceptibility. The 2 patients in this study who had neither hyaline membranes nor alveolar duct fibrosis may be examples of relatively high resistance to toxic effects of oxygen. Each had been treated with oxygen and other modalities for 2 and 13 days, respectively. The latter case began with viral pneumonia; this is the reason that this disease class includes 21 cases in Table 4 and only 20 cases in Table 6.

No clinical test is available to evaluate susceptibility to oxygen toxicity in advance. Therefore, it would appear that the approach to protect patients at the most susceptible end of the spectrum would be to use oxygen therapeutically only when it is necessary and to use the lowest possible effective dose for the shortest possible period of time.

Conclusions

The following conclusions are supported by all participants in the cooperative project:

1. Lung lesions observed at autopsy varied with duration of respiratory failure. Alveolar and septal edema and hyaline membranes were prominent in the first week. Cell infiltration and proliferation of alveolar epithe-

lium and fibroblasts appeared between 7 and 10 days. Beyond 2 weeks, fibrosis was present and usually appeared to be the major factor responsible for death from respiratory failure.

2. Postmortem lesions did not differ by the original disease process.

3. The evolutionary development of the lesions was not altered by the treatment with extracorporeal oxygenation.

4. Fibrosis occurred in a pattern centered on alveolar ducts. Frequently it proceeded to the point of complete effacement of the alveolar duct lumen.

Appendix

Brief characterizations of the lesions listed in Table 1:

A. Lesions relating to pulmonary parenchyma

1. Septal thickening. This simply refers to an increase in the width of alveolar septal tissue and includes both septums related to alveolar ducts and those of individual alveolar spaces. The following five items indicate the nature and relative importance of the components responsible for this overall thickening.
2. Hyaline membranes. These consist of an amorphous eosinophilic layer covering the surface of alveoli, especially those which make up the alveolar ducts. When extent is minimal, they are found at the tips of the alveolar septums which project into the alveolar ducts. With increasing extent, they can cover the entire surface of these alveoli and may involve immediately adjacent alveolar spaces (Figures 1 and 2). Rarely, if ever, do all alveoli show hyaline membranes.
3. Edema. This refers specifically to interstitial edema causing widening of alveolar septums. Free edema fluid in alveolar lumens would be recorded in Table 1 as "estimated percentage of edema-exudate."
4. Capillaries. This refers to prominent congestion and dilatation of alveolar septal capillaries which often bulge above the contour of the alveolar surface and contribute to septal widening.
5. Fibroblasts. This refers to increased numbers of spindle-shaped cells in the interstitial area of alveolar septums. In some cases these are prominent and numerous, but only a few collagen fibers are present. In such cases, congested capillaries are also usually seen.
6. Fibrosis. This refers to the presence of collagen fibers in the interstitial area of alveolar septums. Often this is associated with plentiful fibroblasts, but in some cases fibrosis is prominent while

only small numbers of fibroblasts are seen. In these instances, capillaries also are usually inconspicuous. The fibroblasts and collagen are regularly most prominent in the region of alveolar ducts. They often narrow and can even totally obliterate the lumens of many ducts. Adjacent alveoli usually remain patent, although small (Figures 3 through 10). Because of the characteristic emphasis on alveolar ducts, it is proposed that this pattern of fibroblasts and/or fibrosis should be given the name "alveolar duct fibrosis."

7. Cuboidal epithelium. This refers to the presence of an epithelial layer, visible by light microscopy, on alveolar septums. These cells are often detached from the surface, so that they appear as a row of flat or cuboidal epithelium paralleling the contour of the alveolus. These cells are often seen to involve all alveoli, not limited to those making up the alveolar ducts (Figures 3 through 10).
8. Macrophages. Macrophages often are increased in numbers. They occur mainly in the alveolar lumens but may also be seen in the interstitial area. Some macrophages are always present in alveoli; normal numbers of these were recorded as "0–0" (Table 1).
9. Blood in alveoli. This refers to the presence of erythrocytes in the lumens of alveoli and alveolar ducts. If the figure for "estimated percent edema-exudate" (Table 1) were large and the scores for "blood in alveoli" were also large, it would indicate that hemorrhage was a major component of the pulmonary involvement.
10. Active acute pneumonia. This refers to consolidation of alveoli by purulent exudate. If "estimated percent edema-exudate" were large and this score were also large, it would indicate that pneumonia was an important factor in the terminal illness. If "edema-exudate" were large and both "blood" and "pneumonia" were small, then intra-alveolar edema would be indicated as a major pathologic finding.
11. Organized pneumonia. This refers to the generally recognized intra-alveolar fibrosis of "healed" bronchopneumonia. It involves groups of alveoli and does not have the alveolar ductal pattern described above.

B. Lesions relating to bronchioles and vessels. The remaining findings in Table 1 refer to lesions in bronchioles and vessels. Since these findings are not presented in this report, they are not described here, except for "epithelial extension." This consists in the presence of columnar, or sometimes stratified squamous, epithelium lining groups of alveoli immediately adjacent to bronchioles, not distal to them in the pattern of air distribution.

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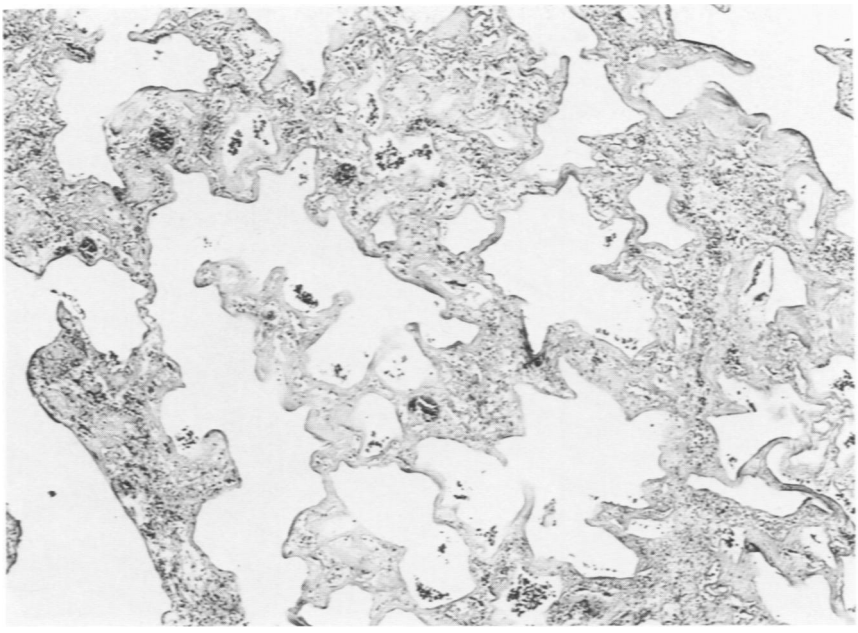

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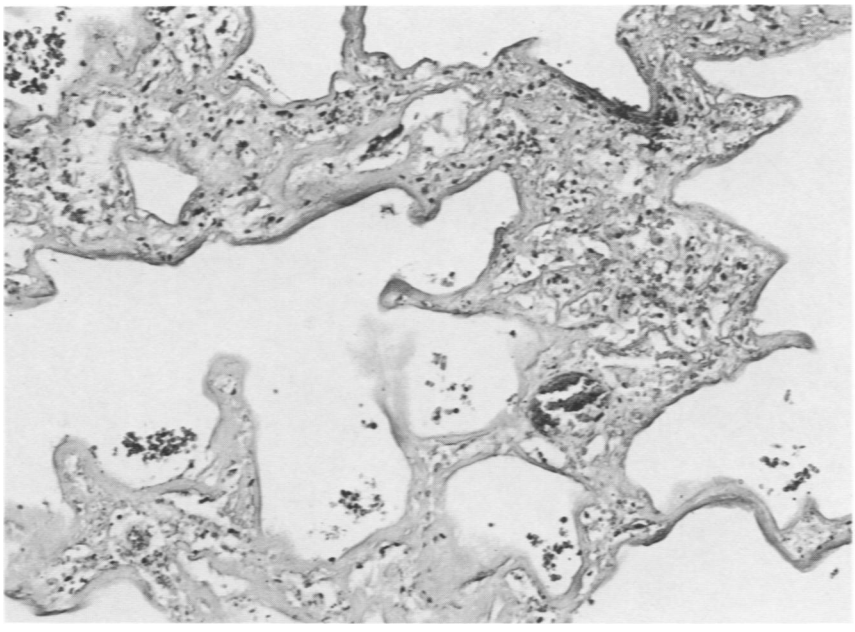

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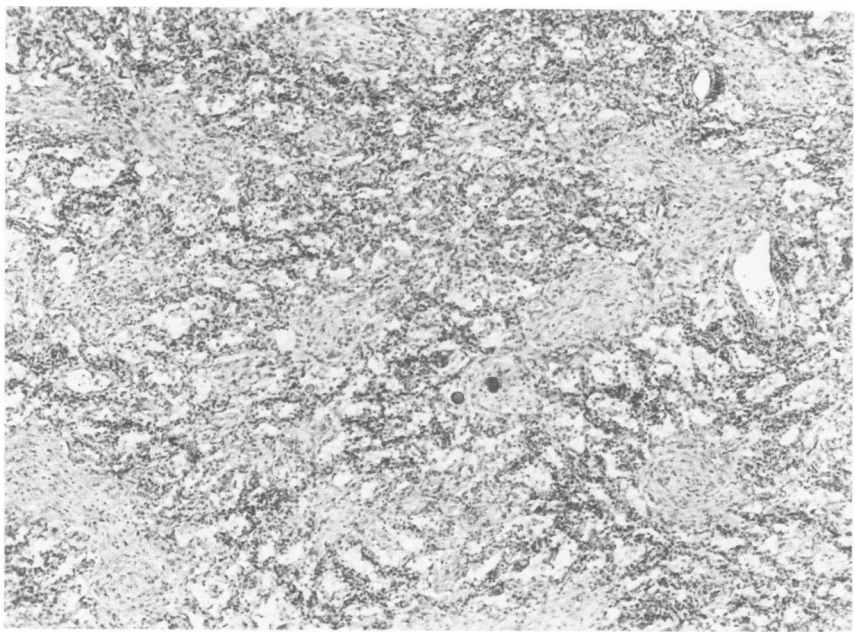
Figure 1—An area of pulmonary infarct in a 23-year-old patient with suicidal drug ingestion, who died after treatment of respiratory distress for 12 days. The lobulated spaces are alveolar ducts seen in longitudinal and cross sections. Most of the ducts are lined by a layer of amorphous material typical of hyaline membranes. The tissue between ducts consists of partially collapsed necrotic alveolar septums. (×50) **Figure 2**—Higher magnification of the alveolar duct at *left center* in Figure 1. The hyaline membranes along the surface are well seen. (×125)



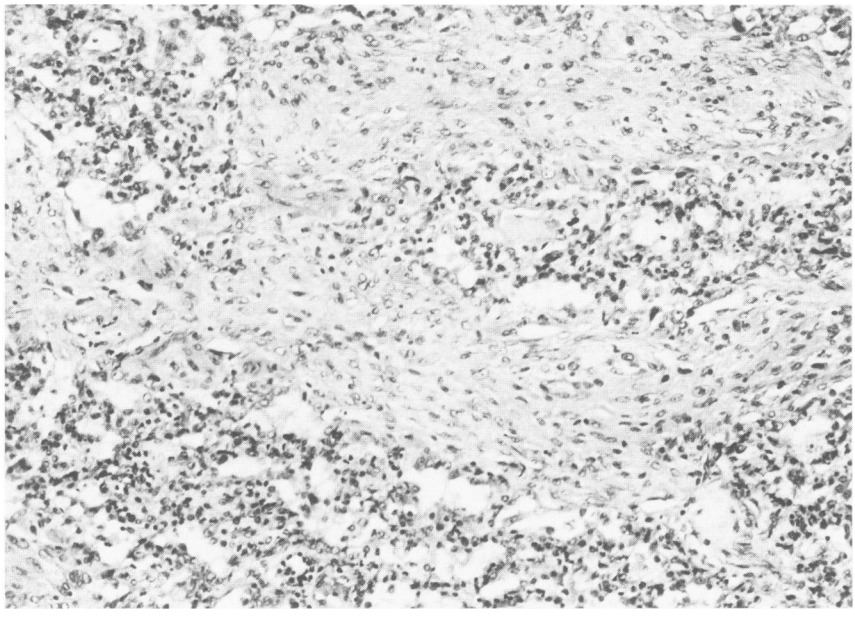
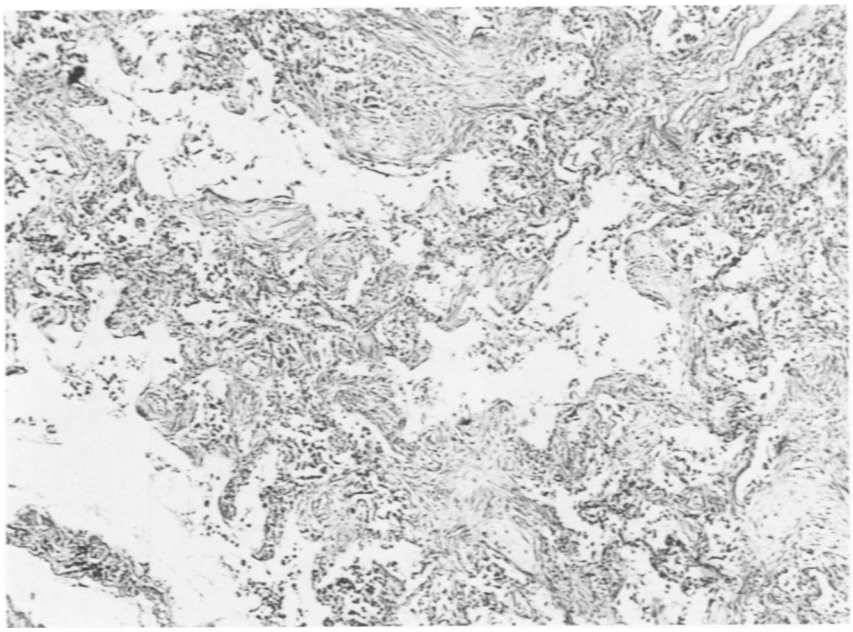


Figure 3—Viable tissue in the same lung as in Figures 1 and 2. Fibrosis is seen in a linear branching pattern and in isolated foci surrounded by alveolar spaces with slightly thickened septums. The pattern of the fibrosis is similar to that of the alveolar ducts in Figure 1, being seen both in longitudinal and cross sections. Lumens are almost completely replaced by the fibrosis. (×50) **Figure 4**—Higher magnification of a longitudinal section of a fibrotic branched alveolar duct in the same case as in Figure 3. Note the intervening alveoli, most of which have cuboidal epithelium and slightly thickened septums with increased cells but little or no fibrosis. (×125)



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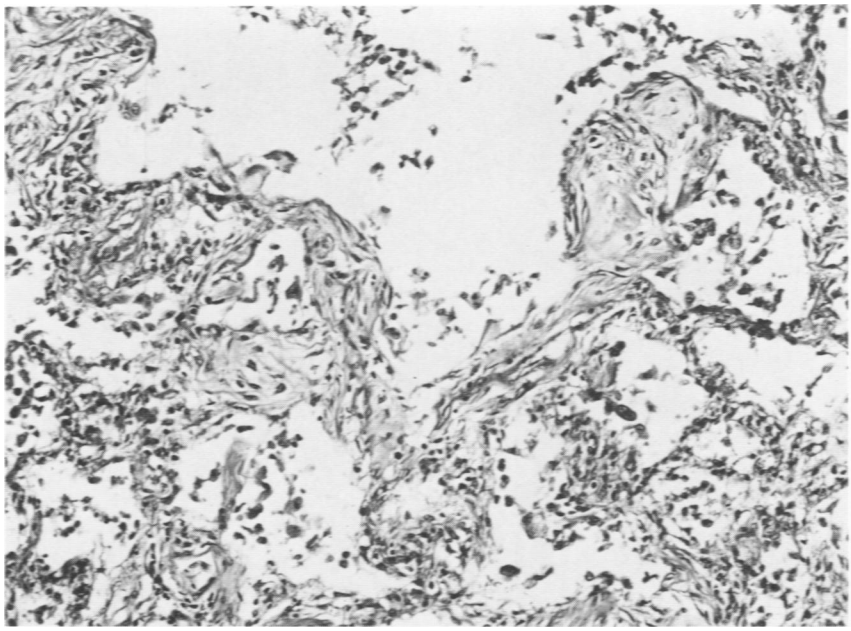

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Figure 5—Alveolar ducts and adjacent alveoli in a 50-year-old patient with massive gastrointestinal hemorrhage and laparotomy, who died after treatment of respiratory distress for 15 days. Alveolar duct lumens are open, but an irregular zone of fibrosis is present at the surface. Alveolar spaces can be seen between the ducts. Some of these septums show fibrosis also, but in much lesser amount than along the ducts. (×50) **Figure 6**—Higher magnification of the same area as in Figure 5, including the right margin of the duct at *right center*. The fibrosis is clear and again there is little involvement of adjacent alveoli. Their septums are slightly thickened and show edema, congestion, and partial epithelialization. (×125)

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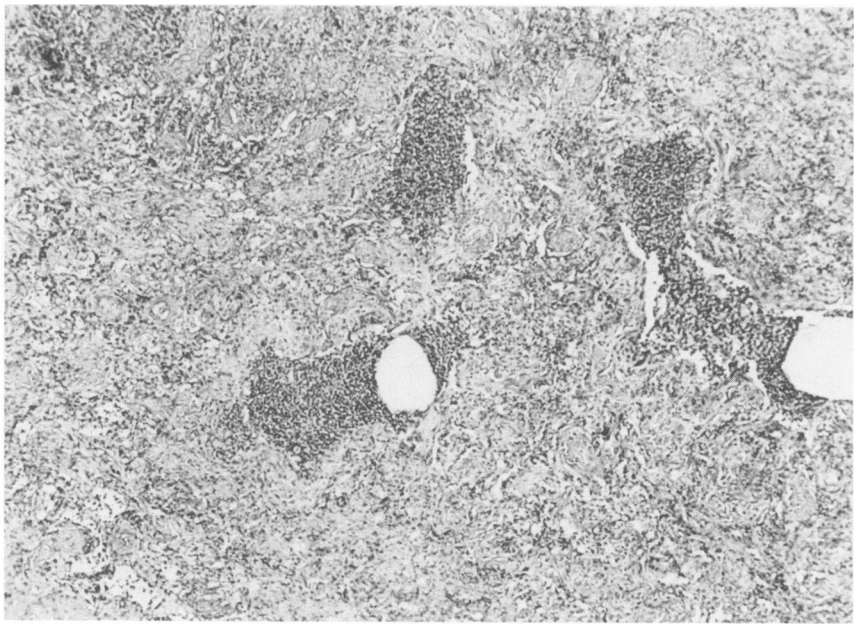

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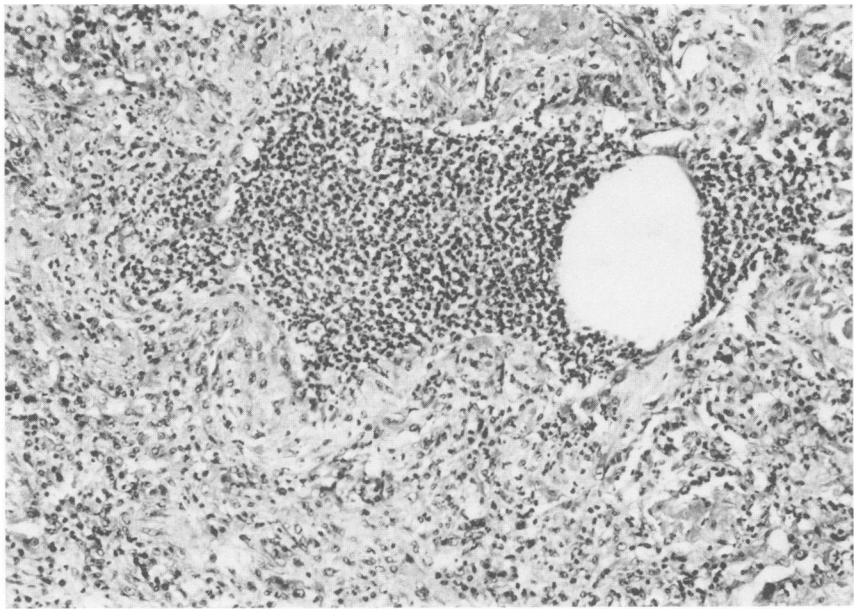
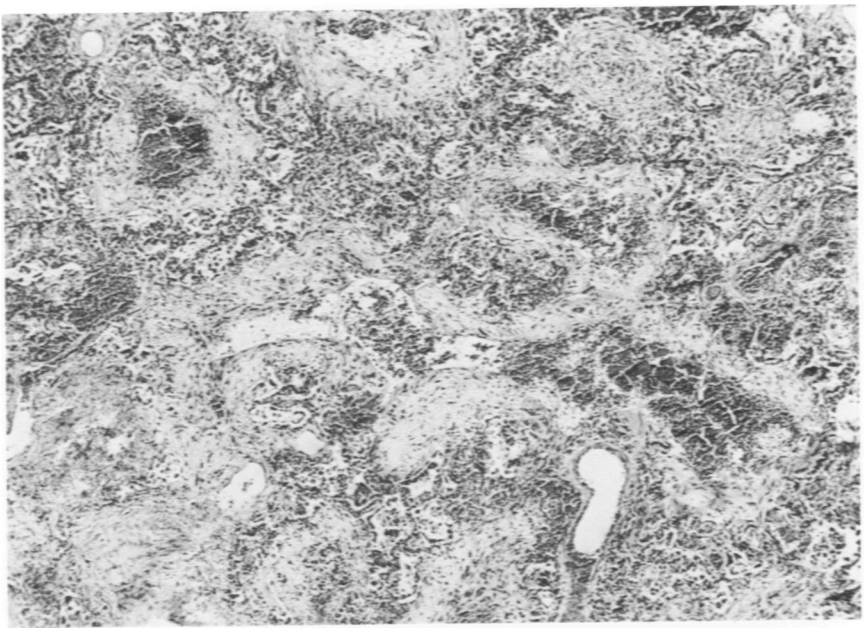


Figure 7—Alveolar ducts and adjacent alveoli in the same patient as in Figures 1 through 4, who died after treatment of respiratory distress for 12 days. The patient had become febrile in the last few days of life. The alveolar ducts show fibrosis and the remaining lumen is filled with polymorphs. The appearance could readily be misinterpreted as microabscess formation. (×50) **Figure 8**—Higher magnification of one of the ducts in Figure 7. Note that the appearance is similar to that in other figures, except for the leukocytes in the lumen of the alveolar duct. (×125)



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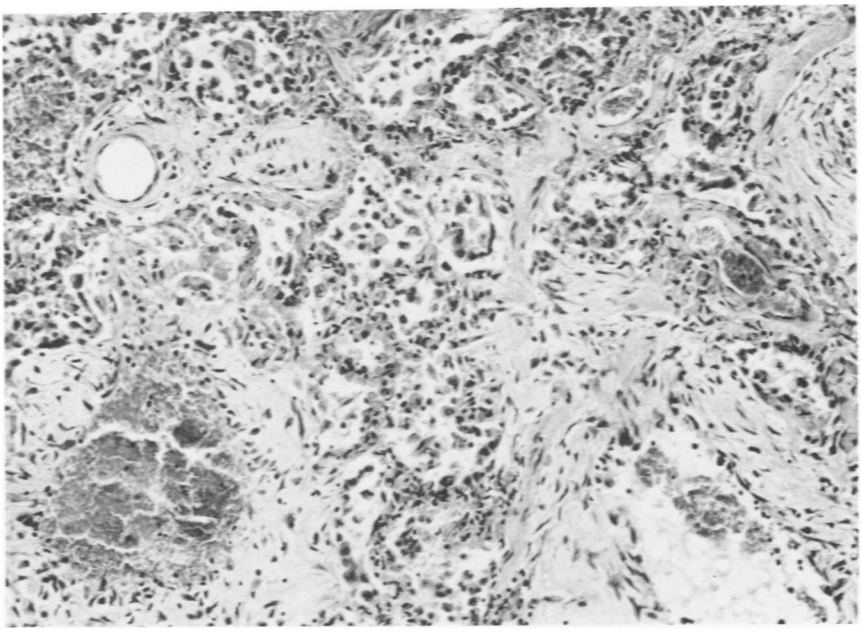

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Figure 9—Alveolar ducts and alveoli in a 33-year-old patient with viral pneumonitis, who died after treatment of respiratory distress for 20 days. Alveolar ducts are seen in longitudinal and cross section. Their walls show fibrosis, and the lumens contain fresh hemorrhage. This appearance, especially when seen in cross section, as at *upper left*, is suggestive of abnormal pulmonary vessels. However, note the normal vessels at *left upper* and *right lower* corners. (×50) **Figure 10**—Higher magnification of the duct at the *upper left* of Figure 9. The morphology is similar to that in other cases, except for the fresh blood in the lumen. (×125)

11

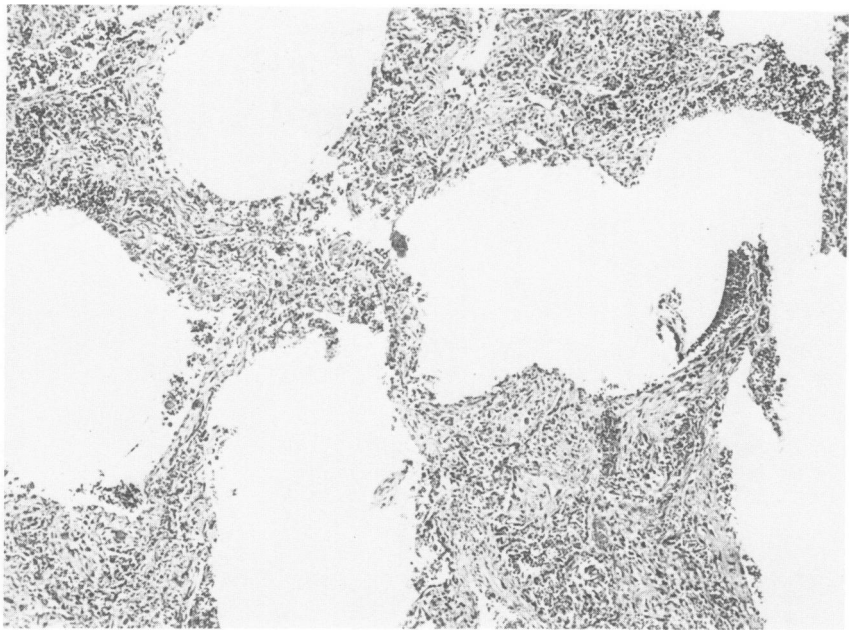

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Figure 11—A group of irregular spaces of excess size and nonanatomic distribution in a 25-year-old patient with viral pneumonitis, who died after treatment of respiratory distress for 10 days. For the last few days respiratory pressures as high as 50 cm of water had been used. These spaces clearly are bubbles of interstitial emphysema; the patient also had subcutaneous emphysema. (×50) **Figure 12**—Higher magnification of one of the spaces in Figure 11. Note the absence of consistent orientation of structures in the wall. A few strands of collagen appear to be layered adjacent to the lumen at the *lower right margin*, but elsewhere the tissue appears simply torn apart. (×125)