Light Microscopic and Ultrastructural Study of the Adverse Effects of Oxygen Therapy on the Neonate Lung

W. Robert Anderson, MD, Martha B. Strickland, MD, Shih H. Tsai, MD and John J. Haglin, MD, PhD

Alterations of lung tissues were evaluated in 74 infants with respiratory distress who received respirator therapy and high concentrations of oxygen for varying durations. Infant survival ranged from 3 hours to 135 days. Sequential pathologic changes were revealed to be an exudative reaction superimposed upon the early stages of typical hyaline membrane disease. This merged with and was eventually replaced by a reparative fibroproliferative response that was most pronounced in those infants who survived for the longest period of time. This response appeared causally related to the development of pulmonary complications of interstitial fibrosis, emphysema, obliterative bronchiolitis and cystic bronchiolectasis. Correlative ultrastructural studies disclosed generalized capillary endothelial damage in early stages of oxygen therapy, interstitial edema and alteration of alveolar cells attributed to the toxic effects of oxygen. Proliferation of type 2 alveolar cells with incorporation of hyaline membranes into septal walls was a notable feature of the reparative reaction and appeared significant in the subsequent development of interstitial fibrosis (Am J Pathol 73:327–348, 1973).

THE ADVERSE EFFECTS of high concentrations of oxygen on function and structure of the adult lung are well recognized and have been a subject of recurrent interest since 1899, when Smith first documented the toxic effects of oxygen in the experimental animal.[1] The detrimental effects of oxygen on the lung of the neonate, however, were not appreciated until recently, when Northway *et al* documented the high incidence of altered lung tissues in infants receiving prolonged oxygen administration in high concentrations for the respiratory distress syndrome.[2] They cited acute, subacute and chronic changes in various pulmonary structures resulting in the syndrome of bronchopulmonary dysplasia and attributed these changes to the manifestations of oxygen toxicity superimposed upon prolongation of the healing phase of hyaline membrane disease. Other observers have subsequently cited similar pulmonary changes in infants receiving oxygen therapy for respiratory distress.[3–5]

From the Departments of Pathology, Pediatrics, Radiology and Surgery, Hennepin County General Hospital and University of Minnesota Medical School, Minneapolis, Minn.

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Address reprint requests to Dr. W. Robert Anderson, Associate Pathologist, Hennepin County General Hospital, Fifth and Portland South, Minneapolis, MN 55415.

The sequence of pathologic changes in lung structures in relationship to the concentration and duration of oxygen therapy has been assessed in infants receiving intensive therapy for respiratory distress in this institution.[6,7] Examination of their lungs disclosed an exudative reaction, in early stages of oxygen therapy, that was superimposed upon typical hyaline membrane disease. This progressively merged with and was replaced by a reparative fibroproliferative response that occurred in those infants who survived for the longest period of time, which appeared causally related to the development of pulmonary complications of interstitial fibrosis, emphysema and cystic bronchiolectasis. These observations are extended in the present study, which evaluates by correlated light and electron microscopy the evolution of pulmonary alterations occurring in 74 infants administered oxygen for varying periods. The ultrastructural features of the early reparative process and cellular damage attributed to the toxic effects of oxygen are emphasized.

Materials and Methods

Clinical Data

The 74 infants in this study were of both sexes and, with 3 exceptions, were all premature at birth. Although birth weights ranged from 600 to 3740 g, the majority of infants weighed less than 1500 g. All manifested respiratory distress of varying severity within the first day of life. A clinical diagnosis of respiratory distress syndrome was made if the infant had increasing tachypnea, sternal and subcostal retractions, expiratory grunting, cyanosis on breathing room air, and a radiographic pattern of diffuse reticulogranularity or opacity with an air bronchogram. All infants required assisted ventilation for varying periods by means of a Bennett PR_2 respirator and received humidified mixtures of air and oxygen adjusted to maintain a blood oxygen tension (pO_2) between 50 and 100 mmHg, a pH between 7.3 and 7.4, and an arterial carbon dioxide tension (pCO_2) less than 60 mmHg. The concentration of oxygen administered thus depended upon clinical response and frequently exceeded 80% The longest duration of oxygen therapy was 135 days. Infant survival ranged from 3 hours to 135 days.

Autopsy Studies

The lungs of all infants were fixed in a buffered 10% formaldehyde solution. Some lungs, in addition, were perfused with 4% formaldehyde under a gravity pressure of 30 cm of water. Representative sections were obtained from all lobes, major bronchi and various levels of the trachea. These were paraffin-embedded and stained routinely with hematoxylin and eosin. Selected sections were also stained with the following special staining technics: PAS, Gomori's reticulin, elastica van Gieson, Gomori's trichrome, mucicarmine and alcian blue, pH 2.5. Histologic examination of these lungs disclosed progressive pulmonary lesions that evolved into three distinctive patterns (Table 1). Tissues from other viscera were examined histologically with hematoxylin and eosin.

To provide a basis for control, the records of infants who died with autopsy-confirmed hyaline membrane disease over a 3-year period prior to the establishment of a newborn intensive care unit were reviewed. Sixteen of these infants had received intermittent oxygen therapy in low concentrations ranging from 30 to 42%, in contrast to the 74 infants in this study in whom administered oxygen was invariably of high concentrations, frequently exceeding 80%. Infant birth weights of the control group varied from 810 to 3550 g, and survival ranged from 7 hours to 3 days.

Electron Microscopic Studies

Correlated electron microscopic studies of the various stages of bronchopulmonary dysplasia were performed in 8 selected autopsies in which lung tissue was sufficiently well preserved for satisfactory ultrastructural studies. Most biopsies were obtained within 30 minutes to 2 hours after death, and in no instances did the time interval exceed 4 hours. Lung biopsies thus included representative tissues from the hyaline membrane and exudative phases and from the early subacute and late reparative proliferative phases. These infants survived for 5, 21, 28, 39 and 68 hours and 13, 111 and 135 days, respectively. The biopsy samples were minced into cubes, 1 mm or less, and fixed for 2 to 4 hours at 0 to 4 C in 3% glutaraldehyde buffered with 0.1 M phosphate; they were then dehydrated in graded alcohols and embedded in Spurr media or Epon 812. Ultrathin sections were cut on a LKB Ultramicrotome III using a diamond knife. Sections were mounted on uncoated copper grids and triple stained with lead citrate and uranyl acetate. They were then examined with an electron microscope.

Results

Histopathologic examination of the lungs of infants receiving intensive therapy revealed the sequential development of pulmonary lesions that generally correlated with infant survival and duration of oxygen therapy. Detailed oxygen concentrations and durations for some individual patients included in this study have been cited previously.[6,7] Although these lesions invariably disclosed merging patterns in their evolution, three predominant stages were apparent in the development of the bronchopulmonary dysplasia syndrome. The acute stage was characterized principally by typical hyaline membrane disease followed by a superimposed exudative reaction. In the longest surviving infants who also received prolonged oxygen administration, this exudative reaction was replaced by a reparative fibroproliferative response together with associated pulmonary sequelae (Table 1).

Hyaline Membrane Disease

Thirty-four infants who had received oxygen therapy for periods ranging from 3 to 60 hours disclosed pathologic features typical of hyaline membrane disease. Twelve of these infants (35.3%) also disclosed a minimal exudative reaction that first became apparent after 22 hours of oxygen therapy. Electron microscopic studies of postmor-

Table 1—Pulmonary Pathology and Sequelae in 74 Infants Following Oxygen Therapy of Varying Duration

Predominant pulmonary reaction	No. of infants	Birth weights (g)	Gestational age (wks)	Survival time	Duration of respirator therapy	Pulmonary pathologic findings and sequelae (percent of infants)						
						Hyaline membranes	Exudative reaction	Proliferative reaction	Interstitial fibrosis	Emphysema	Obliterative bronchiolitis	Cystic bronchiolectasis
Hyaline membrane disease	34	700–3740	22–40	3 hrs–2½ days	3–60 hrs	100	35.3	—	—	—	—	—
Exudative and early reparative reaction	27	600–2700	20–40	2–8½ days	34 hrs–8½ days	77.7	100	77.7	44.4	33.3	11.1	11.1
Reparative fibroproliferative reaction	13	800–1960	25–35	5½–135 days	5½–135 days	23.0	69.2	100	84.6	76.9	38.4	23.0

tem lung tissue of 3 infants representative of this stage revealed changes similar to those previously described.[8] Hyaline membranes were comprised of amorphous material having a granular to fibrillar matrix containing occasional disintegrating and necrotic cell organelles. Fibrin strands were notably absent. Alveolar pneumocytes were frequently denuded, and hyaline membranes lay directly on the underlying exposed basement membrane of the septal wall (Figure 1). Septal capillaries generally were not altered, although occasional capillaries disclosed nonspecific edematous endothelial cell swelling, resulting in some compromise of the capillary lumen.

Exudative Reaction and Early Reparative Response

Examination of the lungs of 27 infants disclosed a predominant exudative reaction superimposed upon hyaline membrane disease. This was minimal in infants surviving less than 30 hours, but became progressively more severe and was invariably present in infants surviving at least 2 days who had received oxygen therapy in excess of 34 hours. Although there was considerable individual variation in the severity and extent of this exudative reaction, necrosis of respiratory epithelium, squamous metaplasia of tracheal and bronchial mucosa, and deposition of eosinophilic slough within bronchi and bronchioles were uniformly present. Focal replacement of ciliated epithelium by squamous metaplastic changes frequently became more prominent with time and was evident at all levels of the trachea, major and minor bronchi, and in occasional bronchioles. Many infants also disclosed an exudate within alveoli and alveolar ducts that was comprised of fibrin, edema fluid, occasional red cells and desquamated pneumocytes or alveolar macrophages (Figure 2). In some foci this was associated with necrosis of the walls of septa and alveolar ducts (Figure 3). Necrosis with effacement was also evident in some medium and small bronchi.

Although an exudative reaction was the predominant histologic pattern in this group of infants, an early transitional reparative proliferative reaction was also apparent in 21 (77.7%). Correlated ultrastructural studies of this reaction in early stages revealed a pronounced proliferation of type 2 alveolar pneumocytes in which extension of cytoplasmic processes encompassed hyaline membranes, incorporating them into septal walls, resulting in mural thickening (Figures 4 and 5). Concomitant with these changes, there was also evidence of a nonspecific cellular damage to other alveolar epithelial cells and capillary endothelium attributed to the toxic effects of high tension oxygen.

Type 2 pneumocytes disclosed marked cytoplasmic edema, blunting of microvilli and dilatation of endoplasmic reticulum. In some areas, alveolar spaces appeared virtually obliterated by swollen pneumocytes (Figure 6). Type 1 pneumocytes also disclosed cellular edema, although to lesser degrees. Capillary endothelial damage was generalized and often of striking proportions. Lumina were variably compromised, and some were virtually obliterated by marked cellular edema, resulting in distortion and disruption of the endothelial lining with the formation of bleb-like vacuoles. Some endothelial cells were detached, and cellular fragments were frequently observed free within capillary spaces (Figure 7). Interstitial edema was usually present in such areas, contributing to the septal wall thickening which was apparent by light microscopy. Hyaline membranes had been replaced in 6 infants by organization and incorporation into septal walls. Early sequelae of this reparative response were manifested by the presence of interstitial fibrosis in 12 infants (44.4%), emphysema in 9 (33.3%) and an obliterative bronchiolitis associated with cystic bronchiolectasis in 3 (11.1%).

Reparative Fibroproliferative Reaction

Transition of the exudative reaction with replacement by a reparative proliferative response was evident in the longest surviving infants who had received continuous oxygen administration which was frequently in high concentrations. A predominant proliferative pattern was present in 13 such infants who survived for 5½ to 135 days. Nine of these infants survived for 12 days or longer. Although persistent exudative reactions were usually evident, these were minimal in infants surviving at least 12 days, and hyaline membranes had disappeared in all but 3 infants. Proliferative lesions by contrast were prominent and widespread, and to varying degrees involved alveoli, walls of septa and alveolar ducts, bronchi and bronchioles. The sequential development of fibroproliferative lesions suggested that these represented reparative phenomena attributable to organization of exudative reactions. Incorporation of hyaline membranes into septal walls resulted in mural thickening, fibroblastic proliferation and deposition of collagen fibers (Figures 8 and 9). Such septa were also invariably lined by prominent hyperplastic alveolar epithelial cells.

Fibroproliferative organization of intraalveolar exudate was also a frequent finding. In such areas, the alveolar exudate was replaced by a proliferation of fibroblasts and deposition of collagen and reticulin fibers resulting in obliteration of alveolar spaces and formation of

patchy nodular scars that were distinct from an organizing pneumonia. Emphysema was usually present in these infants (76.9%) and was characterized by emphysematous alveoli alternating with coalescent alveoli and areas of fibrosis.

An obliterative bronchiolitis present in 5 infants (38.4%) was a further sequela of this reparative fibroproliferative reaction. The lungs of 3 (23.0%) of these infants also disclosed an associated cystic bronchiolectasis manifested radiographically, as honeycomb lesions, which at autopsy consisted of spherical, dumbbell and gourd-shaped cavities measuring up to several millimeters in diameter. Bronchiolar segments terminating in these ectatic cavities were variably compromised by an intraluminal fibroproliferative reaction, suggesting that cystic dilatation occurred through a valvular mechanism that impeded air exit (Figures 10 and 11).

Cor pulmonale developed in 1 infant having the longest survival (135 days) and was attributed to the severe interstitial fibrosis that was present in both lung fields. Hearts of the remaining infants were of normal size and configuration.

Although lungs from infants in the control group disclosed typical hyaline membrane disease, this generally was less extensive than that apparent in those infants receiving high concentrations of oxygen. Furthermore, there was no evidence of the superimposed exudative reaction that was invariably present in the lungs of those infants intensively treated, suggesting that oxygen therapy in high concentrations may contribute to the formation of hyaline membranes as well as the exudative reaction (Figure 12).

Discussion

The findings in this study emphasize that prolonged oxygen therapy in the neonate may result in progressive pulmonary alterations manifested in the chronic stage by interstitial fibrosis, emphysema and, in some instances, cystic bronchiolectasis. The sequence of these changes is characterized by an exudative reaction in acute stages. This is progressively organized and replaced by a reparative fibroproliferative reaction resulting in pulmonary sequelae that are invariably most pronounced in those infants of longest survival. Similar pulmonary lesions cited by others would appear to implicate prolonged oxygen therapy in high concentrations as contributing to these complications.[2-5] In Northway's study, for example, this chronic stage was invariably present in those infants receiving high tension oxy-

gen (80 to 100%) in excess of 150 hours.[2] Previous studies in this institution correlating the sequential development of pulmonary lesions with the duration and concentration of oxygen therapy are also in accordance with these observations.[6,7]

It is well recognized that oxygen in high concentrations will adversely affect pulmonary tissue of the adult[9-16] and newborn animal.[17-20] The pathogenesis of these alterations remains to be clarified, although various observations suggest that these adverse effects may be multifocal. These studies, for example, cite damage to capillaries,[21] alterations of cellular organelles in alveolar type 2 pneumocytes,[12,22,23] necrosis of bronchial and alveolar epithelium,[24] impairment of tracheal mucus flow[25] and inactivation of surfactant.[26,27] Recent ultrastructural studies[12,13,23,28] have implicated the endothelial cell as the "target cell" for the toxic effects of oxygen, resulting in generalized alveolar capillary injury, interstitial edema and subsequent alveolar exudation.

The evolution of pulmonary lesions appears essentially similar in various animal species. Capillary endothelial damage and interstitial edema occurring in the earliest stage[12] are followed by an exudative phase characterized by necrosis of alveolar epithelium, desquamation of pneumocytes, mobilization of alveolar macrophages and formation of hyaline membranes.[11,24] This exudative phase is transient and is progressively replaced by a reparative fibroproliferative response in which septa are uniformly thickened by fibroblastic proliferation and deposition of collagen and reticulin fibers. Furthermore, damaged alveoli are rapidly resurfaced by hyperplasia of granular pneumocytes.[13,28,29] An exudative and proliferative response similar to that observed experimentally may occur in the human lung, so that prolonged high-tension oxygen administration is implicated in the development of pulmonary sequelae of interstitial fibrosis, emphysema, patchy atelectasis and cystic bronchiolectasis.[2,6,22,30,31]

The potentiality of delineating the sequence of these pathologic events by ultrastructural studies is obvious, yet such observations have been infrequent and, with one exception,[22] have been limited to experimental animals. The relative sensitivity of the various septal wall components to toxic effects of oxygen has not been fully elucidated. Although several experimental studies have suggested that the initial insult may be reflected by either interstitial edema[32] or edema of type 1 alveolar pneumocytes,[33] most studies implicate the endothelial cell as the most sensitive to the adverse effects of oxygen. This results in generalized septal capillary damage with endothelial cell destruction, interstitial edema and alveolar exudation.[12,23,28] Denudation of alveolar

epithelial cells may also occur over widespread areas in the early exudative stage, but this is subsequently followed by proliferation of type 2 alveolar cells (granular pneumocytes) that resurface damaged alveoli.[16] The greater proliferative potential of the granular pneumocyte is also supported by Rosenbaum's observations in the rat lung, in which adaptive changes of cellular organelles to oxygen were more pronounced, probably indicating a greater anabolic activity.[34] Septal edema combined with alveolar cell hyperplasia results in mural thickening that may contribute to an alveolocapillary block. The proliferative stage is characterized by persistent septal edema, proliferation of septal cells and deposition of collagen and reticulin fibers, resulting in alveolar septal fibrosis.[13,28,29] It has been suggested that lymphedema due to impaired lymphatic drainage,[35] alveolar collapse with fusion [2] and proliferation of capillaries [36] may serve as stimuli for this septal fibroproliferative reaction.

The ultrastructural alterations of septal wall components in infant lungs observed in this study parallel, in most respects, those changes observed in animals administered high concentrations of oxygen and support a causal relationship. These changes were characterized by: a) alterations of alveolar lining cells in early stages, b) generalized capillary endothelial damage, c) prominent hyperplasia of type 2 alveolar pneumocytes, d) incorporation of hyaline membranes into septal walls by overgrowth of cytoplasmic extensions of type 2 pneumocytes and e) proliferation of septal cells with collagen deposition and fibrosis.

The fine structure of representative lung samples taken from infants in the acute stages of oxygen exposure were generally similar to those features described in typical hyaline membrane disease.[8] Alveolar epithelial cells were denuded in areas of hyaline membrane formation, resulting in direct apposition of these to the exposed basement membrane of the septal wall. Although septal capillaries were not significantly altered at this stage, the lumina of a few had become moderately compromised by endothelial cytoplasmic edema.

Ultrastructural alterations of alveolar epithelium, interstitial tissues and capillary endothelium generally progressed with prolongation of oxygen therapy. Pneumocyte damage characterized by cellular edema, blunting of microvilli and dilatation of endoplasmic reticulum was persistent, however, and was similar to those changes that have been attributed to toxic effects of oxygen.[22,23,33] Furthermore, early proliferative changes were usually present in infants receiving oxygen in excess of 2 days. There was hyperplasia of granular pneumocytes with

resurfacing of alveoli within 2 to 4 days after initiation of oxygen treatment. This profound proliferative activity was considered to reflect the marked regenerative capacity of the granular pneumocyte following nonspecific injury rather than the direct effect of oxygen.

Capillary endothelial damage in the exudative and early proliferative phases was prominent and generalized. Lumina were often severely compromised by marked cellular edema, frequently causing the formation of bleb-like vacuoles. These changes were indistinguishable from those that have been induced experimentally with high-tension oxygen and emphasize the sensitivity of the endothelial cell to these toxic effects. It is of interest that endothelial injury did not antedate damage to pneumocytes as has also been observed in oxygen pneumonitis in the human adult.[22] Septal edema was an associated persistent finding and probably developed secondarily to increased capillary permeability due to generalized endothelial damage.

The incorporation of hyaline membranes into septal walls in the early proliferative phase was a notable departure from the sequence of events described in studies of pulmonary oxygen toxicity in the adult mammalian lung. This organizing process was considered to be of major significance in mural thickening and subsequent septal fibrosis. Proliferation of type 2 pneumocytes with cytoplasmic extensions overgrowing hyaline masses was the principal cellular reaction in this reparative process. Incorporation of hyaline membranes into septal walls probably then served as a stimulus for proliferation of septal cells and fibroblasts, and histiocytic infiltration, as has been proposed by Spencer.[37] This reparative phenomenon is distinct from the cellular toxic effects attributed to oxygen and undoubtedly reflects host response with the prolongation of the healing phase of hyaline membrane disease. Since hyaline membrane formation is a frequent accompaniment of oxygen toxicity in the adult lung, it is probable that septal fibrosis may also develop by a similar reparative–organizing process in some instances.

The severity and extent of this proliferative response leading to advanced lesions of septal fibrosis and related sequelae generally correlated with infant survival and duration and concentration of oxygen therapy. However, prolonged oxygen administration, even in moderate concentrations, appears to adversely affect pulmonary tissues, as exemplified by 9 infants in this study. These infants, surviving from 69 hours to 83 days, developed moderate to severe proliferative lesions, yet oxygen administration usually ranged from 40 to 60% and all infants had received less than 17 hours of oxygen exceeding 80% concentration.

The present study indicates that the neonate lung is sensitive to the toxic effects of oxygen and that this may contribute significantly to the exudative phase through its adverse effects on epithelial, interstitial and capillary endothelial components of the septal wall. Subsequent reparative fibroproliferative response on part of the host frequently leads to pulmonary sequelae that are clinically significant. These observations are in accordance with the thesis that the bronchopulmonary dysplasia syndrome results from prolongation of the healing phase of hyaline membrane disease augmented by the adverse effects of oxygen on lung tissue.

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[*Illustrations follow*]

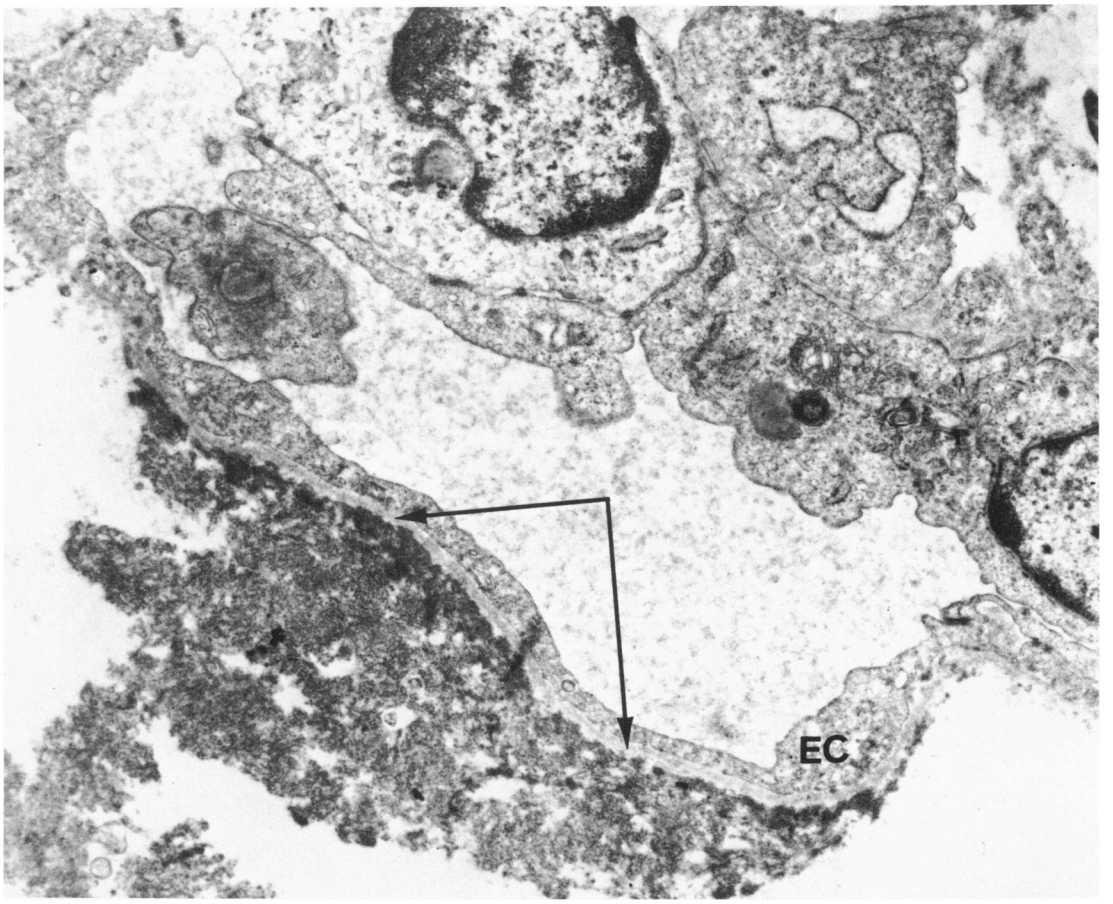

Fig 1—Electron micrograph of lung specimen from infant surviving for 28 hours who received continuous respirator therapy discloses characteristic features of hyaline membrane disease. There is denudation of alveolar epithelium with apposition of hyaline membrane material to the septal capillary basement membrane (*arrows*). The capillary lumen is patent, and the lining endothelium is unaltered (*EC*) (Uranyl acetate and lead citrate, × 9900).

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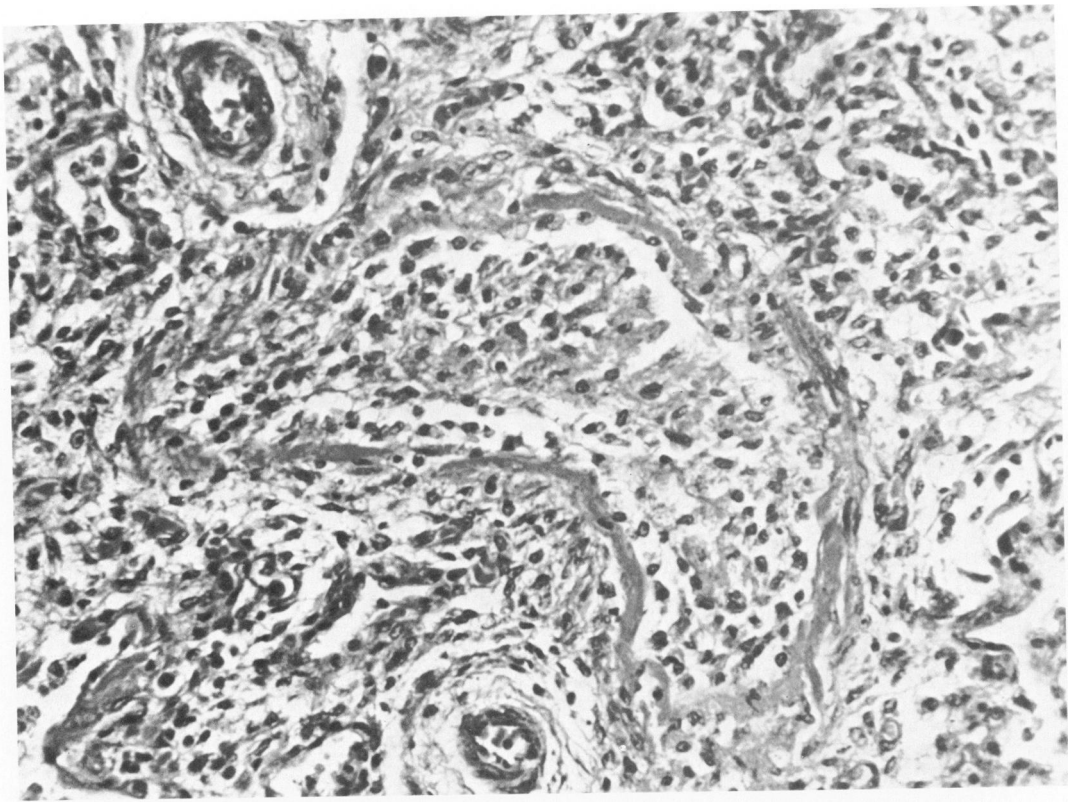

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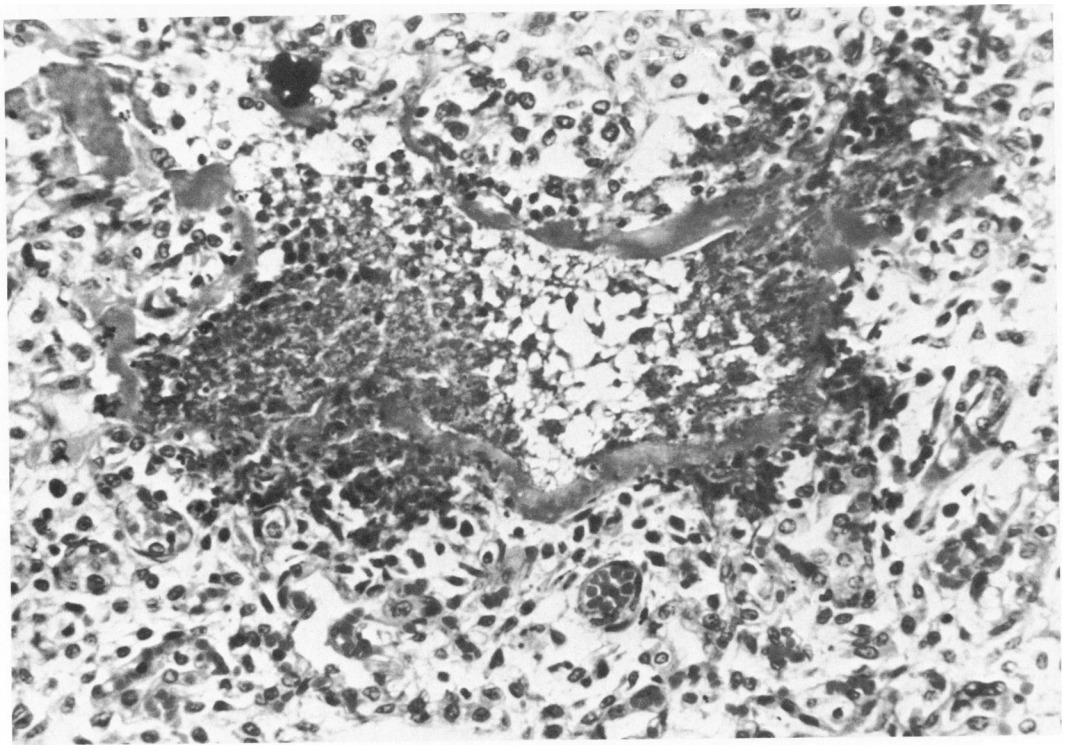
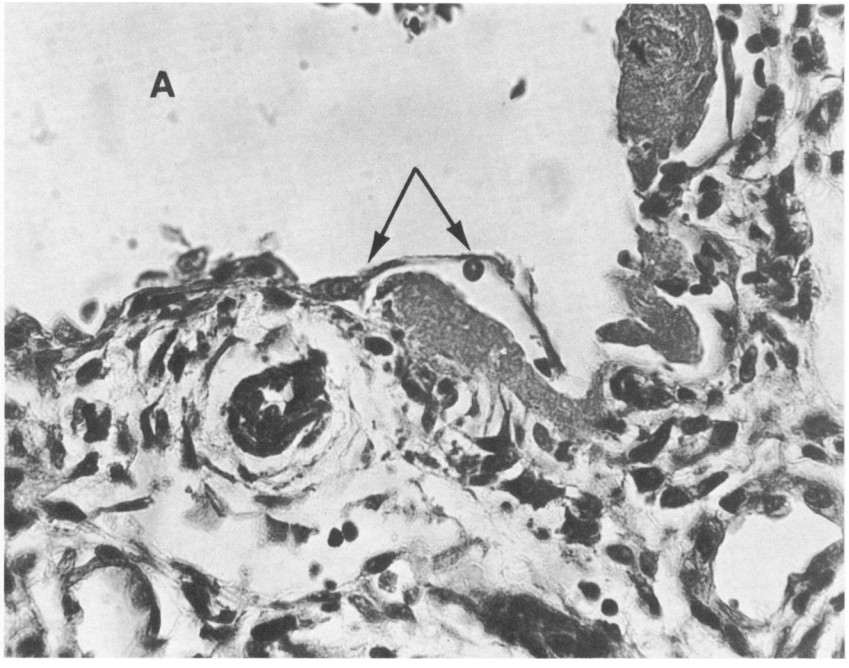


Fig 2—Exudative reaction in infant receiving high concentrations of oxygen for 106 hours is characterized by consolidation of alveolar duct by fibrin admixed with desquamated pneumocytes and alveolar macrophages. Segments of residual hyaline membranes are still apparent (H & E, × 260). **Fig 3**—A less frequent feature of the exudative reaction is focal septal wall necrosis, evident in this infant who survived 52 hours and had received oxygen administration over a 38-hour period. Residual hyaline membranes are interrupted by areas of necrosis extending into septal walls. The alveolar space is filled with fibrin and cellular debris (H & E, × 260).



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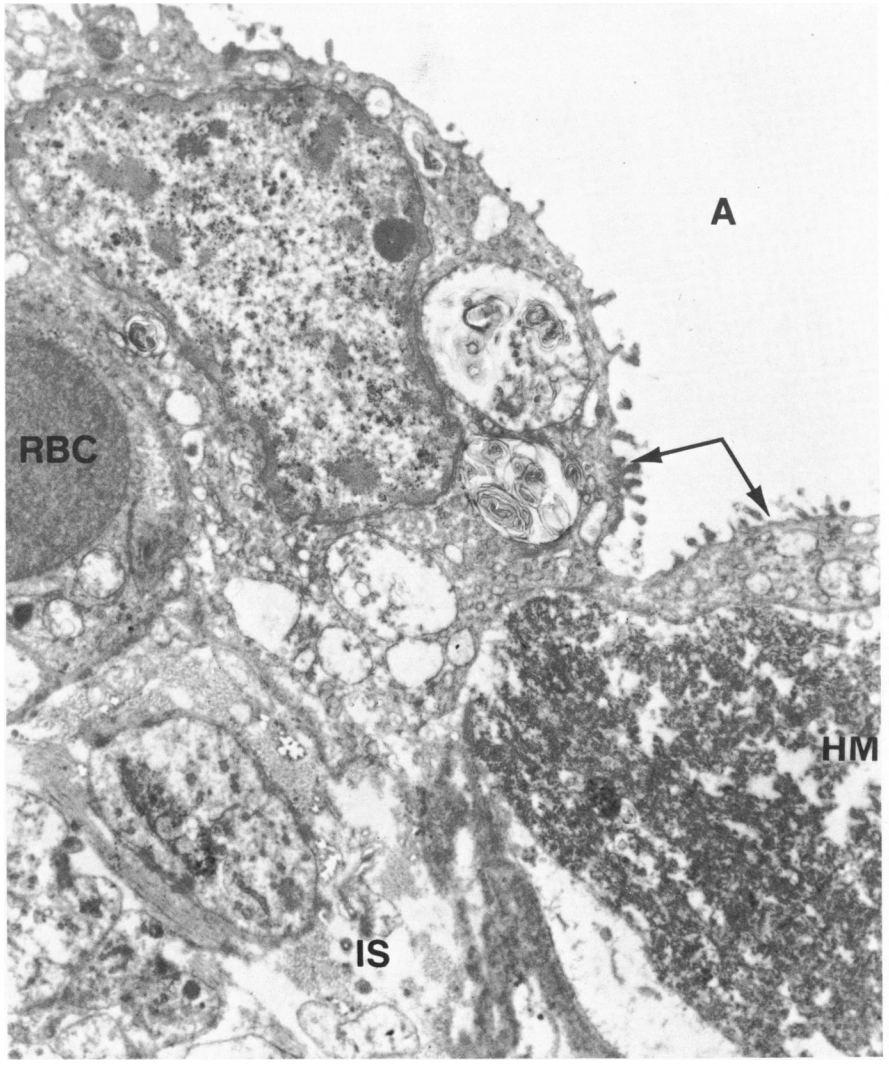

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Fig 4—Lung specimen obtained one-half hour after death in an infant administered continuous high concentrations of oxygen for 68 hours discloses early reparative changes characterized by proliferation of alveolar epithelial cells. Cytoplasmic extension (*arrows*) has virtually incorporated hyaline membrane into septal wall resulting in mural thickening. *A*=aveolar space (H & E, × 520).
Fig 5—Electron micrograph of a comparable area from the same infant lung illustrated in Figure 4 discloses cytoplasmic processes (*arrows*) arising from type 2 alveolar pneumocytes. These encompass and incorporate hyaline membrane material (*HM*) into the septal wall. A red cell (*RBC*) is identified within a septal capillary. Edema is evident within the interstitial space (*IS*). *A*= alveolar space (Uranyl acetate and lead citrate, × 7100).

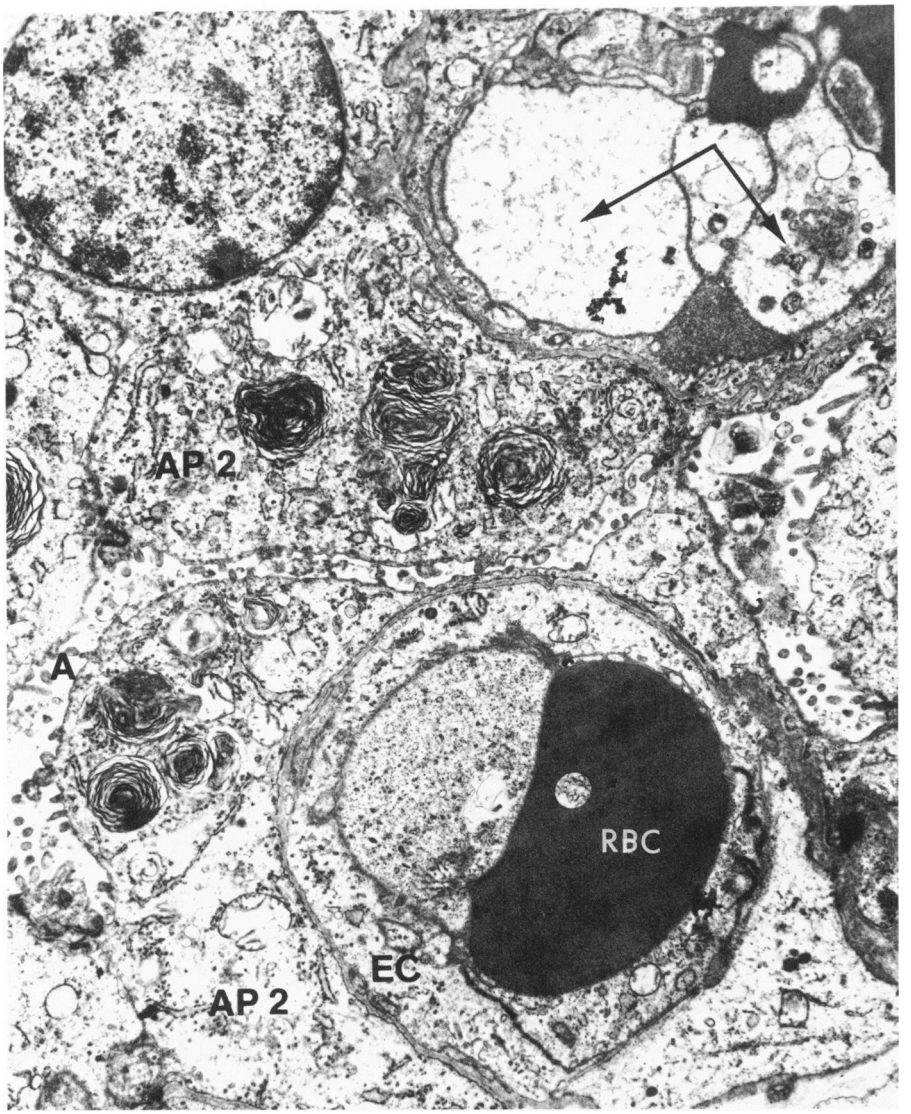

Fig 6—The alveolar space (*A*) in lung biopsy from the same infant (Figures 4, 5) is virtually obliterated by swollen type 2 alveolar pneumocytes (*AP 2*) containing characteristic lamellar inclusions. Septal capillaries disclose prominent endothelial injury concomitant with alveolar pneumocyte alterations. There is marked swelling of endothelium with edematous bleb-like protrusions (*arrows*) that compromise the capillary lumen. A capillary containing a red cell (*lower center*) also shows prominent swelling of endothelial cytoplasm (*EC*) (Uranyl acetate and lead citrate, × 7100).

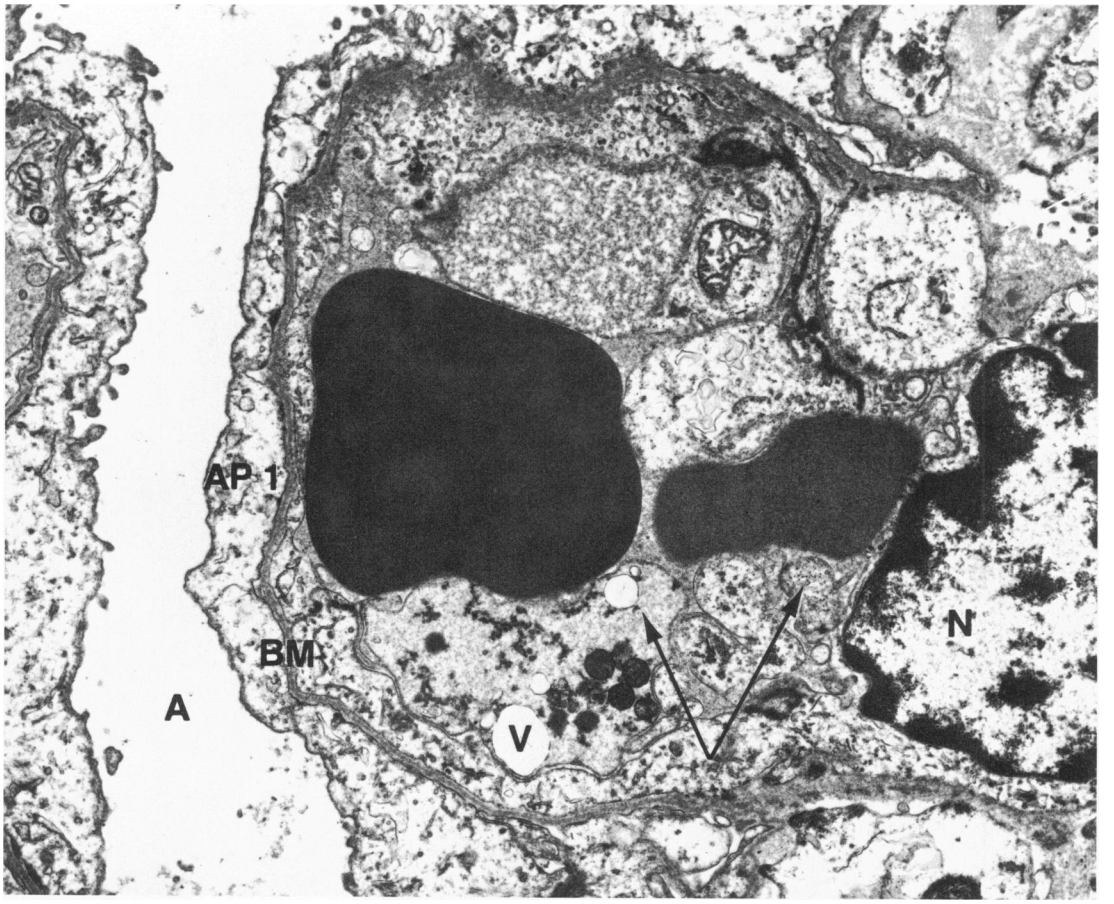

Fig 7—Severe capillary endothelial cell injury is evident in electron micrograph of lung biopsy from the same infant. Cytoplasmic edematous blebs compromise the lumen and distort circulating red cells. There is fragmentation of cytoplasm (*arrows*), dispersion of organelles and vacuolization (*V*) of cytoplasm. Generalized cellular edema of type 1 alveolar pneumocytes (*AP 1*) is also evident. The septal capillary basement membrane (*BM*) is not altered. *N*=nucleus of endothelial cell, *A*=alveolar space (Uranyl acetate and lead citrate, × 9300).

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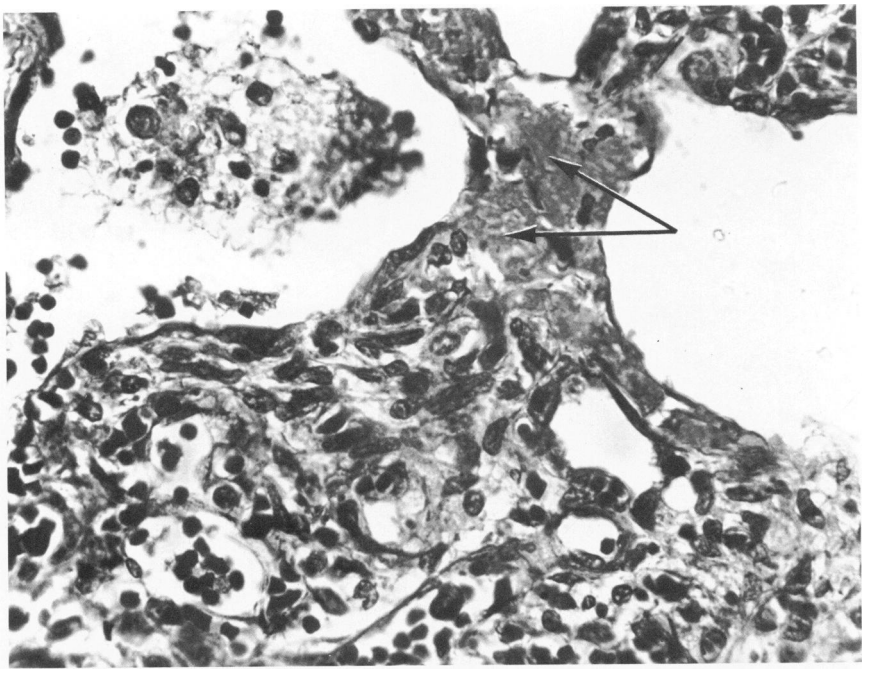

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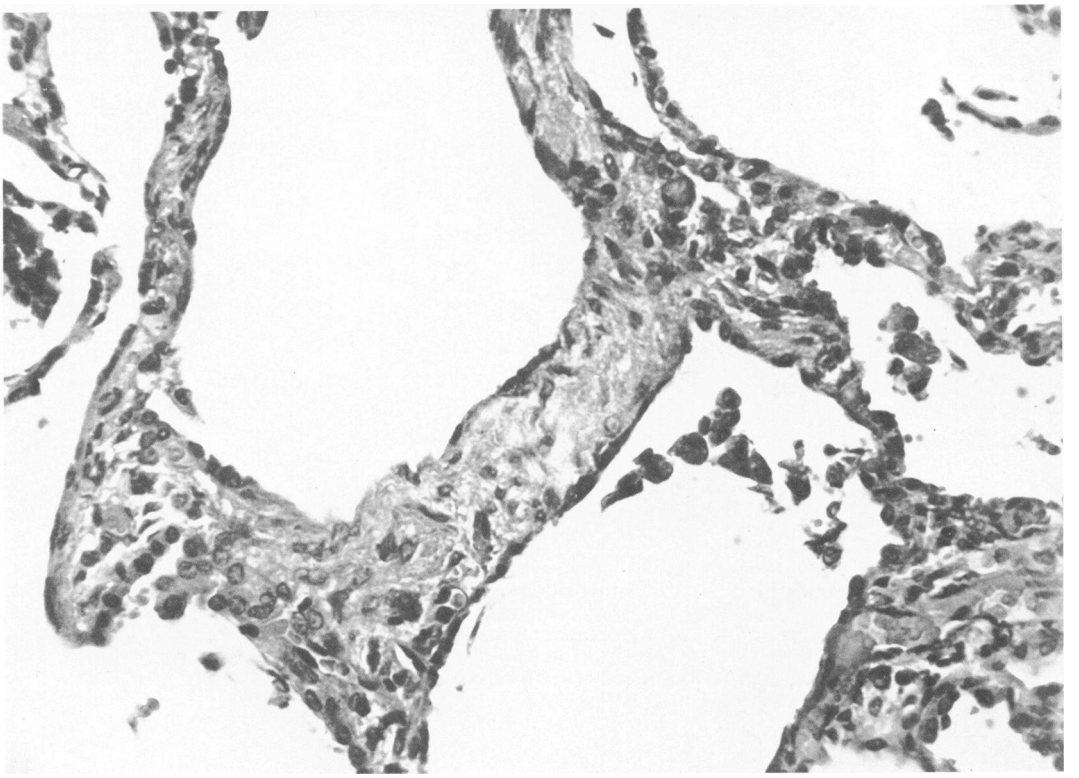
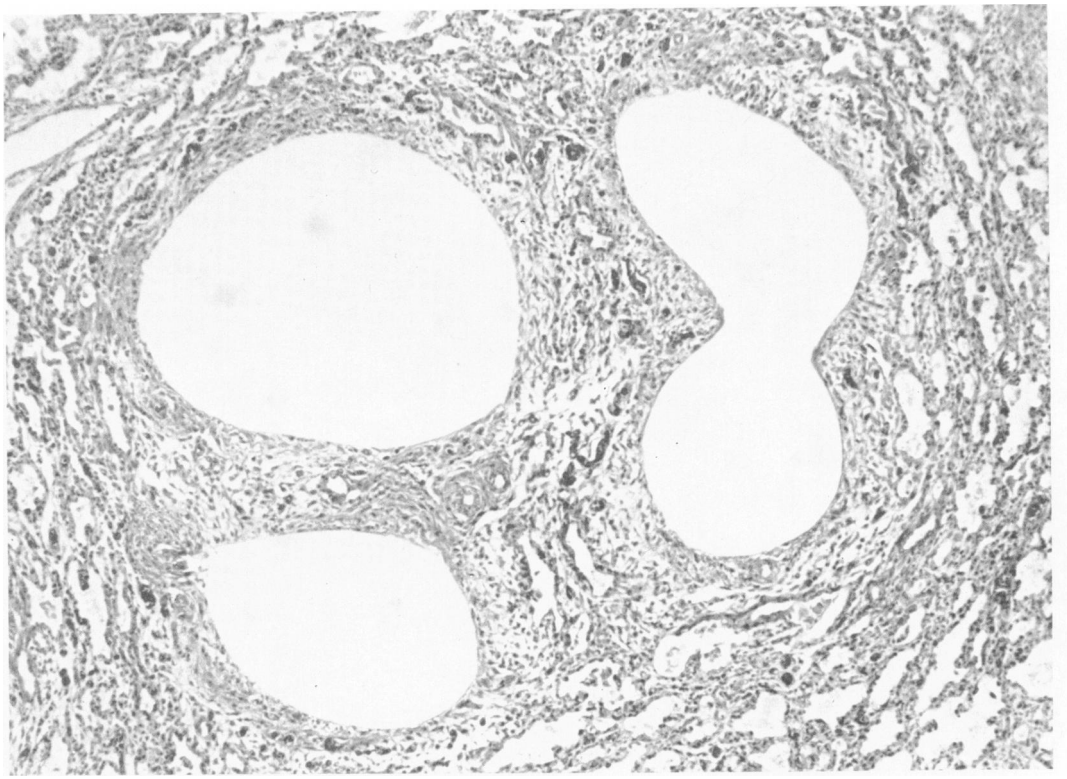


Fig 8—Incorporation of hyaline membrane material (*arrows*) into septa has resulted in mural thickening of septal walls in lungs of infant administered high concentrations of oxygen over a 122-hour period. There is an associated increased cellularity due to interstitial proliferation of fibroblasts and septal cells (H & E, × 260). **Fig 9**—The end-stage of the fibroproliferative interstitial reparative process is exemplified in this infant surviving 135 days who received continuous oxygen therapy during that period. There is marked septal fibrosis and obliteration of septal capillaries. These changes were associated with the development of emphysema, pulmonary hypertension and cor pulmonale (H & E × 260).



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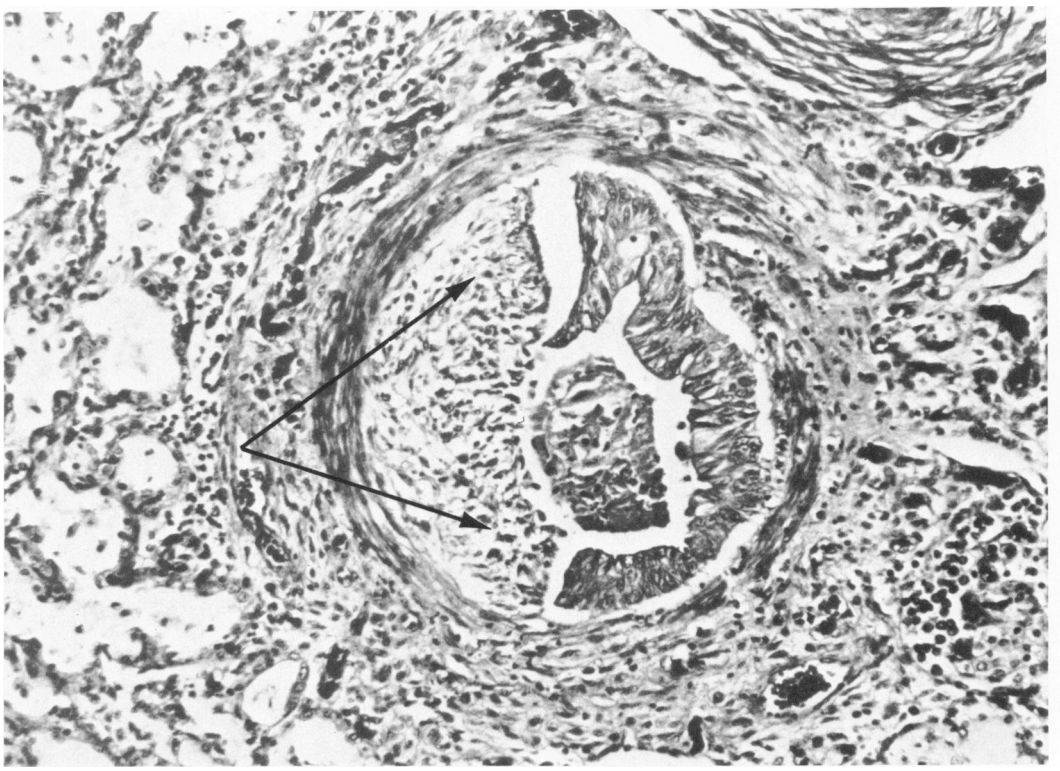

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Fig 10—Spherical and dumbbell-shaped cavities due to cystic bronchiolectasis were infrequent pulmonary complications following respirator therapy exemplified in the lungs of this infant administered high tension oxygen for 278 hours. Immediately adjacent alveoli are atelectatic (H & E, × 50). **Fig 11**—Bronchiolar segments terminating in ectatic cavities in the same infant (Figure 10) frequently disclosed an obliterative fibroproliferative process that occurred internal to the muscularis (*arrows*). Only a portion of bronchiolar mucosa remains and that has been largely replaced by metaplastic squamous epithelium. Residual bronchiolar exudate is present in the center (H & E, × 130).

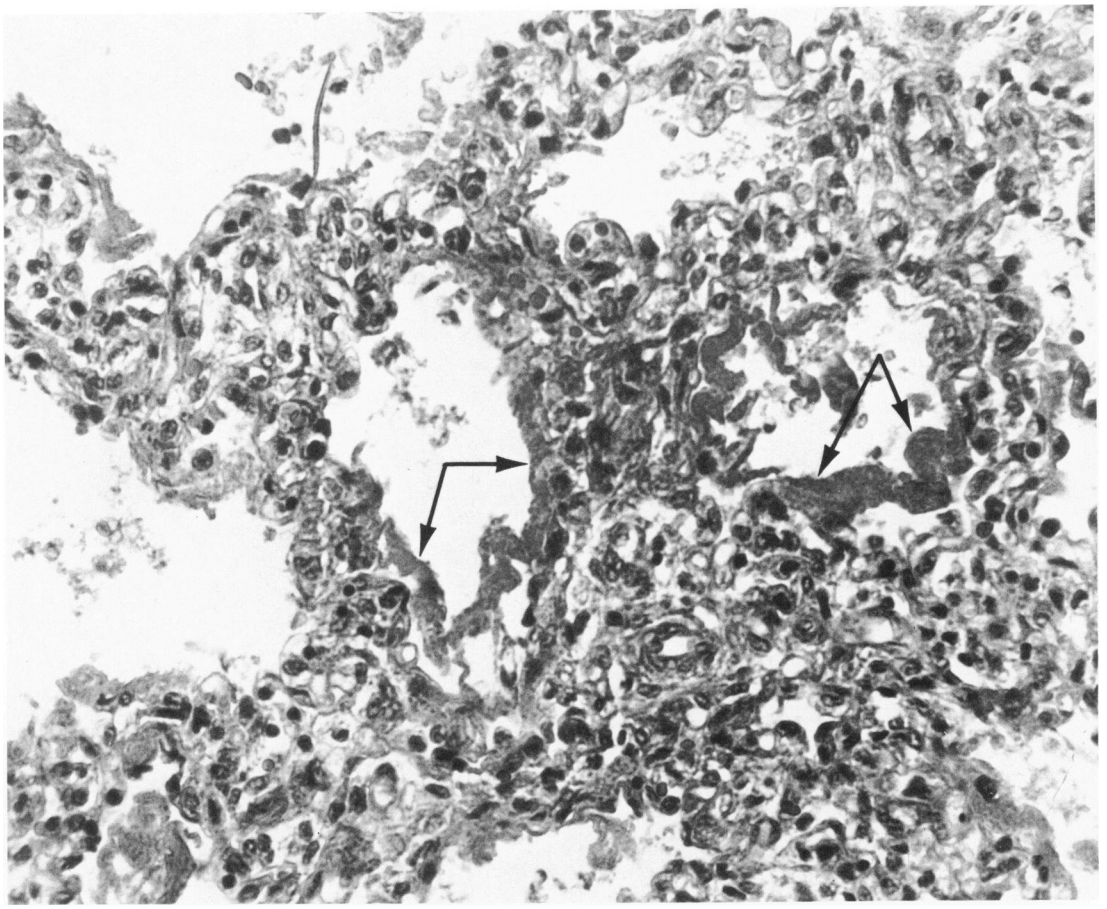

Fig 12—Lung of infant surviving 73 hours who received oxygen therapy only in low concentrations up to 36% discloses persistent hyaline membranes lining some alveoli (*arrows*). There is absence of a superimposed exudative reaction that typified those infants intensivey treated (H & E, × 260).