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Adult Hyaline Membrane Disease:

Relationship to Oxygen Therapy

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HYALINE membrane formation is a response to pulmonary injury of varying etiology. In addition to respiratory distress syndrome of the newborn, it occurs in influenza, chemical and radiation injury, ascent to high altitude, uremia and oxygen intoxication.[1, 4, 15, 26, 31] Although the cause and effect relationship between oxygen therapy and hyaline membrane formation is readily apparent in laboratory models, in humans this relationship is usually obscured by the complexity of the clinical problem which necessitated oxygen administration. In such cases, oxygen as an etiologic factor can be implicated only by exclusion.

The following report concerns six patients from Walter Reed General Hospital who were found at autopsy to have pulmonary hyaline membranes. Review of their clinical records for common factors of possible etiologic significance revealed that all six had had episodes of shock with low arterial oxygen tensions, and that all were mechanically ventilated with volume-cycled respirators which delivered oxygen enriched gas mixtures.

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Case Reports

Case 1. A 25-year-old woman was admitted for evaluation of abdominal pain and low grade fever. She had aborted a 14-week conceptus 7 weeks previously, and at that time had been treated with penicillin and tetracycline for post-abortal sepsis.

Shortly after admission she developed chills, fever and shock. Culdocentesis yielded gram negative bacilli which culture established as *Escherichia coli*. She was treated with intravenous fluids, antibiotics, and steroids. Because of respiratory difficulties which developed on the second hospital day she was given supplemental oxygen by nasal catheter and mask. On the third day a Bennett respirator was tried but was unsatisfactory. The next day an Engstrom respirator was substituted. Following cardiac arrest on the tenth hospital day a tracheostomy was performed.

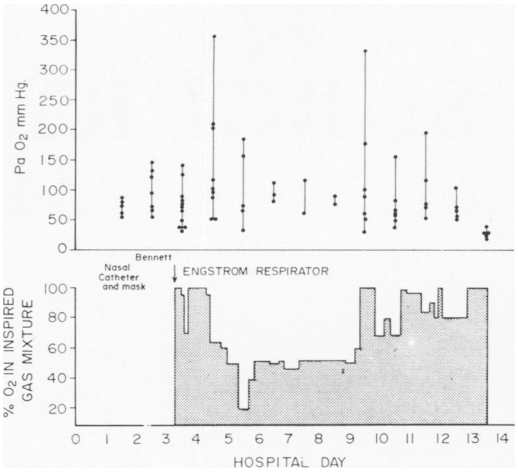

FIG. 1. Case 1.

Ventilation with oxygen-enriched gas mixtures was maintained for a total of 10 days. The patient's terminus was characterized by progressive alveolar-capillary block (Fig. 1). Increasing minute volumes and high concentrations of inspired oxygen failed to raise the PaO_2; one hour prior to death it was 22.4 mm. Hg.

Case 2. A 37-year-old pregnant woman was admitted in active labor complaining of severe headache. Her blood pressure was 260/110 mm. Hg, and the left pupil was larger than the right. During admission examination she convulsed and vomited, and remained comatose thereafter. Following an uncomplicated vaginal delivery, the convulsions stopped, and her blood pressure returned to 110/70.

The postpartum course was complicated by shock, respiratory arrest, two episodes of ventricular fibrillation, hypothermia, marked hyperglycemia (1,000 mg./100 ml.) and multiple clotting factor deficiencies. Shock was treated with blood and intravenous fluids. Ventilation was controlled with an Engstrom respirator using oxygen enriched gas mixtures. The PaO_2 progressively fell and she died on the eighth hospital day without regaining consciousness (Fig. 2).

Case 3. A 22-year-old man with a family history of pheochromocytoma was admitted to the hospital with fulminating pulmonary edema. His blood pressure was 140/110 mm. Hg. The PaO_2 shortly after admission was 37 mm. Hg. He was hemoconcentrated, acidotic and oliguric. Despite phenoxybenzamine therapy and intravenous fluids he had repeated episodes of cardiac arrest and died 41 hours after admission. Ventilation was controlled with an Engstrom respirator for 40 hours (Fig. 3).

Case 4. A 31-year-old woman was admitted with post-radiation recurrence of cervical carcinoma. While in the hospital, she developed a fever of 103° F. and shock. Laparotomy revealed a large infected tumor mass from which *E. coli* were cultured. There were two cardiac arrests during operation. Following these, the pupils became fixed and dilated. Two days after operation, a second procedure was necessary to control bleeding from vessels eroded by the tumor. Over the next 8 days her condition progressively worsened. Three renal dialyses were performed. During the last of these she developed massive intraperitoneal hemorrhage and exsanguinated.

Ventilation was controlled with an Engstrom respirator for 9 days preceding death. During most of this time the respirator delivered 100 per cent oxygen (Fig. 4).

Case 5. A 34-year-old serviceman was transferred to Walter Reed Hospital 24 hours after an automobile accident in which he sustained a closed head injury. Upon admission he was comatose with decerebrate posturing. Examination and diagnostic procedures indicated a midbrain injury. A tracheostomy was performed to prevent aspiration of gastric contents. On the fifth hospital day gastrointestinal bleeding occurred and two units of whole blood were administered. On the tenth day bleeding recurred. Two units of blood per day were required over the next 5 days to maintain a normal hematocrit. On the fifteenth day the central venous pressure became elevated and cyanosis

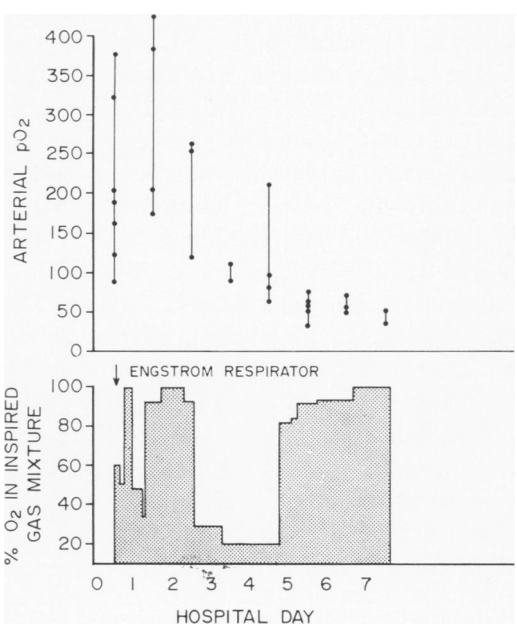

FIG. 2. Case 2.

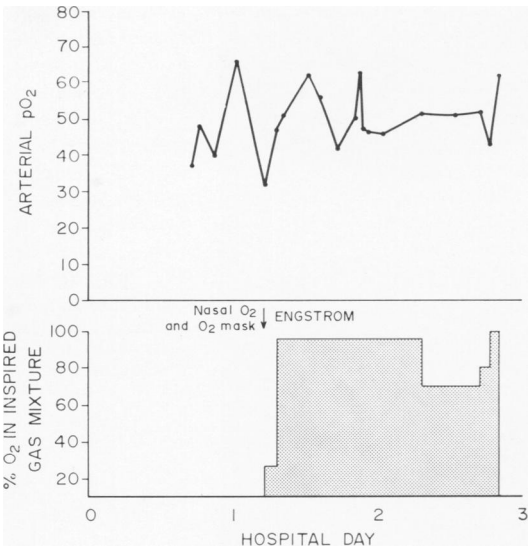

FIG. 3. Case 3.

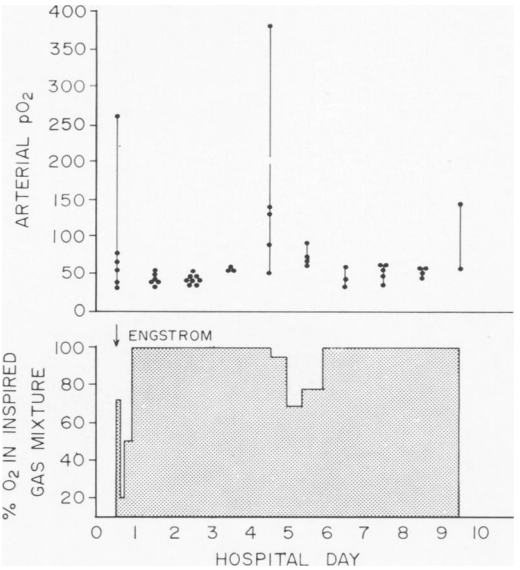

FIG. 4. Case 4.

developed. Positive pressure ventilation was begun by using a Bennett respirator which delivered 100 per cent oxygen. The following day this was replaced with an Engstrom respirator. He died 21 hours later. Mechanical ventilation was performed for 56 hours (Fig. 5).

Case 6. An 8-year-old girl was admitted for correction of Tetralogy of Fallot. At age 3 she underwent a Taussig-Blalock procedure, but cyanosis and dyspnea had returned and was incapacitating. The operation lasted 5½ hours, and the total time on cardiopulmonary bypass was 104 minutes. When she returned to the recovery room her lungs were well aerated. Respiratory difficulties began on the third postoperative day, and an intermittent positive pressure respirator was used to facilitate ventilation. On the fourth postoperative day pulmonary edema developed. The following day a tracheostomy was performed and ventilations were assisted mechanically. The PaO_2 rose from 55 to 110 mm. Hg.

Then 10 days preceding her death were complicated by disseminated intravascular clotting, acute renal failure and progressive cyanosis. Several attempts to wean her from the respirator were unsuccessful. The PaO_2 progressively fell. At the time of her death she was being ventilated with 15 liters per minute of 100 per cent oxygen.

Pathologic Findings

Changes were similar in all cases except for degrees of severity. Prosectors described the lungs as "beefy," "carnacious" and "liver like." The lungs failed to collapse when the thoracic cage was opened, were relatively airless, and oozed frothy fluid from cut surfaces. Light microscopic

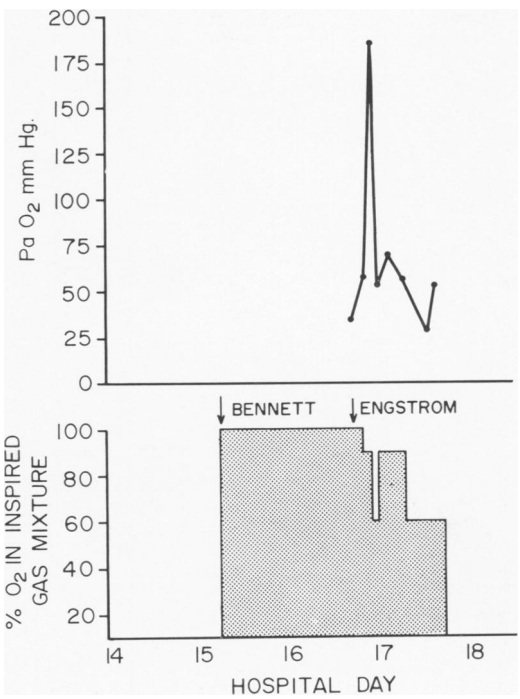

FIG. 5. Case 5.

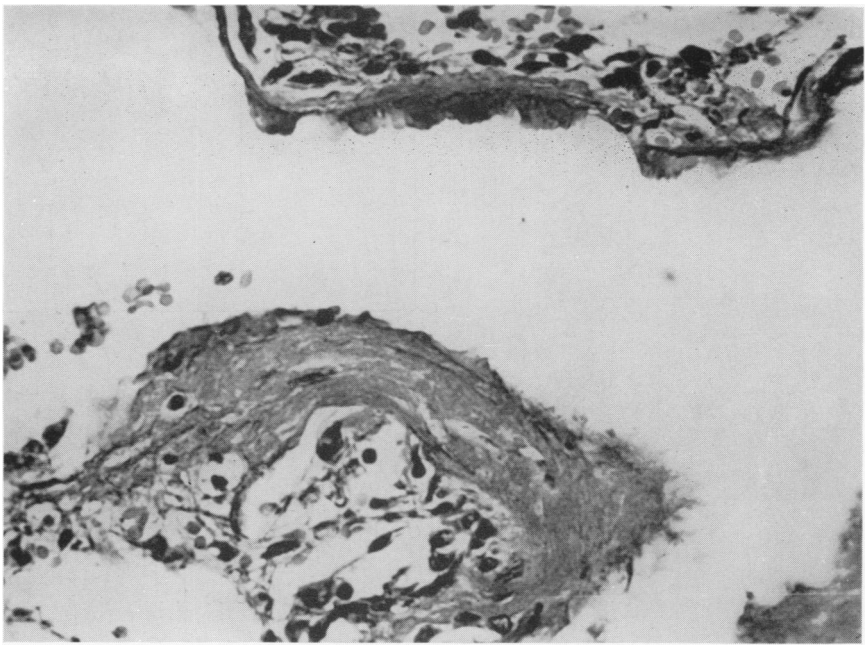

FIG. 6. Hyaline membrane showing its laminated structure.

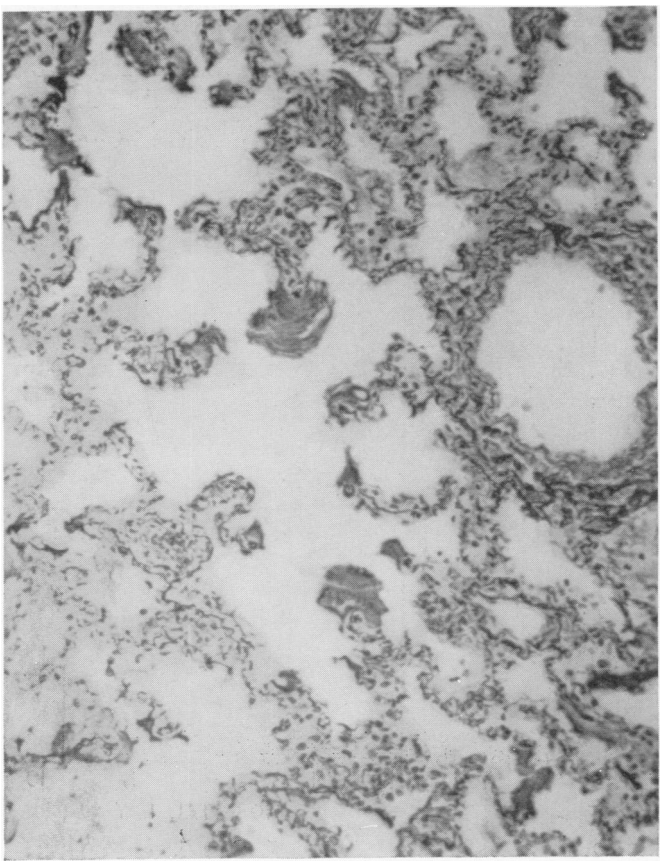

FIG. 7. Prominence of hyaline deposits at junctions of alveolar sacs and alveolar ducts.

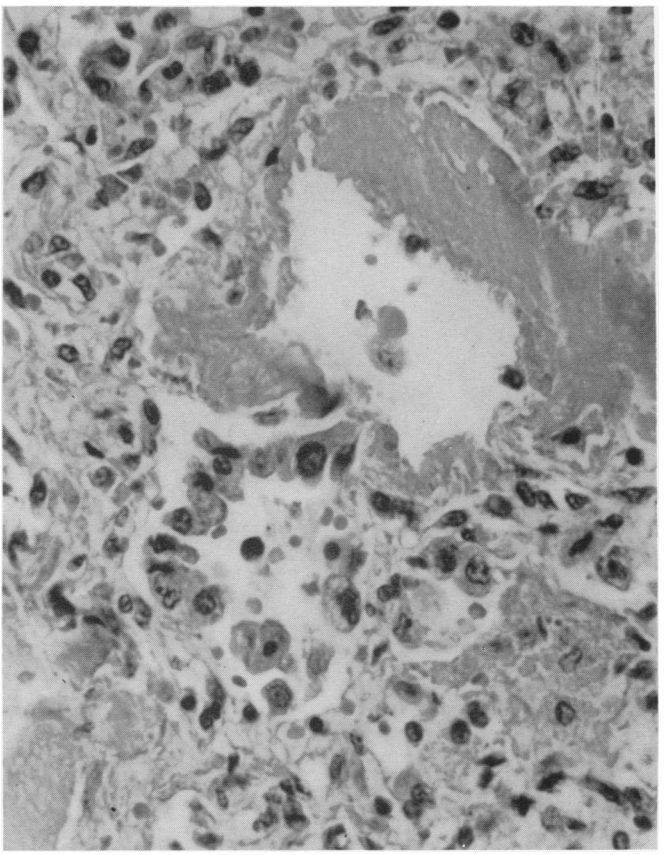

FIG. 8. Upper alveolus is coated with a hyaline membrane. Lining cells are absent. Lower alveolus is lined by swollen partially detached alveolar cells. Hyaline membrane is absent.

examination showed five basic alterations. The most outstanding of these was the dense hyaline membranes which coated alveolar sacs, alveolar ducts and the smaller bronchioles. Lining cells were rarely present between the hyaline membrane and the alveolar wall, which suggests that the cells were sloughed prior to membrane formation and perhaps contributed to the membrane structure. Membranes were laminated and were most prominent at the junction of the alveolar ducts with alveolar sacs (Figs. 6, 7). The significance of this distribution is not apparent.

Swelling of the lining cells and prominence of nuclei was observed in many alveoli which lacked hyaline membranes. Some of these hypertrophied cells were partially or completely detached from the basement membrane (Fig. 8). Rarely was a mitotic figure seen. Histochemical procedures did not permit differentiation of surfactant producing from *non*surfactant producing lining cells.

Interstitial edema was prominent in all six cases and was accompanied by proliferation of interstitial fibroblasts in all but Cases 3 and 5 in which death occurred after 40 and 56 hours of respirator therapy. Pulmonary edema and intra-alveolar hemorrhage were also present in each case. The latter may have resulted from overdistention of alveoli by mechanical ventilation or may be a direct effect of oxygen.[24]

In the two patients with the most advanced lesions alveolar collapse was prominent and numerous hyaline laden macrophages were present within alveoli (Figs. 9 and 10).

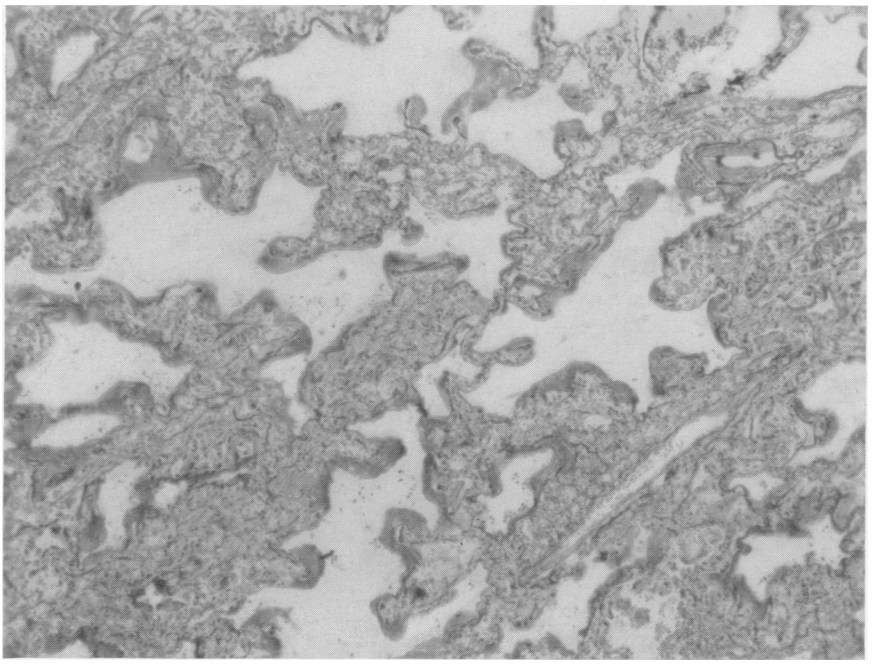

FIG. 9. Advanced lesion. Hyaline membranes, alveolar collapse, and marked interstitial inflammatory and proliferative response.

Discussion

Changes in the lungs following prolonged shock include pulmonary edema, intra-alveolar hemorrhage, perivascular hemorrhage, congestive atelectasis and microthrombosis.[12, 16, 21, 25] Hyaline membranes have not been described unless oxygen therapy has been administered. Volume cycled respirators such as the Engstrom produce a number of pathologic changes, but these may result from high concentrations of oxygen in the inspired gas mixtures rather than the effects of mechanical ventilation. Oxygen, in the absence of shock or mechanical ventilation, does produce pulmonary lesions in experimental animals similar to those described in the above cases. Since no other predisposing conditions to the development of hyaline membrane were known to have existed, it appears likely that oxygen was the major, if not the only etiologic factor.

Pulmonary oxygen intoxication begins insidiously with changes in physiologic parameters preceding the onset of symptoms by several hours. The latent interval is inversely proportional to the partial pressure of inspired oxygen and a minimum of 300 mm. Hg oxygen is required to produce damage.[27] At one atmosphere volunteers breathing 78 to 88% oxygen develop symptoms in 12 to 24 hours[6, 19] while at two atmospheres pure-oxygen induces symptoms in 3 to 6 hours and physiologic changes in less than one.[5]

The time sequence for the development of anatomic lesions has been studied in several species excluding man.[3, 4, 17, 23, 32] In all species studied the lesion evolves similarly, although the time required is quite variable. The earliest changes are edema, congestion of alveolar septae and disruption of capillary endothelium.[17, 32] Pulmonary edema follows accompanied by swelling and necrosis of alveolar and bronchiolar epithelium.[3, 32] As the damaged epithelial cells are sloughed, the hyaline membrane laminates on the denuded surfaces. In those alveoli which are less severely affected there is proliferation of alveolar lining cells.[17]

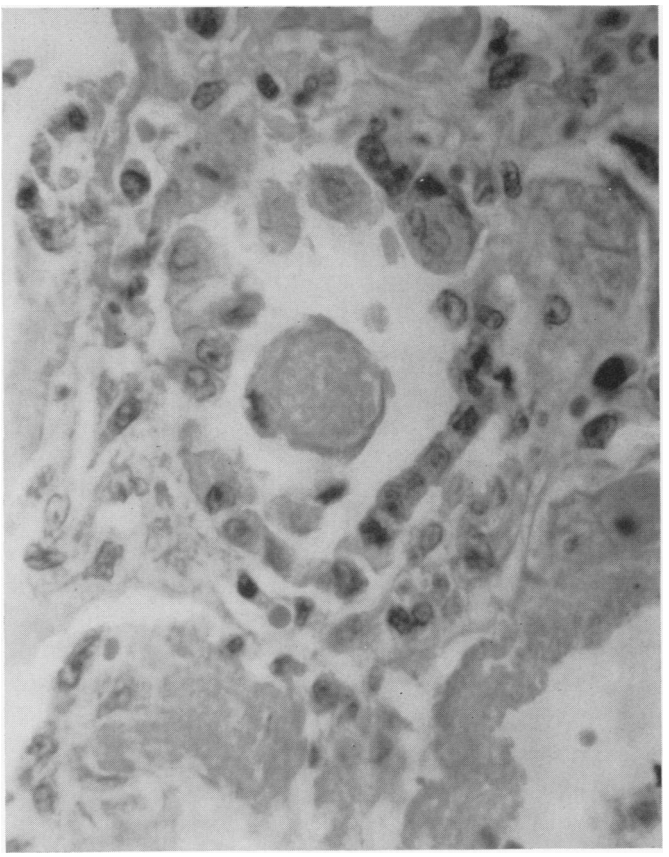

FIG. 10. Macrophage with ingested hyaline.

Capillary proliferation [20] and vascular spasm [33] have been reported by different investigators as components of oxygen intoxication but were not apparent in our material. Atelectasis [32] which has also been described, was present in the two cases which showed the most severe lesions.

Hyaline membranes are the most conspicuous feature of pulmonary oxygen intoxication but are not pathognomic.[1, 4, 6, 15, 26, 31] The membranes are said to consist of fibrin, fat, hemoglobin, basement membrane material and mucus.[7, 9, 10, 29, 30] The mean duration of therapy preceding development depends upon numerous variables including species, partial pressure of inspired oxygen, temperature, and therapy prior to exposure to oxygen.[4, 5, 6, 14, 19] There is insufficient data to generalize about the duration of therapy which will produce membranes in humans, but they can occur after as little as 40 hours (Case 3).

Recovery from oxygen intoxication after development of hyaline membranes is uncommon, but if life can be sustained the membranes will be removed by phagocytosis (Fig. 10). The end state lesion has yet to be defined, but the prominence of reactive fibroplasia in subacute stages suggests that interstitial fibrosis and emphysema may represent healed lesions of acute oxygen intoxication. Experimental studies are currently in progress to test this hypothesis.

The mechanism of oxygen intoxication is only partially understood. At the molecular level excessive oxygen inactivates sulfhydryl dependent dehydrogenases [22] interferes with the formation of high energy

phosphate bonds,[13] inhibits proteolysis,[22] stimulates histamine release,[11] and decreases pulmonary surfactant.[8] How inactivation of surfactant contributes to membrane formation is not known. Certainly the latter two processes are inter-related, for in respiratory distress syndrome of the newborn surfactant activity is almost totally lacking, and the lungs contain characteristic hyaline membranes.[2] Attempts to inactivate surfactant by oxygen *in vitro* have been unsuccessful, although inactivation occurs readily *in vivo*. Obviously, therefore, the effects of oxygen upon surfactant are mediated indirectly.

Electron microscopic studies from this laboratory [28] and elsewhere [17] show marked swelling of mitochondria in altered alveolar cells. Whether this is a manifestation of oxygen intoxication or a nonspecific degenerative change is not known, but it probably represents the morphologic counterpart of defective formation of high energy phosphate bonds.[13]

Alveolar lining cells can be differentiated into two types by electron microscopy: those that produce surfactant, and those that do not. The former can be identified by the presence of specific organelles in their cytoplasm. By light microscopy it was not possible to determine which type the damaged alveolar cells were; but by electron microscopy, it was clearly demonstrated that both variety of cells sustained damage. Thus it is likely that the decrease in pulmonary surfactant results from damage to the cells which produce it, rather than to a biochemical interference in its synthesis.

From the clinical standpoint oxygen intoxication represents an iatrogenic calamity which is better prevented than treated. Once alveolar-capillary block is initiated the process is self perpetuating, as it requires increased concentrations and volumes of oxygen to maintain the PaO_2. This in turn produces further lung damage, hypoxemia, and eventually death. The rapidity with which hyaline membranes can form is illustrated by Cases 3 and 5 in which membranes developed after 40 and 56 hours of oxygen therapy. Both patients had pulmonary edema at the inception of therapy and it is likely that this hastened the development of membranes. Of the remaining patients, none had pulmonary edema at the time oxygen therapy was instituted, and the latent interval preceding the development of alveolar capillary block (the clinical counterpart of hyaline membranes) was considerably longer.

Summary

Six cases of pulmonary hyaline membrane diseases are presented which are thought to have resulted from oxygen intoxication. Pathologic findings included pulmonary hemorrhage, interstitial edema and fibrosis, swollen alveolar lining cells and characteristic hyaline membranes. Resolution of the lesions occurs by phagocytosis of hyaline together with intense interstitial fibroplasia.

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