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Lung disease in the very immature neonate: radiographic and microscopic correlation* **

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Abstract. Radiographic-pathologic correlation of pulmonary patterns has not been performed in very small preterm infants below 28 weeks of gestation. The radiologic findings of linear intersititial densities or generalized airspace opacity coincided with histologic changes of edema and hemorrhage and indicate that this is the most frequent abnormality producing radiographic pulmonary opacification in infants of 23-27 weeks gestation. On occasion, parenchymal immaturity alone results in lung opacification, reflecting the established interpretation of diffuse atelecatasis as the histologic-radiographic finding in respiratory distress syndrome.

A clinical diagnosis of respiratory distress syndrome (RDS) is made according to specific respiratory criteria noted on physical examination. They include tachypnea, expiratory grunting, cyanosis, and retractions. The pulmonary abnormalities identified radiographically are very difficult to categorize. This study was performed to determine the specificity of pulmonary abnormalities identified on the chest radiographs of very small preterm infants (23-27 weeks gestation). Infant lungs, considered radiographically as showing RDS, initially may be well expanded but in the ensuing 6-12 hours of life develop a pattern of fine reticular, coarse linear, or homogeneous confluent densities with well visualized air bronchograms. The radiographic pulmonary findings may be as nonspecific indicators of the underlying pulmonary pathology as is the clinical syndrome of RDS. We have correlated the microscopic pulmonary pathology with the radiographic appearance of the lungs in infants who died with a diagnosis of RDS. This is to clarify the recognized patterns of pulmonary disease in immature lungs and evaluate the radiologist's ability to accurately diagnose the underlying lung disease.

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Previous correlative studies of more mature infants (above 30 weeks of gestation) have generally shown atelectasis as the pulmonary abnormality accounting for radiologic lung densities [1-5]. Edema, hemorrhage, and pneumonia were less often identified. This study incorporates less mature infants.

Materials and methods

The babies included in this study ranged in gestational age from 23-27 weeks (mean 24.2 weeks), in birth weight from 500-1525 grams (mean 726 grams), and survival time from eight hours to seven days (mean 3.1 days). Infants surviving longer than seven days were excluded from the study to avoid pulmonary artifact produced by developing bronchopulmonary dysplasia or multifaceted lung injury related to mechanical ventilation.

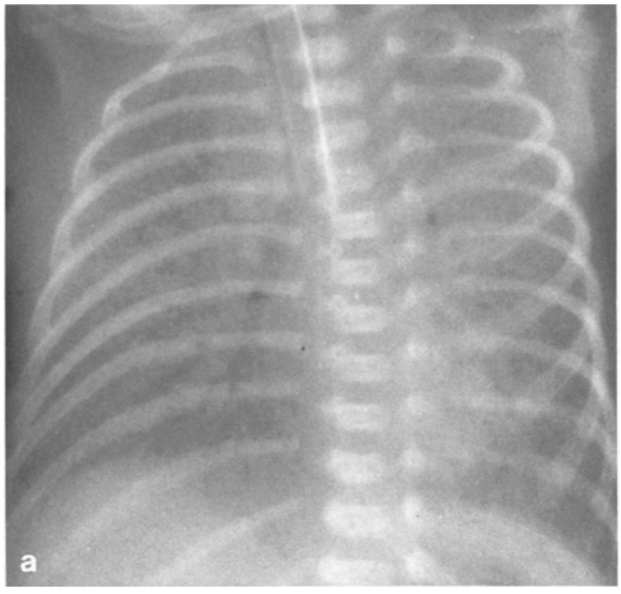
The microscopic appearance of the lungs of 26 preterm infants (19 males, 7 females) was reviewed to determine the type and the severity of parenchymal changes present. The cases were retrospectively ascertained and lung inflation was the routine fixation method in use. Lung inflation was by intratracheal instillation of 10% buffered formalin via gravity. Instillation was stopped after maximal lung distension was reached. Often the very small lungs would not expand much. The high incidence of identifiable alveolar hemorrhage indicates that there was no significant washout of air sac contents.

All infants included had an initial radiograph obtained between 30 minutes and four hours after birth and a chest radiograph within less than two hours of the time of death.

The radiographs were examined and evaluated by two radiologists without knowledge of the clinical status, the microscopic pathology, or background information. Radiologic assessment included a description of interstitial or airspace disease, pleural changes, visualization and appearance of air bronchograms, degree of parenchymal opacification, and degree of inflation. The microscopic examination, done by a pathologist and a senior medical student, included evaluation of the stage of lung maturation, presence of hyaline membranes, and observation of specific pulmonary interstitial and air sac abnormalities. The patient records were assessed for infant maturity, pertinent perinatal information, details of ventilator and oxygen use, and the infant's blood gas determinations.

Representative case material

Case 1. A male twin, weighing 650 gm at 25 weeks of gestation, was delivered of a febrile mother with chorioamnionitis. The infant survived 24 hours. During this time he required inspiratory oxygen concentrations of 100% and constant mechanical ventilation with high pressures. The initial radiograph at 2 hours was nor-



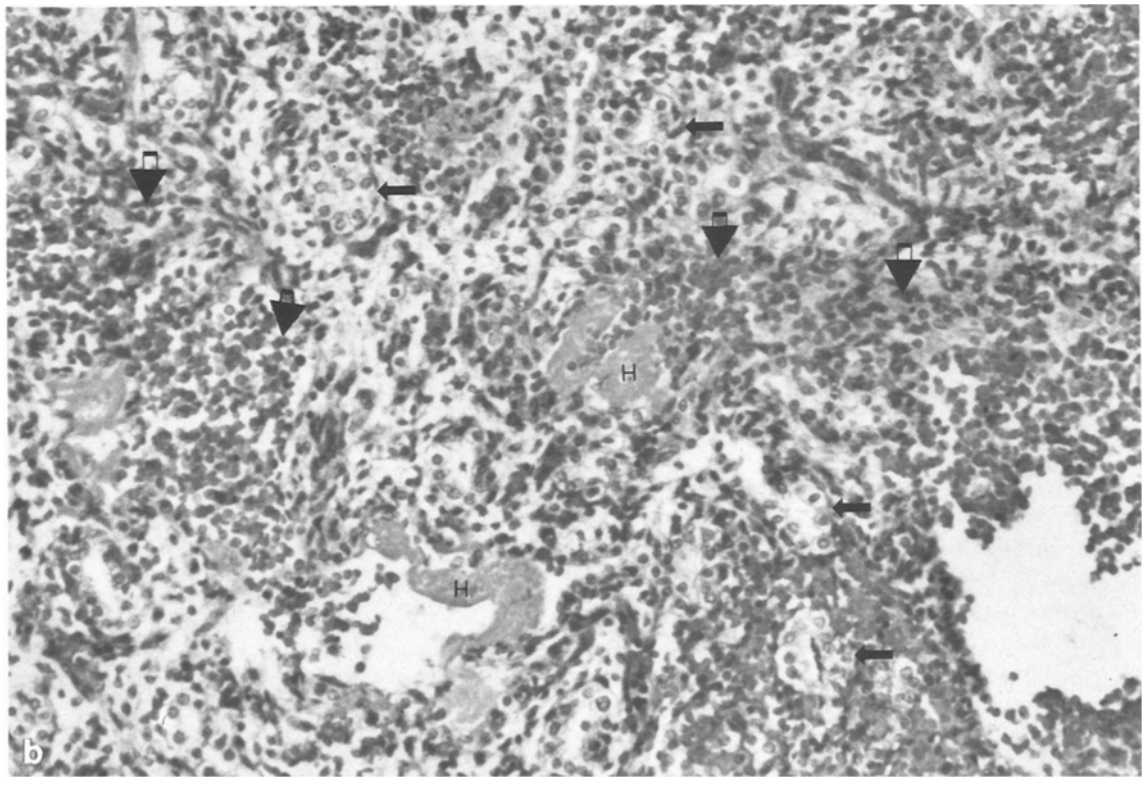


Fig. 1. a Case 1 at 23 hours shows extensive lung parenchymal opacification. **b** Early canalicular lung development (arrows indicate residual cuboidal epithelium) with diffuse interstitial and airspace hemorrhage (large arrow). Hyaline membranes are present in bronchioles. (Photo 9X)

mal, but at 23 hours of age the lungs showed homogeneous opacification with extensive air bronchograms (Fig. 1 a).

Microscopic examination of the lungs showed early canalicular stage parenchymal development, severe hyaline membranes in airspaces, and hemorrhage filling almost all of the airspaces visible (Fig. 1 b).

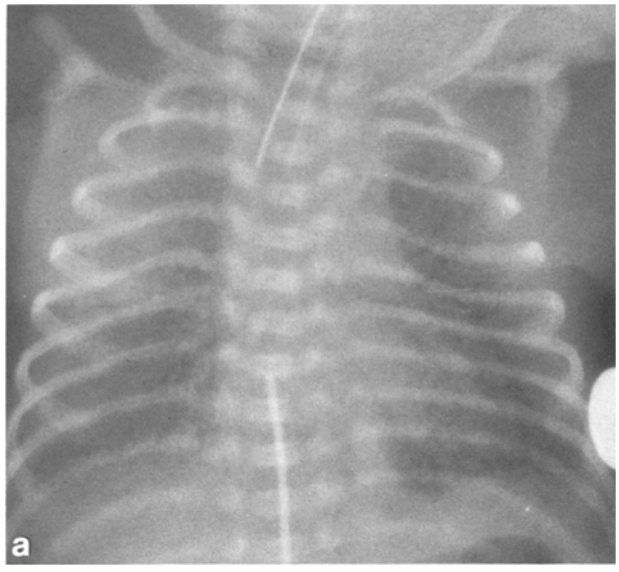
Diagnosis: Diffuse pulmonary hemorrhage.

Case 2. This male infant is the first of twins born at 25 weeks of gestation and weighing 854 grams. The mother's membranes had ruptured three weeks before delivery. The infant received 100% inspired oxygen concentration and was maintained on high mechanical respirator settings of 57 mm Hg and 6.0 mm Hg, inspiratory and expiratory pressures respectively. Initial chest radiograph at 30 minutes of age showed interstitial density and peripheral mild alveolar opacification of the lungs, poor aeration, and air bronchograms. Examination one hour before death on day 2 was unchanged (Fig. 2 a).

Histologic examination of the lung showed immaturity (early canalicular stage development), severe hyaline membranes lining bronchioles, and diffuse interstitial changes of severe edema and hemorrhage (Fig. 2 b).

Diagnosis: Interstitial pulmonary edema and hemorrhage.

Case 3. An infant girl, a 620 gram product of a 24 week gestation survived five days. The mother had developed preeclampsia two weeks before delivery necessitating early delivery. The infant was maintained on inspired oxygen concentrations from 50 to 78%



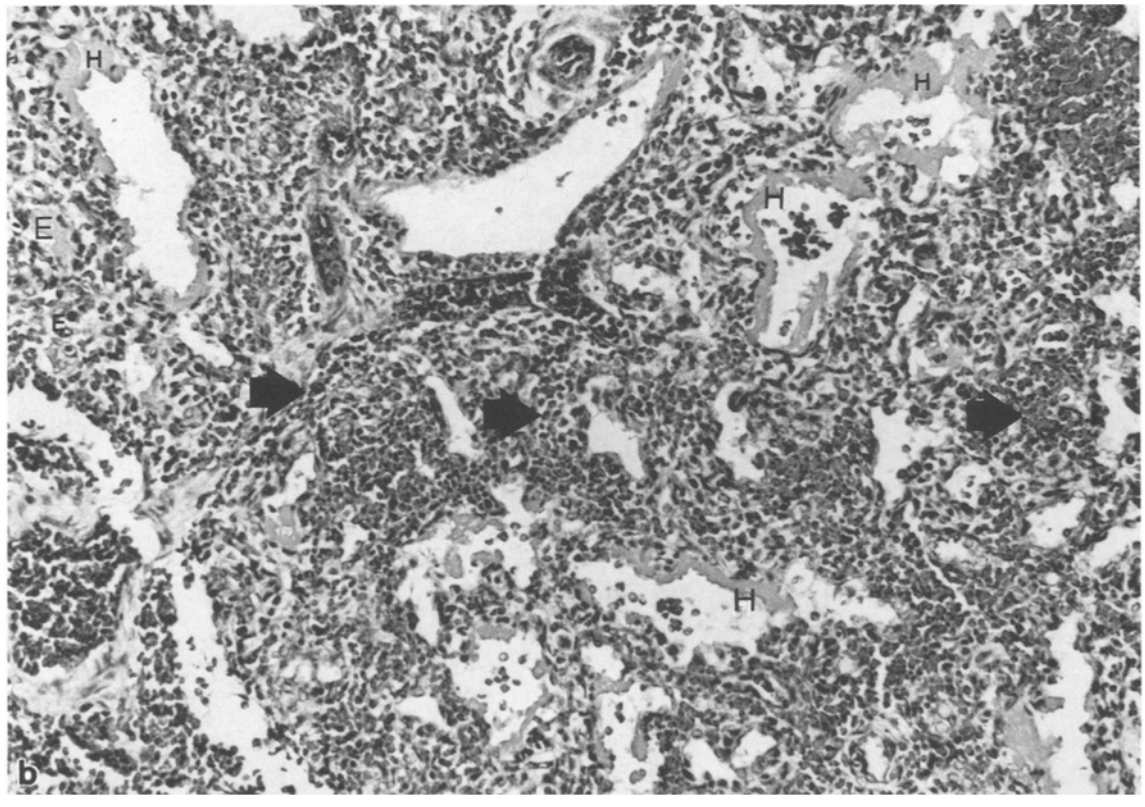


Fig. 2. a Case 2 shows diffuse coarse interstitial streaks of parenchymal density bilaterally and early airspace consolidation. **b** Hyaline membranes (H) line the bronchioles which still contain air. Diffuse interstitial hemorrhage (dark arrowhead) and edema (E) result in consolidation lung parenchyma. (Photo 2.3X)

with inspiratory pressure of approximately 20 mm Hg and expiratory pressure of 3 mm Hg. Initial radiographs (at 2 and 4 hours) appeared normal but by 18 hours there was development of diffuse, very dense interstitial streaks, central alveolar densities and air bronchograms (Fig. 3 a, b).

Histologic examination showed early alveolar lung development, the presence of severe hyaline membranes, moderate airspace hemorrhage, interstitial edema, and early interstitial fibrosis (Fig. 3 c).

Diagnosis: diffuse hemorrhage, interstitial edema, early pulmonary fibrosis.

Case 4. This infant born after a 24 week gestation, weighed 720 grams. The pregnancy was complicated by intermittent bleeding and premature labor. The infant survived 26 hours. He was maintained on 63% inspired oxygen with respirator pressure of 16 mm Hg/3 mm Hg, inspiration/expiration. Initial (2 hours) and final (26 hours) chest x-rays showed diffuse, finely reticular parenchymal opacification of the lungs, particularly the lower lobes and some central air bronchogram effect (Fig. 4 a).

Pathologic examination showed canalicular development, slight hyaline membrane production, marked hemorrhage into the airspaces and interstitium, and moderate edema throughout the interstitium (Fig. 4 b).

Diagnosis: Interstitial and air space hemorrhage and edema.

Case 5. A male infant, the product of an uncomplicated 27 week pregnancy and weighing 1016 grams, survived 48 hours. Although

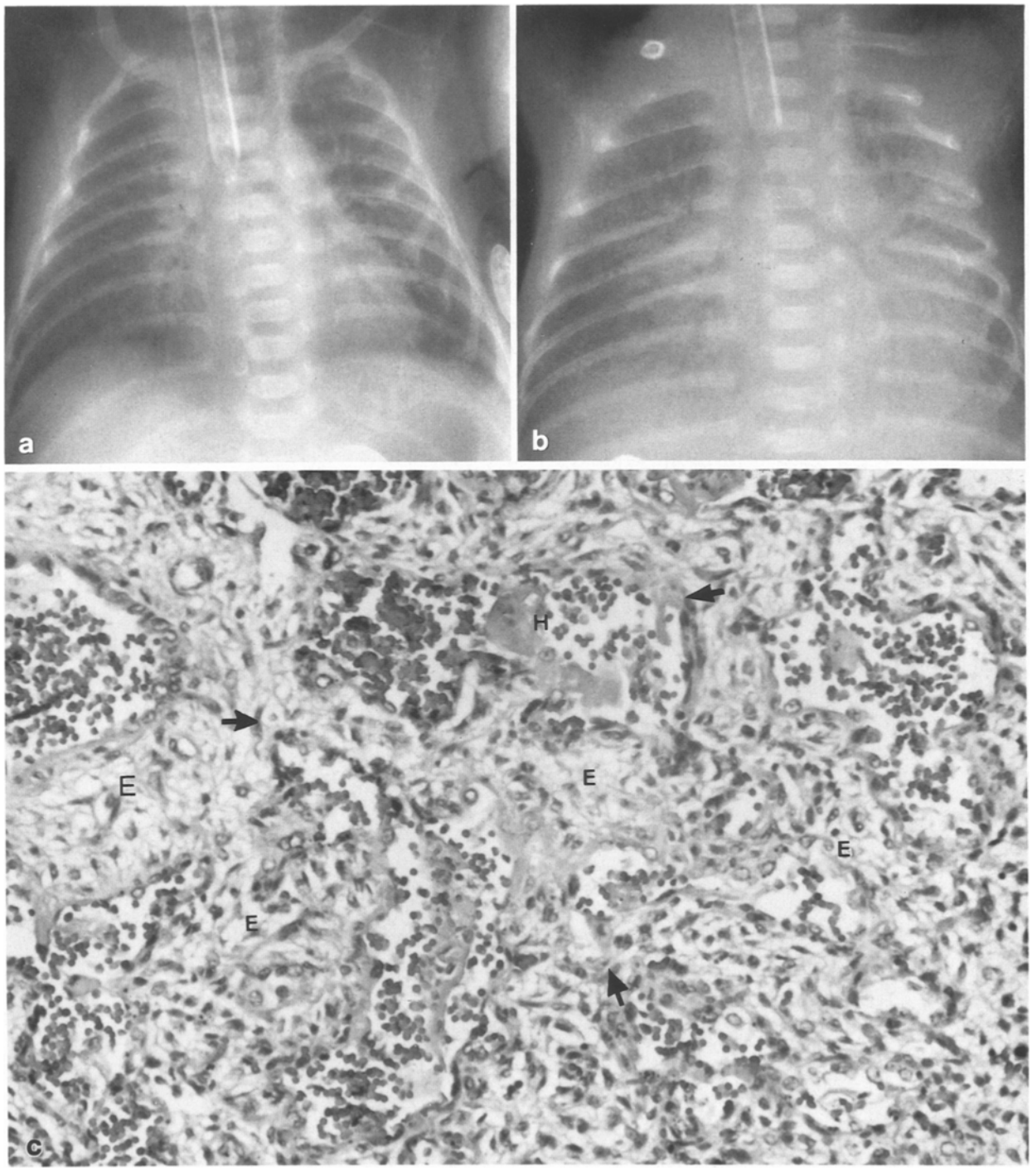


Fig. 3. a Case 3. Initial examination shows good lung expansion and aeration (2 hours of age). **b** AT 18 hours of age the infant shows dense patchy interstitial streaks and early central airspace consolidation of parenchyma. **c** Hyaline membrane development (H), widespread interstitial edema (E), hemorrhage and early interstitial fibrosis (arrows)

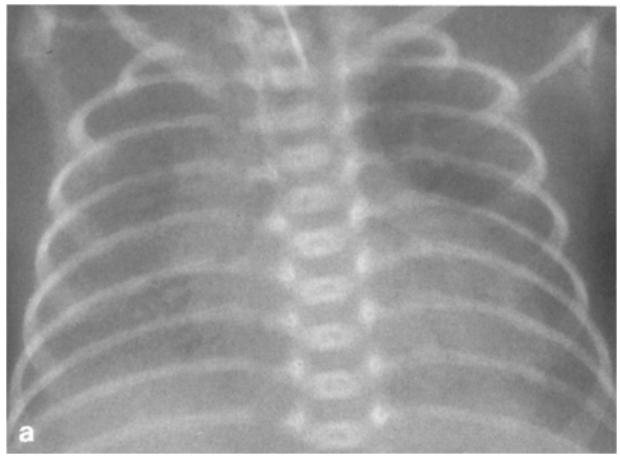
the initial chest x-ray was normal, at eight hours and prior to death there was a pulmonary pattern of generalized, fine interstitial density with overall parenchymal opacification, and air bronchograms (Fig. 5 a).

Histologic examination showed alveolar stage lung development, severe hyaline membranes, and very severe interstitial edema present throughout the lungs with slight to moderate interstitial hemorrhage (Fig. 5 b).

Diagnosis: Severe interstitial edema, moderate hemorrhage.

Case 6. This infant girl, first of twins, and product of a 24 week gestation weighed 610 grams. She survived 30 hours. During this time she required 88% oxygen and ventilator inspiratory/expiratory pressures of 13/3 mm Hg.

Chest radiographs throughout her life showed diffuse, very marked generalized pulmonary airspace opacification and well visualized air bronchograms (Fig. 6 a).



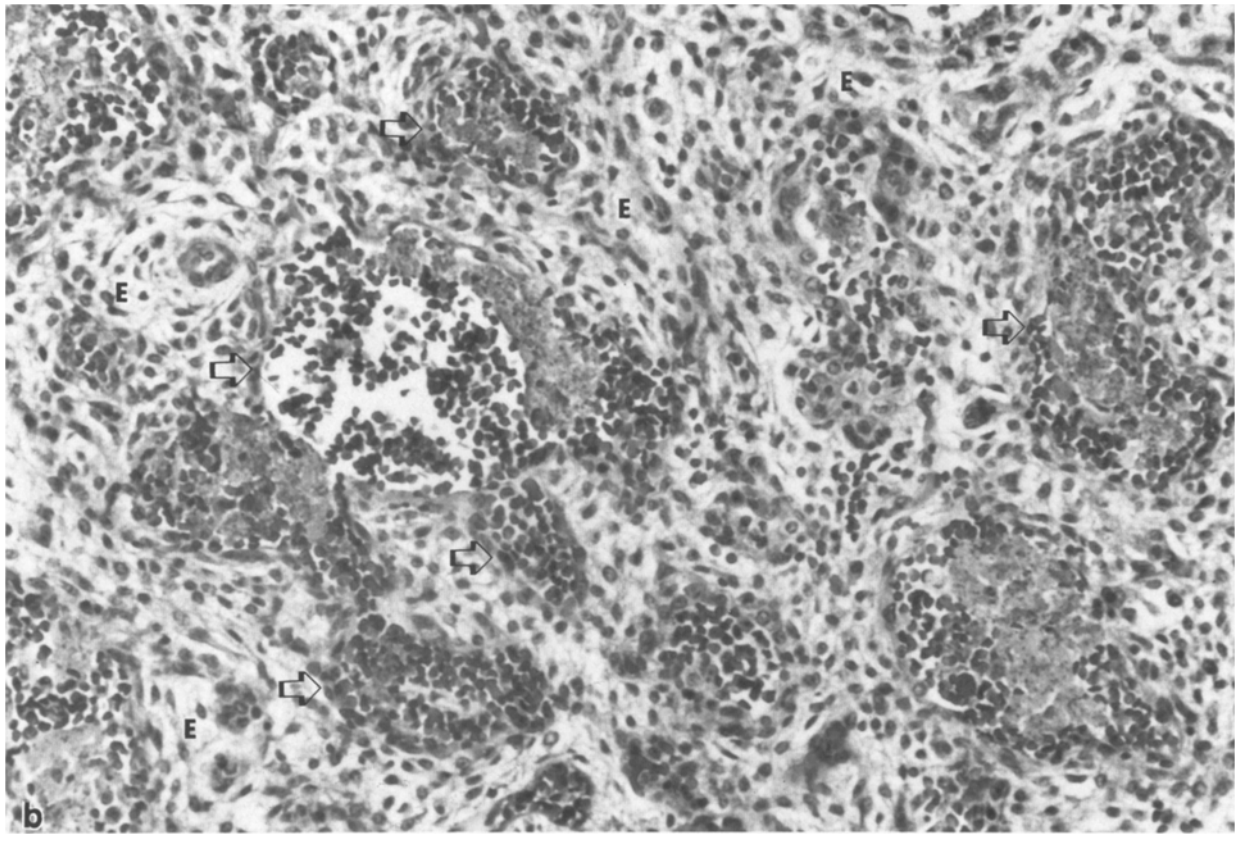


Fig. 4. a Very fine reticular and nodular pattern of parenchymal consolidation (26 hours). Peripheral air bronchograms are not seen. **b** Early hyaline membrane formation, moderate edema of interstitium (E) and bronchiolar hemorrhage (arrows). (Photo 9X) Hemorrhage filled bronchi prevent visualized air bronchograms

Pathologic examination showed very immature canalicular stage lungs with moderate early hyaline membrane formation. Although very mild interstitial edema and hemorrhage was present, the major factor contributing to the pulmonary opacification was the notable immaturity of the lungs, the inability to maintain distention of these immature airspaces, and expectedly thickened interstitium (Fig. 6b).

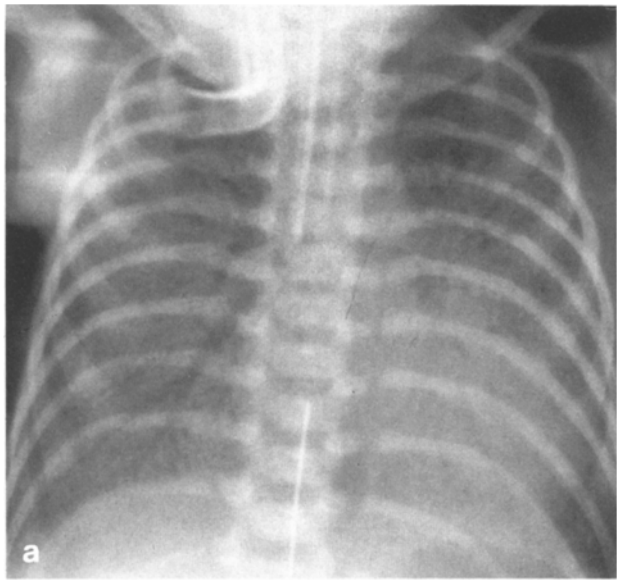
Diagnosis: Canalicular stage, very immature lungs.

Table 1. Pulmonary abnormalities identified histologically

Total number of infants	26
Hyaline membranes	23
Terminal air sac hemorrhage	23
Interstitial edema	24
Interstitial air	13
Interstitial hemorrhage	26
Interstitial inflammation	7

Results

The lungs of viable preterm infants pass developmentally through two states of maturation: canalicular development and saccular/early alveolar development. In the former, the interstitium or parenchyma is thick, the microvessel walls are thick and there is poor association of the pulmonary capillaries with the epithelium lining the aerating surfaces (respiratory bronchioles). The airspaces show a simple branching pattern and are lined by high



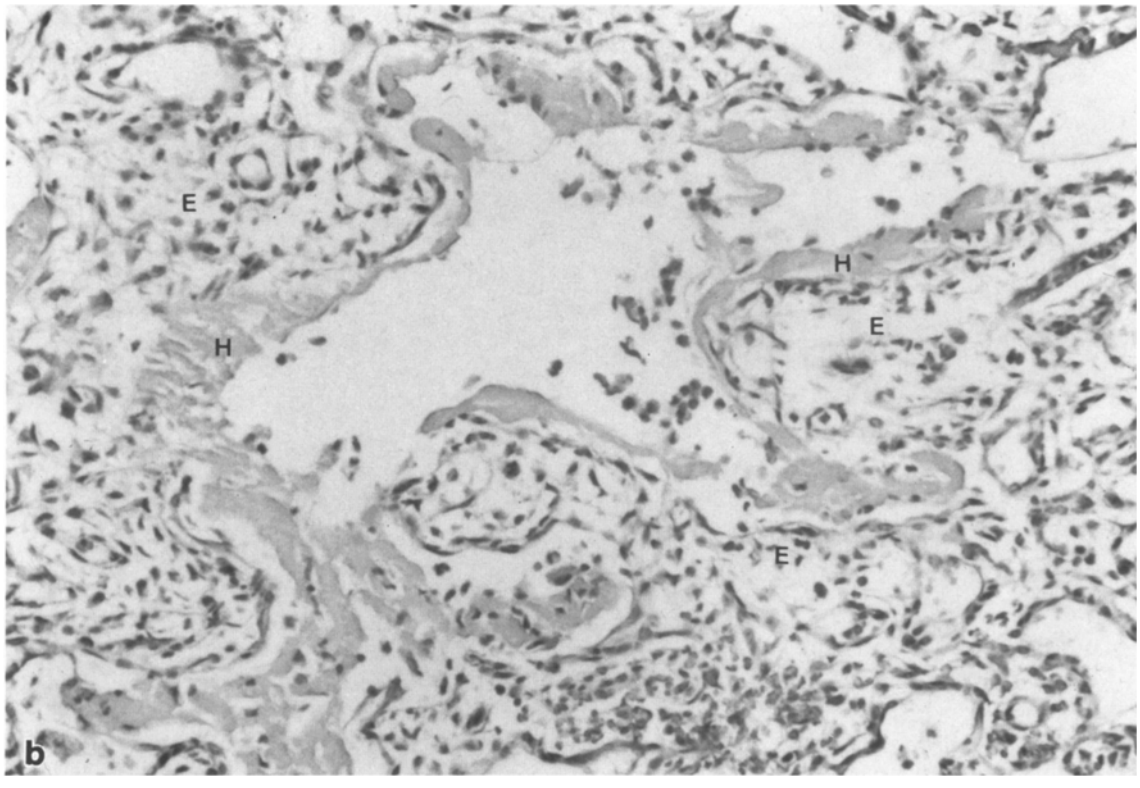
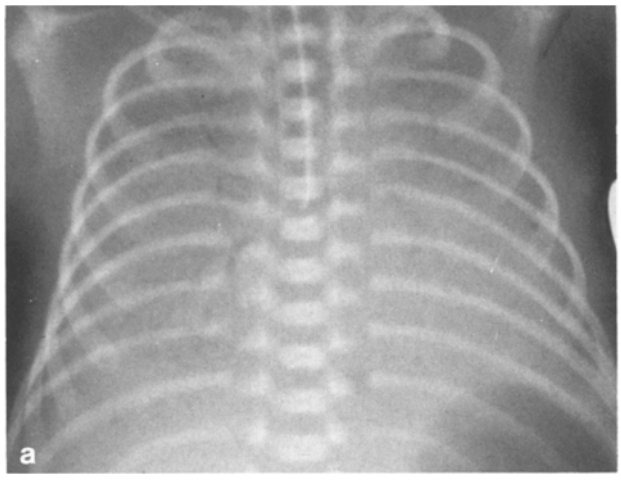


Fig. 5. a Prior to death a diffusely consolidated lung with peripheral air bronchograms (48 hours). **b** Hyaline membranes (H) line bronchioles, severe interstitial edema (E) throughout the parenchyma. (Photo 9X)

cuboidal epithelium further hindering gas diffusion. As maturation progresses to the saccular/early alveolar stage of development, the interstitium becomes thinner, capillaries are more closely associated with the exchanging epithelial surfaces and are thinner-walled, the respiratory bronchioles progressively branch and increase in number, and lining epithelium becomes flattened [6, 7]. Physiologically, the endogenous surfactant production cycle is not mature with surfactant synthesized, released, and adsorbed onto the respiratory surface until approximately 30 weeks gestation. The effect is responsible for developing more compliant lungs with more efficient and extensive surfaces for gas exchange, and better pulmonary blood flow and distribution.

Hyaline membranes were identified in most of the infants studied, occurring in 23/26 infants. The most important finding in the terminal air sacs was hemorrhage. The significant interstitial changes were edema, interstitial air, hemorrhage, and occasionally inflammation (Table 1). The corresponding radiographic patterns observed consistently were reticular interstitial density; thick, dense linear streaks; air



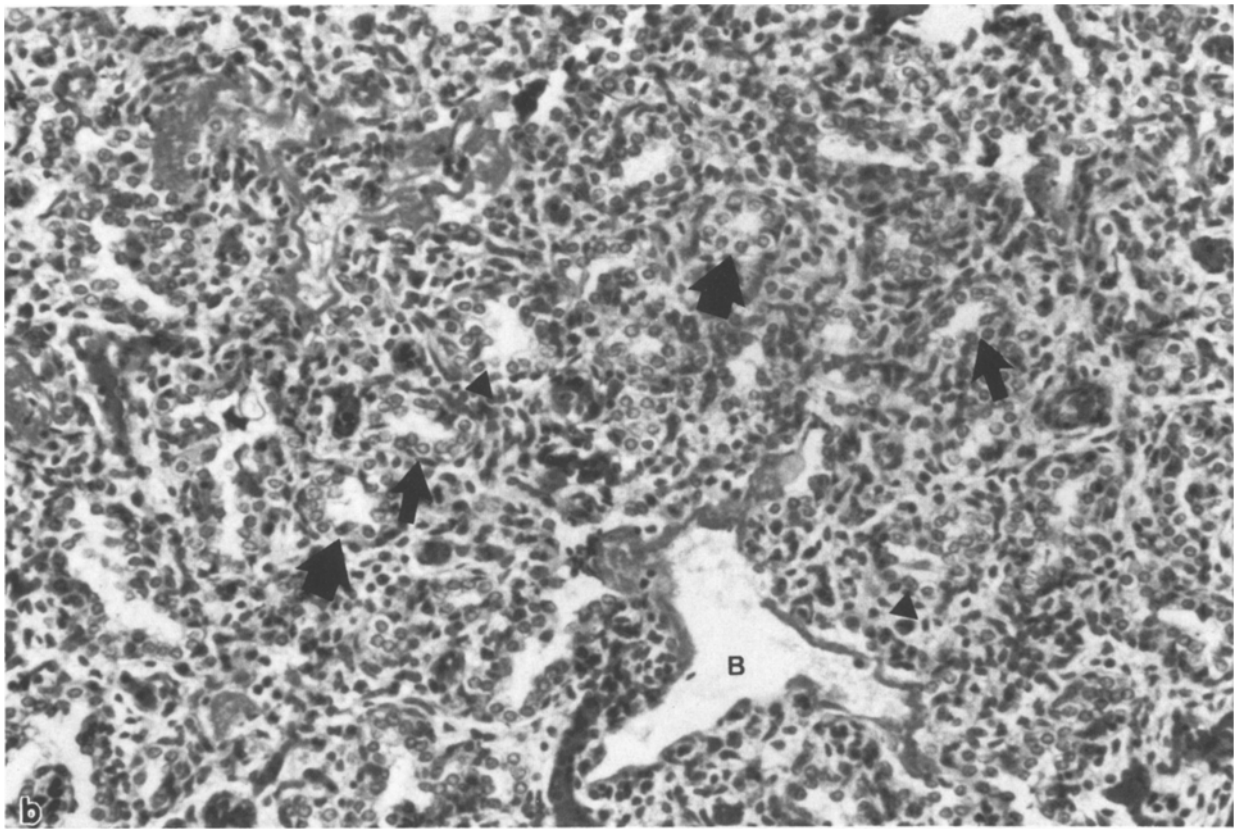


Fig. 6. a At 28 hours of age the lung is poorly expanded and shows diffusely, consolidated, opacified airspaces. **b** Immature canalicular stage lungs with early hyaline membrane formation and mild interstitial edema and hemorrhage. Note primitive branching bronchioles (B), poor sacculation, and high cuboidal lining epithelium of airspaces (A). (Photo 9X)

bronchograms; patches of consolidation; or complete parenchymal consolidation.

Discussion

The term hyaline membrane disease has been used synonymously with respiratory distress syndrome (RDS) and is a useful description for clinical difficulty in adequately oxygenating an immature infant. Insufficient airspace expansion, airspace collapse on exhalation, and poor gas exchange are the key contributors to this disease. It is characterized clinically by tachypnea, expiratory grunting, hypoxia and acidosis. Those who have previously made radiographic/pathologic correlations have studied infants of 30 weeks or greater gestational age and invariably identified massive atelectasis: a reflection of lung immaturity and inadequate surfactant [8].

Hyaline membranes themselves are a constant feature in airspaces of infants surviving at least 8 hours with lung disease and particularly those receiving rich inhaled oxygen mixtures and mechanical ventilation. These eosinophilic staining membranes are a result of bronchiolar epithelial necrosis related to a combination of barotrauma, inhaled

oxygen effect, and underlying hypoxic damage and they represent deposited exudate, necrotic epithelial lining cells, and serum proteins. They are not likely a visible radiographic entity as they are not thick although they may contribute to the patient's clinical condition hampering gas exchange. Radiographically normal lungs may histologically show extensive hyaline membranes.

In this study of extremely immature infants, an overall pattern of coarse linear density or patchy consolidation invariably reflected pulmonary hemorrhage, interstitial edema, airspace edema, and occasionally underexpansion with severe immaturity. Profound edema, (with associated hemorrhage) was the underlying abnormality in most of the babies examined, accounted for deterioration of the infant's condition, and produced the major radiographic changes.

There are several factors allowing edema to occur. Immature arterioles have a highly permeable basement membrane, a defect which is enhanced by anoxia and acidosis. In the presence of a large intravascular volume and increased pulmonary blood flow (enhanced by a patent ductus arteriosus) hydrostatic loss of intravascular fluid increases. Immature vessels may lack sufficient smooth muscle to compensate adequately for hemodynamic and osmotic changes. Interstitial pericapillary pressures less than alveolar pressure produce transmural pressure gradients which cause capillaries to leak. When intercellular junctions leak at the Type 1 pneumocyte lining layer, protein molecules in the alveolar lining fluid exert a colloid osmotic pressure drawing water into the alveolus. At low lung volumes, interstitial tissue pressure (which is less negative) hampers fluid movement into the usual lymphatic sumps [7].

Pulmonary hemorrhage occurs because of immature sequence of clotting factors, platelet sequestration, or vitamin K and enzymatic deficiency. Immature capillaries have poorer wall integrity, also.

The radiographic appearances of those infants studied were not diagnostic of the pathology identified. Most infants initially showed well aerated lungs which progressively, over 6–12 hours, developed a pattern of diffuse reticular density or more consolidated homogeneous lung density. A pattern of air filled bronchi to the fourth or farther divisions was present. The radiographs obtained shortly before death did not differ from others during the course of the patients' illnesses, or from the pattern commonly seen in surviving infants in difficult respiratory status. The worsening of the pulmonary pattern paralleled declining respiratory status, increasing hypoxia and acidosis.

The degree of pulmonary opacification radiographically correlated with the amount of overall airspace obliteration identified microscopically.

The clinical diagnosis of RDS in the premature newborn is a course of progressive respiratory failure caused by inadequate surfactant function superimposed upon a structurally immature lung. The pathologic study of the lung reflects features of poorly developed and expanded terminal air sacs further compromised by edema and hemorrhage. These findings reflect the effect of immaturity compounded by lung injury. The radiologic representation of diffuse airspace opacification does not provide specific differentiation of the underlying pathology.

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References

1. Tudor J, Young L, Wigglesworth JS, Steiner RE (1976) The value of radiology in the idiopathic respiratory distress syndrome: a radiological and pathological correlation study. Clin Radiol 27: 65
2. Edwards DK, Jacob J, Gluck L (1980) The immature lung: radiographic appearance, course and complications. AJR 135: 659
3. Bomsel F, Couchard M, Larroche J-Cl, Magder L (1975) Diagnostic radiologique de l'hemorragie pulmonaire massive du nouveau-ne (Radiologic diagnosis of massive pulmonary haemorrhage of the newborn). Ann Radiol (Paris) 18: 419
4. Berger G, Rupprecht E, Hinkel G-K, Schwarze R (1975) Comparative assessment of clinical, roentgenological and anatomicopathological pulmonary findings in prematures and newborns. Pediatr Radiol 3: 61
5. Capitanio MA, Kirkpatrick JA (1969) Roentgen examination in the evaluatin of the newborn infant with respiratory distress. J Pediatr 75: 896
6. Langston C, Kida K, Reed M, Thurlbeck WM (1984) Human lung growth in late gestation and in the neonate. Am Rev Respir Dis 129: 607
7. Kotas RV (1982) Clinical relevance of pulmonary surfactant. In: Farrell PM, (ed) Lung development: biological and clinical perspectives, vol II: Neonatal respiratory distress. Academic Press, New York, pp 18–19
8. Thompson TR (1983) Intensive care of newborn infants: a practical manual. University of Minnesota Press, Minneapolis, pp 226–242

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