

Surfactant and RDS in Premature Infants

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Originally published in the *The ASIP Bulletin*, Volume 7, Issue 1 - January 2004

MILESTONES

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The history of investigations that solved the mechanistic enigma of Respiratory Distress Syndrome (RDS) in premature infants is a splendid example of how multidisciplinary research drives medical progress. Until about 25 years ago RDS was a major health problem that affected approximately 25,000 newborns in the United States each year, with 10,000 of those infants dying early in the post-partum period. Today, RDS is uncommonly the cause of neonatal mortality in developed countries. This striking change is the result of research efforts that identified the pathologic mechanism underlying RDS and provided the scientific rationale for designing therapies that effectively prevent and manage this disease.

RDS in premature infants was commonly referred to as Hyaline Membrane Disease because at autopsy the lungs contained microscopic protein aggregates that formed characteristic membranes in the distal airways. Numerous theories were proposed to account for the origin and significance of the membranes, and for decades a prevailing view was that they consisted of debris present in amniotic fluid that had been aspirated by the fetus prior to birth. However, pathologists had long recognized that the most common autopsy finding in RDS lungs was severe atelectasis, the condition in which lungs are collapsed and airless, and pediatricians had observed that the degree of atelectasis progressively worsened as the clinical condition of the infant deteriorated. The obvious critical question was "Why did the lungs of premature infants become airless?"

Since early in the 20th century, physiologists and anatomists had speculated about the effects of surface tension in the air spaces of the lung. The pulmonary alveolus, the terminal anatomic structure of the lung, is a roughly spherical structure whose surface is a curved gas-liquid interface with physical properties that approximately fit the Law of Laplace: $P=2T/R$, where P is the pressure difference across the

surface, T is the surface tension, and R is the radius of curvature. The Laplace relationship predicts an inherent instability of the pulmonary alveolus because if surface tension remains constant then the decrease in alveolar size upon expiration would increase intra-alveolar pressure and this would promote further decrease in alveolar size. To account for the observed stability of normal pulmonary alveoli, a surface active material (surfactant) capable of reducing alveolar surface tension had been proposed by some early investigators, but never demonstrated. In 1955, the English physicist R.E. Pattle¹ published the results of experiments he had conducted on the stability of bubbles produced in various fluids including serum and pulmonary edema fluid. He observed a remarkable stability of the bubbles that were contained in the foam of pulmonary edema fluid compared to bubbles produced in serum and other fluids. He concluded that the bubbles of pulmonary edema fluid contained "a protein layer that can abolish the tension of the alveolar surface". Further insight into the pathogenesis of RDS was provided in a presentation² made to the New York Pathological Society in 1956 by Peter Gruenwald, a pathologist who worked at a maternity hospital in New Jersey. Based on autopsy findings, Gruenwald proposed that three factors contributed to the pattern of atelectasis of premature infants: a) "a low ratio of capacity of alveoli versus bronchi in premature infants favors the loss of air from the alveoli when only part of the total volume of air leaves the lungs," b) "in conditions of collapse following air breathing the respiratory surfaces have an increased adhesiveness tending to perpetuate atelectasis caused by the first factor," and c) "surface tension favors the development of large bubbles in the bronchioles, rather than smaller ones in the alveoli." In 1956, J.A. Clements presented evidence for the presence of a surface tension-reducing material in lung extracts that was not present in serum or other tissues.³ This was soon followed by the breakthrough discovery of Avery and Mead⁴ that surfactant could not be detected in the lungs of infants who died with RDS, while it was readily detected in the lungs of infants who died of non-pulmonary disease,

provided their birth weight was greater than 1,000 grams. They proposed that prematurity and lack of surfactant were responsible for RDS.

The findings of Avery and Mead created widespread interest and stimulated investigations aimed at determining the chemical composition of surfactant, the site of its production, and the factors that regulated its expression. Numerous studies began to address these issues. An important set of observations was reported by Kikkawa and colleagues⁵ who studied respiratory distress in newborn lambs. In their model system, lambs delivered prematurely developed respiratory distress with loss of pulmonary surfactant, while full term lambs did not. Sequential electron microscopic analysis of the developing fetal lung revealed the appearance of osmiophilic inclusion bodies in certain alveolar lining cells (Type II pneumocytes) at about 121 days gestation. The number of inclusion bodies increased with further fetal maturation. Normal surfactant activity was first detected in lung extracts a few days after the initial appearance of the inclusion bodies. At the time this research was performed, the chemical structure of pulmonary surfactant had not been established, but it was known that the major component of surfactant was the saturated lipid dipalmitoyl phosphatidylcholine, an osmiophilic compound. The experiments of Kikkawa and colleagues⁵ confirmed the excretory properties of the Type II pneumocytes and the phospholipid nature of the osmiophilic inclusion bodies. These investigators concluded that the inclusion bodies were the source of surfactant because respiratory distress and loss of surfactant activity were associated with a decrease in the number and density of inclusions. In addition, the electron micrographs showed that the alveoli of normal lambs were lined by a dense osmiophilic layer, which implied that the secreted surfactant was distributed along the curved gas-liquid interface.

The research that solved the pathogenesis of RDS in premature infants resulted in the development of treatments aimed at preventing alveolar collapse. Surfactant replacement therapy and the use of ventilators to maintain a positive endrespiratory pressure were shown to be highly effective. The research also opened up an entirely new field of investigation that is ongoing. Much is now known about the biosynthesis, assembly and turnover of surfactant. The structures of four proteins present in pulmonary surfactant have been determined. Insights into the functions of these proteins have come from studies of mice with engineered mutations and of humans with inherited mutations. A growing number of publications have presented evidence that some of these proteins function in host innate immune responses, findings that implicate pulmonary surfactant in physiological functions that go beyond lowering alveolar surface tension.

References

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