Pediat. Res. 7: 842–845 (1973)

What is New in Our Understanding of Perinatal Pulmonary Problems?

Presidential Address to the Society for Pediatric Research, May 19, 1973

MARY ELLEN AVERY[36]

Department of Pediatrics, McGill University, Montreal, Quebec, Canada

Thank you for the honor of having been your president this past year, and for the special pleasure of addressing you this morning on a topic of my choice without previous announcement of the title. It is about the equivalent of having an article published in your favorite journal without editorial review.

I have entertained the possibility of speaking on neonatalogy: is it a specialty, or what is it, or where is it going, or even "how did it get started"? After months of reflection, I decided it would not take me 15 minutes to say "I don't know," hence, I have chosen a more focused aspect of the newborn, the lung. The title is "What is new in our understanding of perinatal pulmonary problems?".

One way to find out what is new is to read the relevant abstracts in the program issue of *Pediatric Research;* the April 1973 issue contains 855 abstracts. Forty-seven relate to the lung of the fetus and neonate, and 26 of these are concerned with aspects of the pulmonary surfactant. Surmising that there is considerable interest in this topic, I shall try to make use of the information in the abstracts, and that published in the past few years to assess the state of the art. Unfortunately, time will not permit acknowledgment to all the investigators individually; I am certain they at least will recognize themselves, and I trust the rest of you will realize that I am attempting to synthesize the observations of a number of people, rather than to discuss only our own small contributions to this topic.

One question that has been asked for at least a decade is whether hyaline membrane disease is entirely due to a delay in lung maturation with respect to surfactant production, or whether it is the result of immaturity plus some associated insult. The pendulum has swung with respect to this issue. When the measurement of lecithin in amniotic fluid, expressed as lecithin-sphingomyelin ratio, or lecithin concentration was introduced (and found so helpful in a number of instances), it was tempting to say that failure of surfactant production by the fetus was a primary predisposing event in the disease. The argument was based on knowledge that dipalmitoyl lecithin was an essential component of the surfactant; that it contributed significantly to the lecithins in amniotic fluid that were acetone precipitable and surface active; that it was the product of the differentiated pulmonary alveolar *type II* cells, and hence, a reduction in surface active lecithins in amniotic fluid would be predictive of infants who, when delivered, would have respiratory distress [19]. Subsequently, a foam stability test has been widely used [7] for the same purpose. In an abstract in this program, the Wisconsin group suggest another approach, namely, that a relative excess of stearic acid on lecithin is a better predictor of respiratory distress than the lecithin concentration alone [16]. However, the same group reminds us that typical hyaline membrane disease can occur in infants whose amniotic fluid lecithin is within the normal range, raising the possibility that factors other than immaturity alone may be at work [33].

The near future will surely be marked by a search for a more specific indicator of surfactant presence in amniotic fluid. Encouraging reports from Clements' group about a protein of approximately 10,700 molecular weight, specific for the lung, and surfactant related, suggests the possibility of its use as a marker of lung maturity [6].

Clinical observation would lead to the suggestion that surfactant is not always deficient at birth in infants who subsequently die of hyaline membrane disease. For example, some infants show minimal retractions or interference with gas exchange in the first hours of life, but later have classic hyaline membrane disease. Such infants must have had some surfactant present to permit the initial nearly normal lung function. Three explanations seem logical. The infants may represent a group with suboptimal amounts of surfactant synthesized, with an abnormality of release onto the alveolar surface, or with utilization in excess of the capability for further synthesis and release. Evidence in support of humoral factors that may hasten release exists in the studies of Goldenberg *et al.* [20] with pilocarpine, and in recent studies of Taeusch [31] with isoxsuprene. Release in association with air breathing after birth is now well documented [31].

Among the recent advances in our understanding of the pulmonary surfactant is recognition that the pattern of breathing can alter its rate of utilization. This effect was first shown on the excised lungs of dogs by Faridy [11] by ventilation at different frequencies and volumes. It is evident that permitting the lung to return to airlessness on end-expiration increases the change of the alveolar surface area with each breath and the consequent large ventilatory excursions accelerate surfactant utilization [11]. The remarkable benefit of continuous distending airway pressure, whether applied as a positive end-expiratory pressure, or continuous negative pressure around the chest serves to illustrate the significant improvement in ventilation-perfusion relations in a lung prevented from returning to airlessness on expiration. Upon the application of such pressures, arterial oxygenation improves within minutes; upon their removal, arterial oxygen tension falls, also within minutes [21]. Ten abstracts submitted for this meeting relate experiences with distending airway pressure, and are overwhelmingly in its support. Apparently, preventing alveolar collapse reduces the extent of area change of the alveolar surface, and hence conserves the existing surfactant, or enhances surface film formation. The efficacy of this form of ventilatory support is the strongest single argument for the role of abnormal surface forces promoting atelectasis as central in the pathophysiology of the disease. One word of caution from San Diego is the observation, in some infants, of fluid retention while on distending airway pressure, an effect that probably indicates excessive pressures, or their use after the infant's lung is making adequate amounts of surfactant [8].

To return to our original question then, whether immaturity alone, or some additive adverse factors predispose to the disease, I believe that the best answer at this time in that lung immaturity, usually associated with premature birth, is the most significant predisposing factor, but that other events can set the stage for the disease, presumably by interference with the normal balance between surfactant production and utilization. Biologic variability with respect to the timing of lung maturation is surely a central issue, as illustrated by the familial predisposition and the occasional expression of the disease in term infants.

The second question that seems relevant, in the light of the 26 abstracts that pertain to it, is the role of glucocorticoids in accelerating lung maturation. This represents one illustration of an event that can influence the likelihood of postnatal respiratory distress. I believe the existing data permit the following statements.

1. Unequivocal evidence of glucocorticoid induced acceleration of maturation of the lung just before the time of normal differentiation of *type II* cells is now available in lambs, rabbits, rats, and monkeys [9, 10, 13, 24, 25]. Presumptive evidence is at hand from the studies of Liggins and Howie [25] and Spellacy [30] in man that lung maturation can be accelerated by glucocorticoids.

2. There is a critical period in lung growth that permits an acceleration in maturation with exposure to glucocorticoid, and that period is just before the event would occur normally. Glucocorticoid exposure in early fetal life may accelerate growth rather than differentiation [29]; at the critical period, differentiation appears at the expense of growth [5], with some reduction in cell number, and later, or postnatally, no effect is seen with glucocorticoids [2, 12]. The density of nuclear glucocorticoid receptors in the rabbit, at least, is at its greatest when the effect on differentiation is greatest; on the other hand, cytosol receptor density remains nearly constant [3, 17].

3. The lung can differentiate in the absence of fetal adrenal corticol activity, as shown by Kenny *et al.* [22] in an infant with congenital absence of the adrenals, and in some anencephalic infants with atropic adrenals, as long as they are delivered at term, or later.

4. The time required for glucocorticoid effects on lung maturation after exogenous administration appears to be at least 24 hr, and perhaps 48 hr in rabbits and lambs [10, 24].

5. The magnitude of the effect on surfactant production rates from prenatal glucocorticoid administration in the premature fetal lamb is more than 20-fold, according to the data of Platzker and colleagues [27]. The choline incorporation pathway appears to be the most responsive to glucocorticoid administration [14].

6. A number of abnormal situations that might be thought of as "stressful" to the fetus are associated with less than the expected incidence of respiratory distress syndrome. These include rupture of the membranes more than 16 hr prematurely, even in the absence of infection. A possible mechanism is suggested by the observations of Bauer *et al.* [4] that cord blood and subsequent cortisol levels are elevated in the infants after premature rupture of membranes and such elevations are associated with less respiratory distress. All of the published prospective studies that have sought this correlation of a sparing effect of premature rupture of the membranes have reported its presence [28, 32]. In some retrospective studies the correlation has not been evident, but frequently those studies have included a number of term infants who can dilute the observations on low birth weight infants [18]. In infants under 1,000 g, Alden *et al.* [1] found that the best predictor of postnatal survival was premature rupture of the membranes, although they did not relate it to less respiratory distress. How the infant perceives the fact of membrane rupture is intriguing and the mechanism awaits further study. Another stress would appear to be caesarean section in the absence of labor in premature infants. The British Perinatal Study showed an overall 15-fold increase in deaths from the disease when delivery was by section in the absence of labor, or a 20-fold increase in that group compared with the outcome after vaginal delivery [15], a point I wish our obstetric colleagues would take more seriously. Because cortisol levels are higher in cord blood after labor, it is possible the beneficial effect of labor is mediated hormonally [26].

Finally, it is tempting to suggest that the 3-day natural course of the sublethal forms of hyaline membrane disease probably represents the time required for postnatal maturation of the lung. The infants are known to be exposed after birth to elevations in endogenous cortisol production, perhaps induced by the stress of the disease.

A moment of reflection on the preceding remarks may be permissible in this setting. None of the comments I have just made on prenatal detection, or aspects of pathogenesis, or the role of glucocorticoids could have been made 5 years ago. Most of them could not have been made 1 year ago, and some of them depended on the arrival of abstracts for this meeting. This crescendo of research on metabolic functions of the developing lung suggests that not only are those concerned with the care of the infant quick to perceive the implications of these studies for the prevention of hyaline membrane disease, but students of developmental biology are aware that some insights into the regulation of timing of cell differentiation are at hand. The endocrinologists and lipid chemists doubtless feel a compulsion to enter into the field, alert to the dangers that can evolve when pulmonary physiologists begin talking about hormones.

Finally, I am reminded of the famous exercise in logic, where the professor and the student stood on the shores of a pond upon which were six black swans. The professor asked the student what were his three conclusions from the observation. The student answered that swans could swim; there were six of them, and that all swans were black. To some extent the nature of our conclusions about hyaline membrane disease may be analogous to concluding all swans are black. Caution dictates that we conclude with the comment that within the constraints of our vision, and our experiments to date, it appears that we are on the threshold of understanding some of the hormonal regulators of organ maturation aand the clinical consequences of alterations in that regulation.

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34. This address was presented at the 43rd Annual Meeting of the Society for Pediatric Research, San Francisco, May 17–19, 1973.
35. Dr. M. E. Avery is Professor and Chairman, Department of Pediatrics, McGill University, Montreal, Quebec, Canada.
36. Requests for reprints should be addressed to: MARY ELLEN AVERY, M.D., 2300 Tupper St., Montreal, Quebec, Canada.
37. Received for publication June 7, 1973.

Printed in U.S.A.