

deafness, and the visually impaired). This paper not only encouraged clinical trials of physical therapy but also challenged academicians and practitioners to use other methods of treatment for improvement of motor function of children with cerebral palsy. Since that time, neurosurgery, along with orthopedic surgeons has devised newer methods of treatment using baclofen, oral and intrathecal botulinum toxin, and rhizotomies. Newer methods of physical therapy

have been also devised, such as, neurodevelopmental therapy for enhancing the functioning of these children.

Therapy studies should continue to receive high priority in the subspecialty of neurodevelopmental disabilities. The goal of such studies should be the continued clinical benefit of children with motor dysfunction.

COMMENTARY

The Alveolar Lining Layer: A Review of Studies on Its Role in Pulmonary Mechanics and in the Pathogenesis of Atelectasis, by Mary Ellen Avery, MD, Pediatrics, 1962:30:324–330

Comments by Alan H. Jobe, MD, PhD

ABSTRACT OF ORIGINAL ARTICLE. The alveoli of the normal lung are lined by a substance that exerts surface tension at the air–liquid interface. In the expanded lung, the tension is high and operates to increase the elastic recoil of the lung. In the lung at low volumes, the surface tension becomes extremely low. This confers stability on the air spaces and thus prevents atelectasis. This lining layer is a lipoprotein film, which is not found where alveoli still are lined by cuboidal epithelium. Its appearance coincides with the appearance of alveolar lining cells. Electron microscopic evidence of secretory activity in alveolar cells suggests that they may be the source of the surface-active film. The normal alveolar lining layer is not present in lungs of infants who die from profound atelectasis and hyaline membrane disease. Whether its absence is a failure of development or attributable to inactivation is not established.

COMMENTARY

Dr Avery published this review article on the alveolar lining layer or surfactant in *Pediatrics* just 3 years after the seminal article with Jere Mead that demonstrated that saline extracts of lung homogenates from infants with hyaline membrane disease had high minimum surface tensions.¹ Although the pathology of and epidemiologic associations with hyaline membrane disease were known at that time, the controversy was whether the membranes caused the disease or were the result of some unknown process peculiar to preterm infants.^{2,3} With the “rediscovery” of surface tension lowering materials in the lungs by Pattle and Clements in the mid-1950s,^{4,5} the mechanical effects of surface tension-lowering

substances on the lungs were investigated intensively.⁶ Avery and Mead¹ made the first direct connection between hyaline membrane disease and surface tension abnormalities in 1959, and in the same year, Gribetz, Frank, and Avery⁷ reported that the pressure volume curves of lungs from infants with hyaline membrane disease had low lung volumes and decreased stability on deflation. These observations occurred concurrently with the initial development of neonatal intensive care and an interest in treating preterm infants with respiratory failure.⁸ The result was an explosion of information about hyaline membrane disease and surfactant that ultimately has led to our spectacular progress in treating what we now call respiratory distress syndrome (RDS). Fortunately the opportunity to observe hyaline membranes on pathologic specimens is much less frequent now.

Dr Avery’s 1962 article is particularly interesting because it was written when just a few pieces of critical information about hyaline membrane disease and surfactant were available. The article explained the effects of the alveolar lining layer on lung pressure volume physiology and the implications for the preterm infant as completely as is found in current texts on neonatology. The article pointed out a number of unknowns in 1962 that were quickly explored over subsequent years by many of the founders of what would become the subspecialty of neonatology. The predominately lipid nature of surfactant was characterized by Klaus, Clements, and Havel in 1961.⁹ Investigators such as Adams and Fujiwara demonstrated that infants with hyaline membrane disease had low amounts of phospholipids in lung tissue and alveolar washes.¹⁰ In 1967, Brumley, Hodson, and Avery¹¹ published in this journal an elegant demonstration of the relationship between surface tension and the amount of phospholipid in lung tissue and hyaline membrane disease. By 1972, King

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and Clements had characterized the lipid composition and the biophysical properties of surfactant.¹²

The 1962 article ends with the comment that the information about the surface lining layer “does not at this time point to any specific therapy.” Unsuccessful attempts to treat infants with RDS with aerosols of pure dipalmitoylphosphatidylcholine were reported in 1964 and 1967.^{13,14} Other investigators sought to learn more about cardiopulmonary function and maturation using animal models of prematurity. Stahlman published her observations of cardiovascular performance using lambs in 1964.¹⁵ In 1965, in back-to-back articles in *Pediatrics*, Orzalesi et al¹⁶ described the relationship between gestational age and surfactant appearance, and Reynolds et al¹⁷ explored the effects of asphyxia on RDS in preterm lambs. Evaluations of surfactant lipid metabolism during development^{18,19} provided the basis for the development of the L/S ratio for the prediction of infants at risk of RDS by Gluck et al in 1971.²⁰ Another improvement in outcome for infants with RDS resulted from the use of continuous positive airway pressure based on an appreciation of the physiology of surfactant deficiency by Gregory et al in 1971.²¹ This report stimulated many neonatologists to improve mechanical ventilatory techniques, an effort that continues to the present. Liggins’ observation in 1969²² that fetal cortisol infusions resulted in the preterm delivery of lambs that were able to breathe resulted in the randomized controlled trial demonstrating that antenatal glucocorticoids decreased the incidence of RDS after preterm delivery in humans.²³ All of these advances resulted from the recognition that surfactant abnormalities were associated intimately with hyaline membrane diseases.

The final sentence of the summary for the 1962 article stated that it was not known whether the alveolar lining layer was absent because of a failure of development or because of inactivation. The developmental explanation for the lack of surfactant was established soon after the question was raised.^{16,19} In 1965, Tierney and Johnson²⁴ demonstrated that blood or serum interfered with surfactant function. Balis et al²⁵ noted that surfactant was a thromboplastin and that it participated in hyaline membrane formation, and we found that airway samples from infants with RDS had surfactant with good surface tension-lowering properties if the surfactant was separated from inhibiting proteins.²⁶ We know now that both developmental lack of surfactant and inhibition cause surfactant deficiency in the preterm infant with RDS.

In retrospect, it is surprising that the concept that RDS could be treated with surfactant was not pursued until Enhorning and Robertson²⁷ reported for the first time in *Pediatrics* in 1972 that preterm rabbit lungs could be expanded with a natural surfactant recovered by lavage of adult rabbit lungs. Their initial and subsequent demonstrations of surfactant treatment in animal models were successful because they used natural surfactants that contained the yet to be identified surfactant proteins, and they gave the surfactant by tracheal instillation. The first clinical report of treatment of RDS with surfactant by Fuji-

wara et al²⁸ in 1980 was followed by the initial successful randomized trial published in 1985 by Enhorning et al²⁹ that was published in *Pediatrics*. Surfactant treatments have turned out to be the most studied and successful pharmacologic interventions for preterm infants.³⁰ Fortunately for preterm infants, Dr Avery’s initial studies of surfactant did point to very successful therapies for RDS.

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COMMENTARY

A Simple Phenylalanine Method for Detecting Phenylketonuria in Large Populations of Newborn Infants, by Robert Guthrie and Ada Susi, Pediatrics, 1963;32:318–343

Comments by Charles R. Scriver, MDCM

ABSTRACT OF ORIGINAL ARTICLE. The article describes a “microbial inhibition assay” for rapid and economical measurement of phenylalanine levels in whole blood. Capillary blood, from a heel prick, is collected from the newborn infant onto Schleicher and Schuell no. 903 filter paper; a disk of the sample is then transferred to an Agar plate containing a heavy inoculum of *Bacillus subtilis* ATCC 6051; an inhibitor of bacterial growth (β -2-thienylalanine) is counteracted by any significant excess of phenylalanine in the blood sample; and semiquantitative positive tests (hyperphenylalaninemia) are recorded by size of the bacterial growth zone in the Agar around the filter paper disc. The method permits mass screening for hyperphenylalaninemia.

COMMENTARY

The article I selected for the 50th anniversary supplement to *Pediatrics* describes a method. Its application has gone around the world, changed the natural history of a disease (phenylketonuria), and, through genetic screening, has introduced new concepts and approaches to the practice of medicine and health care.

Context

Lionel Penrose¹ recognized phenylketonuria (PKU) as the first example of chemically impaired human cognitive development. He anticipated that this multifactorial disease, in which the necessary and sufficient components were recessive mutation in a gene and exposure to an essential nutrient (phenylalanine), might be treated to restore metabolic homeostasis and prevent disease. A decade later, three groups^{2–4} reported a successful chemical response to dietary restriction of phenylalanine in pilot studies on patients with

PKU. The next obvious requirement was for a simple screening test that could be applied soon after birth, in the live birth population, before the postnatal cognitive impairment begins in the infant with PKU; a test sufficiently sensitive to detect one affected infant among 10 000 unaffected. Although other methods met the requirements of a screening test,⁵ it was the Guthrie test that became most widely used.

The prospect of screening thousands of newborns became a fact; the particular prospect of a false-negative test result came to haunt its users. Newly recognized ethical, legal, social, and economic issues soon attached themselves to the Guthrie test and the universal newborn screening it catalyzed. The issues became a major challenge for the American health care system (a challenge both lesser and different in societies where universal health care was emerging or already existed). The National Academy of Science (USA) convened an international committee of experts and consultants to examine the issues. The corresponding report⁶ provided universal guidelines for “genetic screening” as it became known. Another report⁷ came 2 decades later from the Institute of Medicine, offering renewed guidelines for the somewhat different procedure known as genetic testing.

Both genetic screening and genetic testing are searches for persons possessing certain genotypes that 1) cause or predispose to disease; 2) may lead to disease in descendants; and 3) identify other variations of interest. A positive test result can lead to three results: 1) early diagnosis and effective treatment to prevent disease; 2) counseling about reproductive options to avoid the consequences of heredity; and 3) knowledge of the frequency and distribution of genetic variation in society. Genetic screening is an activity directed at populations; genetic testing is one directed at persons or families already known to be at elevated risk for a genetic disease. An emerging societal view of genetic disease and the relevance of genetic screening and testing to alter its effect on persons, families, and communities is one legacy of the Guthrie test.

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