
History of Surfactant up to 1980

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Key Words

History of neonatology · Preterm infant · Respiratory distress syndrome · Surfactant composition · Surfactant deficiency · Surfactant function · Surfactant substitution

Abstract

Remarkable insight into disturbed lung mechanics of preterm infants was gained in the 18th and 19th century by the founders of obstetrics and neonatology who not only observed respiratory failure but also designed devices to treat it. Surfactant research followed a splendid and largely logical growth curve. Pathological changes in the immature lung were characterized in Germany by Virchow in 1854 and by Hochheim in 1903. The Swiss physiologist von Neergard fully understood surfactant function in 1929, but his paper was ignored for 25 years. The physical properties of surfactant were recognized in the early 1950s from research on warfare chemicals by Pattle in Britain and by Radford and Clements in the United States. The causal relationship of respiratory distress syndrome (RDS) and surfactant deficiency was established in the USA by Avery and Mead in 1959. The Australian obstetrician Liggins induced lung maturity with glucocorticoids in 1972, but his discovery was not fully believed for another 20 years. A century of basic research was rewarded when Fujiwara introduced surfactant substitution in Japan in 1980 for treatment and prevention of RDS.

Introduction

A condition as impressive and gruesome as respiratory distress syndrome (RDS) had been described long before book printing became available. Common terms for the disease were prematurity, weakness, or atelectasis, and the disorder was poorly distinguished from birth asphyxia. Obstetrics became a science-oriented field of medicine during the 18th century, mainly in the big maternity hospitals of London and Paris. By establishing obstetrics as a science, Mauriceau [1], Smellie [2], Raulin [3], and Baudelocque [4] also laid the foundation stone for effective treatment of the newborn infant. Neonatal medicine evolved in the foundling hospitals more than a century before hospitals for sick children were built.

Respiratory Support to the Neonate

In 1774, the reverend Priestley [5] discovered oxygen in an attempt to isolate various gases from mercuric oxide in his bathroom in Birmingham. During the course of his amateur experiments, he also discovered ammonia and carbon monoxide. Two years later the Scottish surgeon Hunter [6] constructed a bellows-type ventilator with a pressure-limiting valve and he suggested using oxygen instead of air. Shortly thereafter, the famous Paris chemist Lavoisier [7] fully understood Priestley's discovery, gave oxygen its name, and showed that burning is associated with oxygen consumption. His book inspired Chaussier

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[8], who at this time was a young physiologist in Dijon, to construct an apparatus for resuscitation of the newborn infant with a bag and mask that allowed artificial ventilation with variable inspiratory pressure and oxygen concentration (fig. 1). Called to the Paris chair of anatomy and physiology in 1794, Chaussier constructed different types of curved silver endotracheal tubes for neonates, which were closed at the end and had oval lateral holes. Being a republican, a systematic researcher, a hard worker of quakerian seriousness, and a gifted teacher, he made a splendid career and became director of the Paris maternity hospital and dean of the faculty during the imperial times. He published many papers on obstetrics and diseases of the neonate from 1805 to 1813, but was kicked out of the faculty during the big royalist revival in 1822. Five years after his retirement, artificial ventilation suffered a major setback when Leroy d'Étiolles [9] showed that inflation of the lung might cause pneumothorax.

For exactly 100 years, intermittent positive pressure ventilation made no progress, a fact that limited the development of both anesthesiology and thoracic surgery. In 1871, the Jena obstetrician Schultze [10] observed that in asphyxiated neonates right-to-left shunting through the persisting ductus arteriosus may occur. He believed that abrupt swinging of the infant's body closed the ductus arteriosus and would be useful for resuscitation. Schultze's method must have been totally ineffective in infants, whose lungs had never been ventilated, and probably caused tremendous hypothermia and intraventricular hemorrhage. He published his recommendations in a monograph which had the form of a letter to the highly influential Leipzig physiologist C. Ludwig. This, and the fact that his technique did not require as much skill as artificial ventilation, made 'Schultze's swingings' very popular throughout Europe, and they were widely used up to the Second World War.

In 1889, Alexander Graham Bell, the Canadian inventor of the telephone, constructed a body-enclosing ventilator for newborn infants [11]. Bell correctly stated that many preterm infants 'die from inability to expand their lungs sufficiently when they take their first breath. I have no doubt that in many of these cases, lives could be saved by starting the respiration artificially'. His ventilator, however, remained unaccepted. Preterm infants continued to die, and it was not until 1929 that Drinker and Shaw [12] developed an instrument suitable for long-term ventilation. However, it was not before the report of Donald and Lord [13] in 1953 that artificial ventilation of the neonate became an accepted, although largely unsuccessful, treatment for RDS. Even after Avery and Mead's

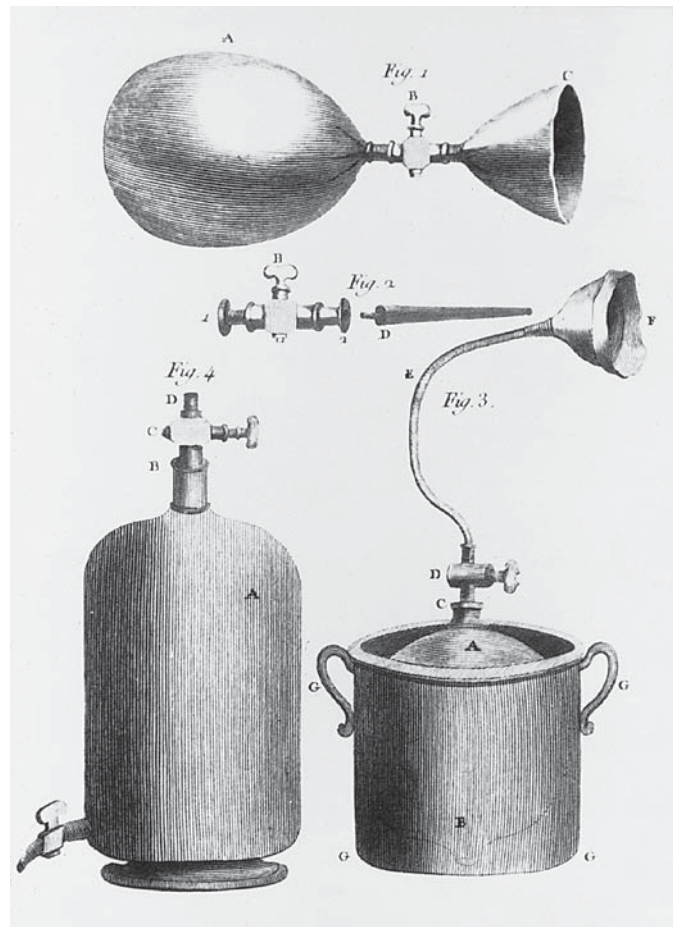


Fig. 1. Francois Chaussier's ventilator for neonates, model 1791. Top: Bag and mask; center: adapter for endotracheal tube; bottom left: oxygen tank; bottom right: device for spontaneous breathing with enriched oxygen [8].

paper [14] had clearly shown that the disease was caused by surfactant deficiency, treatment consisted of oxygen and minimal handling, and the mortality rate exceeded 50% [15]. It took another 10 years until George Gregory, an anesthesiologist working with the San Francisco group of neonatologists, drew the right conclusions from the pathophysiology of this disorder. As grunting correctly was understood as an adaptive mechanism in atelectasis [16], Gregory [17] developed continuous positive airway pressure, the first really successful treatment for RDS, which lowered the mortality of this disorder to around 20%. However, in 1973 RDS remained responsible for a quarter of all neonatal deaths [18].

Pathophysiology of the Immature Lung: Early Views

The first observations of neonatal RDS were published by obstetricians in England, France, and Germany in the second half of the 18th century. Raulin [3] revealed a high degree of understanding of the immature lung as early as 1768: 'The countless lung vesicles must fill with air, and must chase it away again. The largest part of the lung's blood vessels, hitherto collapsed, must open and fill with blood, whose circulation is required unless the life extinguishes instantly. If the lung vesicles are too weak, without power, or obstructed with phlegm, they do not accept the atmosphere's air, and the blood vessels collapse. Both functions (i.e. ventilation and perfusion) become impossible or very imperfect, and the loss of the infant is close'. Detailed texts on neonatology originated from the hospices for foundlings, mainly in France, after these institutions had been made mandatory for every county by Napoleon in 1811 [19–22]. Initially, no distinction was made between immaturity, 'life weakness', and birth asphyxia. The pulmonary changes observed in deceased infants were generally termed 'atelectasis' if the lung did not float at the postmortem examination. Despite this knowledge, the 'floating test' of an excised lung was still used at this time to judge if an infant had lived after birth, and continued to play a sad role in infanticide trials.

After the end of the Napoleonic wars, the stage was set for scientific research and major progress in basic sciences and clinical medicine. The French revolution had abolished religious restrictions, which for centuries had impeded scientific progress. The ban on postmortem examination, on blood investigation, and on the use of chemistry in analytical medicine was lifted and medicine was reunited with surgery which for centuries had made its progress in the twilight of barber shops and field surgeons. Billard's [22] fundamental 'Traité des Maladies des Enfants Nouveau-Nés et à la Mamelle' gave a detailed and largely correct classification of neonatal lung disorders in 1828. Billard pointed out that newborn infants may be born sick, or may contract disease postnatally, or may show sequelae of diseases that have occurred during fetal life. In the same year, 1828, the Paris surgeon Leroy d'Etiolles [23] wrote a memoir which reveals his understanding of surfactant deficiency. Leroy used to work in urology and had developed several instruments for intravesical lithotripsy which he had to defend in life-long and bitter struggles against his competitors. In his leisure time he was busy with experiments on the physiology of resuscitation and artificial ventilation. He ventilated the lungs

of different living animals, of adults drowned in the river Seine, and of stillborn or deceased neonates, and measured the inflation pressure required to cause pneumothorax. Without using Hunter's valve [6] he found that a given pressure was always tolerated by the lung of stillborn infants, whereas in adults or animal lungs pneumothorax occurred. He concluded 'the reason may be that the lung of the neonate is more compact'.

In 1835, the German obstetrician Jörg [24] published an extensive monograph on RDS, 'Die Foetuslunge im gebornen Kinde'. The name, which he used for the disease 'fetal lung in the baby who is born', has never been replaced by a better term thereafter. The book contains many features of modern understanding of RDS and showed that the disease occurred almost exclusively in preterm infants, that birth asphyxia, weakness, and right-to-left shunting contributed to its pathogenesis, and that minimal handling and warming improved survival from this disorder. Jörg's book even reports an inflammatory response of the small airways to oxygen administration, which present physicians believe was only discovered in recent years.

Pathology of the Hyaline Membrane

The invention of the microscope around the middle of the 19th century was led by the Würzburg pathologist Rudolf Virchow. He had been exiled from Berlin, where he had joined the 1848 revolution, but returned to the capital in 1859 to become director of the Institute of Pathology at the Charité and a radical deputy to the parliament. As early as 1854, he described a substance similar to the nerve medulla in various animal tissues and especially in the alveoli of diseased lungs. This substance stained blue with hematoxylin and was termed 'myelin' by Virchow [25].

The first correct description of the characteristic hyaline membranes of the lung was published by Hochheim in 1903 [26]. He believed that they represented aspiration of amniotic fluid contents, and, what was worse, published his findings in German. Therefore, hyaline membranes had to be rediscovered by Farber and Sweet [27], who described 18 cases in 1931, still believing that the membranes were aspirated vernix, and therefore called them vernix membrane. The hyaline membrane, being an end product rather than a cause, did not shed light on the pathogenesis but stimulated wrong theories and ineffective therapies. Many clinicians tried to correct pulmonary or systemic hypotension, described by Smith [28] to

be 'in relation to idiopathic respiratory distress (hyaline membrane disease; HMD) in the newborn'. Others tried to counteract fibrinolysin deficiency, which had been described as 'a new concept of HMD' by Liebermann in 1959 [29]. In 1956, Gitlin and Craig [30] published a study which connected hyaline membranes with birth asphyxia and which showed that they were composed largely of fibrin. They speculated that 'pulmonary hyaline membranes can be produced as the result of: (1) effusion from the pulmonary circulation or (2) conversion by fibrinogen in the effusion to fibrin'. They still regarded aspiration of lipid and squamous cells from vernix in the amniotic fluid as pathogenetic variables. The theory that hyaline membranes resulted from shock, fibrinolysin deficiency or disseminated intravascular coagulation, persisted for 20 years and stimulated several therapeutic approaches directed at influencing coagulation. Plasminogen infusions, recommended in 1977 by Ambrus et al. [31] following a double-blind study of 500 preterm infants, was believed to decrease the severity of HMD and overall neonatal mortality. Infants with HMD were thought to have low levels of serum plasminogen. Therapeutic administration of plasminogen was believed to enhance fibrin degradation in the alveoli with subsequently improved alveolar expansion.

Considerable energy was spent discussing the correct nomenclature: RDS with or without idiopathic? Hyaline membrane syndrome or disease? De and Anderson [32], in a review of the literature in 1953 listed 9 different terms used to describe the same histological findings. Comroe [33] commented sarcastically on this discussion: 'the amount of knowledge of the cause of a disease is inversely proportional to the square of the number of names acquired by the disease'.

Surfactant Function and Surfactant Deficiency: Modern Views

The theory of surface forces had been elaborated at the end of the 19th century by Rayleigh [34], who determined molecular size by preparing monomolecular films and who obtained the Nobel prize in 1904. Pulmonary surfactant was definitely detected in 1929 by Kurt von Neergaard, a Swedish physiologist working in Basel, Switzerland. In his paper: 'New opinions on a basic principle of breathing mechanics. The retractile force of the lung, dependent on the surface tension in the alveoli' [35], he studied excised pig and dog lungs and measured the pressure-volume curves (fig. 2) either with air or with gum

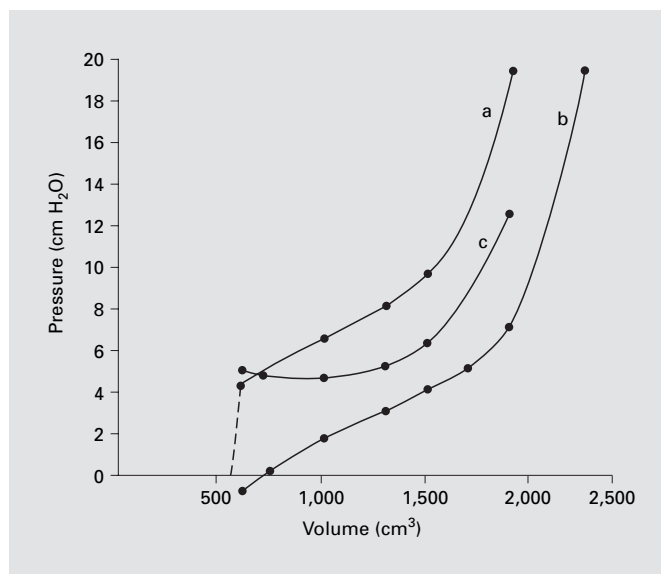


Fig. 2. Kurt von Neergaard's recoil pressure-volume recordings of isolated porcine lung, published in 1929. **a** Total lung recoil with air filling; **b** tissue elasticity after eliminating surface tension by liquid filling; **c** retractile force due to surface tension [35].

arabic and Tyrode solution: 'To eliminate surface tension, the lung was filled with a liquid to remove the effect of the air tissue interfaces'. He concluded 'in all states of expansion, surface tension was responsible for a greater part of total lung recoil than was tissue elasticity' and found that the law of Laplace [36] had to be applied for the expansion and retraction of pulmonary alveoli.

Von Neergaard was well aware of the significance of his findings for the newborn infant: 'The considerable force of the surface tension, which later is responsible for the greater part of lung recoil, hampers the initial opening of the lung'. The problem with his discovery was that his paper was published in German and that, for 25 years, no scientists in the evolving field of surfactant research really took note of his publication. In 1929, the year in which his paper appeared, von Neergaard moved to Zurich and began to work at the Institute of Physical Therapy. He did not pursue his research on lung mechanics and did not publish further physiology papers. However, he became a philosopher, got interested in the relation of medicine to politics and social sciences, and wrote several books on scientific thinking and on the researcher's task in the 20th century.

In 1933, Wilson and Farber [37] recognized 'cohesion of the moist surfaces in collapsed and airless lungs' of newborn infants and pointed out that 'the initial resis-

tance of the atelectatic lungs to expansion is always present and contributes to the maintenance of atelectasis'. In 1947, the pathologist Gruenwald [38], working at that time at the Brooklyn Long Island College of Medicine, described 'surface tension as a factor in the resistance of neonatal lungs to aeration'. Without knowledge of von Neergaard's work, Gruenwald had repeated his experiments and determined the smallest pressure necessary to expand the lungs of stillborn or deceased newborn infants either with stained saline solution or with air. From the difference in pressure required, he postulated the existence of surface tension at the tissue/air interface: 'The resistance to aeration is due to surface tension which counteracts the entrance of air but has no effect on the aspiration of fluid. Surface active substances reduce the pressure necessary for aeration'. It may have been important that Gruenwald was the teacher of Mary Ellen Avery at the Johns Hopkins Hospital in Baltimore.

After the end of World War II, research on warfare chemicals had a major impact on the understanding of pulmonary surfactant. With the aim of preventing, diagnosing, and treating injuries caused by war gases – notably lung edema caused by phosgene – military research laboratories had been established in the USA, in Canada, and in Great Britain. Supported by the Canadian chemical warfare laboratories, Macklin [39] had found the 'residual' cells of the lung and determined alveolar size in 1950 [40]. In 1954, he published a paper in which he described both 'the pulmonary alveolar mucoid film and the pneumonocytes' [41]. He assumed the presence of an aqueous mucopolysaccharide film on the pulmonary alveolar walls which is able to maintain 'a constant favourable surface tension': 'There is evidence pointing to the granular pneumonocytes as the originators of the secretion which composes this film'. At Harvard and with support of the US Army Chemical Center, Radford [42] wanted to determine alveolar surface area and again filled isolated lungs sequentially with saline and air. His findings meant that either the respiratory surface was only one tenth of that determined by histological methods, or that the lung 'consisted of a highly surface active substance', and both conclusions seemed unlikely to Radford.

In 1955, Pattle [43], who worked at the British chemical defense experimental establishment at Porton Down, examined pulmonary edema foam and measured surface tension by the rate of contraction of the foam bubbles. He not only proved that the stable foam bubbles expressed from lung originate from the alveolar lining layer, but also speculated that 'absence of the lining substance may

sometimes be one of the difficulties with which a premature baby has to contend'. At the same time, Clements [44] who worked at the US Army Chemical Center in Edgewood, Maryland, began quantitative studies using a modified surface balance consisting of a Langmuir trough and a Wilhelmy platinum plate. With this device, he studied surface films from rat, cat, and dog lungs and recognized that surface tension fell from 45 to less than 10 dyn/cm upon compression of the surface to 30% of its area [45]. Shortly after his fundamental paper, Clements left the Army Chemical Center and continued surfactant research at the Cardiovascular Research Institute in San Francisco. Gifted with an unlimited curiosity, diligent and systematic work style, and always a friendly personality, Clements became the unchallenged master in this field. Most people in surfactant research will gratefully acknowledge his readiness to critically evaluate and support their work.

In 1959, Avery – at that time a research fellow at the Boston Lying-in Hospital – and Mead [14] – from the Department of Physiology at the Harvard School of Public Health – published the paper that confirmed that HMD was due to surfactant deficiency. Using a similar surface balance as that designed by Clements, they studied the surface tension of lung extracts from newborn infants who died of HMD and from other causes. In the latter, the mean minimal surface tension, measured during surface compression, was 7.6 dyn/cm compared to 30.4 dyn/cm in infants dying of RDS. They concluded that 'the disease is associated with the absence or the late appearance of some substances which in the normal subject renders the internal surface capable of attaining a low surface tension when lung volume is decreased'.

Surfactant Biosynthesis and Analysis

By 1946, Thannhauser et al. [46] had shown that the lung contains unusually high amounts of dipalmityl lecithin (now known as dipalmitoylphosphatidylcholine or DPPC) but they did not connect this finding with the postulated surface-active properties at the alveolar wall. In 1961, Klaus et al. [47] in San Francisco isolated alveolar surfactant from bovine lungs and they could extract a phospholipid fraction that displayed surface-active behavior in the Wilhelmy balance.

In 1967, Gluck et al. [48] showed that during the development of the mammalian lung, DPPC is produced and secreted into amniotic fluid and in 1971 they developed the first useful test to determine fetal lung maturity

by amniotic fluid analysis: the lecithin/sphingomyelin ratio [49]. Scarpelli [50] had by 1967 opened the field of research on fetal pulmonary phospholipid metabolism. In 1975, Hallman [51], a Helsinki neonatologist working as a research fellow in Gluck's laboratory in La Jolla, San Diego, discovered that phosphatidylglycerol seems to contribute to surfactant spreading, and that this lipid invariably is absent in RDS. In the same laboratory near the Pacific coast, Jobe and Gluck [52] showed that pulmonary phospholipids have both an intracellular and an alveolar pool and they determined their biological half-lives.

In a series of papers published in 1972 and 1973, King [53, 54], trained and mentored by Clements, showed that surfactant contains several specific apoproteins and that the major surfactant protein SP-A is glycosylated, interacts with phospholipids, and is responsible for surfactant interaction with the cell surface. The low-molecular-weight hydrophobic surfactant proteins SP-B and SP-C were first identified by Phizackerley et al. [55] in 1979. Gil and Reiss [56] identified the lamellar bodies of the type II cell as a site of surfactant storage and Williams [57], also a long-time member of the San Francisco group, documented the intra-alveolar transformation of lamellar bodies to tubular myelin.

Accelerated Lung Maturation

In 1968, the New Zealand obstetrician Liggins [58] noted that following infusion of adrenocorticotrophic hormone, cortisol, or dexamethasone to the pregnant ewe premature lambs had unexpectedly mature lungs due to enzyme induction. He concluded that this may be used to reduce morbidity and mortality from RDS and, together with Howie, a pediatrician, Liggins [59] performed a controlled trial of betamethasone which proved his hypothesis that: 'RDS occurred less often in treated babies'. Antenatal glucocorticoid treatment significantly reduced the risk, severity, and mortality due to HMD in infants born at less than 32 weeks. Even though the study was published in English in 1972 and was quickly confirmed by other trials, sadly, it was not rapidly accepted by the scientific community. The obstetricians' reluctance increased further when a large collaborative trial of the National Institutes of Health, initiated in 1976 and published in 1981, failed to confirm the beneficial effect of antenatal steroids [60]. This delayed the universal adoption of Liggins' pioneering discovery, an intervention which also significantly reduced the incidence of cerebral

hemorrhage, for another 10 years, and illustrates how difficult it is for scientists in the USA to acknowledge progress achieved in other countries.

Surfactant Substitution

In his paper published in 1947, in which he demonstrated the correlation between surface tension and lung elasticity, Gruenwald [38] used amylnitrite as an exogenous surfactant to lower the surface tension at the air-water interface and speculated 'the addition of surface active substances to the air or oxygen which is being spontaneously breathed in or introduced by a respirator might aid in relieving the initial atelectasis of newborn infants'. A nebulized detergent mist, commercially available as 'Alevaire', was recommended by Ravenel [61] in 1953 as 'an almost infallible weapon for combating neonatal asphyxia due to the inhalation of amniotic fluid with or without atelectasis'. In 1955, however, Silverman and Andersen [62] published a controlled trial of 'Alevaire' which did not prove any 'therapeutic benefit as judged by death rate and autopsy findings that could be credited to Alevaire mist therapy of premature infants in the first 3 days of life'.

After Avery and Mead [14] had proved that infants who had died from HMD lacked pulmonary surfactant, and after the major surfactant component had been identified to be DPPC [47], this substance was employed in several clinical trials, usually in nebulized form. Robillard et al. [63] and later Shannon and Bunnell [64] treated a small number of infants, but their results did not encourage them to continue these studies. In a more extensive study directed by the Clements' Group from San Francisco and performed in Singapore in 1967, Chu et al. [65] showed that aerosolized DPPC did not have a positive effect and might even have had a negative effect on the clinical course of RDS. Therefore, it was clear that besides DPPC other components of natural surfactant were required for optimal effects *in vivo*. Starting in 1972, Enhorning and Robertson [66, 67] used surfactant extracts from adult rabbits to treat prematurely born rabbit pups and showed significant improvement in pulmonary mechanics. Similar studies were performed by Adams et al. [68] (including Tetsuro Fujiwara) in premature lambs in 1978 and from this work Fujiwara [69] used the recipe for the exogenous natural surfactant that first proved effective for the treatment of newborn infants with RDS. This surfactant was isolated by saline extraction from minced bovine lung and enriched with synthetic lipids.

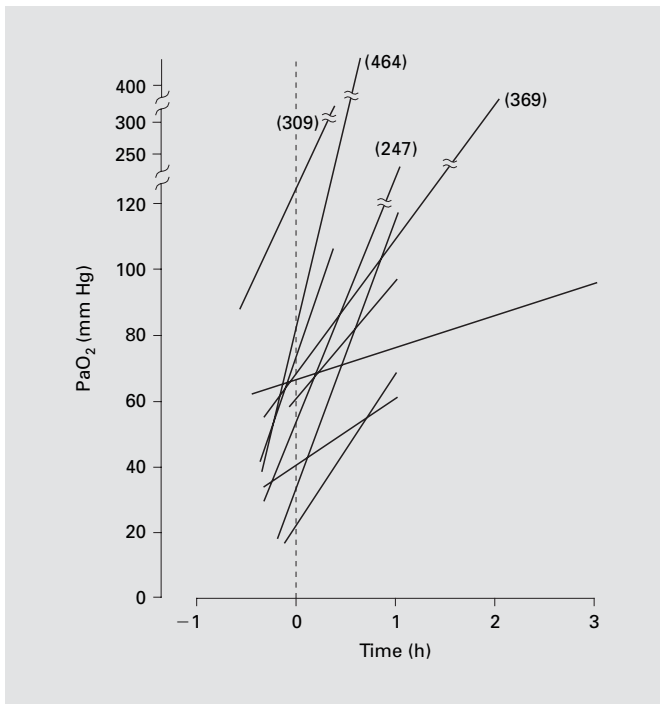


Fig. 3. Tetsuro Fujiwara's first 10 infants treated with surfactant, published in 1980. Changes of PaO₂ within 45 min before and 1–3 h after administration of surfactant extracted from bovine lungs and enriched with synthetic lipids [69].

At the Akita University in Japan, he treated 10 infants with severe RDS requiring ventilator support with high oxygen concentration. Within 3 h after endotracheal administration, arterial PO₂ rose from a mean of 45 (5.9) to 212 (27.9) mm Hg (kPa) and inspired oxygen could be lowered from 81 to 38% (fig. 3). After his pioneering report, several effective natural surfactants were prepared from calf lung lavage fluid [70], minced bovine and porcine lung [71], and human amniotic fluid [72]. A series of carefully controlled multicenter clinical trials has not only made surfactant substitution an exceptionally well-studied form of treatment [73–75], but also set high standards for the introduction of new drugs into pediatrics.

Conclusions

To identify the scientific hallmarks of surfactant research, it is very helpful to read Comroe's wise chapter 'Premature Science and Immature Lungs' in his book '*Retrospectroscope*' [33], Cone's [76] comprehensive '*History of the Care and Feeding of the Premature Infant*', and

Rooth and Saugstad's [77] collection of personal views in their '*The Roots of Perinatal Medicine*'. At least three lessons may be learned from the history of surfactant research:

First, not everything has been achieved within the last 5–10 years, the time interval to which we are educated to restrict the reference list of our publications. Even before nutrition and temperature-control became available for preterm infants, remarkable knowledge of the neonatal lung had accumulated by careful clinical and postmortem examination. Also, our present information, based on biochemical and physical studies as well as scientifically controlled trials, is only one point in a continuing process of learning. Research rarely leads to final answers, but often to better questions.

Second, the history of surfactant research illustrates how dramatically scientific progress changed from empiric knowledge to scientific observation at the end of the 18th century, then from systematic measurement to application of basic sciences during the 19th century, and from single experiments to the multidisciplinary teamwork in the 20th century.

Third, remarkable discoveries in perinatal medicine which were rejected, ignored, or forgotten after publication, also illustrate that the right idea of a talented researcher is not enough to ensure scientific progress: new findings have to be communicated at the right time, in the right language, and to the right readers who are capable of fully understanding their significance in order to promote future progress.

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