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SPECIAL ARTICLE

A History of Neonatal Medicine—Past Accomplishments, Lessons Learned, and Future Challenges. Part 1—The First Century

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This is the first of two articles that will review the history of neonatal medicine. This article will describe the beginnings of the modern era of newborn medicine, review pharmacological misadventures, and describe recent advances in the fields of neonatal and perinatal medicine.

KEYWORDS: incubator, infant mortality rate, neonatal medicine, pharmacological misadventures, surfactant

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INTRODUCTION

Historically, newborn medicine has been surrounded by controversy and affected by the ethical, cultural, and political values of the society in which it is practiced. The past 150 years have produced dramatic changes in neonatal and infant mortality and morbidity (Figures 1, 2);[1,2] the latter half of the 20th century in particular saw an explosion of new concepts and technology in perinatology and neonatology. The current practice of newborn medicine has been sculpted by significant recent accomplishments as well as by well-intentioned medical misadventures.

19TH CENTURY: FIRST INCUBATOR

Before the late 19th century, physicians essentially ignored infants. There were no institutions dedicated to the care of infants except foundling homes, where mortality rates were as high as 85% to 95%.[3] Industrialization in the 19th century, including the employment of women in factories, the associated increase in the use of artificial feeding (i.e., dry nursing), and child abandonment and the related development of foundling homes, resulted in the highest recorded infant mortality: more than 230/1,000 births in 1870.[4] These high infant death rates, coupled with falling birth rates in the late 19th century, provoked fears of depopulation and national defense vulnerability, spawning in Europe the Infant Welfare Movement (IWM) from 1870 to 1920. Seeking to preserve the lives of all infants, even those prematurely born, the IWM marked one of the first times newborn medicine was affected by political and social concerns. Incubators were built, special care nurseries were expanded, and

ABBREVIATIONS: AAP, American Academy of Pediatrics; AGA, appropriate for gestation; BPD, Bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; HMD, hyaline membrane disease; IWM, Infant Welfare Movement; LGA, large for gestation; NICU, Newborn Intensive Care Unit; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; RLF, retrolental fibroplasias; ROP, retinopathy of prematurity; SGA, small for gestation

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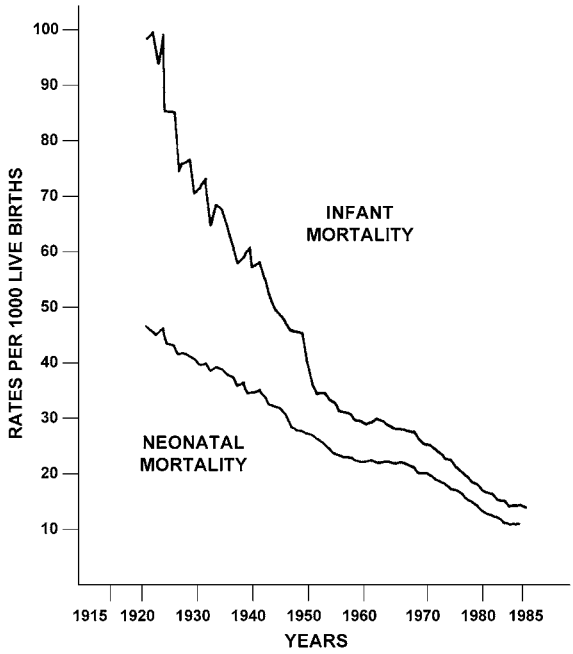

Figure 1. Infant and neonatal mortality rates for the United States, 1916–1985. The greatest decline in infant mortality occurred in the decade of the 1920s and between 1935 and 1949. In 1915 neonatal mortality accounted for 44% of infant mortality; in recent years it is 75% of the total. (Reprinted with permission of the American Journal of Perinatology, reference 1).

preventive "well baby" care was practiced.

A significant accomplishment in obstetrical and newborn care occurred in 1857 when Jean Louis Paul Denucé reported the first use of an incubator in the care of a premature infant.[5] Parisian obstetrician Stéphane Tarnier advanced this by modifying a warming chamber for the rearing of poultry to develop the Tarnier-Martin Couveuse (Figure 3) in 1878, an incubator that decreased the neonatal death rate from 66% to 38% among infants with birth weights of less than 2,000 grams.[6,7] Another Parisian obstetrician, Pièrre-Constant Budin, extended Tarnier's work,[8] and, as director of the Pavilion des Debiles at the Maternité in Paris, in the late 19th century established the principles and methods that form the basis of newborn medicine.

Martin A. Couney, the "Incubator Doctor" and a student of Budin's, moved to the United States in 1896 and became the first person there to offer specialized care for premature infants (Figure 4).[6] Carl Credé in Vienna introduced the use of silver nitrate to prevent ophthalmia neonatorum.[9] Cerebral palsy had previously been thought to be secondary to the irritation and convulsions of teething; however, William

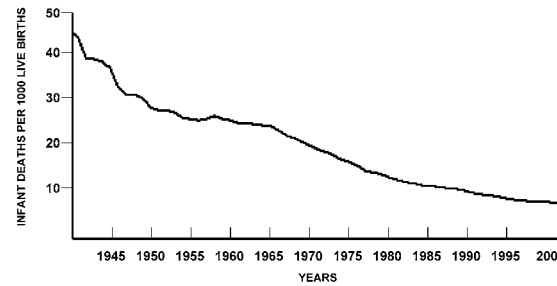

Figure 2. Deaths under 1 year of age per 1,000 live births. (National Vital Statistic System, NCHS, CDC, reference 2).

Little, an English orthopedic surgeon, linked birth trauma with cerebral palsy.[10] In addition, John Ballantyne, an Edinburgh obstetrician, designed the blueprint for the continuity of maternal-infant care. This marked the beginning of antenatal care, as Ballantyne, besides arguing for continuity of care, stated that maternal diseases such as syphilis, typhoid, and tuberculosis, and maternal ingestion of toxins adversely affected fetal health and growth.[11]

At the end of the 19th century, these medical and technical advances paralleled significant developments in care delivery. Foundling homes, originally opened for the care of abandoned children, were replaced with children's hospitals. Home deliveries gave way to hospital births. With hospital births increasing from less than 5% in 1900 to more than 50% in 1921, hospital nurseries began appearing and pediatricians assumed a larger role in neonatal care.[12]

1900s: INFANT MORTALITY RATES—A MIRROR OF THE NATION'S HEALTH

In this era, care of the premature infant was centered in the home, hospital "stations," and commercial premature institutions (exhibits). High institutional mortality in the United States, called "hospitalism" was prevalent, with infant mortality of 50% secondary to malnutrition and recurrent infections,[13] and as high as 78% for admitted premature infants.[14] With the expansion of the European IWM to the United States came a growing awareness that infant mortality rates reflected the overall health and welfare of the nation. A social movement to reduce infant mortality led to the establishment of a Federal Children's Bureau in 1912. Compared with their European colleagues, American physicians were slow to realize the

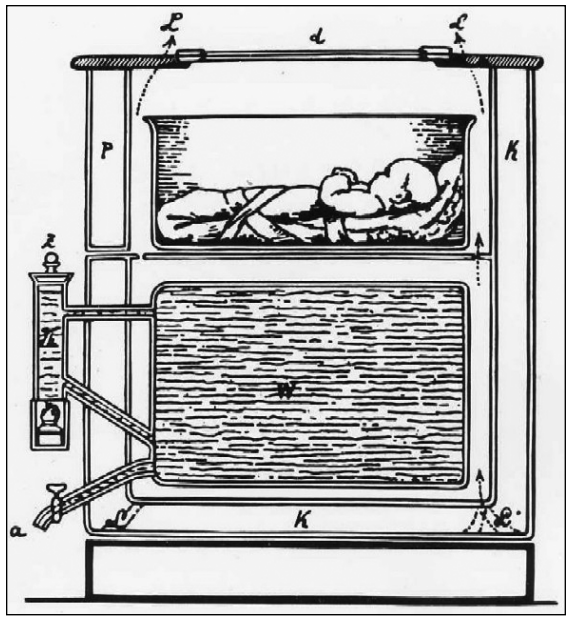

Figure 3. Tarnier-Martin Couveuse. A double-walled chamber (K) with a glass top (d). Warming was accomplished by heating water with an oil flame in an external "thermosyphon" (Th). The closed incubator was ventilated by a rising current of warm air (L). Water fill was via (Z), and drained through a pet-cock (a). (Reprinted with permission of the American Academy of Pediatrics, reference 6).

benefits of breastfeeding and the impact of the social environment on medical outcomes.

The early 1900s saw pediatricians beginning to contribute to the science of newborn medicine. Thomas Rotch's "percentage" feeding method, with precise proportions of milk, cream, and sugar modified and mixed daily to meet individual infant's needs, gave pediatricians the role of supervising the use of artificial infant formula when breast milk was unavailable.[15] Despite his now discredited recommendation of one or two drops of brandy or strychnine (1:1,000) for "stimulation" of cyanotic infants,[16] John Lovett Morse advanced newborn care by promoting the use of growth curves to establish energy demands.[17] At the Kaiserin Auguste Victoria Haus in Berlin, Leo Langstein and Arvo Y'ppo studied the pathology of prematurity, pre- and postnatal growth, and mortality rates of premature infants in relation to birth weight.

1910s: NEWBORNS IN A "NO-MAN'S LAND"

With a newly constructed U.S. birth registry in 1915 showing an infant mortality rate of 99.6/1,000 live births,[18] national awareness of the newborn's plight grew. Yet, the doctors

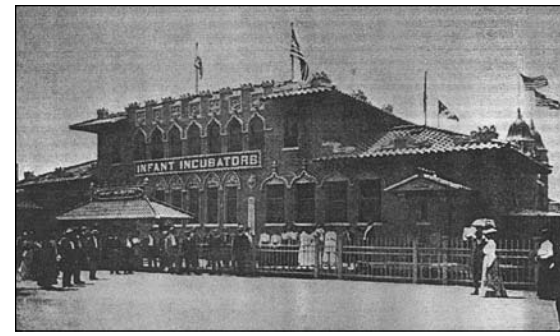

Figure 4. Martin A. Couney traveled to World's Fairs setting up public exhibits. This is a photograph of an infant incubator building at the Pan-American Exposition in Buffalo, New York in 1901. The facility included sleeping accommodations for two wet nurses, a nursery for bathing and feeding infants, a public viewing room, and a small pharmacy. (Reprinted with permission of the American Academy of Pediatrics, reference 6).

caring for newborns debated the merits of the obstetrician's focus on the incubator and prevention of early mortality vs. the pediatrician's focus on feeding and the prevention of infection. The relative merits of hospital-based physician care vs. home-based maternal care also were debated because of the high hospital mortality rates of this era. John Ballantyne in 1916 stated the newborn infant was in a "no-man's land" between obstetrics and pediatrics.[19]

Pediatricians like L. Emmett Holt, author of the influential 1897 textbook "The Diseases of Infancy and Childhood,"[20] nudged pediatrics further into newborn care. The care of the newborn entered the academic setting through the work of Julius Hess, chief of pediatrics at Michael Reese Hospital in Chicago. Hess established concepts of research in the newborn, developed the Hess Incubator (Figure 5), and became the leading American expert on prematurity.[6,21,22] The Sarah Morris Hospital affiliated with Michael Reese Hospital promoted advances in aseptic techniques, neonatal transport service, and nasal feeding under the leadership of the unit's nursing director, Evelyn Lundeen.[23]

1920s: INFANT CARE CARVES ITS OWN NICHE

The 1920s represented a time of consolidating and organizing the significant technological advances of the preceding decade. The Sheppard Towner Act of 1921 promoted maternal and infant welfare and supported birth and death

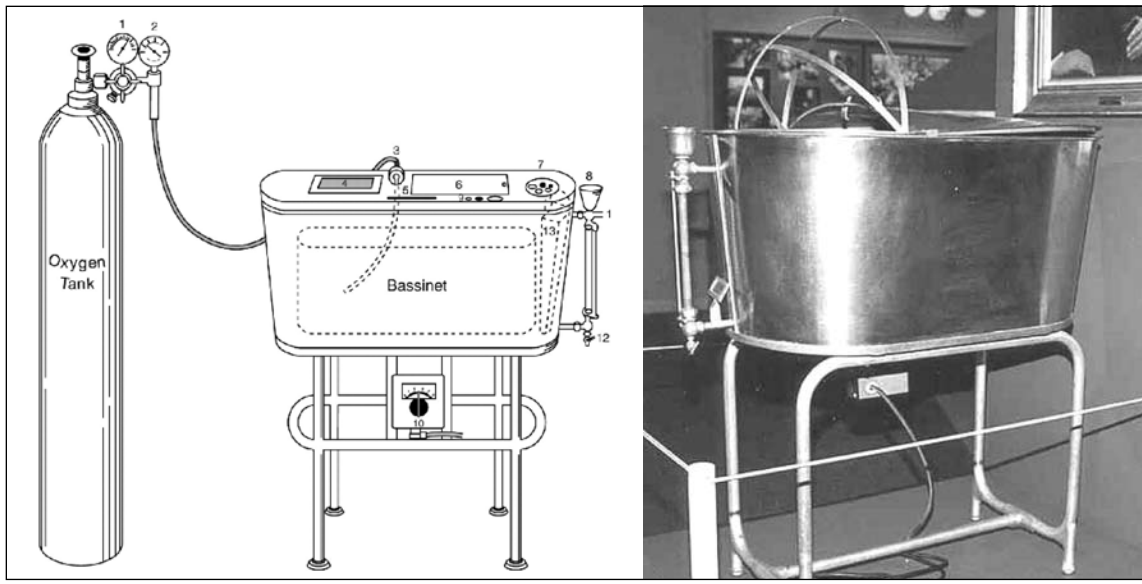

Figure 5. The Hess incubator. (reproduced with permission of the British Medical Journal Publishing Group, reference 22. Photograph courtesy of Tonse N. K. Raju, MD).

registries, state divisions of child hygiene, principles of infant care, and proposed scientific solutions for the social problems facing mothers and infants. As hospital deliveries increased and middle-class women arrived in maternity wards, pediatricians took further interest in newborn care. In 1922, premature infant care carved its own niche with the opening of the Sarah Morris Premature Center, the first unit solely for premature infants,[24] translating its experience into the Julius Hess textbook "Premature and Congenitally Diseased Infants,"[25] the first book devoted to this topic.

But the 1920s was not all progress. Misplaced concerns about infectious complications spelled the temporary downfall of the incubator. Spirit of ammonia and a small dose of whiskey were advocated for the management of infant apnea (Sarah Morris Hospital, 1922).[25] Infants were subjected to regimented feeding schedules that included awakening them for feedings, placing bottle nipples in boric acid, timing feedings strictly, and giving water before feeding to manage thirst and regulate temperature. Strict patient isolation protocols in newborn nurseries reduced newborn epidemics but resulted in maternal-infant separation, impaired mother-infant bonding, and less breastfeeding.

1930s: REBIRTH OF THE INCUBATOR

Infections and diarrhea in newborns declined with improved nursery protocols, better hygiene, and the use of breast milk. For the first time, death secondary to prematurity exceeded those caused by infection. The '30s also saw the revival of the incubator, with the development of the Hess oxygen box in 1934,[26] which could deliver oxygen to treat respiratory distress.

Although the first clinical report of oxygen use for premature or cyanotic infants appeared in 1891,[27] oxygen in the decade of the '30s was treated as a pharmacological agent and often was administered with a second stimulant, such as brandy. The Hess Incubator was used in the United States' first dedicated neonatal transport vehicle in Chicago. The incubator, which was heated by hot plate-like coils that plugged into the ambulance, also contained holy water (perhaps an indication of the high mortality rates).

1940s: CLINICAL TRIUMPHS, NEW CHALLENGES

As the guns of World War II quieted, a "therapeutic explosion" in newborn medicine, with advances in blood banking, fluid therapy, and antibiotics, heralded modern neonatology with both clinical triumphs and iatrogenic diseases. Ninety percent of deliveries now occurred in hospitals, resulting in the construction of new nursery facilities. Pediatricians were increas-

ingly involved in the delivery room and began ordering tests from clinical laboratories and radiological facilities, assessing infant electrocardiograms, administering fluids through peripheral veins (rather than the peritoneal cavity, the sagittal sinus, or subcutaneous tissues), and treating newborns with an expanding arsenal of antibiotics. Fifty percent survival at 28 days of age was achieved for infants with birth weights under 1,800 grams (Figure 6).[28]

Advances in diagnosis included N. McAlister Gregg's discovery of the link between maternal rubella infection and congenital rubella syndrome, and Louis K. Diamond's description of the link between Rh factor and erythroblastosis fetalis. New therapy followed shortly with Diamond's introduction of double volume exchange transfusion, which prevented most cases of kernicterus and saved an estimated 8,000 lives per year in the United States.[29] The prevention of erythroblastosis fetalis was eventually made possible by the introduction of RhoGAM in 1963.[30]

Hemorrhagic disease of the newborn was first described in 1894.[31] In 1939 W.W. Waddell and D. Guerry discussed the role of vitamin K in preventing hemorrhagic disease of the newborn.[32] This disease was most prevalent in breastfed infants because of the low vitamin K content of breast milk. The prophylactic use of vitamin K in newborns began in the early 1940s and was the second routine pharmacological treatment used in newborns. The first was the use of silver nitrate to prevent ophthalmia neonatorum by Carl Segmund Crede in 1881.[7]

With technological advances came a significant iatrogenic disease, retrolental fibroplasia (RLF), currently redefined as retinopathy of prematurity (ROP), from excessive oxygen administration. RLF was responsible for more childhood blindness, an estimated 8,000 cases, than all other causes combined. The association between oxygen therapy and RLF was eventually determined by Kate Campbell of Australia in 1951.[33] An interesting part of the medical dilemma of RLF was the proposed treatment with adrenocorticotropin. Early results were promising, but a controlled trial was performed and showed no benefit. This was the first randomized controlled trial in newborn medicine.[34]

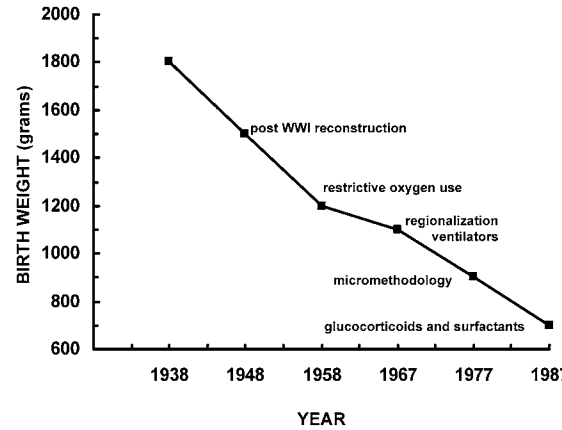

Figure 6. Approximately 50% survival (28 days) by birth weight for 1938–1987. Survival is juxtaposed with some of the significant perinatal advances of the decade. (Reprinted with permission of Neonatal Network, reference 28).

1950s: NEWBORNS AS BONA FIDE PATIENTS

Before 1950, little scientific effort was directed at the premature and seriously ill infant. There was limited peripheral or central intravenous access, and no means of mechanical ventilation or laboratory micro-methods for analysis of blood samples. Women were not allowed in the "premature nursery" because of concern about exposing infants to infectious diseases. There were no cardio-respiratory monitors. Infant apnea was managed solely by observation, and apnea episodes were managed by pulling on a gauze string attached to the infant's foot. Insights into fetal and neonatal physiology, perinatal diseases, and the pathogenesis of in utero and neonatal diseases produced clinical benefits in infant nutrition, RLF, hyaline membrane disease (HMD), and antibiotic therapy.

Basic science led to clinical treatment, with Richard Pattle's discovery of the surface-tension-lowering properties of the alveolar lining layer[35] and John Clements's finding in 1957 that surface tension depends on surface area.[36] Mary Ellen Avery's and Jere Mead's description of surfactant deficiency as the etiology of HMD,[37] a disease that caused an estimated 25,000 deaths per year,[38] soon followed. This laid the foundation for the eventual administration of surfactant to premature infants, a treatment that revolutionized the field, reducing neonatal mortality from HMD (now known

as respiratory distress syndrome, [RDS]) by 40%.[39] William A. Silverman demonstrated that maintaining body temperature by controlling the thermal environment significantly decreased low-birth-weight mortality.[40] Due to this discovery, thermal management and the concept of a "neutral thermal environment" (the environmental temperature at which an infant can maintain a normal central temperature without physiological changes) became cornerstones of neonatology.

In this decade, newborn infants came to be viewed as patients. Virginia Apgar, MD, MPH, developed the Apgar Scoring System, which changed the newborn from a delivery room "byproduct" to a new patient.[41] In the '50s and '60s, premature and seriously ill infants began to be transported to regional centers to receive the best care available. The change in name from premature nursery to special care nursery reflected the new significance of critically ill newborns.

An unusual neonatal resuscitation device called the Bloxsom air-lock was introduced in 1950 (Figure 7).[42,43] It consisted of a tightly closed chamber with humidified oxygen at approximately 60%, with the ability to cycle changes in pressure. Eventually, a properly performed study showed no benefit from its use.[44] This is another example of a well intended therapeutic intervention being introduced into clinical care before it was critically evaluated; a theme that recurs throughout the early history of newborn medicine.

As much as newborns benefited from medicine's advances, they unfortunately also suffered from its faulty knowledge. The '50s and early '60s were the years of early starvation, when the first feeding was delayed for two to three days in sick or premature infants because of concerns about aspiration pneumonia[45] resulting in severe weight loss, frequently as great as 20%. In the '50s, with Jonathan Lanmann's recognition that hyperoxia was causing RLF,[46] restricted oxygen use caused increased deaths from respiratory distress and in the survivors an increased incidence of cerebral palsy. Two iatrogenic diseases related to drug use, the lethal "gray baby" syndrome (from the use of chloramphenicol in premature infants) and kernicterus (from sulfisoxazole prophylaxis) were identified and their pathogenesis clarified. This period's frequent medical misadventures provoked this comment in *Lancet:* "Modern neonatal iatrogenesis reached a peak when almost every major error in newborn care was widely practiced, at least for a time."[47]

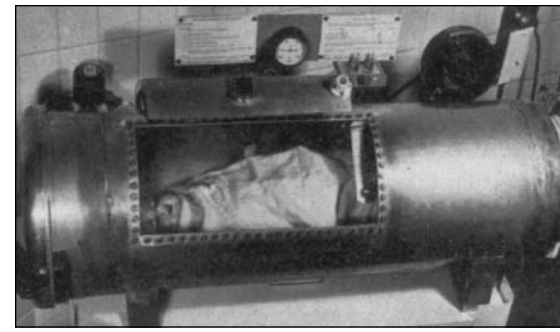

Figure 7. The Bloxsom Positive Pressure Oxygen Air Lock Device (Reprinted with permission of the American Academy of Pediatrics, reference 43).

Newborns didn't reap the expected benefits of this era's technological advances. Poverty and deterioration of maternal infant care in America's inner cities prevented the expected annual decrease in infant mortality. Infant mortality rates were 28/1,000 births in the '40s and 21/1,000 births in the '50s.[48] Although newborn medicine had made significant gains in the first half of the 20th century, clearly there was much more to accomplish.

1960s: CONTEMPORARY NEWBORN MEDICINE

Most consider this decade the start of the current "modern practice" of newborn medicine, and the time when the premature nursery became the Newborn Intensive Care Unit (NICU). Sparked by the much-publicized 1963 birth and subsequent death secondary to RDS of President Kennedy's son at 32 weeks gestation, the focus of preterm infant care shifted from temperature control, feeding, and vulnerability to diseases to a more comprehensive and scientific approach to newborn infant care. Declaring neonatal mortality unacceptably high, Congress significantly increased neonatal research funding to the National Institutes of Health. Advances occurred in respiratory support, fluid therapy, assessment of low-birth-weight infants, temperature regulation, and the treatment of erythroblastosis fetalis. The terms "neonatology" and "neonatologist" were

introduced by Alexander Schaeffer in his landmark textbook "Diseases of the Newborn."[49]

Initial neonatal ventilators, such as the Puritan Bennett and the Baby Bird, were adapted from adult models of the Bird Respirator and the Bloxom Air Lock Respirator (iron lung type) and delivered ventilation without continuous positive airway pressure (CPAP).[50] Prior to this time, attempts to treat RDS consisted of little more than a towel clip around the xiphoid process suspended from the incubator roof with a rubber band.[51]

By the middle of this decade, disposable butterfly scalp vein needles facilitated the use of intravenous fluids, replacing clysis (in which 30 to 60 mLs of glucose solution with hyaluronidase was injected subcutaneously over the scapular and lumbar regions, rotating the sites and sealing over the injection site with collodion),[52] rectal, sagittal sinus (also used for blood draws), and intraperitoneal infusions.[53] During this time it was routine not to feed infants experiencing respiratory distress**.** This resulted in a catabolic state with accompanying acidosis and azotemia. Robert Usher introduced intravenous dextrose water with sodium bicarbonate to buffer the respiratory acidosis. This approach, referred to as the Usher Regime, reduced mortality from 37% to 17% among affected infants with birth weights of 900 to 2,500 g.[54] In 1968 total parenteral nutrition was first used for surgical long-term NPO patients, and soon after for non-surgical infants.

The development of the Rh antibody prophylactic program for Rh-negative mothers in the late 1960s is considered by many as one of the most important developments in perinatal medicine of our time. Prior to the use of RhoGAM, 1 in 100 babies were affected with a high risk of intrauterine demise or neonatal hydrops.[55] Ninety-five percent of the cases are now prevented, with an accompanying dramatic decrease in the need for double volume exchange transfusions and the occurrence of kernicterus.

Lula O. Lubchenco introduced the concept of small (SGA), large (LGA), and appropriate for gestation (AGA) infants by correlating intrauterine growth with gestational age.[56] This improved the assessment and management of problems unique to the premature, SGA, and the LGA infant, and provided a standard for postnatal growth of prematurely born infants. This was followed by a more comprehensive description of newborn infants based on birth weight and gestational age.[57] Despite this decade's progress, at its end, infants of 28 weeks gestation or less were still frequently considered pre-viable.

1970s: BREATHING EASIER

Remarkable advances in the respiratory management of the premature infant occurred during the 1970s. The landmark study by George Gregory illustrating the benefits of CPAP[58] resulted in a dramatic improvement in the successful respiratory support of premature infants, which at the start of this decade was only 10% for infants with birth weights under 1,500 grams.[52] The first generation of ventilators designed specifically for neonatal use (Baby Bird I and Bournes BP 200) introduced time-cycled, pressure-limited, continuous flow with CPAP, intermittent mandatory ventilation. Respiratory monitoring improved with the introduction of transcutaneous oxygen assessment,[59] followed by transcutaneous carbon dioxide, pulse oximetry, routine blood gas monitoring, and noninvasive apnea, heart rate, and blood pressure monitoring.

Families and nurse practitioners expanded their roles in the neonatal intensive care unit. Recognizing the need for specialized neonatal nursing care, Steven Boros at St. Paul Children's Hospital developed and implemented the role of the advanced practice nurse.[60] At the same time, pharmacists with advanced clinical training and skills were beginning to provide pharmacologic and therapeutic interventions. Activities included improved drug dosing, often guided by therapeutic drug monitoring and pharmacokinetic adjustments;[61,62] assistance with optimum drug selection and monitoring strategies;[61] detection of fetal drug effects by improved maternal drug histories;[63] and managing parenteral nutrition strategies.[64] Many pharmacists subsequently made important contributions in defining the unique pharmacokinetics and therapeutic ranges of drugs in neonates, and created excellent dosing handbooks.[65-67] The early activities of these pioneers and subsequent valuable contributions of

other pharmacists to service and research in neonates has lead to a widespread appreciation by most neonatologists of the need for a pharmacist presence in the NICU.

Not only did a variety of healthcare practitioners expand their roles in NICU, but families who were previously excluded from the NICU because they were considered infectious disease risks became an integral part of the health care team. Parent support groups were developed, fathers obtained "nonvisitor" status, and breastfeeding was encouraged. This decade witnessed the introduction of routine eye exams to evaluate for ROP, head ultrasounds to assess for intracranial hemorrhage, organized follow-up of the high-risk NICU graduate, and research-based quality outcome assessments. It also saw the use of prenatal glucocorticoids to induce lung maturation and decrease the incidence of RDS, the initial trials of surfactant replacement therapy in animals, continued improvement in incubator design, and the first successful use of extracorporeal membrane oxygenation (ECMO) in 1975.[68] ECMO eventually reduced infant mortality from 80% to 25% for critically ill infants with acute reversible respiratory and cardiac failure unresponsive to conventional therapy in conditions such as persistent pulmonary hypertension, meconium aspiration, and sepsis.

In the late 1970s extensive clinical investigations ensued after the discovery in 1971 by J. R. Vane that non steroidal anti-inflammatory drugs block the activity of prostaglandins acting on the cyclooxygenase enzyme which catalyzes a key step in prostaglandin synthesis.[69] The use of indomethacin in the management of the patent ductus arteriosus was then established.[70] A review of the literature in 2003 showed no significant benefit to the use of ibuprofen and recommended that indomethacin should remain the drug of choice. An extended use of indomethacin emerged in 1988 as prophylactic treatment of intraventricular hemorrhage in very low birth weight infants.[71] As early as 1985 a serious side effect of indomethacin was reported, isolated intestinal perforation.[72] Conversely, the use of prostaglandin E_1 was instituted to maintain patency of the ductus arteriosus in ductus-dependent congenital heart disease.[73] Indomethacin was also being used as a tocolytic agent.[74] By the end of this decade, newborn medicine had achieved a 50% survival rate for infants with birth weights of 900 grams and gestational ages of 27 weeks (Figure 6).[28]

1980s: SURFACTANT THERAPY

The single most significant accomplishment of the '80s was Tetsuro Fugiwara's first successful administration of surfactant to a newborn in 1980.[75] This was a period of extensive worldwide clinical research in the use of surfactant therapy for premature infants born with RDS.[76] Surfactant replacement therapy revolutionized newborn care, dramatically decreasing mortality and morbidity rates.

Persistent pulmonary hypertension of the newborn (PPHN) secondary to sepsis, meconium aspiration syndrome, or pulmonary hypoplasia was associated with high rates of neonatal mortality and morbidity. In 1980 Furchgott and Zawadzki identified a vasodilator called endothelium-derived growth factor.[77] Ignarro eventually characterized this as nitric oxide in 1987.[78] Initial trials using this gas showed a decrease in the need for ECMO by 40%.[79] The FDA approved the use of inhaled nitric oxide for PPHN in 1999.

In the late '80s, family-centered care expanded, with sibling visitation policies, support groups, antepartum consultations, parental rooming-in, kangaroo care (skin-to-skin contact between parents and their infants), and multidisciplinary developmental committees becoming common place.

Bedside pulmonary function tests were introduced by Cunningham and Desai,[80] follow-up outcome studies were published, cryosurgery for ROP was introduced, and the American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists published the first edition of "Guidelines in Perinatal Care" in 1983.[81] The AAP and the American Heart Association introduced neonatal advanced life support with the goal of having qualified personnel in neonatal resuscitation readily available for every delivery in the country.

As technological progress resulted in smaller and sicker infants admitted to the NICUs, complex ethical issues emerged. Corporate America entered the NICU. Competition in-

creased among corporate health care systems, and neonatal physicians then numbered 2,000. The regionalization of the '60s and '70s was unraveling.

PHARMACOLOGICAL MISADVENTURES IN NEWBORN MEDICINE

Newborn medicine has been a rapidly changing field of practice with a history of a long list of treatments and procedures instituted into clinical practice without controlled outcome measurements and therefore an inability to critically assess risks and benefits. There have been periods of "therapeutic exuberance"[82] where physicians entered into clinical care with a "great spirit of innovation, somewhat lacking discipline".[83] These misguided efforts were always with the best of intentions, unfortunately sometimes with devastating results. The following is a review of this topic in newborn medicine as it pertains to the field of pharmacology.

Synthetic vitamin K prophylaxis

In the 1950s premature infants were being treated with large doses of vitamin K in an attempt to prevent bleeding. In some infants the cumulative doses exceeded 50 mg. During this time period there was an associated dramatic increase in hemolytic anemia, hyperbilirubinemia, and kernicterus.[84] The exact mechanism of this associated toxicity has not been elucidated. Interestingly, a review of this topic could not find any publications that gave a rationale for, or even advocated this large dose of vitamin K.

Sufisoxazole prophylaxis

The historical basis for antibiotic prophylaxis in newborn infants was laid by the puerperal sepsis epidemics of the mid-1800s. In 1953 sulfisoxazole, a newly available sulfonamide, was introduced. The purported advantage was a less frequent dosing to maintain adequate blood levels. Subsequently, it was shown that there was an increased mortality rate and occurrence of kernicterus.[85] G.B. O'Dell showed that the kernicterus was caused by the competition of the sulfonamide with bilirubin for albumin binding sites resulting in increased levels of free bilirubin that easily crossed the blood brain barrier.[86] It is important to note that the FDA requires no screening of drugs for their effect on bilirubin-albumin binding, and that few laboratories currently have expertise in this area.

Chloramphenicol prophylaxis

Chloramphenicol was discovered by Burkholder of Yale in 1947. The drug was synthesized in the research laboratories of Parke, Davis & Co. and placed on the market in 1949 as the first broad spectrum antibiotic. Despite Alexander's advice in 1956 recommending a trial before its use in newborn infants[87] widespread use ensued. Sutherland first reported the cardiovascular collapse of newborns exposed to high serum concentrations of chloramphenicol in 1959.[88] These infants developed a slate-colored, or pallid, cyanosis shortly before their demise (hence the term "gray baby" syndrome). The use of chloramphenicol in neonates was stopped in 1960. An important result of this experience was the development of the recommendation that serum drug concentrations be determined during antibiotic therapy.[88]

Hexachlorophene

In the 1960s 3% hexachlorophene (HCP) soap was used on infants upon admission to the nursery and then every other day during their hospitalization. This was done to decrease the high rate of *staphylococcus aureus* infections in nurseries at the time. HCP (2,2'-Methylenebis [3,4,6-trichlorophenol]) was patented in 1941 and was widely used in soaps, cosmetics, and antiseptic solutions. It was not until 1973 when a *Morbidity and Mortality Weekly Report* described the spongiform myelinopathy of the brainstem of exposed infants that an association was made with the clinical neurological deterioration previously described in case reports in the 1960s.[89]

Benzyl Alcohol

Benzyl alcohol is a constituent of jasmine, hyacinth, ylang-ylang oils and balsam. It was synthesized in 1853. In 1942 The United States Pharmacopeia required all medications in multiple dose vials to contain a bacteriostatic agent.[90] Umbilical venous and arterial catheters came into routine use by 1972, and these catheters were frequently flushed with

normal saline containing bacteriostatic 0.9% benzyl alcohol. In 1981 a "gasping" syndrome was described that included a metabolic acidosis, hepatic and renal failure, neurological deterioration, and gasping respiratory efforts.[91] The causative agent was felt to be benzoic acid, a metabolite of benzyl alcohol. In 1982 the FDA issued a recommendation to discontinue the use of benzyl alcohol. At this time it was estimated that approximately 70% of NICUs were using this agent.[92] It has been estimated that the annual number of deaths attributed to benzyl alcohol during this period of time exceeded 1,800.[93] After the discontinuation of its use there was a significant decrease in the rate of kernicterus and intraventricular hemorrhage in autopsies of preterm infants. Benzoate, a metabolite of benzyl alcohol, is known to displace bilirubin from albumin binding sites.[94]

Intravenous vitamin E

Vitamin E was discovered in 1922 by Evans and Bishop.[95] In 1949, W.C. Owens and E.U. Owens postulated that the pathogenesis of RLF was related to a deficiency of vitamin E. Early trials showed no benefit from supplementation. Preterm infants were often not fed for extended periods and because of valid concerns related to painful intramuscular shots an intravenous form of vitamin E (E-ferol Injection, Carter-Glogau Laboratories) was developed and made available in 1983. Even though there was no good evidence of efficacy in the prevention of RLF, nor FDA approval of its use, E-ferol Injection was widely accepted by neonatologists, ultimately resulting in the deaths of approximately 40 infants. The clinical course consisted of hepatomegaly, thrombocytopenia, cholestatic jaundice, ascites, and azotemia. The most likely agent causing these deaths was the solubilizer polysorbate in the E-ferol preparation.[96] Both Carter-Glogau Laboratories and O'Neal, Jones and Feldman Pharmaceuticals (the distributor) were forced out of business because of these events.

Steroids

Bronchopulmonary dysplasia (BPD) was first described by Northway in 1967.[97] BPD, in clinical practice defined as ongoing oxygen requirements at 36 weeks postmenstrual age, occurs most frequently in prematurely born infants who require prolonged mechanical ventilation and supplemental oxygen. BPD is associated with other long-term pulmonary complications, growth impairment, cardiovascular sequelae, and neurodevelopmental problems. It has been characterized as an iatrogenic nightmare and one of the greatest disappointments in neonatal care.[91] It is therefore understandable that neonatologists embraced the use of dexamethasone in the management of BPD. In routine clinical care dexamethasone caused rapid improvement in lung function allowing a faster weaning from mechanical ventilation and oxygen requirements. However, there was no data showing long-term benefit from a pulmonary perspective. As its use became more widespread there was accumulating evidence of side effects consisting of growth retardation, hyperglycemia, increased rates of infections, systemic arterial hypertension, gastrointestinal perforation and hemorrhage, and adrenal insufficiency. Regardless of these serious side effects the use of dexamethasone continued as clinicians tilted the scale towards the beneficial pulmonary effects. In 2002 with growing concerns about neurological sequelae, the AAP Committee on Fetus and Newborn recommended against the use of corticosteroids in all but "…exceptional clinical circumstances."[98]

CONCLUDING COMMENTS

A.F. Robertson, of the Brody School of Medicine at East Carolina University, cautions: "New pharmacological agents have been and will continue to be a danger in neonatology. Many adverse affects may not be seen in small population studies performed for drug licensing. Manufacturers often prefer to avoid the issue and exclude neonates from the drug's indications for use."[93] In clinical practice this exclusion has little effect because "off-label" use of drugs (in a formulation, dosage, or condition not covered by licensure) in neonatology is extremely common.[99] In addition, the AAP Committee on Drugs states "Physicians who choose to prescribe a medication with limited pediatric data have a public and professional responsibility to assist in the systematic development of the information about that drug for the benefit of other patients."[99]

The second and final article in this series will cover the decade of the 1990s. The Micropremie, current mortality and morbidity outcome data, and future challenges in the fields of neonatal and perinatal medicine will be reviewed.

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