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A Century of Neonatal Medicine

Technological advances and changing social values have led to stunning gains in newborn medicine.

By Richard C. Lussky, M.D.

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 (Figure 1); the latter half of the 20th century in particular has seen 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 medical misadventures. Here are some of the highlights.

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%.[1] Industrialization in the 19th century, including the employment of women in factories, the associated increase in 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.[2]

These high infant death rates, coupled with falling birth rates in the late 19th century, provoked fears of depopulation and national defense vulnerability, and in Europe spawned 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 preventive "well baby" care was practiced.

Parisian obstetrician Stéphane Tarnier modified a warming chamber for the rearing of poultry to develop the Tarnier-Martin Couveuse (Figure 2) in 1878, an isolette that decreased the neonatal death rate to 38% from 66% among infants with birth weights less than 2,000 grams.[3] Another Parisian obstetrician, Pièrre-Constant Budin, extended Tarnier's work,[4] and, as director of the Pavilion des Debiles at the Maternité in Paris, in the late 19th century developed the principles and methods that form the basis of newborn medicine.

Still other significant accomplishments occurred in obstetrical and newborn care during this era. Jean Louis Paul Denucé in 1857 reported the first use of an incubator in the care of a premature infant.[5] 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.[6] (See Figure 3.) Carl Credé in Vienna introduced the use of silver nitrate to prevent ophthalmia neonatorum,[7] and William Little, an English orthopedic surgeon, linked birth trauma with cerebral palsy.[8] (Cerebral palsy had previously been thought to be secondary to the irritation and convulsions of teething.) 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.[9]

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 being 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,[10] hospital nurseries began appearing, and pediatricians assumed a larger role in neonatal care.

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,[11] and 78% for admitted premature infants.[12] 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 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 infants' needs, gave pediatricians the role of supervising the use of artificial infant formula when breast milk was unavailable.[13] Despite his now discredited recommendation of one or two drops of brandy or strychnine (1:1,000) for "stimulation" of cyanotic infants,[14] John Lovett Morse advanced newborn care by promoting the use of growth curves to establish energy demands.[15] 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,[16] national awareness of the newborn's plight grew. Yet the doctors 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 said the newborn infant was in a "no-man's land" between obstetrics and pediatrics.[17]

Pediatricians like L. Emmett Holt, author of the influential 1897 textbook "The Diseases of Infancy and Childhood,"[18] 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 4), and became the leading American expert on prematurity.[6] The Sarah Morris Hospital at 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.[19]

1920s: Infant Care Carves Its Own Niche

The 1920s represented a time of consolidating and organizing the dramatic technological advances of the preceding decade. The Sheppard Towner Act of 1921 promoted maternal and infant welfare and supported birth and death registries, principles of infant care, state divisions of child hygiene, and scientific solutions for the social problems facing mothers and infants. As hospital deliveries increased and middle-class women arrived in maternity wards, pediatricians took new 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,[3] and with the publication of Julius Hess's textbook "Premature and Congenitally Diseased Infants,"[20] 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).[21] 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. Strictly isolating 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, deaths 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,[22] which could deliver oxygen to treat respiratory distress.

Although the first clinical report of oxygen use for premature or cyanotic infants appeared in 1891,[23] oxygen in this decade 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 (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 increasingly involved in the delivery room and began ordering tests from microchemical laboratories and radiologic facilities, examining infant electrocardiograms, administering fluids from peripheral veins (rather than the peritoneal cavity, the sagittal sinus, or subcutaneous tissues), and treating newborns with an expanding pharmacy of antibiotics. Fifty percent survival at 28 days of age was achieved for infants with birth weights under 1,800 grams.[24] (See Figure 5, page 52.)

Advances in diagnosis included N. McAlister Gregg's 1941 discovery of the link between maternal rubella infection and congenital rubella syndrome, and Louis K. Diamond's 1942 description of the link between Rh factor and erythroblastosis fetalis. New therapy followed shortly in 1946 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.[25] The prevention of erythroblastosis fetalis was eventually made possible by the introduction of RhoGAM in 1963.[26]

With technological advances came a significant iatrogenic disease, retrolental fibroplasia (RLF), 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 Cambell of Australia in 1951.[27]

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 microchemical laboratory determinations. Women were not allowed in the "premature nursery" because of concern about exposing infants to infectious diseases. There were no cardiorespiratory monitors. Infant apnea was managed solely by observation, and apneic infants were stimulated 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[28] and John Clement's finding in 1957 that surface tension depends on surface area.[29] Mary Ellen Avery's and Jere Mead's description of surfactant deficiency as the etiology of HMD,[30] a disease that caused an estimated 25,000 deaths per year,[31] 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%.[32] William A. Silverman demonstrated that maintaining body temperature by controlling the thermal environment significantly decreased low-birth-weight mortality.[33] With this discovery, thermal management became a cornerstone of neonatology.

In this decade, newborn infants came to be viewed as patients. Virginia Apgar, M.D., M.P.H., developed the Apgar Scoring System, which changed the newborn from a delivery room "byproduct" to a new patient.[34] In the '50s and '60s, premature and seriously ill infants began to be transported to regional centers to receive the best care available. The changes in name from premature nursery to special care nursery, and then to newborn intensive care unit (NBICU) reflected the new significance of critically ill newborns.

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.[35] The result was severe weight loss, frequently as great as 20%. In the '50s, with Jonathan Lanmann's recognition that hyperoxia was causing RLF,[36] restricted oxygen use caused increased

deaths from respiratory distress. 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." [37]

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.[38] 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 physicians consider this decade the start of the current "modern practice" of newborn medicine, and the time when the premature nursery became the NBICU. Sparked by the much-publicized 1963 birth and subsequent RDS death of President Kennedy's son, Patrick Bouvier Kennedy, 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 by 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." [39]

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).[40] The Usher Regime, which consisted of intravenous dextrose water with sodium bicarbonate to buffer the respiratory acidosis and Ce-Vi-Sol to decrease pulmonary capillary permeability, was used to treat RDS. In contrast, the earliest 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.[41]

By the middle of this decade, disposable scalp vein needles enabled the use of intravenous fluids, replacing clysis (in which 30 mls to 60 mls of glucose solution with Wydase® were injected subcutaneously over the scapular and kidney regions, rotating the sites and sealing over the injection site with collodion), [42] rectal, sagittal sinus (also used for blood draws), and intraperitoneal infusions.[43] In 1968 total parenteral nutrition was first used for surgical long-term NPO patients, and soon after for nonsurgical infants.

Lula O. Lubchenco introduced the concepts of small (SGA), large (LGA), and appropriate for gestation (AGA) infants with her publication of data correlating intrauterine growth with gestational age.[44] This improved the assessment and management of problems unique to the premature and SGA or 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.[45] Despite this decade's progress, at its end, infants of 28 weeks gestation or less were still frequently considered previable.

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 success of CPAP[46] 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.[42] 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,[47] 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, Steve Boros at St. Paul Children's Hospital developed and implemented the role of the advanced practice nurse.[48] Families, previously excluded because they were considered infectious disease risks, became an integral part of the NBICU 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 retinopathy of prematurity (ROP); head ultrasounds to assess for intraventricular hemorrhage (IVH); organized follow-up of the high-risk NBICU graduate; and research-based quality outcome assessments. It also saw the use of prenatal glucocorticoids to decrease RDS, initial trials of surfactant replacement therapy in animals, continued improvement in isolette design, and the first successful use of extracorporeal membrane oxygenation (ECMO) in 1975.[49] 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, meconiumaspiration, and sepsis.

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 5).

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.[50] This was a period of extensive clinical research in the use of surfactant therapy for premature infants born with RDS.[51] Surfactant replacement therapy revolutionized newborn care, dramatically decreasing mortality and morbidity rates.

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 infants), and multidisciplinary developmental committees.

Bedside pulmonary function tests (PFTs) were introduced by M. Douglas Cunningham,[52] follow-up outcome studies were published, cryosurgery for ROP was introduced, and the AAP and American College of Obstetricians and Gynecologists published the first edition of "Guidelines in Perinatal Care" in 1983.[53] The AAP and the American Heart Association introduced neonatal advanced life support with the goal of having qualified personnel in neonatal resuscitation attending every delivery in the country.

As technological progress resulted in smaller and sicker infants in NBICUs, difficult ethical issues emerged. And corporate America entered the NBICU. Competition increased among corporate health care systems, and neonatal physicians now numbered 2,000. The regionalization of the '60s and '70s was unraveling.

1990s: The Micropreemie

The '90s has been the decade of the micropreemie. Successful treatment of these newborns, with gestational ages of 23 to 25 weeks and birth weights of 500 to 750 grams, has been made possible by surfactant replacement therapy, improved perinatal management (including prenatal steroids), new technologies for maintaining temperature, precision micromanagement of fluid delivery, sophisticated nutritional management, and continued improvement in ventilatory management (e.g., patient-triggered ventilation, high-frequency ventilators, pressure and volume support ventilators, and in-line PFTs).

A number of significant accomplishments have occurred in the past 10 years. In 1992, the AAP initiated what eventually became the "Back to Sleep" campaign, which reduced the rate of SIDS by two-thirds, to 0.694/1,000, in 1997.[54] In 1994 the Pediatric AIDS Clinical Trials Group Protocol 076 was published, recommending perinatal zidovudine, which decreased the perinatal transmission of HIV by two-thirds.[55] Heidelise Als introduced the Newborn Individualized Developmental Care and Assessment Program, which supported family-centered, individualized developmental care for premature infants[56] while shortening ventilator days and improving developmental outcomes of NBICU graduates.[57] The development of interinstitutional, randomized, prospective studies and databases continued. There was increased awareness of the "neonatal golden hour" of delivery room and early management and how it affects long-term outcome, with the beneficial use of prophylactic surfactant, institution of early CPAP, and use of indomethacin for the prevention of severe IVH. Other significant developments were the introduction of nitric oxide for pulmonary hypertension, erythropoietin administration and the rethinking of indications for blood product transfusions for anemia of prematurity, and Group B Beta hemolytic streptococcus maternal prophylaxis and neonatal evaluation/treatment guidelines by the AAP and ACOG.[58] With improved perinatal management of neonatal sepsis, mortality rates decreased from 90% in the early '30s to the current 4% to 6%.[59]

The Future

As the 20th century ends, significant challenges remain for neonatal and perinatal medicine:

1) an unchanging premature delivery rate of 6% to 7% with significant associated mortality and morbidity;

2) new technology gains, with both clinical benefits and associated higher economic and social costs, increasing concerns about "how small is too small" and how this care will be paid for;

3) maternal-fetal conflict and best-interest arguments including discussion of the best role for parents in end-of-life decisions;

4) the urgent need to address the societal problems that are reflected in the great disparity in premature delivery and infant mortality rates between races, and the United States' infant mortality rank as 20th out of 23 industrial nations;

5) the safe introduction of new technologies with steep, unforgiving learning curves;

6) the deterioration of regionalized perinatal care due to competition;

7) managed care constraints, with the issues of costs vs. quality arguments and resource allocation; and

8) the associated issues of burden of survival morbidity, short hospital stays, and increasing social scrutiny of the field.

With challenges come opportunities, however. Medical science needs to continue to improve the general health of women through socioeconomic initiatives, reproductive technology, and greater access to health care to decrease infant morbidity and mortality, and to create a bright future for American families and babies.

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Richard Lussky is assistant medical director of the NBICU at Hennepin County Medical Center and assistant professor of pediatrics at the University of Minnesota.

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