7 The Field of Neonatology

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During the eighteenth century, the care of sick infants was extremely primitive resulting in an extremely high infant mortality rate: 290/1,000 live birth or a whopping 29%. In the next century, persistently high infant mortality rate raised concerns of depopulation and potential lack of military enrollees which prompted the European governments' initiatives to improve maternal and child health. The late nineteenth century witnessed the beginning of some attempts to improve neonatal care with the advent of primitive but effective warming devices. This simple intervention resulted in improvement of infant mortality rate. In the United States the reduction of infant mortality was dramatic dropping from 100/1,000 to approximately 35/ 1,000 live birth from 1915 through 1940s (*Fig. 7.1*). This reduction was in part a result of the decline in neonatal mortality rate from 44 to 25/1,000 live births.

In the nineteenth century, attempts to provide better care of the high risk infants were done by midwives and obstetricians. Ironically, pediatricians were not involved. A French obstetrician Stephane Tarnier was credited for developing the incubator, which markedly reduced the mortality rate of infants under 2,000 g from 66% to 38%. Pierre Budin another French obstetrician was generally considered as one of the pioneers in improving neonatal care by extending the works of Tarnier and introducing the principles and methods of neonatal care. Martin Couney, a physician who championed the cause of premature care immigrated to the United States and brought the idea of improving premature care by the use of incubators. He was a clinician as well as a showman. He took the advantage of novelty of the care of premature infants with incubator and brought it to the public by showing them in various venues including fairs in cities such as Buffalo, New York, and Chicago. One vignette regarding the Chicago exhibition is that Dr. Couney presented the premature babies in the incubators to the public charging fees and made quite a bit of profit. Unfortunately, many of the infants developed diarrhea ending in death to some that prompted the closure of the show.

At about the same time, the first premature nursery was established at Sarah Morris Hospital of Michael Reese Hospital in Chicago in 1934. The nursery was directed by Dr. Julius Hess with the assistance of a very dedicated nurse, Evelyn Lundeen. This probably marked the beginning of modern Neonatology because in addition to being an excellent and dedicated clinician for this nursery, Dr. Hess started to engage in research for new knowledge to improve the care of the premature infants. The two pioneers also published textbook devoted to the principles and methods of premature care, many of which are still valid today. Other publications that enhanced the knowledge in the care of newborn soon followed and a new science was born. This era also marked the gradual introduction of pediatricians into the care of the newborns both in the delivery room and in the nursery.

At the end of World War II, several advances were responsible for the marked improvement of neonatal care. In addition to continued use of the incubator as a warming device for premature and other high risk infants, the discovery of blood type, introduction of blood transfusion, use of oxygen, fluid therapy, and antibiotics markedly improved the outcomes of the high risk infants. Advances in knowledge through clinical investigation such as establishing the diagnosis of congenital rubella syndrome, and identification of the cause of Rh erythroblastosis continued to improve the progress of the field. Some notable technological advances included the use of tiny needles (butterfly needles) designed by Dr. Robert Usher that allowed for intravenous fluid infusion as well as provision of sodium bicarbonate that improved outcomes of infants with respiratory distress syndrome. The technique of exchange transfusion was extremely valuable for the treatment of severe Rh erythroblastosis.

Some of the interventions were made without solid evidence of efficacy or freedom from potential harms. An example of this phenomenon was clearly illustrated with the oxygen treatment story. Liberal use of oxygen became commonplace in the 1950s not only to treat respiratory distress, but also more benign conditions, such as periodic breathing. While oxygen was responsible for saving many infants by reducing death or morbidity form hypoxia, ignorance of its potential adverse effects led to the tragic epidemic of retrolental fibroplasia (now known as retinopathy of prematurity) that blinded thousands.

During the past 5 to 6 decades, the emergence of the vibrant and productive subspecialty of Neonatology within Pediatrics has been witnessed; the evolution of the

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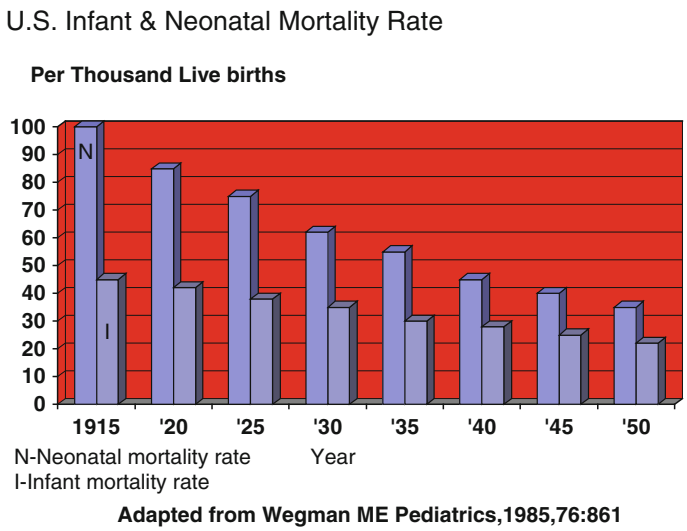

Figure 7.1
US infant and neonatal mortality rate per thousand live births

specialty was very nicely documented by Alistair Philip. It is not entirely clear when and how the term Neonatology came about, although it is most likely that the term was introduced by Alexander Shaffer who used the term in his textbook in 1960. The emergence of this subspecialty along with tremendous advances in medical care for the high risk infants have resulted in marked improvement in neonatal mortality rate in industrialized countries. Lee et al have shown that from 1950 to 1975, the US neonatal mortality rates have fallen significantly from 20 to 11.5/1,000 live births. This fall was not associated with any change in important demographic variables such as birth weight and gestational age that might affect neonatal mortality rates, clearly suggesting that the improvement is a result of improved medical care provided by the clinicians in this specialty. In 2005, the US neonatal mortality rate has fallen further to a low of 4.54/1,000 live births. This remarkable change in statistics was associated with the lowering of gestational age range for viability. In the 1950s and 1960s, only the very preterm infants (32 plus weeks of gestation) had a realistic chances of survival. In fact, in those days, in many countries, the neonatal survival statistics only list those who are 28 weeks in gestation or above. Today, the threshold of viability in the developed countries is close to 24–25 weeks. Unfortunately, the improvement in survival rate in the most immature infants has not been associated with improved outcomes of these infants at 2 years corrected age and in resource-limited circumstance, provision of intensive care to these infants may not be appropriate. The lowering of the threshold of viability also sparks intense debate among neonatologists, ethicists, and many concerned parties as to how far is too far in saving these tiny babies. The debate is also a result of very high morbidity rates among survivors of the extremely low birth weight and preterm infants. Most parties in this debate consider 22–23 weeks gestation as futile while the center of intense disagreement is for infants in the 24–25 weeks gestation because of increasing chances of survivors but the rate of poor neurodevelopmental abnormality remains high. Substantial differences exist even between industrialized countries with the Dutch drawing the line for intensive care at 25 weeks and the Japanese attempting to save infants as immature as 22 weeks. These difficult issues are further addressed in the chapter on Chap. 37, "Ethics and Decision Making in Neonatology" elsewhere in this section.

The improvement in neonatal mortality rates during the past half century is a result of many advances derived from plethora of accomplishments in basic science, translational and clinical research, and the implementation of these research findings into clinical practice by the neonatologists as the core clinician leaders working with obstetricians, medical and surgical subspecialists, along with a cadre of multidisciplinary personnel who are involved in

neonatal care. These advances include, among others, the use of antenatal steroids for acceleration of fetal maturation, surfactant for the treatment of hyaline membrane diseases, antibiotics for neonatal sepsis, inhaled nitric oxide for persistent pulmonary hypertension, and hypothermia for infants with hypoxic ischemic encephalopathy just to name a few. A more detailed list of these advances is presented in *Table 7.1*. These therapies are also described in detailed in various chapters of this section.

Historically, in the 1950s and 1960s the venue for the care of sick neonates was primarily located in a number of premature nurseries around the country which were associated with obstetrical wards and were designed primarily for the care of premature babies. The high risk term infants were generally cared for in the pediatric wards. The responsibility for the care of these infants was generally assumed by pediatricians who were interested and dedicated to this particular group of high risk infants. These clinicians were ably supported by dedicated and experience nurses. As more sophisticated and useful medical advances such as mechanical ventilation, were introduced to the field, there was a transition of the venue from premature nurseries to neonatal intensive care units (NICUs). The high risk term infants were integrated into the neonatal intensive care units. The clinicians who were responsible for the delivery of care in these units gradually organized themselves into a distinct group of physicians and over time, the specialty of Neonatology became a reality.

At around the mid-1960s an important event occurred that was in part responsible for improved neonatal outcomes: the implementation of perinatal regionalization. The concept emerged from the clear demonstration in a Canadian study that neonatal mortality rate was markedly lower when the high risk infants were cared for in institutions with neonatal intensive care units. At about the same time, there was strong interest in regionalizing medical programs which include cardiac care and others; the neonatal regionalization program was benefitted by the endorsement of the American Medical Association which strengthened its implementation. The strategy was further enhanced by the publication by March of Dimes and supported by key medical organizations including American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecology (ACOG) of a document entitled "Toward Improving the Outcomes of Pregnancy." The Program called for the designation of various levels of obstetric and neonatal facilities in a region in accordance with their capabilities to care for infants with graded levels of risk. The Program established the core infrastructure nationwide of having the Tertiary Care Center in a region serving as the leader in providing care to the high risk

Table 7.1
Introduction of perinatal therapies that improved neonatal care and outcome during the past six decades

Decades	Therapy
1950s	First-generation antibiotics
	Blood transfusion; exchange transfusion
	Incubators: Armstrong, Hess bed
1960s	Assisted ventilation: Intermittent positive pressure ventilation
	Incubator: Air shields isolette
	Negative pressure ventilator
	Usher's butterfly needles; umbilical vessel catheterization
	Newborn screening (PKU and Hypothyroidism)
1970s	Assisted ventilation: Continuous positive airway pressure
	Antenatal steroids
	Tocolysis for preterm labor
	Phototherapy for hyperbilirubinemia
	Central line placement/parenteral nutrition
	Rhogam for prevention of Rh disease
	Cyclooxygenase inhibitors for patent ductus arteriosus
	Noninvasive diagnostic technology (echocardiography, cranial ultrasound, other advanced imaging techniques)
1980s	Assisted ventilation: High-frequency ventilation; extracorporeal membrane oxygenation
	Cardiac surgery for congenital heart disease
	Extracorporeal oxygenation for cardiac surgery and cardiorespiratory failure
1990s	Surfactant therapy for hyaline membrane disease
	Inhaled nitric oxide for pulmonary hypertension
	Indomethacin prophylaxis for intraventricular hemorrhage
	Intraparatum antibiotic prophylaxis for neonatal group B Streptococcus sepsis
	Fetal surgery
	Laser therapy for severe retinopathy of prematurity
	Assessment of neurodevelopmental outcomes of high risk infants
2000s	Hypothermia for term infants with hypoxic ischemic encephalopathy
	Gentle ventilation to prevent bronchopulmonary dysplasia
	Probiotics for prevention of necrotizing enterocolitis

mothers and infants. Each tertiary care center is associated with several Level I and II facilities with appropriate transfer and retrotransfer guidelines for the high risk mothers and infants. The AAP and ACOG published specific guidelines that defined the various levels of perinatal care facilities that serve as the blue print for local implementation.

To support the medical staffing of these facilities, the American Board of Pediatrics have approved a 3-year Fellowship Program for Neonatal Perinatal Medicine to train a cadre of neonatologists to deliver high-quality clinical care. The 2007 statistics showed that there are approximately 5,000 + board certified or eligible neonatologists in North America who served this function. Because of unabated high preterm birth in the United States, it appears that there will be continuing need for this workforce to staff the neonatal intensive care units. Many of the trainees came from various parts of the world. Most of them returned to their home countries and set up neonatal programs to deliver intensive care for the high risk newborns. The establishment of these programs in part account for the improvement of the neonatal mortality rates worldwide, particularly in the developing countries.

The Future

Clinicians and scientists in the field of Neonatology have come a long way in achieving improved outcomes of the high risk newborns worldwide. There are many challenges ahead that may positively or negatively impact continuing efforts to achieve the goal of improving the outcomes of pregnancy. The list below in by no means all inclusive but deserves consideration.

- Preterm birth – Over the past decades, there have been significant monetary investment and efforts by many scientists to uncover the cause of preterm birth with the goal of reducing its incidence. Unfortunately, to date, the etiology of preterm labor is still incompletely understood and during the past several years, the incidence of preterm birth has inched up, in part due to an increase in the birth of late preterm infants. This group of infants has higher neonatal morbidity rate than term infants and has required NICU admission. The reduction of late preterm birth from planned cesarean section by quality improvement approach would be an appropriate and likely an effective approach.
- Congenital anomalies, which occur in approximately 3% of live birth, represent an important risk factors for admission to the NICU. Both syndromic and nonsyndromic congenital anomalies account for a significant portion of admissions to the NICU, taxing medical and surgical resources in their care. To date, very little is known in regard to the causes of various significant anomalies. Research in this area should be of high priority.
- Treatment-related Injury – This is another area that deserves high priority in basic science and clinical investigation. Our attempts to increase survival involve therapies that often produce iatrogenic consequences. Prime examples are bronchopulmonary dysplasia from treatment of neonatal respiratory failure in very low birth weight infants, retinopathy of prematurity in extremely low birth weight infants due to oxygen toxicity, and short bowel syndrome in very low birth weight infants with surgical necrotizing enterocolitis. Strategies that will prevent the occurrence of these posttreatment complications are urgently needed, because these conditions produce long-lasting disability, often with poor neurodevelopmental outcomes. Adoption of lower oxygen saturation targets may be one effective intervention, because virtually all complications of prematurity are meditated to some degree by oxygen radical injury.
- Technology evaluation – Delivery of care to high risk infants often requires sophisticated technology. The intervention may produce harms if its safety is not fully evaluated. The use of the technology should be evidence based and fully evaluated for safety and potential adverse effects. Drugs used in newborns should undergo similar rigorous evaluation for safety and efficacy.
- The impact of noxious environmental stimuli on the neurodevelopmental outcome of critically ill newborns is being increasingly recognized. Attention to these environmental factors and on pain control along with developmentally supportive care hold promise for improving functional outcomes in extremely preterm survivors of neonatal intensive care.
- Behavioral research – As the survival of high risk infants (particularly the extremely low birth weight infants) increases there is a need to evaluate the neurodevelopmental and behavioral outcomes of the survivors. The goal is to identify potential deficits and formulate appropriate neuroprotective and other behavioral interventions to improve outcomes.
- Family Center Care – Involvement of families in the care of high risk infants has been shown to benefit both patients and their families. Future model of care in neonatal intensive care unit needs to incorporate the family center concept in its construction and design to allow for operational implementation of this important concept.

While the history of neonatology is a story of triumph over life-threatening conditions and enormous improvements in survival of extremely premature infants it has been punctuated by a multitude of serious missteps and errors that led to unnecessary morbidity and mortality in thousands of infants. Sadly, the well-publicized retrolental fibroplasia epidemic is but one example of the consequences of uncritical acceptance of new therapies. Other examples include such apparently benign interventions as routine use of Sulfa drug prophylaxis in all preterm infants, which led to a sixfold increase in kernicterus and a doubling of mortality affecting thousands of infants and empiric treatment with large doses of Chloramphenicol, which led to the Gray baby syndrome and numerous unnecessary deaths in the 1950s. Hexachlorophene baths for prevention of staphylococcal infection led to neurotoxicity and permanent brain damage in thousands of infants in the 1960s. More recent examples from the 1990s and beyond indicate that modern neonatology is not immune from serious errors in judgment. Hyperventilation/hyperoxia was widely used to treat persistent pulmonary hypertension without ever being subjected to prospective clinical trials and resulted in increased rates of chronic lung disease, periventricular leukomalacia, and sensorineural hearing loss in large number of term infants. Liberal use of dexamethasone for treatment/prevention of bronchopulmonary dysplasia was a universally accepted therapy for more than a decade before a significant increase in cerebral palsy was recognized.

The urgent nature of our work makes it tempting to embrace new promising therapies without waiting for adequate evidence of safety and efficacy. The examples cited above should serve as a cautionary note for neonatologists around the world to remember the first dictum of medicine: "Primum non nocere" (first, do no harm).

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