

## SPECIAL ARTICLE

## A History of Neonatal Medicine—Past Accomplishments, Lessons Learned, and Future Challenges: Part II—The 1990s, the New Millennium, Future Challenges

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This is the second of two articles reviewing the history of newborn medicine. This article will discuss recent accomplishments in the field of newborn medicine, current health outcome data, and future challenges facing the fields of neonatal and perinatal medicine.

**KEYWORDS:** ethics, health disparities, health outcomes, micropremie, neonate, public health

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### INTRODUCTION

The epidemic of preterm birth continues to be a public health crisis for the United States. Approximately 12% of all pregnancies result in a preterm birth, a rate that has increased

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by 29% over the past two decades.<sup>1</sup> Low-birth-weight infants (birth weight of < 2,500 grams) comprise 11% of all deliveries, yet result in over 90% of the neonatal deaths.<sup>2</sup> Very-low-birth-weight infants (birth weight < 1,500 grams) comprise 1% of all deliveries and result in greater than 60% of neonatal deaths.<sup>3</sup> Prematurity and low-birth-weight continue to be the leading causes of neonatal mortality.

Improved survival of newborns with gestational ages of 23–25 weeks and birth weights of 500 to 750 grams has been made possible by surfactant replacement therapy, improved prenatal management (including the use of prenatal steroids), new technologies for temperature regulation, availability of precision

delivery infusion pumps for fluid and medication administration, more refined nutritional management, and continued improvement in

**ABBREVIATIONS:** AAP, American Academy of Pediatrics; ACOG, American College of Obstetrics and Gynecology; ADE, adverse drug events; ADHD, attention-deficit hyperactivity disorder; AIDS, Acquired Immunodeficiency Syndrome; BPD, bronchopulmonary dysplasia; DNA, deoxyribonucleic acid; ELBW, extremely low-birth-weight; HRF, hypoxic respiratory failure; IMR, infant mortality rate; iNO, inhaled nitric oxide; NICHD, National Institute of Child Health and Human Development; NICU, Newborn Intensive Care Unit; PPHN, persistent pulmonary hypertension; RDS, respiratory distress syndrome

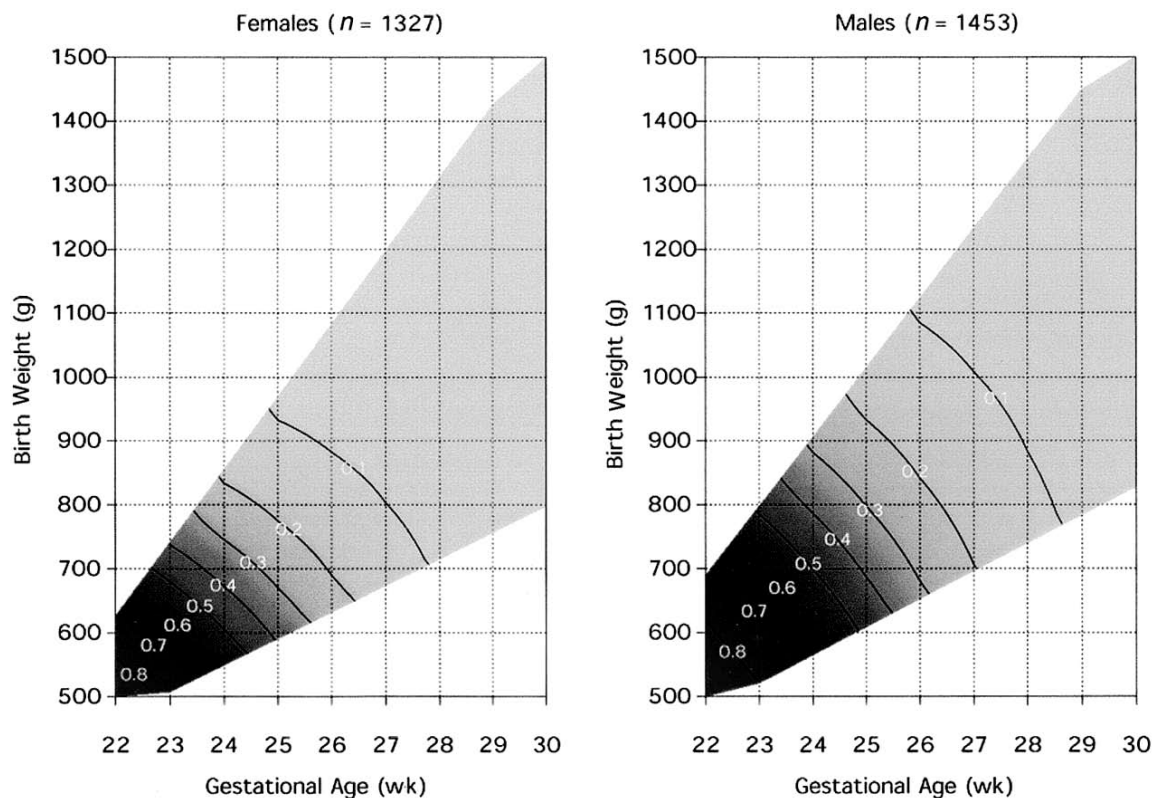
ventilatory support (e.g., patient-triggered, high-frequency, pressure and volume support ventilation modalities, and in-line pulmonary function testing capabilities). This article will discuss recent accomplishments in the field of newborn medicine, current health outcome data, and future challenges facing the fields of neonatal and perinatal medicine.

### OUTCOME DATA FOR INFANT MORTALITY AND MORBIDITY

#### Mortality

For the first time in 45 years, the infant mor-

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**Figure 1.** Logistic estimates of mortality risk by birth weight and gestational age based on singleton infants born in NICHD Neonatal Research Network Centers. The limits of the gray scale area indicate the upper 95<sup>th</sup> and lower 5<sup>th</sup> percentiles of birth weight for each gestational age. The curved lines indicate combinations of birth weight with gestational age with the same estimated probability of risk mortality, from 10% to 90%. Note that at each gestational age, a lower birth weight carried a higher mortality risk. (Reprinted from Lemmons JA, Bauer CR, Oh W, et al: Very-low-birth-weight outcomes of the NICHD Neonatal Research Network. *Pediatrics* 107, 1999 with permission of *Pediatrics*<sup>12</sup>)

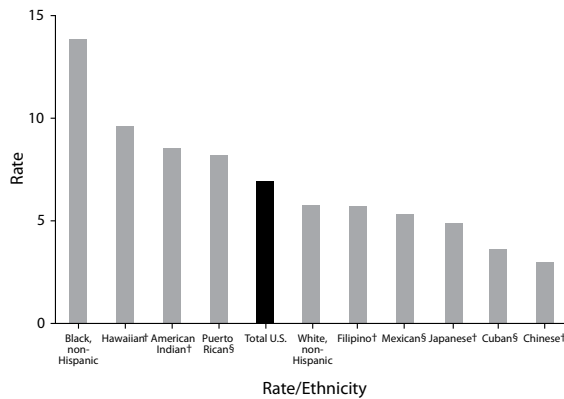
tality rate (IMR) increased in the United States in 2002 from 6.8/1,000 live births to 7.0/1,000 live births.<sup>1,4</sup> In year 2000, twenty-four other countries had lower IMRs than the United States, with Sweden's rate approximately one-half of the U.S.'s at 3.6/1,000 live births.<sup>5</sup> If the U.S. were to achieve the IMR of Sweden, 13,940 fewer infants would die each year.

An extremely-low-birth-weight infant (ELBW) is defined as a neonate with a gestational age of  $\leq 25$  weeks and a birth weight of  $\leq 750$  grams. A dramatic improvement in the survival of these infants has occurred over the past two decades. A National Institute of Child Health and Human Development (NICHD) survey of participating Neonatal Intensive Care Units (NICUs) documented survival rates of 21% at 22 weeks, 30% at 23 weeks, 50% at 24 weeks, and 75% at 25 weeks gestational age.<sup>6</sup> The survival rate was 11% and 29% in newborns with birth weights of 401 to 500 grams and 501 to 600 grams, respectively (Figure 1). Data from the Vermont Oxford

Neonatal Network showed similar survival rates.<sup>7</sup> The remarkable improvement in birth weight-specific neonatal mortality rates is primarily a reflection of technological advances in neonatal medicine and an improvement in the understanding of neonatal physiology.

Significant health disparities exist between racial and ethnic groups. In 2001, infant mortality rates were greatest for infants born of non-Hispanic black mothers (13.5 deaths per 1,000 live births).<sup>4</sup> African American infants have a greater than two-fold higher rate of low-birth weight and infant mortality than Caucasians.<sup>8</sup> The African American:White ratio of infant deaths has actually increased by 45% over the past six decades from 1.69 to 2.46.<sup>4</sup> American Indians/Alaska Natives have an IMR 22% higher than the general population, and 60% higher than Caucasians (Figure 2).<sup>5</sup>

Infant mortality rates are widely viewed as a reflection of social conditions and societal equity in the areas of social well-being and distributive justice (e.g., health care resource allo-



**Figure 2.** Infant Mortality Rates\*, by Selected Racial/Ethnic Populations—United States 2002.

\*per 1,000 live births

†Can include persons of Hispanic and non-hispanic origin

§Person of Hispanic origin may be of any race

([http://www.CDC.gov/nchs/data/nvsr/nvsr53/nvsr53\\_10.pdf](http://www.CDC.gov/nchs/data/nvsr/nvsr53/nvsr53_10.pdf))

caution). In fact, measures of social disadvantage are highly correlated with prematurity.<sup>9</sup> As a mother's educational level decreases, the IMR increases.<sup>4</sup> The mortality rate for infants whose mother had less than a high school education was 49% higher than that of mothers with more than 13 years of education.<sup>4</sup> It is estimated that the reduction of social class differences could prevent over one-half of post-neonatal deaths as well as a significant number of perinatal deaths.<sup>10</sup>

### Morbidity

Although survival rates have increased, there has not been a parallel improvement in the rate of morbidities in ELBW infants. A co-morbidity of prematurity is bronchopulmonary dysplasia (BPD). This is defined as ongoing oxygen requirements at 36 weeks postmenstrual age and occurs most frequently in prematurely born infants who require prolonged mechanical ventilation and supplemental oxygen. Recent data has shown that 86% of survivors with birth weights of 401 to 500 grams and 62% of infants with birth weights of 501 to 600 grams develop BPD.<sup>2</sup>

Neurological and neurodevelopmental outcomes of extremely prematurely born infants remain a primary concern of neonatologists, perinatologists, and developmental pediatricians. A NICHD follow-up study of 1,151 ELBW infants found that 17% had cerebral palsy, 11% had hearing impairment, 9% had visual impairment, and 49% had abnormal

neurodevelopment.<sup>11</sup> Bayley scores < 70 (the subnormal range) for the mental developmental index were found in 37%, and psychomotor developmental index scores < 70 were noted in 29%. The EPICure study followed 1,185 30-month olds who had been born at  $\leq 25$  weeks gestation, surveying all of the perinatal centers in the United Kingdom and the Republic of Ireland, to evaluate outcomes.<sup>12</sup> Fifty percent of these children had no disability; however, 25% had mild disability, and 23% had a severe form of disability (i.e., likely to need physical assistance to perform daily activities). Thirty percent had Bayley scores < 70, 18% had cerebral palsy, 10% had severe neuromotor disability, 2% were blind, and 3% required hearing aids. Some infants considered to have no disabilities were later found to have higher rates of attention-deficit hyperactivity disorder (ADHD) and learning disabilities in the areas of writing, math, and reading, in comparison to the general population.<sup>13</sup>

ELBW infants have been followed to adolescent age. Saigal and colleagues conducted a longitudinal follow-up study in adolescents.<sup>14</sup> The authors compared psychometric assessments and frequency of school difficulties in 150 ELBW survivors and 124 full-term controls. Twenty-eight percent of the ELBW survivors had neurosensory impairment, 57% experienced visual problems, 7% had a seizure disorder, and 9% were considered hyperactive. Evaluations revealed lower IQ scores as well as lower scores in math, reading, and spelling. Approximately 50% received special education, with 22% receiving full-time assistance. In addition, there was shorter stature and lower weight attainment in comparison to a control group. Chapieski and Evankovich found an increased rate of negative temperament characteristics, ADHD, and lower levels of social competence in adolescents who were born prematurely.<sup>15</sup> In relation to long-term follow-up data, it is also important to be aware of the fast pace of change in perinatal and neonatal practice. The above referenced follow-up studies do not reflect such components of contemporary practice as antenatal steroids, prophylactic surfactant, and the virtual elimination of postnatal steroid use. There is also now an increased emphasis on broadening the approach to health measurements in neonatal follow-up studies,

incorporating quality of life assessments.<sup>16</sup> Outcome studies over the next 5 to 15 years will reflect more accurately the current perinatal and neonatal practice environments. It is also important to note that if we are truly going to optimize the outcome of high-risk infants, we need to address the socioeconomic factors that adversely affect children's development after they are discharged from the hospital (e.g., poverty, lack of adequate health care insurance and access, exposure to violence, etc.).

### **Evaluation of the Literature**

There are important caveats to consider when analyzing the current neonatal follow-up literature as there is significant variation in both definitions and care philosophy between perinatal centers. There are differences between centers on whether all live births or just those births that were actively treated in the delivery room are included in survival and outcome statistics. When evaluating the outcome literature, factors to be aware of are: 1) whether every live birth above a specific birth weight and gestational age was resuscitated in the delivery room, or if infants were selectively treated in the delivery room based on their condition; 2) the criteria used to judge viability; 3) indications for withdrawal of support; 4) the experience and skill level of team members for these high-risk deliveries; 5) comparability of racial, ethnic, socioeconomic, and demographic variables; and 6) percentage of inborn versus transported infants. The latter is important since infants who require transport have a higher level of morbidity and mortality. Outcome evaluations among the NICHD Neonatal Network perinatal centers have shown "large and disturbing" differences between centers in both survival and neurodevelopmental sequelae after adjustment for demographic variables and antenatal interventions.<sup>17</sup> There is also a significant effect on long-term developmental outcome of family factors and social support, including early educational intervention.<sup>18</sup>

### **Outcomes Research**

Higgins et al. list a number of the gaps in current knowledge that need to be addressed in both the obstetric and neonatal fields in the assessment and treatment of periviable infants and their mothers.<sup>19</sup> Included in these are the

following: 1) identifying sensitive markers for periviable birth that can help direct treatment before delivery; 2) developing tools to assess and treat subclinical intrauterine infections/inflammation and uteroplacental dysfunction; 3) identifying prenatal markers for poor neonatal outcomes after periviable birth that would allow individualized counseling and treatment of patients at risk; 4) developing better understanding of survival and morbidity rates after periviable birth, with respect to racial, ethnic, and gender variables; 5) establishing evidence-based standards for fluid, electrolyte, nutrition, and environmental care; 6) making available infection prevention and treatment modalities to improve short-term and long-term outcomes; 7) encouraging heightened attention to brain injury and healing, with specific attention to the affect of cytokines, drug, and oxygen on the developing brain and the development of neuroprotective mechanisms; 8) improving delivery room treatment of infants with attention to resuscitation, oxygen use, and surfactant administration; and 9) enhancing long-term outcomes for extremely-low-birth-weight infants, with attention to functional outcomes; psychiatric, behavioral, and attention issues; effects of developmental interventions on outcomes; and chronic medical illnesses such as BPD.

### **ADVANCES IN THE 1990s**

The 1990s was considered the decade of the micropremie (Figure 3). In 1992, the American Academy of Pediatrics (AAP) initiated what eventually became the "Back to Sleep" campaign, which reduced the rate of Sudden Infant Death Syndrome by two-thirds, to 0.7/1,000 live births.<sup>20</sup> In 1994, the Pediatric AIDS Clinical Trials Group Protocol 076 was published, recommending the use of perinatal zidovudine, which decreased the rate of perinatal transmission of Human Immunodeficiency Virus by two-thirds.<sup>21</sup> Als and Gilkerson introduced the Newborn Individualized Developmental Care and Assessment Program, which supported family-centered, individualized developmental care for premature infants,<sup>22</sup> resulting in fewer ventilator days and improved developmental outcomes of Newborn Intensive Care Unit graduates.<sup>23</sup> The development of databases and inter-institutional, randomized, prospec-



**Figure 3.** Twenty-three week gestational age infant at 1 week of age.

tive studies continued to progress. One of the better known neonatal databases is the Vermont Oxford Network,<sup>24</sup> and the Cochrane Collaboration is the best known meta-analysis in the field.<sup>25</sup> There was an increased awareness of the “neonatal golden hour” of delivery room and early newborn intensive care unit (NICU) management and its potential to affect long-term outcome. Increased emphasis was placed on the benefits of prophylactic surfactant, the institution of early continuous positive airway pressure, the maintenance of normal body temperature, and the optimization of a gentler transition to the ex-utero environment for extremely low-birth-weight infants. Other significant developments were the introduction of erythropoietin administration for the prevention of anemia in premature infants, a rethinking of indications for blood product transfusions based on an increased emphasis on physiological principles, and the formulation of Group B Beta hemolytic streptococcus maternal prophylaxis and neonatal evaluation/treatment guidelines by the AAP and the American College of Obstetrics and Gynecologists (ACOG).<sup>26</sup> With improved perinatal management of neonatal sepsis, the mortality rates decreased from 90% in the early ‘30s to the current 4% to 6%.<sup>27</sup> In 1999, the Food and Drug Administration approved the use of inhaled nitric oxide (iNO) for use in near-term and term infants with hypoxic respiratory failure (HRF) complicated by persistent pulmonary hypertension (PPHN). HRF affects between 16,000 and 25,000 infants each year in the United States with about half of these infants presenting with PPHN.<sup>28</sup> In 2000, the

AAP recommended iNO for infants with progressive hypoxic respiratory failure.<sup>29</sup> The need for extracorporeal membrane oxygenation decreased by 40% in infants treated with iNO in a National Institute of Child Health and Human Development (NICHD) sponsored study.<sup>3</sup>

## PERSPECTIVES ON CURRENT CHALLENGES

Many challenges and opportunities face perinatal and neonatal medicine in the 21<sup>st</sup> Century. There needs to be a proactive discussion on how to balance prioritizing the care of ELBW infants versus the impact the care has on the physical integrity of the infant, the psychosocial health of the family, and the fiscal strength of the health care system. Increasingly, there are discussions among leaders in the field of neonatology regarding the question, “Is more neonatal intensive care always better?”<sup>30</sup> Kirby made the following relevant comment: “My hope is that it won’t be the epitaph of our generation that people will say: ‘Here was a community which developed the most amazing, dazzling fields of science and yet proved themselves so indifferent or incompetent, that they didn’t address the serious social and ethical consequences of what they were up to.’”<sup>31</sup>

### Impact on the family

The impact of the birth of an ELBW infant on family dynamics has also been examined. Taylor found lower perceptions of parenting competence, an increased rate of child attachment disorders, a general negative impact of the child’s health on the family, and higher rates of both child-related family stress and adverse family outcomes in comparison to a control group.<sup>32</sup> These findings suggest that family sequelae persist into the school-age years. The degree of family impact was found to correlate with the severity of neonatal medical risks and complications.

In reviewing the impact of a premature birth on the family, it is important to be aware of a growing body of information regarding the perceptions of, and preferences for, neonatal outcomes of ELBW infants among health care professionals, parents, and adolescents (who were born extremely prematurely). Consistently, children and their parents had a more optimistic assessment of their current health

status in comparison to that of health care professionals.<sup>33,34</sup>

### **Ethical concerns**

The American Academy of Pediatrics' Committee on Fetus and Newborn published "Perinatal Care at the Threshold of Viability"<sup>35</sup> and the Canadian Paediatric Society and Society of Obstetricians and Gynecologists published guidelines pertaining to the care of women at risk for the birth of an ELBW infant.<sup>36</sup> The limit of viability is generally considered to be at 23 weeks of gestation; however, some countries, notably Japan, provide care at 22 weeks of gestation. Because the outcome has not always been that of a healthy child, relevant ethical questions have been raised for the treatment of those infants born at 23 and 24 weeks gestation.

Futile care is frequently defined as "medical care that prolongs suffering, does not improve the quality of life, or fails to achieve a good outcome for the patient."<sup>37</sup> Efforts to prolong life, once considered an outcome of healing, are increasingly viewed by some as harmful acts of prolonging suffering. Because of the advances in neonatal care, and the accompanying ability to provide care to increasingly premature infants (with the associated increased risk for significant disability), there is a heightened awareness of the concept of futile care and quality of life issues for NICU survivors. The scope of this paper does not allow for a full discussion of this topic; hence, the reader is referred to a number of recent publications on this topic.<sup>38,39</sup>

The existing standard is to recognize the primary responsibility and rights of the parents to make decisions on behalf of their children. The AAP, ACOG, and the Canadian Pediatric and Obstetrical Societies recommend providing parents with reliable prenatal and postnatal outcome data, based on both the perinatal center's outcome data and a regionally or nationally recognized comparison group, which are updated as the infant's medical condition changes. This information will improve their decision making abilities and empower them to advocate for their infant both in the short term and long term. In a rapidly evolving field, where there is great variability in practices, it is hard to reach consensus in these matters.

The majority of practices are reflected in the following guidelines: 1) do not offer support to infants born at less than 23 weeks of gestation; 2) at 23 and 24 weeks gestation the primary decision maker for resuscitation is a fully informed parent; and 3) at 25 weeks of gestation and greater the standard of care is to provide medical care.

There is a general consensus that "...where the risk of mortality and morbidity is significant and the prospects of benefit are suffused in ambiguity and uncertainty—the decision on whether or not to institute medical treatment properly belongs to the parents."<sup>40</sup> There are times where agreement can still not be reached. In these situations, consultation with colleagues and a pediatric ethics committee may be helpful. Unfortunately, increasingly, legal recourse is being sought on both the part of the family and health care organizations in these matters.<sup>41</sup> The increasing use of the courts highlights the importance of effective anticipatory guidance and ongoing communication with parents, serving to keep them involved as partners with the health care team that is caring for their infant. These issues require that the practitioner attempt to balance the principles of parental autonomy and their own duties of beneficence, non-maleficence, and distributive justice.

### **Societal Challenges**

In 1989, Rosenblatt coined the term "perinatal paradox" to highlight the ongoing challenges facing perinatal and neonatal medicine.<sup>42</sup> In his commentary, he called attention to this "tyranny of the individual case over the public good."<sup>42</sup> The NICU is probably the most striking example of the lack of balance in the health care system where high-risk mothers often find it difficult to receive health insurance and find health care providers for their prenatal care despite its proven effectiveness, yet neonatal care is an "inalienable" right for all infants in NICUs with its much more uncertain outcomes. As a country, the United States' health care systems can deliver high-quality care to an individual with a high-risk pregnancy or to an extremely low-birth weight infant, yet in aggregate continue to lag behind most other countries in perinatal health outcomes.<sup>43</sup> We also fail to address the larger societal problems

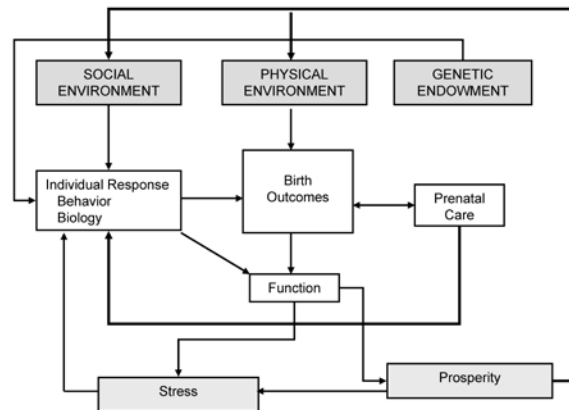
that are in part responsible for these high-risk clinical situations. The National Commission to Prevent Infant Mortality stated in 1988, “The basic incongruity in American perinatal care lies in our superb ability to care for the individual patient and our dismal failure to address the problems of the larger society.”<sup>44</sup>

In 2002, hospital charges for all infants, including healthy newborns, totaled \$33.8 billion. Nearly half of that, \$15.5 billion, was spent on babies born either prematurely or with low-birth-weight.<sup>1</sup> Rates of prematurity, very-low-birthweight, and infant mortality have not improved despite these costs, including an investment of billions of dollars into basic research on maternal and neonatal disease and funding of delivery programs that attempt to make products of this research available to women and their health care providers. There is also an inconsistency in public policy, funding, and societal asset allocation with an emphasis on very expensive cure-oriented and technologically-focused neonatal intensive care and less focus and decreasing funding support for the long-term health and educational needs of NICU graduates. Kliegman cautions: “The enthusiasm for the remarkable scientific advances in neonatology must be tempered by the significant neonatal, postneonatal, and childhood problems of low-birth-weight infants, and by the environment in which they are born and to which they return after surviving the hazards of premature birth.”<sup>38</sup>

Finally, an open and honest dialogue of factors that contribute to racial and ethnic health disparities is urgently needed within the health care sector. Some of the proposed causes include the following: poor quality of care by some providers, racial bias and stereotyping, a lack of trust in health care providers, and differences in the preferences of patients for some medical interventions.<sup>45</sup> The multifactorial causes in the health care system of health disparities is addressed in the report of the Institute Of Medicine entitled *Unequal Treatment: confronting racial and ethnic disparities in health care*.<sup>46</sup>

#### **Medical vs. Social models of causation and the public health approach**

The health care system must eliminate the “conceptual tension” and the “disciplinary an-



**Figure 4.** The interactive nature of social, physical environment, and biological influences on perinatal health.

tagonism” between the social model (emphasis on social variables such as poverty and the need for societal change) and the medical model (emphasis on pathophysiology and clinical interventions). There is currently an isolation between these two models that is reflected in public policy, empirical research, and clinical care. A model needs to be developed based on the interactive nature of social and biologic influences. Figure 4 provides a schematic overview that incorporates components of both the traditional medical model and the social model. The paradigm needs to shift from the current ineffective medical crisis intervention model for the prevention of prematurity (that frequently involves trying to prevent a premature delivery by a woman that presents in advanced preterm labor) to a public health, population-based perspective that includes a better understanding of the proximate and antecedent risk factors and their inclusion in predictive models.

Interventions and resources need to be redirected to “upstream” aspects of perinatal health care provision. Universal access to health services may be ensured by removing barriers to care, including those that are financial, cultural, educational, and those rooted in the health care system (e.g., institutional racism and bias). Whitehead’s and Dahlgren’s classic “rainbow” model incorporates a broader perspective on the determinants to health, including general socioeconomic factors, cultural and environmental conditions, social and community networks, in addition to the traditionally addressed individual lifestyle and biological factors.<sup>47</sup>

### Women's health

Early prenatal care (i.e., first trimester), and the attainment of optimal preconceptional health, reduces both infant mortality and poor birth outcomes. Infants born to women who do not receive prenatal care have increased rates of prematurity and low birth weight when compared to women receiving prenatal care.<sup>48-53</sup> Additionally, these infants have higher complication rates and more NICU admissions than those born to women who received prenatal care.<sup>48,49,53</sup> This lack of prenatal care leads to increases in neonatal morbidity, mortality, and costs for low-birth-weight births.<sup>48,49</sup> The percent of women who received prenatal care during the first trimester increased from 68% to almost 84% from 1970 to 2002, respectively.<sup>1</sup> Although the increases were noted in all of the major racial and ethnic groups, disparities continue with the lowest rates reported for American Indian or Alaska Native women.<sup>1</sup>

In order to achieve optimal perinatal outcomes for women and infants, it is necessary to focus on the health of women throughout their life, not just during pregnancy. This is increasingly important because of the shifting of infant mortality and disparities to lower birth weights and younger gestational ages, which will limit the time available for early prenatal care in these pregnancies. In order to accomplish this, it will be necessary to design a rational perinatal health care system for all women that incorporates social influences on maternal and child health. There is also a need to operationalize and measure social structural factors (e.g., segregation, neighborhood context, wealth inequalities, social stressors, and health care service inequalities).

### Adequate health insurance

Financial concerns and a lack of adequate health insurance are major obstacles to adequate prenatal care; hence, universal health care coverage for women and children is critically important. Providing medical insurance, and thereby enabling access to and utilization of preventive health services, is cost effective and results in better health outcomes. Rates of no insurance and underinsurance have been increasing and disproportionately affect minority populations and families with lower socioeconomic status.<sup>54</sup> Over one-half million women

give birth each year with no insurance coverage,<sup>42</sup> and 17% of women in childbearing years (approximately 10 million) have neither private nor public health insurance.<sup>55</sup> A significant percentage of children with special health care needs also lack adequate insurance coverage.<sup>56</sup> Although Medicaid coverage for pregnancy-related services has allowed more women in low income brackets to access care, reductions in Medicaid funding will increase health disparities because a larger percentage of minorities rely on Medicaid for health insurance.

## PERSPECTIVES ON RESEARCH CHALLENGES

### Evidence-based medicine

Sackett defined evidence-based medicine as "the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients."<sup>57</sup> He further described it as a means of integrating individual clinical expertise with the best available external clinical evidence from systematic research. There are a number of recently published reviews pertaining to the practice of evidence-based medicine in pediatrics and neonatology.<sup>58-62</sup> It is imperative that neonatology incorporate quality clinical outcome follow-up data into evidence-based decisions in clinical practice. An example of this is the recent history of the use of postnatal steroids to decrease the ventilatory requirements of infants with BPD, which was eventually shown to double the risk for the development of cerebral palsy, and has resulted in a caution from the AAP regarding the use of steroids in this patient population.<sup>63,64</sup> Collaborative quality improvement efforts among perinatal centers with the objective of identifying best practices are needed, followed by encouragement of wide-spread adoption of these clinical practice guidelines.<sup>65</sup> There is also a growing body of literature that questions the effectiveness of traditional continuing medical education approaches. Davis showed that the often used approach of conferences has little impact on professional practice, with patient-mediated interventions, outreach visits, and multifaceted activities being much more effective.<sup>66</sup>

### Priorities for clinical research

**Genetics.** With the mapping of the human



genome by the Human Genome Project, there is a promise to better understand genetic and gene-environment causes of preterm birth. Areas of research will include host susceptibility to infections, genetic contributions to the regulation of “host responses”, and the molecular biology underlying parturition.<sup>67,68</sup> Research initiatives will involve evaluating: 1) high-risk phenotypes, 2) biobanking of biologic specimens of preterm births for future investigations; and 3) advances in the areas of bio-information and animal models.<sup>69</sup> There is great potential for the prevention of preterm births in furthering the understanding of the interactions between the social environment, individual patient factors, and genetics.

**Respiratory.** In current practice, the variability in oxygenation status places infants at increased risk for hyperoxia and free oxygen radical exposure in addition to associated morbidities such as retinopathy of prematurity and BPD. In order to further decrease morbidity and mortality due to respiratory disease, there needs to be a means to servo-control oxygen delivery based on an infant’s oxygen saturation determination by pulse oximetry. This would avoid the wide swings in oxygenation that are now seen in clinical practice.

Future research efforts are needed to determine oxygen saturation goals that optimize neurodevelopmental outcomes while minimizing damage from oxygen toxicity to developing organs. The clinical goal is to minimize the risks of four competing outcomes: mortality, retinopathy of prematurity, cerebral palsy, and BPD. A more detailed discussion of research needs is provided by Tu, who reviews a history of the past fifty years of neonatal oxygen therapy, exploring monitoring strategies, recommended upper and lower limits of oxygenation, and future research needs.<sup>70</sup>

The development of complete synthetic surfactants that contain both phospholipids and apoproteins will provide infants with the benefit of surfactant administration while eliminating potential consequences of foreign protein exposure. A second area of focus should be to improve the respiratory management of RDS with the goal of decreasing the incidence and severity of BPD. An increased understanding of the therapeutic uses of surfactant in respiratory distress syndrome (RDS) and other

respiratory disorders (e.g., meconium aspiration syndrome, pneumonia) is also needed.

The optimal level of supplemental oxygen for resuscitation of infants at different gestational ages and the best means to monitor oxygenation status needs to be determined. The effect of 100% oxygen on cell growth and death, gene activation, and DNA damage needs further study. The differential effect of room air versus 100% oxygen on oxidative stress, cerebral blood flow, cerebral microcirculation, brain cell injury, pulmonary and cardiovascular systems, and ultimate survival are also critical areas for further research.<sup>71</sup>

**Cardiovascular.** Research that improves both the definition of, and our understanding of, the normal ranges of systemic blood pressure will help to optimize cerebral blood flow. The advent of prostaglandin E<sub>1</sub> and E<sub>2</sub> have greatly altered care of the neonate with congenital heart disease. Although the use of prostaglandin inhibitors (NSAID) has improved the standard of care of patent ductus arteriosus in infants, there needs to be consensus on the optimal prophylactic and therapeutic management of the patent ductus arteriosus in high-risk ELBW infants.

**Neurodevelopment.** Enhancements in continuous video-electroencephalogram monitoring with correlation to clinical seizure activity will enable the practitioner to optimize therapeutic interventions. This would require the institutional commitment to fund the equipment purchases and have the technologists available to use the equipment, along with the availability of personnel (i.e., pediatric neurologists) to help interpret and manage the patient based on these findings. It should also be a priority for NICUs to improve the monitoring of cerebral blood flow and cerebral metabolism, and to incorporate these parameters into clinical practice. Finally, we need an improved understanding of the biologic basis of injury to the developing brain, potential neuroprotective factors, and the role of cytokine and inflammatory mediators in both brain injury and protective mechanisms.

**Growth and nutrition.** Although significant strides have been made in our understanding of substrate utilization and growth needs in the neonate, clinical studies that further evaluate the optimal parenteral and enteral

administration of nutrition are needed. A better understanding of what is ideal growth for the ELBW infant, and what is the optimal way to monitor this (e.g., growth curves [derived from fetal or postnatal data], anthropometric measurements, or biochemical assessments), is essential if improved outcomes are to be achieved.

Growth and nutrition have significant potential impact on the long-term health and neurodevelopmental outcome for prematurely born infants. The typical ELBW infant is discharged from the hospital with significant nutritional compromise. The “Barker hypothesis” postulates that a number of organs, affected by fetal nutrition, undergo programming during embryonic and fetal life.<sup>72</sup> This programming can increase the risk for cardiovascular disease, type-2 diabetes, and other diseases in adulthood; hence, fetal and early infant nutrition can have a life-long impact on an individual’s health.

**Pharmacotherapy.** Almost 40 years ago, Harry Shirky coined the term “therapeutic orphans” to describe the lack of research on medications in infants and children.<sup>73</sup> The advent of recent legislation (i.e., FDAMA, the Pediatric Rule, ICH E-11, and the Final Rule) has been an important advance for the field of pediatric pharmacotherapy.<sup>74</sup> The reader is referred to a review of these legislative initiatives.<sup>74</sup> Spielberg wrote, “The challenges remain to maintain a collaborative and cooperative focus on the needs of sick children among governmental agencies, academia and practice-based pediatricians, pharmacy groups, pediatric societies and hospitals, and the pharmaceutical industry.”<sup>74</sup> The NICHD Network of NICUs and the Pediatric Pharmacology Research Unit must work in a collaborative manner to identify and address many of the critical issues in neonatal pharmacokinetics and pharmacodynamics. The groups could better define the ontogeny of hepatic and gut cytochrome P450 isozymes that are necessary for drug absorption and elimination. Likewise, it is imperative that federal funds be allocated to basic and translational science if we are to better understand the pathogenesis and pharmacological therapy for neonatal disease. Prospective studies should also be conducted assessing the long-term effects of maternal therapeutic drugs on

perivable infants (gestational ages of 23-25 weeks) and on the effects of medication on organogenesis and neurodevelopment. It is critically important, considering the increasing rate of preterm delivery, for future interventional studies in the field of obstetrics to include long-term outcome assessment as a component of the evaluation of prenatal therapies. Very little work has been done in evaluating the long-term effects on the fetus and infant of such prenatal therapies as antibiotic use with perivable pregnancies, tocolytics, and thyrotropin-releasing hormone.<sup>75</sup> A database pertaining to the short-term and long-term safety and effects of antibiotic therapy on perivable infants should also be developed.

A glaring example of the therapeutic neglect of the newborn infant was that pain control was not adequately addressed until the ‘80s, when discussions were centered on neonatal circumcisions.<sup>76</sup> It was not until the misperception that immature, and even the mature newborn infant, did not experience pain was challenged and proved wrong, that the benefits of analgesia and anesthesia were routinely provided to this vulnerable population.<sup>77</sup> Pain assessment and control guidelines have now become part of standard care.<sup>78-80</sup> Unfortunately, the therapeutic armamentarium remains relatively limited, and the risk/benefit analysis will take years of clinical practice to be fully completed. Today, neonatal pain management is increasingly a comprehensive approach, incorporating comfort measures, behavioral approaches, oral sucrose, non-steroidal anti-inflammatory agents, and natural and synthetic opioid agents.<sup>78</sup>

Mello et al. described wide variations in how academic medical centers work with sponsoring pharmaceutical companies in the analysis and publication of sponsored clinical trials.<sup>81</sup> Fifty percent of centers would allow sponsoring companies to write the manuscripts, 24% allowed companies to perform their own statistical analysis, and 41% would allow contracts to restrict physicians and scientists from independently disclosing trial results. These practices raise serious concerns regarding the integrity of the scientific literature. A number of professional organizations, including the American Medical Association, the International Committee of Medical Journal Editors, and the Association of American Medical Colleges are

in the process of creating principles and policies pertaining to company sponsored research and reporting that will address these issues.

**Medication Errors.** The 1999 Institute of Medicine report, *To err is Human: Building a Better Health Care System*,<sup>82</sup> brought national attention to medical errors in hospitals and their impact on patient safety. Pediatric patients were identified as being at particularly high risk for experiencing injury and even death due to medication errors. Medication errors cause the greatest harm to the very-low-birth-weight infants cared for in NICUs.<sup>83</sup> Factors contributing to this increased risk are weight-based dosing, decreased communication abilities of children and infants, and a use of stock medicine dilution. In a prospective cohort study in a NICU, there were 91 medication errors and 50 potential adverse drug events (ADEs) per 100 admissions.<sup>84</sup> The three most common types of medication errors and potential ADEs were physician ordering errors (79%), transcription and dispensing errors, and medication administration errors. Potential solutions include an increased research focus in developing process-oriented and accountable prevention strategies, prioritizing this area in hospital-based quality assurance and improvement programs, use of computerized physician order entry and bar code identification, and the elimination of selected abbreviations.<sup>85,86</sup> Guidelines for preventing medication error in pediatrics were jointly developed by The Pediatric Pharmacy Advocacy Group and Institute for Safe Medication Practices.<sup>87</sup> In order to reduce or eliminate medication errors, a national registry should be created to identify and track medication errors in pediatric patients.

**Technology and Systems Integration.** Cautious inclusion of new technologies into clinical practice based on a critical evaluation of their efficacy, safety profile, and effect on the larger system of care is critically needed.<sup>88</sup> One example of this is the routine use of electronic fetal monitoring in obstetrics today where it has been shown that in the low-risk patient population there is an increased rate of cesarean sections with no improved health outcomes.<sup>89</sup> All too often, promising innovations, studied in limited numbers of patients under controlled conditions, have had unanticipated side effects when applied to larger populations. In the care

of prematurely born infants, it has been said that the “technological throttle is stuck open.” As technologies are introduced in the fields of neonatal and perinatal medicine, a prospective evaluation of their impact on clinical outcomes is an absolute necessity.

**Advocacy/community participation and professionalism.** Individual health outcomes are significantly affected by social, economic, and environmental factors. Health care professionals have a primary ethical and professional responsibility to address these factors that affect their patients. Advocacy efforts in health care policy and an increased engagement in improving systems of care and population health offer an opportunity to have a much wider impact on improving the health of populations than that offered by the traditional individual patient-physician relationship. In this regard, Gruen states, “Successful advocacy requires clarity of purpose, good data, and effective strategies.”<sup>90</sup> Importantly, “It relies on promotion of the skills and attitudes of good citizenship in medical education.”<sup>91</sup>

Most current maternal interventions, including enhanced prenatal care programs, nutritional support, home monitoring for early detection of labor, and bed rest,<sup>92</sup> have proved to be ineffective in preventing premature births.<sup>93</sup> Tocolytic agents are effective in the initial management of acute preterm labor and may provide time to use prenatal steroids.<sup>94</sup> However, there is no documented long-term benefit of tocolytic therapy beyond this acute management.<sup>95</sup> The March of Dimes has developed a national Prematurity Campaign with the goal to decrease the rate of premature birth from 12.1% in 2002 to 7.6% in 2010, in accordance with the U.S. Public Health Service *Healthy People 2010* objective. This will result in 186,000 fewer prematurely born infants each year. The aims of the Campaign are to: 1) generate concern and action around the problem of prematurity; 2) educate women of childbearing age about risk reduction and warning signs of premature birth; 3) provide affected families with information, emotional support, and opportunities to help other families; 4) assist health practitioners in improving prematurity risk detection and addressing risk-associated factors; 5) encourage investment of more public and private research dollars to identify causes



Figure 5.

of preterm labor and prematurity, and to identify and test promising interventions; and 6) advocate to expand access to health coverage in order to improve maternity care and infant health outcomes. The March of Dimes has developed a prevention strategy that is multifactorial, that uses a population-based approach, and that incorporates an emphasis on improved health of women throughout their life span. Considering the heterogeneous causations of preterm birth, single therapeutic interventions are not likely to significantly impact the public health problem of prematurity. For additional information, see <http://www.marchofdimes.com>.

Neonatal and perinatal medicine have made great gains. Yet, there is much more to do if we are going to truly optimize the health of all women, children, and families throughout their lifetimes. The future is truly in our hands (Figure 5)!

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