THE PPB STRATEGIC PLAN

Based on workshop discussions and on input from the PPB research community, the Branch developed a Strategic Plan to guide its activities for fiscal year 2005 through fiscal year 2010. The Strategic Plan will help guide the Branch's investments in areas of need that are important to the field, and in identifying new strategies for solving old problems. The Strategic Plan will also be a useful tool for the scientific community to use for stimulating research interests. The plan will help to refine the Branch's goals, but not narrow its mission.

Within the scope of the Center for Developmental Biology and Perinatal Medicine, the PPB will use the Strategic Plan to recommend workshops, conferences, and RFAs. Additionally, in accordance with the mission of the National Institutes of Health (NIH), the PPB will continue to welcome, assist, and support investigators who propose applications relevant to the PPB mission, regardless whether the applications relate specifically to the Strategic Plan.

The Strategic Plan includes *Ongoing Areas of Emphasis* and *New Areas of Emphasis,* and, where possible, action steps and priorities for each area. Given the broad nature of the PPB mission, the Plan is not intended to be comprehensive. The Branch anticipates that research conducted within the grants and contracts portfolios will continue to address many issues not covered in this plan. With this in mind, the Strategic Plan was developed to be flexible, so that the PPB can address new and emerging areas relevant to the field as they use. Rather than being a restrictive entity, the PPB Strategic Plan will allow for the expansion of research, both within this framework, and outside of it.

ONGOING AREAS OF EMPHASIS

The ongoing areas of emphasis include critical topics of research that are currently underway and are crucial to the PPB mission. Some of these areas, such as the Networks, have a long history in the Branch and provide a mechanism for timely, cost-effective clinical investigations. Others, such as stillbirth and obstetrical-fetal pharmacology, are more recent efforts to fill gaps that were identified by the field, which now have initiatives planned for implementation.

EVIDENCE-BASED MEDICINE IN OBSTETRICS AND NEONATOLOGY

Modern medical management has, in some instances, adopted solid principles of care, while at other times it has employed pharmaceuticals and methodologies without rigorous use of the controlled observation necessary for objective evaluation. This disconnect sometimes results in the enthusiastic initial adoption of concepts and procedures, followed by their modification or replacement, sometimes decades later, after extensive experience has failed to support their usefulness or has shown unexpected consequences. To respond to the need for well-designed clinical trials in maternal-fetal medicine and neonatology, the NICHD established the MFMU Network and the NRN in 1986. Each Network is guided by its respective Steering Committee, which consists of representatives from each clinical center, the NICHD, and the data-

coordinating center. Protocols are developed and approved by the Steering Committee. Typically each Network has two to three randomized controlled trials and two to three observational studies ongoing at any given time. These Networks allow for a timely response to urgent clinical questions in a cost effective manner. Currently, the MFMU Network has 14 sites, and the NRN has 16 sites. Sites are selected every five years following an open competition.

ACTION STEPS:

1. Continue to support the MFMU Network and the NRN.
2. Facilitate the collaboration between the two Networks through improved communication among various groups, interaction beyond the Network meetings, and input on protocols from one group to the other.
3. Encourage research through clinical trials that are not Network activities. Because the Networks are competed every five years and, thus, are not open to all institutions at all times, the Branch recognizes the need to support researcher-initiated investigations that evaluate evidence-based practice in maternal-fetal medicine and neonatology outside these Networks. Examples include the ongoing *Vaginal Ultrasound Cerclage Trial* (1 U01 HD039939-01A1; Principal Investigator: John Owen, MD), a multicenter, randomized clinical trial, designed to determine the efficacy of cerclage (a purse-string suture placed around the uterine cervix) for the prevention of spontaneous preterm birth prior to 35 weeks' gestation; and the *Twin-Twin Transfusion Syndrome Trial* (5 R01 HD041149-02 Principal Investigator: Tim Crombleholme, MD), a prospective, randomized multicenter trial of pregnancies complicated by twin-twin transfusion syndrome (TTTS) to compare serial amnioreduction with selective fetoscopic laser photocoagulation. The overall goal of the latter study is to improve the outcome of twins with TTTS by determining which treatment for TTTS improves survival as well as cardiac, neurologic, and developmental outcomes.

SUDDEN INFANT DEATH SYNDROME (SIDS)

In the United States alone, about 2,500 infants now die each year from SIDS; but SIDS occurs worldwide. The majority of SIDS deaths occur before babies reach six months of age. These deaths, although associated with a sleep period, are sudden and unpredictable. In most cases, infants appear healthy before succumbing to SIDS. No explanation for these deaths can be found, even when a complete postmortem is performed, including an autopsy, an examination of the death scene, and a review of the infant's clinical and family history. In the absence of an identifiable cause of death, these infant deaths are, by standard definition, labeled SIDS.

SIDS exacts a devastating emotional toll on affected families and caregivers. In 1974, landmark legislation—the Sudden Infant Death Syndrome Act (P.L. 93-270)—gave the NICHD the statutory responsibility to oversee SIDS research and to develop a public education and information program about SIDS. The Institute's ultimate goal is to eliminate SIDS in all populations. To reach this aim, it is important to understand the underlying causes and mechanisms of the syndrome, develop strategies to identify infants at high risk for SIDS, and develop and implement preventive strategies that can effectively reduce the incidence of SIDS across diverse populations.

The research agenda of the NICHD's SIDS program is outlined in *Targeting Sudden Infant Death Syndrome (SIDS): A Strategic Plan*, one of several NICHD strategic planning documents available on the NICHD Web Site, at http://www.nichd.nih.gov/strategicplan/cells/.

Since 1994, as a way to address the second part of the SIDS Act, the NICHD, the Maternal and Child Heath Bureau, the AAP, the SIDS Alliance and the Association of SIDS, and Infant Mortality Programs have sponsored the *Back to Sleep* campaign; to educate caregivers that healthy infants be placed on their backs to sleep to reduce the risk of SIDS. The campaign also explains other ways to reduce the risk of SIDS, including placing an infant on a firm mattress. Information about the *Back to Sleep* campaign is available at the NICHD Web Site, at http://www.nichd.nih.gov/sids/sids.cfm.

AREAS TO INVESTIGATE:

The NICHD's SIDS Strategic Plan is divided into four sections; each section recommends a number of research questions related to SIDS. These sections are explained below.

Etiology and Pathogenesis

The recommendations in this section are targeted toward understanding:

- How the neural abnormalities observable in SIDS infants develop;
- How these neural abnormalities affect infant health and development before and after birth;
- How environmental factors in the Neonatal Intensive Care Unit (NICU) and beyond affect the growing brain of preterm infants;
- Whether there are genetic factors that predispose infants to sudden death; and
- How specific characteristics of the fetal and postnatal environment either contribute to the pathological process or serve to protect infants.

Prognostics and Diagnostics

The recommendations in this section address:

- Assessment of neural maturity through infancy; and
- Development of tools to assess the neurological and developmental maturation of newborn infants through early infancy and the predictive value of screening tools used in the neonatal period.

Preventive Strategies

The recommendations in this section emphasize the need for:

- Strong community partnerships;
- Knowledge of cultural variations;
- Rigorous evaluations of interventions and feedback from the lay community;
- Comprehensive and consistent assessments of fetal and infant deaths; and
- Understanding of how multiple risk factors may interact.

Health Disparities

The recommendations in this section emphasize:

- Creation and maintenance of strong community resources for research and intervention;
- Investigation of both protective and adverse forces operating within and across populations; and

- Investigation of both macro- (e.g., equity of care) and micro-level (e.g., genetic predisposition) forces that operate within and across populations.

ACTION STEPS:

1. Support the RFA: HD-03-004—*Prenatal Alcohol Exposure Among High-Risk Populations: Relationship To Sudden Infant Death Syndrome*. The NICHD and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) invited cooperative agreement applications for the development of community-linked studies to investigate the role of prenatal alcohol exposure in the risk for SIDS and adverse pregnancy outcomes, such as stillbirth and fetal alcohol syndrome (FAS), and how they may be inter-related. The investigators will work collaboratively under cooperative agreements with NICHD and NIAAA over a three-year period to plan and pilot multidisciplinary investigations, using common protocols, within communities at high risk for prenatal maternal alcohol consumption. The long-term goals of this initiative are to decrease fetal and infant mortality and improve child health in these communities. Applications were due March 17, 2003; funding plans were reviewed at the September 2003 meeting of the National Advisory Child Health and Human Development (NACHHD) Council.
2. Issue a Letter of Invitation: HD-02-104—*Data Coordinating and Analysis Center, Event Recordings of High Risk Infants on Apnea Monitors: The Collaborative Home Infant Monitoring Study (CHIME)*. This grant, awarded in 2003, continued the National Infant Sleep Position Study (NISP), which evaluates trends in infant sleep practices, the dissemination of the *Back to Sleep* recommendations, and the factors that influence these trends. This invitation also facilitated the scientific community's access to the databases collected by NISP and the CHIME efforts.
3. Support the RFA: HD-02-08—*Development of Community Child Health Research*. The purpose of this solicitation was to support community/research institution partnerships that will span two-and-a-half years. These partners planned a multi-site, multi-level study to examine: how community, family, and individual-level influences interacted with biological influences; and how these interactions resulted in health disparities in pregnancy outcomes and in infant and early childhood mortality and morbidity. The funding plan was reviewed at the January 2003 meeting of the NACHHD Council.

STILLBIRTH

Stillbirths account for a large proportion of perinatal mortality. According to annual national vital statistics, the number of fetal deaths (defined as deaths at 20 weeks or more gestation) is similar in magnitude to the total number of infant deaths in the United States. While the infant mortality rate declined by about 32 percent to 7.2 deaths in 1000 live births between 1985 and 1998, the stillbirth rate declined by only about 14 percent to 6.7 deaths in 1000 live births. Despite the significant and persistent burden of stillbirth, the phenomenon has remained largely unstudied. For at least half of all stillbirths, the cause remains undetermined.

AREAS TO INVESTIGATE:

- In-depth studies of the causes, reproductive and fetal risks in predicting stillbirth;
- The role of placentation in fetal demise, including the role of genetic mosaicism in the placenta;
- Unexplained stillbirths and the potential role of fetal autonomic dysfunction;
- The relationship of stillbirths to other adverse pregnancy outcomes, particularly those with a potential infectious etiology; and
- Quantitative evaluation of the role of thrombophilias to aid in screening and management decisions.

ACTION STEPS:

1. Convene a workshop. The NICHD held a workshop in March 2001, *Setting a Research Agenda for Stillbirth*, to explore the current knowledge in the field and identify research topics. The findings from this workshop were published in the February 2002 issue of *Seminars in Perinatology*.
2. Support the RFA: HD-02-025—*Research on the Scope And Causes of Stillbirth in the United States*. This 2002 RFA created a network of clinical sites, with central data collection and analysis, to develop and implement common research protocols to study stillbirth (defined as fetal death at 20 weeks' or greater gestation). The resulting network of multidisciplinary investigators will develop research diagnostic protocols, as well as a body of data on the scope and causes of stillbirths among varied populations within the United States, while encouraging community involvement to obtain an adequate sampling of rural and urban populations and a diverse ethnic/racial makeup. The information obtained from this effort will aid in future research in improving preventive and therapeutic interventions and in understanding the pathologic mechanisms that lead to fetal death. Applications were due on March 13, 2003; the funding plans were reviewed at the September 2003 meeting of the NACHHD Council.
3. Encourage and create other research opportunities. Initiatives to address the Areas to Investigate for stillbirth not covered above will be considered by the Branch for its yearly initiatives.

OBSTETRICAL-FETAL PHARMACOLOGY

The study of drugs used during pregnancy is one of the most neglected areas in the fields of clinical pharmacology and drug research. The data available on drug biodisposition and effect are scarce, fragmentary, and frequently contradictory. The lack of Food and Drug Administration (FDA) obstetric labeling and the universal off-label use of drugs are a direct result of the lack of research and clinical trials in this special population. Epidemiological surveys have determined that nearly two-thirds of all pregnant women take at least four or five drugs during pregnancy and labor. These data demonstrate that drug use during pregnancy is of great public concern because it is mostly based on an empiric approach, rather than on a scientific basis; further, current use does not take into account the profound physiologic changes characteristic of the pregnant state.

ACTION STEPS:

1. Convene the experts. The PPB, in collaboration with the NICHD's Endocrine, Nutrition, and Growth Branch (ENGB), the NICHD Office of the Director, the CRMC, and the FDA, held a series of workshops in the fall and winter 2001-2002 to identify research topics and determine the status of the field. In addition, within NIH, presentations to Office of Research on Women's Health's liaisons were made in an attempt to develop inter-Institute initiatives.
2. Support a new RFA. The NICHD issued a RFA (HD-03-017) on July 29,2003 for Obstetric-Fetal Pharmacology Research Units, to support integrated basic, translational, and clinical research centers that will:

    - Conduct pharmacologic studies of drug disposition and effect during normal and abnormal pregnancies;
    - Conduct single-site and multi-site cooperative clinical trials;
    - Conduct pharmacogenetic studies on the effect of pregnancy on drug metabolizing enzymes, transporters, and effectors;
    - Perform studies of placental transfer of drugs;
    - Conduct studies of fetal and maternal pharmacology;
    - Facilitate the utilization of clinical materials for basic research studies; and
    - Enhance the exchange of information between basic scientists and obstetricians, and among various specialists involved in treating pregnant women.

    The receipt date is November 24, 2003, and the funding plan will be reviewed in June 2004 at the NACHHD Council meeting.
3. Identify future initiatives, based on the progress of the grants awarded in response to the new RFA, and on the status of researcher-initiated investigations.

NEONATAL PHARMACOLOGY

Similar to the paucity of research on drugs used during pregnancy, the field of neonatal pharmacology is also a highly neglected field. The mandates of the Best Pharmaceuticals for Children Act (BPCA) provide an excellent opportunity for addressing many of the unresolved issues related to research and clinical practice of drugs used in newborn infants. This work is in cooperation with the ENGB, which maintains primary responsibility for the Pediatric Pharmacology Research Units (PPRUs) and the BPCA.

ACTION STEPS:

1. Partner with the PPRU Network, and with the FDA's Newborn Drug Development Initiative. Two program officers from the PPB are participating in a series of planning workshops that will lead to a multidisciplinary national workshop, planned for the winter/spring of 2003-2004, on this topic. PPB staff anticipates that the executive summary issued from the workshop will prioritize research and regulatory issues related to neonatal pharmacology. This summary will provide a background for future studies including clinical trials to foster the development of safe and effective drug therapies for preterm and neonatal populations.

MATERNAL-FETAL SURGERY

An increasing number of maternal-fetal surgeries for non-lethal conditions, such as meningomyelocele are being performed; yet, *in utero* surgery has not been validated to show improvement over postnatal repair. In addition, the risks to the fetus (i.e., death, preterm delivery) and to the mother (e.g., two classical uterine incisions within one pregnancy, all future pregnancies to be delivered by cesarean section, and complications such as placenta increta, uterine rupture) have not been evaluated. To address this research need, the NICHD established the Maternal-Fetal Surgery Network within the MFMU Network in 2001 to evaluate *in utero* fetal surgery versus standard postnatal repair as a treatment for antenatally diagnosed spina bifida in a randomized clinical trial.

ACTION STEPS:

1. Monitor the trial closely for adverse events and protocol compliance. The Branch, through an Inter Personnel Agency agreement, hired maternal-fetal medicine specialist and fetal surgeon, Dr. Nancy Chescheir, to act as the NICHD Program Scientist.
2. Assemble the field. The Branch will plan a workshop on the ethics and role of maternal-fetal surgery, to clarify conditions that might benefit from *in utero* repair, and to identify future trials needed in this progressive area.

NEW AREAS OF EMPHASIS

PREMATURITY

Preterm delivery accounts for 70 percent of perinatal mortality, and for nearly half of the long-term neurologic morbidity of newborns. Despite years of intense effort to reduce preterm delivery rates, approximately 10 percent of all births in the United States are still preterm, and the incidence of very preterm births has been rising in recent years. The understanding of the underlying mechanisms of preterm birth is limited; less than half of all preterm births have an identifiable risk factor.

The PPB staff and the Workshop participants recognized that significant research has been devoted to this condition; but noted that much remains to be understood. The Branch selected this topic as one that needed novel approaches for the future. Participants added that into the etiology of preterm birth should take into consideration its multi-factorial nature, including utero-placental insufficiency, fetal growth abnormalities, and fetal stress.

AREAS TO INVESTIGATE:

- New tools are needed for:
  - Fetal growth assessment; and
  - Non-invasive methods to assess cervical, myometrial, and placental changes longitudinally.

- Research should focus on the:
  - Pre-pregnancy and early pregnancy periods;
  - Role of the cervix;
  - Variability in host response; and
  - Role of the placenta; including:
    - Functional mechanisms related to pregnancy outcomes and fetal well-being, such as fetal growth and preterm delivery; and
    - Innovative technologies to study function *in utero*.
- Strategies for predicting preterm birth should include multivariate analysis, such as that used in neural network analysis, and should focus on identifying the potentially reversible changes that take place in pre- and early pregnancy stages.
- Research should focus on the cases with highest mortality and morbidity and should not be diluted by inclusion of less relevant cases of preterm birth that are close to term.
- The field needs to develop clinically applicable methods to identify pregnancies for which delaying delivery is futile or detrimental, and the effects of intervention on outcome.

ACTION STEPS:

1. Support the RFA: HD-01-005—*Health Disparity In Preterm Birth: The Role Of Infectious And Inflammatory Processes*. The PPB funded six grants under this RFA from fiscal year 2001 and will follow closely the findings from these grants. The disparity in the rate of preterm births between African American and all other ethnic minorities remains one of the most striking of U.S. health disparities. Preterm births are twice as high among African American women as among any other group of women in the United States; with an even greater discrepancy exists in the rate of very early preterm birth. The findings from these studies may provide groundwork for new initiatives.
2. Issue a new Program Announcement (PA). In conjunction with the National Institute of Environmental Health Sciences (NIEHS) and the National Institute of Nursing Research (NINR), the PPB issued PA-02-102: *The Role of Gene-Environmental Interactions Underlying the Health Disparity of Premature Birth*, to address the need to better understand how adverse societal, behavioral, and environmental conditions alter gene expression, and how these factors interact with diverse genetic backgrounds to increase a woman's susceptibility for premature birth in high-risk racial and ethnic groups. The solicitation encourages multidisciplinary approaches to clarify the potential role of genetics in the increased risk of premature birth among certain populations. This PA will close on January 1, 2005. The Branch will closely follow the number and caliber of applications submitted in response to this PA. If the research community does not adequately respond to the PA, the PPB will consider issuing an RFA.
3. Issue a new RFA. In 2004, the Branch plans to issue the RFA *Research into Mechanisms of Fetal Growth Restriction*. The aim of this initiative is to stimulate research into the mechanisms of fetal growth restriction, and to gain a better understanding of the factors that regulate fetal growth during pregnancy.

4. Increase participation in the National Children's Study (NCS). The Branch has begun these activities:
    - The PPB, in conjunction with the NCS, held a workshop on the assessment of fetal growth and integrity on December 15-16, 2002, in Baltimore, Maryland. This workshop reviewed the current models of fetal growth assessment.
    - The PPB is working with NCS staff to develop the requirements for a pilot study of the feasibility of three-dimensional ultrasound data acquisition, storage and retrieval for the measurement of fetal growth.
    - The Pregnancy and the Infant Working Group is encouraging collection of data that will allow for novel assessments of fetal growth and integrity.
5. Create other research opportunities. Initiatives to address the Areas to Investigate for Prematurity, which is not covered above, will be considered by the Branch for its yearly initiatives. Given the importance of this topic to the Branch, an initiative on prematurity will be proposed each year once the findings from ongoing grants and trials are reviewed.

FETAL DEVELOPMENT, INCLUDING MATURATION OF INDIVIDUAL ORGAN SYSTEMS AND IMPACT OF INTERVENTIONS ON LONG-TERM FUNCTION

Within this area, participants noted the following:

- New tools for defining fetal growth are needed.
- The gender-specific effects of "stressors" on prenatal organ maturation at critical windows of development are not well understood.
- The epidemiological associations of specific intrauterine stressors and later outcomes are ripe for further study.
- The integration of the complex effects intrauterine stress has been little studied.
- New treatment offerings need to be developed for use once undergrowth and/or fetal stress are detected.
- The phenomenon of intergenerational programming is not well understood.
- The mechanisms that determine embryonic and fetal growth trajectory during the post-fertilization period are not known.
- The role of maternal stress during pre- and post-natal life requires further investigation
- There is a great need to determine the role of the placenta in programming.
- The field of human and animal development needs a structured repository of developmental information that allows computerized retrieval methods.
- The role of maternal nutrition on fetal growth and growth restriction requires further investigation.
- Assessment of outcome should focus on the long-term (into adulthood) functional outcome of high-risk infants. Developing a nation-wide database to prospectively record high-risk infant outcomes should be given a priority so that researchers can evaluate the effectiveness of therapeutic interventions in perinatal and neonatal periods on the health and well-being during adult life.

ACTION STEPS

1. Convene the experts. In collaboration with the Pregnancy and the Infant Working Group of the NCS, members of the PPB held a workshop December 15 and 16, 2002, on the *Evaluation of Fetal Growth and Integrity.* In addition, the PPB and the Pregnancy and the Infant Working Group of the NCS plan to hold workshop to evaluate the measurement and identification of stress in pregnancy, in late 2003.
2. Issue the RFA: HD-03-018—*Research into Mechanisms of Fetal Growth Restriction*. The aim of this initiative is to stimulate research into the mechanisms of fetal growth restriction, and to gain a better understanding of the factors that regulate fetal growth during pregnancy. The target receipt date was July 23, 2003, and the funding plan will be reviewed at the January 2004 meeting of the NACHHD Council.
3. Create other research opportunities. In addition to the above, Branch staff will consider the avenues for investigating fetal development, maturation of individual organ systems, and impact on long-term function in the yearly Branch initiatives.

MATERNAL MORBIDITIES

Hypertension

Workshop participants identified the following needs for hypertension research:

- Understand pathophysiologic abnormalities that lead to adverse pregnancy outcome in hypertensive women;
- Identify the risk factors for adverse outcome (i.e., preeclampsia, abruption, preterm birth) in hypertensive women and design prevention strategies based on these risk factors.
- Understand the genetic diversity that underlies hypertension in pregnancy and that could: 1) Lead to a role for pharmacogenetic therapy; and 2) Identify a subset of women at risk for preeclampsia or cardiovascular complications in the future.
- Generate a program of long-term follow-up of hypertensive women, from preconception to ten years postpartum, similar to studies in non-pregnant hypertensive individuals. Identify risk factors for cardiovascular complications from these data.
- Initiate career development programs to enhance the research capabilities of scientists interested in hypertension during pregnancy.

Thrombophilias

Workshop participants cited a need to understand the fundamental pathologic processes in patients with thrombophilic conditions, in order to:

- Enable accurate counseling regarding personal, fetal, and neonatal risk assessment surrounding pregnancy.
- Stratify the at-risk patient population to assess risk for thromboembolic events and adverse pregnancy outcomes.
- Build base prevention and treatment strategies on risk assessment.
- Focus on specific prevention and treatment strategies, once the natural history of the individual thrombophilic mutations and pathologic mechanisms have been elucidated.

- Develop a comprehensive database, with epidemiologic information, tissue, biologic fluids, and biophysical components, and make it available for future investigations.
- Establish regional Centers of Excellence comprising of scientists, researchers, and clinicians, with special interest in thrombophilias. Such Centers would optimize resources and patient care, and, most importantly, would strengthen research.

Maternal Obesity
The patients explained the need to understand the fundamental pathologic processes in patients with obesity, in order to:
- Evaluate the impact of the obesity epidemic on pregnancy outcome, and, specifically, determine the impact on fetal growth and assessment.
- Evaluate the role of obesity on stillbirth, given the known association between obesity and stillbirth.
- Evaluate the association between the maternal metabolic syndrome and pregnancy outcome.

ACTION STEPS:

1. Continue to participate in the U.S. Department of Health and Humane Services (DHHS) Safe Motherhood Group. This Group, which includes the NIH, the DHHS, the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA), and the Substance Abuse and Mental Health Services Administration (SAMSA); aims to facilitate collaboration across agencies and Institutes on issues including maternal morbidity.
2. Encourage applications in these areas. A large application (more than $500,00) that incorporated some of the aims under thrombophilias was accepted for review by the NICHD, as a result of a Branch-initiated request. The Branch will seek co-funding from other Institutes and agencies to support this and future projects.
3. Consider the other needs regarding maternal morbidities for yearly Branch initiatives.

NEONATOLOGY (SPECIFICALLY INTENSIVE CARE, AND LONG-TERM OUTCOME ISSUES)

In spite of major advances in the management of high-risk newborn infants, substantial progress is still needed in reducing both acute and long-term morbidity. Particular concern remains in regard to acute issues, such as bacterial and fungal infection, optimizing nutrition of the growing preterm infant, medical decision making at the border of viability, and optimizing the intensive care environment to foster optimal developmental care. Additional concerns include: the high rates of chronic lung disease in survivors of neonatal assisted ventilatory support; concerns about high rates of long-term morbidities and deficits in cognitive functions in very low birth weight infants; and the unresolved issues concerning the effect of perinatal/neonatal and family environment on outcomes during childhood, adolescent and adult lives.

One major obstacle to understanding the toll of long-term morbidity on the survivors of neonatal intensive care is the lack of nation-wide data on outcome. While some investigators have carried out excellent studies on outcomes, all such studies have been limited to the researcher's institution, and no national trends on morbidity can be discerned from these studies alone. There

is a great need for developing a National Registry of Outcomes for the survivors of neonatal intensive care.

AREAS TO INVESTIGATE

- Research regarding the cause, prevention, and treatment of prematurity could lead to improvement in the neurological outcomes for the infant. Basic research in neuroscience and translational research should be a priority. The early identification of infants at high risk for long-term neurodevelopmental impairment is needed.
- Basic and translational research on organ development, and on the effects of intensive care interventions and prenatal and postnatal influences on development and long-term potential for function should be a priority.
- Basic and translational research in fetal nutrition and gastrointestinal development are key to preventing extrauterine growth retardation and malnutrition, and to addressing developmental issues in organ development during critical windows of development.
- Information regarding factors that impact on medical decision making at the limit of viability, including factors that relate to maternal health, parental involvement, physician/nursing/staff involvement, societal norms, and cost-effective use of therapies, is necessary to provide optimum medical care and to improve outcomes.
- A collaborative effort is needed to developing a comprehensive registry for long-term outcomes. The collaboration may include several federal agencies (i.e., the NICHD, CDC, the Agency for Healthcare and Research Quality, etc.) and may utilize network databases and state health department information.

ACTION STEPS:

1. Develop and coordinate a workshop, in collaboration with the AAP, to identify the research priorities specific to neonatology. This workshop will occur in late 2003 or 2004.
2. Consider other areas for investigation under neonatology for yearly Branch initiatives.

FETAL/NEONATAL BRAIN DEVELOPMENT AND DAMAGE (INCLUDING PRENATAL, PERINATAL, NEONATAL, AND INFANT PERIODS)

Specifically, this discussion addressed the following topics:

- Neonatal/infant nutrition and the long-term impact on growth and maturation; and
- Prevention of brain injury in the newborn period, such as from hyperbilirubinemia, hypoglycemia, and other metabolic abnormalities in the preterm and term infants.

AREAS TO INVESTIGATE

- Interaction of the environment and the genome in developing brain, including molecular, cellular, and animal models of injury and repair:
  - Identification of common pathways of injury to developing brain, including metabolic, infectious, and xenobiotic agents;

  - Genomic factors that render the developing brain resistant and/or susceptible to injury; specific complications, including intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy, retinopathy, and speech and language disorders are potential areas of research to target genomic influences on diseases;
  - Environmental factors which promote plasticity or enhance defect; and
  - Development of strategies to prevent injury and promote neural repair.
- Translation of the basic science data to the newborn unit and beyond; for example:
  - Collaborative use of the MFMU Network to validate animal models of injury and repair; and
  - Development of intervention and prevention trials.
- Improved methodologies for assessment of normal neurobehavioral development, for diagnosis of injury, and for documentation of efficacy of therapies and repair of developmental injury applicable in the clinical situation; this effort may entail:
  - Implementation of comprehensive infant follow-up studies as projected for the NCS;
  - Development of behavioral methodologies and probes to evaluate continuities and trajectories relevant to long-term outcome;
  - Development of improved fetal imaging strategies (e.g., fetal MRI, fMRI, volumetric studies);
  - Development of improved neonatal imaging strategies (MRI, MRS, DTI); and
  - Development of standardized strategies to assess early language abilities.
- Research involving brain development in the preterm infant for improvement of outcomes, including the assessment of optimal developmental care in the NICU.

ACTION STEP:

1. Consider the areas above for investigation as yearly Branch initiatives.

TRAINING FOR THE FUTURE: SCIENTISTS AND PHYSICIAN-SCIENTISTS

Areas for future emphasis include the following:

- Increase research exposure, involvement, and interest among medical students, undergraduate, and graduate students through support of perinatal research programs.
- Provide funding to reduce clinical service demands, in exchange for greater research training time; ensure liability costs do not necessitate a volume of clinical practice that precludes substantive research time; increase levels of funding for research training to compete with clinical compensation.
- Develop programs that will facilitate continuing research by MD, PhD, and other trainees who have already been involved in, and wish to continue, the perinatal research track. This item is particularly important at the junior faculty stage of career development.
- Incorporate and fund PhD and Masters of Public Health (MPH) tracks in training.
- Assure consistent and capable mentoring and rigorous oversight and quality control of training programs.
- Encourage interdisciplinary programs, including reproductive biology, and development of graduate studies programs in reproductive biology.
- Simplify methods for obtaining funding for pre-doctoral and postdoctoral positions.

- Allow a principal investigator to apply for a pre-doctoral or postdoctoral award without having a named candidate.
- Remove U.S. citizen/permanent resident requirement from training eligibilities.
- Allow a supplement to R01 grants that allow addition of a training position.
- Provide postdoctoral grants for salary, supplies, and technical support for which trainees can apply during the postdoctoral training period; or consider extension funds to secure faculty position.
- Fund a bridge grant to include salary, supplies, and technical support for which a postdoctoral student can apply.
- Re-establish a starter grant mechanism similar to the R29 to foster development of new and/or junior faculty.
- Increase flexibility of programs such as Women's Reproductive Health Research (WRHR), and establish WRHR-type programs for non-physician scientists in reproductive biology.
- Expand loan forgiveness programs for physicians and establish loan forgiveness program for non-physician scientists.

Recruitment, training, and retention activities would involve the following items:

- Recruitment efforts should be emphasized to draw potential candidates into the research arena.
- To influence younger generations of potential scientists, efforts should focus on the depth of training and enhancement of candidate pool.
- The current support provided by the NICHD is valued, but the consensus is that fellows are not getting support early or often enough. Can NICHD direct support to medical students, residents, and early post-docs by speaking to these audiences? How about to undergraduates?
- More unified training efforts in both fields of maternal-fetal medicine and neonatology are crucial.
- Training needs to enhance the capacity of instructing teachers how to teach.
- Flexibility in the awards is important.
- International collaborations could be useful in training.
- Consider adding a PhD component to the WRHR program, or starting a similar program at WRHR sites, to facilitate interaction between PhD and MDs in reproductive sciences.
- Add flexibility of training to awarded R01 grants.
- With regard to neonatal training for fellows, increasing the funding mechanisms after the first year is critical. It was also suggested that the NIH extend the current program from three to four, or perhaps five years.

ACTION STEPS:

1. Propose an initiative(s) to increase the availability, scope, flexibility, and length of training in perinatology and neonatology. Conceivably a K12 mechanism that specifically focused on enhancing training could be used to incorporate many of the recommendations made by the workshop participants such as:

    - Increasing research exposure, involvement, and interest among medical students, undergraduate, and graduate students;

- Developing programs that will facilitate continuing research by MD, PhD, and other trainees who have already been involved in, and wish to continue, the perinatal research track;
- Incorporating and funding PhD, MPH, MSCE tracks in training;
- Encouraging interdisciplinary programs, including reproductive biology, and developing graduate studies programs in reproductive biology;
- Recruiting potential candidates into the research arena;
- Influencing younger generations of potential scientists, with efforts focusing on the depth of training and enhancement of candidate pool;
- Providing unified training efforts in both fields of maternal-fetal medicine and neonatology;
- Providing training needs to enhance the capacity of instructing the teachers how to teach.
- Expanding international training collaborations;
- Facilitating interactions between PhDs and MDs in reproductive sciences; and
- Increasing the trainee support from three to four, or perhaps five years.

2. Encourage existing T32 programs to promote their programs to medical students, undergraduates, and graduate students.
3. Promulgate this grant mechanism at society meetings and interaction with investigators. The K25 mechanism may not be readily known to the scientific community as a means for protecting research and mentoring time.
4. Encourage institutions and individuals involved in perinatal research to apply for National Research Service Awards such as fellowship, training, and career awards.
5. Continue to be vigilant in monitoring the quality of PPB training grants in terms of mentoring and training.
6. Encourage existing research programs to promote interdisciplinary training, such as the Mentored Specialized Clinical Investigation Development Award grants through the NRN and MFMU Networks.
7. Forward several of the recommendations that involve changes to the current NIH policy to the director of the Office of Extramural Programs for consideration, including:
    - Increasing the monetary compensation of the K25 grant to compete with clinical compensation;
    - Allowing a principal investigator to apply for a predoctoral or postdoctoral award without having a named candidate;
    - Removing U.S. citizen/permanent resident requirement from training eligibility;
    - Allowing a supplement to R01 grants to allow addition of a training position;
    - Providing postdoctoral grants for salary, supplies, and technical support for which trainees can apply during the postdoctoral training period;

- Funding a bridge grant to include salary, supplies; and technical support for which a postdoctoral applicant can apply;
- Reestablishing a starter grant mechanism similar to the R29 to foster development of new and/or junior faculty; and
- Expanding the loan forgiveness programs for physicians and establishing loan forgiveness program for non-physician scientists.

DEFINE AND IMPROVE THE LINK BETWEEN FETAL, OBSTETRICAL, AND NEONATAL INTERVENTION AND INFANT/CHILD OUTCOMES

- The mechanism/s that underlie fetal growth retardation (FGR) and the development of chronic adult disease are not known.
- Although short-term impact of nutritional and other interventions in the neonate are well known, their impact on health during adolescence and adulthood is not known.
- Prospective studies in humans, using state-of-the-art methods in a carefully identified contemporary cohort are required to distinguish the genetic, nutritional, metabolic, and hormonal influences during pregnancy that impact fetal growth, and to examine the relationship between size-at-birth and adolescent and adult health.
- Development of sophisticated techniques for animal models, including physiological phenotypes and non-invasive methods for physiological data are needed.
- The physiological mechanisms of early life experiences within socioeconomic disadvantaged individuals and their health during childhood, reproductive life, and adulthood need further study.
- The community needs to examine the biological basis of nutritional and pharmaceutical interventions, to determine the impact of timing of the intervention (i.e., early or late in pregnancy, intrapartum or the neonatal period).
- The field should support the development of new algorithms to examine outcomes, including sensitive techniques to address functions, including functional imaging methods (MRI), anthropometric studies (body composition measurements), and other methods to assess neurodevelopment early in life.
- Evaluation of intrauterine genetic environment, including fetal polymorphism and its relation to IUGR, preeclampsia, hypertension, and stroke is also needed.
- More data are needed on infections not related to prematurity that continue to result in significant fetal and neonatal morbidity such as hepatitis C, HIV, cytomegalovins, etc.
- Studies that focus on morbidity due to prematurity, particularly from high bilirubin, abnormalities of glucose and calcium metabolism, and from nutritional deficiencies are required.
- Studies to optimize nutritional support for a preterm infant receiving intensive care are necessary.

ACTION STEPS:

1. Support the Newborn Drug Development Initiative. The goal of this NICHD/FDA project is to foster the development of safe and effective drug therapies for pre-term and neonatal

populations. This five-year initiative will initially focus on defining the state-of-the-art and determining research priorities for cardiac, neurological, pulmonary diseases, and pain control.

2. Support the RFA: HD-00-010—*Cooperative Multicenter NRN*. The PPB funded 16 clinical centers through this RFA to create multimember clinical programs that investigate the safety and efficacy of treatment and management strategies to care for newborn infants, particularly programs related to management of low-birth-weight infants. The NRN has the unique capability of conducting multicenter clinical trials research in the neonatal population and developing high-impact modalities of treatment for newborn infants. Follow up of high-risk infants is an integral part of the program for determining long-term outcomes. A Genomics Subcommittee was recently created to institute projects related to the impact of genetics on health and disease in the NRN.
3. Support the PAR-02-105: *The Fetal Basis of Adult Disease: Role of the Environment.* This effort is an ongoing PA that may add to improving the link between fetal, obstetric, and neonatal outcomes.
4. Issue the RFA: HD-03-018—*Research into Mechanisms of Fetal Growth Restriction*. The aim of this initiative is to stimulate research into the mechanisms of fetal growth restriction, and to gain a better understanding of the factors that regulate fetal growth during pregnancy. The target receipt date was July 23, 2003, and the funding plan will be reviewed at the January 2004 meeting of the NACHHD Council.
5. Facilitate interaction between the NRN and the MFMU Network. Having a steering committee member from the MFMU present at the NRN meetings, and vice versa, was one recommended way to improve interaction. Program officials and program coordinators would also be present at both Network meetings to facilitate possible areas of overlap in projects. Joint projects could also be developed to maximize assessment of outcome variables (e.g., maternal, fetal, neonatal).