Pregnancy and Perinatology Branch

NICHD

Strategic Plan 2005-2010

U.S. Department of Health and Human Services
National Institutes of Health
National Institute of Child Health and Human Development

Pregnancy and Perinatology Branch (PPB)
Strategic Plan

Fiscal Year 2005 through Fiscal Year 2010

U.S. Department of Health and Human Services
National Institutes of Health
National Institute of Child Health and Human Development

For Administrative Use
October 2003

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BACKGROUND

The Pregnancy and Perinatology Branch (PPB) is one of three branches in the Center for Developmental Biology and Perinatal Medicine at the National Institute of Child Health and Human Development (NICHD). The mission of the Branch is to improve the health of mothers and children, with focuses on maternal health, pregnancy, fetal well-being, labor and delivery, and the developing child.

The purpose of research supported by the Branch is to promote the acquisition of scientific information through basic, translational, and clinical investigation, that supports the Branch mission. Important research areas for PPB include: basic mechanisms underlying normal and disease processes; the identification of new treatments, methodologies and preventative strategies arising from translational and evidence-based research; and assessment of the dissemination and impact of therapeutic and preventative interventions. In addition, the Branch aims to increase scientific resources for these fields of study through recruitment and training of investigators.

In March 2001, the Branch began a process of self-assessment, reviewing the goals and mission of the Branch, its initiatives, and its portfolio in preparation for a PPB Planning Workshop to be held in 2002. This extensive internal review included large projects, such as the PPB-supported Networks, the Maternal-Fetal Medicine Unit (MFMU) Network and the Neonatal Research Network (NRN), as well as various program projects (P01s). To familiarize Branch members with the PPB portfolio, each program project was assigned to three Branch members, who reviewed, discussed, and assessed the project's progress since initiation, contributions to the field, and novelty. Seminars held by the NICHD Center for Research on Mothers and Children (CRMC) also gave Network program officers the opportunity to present updates on their projects to Branch members; other discussions were held on projects within the sudden infant death syndrome (SIDS) portfolio. Prior to the PPB Planning Workshop, the Branch members also reviewed the NICHD SIDS Strategic Plan, the Society for Maternal Fetal Medicine's *Research Priorities in Maternal Fetal Medicine*, and the *Committee Research Agenda* from the American Academy of Pediatrics (AAP) Section on Perinatal Pediatrics.

As a result of these inquires, Branch staff identified research priorities in three areas: 1) Areas already under investigation that remained important; 2) Areas that needed stimulation; and 3) Areas that needed new approaches or directions. Based on these general areas, Branch staff identified 10 target research areas for the PPB Planning Workshop. In addition, the Branch prepared background information for the Workshop, including the Branch's history, the Request for Applications (RFAs), contracts, workshops and conferences, grant portfolios, ongoing activities, and planned activities for fiscal year 2003 and fiscal year 2004 (See Appendix A).

SUMMARY OF THE PPB PLANNING WORKSHOP

In December 2002, the PPB convened its two-day Planning Workshop to develop a research agenda that would help guide Branch activities and priorities for the years 2005 through 2010. The Branch invited 14 eminent scientists to the Workshop to identify the needs of the scientific community served by the PPB and to prioritize Branch scientific areas and research issues.

During the bulk of the Workshop, participants discussed the Areas of Opportunity, based on prepared statements that detailed important new directions for research, and on the recommendations of PPB staff. The final half-day focused on priority setting by the group. Additional follow-up activities included the development and finalization of the group's recommendations. The findings from and recommendations of this PPB Planning Workshop formed the basis for this Strategic Plan document.

The participants were assigned as champions for one of the Areas of Opportunity and developed summary sheets on each topic. These summations were revised after the workshop to include items from these discussions (see Appendix B).

The Areas of Opportunity discussed during the Workshop included:

- Prematurity;
- Fetal development, including maturation of individual organ systems and impact of interventions on long-term functional outcomes;
- Maternal morbidities;
- Neonatology, specifically intensive care and long-term outcome issues;
- Fetal/neonatal brain development and damage (including prenatal, perinatal, neonatal, infant periods, and environmental effects on child development);
- Training for the future: scientists and physician-scientists; and
- Links between fetal, obstetrical and neonatal intervention and infant/child outcome.

In addition, workshop participants discussed several cross-cutting themes that were relevant to all areas of opportunity, including:

- Infrastructure resources;
- Environmental and genetic influences;
- Health disparity issues;
- Technology development, including the application of new technologies (e.g., genomics, proteomics, fMRI, bioinformatics, etc.) in pregnancy and perinatology research; and
- Research risk and ethical aspects of research.

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).

APPENDIX A: PPB SUMMATION FOR THE 2003 PLANNING WORKSHOP

HISTORY OF RFAS
FISCAL YEAR 1994 TO FISCAL YEAR 2002

FISCAL YEAR 2002

RFA-HD-02-025: Research on the Scope and Causes of Stillbirth in the United States
The purpose of this solicitation was to create a network of clinical research sites with central data collection and analysis, which would develop and implement common research protocols to study stillbirth (defined as fetal death 20 weeks or greater gestation). According to annual national vital statistics, the number of fetal deaths at 20 weeks or greater gestation is similar in magnitude to the total number of infant deaths in the United States. Despite this significant and persistent burden, stillbirths remain largely unstudied. For at least half of all stillbirths, the cause remains undetermined. This RFA sought to create a network of multidisciplinary investigators to develop research diagnostic protocols, as well as to build 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 will aid in future research to improve preventive and therapeutic interventions, and to understand the pathologic mechanisms leading to fetal death.

RFA-HD-02-008: Development of Community Child Health Research
The NICHD invited cooperative agreement applications for the development of a community-linked collaboration to investigate disparities in maternal and child health. The purpose of the solicitation was to support community/research institution partnerships that would work together over a two and one-half year span. The partners planned a multi-site, multi-level study to examine how community, family, and individual level influences interact with biological influences, to result in health disparities in pregnancy outcome and infant and early childhood mortality and morbidity. The long-term goals were to decrease fetal and infant mortality and improve child health in minority urban and rural communities.

FISCAL YEAR 2001

RFA-HD-01-005: Health Disparity in Preterm Birth: The Role of Infectious and Inflammatory Processes
This RFA aimed to determine the role of infectious and inflammatory processes in preterm birth and adverse neonatal outcomes in different ethnic populations. The research proposed in response to this solicitation involved multidisciplinary investigations to clarify the potential role of infectious diseases and the associated immune response as a cause of early preterm birth and fetal and neonatal morbidity.

FISCAL YEAR 2000

RFA-HD-00-010: Cooperative Multicenter NRN
The NICHD invited applications from investigators willing to participate, under a cooperative agreement (U10), in an ongoing multicenter clinical program designed to investigate the safety and efficacy of treatment and management strategies to care for newborn infants, particularly those related to management of low birth weight infants. The program sought to facilitate evaluation of these strategies by establishing a network of academic centers that, by rigorous patient evaluation using common protocols, studied the required numbers of patients and provided answers more rapidly than individual centers acting alone. The NICHD program staff assisted the principal investigators of the NRN and its Advisory Board in identifying research topics of high priority, and in designing and implementing protocols appropriate to the evaluation of optimal management in these areas.

RFA-HD-00-009: Cooperative Multicenter MFMU Network
The NICHD invited applications from investigators willing to participate, under a cooperative agreement (U10), in an ongoing multicenter clinical program designed to investigate problems in clinical obstetrics, particularly those related to prevention of low birth weight, prematurity, and medical problems of pregnancy. This program sought to facilitate resolution of these problems by establishing a network of academic centers that, by rigorous patient evaluation using common protocols, studied the required numbers of patients and provided answers more rapidly than individual centers acting alone. The NICHD program staff assisted the principal investigators of the MFMUs and the Advisory Board in identifying research topics of high priority, and in designing and implementing protocols appropriate to the evaluation of optimum management in these areas.

FISCAL YEAR 1997

RFA-HD-97-010: Data Coordinating Center (DCC) for the Cooperative Multicenter NRN
The NICHD supported clinical research in neonatal medicine through its ongoing 14-center NRN to do clinical research investigating the safety and efficacy of treatment and management strategies to care for newborn infants, particularly those of low birth weight. The Network, funded by cooperative agreements, included a DCC that provided statistical expertise, data management, and analysis for Network trials and studies. The DCC had served the NRN since the Network's inception; support for this DCC continued through March 31, 1998. NICHD invited all potential applicants to apply for the cooperative agreement to participate as the DCC for the NICHD NRN. The successful applicant is now responsible for completing ongoing trials and studies and initiating new research in neonatology and perinatology.

RFA-HD-97-009: DCC for the Maternal-Fetal Research Network
The NICHD fostered its strong and ongoing interest in clinical research in maternal-fetal medicine by establishing the MFMU Network in 1986. Support of the Network has continued until the present time, with recompetition of the clinical centers in 1991, and again in 1996. At the time of this RFA, the Network consisted of 13 clinical centers, a single data coordinating center independent of any of the clinical centers, and NICHD program staff. The Network DCC

was supported with a cooperative agreement. The incumbent grantee at this time had served the Network since the Network's inception, providing statistical consultation, data management, and data analysis, in addition to various logistical services required in the multicenter research program of the Network. The competitive segment for the initial DCC ended March 31, 1998. The NICHD continued support of the DCC for five years to permit completion of ongoing studies and initiation of several new randomized clinical trials and other studies in obstetrics. The NICHD did not limit the competition to the incumbent grant for the DCC, but invited other applications as well.

FISCAL YEAR 1995

RFA-HD-95-009: Perinatal Emphasis Research Centers (PERC)
The NICHD invited applications from investigators to develop multidisciplinary research efforts that would advance knowledge about diseases and disorders of pregnancy and infancy, with the aim of reducing infant morbidity and mortality in rural populations. The resulting grant was part of the PERC program. These centers were intended to support hypothesis-testing research efforts, not service or demonstration projects. PERCs were organized around problem/need themes and were established where research could be coordinated within existing programs of health care to ensure the rapid assimilation of new scientific knowledge into health care delivery. PERCs active when this RFA was issued addressed issues in high-risk pregnancies (e.g., diabetes, hypertension), prevention of prematurity, fetal hypoxia, IUGR, and infant sleep physiology. The PERC was to work closely with the NICHD in participating in the PERC network, and in carrying out its objectives in a manner consistent with NICHD goals and missions.

RFA-HD-95-007: Cooperative Multicenter MFMU Network
The NICHD invited applications from investigators willing to participate, under a cooperative agreement (U10), in an ongoing multicenter clinical program designed to investigate problems in clinical obstetrics, particularly those related to prevention of low birth weight. The program aimed to facilitate resolution of these problems by establishing a network of academic centers that, by rigorous patient evaluation using common protocols, studied the required numbers of patients and provided answers more rapidly than individual centers acting alone. The NICHD program staff assisted the principal investigators of the MFMUs and the Advisory Board in identifying research topics of high priority, and in designing and implementing protocols appropriate to the evaluation of optimum management in these areas.

RFA-HD-95-006: Cooperative Multicenter NRN
The NICHD invited applications from investigators willing to participate, under a cooperative agreement (U10), in an ongoing multicenter clinical program designed to investigate the safety and efficacy of treatment and management strategies to care for newborn infants, particularly those related to management of low birth weight infants. The program sought to facilitate evaluation of these strategies by establishing a network of academic centers that, by rigorous patient evaluation using common protocols, studied the required numbers of patients and provided answers more rapidly than individual centers acting alone. The NICHD program staff assisted the principal investigators of the NRN and its Advisory Board in identifying research

topics of high priority, and in designing and implementing protocols appropriate to the evaluation of optimal management in these areas.

FISCAL YEAR 1994

RFA-HD-94-013: PERC Program
The NICHD invited applications from existing members of the PERC program (competitive continuation applications), and from prospective members (new applications) with the objective of encouraging investigators to develop multidisciplinary research efforts that would advance knowledge about diseases and disorders of pregnancy and infancy, and about special issues relevant to rural populations. These grants supported hypothesis-testing research efforts, not service or demonstration projects. PERCs were organized around problem/need themes and were established where research could be coordinated within existing programs of health care to ensure the rapid assimilation of new scientific knowledge into health care delivery. PERCs active at the time this RFA was issued addressed issues in high-risk pregnancies (e.g., diabetes, hypertension), prevention of prematurity, fetal hypoxia, IUGR, and infant sleep physiology. PERC centers worked closely with the NICHD in participating in the PERC network, and in carrying out its objectives in a manner consistent with NICHD goals and missions.

RFA-HD-94-011: Diagnostic Methods to Assess Neurologic Integrity in Fetus/Neonate
This RFA sought to stimulate research on the development of effective technologies to assess the integrity and function of the developing brain in human fetuses and newborns. The long-term goal of this research was to identify newborns with brain dysfunction due to early, repetitive, or chronic intrauterine central nervous system influences/insults, which may result in SIDS and developmental disabilities including cerebral palsy. Postnatally acquired and acute perinatal deficits were not within the scope of this RFA. The NICHD and the National Institute of Neurological Disorders and Stroke (NINDS) invited applications for studies in animals and/or humans that: (1) Elucidated the physiological parameters that would serve as reliable markers of central nervous system integrity/pathology; and (2) Explored the development of technologies/clinical tools that would identify infants who had, or were at risk for, abnormal neurologic development or sudden death from prenatal insults.

PPB-RELATED WORKSHOPS AND CONFERENCES, FISCAL YEAR 1991 TO PRESENT

- *The NIH Workshop on Defining the Content of Follow-Up Care*, June 19-20, 2002, Bethesda, Maryland
- *SIDS Pathogenesis in the New Millennium*, November 29-30, 2000, Rockville, Maryland
- *Prenatal Alcohol Exposure and Risk for Adverse Pregnancy Outcomes and SIDS*, August 6-7, 2001, Bethesda, Maryland
- *The Role of Genetics in the Health Disparity of Premature Birth and Low Birth Weight Infants*, May 4, 2001, Rockville, Maryland
- *Setting a Research Agenda for Stillbirth*, March 26, 2001, Rockville, Maryland
- *Nausea and Vomiting during Pregnancy*, September 20-21, 2000, Bethesda, Maryland
- *Maternal-Fetal Surgery Conference*, July 16-18, 2000, Bethesda, Maryland
- *From Bronchopulmonary Dysplasia (BPD) to Chronic Lung Disease (CLD): The Evolution of a New Disease*, Chronic Lung Disease Workshop, May 31-June 2, 2000, Rockville, Maryland
- *Fetal Origins of Adult Disease*, September 2-3, 1999, Bethesda, Maryland
- *Workshop of Sleep Needs, Patterns, and Difficulties of Adolescents*, Forum on Adolescence, Board on Children, Youth, and Families, National Academy of Sciences, September 22, 1999, Washington, DC
- *Endothelial-Derived Vasoactive Substances and Free Radicals in Perinatal Biology*, May 6-8, 1999, Alexandria, Virginia
- *Epidural Conference*, February 19-20, 1999, Bethesda, Maryland
- *Bed Coverings for Infants: What is Safe?* December 8, 1998, Bethesda, Maryland
- *Colloquium on Perinatal Endocrinology*, September 20-22, 1998, Nancy, France
- *SIDS Pathogenesis: Approaches to Identifying High-Risk Infants*, September 13, 1998, Lake Arrowhead, California
- *Postpartum Hemorrhage and Placenta Accreta Conference*, February 11-12, 1998, Detroit, Michigan
- *Mi in a kin towani ewaktonji kte ni: "I will never forget my child,"* September 17-19, 1997, Rapid City, South Dakota
- *Placenta and Child's Brain*, July 18-19, 1996, Bethesda, Maryland
- *Infant Sleep Environment and SIDS Risk*, January 9-10, 1997, Bethesda, Maryland
- *4th SIDS International Conference*, June 23-26, 1996, Bethesda, Maryland
- *Pregnant Women in the Workplace: Sound and Vibration Exposure*, February 22-23, 1996, Gainesville, Florida
- *Electronic Fetal Heart Rate Monitoring: Research Guidelines for Interpretation*, May 15-16, 1995, Bethesda, Maryland
- *Fetal Growth: Its Regulation and Disorders*, April 18-19, 1995, Providence, Rhode Island
- *Early Discharge and Neonatal Hyperbilirubinemia*, March 28, 1995, Rockville, Maryland
- *Nitric Oxide (NO) in the Perinatal Period*, December 7, 1994, Rockville, Maryland
- *Placental Growth and Function*, July 7-8, 1994, Bethesda Maryland
- *Neonatal Pain: Physiology and Management*, June 3-4, 1994, Philadelphia, Pennsylvania

- *Animal Models of SIDS*, June 2-3, 1994, Bethesda, Maryland
- *Infant Sleep Position and SIDS Risk*, January 13-14, 1994, Bethesda, Maryland
- *NIH Consensus Development Conference on Antenatal Steroid Treatment*, February 28-March 2, 1994, Bethesda, Maryland
- *Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS)*, September 23, 1993, National Press Club, Washington, DC
- *Acute Perinatal Asphyxia*, August 30-31, 1993
- *Research Definition of Birth Asphyxia*, April 2-3, 1992, Chevy Chase, Maryland
- *Sleep Position and SIDS Risk*, March 30, 1992, Bethesda, Maryland
- *The Global Strategy Meeting on SIDS*, February 17-18, 1992, Sydney, Australia
- *Fetal Therapy: Current Status and Future Prospects*, October 31-November 1, 1991, Bethesda, Maryland
- *Roles of Endothelial-Derived Vasoactive Factors in Perinatal Biology*, August 17-19, 1991, San Diego, California

PPB ONGOING ACTIVITIES

GRANTS PORTFOLIO

In the last five years (fiscal years 1997-2001) a total of 11,450 competitive grant applications were received by the NICHD. 1,075 or 9.4 percent were assigned to the PPB. The largest majority of the applications were R01s, which represented 45.4 percent of all assigned applications. A total of 304 assigned applications were awarded, representing a success rate of 28.8 percent; this rate is similar to the overall NICHD success rate of 29.3 percent. Overall competitive renewals had a much higher success rate than new applications (48.4 percent vs. 23.2 percent). The number of awards broken down by general or specific mechanism type and their relative percentage are listed below.

MECHANISM TYPE	NUMBER	RELATIVE PERCENTAGE (%)
Fellowship Awards (F series)	12	3.9
Career Awards (K series)	20	6.6
Program Projects (P01)	10	3.3
Research Projects (R01)	138	45.4
Small Research Projects (R03)	40	13.1
Conferences Grants (R13)	4	1.3
Academic Enhancement Grants (R15)	2	0.6
Exploratory/development Grants (R21)	2	0.6
FIRST Awards (R29)	6	2.0
MERIT Awards (R37)	2	0.6
STTR/SBIR Grants (R41, R43, R44)	21	6.9
Institutional Training Grants (T32)	9	2.9
Cooperative Agreements (U series)	38	12.5

The success rates varied significantly based on a particular mechanism type. For example, R01s had the lowest success rate (23.9 percent), while P01 applications had the highest success rate (55.5 percent).

The success rates for selected mechanisms are tabulated below.

MECHANISM	TOTAL	AWARDED	SUCCESS RATE (%)
F31 & F32	35	12	34.3
K08	14	6	42.9
K23	8	4	50.0
K24	9	5	55.6
P01	18	10	55.5
R01	576	138	23.9
R03	156	40	25.6
T32	18	8	44.4

PROGRAM PROJECT (P01) DESCRIPTIONS

Initiation of Human Labor: Prevention of Prematurity
PI: MENDELSON, CAROLE; 5 P01 HD011149-25
The long-range goals of this program-project are to: 1) Define the functional phenotypes of the uterus and the cellular changes that account for the differences in these phenotypes during pregnancy/parturition; 2) Evaluate the mechanisms by which the transitions in the uterine phenotypes are effected at the cellular/gene level; 3) Define the ontogeny/regulation of interstitial collagen formation in amnion and the impact of selected risk factors for pre-term, premature rupture of the fetal membranes (PT-PROM) on pro-collagen synthesis/processing; and 4) Define the cellular interactions in the fetal membranes that contribute to the tensile strength of this tissue and to liability for PT-PROM.

Hypoxia in Development: Injury and Adaptation Mechanisms
PI: HADDAD, GABRIEL G; 5 P01 HD032573-05
One main consequence of numerous cardiovascular and respiratory disorders, whether in the neonate, older infant or at a later more mature age, is tissue O_2 deprivation. Our overall program hypothesis is that O_2 deprivation leads to alterations in cytosolic, membrane and nuclear events that form the underlying basis for cellular adaptation, sublethal injury, or cell death. The extent of these alterations depends on many factors including age, type of cell, its endowments in excitable cells (e.g., neurons) and non-excitable cells (e.g., glia, renal tubular epithelium), interactions between cells, and severity and chronicity of hypoxia. The central aims of this program will therefore be to: 1) Define the nature of the response to hypoxia in neurons, glia, and renal tubular epithelium in mature and immature cells; and 2) Delineate the underlying mechanisms at the cellular and molecular levels.

Metabolic Regulation of Fetal Growth
PI: HAY, WILLIAM W; 5 P01 HD020761-14
The focus of this program grant is metabolic regulation of fetal growth, emphasizing experiments in comparative reproductive and developmental physiology to determine pathogenesis and

metabolic consequences of fetal growth restriction (FGR). FGR affects a large number of human pregnancies and is responsible for increased fetal, neonatal, and adult morbidity and mortality. Three projects will address the following experimental aims and hypotheses: 1) In pregnant sheep, deprivation of glucose and amino acid supply to the fetus produces fetal insulin deficiency and insulin resistance, resulting in FGR and a limitation to nutrient therapy; 2) In pregnant sheep, placental insufficiency from abnormal growth and function produces severe FGR and limitation to nutrient therapy; 3) Clinical studies in normal and FGR pregnancies are directed at fetal surveillance and fetal and placental amino acid metabolism using techniques comparable to those in the animal models; these studies also provide measures of placental and fetal responses to nutrient therapy.

Perinatal Studies of Disorders of Fetal Metabolism
PI: KALHAN, SATISH C; 5 P01 HD011089-25
The long-range objective of the PERC is to explore the influence of maternal metabolic environment and its perturbations on maternal, fetal, and newborn metabolism and growth. Because fetal and neonatal growth, differentiation, and organization can be affected by both environmental and genetic programming, additional goals of these studies are to identify the influences of these factors, metabolic or genetic, on key regulatory events in the newborn and to explore the mechanism(s) involved.

Ventral Medulla and the Sudden Infant Death Syndrome
PI: KINNEY, HANNAH C; 5 P01 HD036379-05
The overall hypothesis is that SIDS, or a subset of SIDS, is due to developmental abnormalities of the ventral medulla, which interferes with normal protective cardiorespiratory responses to potentially life-threatening, but often-occurring events during sleep, such as hypoxia, hypercapnia, and apnea. We recently reported neurotransmitter receptor binding deficiencies in the arcuate nucleus of SIDS victims; this region contains ventral medullary surface neurons that are considered homologous to neurons located in similar areas in cats' brains, which are necessary for the protective responses to hypercapnia and asphyxia. We propose a triple-risk model of SIDS, in which an infant dies of SIDS only if he/she possesses: 1) An underlying vulnerability (e.g., an abnormality in the ventral medulla); 2) A critical period in the development of homeostatic control (i.e., early infancy); and 3) An exogenous stressor (e.g., positional asphyxia).

Fetal and Adult Adaptations to Long-Term Hypoxemia
PI: LONGO, LAWRENCE D; 5 P01 HD031226-08
The overall theme of this proposal is to explore the fundamental mechanisms whereby the fetus and adult adapt to long-term, high-altitude hypoxemia. In addition, we will examine several of these mechanisms in association with development of the fetus into an adult. This proposal is a broadly based, multidisciplinary program that uses physiologic, pharmacologic, biochemical, and molecular approaches to explore adaptations of the cardiovascular system, the cerebral blood vessels, uterine vessels, the fetal hypothalamic-pituitary-adrenal axis, and the myometrium in response to long-term hypoxemia.

Placental Angiogenic Factors and Uterine Artery Endothelial Cells (UAEC) and Placental Artery Endothelial Cells (PAEC) Nitric Oxide Production
PI: MAGNESS, RONALD R; 5 P01 HD038843-02
The body of a pregnant woman faces the unique physiological challenge of reorganizing the maternal uterine vascular network to accommodate the metabolic demands of the feto-placental and uteroplacental blood flow by angiogenic growth factors (with particular focus on bFGF and VEGF), and by the vascular regulator, nitric oxide. This grant has two overall specific aims: 1) To establish molecular and cellular models of the regulation of the vascular endothelium at the maternal-fetal interface; and 2) To investigate these basic mechanisms in clinical settings where changes in placental regulator factors are hypothesized to control vascular adaptation to pregnancy. Data from these studies will further our understanding of the basic control of placental and uterine angiogenesis and mechanisms contributing to fetal pathophysiology in diabetes, in ethanol exposure, as well as in preeclampsia and IUGR.

Fetal Neuroendocrinology, Parturition, and the Myometrium
PI: NATHANIELSZ, PETER W; 5 P01 HD021350-14
The focus is on fetal neuroendocrine maturation and parturition. The hypotheses are related to fetal endocrinology, placental and fetal membranes, and decidual and myometrial regulation. In parallel experiments the present proposal will continue to utilize chronically instrumented pregnant sheep and non-human primates. The work is unique in several aspects, particularly in focused efforts to correlate and compare work in ovine and non-human primate pregnancy.

Biological Basis for Perinatal Transition
PI: PADBURY, JAMES F; 5 P01 HD011343-22
This program project will focus on the development of the mammalian fetus and its transition to postnatal life to define how these events impact fetal and newborn development. We will study the following as model systems: 1) The factors that regulate proliferation and differentiation of developing the trophoblast factors, which regulate the growth and proliferation of fetal and neonatal hepatocytes; 2) Unique mechanisms for hormonal regulation of gene transcription between fetal and adult life; and 3) The role of glucocorticoids in the regulation of critical aspects of brain maturation.

Preeclampsia: Mechanisms and Post-Pregnancy Implications
PI: ROBERTS, JAMES M; 2 P01 HD030367-09
In the past five years, we have characterized and identified mechanisms of abnormal trophoblast invasion in preeclampsia, which supports the involvement of oxidative stress in the linkage of abnormal implantation to the systemic syndrome. This program extends the studies to include detailed mechanistic examination and tests the long-range significance to mother and baby. Abnormal implantation and reduced placental perfusion are insufficient to explain the syndrome. Apparently, similar changes are present in pregnancies complicated by IUGR, and in one-third of preterm pregnancies.

Biology at the Maternal-Fetal Interface
PI: SOARES, MICHAEL J; 1 P01 HD039878-01A1
The overall goal of the program project is to understand regulatory processes that lead to the development of therapeutic strategies for the purpose of improving the quality and success of

pregnancy. The program project grant studies uterine decidual cell-signaling mechanisms involved in the regulation of maternal uterine inflammatory cells, multi-drug resistant efflux systems used by the placenta to protect the fetus, and the impact of soluble placental major histocompatibility complex proteins on maternal inflammatory and immune cell responses.

Response to Hypoxia and Nutrition during Development
PI: STARK, RAYMOND I; 5 P01 HD013063-23
The central theme of this program is based on the axiom that, during early stages of development, organisms are uniquely vulnerable to environmental challenges, which constrain the physiological and behavioral phenotypes that are manifest throughout the rest of the lifespan of the organism. Understanding the mechanisms that confer risk or resistance to these challenges is the fundamental goal of these projects.

Maternofetal Signaling and Life-Long Consequences
PI: THORNBURG, KENT L; 2 P01 HD034430-06
The program is designed to test the umbrella hypothesis that stressors of the fetal cardiovascular and renal systems irreversibly alter early gene expression patterns and, thereby, predispose the offspring for disease in later life.

INSTITUTIONAL TRAINING GRANT (T32) DESCRIPTIONS

Physiology of Reproduction
PI: CARR, BRUCE; 5 T32 HD007190-24
This program has been in place for several decades at the Cecil H. and Ida Green Center for Reproductive Biology Sciences. Investigators from the departments of obstetrics and gynecology, pediatrics, biochemistry, cell biology-neuroscience, microbiology, and physiology participate in this training program. Basic scientists (e.g., biochemists-molecular biologists, physiologists, immunologists, microbiologists, cell biologists, and pharmacologists) and clinical scientists (e.g., obstetricians and gynecologists specializing in endocrinology, oncology, and maternal-fetal medicine, and pediatricians specializing in perinatal medicine) work side-by-side in contiguous, well-equipped, modern laboratory spaces. Over the years, this program has maintained a similar number of MD and PhD postdoctoral trainees, who also work side-by-side. Each of the research faculty spends more than 85 percent of their time in the conduct of research, research-related endeavors (i.e., preparations of grant applications, manuscript and abstract preparation), and other research training activities. Each of the trainees is supervised by one or more of the senior faculty; the primary or secondary mentor of the MD trainees is a senior basic scientist in all cases.

Mechanisms of Disease in the Newborn Human Infant
PI: COLE, F. S; 1 T32 HD041925-01
This project is a recent institutional research training grant within the department of pediatrics at the Washington University School of Medicine. The long-term objective is to foster the growth and development of physician-scientists in newborn medicine and developmental biology. The aim of this program is to utilize the unique resources of the institution, including the developmental biology group in the department of pediatrics and the developmental biology

program in the division of biology and biomedical sciences, for a training program with a participating faculty of pediatricians and basic scientists, who share common interests and frequent investigative and scholarly interactions. The program provides funding for an initial two years of laboratory investigation and emphasizes the application of cell and molecular biologic approaches to address fundamental issues in the most important problems of newborn infants. The substantive collaboration of established pediatric physician-scientists and basic investigators pursuing questions in developmental biology provides a unique opportunity for the training of selected individuals in the application of fundamental experimental methods to the treatment and prevention of diseases of the newborn infant. As such, the program provides new pediatric scholars to lead the way for future advances in this important area of child health.

Training in Neonatal and Developmental Diseases
PI: DEVASKAR, SHERIN U; 5 T32 HD007549-02
This project is a new training program in neonatal and developmental diseases, which was established within University of California, San Francisco, School of Medicine's existing neonatology program. This five-year program is geared toward training post resident neonatology fellows (MD and MD/PhD) with the idea of developing independent and productive physician-scientists, and of training of postdoctoral PhD fellows in the areas of neonatal and developmental diseases. This program strives to attract individuals with a commitment to academic medicine, and to provide a scientifically rich environment where MD and PhD post-resident and postdoctoral trainees are afforded the opportunity of training side-by-side in established laboratories with expertise in developmental biology, genetics, molecular biology, and cell biology. The program is structured to include clinical neonatology training (as per the requirements spelled out by the American Board of Pediatrics), the bulk of which occurs during the first year, the second and third years are devoted to training in laboratory-based research for the post-residency fellows. Following the initial training period, and after rigorous evaluation, the post-residency fellows progress into the postdoctoral portion of their fellowship, which consists of two additional years (four and five). After this time, they are expected to obtain independent funding for their research programs.

Research in Perinatal Medicine
PI: GROSS, IAN; 5 T32 HD007094-26
This program offers an intensive laboratory experience in experimental biology and structured training in clinical research and epidemiology. The goal of this postdoctoral program, since its inception in 1977, has been to provide pediatricians and PhD graduates who are interested in developmental medicine with an environment that will permit them to gain the skills necessary for a successful academic career. Both clinical and basic science departments at Yale University are involved with this program including pediatrics, genetics, molecular biophysics and biochemistry, cell biology, pathology, and epidemiology. Trainees who elect to do clinical research are required to take courses in designing clinical trials, in statistics, and in epidemiology. They may also become candidates for the MPH degree at the Yale School of Public Health. Trainees are appointed for three years and must be committed to pursuing a career in academic medicine. MD trainees complete their residency prior to entering the program. PhD graduates will have a demonstrated interest in developmental biology. This program has been functioning successfully for more than 23 years. Graduates hold academic positions throughout the United States, and many have become leaders in perinatal medicine.

Training in Developmental and Perinatal Endocrinology
PI: HANDWERGER, STUART; 5 T32 HD007463-09
This program provides training in developmental and perinatal endocrinology at the University of Cincinnati College of Medicine and the Children's Hospital Medical Center in Cincinnati. The faculty advisors consist of 20 established investigators with major interests in developmental and perinatal endocrinology from three clinical and three basic science departments. The research themes include: the regulation of trophoblast differentiation and function in the regulation of decidualization; the role of growth factors in mammalian development; the molecular biology of the growth hormone, prolactin, and placental lactogen gene family; and mechanisms of hormone action. Pre-doctoral trainees obtain their PhD degrees in the department of cell biology, neurobiology, and anatomy, in the department of molecular and cellular physiology, in the department of molecular genetics, biochemistry, and microbiology, and in the program in developmental biology of the University of Cincinnati College of Medicine. Postdoctoral trainees must have the MD or PhD degree, or both.

Training in Perinatal Medicine
PI: WILLIAM HAY; T32-HD007186-23
The purpose of this training program is to provide basic and clinical postdoctoral research training for pediatric (neonatology) and obstetric (maternal-fetal medicine) physicians and basic scientists who have completed residency training or hold a PhD degree. The research training, in perinatal/developmental physiology and biology, lasts for three years in preparation for academic careers in reproductive medicine within departments of pediatrics and obstetrics and gynecology. During the first year, which is largely clinical and is not funded by this grant, trainees work with faculty advisors to select basic research projects and mentors. Three areas of research excellence are offered: 1) Fetal nutritional metabolism and growth; 2) Placental development and function; and 3) Vascular development and regulation of blood flow. During all three years of training, trainees attend seminars that review: intrauterine development and fetal, maternal, and neonatal physiology courses in the graduate school, as well as those dealing with cell culture, cell and molecular biology, isotope applications, biostatistics, microcomputer applications to data processing, statistics, graphics, bioethics, and ethical conduct of research. The second and third years are devoted to the completion of the basic research projects begun in the first year and to expansion into new areas of research that includes new research techniques. Trainees plan and conduct their research projects independently, but with full faculty guidance.

Neonatal Training Grant
PI: JOBE, ALAN H; 5 T32 HD007541-02
This program provides training for third and fourth year MD neonatology fellows to develop sufficient research experience to initiate careers in academic neonatology. This training program supplements the clinical neonatology fellowship at Children's Hospital Medical Center. The program supports only those select fellows who demonstrate real research potential and motivation after the first two years of fellowship. The research training is structured to provide a mentored experience, with the fellow-in-training working with a senior mentor and often with an associate mentor. All mentors are researchers who work as a large collaborative group and focus on the common research themes of lung development and lung injury. The group uses state-of-the-art technology to explore questions in lung biology that range from molecular genetics and transgenic models to lung physiology. The lung research is supplemented by clinical research

supported by the NICHD's NRN. The goal for this training grant is to support only research training for neonatologists who have the potential and motivation to become successful research-oriented academic neonatologists.

Graduate Research Training in Perinatal Biology
PI: KITTERMAN, JOSEPH; T32-HD007162-23
This program is designed to train physicians to conduct fundamental research in perinatal biology, and to integrate advances in basic and clinical research with clinical care for improving treatment of pregnant women, their fetuses, and newborn infants. The faculty (e.g., basic scientists, clinical researchers, and health policy researchers) conducts research in cardiovascular biology, lung biology, neurobiology, perinatal epidemiology, and reproductive biology. Disciplines employed include cellular and molecular biology, integrative physiology, clinical investigation, and health policy research. Trainees enter the program after completing a residency in obstetrics and gynecology or in pediatrics and are appointed for three to four years, of which, at least two are devoted to research. Trainees also complete clinical training in an accredited fellowship program in maternal-fetal medicine or neonatal-perinatal medicine.

Perinatal Biology Training Grant
PI: PADBURY, JAMES F; 5 T32 HD007511-04
The grant at Women & Infants' Hospital is an interdisciplinary program to prepare neonatal, maternal-fetal medicine, and post-doctoral fellows who are recognized early in training to have great potential for an academic career. The faculty are in the Brown University School of Medicine and Biology. The emphasis includes understanding cell-to-cell signaling and signal transduction pathways, mechanisms of morphogenesis and differentiation, and the role of transcription factors and transcription regulation in development and the control of cell division and cell death during organ formation. The clinical relevance of these areas of investigation is borne out by their likelihood to identify important mechanisms for: the regulation of fetal growth and of the growth and differentiation of major organ systems and the developing oocyte; the role of transcription factors in development; and the mechanisms for brain development and the prevention of brain injury during the transition from fetal to newborn life.

Developmental and Neonatal Biology Training Program
PI: STEVENSON, DAVID K; 5 T32 HD007249-19
The aim of this training program is to provide educational opportunities for young people to achieve excellence in clinical newborn medicine, scholarly basic science and clinical research, and medical education. The program is designed to encourage the cross-fertilization of ideas that will enrich the ideas of both the basic- and the clinically oriented scientist. For those trainees interested in clinical training, the program offers intensive clinical experiences with newborns, including the opportunity for clinical investigation, as well as the opportunity for advanced study in developmental biology, especially at the cellular and molecular levels.

MULTICENTER TRIAL DESCRIPTIONS

The NICHD Maternal Fetal Medicine Units Network

The NICHD created the MFMU Network in 1986 to focus on clinical questions in maternal fetal medicine and obstetrics, particularly with respect to the continuing problem of preterm birth. Operating under cooperative agreements, the current Network comprises 14 university-based clinical centers and a DCC. More than 24 randomized clinical trials, cohort studies, and registries have been completed or are in progress through the MFMU Network. MFMU Web site is http://www.bsc.gwu.edu/mfmu/.

The Neonatal Research Network

The NICHD's NRN was established in 1986 to improve the care and outcome of neonates, especially VLBW infants. Operating under competitive cooperative agreements, the NRN includes investigators from 16 university-based clinical centers, a Network DCC, and NICHD program staff. The Network has addressed the major problem areas in neonatology with randomized controlled trials, studies, and outcomes research in the prevention and treatment of sepsis, intraventricular hemorrhage, CLD, pulmonary hypertension, anemia, acute perinatal asphyxia, and nutrition. For more information about the NRN, please go to http://neonatal.rti.org.

Fetal Surgery Network

The NICHD created the Fetal Surgery Network in 2001 to evaluate *in utero* fetal surgery as a treatment for antenatally diagnosed spina bifida in a randomized clinical trial. The objective of this program is to establish a network of three academic centers as Fetal Surgery Units, as well as a Data and Study Coordinating Center that, by rigorous patient evaluation using a common protocol, can study the required numbers of patients and can provide a valid answer more rapidly than individual centers acting alone.

Vaginal Ultrasound Cerclage Trial

PI: OWEN, JOHN MD; 1 U01 HD039939-01A1

This trial is 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. Women at significant risk for recurrent spontaneous preterm birth (i.e., those with a prior spontaneous birth at 17-32 weeks' gestation), and those who have an increased risk based on mid-trimester ultrasonographic findings of a cervical length <25mm will be studied at seven centers. This topic is one of the most controversial issues in obstetrics/maternal-fetal medicine at present. Prior studies have demonstrated that the presence of a short cervix significantly increases the risk of preterm delivery; however, there is no consensus or scientific evidence on the proper clinical management. This trial will provide significant evidence for the specialty, for women, and for their pregnancies.

Twin-Twin Transfusion Syndrome (TTTS) Trial

PI: CROMBLEHOLME, TIM MD; 5 R01 HD041149-02

This is a prospective randomized multicenter trial of pregnancies complicated by TTTS to compare serial amnioreduction with selective fetoscopic laser photocoagulation. There are 16

participating centers; two centers perform selective fetoscopic laser surgery. Long-term neurodevelopmental outcome will be evaluated by the NICHD NRN at 18 to 22 months of age. The overall goal of the study is to improve the outcomes of twins with TTTS by determining which treatment for TTTS has a better survival outcome, as well as better cardiac, neurologic, and developmental outcomes.

Prophylaxis of Adrenal Insufficiency to Prevent CLD
PI: WATTERBERG, KRISTI MD; 5 R01 HD038540-02
This project is a multicenter, randomized trial of 712 extremely low birth weight (ELBW) births, to further define the benefits and assess the risks of hydrocortisone prophylaxis against adrenal insufficiency in these infants. Primary outcome measures will be: (1) Benefit: increased survival without CLD at 36 weeks postmenstrual age; (2) Risk: no increase in cerebral palsy at 18 to 22 months adjusted age. Other measures of neurodevelopmental outcome will also be assessed. The sample size will detect a change of 10 percentage points in successful outcome, and in the incidence of specific adverse effects, with a power of 80 percent. Baseline data on mother and infant, daily clinical data for the first 28 days of life, outcome data at 36 weeks postmenstrual age, and outcome data at 18 to 22 months adjusted age will be collected. If this study confirms the benefits seen in the pilot study, the results will mean a significant improvement in health care for premature infants, both by introducing a beneficial new therapy, and by avoiding higher dose dexamethasone.

Maternal Lifestyles Study
NICHD and National Institute on Drug Abuse (NIDA)—LOI-HD-02-103
This cooperative agreement (U10) is for a clinical research program designed to evaluate the effects of *in utero* drug exposure to cocaine and/or opiates on child and family outcomes. The objective of this program is to continue the research of four academic centers that are currently participating as centers in the Maternal Lifestyle Study (MLS) protocol. These centers, the Maternal Lifestyle Study Centers, are the only four academic institutions currently participating in the study, and represent a subgroup of the existing NICHD NRN performing the MLS Phase 4. Data coordination is performed by the two participating data and study coordinating centers at the Research Triangle Institute and the Brown University Neurodevelopmental Data Center.

SUDDEN INFANT DEATH SYNDROME (SIDS)

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

Since 1994, 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: http://www.nichd.nih.gov/sids/sids.cfm.

NATIONAL CHILDREN'S STUDY (NCS)

The NCS is a large, long-term study of environmental influences on children's health and development. This Study will explore a broad range of environmental factors, both helpful and harmful, that influence the health and well-being of children. For this Study, environment is broadly defined to include chemical, physical, social, and behavioral influences on children, which will allow better understanding of the role of these factors on health and disease.

The Study grew out of the President's Task Force on Environmental Health Risks and Safety Risks to Children and was authorized in the Children's Health Act of 2000. The Act directed the NICHD to conduct the study along with a consortium of federal agencies, including the Environmental Protection Agency, the CDC, and the NIEHS.

The study will examine about 100,000 children across the United States and will follow them during prenatal development, through birth, childhood, and into adulthood. The Study will allow the evaluation of exposure and outcome links in the context of life stages of development. Planning and organization of the Study are underway, including the formation of Working Groups to consider issues such as hypotheses and study design, ethics, development and behavior, chemical and physical exposures, injuries, emerging technologies to measure exposures and outcomes, and community outreach/participation.

The PPB is participating in the planning process of this large effort. Drs. Marian Willinger and Cathy Spong are the federal co-chairs of the Pregnancy and the Infant Working Group. Dr. Gary Hankins (UTMB-Galveston) is the non-federal co-chair of the Working Group.

PA-02-102: THE ROLE OF GENE-ENVIRONMENTAL INTERACTIONS UNDERLYING THE HEALTH DISPARITY OF PREMATURE BIRTH

Expiration Date: January 1, 2005, unless reissued.
The NICHD, the NIEHS, and the NINR are seeking research grant applications on the role of gene-environmental interactions that underlie the health disparity of premature birth in the United States. This solicitation specifically addresses 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 in these disadvantaged populations.

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 cooperative agreement (U10) aims to continue specific analyses of the CHIME Study (U10 HD 29067-08), to continue to conduct the NISP study, and to serve as a resource for public-use datasets from CHIME and NISP, which were developed during the previous grant award period.

CONTRACT: COCHRANE COLLABORATION

The Cochrane Collaboration is an international effort whose mission is the preparation, maintenance, and dissemination of frequently updated systematic reviews of health care interventions in all fields of medical practice. The reviews are prepared using systematic methods that are designed to produce unbiased and precise estimates of the effect of a treatment on each of the major outcomes of clinical importance. The Neonatal Cochrane Collaboration is one of 40 such groups. The NICHD funds the infrastructure of the Neonatal Collaborative Review Group to prepare up-to-date systematic reviews of the effectiveness of interventions in the field of neonatology to help neonatologists, researchers designing clinical trials, funding agencies, and individuals making decisions about the allocation of resources for neonatal care make more informed decisions. The Neonatal Cochrane Review Group's systematic reviews are available on the NICHD Web site, at http://www.nichd.nih.gov/cochrane.

PPB PLANNED ACTIVITIES
FISCAL YEAR 2003 TO FISCAL YEAR 2004

RFAS, FISCAL YEAR 2003

RFA HD-03-004: Prenatal Alcohol Exposure Among High-Risk Populations: Relationship to SIDS

The NICHD and the NIAAA invite 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 FAS, and how they may be inter-related. The investigators will work collaboratively under cooperative agreements with the 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 to improve child health in these communities.

RFAS PLANNED FOR FISCAL YEAR 2004

Research into Mechanisms of Fetal Growth Restriction

The aim of this initiative is to stimulate research into the mechanisms of FGR, and to gain a better understanding of the factors that regulate fetal growth during pregnancy. FGR is the second-leading cause of perinatal morbidity and mortality, after only prematurity. The incidence of FGR is estimated to be approximately 5 percent in the general obstetric population. Further research into the mechanisms that control normal fetal growth will increase understanding of and prevention of situations of abnormal fetal growth. Providing the best possible environment for the fetus would not only ensure adequate fetal growth and health in the newborn period, but also protect against the development of diseases in adult life.

Obstetrical-Fetal Pharmacology Research Units

The purpose of this initiative for cooperative research is to support integrated basic, translational, and clinical research centers for conducting: pharmacologic studies of drug disposition and effect during normal and abnormal pregnancies; single-site and multi-site cooperative clinical trials; pharmacogenetic studies of the effect of pregnancy on drug metabolizing enzymes, transporters, and effectors; studies of placental transfer of drugs; and studies of fetal and maternal pharmacology. The units will also 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 the treating pregnant women.

WORKSHOPS/CONFERENCES

PPB Planning Workshop

The PPB supports basic and clinical research directed toward improving the outcome of pregnancy, reducing infant mortality, and minimizing maternal and infant morbidities. Activities

in the Branch have been focused around six emphasis areas: maternal, fetal, placental, labor and delivery, neonatal, and SIDS. The major emphasis areas within the Branch were internally evaluated to determine areas of opportunity and to develop plans to implement changes. The objective of this workshop was to obtain outside evaluation of the PPB vision statement and long-term plan, developed by careful review within the Branch, and by experts in the fields of maternal-fetal medicine, neonatology, obstetrics, pediatrics, SIDS, and in related targeted fields. These experts evaluated, refined, and adapted the Branch's plan. Evaluation by outside experts helped to solidify the goals of PPB and to improve its relationship with the participating fields in attaining the goals.

Investigation of Fetal Origins of Adult Health in Twin Cohorts
The purpose of the meeting was to evaluate research to date, and to identify new approaches of using twin cohorts to elucidate mechanisms of fetal origins of health throughout the lifespan. Twin cohorts enable investigators to separate environmental and genetic effects through comparison of monozygotic and dizygotic pairs, and to investigate the contribution of maternal factors using within pair analysis. Studies in the literature, which explore fetal origins hypotheses, vary in their capacity to fully exploit the opportunities that twin cohorts provide. While twins represent valuable experiments in nature, it is also necessary to address whether information from twin pregnancies can be generalized to singletons. In addition, the outcome of twin pregnancies, which are increasing due to assisted reproductive technologies, are important in their own right because these twins are at higher risk for SIDS, cerebral palsy, and other morbidities in infancy and childhood. By exploring how to utilize information gained from the study of twin pregnancies, it is hoped that effective public health interventions can be developed to improve health throughout the lifespan and across generations.

Poorly Explored Genetic Factors Affecting Pregnancy Outcome
The purpose of the workshop was to discuss the current scientific knowledge, and to stimulate research interest in and collaboration with the scientific community in this poorly developed research area. This topic involves certain genetic factors that affect pregnancy outcome. The topics covered include genomic imprinting, uniparental disomy, and confined placental mosaicism. The basic science and clinical aspects underlying these topics were presented and potential future directions in research were discussed.

Bilirubin-Induced Brain Injury (BIBI)
This conference focused on BIBI and kernicterus. The workshop was designed around three themes: 1) Evaluating the neurobiology of BIBI, including exploration of the molecular and cellular basis for breakdown of blood brain barrier function for bilirubin, factors modulating regional susceptibility or resistance of neurons to damage from bilirubin, etc.; 2) Evaluating various system-related causes that have led to a mini epidemic of BIBI and kernicterus, so that appropriate strategies and practice guidelines can be developed; and 3) Evaluating the value and limitations of the existing and evolving methods for rapid diagnosis of hyperbilirubinemia and its effective treatment. The final topic also focused on the photobiology as it relates to phototherapy.

APPENDIX B: AREAS OF OPPORTUNITY STATEMENTS COMPILED AT THE PPB WORKSHOP

AREA OF OPPORTUNITY: PREMATURITY

Prematurity remains the most prevalent cause of perinatal mortality and morbidity, as well as a significant contributor to high health-care costs. Other than improvement in neonatal care, one that comes at a considerable cost and morbidity, research into prematurity and preterm labor has not lead to significant tangible benefits.

Research into preterm delivery can be divided into investigations related to its etiology, prediction, prevention, diagnosis, and management. These categories do overlap, which means advances in one are could significantly impact the course of action in the others.

RESEARCH GAPS AND OPPORTUNITIES

Significant research effort and resources have been invested into discovering the etiology of preterm birth, but have resulted in limited success. Much of the previous work has been invested in studying single mechanisms. Recent advances have focused on the role of infection/inflammation; however, the infectious source and the cascade of events linking this process to preterm delivery are still not well understood. Moreover, infection alone may not be the only determinant; the process leading to preterm delivery appears to be multifactorial and includes a dependency on host response.

Other areas that have received little attention but may have potential impact on the etiology of prematurity include utero-placental insufficiency, fetal growth abnormalities, and fetal stress. Investigation into the etiology of premature birth has traditionally focused on the period immediately preceding the onset of contractions or preceding Premature Rupture of Membranes (pPROM). The period in early pregnancy, and even pre-pregnancy, has received little attention.

Additional areas needing attention include infection/inflammation predating pregnancy or implantation, deficient placentation, and utero-placental insufficiency. While there is a plethora of data regarding myometrial function in labor, there is also a dearth of information regarding the role of the cervix, fetus, and placenta in labor. In addition, most of the *in vitro* data related to myometrial function are gathered from studies involving tissues obtained from the lower segment at the time of delivery. This limitation is mostly due to the difficulties in conducting longitudinal non-invasive molecular and biochemical studies involving the myometrium and cervix in pregnancy.

Identifying women at risk of preterm birth will also allow targeted use of modalities to improve neonatal outcome, such as maternal administration of corticosteroids. More optimistically, identification of these women will allow the use of strategies to prevent preterm delivery. Until recently; however, these strategies have been largely ineffective. One reason is that available

methods to identify women at risk of preterm delivery had positive and negative likelihood ratios that were not in the clinically useful range and, therefore, did not significantly modify *a priori* risks. More importantly, however, the methods currently available identify at-risk women at an advanced stage in the process that leads to preterm delivery, making them unamenable to prevention. Structural and biochemical changes in the cervix and amniotic fluid are underway weeks before the onset of labor. As the process gets closer to delivery of the fetus, these changes become irreversible. Unless women are identified at an early stage in this process, sometimes as early as the first half of gestation, prevention of preterm delivery may prove to be futile. Identification of such preventive strategies may also impact pPROM, a condition that accounts for a large proportion of preterm births. Moreover, prediction strategies have been mostly limited to univariate analysis and have not taken into consideration the multifactorial nature of the problem.

Every year, millions of women are admitted to hospitals and treated for preterm contractions. Only a minority of these women can be considered in true preterm labor and, if left untreated, go on to have preterm deliveries. Admitting and treating only women who are at risk of preterm delivery, rather than all those with preterm contractions, would result in substantial cost savings, as well as in a decrease in maternal morbidity from unnecessary admissions, bed rest, and therapy. T he available methods for diagnosing labor have very low specificities. Even the presence of cervical change, once thought to be the hallmark of labor, is associated with false-positive diagnosis prior to term.

The management of preterm labor has mostly focused on tocolysis and bed rest despite the lack of strong evidence to support such practices. Moreover, there is no consensus as to the type of tocolytic or regimen (including maintenance) to use. Despite the reasonable assumption that, in some cases, treatment of preterm labor may be futile and even detrimental (resulting in infection, utero-placental insufficiency), there are no clinically applicable tests to guide management.

NEW DIRECTIONS AND APPROACHES TO ADDRESS GAPS

Investigations into the etiology of preterm birth should take into consideration the multifactorial nature of the problem, including utero-placental insufficiency, fetal growth abnormalities, and fetal stress. With regard to fetal growth, a better approach than currently available is needed; individualized growth assessment appears to hold the most promise. Research should also focus on early pregnancy and pre-pregnancy periods and should include into the role of the cervix and variability in host responses. Similarly, strategies for the prediction of preterm birth should include multivariate analysis, such as neural networks, and should focus on identifying the preparatory and potentially reversible changes in early pregnancy or pre-pregnancy. Non-invasive methods to assess cervical, myometrial, and placental changes, both longitudinally and in early pregnancy, should be pursued. In order to tailor management, methods of differentiating between women who are and are not in true labor are needed. As for the prevention of preterm delivery, treatments geared toward the early changes, rather than tocolysis, should be pursued; however, studies to determine the role of tocolytics are still needed. Many of the proposed studies discussed require access to a large and diverse patient population, as well as to representative tissue samples.

In order to achieve the aims proposed above, a consortium of centers involved in preterm labor research is recommended; tissue and data banks should also be included in the design. Consolidation, coordination, and collaboration between the various groups involved in this area of research, including neonatology, would be more efficient than the present system. Categorization of preterm birth should be improved. In addition, studies should focus on the cases with highest mortality and morbidity, and not be diluted by inclusion of preterm birth close to term, which is clinically less relevant. Finally, clinically applicable methods for identifying pregnancies in which delaying delivery is futile or detrimental may be useful.

PRIORITY OF AREA OF OPPORTUNITY WITHIN THE PPB

Prematurity is obviously a priority for the PPB as evidenced by prior funding in this area. Some existing resources, as well as additional ones, may have to be reassigned. Funding should be made available for both clinical and laboratory investigation.

INFRASTRUCTURE RESOURCES NEEDED

RFAs, research funding, data analysis resources, and established consortiums and tissue/data banks are important resources necessary to adequately address the research gaps in prematurity research.

Environmental and Genetic Influences

Prematurity is the model area to investigate environmental and genetic influences. These studies would obviously require large sample sizes and extensive databases.

Health Disparity

It is well known that a health disparity exists in the rate of premature birth, as well as in perinatal outcomes, among different racial and socioeconomic groups.

Technology Development

Proteomics, genomics, as well as high-throughput screening for polymorphisms will be essential for investigating the multifactorial nature of preterm birth. In addition, nuclear magnetic resonance and other fetal and placental imaging techniques will allow non-invasive assessment of the early changes leading up to preterm birth. Bioinformatics will be needed to manage and analyze the required large databases, and to provide a clinically applicable model for prediction and diagnosis.

Research Risk and Ethical Aspects of Research

Pregnancy is always a challenging area with regard to risks and ethical considerations. In fact, this issue may be one of the major factors that has affected advances in this area. Safe, non-invasive methods of investigation are a priority.

AREA OF OPPORTUNITY: FETAL AND EMBRYONIC DEVELOPMENT— MATURATION OF INDIVIDUAL ORGAN SYSTEMS AND IMPACT OF INTERVENTIONS ON LONG-TERM FUNCTION

There is growing evidence that adult coronary disease, hypertension, obesity, insulin resistance (Syndrome X), cerebral palsy, osteoporosis, and a host of other adult diseases have their roots in prenatal and early postnatal life. Numerous studies from around the world show an increased risk for ischemic heart disease with decreased birth weight. Fetal overgrowth may carry similar risks. There appear to be critical windows during early post-fertilization, organogenesis, and later maturation stages where stressors (defined broadly) are potent in stimulating defensive biological adaptations that may have survival value. However, fetal adaptations to stress may also "inadvertently" bring postnatal harm by "programming" an individual for increased risk of adult-onset disease. Programming is the initiation of adaptive gene-expression patterns that alter the normal growth and development trajectories, and that become disadvantageous during postnatal life. There is evidence that interruption of the fetal nutritional supply line, maternal stresses that increase circulating cortisol levels, and intrauterine hypoxia all lead to programming of offspring.

The programming hypothesis brings a new perspective to public health. Diseases that were once thought to arise near the time of their manifestation in adult life are now known to have roots in pre- and early post-natal life and, in some cases, in previous generations. For example, coronary disease, the number one cause of death among adult men and women, is more closely related to low birth weight than to known behavioral risk factors. Thus, a significant portion of the disease burden borne by adults may have roots in antenatal nutrition and a poor transgenerational maternal health history. The mechanisms that cause fetal undergrowth are complex, multifactorial, and mysterious, but several facts about growth are known. For example, it is known that the early fetal growth trajectory is strongly influenced by maternal weight, physiological status, and body composition at the time of conception. A significant improvement in maternal-fetal health has the potential to yield more benefit to population health than strategies that depend upon unraveling the pathophysiological underpinnings of diseases one at a time after they appear in adult life. However, there are enormous gaps in our understanding of programming that will impede the recognition and reversal of programmed disease.

RESEARCH GAPS AND OPPORTUNITIES

The information gaps that need attention over the next decade include:

1. Tools for Defining Fetal Growth

In past decades, growth has been primarily defined by weight at a given gestational age. However, it is becoming increasingly clear that fetuses of the same weight and gestational age may have internal organs of different sizes and levels of maturity. While the continuous improvement of imaging technologies over the past three decades to monitor growth of individual fetal structures has become increasingly accurate, imaging remains a rather crude tool for fetal assessment. Ultrasound technology has the limitations placed upon it by dispersion of

sound by tissues of varying density; other new technologies should be sought. In addition, growth norms for fetal organs, which could be used as sensitive growth standards, have not yet been developed.

2. Gender-Specific Effects of " Stressors" on Prenatal Organ Maturation at Critical Windows of Development

Organs such as the kidney and pancreas have critical windows of vulnerability during phases of rapid growth and differentiation. For example, the kidney is particularly vulnerable to permanent damage during nephrogenesis; the pancreas is vulnerable during at least two waves of differentiation of islet beta cells. A single form of stress may lead to changes unique to each fetal/newborn organ, depending upon the age of gestation, the sex of the offspring, and the postnatal age at which it is studied. Thus, the further development of animal models (including genetic models) that determine how stressors lead to altered growth of specific organs during embryonic and fetal life are greatly needed. The judicious use of gene and protein expression technology (profiling) along with organ-specific outcomes (i.e., size and shape, physiology, histology, biochemistry, *in vitro* cell behavior, etc.) would be required to characterize the insult. Advantage should be taken of new technologies already in existence, and of those that will emerge in the next few years. These include MRI, PET scans, genomics, proteomics, gene therapy, as well as 3-D gene localization (spatial genomics).

Examples of stressors include:

- Hypoxia, hyperoxia (reactive oxygen species)
- Receptor-mediated growth/maturation (hormones, growth factors, cytokines etc)
- Mechanoreceptor (heart, blood vessels, lung, kidney)
- Maternal emotional/disease stressors
- Fetal nutrient supply-line disruption
- Exogenous toxicants (drugs, etc.)
- Iatrogenic factors

3. Epidemiological Associations of Specific Intrauterine Stressors and Later Outcomes

Organ-specific studies are necessary to study fetal under- and over-growth in human populations. There is an urgent need for epidemiological studies to determine relationships between prenatal environmental insults (including gene expression patterns) and adult disease, as well as intermediate markers for adult outcomes. To take advantage of mechanistic animal studies, the development of clinical studies driven by parallel animal studies that will foster translational discoveries is vital. At present, the role of fetal undergrowth in adult-essential hypertension is highly controversial, even though several studies show that a low-protein diet during pregnancy programs for a form of adult high blood pressure that is evident in offspring early in life. Parallel studies between animals and humans would bring new information to the pathophysiology of hypertension in the human population.

Examples of needed studies include:

- Human nutrition (diets and outcomes in subsets of pregnant women)
- Postnatal heart, pancreas, kidney, hypothalamic-pituitary-adrenal (HPA) function in individuals born undergrown at term
- Premature birth: short and long term outcomes

- Specific intrauterine complications (Rh disease, fetal infections, etc.)

4. Biological Integration of Effects during Intrauterine Stress

There are very few studies that analyze programming as a multi-organ disease. Yet, it is clear that humans who suffer from pre- and postnatal undergrowth are at risk for diseases in multiple organs. For example, there is a heightened risk for obesity, insulin resistance, and hypertension all within a single individual who is undergrown at birth. Thus, there is a need for animal studies to determine the interactive responses of organ growth/maturation via signaling (systems integration).

Examples include:

- Heart, kidney, placenta
- HPA, pancreas, leptin, etc.
- Immune system

5. Treatment Offerings for when Undergrowth and/or Fetal Stress is Detected

As evidence for associations between early developmental patterns and adult onset disease increases, there is increasing pressure from the medical community and the lay public to make diet recommendations to women for preventing fetal undergrowth. Some physicians have succumbed to the pressure and have recommended unproven dietary regimens. However, either low- or high-protein diets depress fetal growth by unknown mechanisms. Furthermore, there are many organ-specific growth deficits that could theoretically be corrected if the pathophysiology was understood. Thus, it might be possible to develop rescue strategies, ranging from dietary to gene therapies, for abnormal developmental patterns based upon the underlying pathophysiology, once it is known. This course of action would require the establishment of research programs designed to change biological patterns and reverse deleterious effects *in utero* in animal models.

6. Intergenerational Programming

There is evidence from epidemiological studies and from animal studies that growth effects are passed on from one generation to the next, over and above ethnic and genetic backgrounds. The mechanisms that cause this multigenerational underdevelopment are not understood.

7. Post-Fertilization Biology

Several lines of evidence point to the large effects of environmental temperature and chemical composition in determining the growth trajectory of an embryo from the moment of conception. For example, the protein or amino acid composition of the surrounding medium in which an early post-fertilization embryo grows may determine the allocation of cells between the trophectoderm and the inner cell mass, which may ultimately affect the birth weight of that individual. Because the relative importance of the early growth trajectory of an embryo versus the later nutritional provision of the placenta is not known, research strategies to study this issue are needed.

8. Maternal Stress during Pre- and Postnatal Life

The biology of maternal stress is complex, but it its importance in reproductive success and fetal growth and development is virtually unknown. There is evidence that severe emotional stress during pregnancy leads to impaired fetal growth, and that maternal stress-related baby neglect

alters growth of the newborn. Animal evidence points to postnatal care as important for neurological and psychological health of offspring. The investigation of this problem will require a multidisciplinary team approach, including psychologists, sociologists, obstetricians, fetal physiologists, placental physiologists, and endocrinologists.

9. The Role of the Placenta in Programming

All nutrient exchange between mother and fetus takes place at the placental interface. While placental nutrient transporters are known to be down regulated in cases of growth restriction, little is known about the regulation of placental growth, the establishment of the maternal/fetal circulations, or the regulatory systems that sense and regulate fetal growth. The profiles of gene expression that reflect normal and abnormal placenta function have not been determined. Thus, fetal growth regulation will not be understood without further investigation of placental physiology and its association with gene expression.

10. Structured Repository of Developmental Information

Rapid progress in understanding fetal/neonatal development depends upon ready access to information across a wide variety of disciplines. For example, searching for current information on fetal/neonatal organ development and programming would require labor-intensive searches in obstetrics, fetal physiology, pediatric and adult cardiology, endocrinology, epidemiology, medicine, and adult sports physiology because there is no long standing discipline where the subject is often reviewed. While computerized word searches are very helpful, every scientist knows that perhaps the majority of articles sought by a single search are not identified because of inadequate retrieval algorithms. In addition, much of the background information in the area of fetal growth was published before search engines were developed, so they are no longer easy to find. Information retrieval science has made it possible to get broad-based links between digital databases and intelligent links that find related words and concepts in a search session. Thus, it is possible to categorize, using informatics, methodologies from the key studies of prenatal (and early postnatal) development of organs that are most important in causing adult human disease, and to create database links with genetic information from the late 1980s to the present. There is a need, in this field particularly, to develop new retrieval systems that would allow scientists to more easily identify knowledge gaps in organ development.

AREA OF OPPORTUNITY: MATERNAL MORBIDITIES— HYPERTENSION AND THROMBOPHILIAS

HYPERTENSION

Hypertensive disorders are the most common medical disorders during pregnancy, with a reported rate of 7 percent (Samali et al 1996). The estimated rate is projected to increase to approximately 10 percent by 2005 because of the epidemic of obesity in women, and because of the trend of delaying pregnancy to an older age. These disorders are a major cause of adverse maternal and perinatal outcomes, both acute and long-term (i.e., renal failure, stroke, cardiovascular complications). The direct and indirect costs attributable to the above complications are extremely high considering acute and/or IUGR, and the long-term care of women with these complications.

Research Gaps

- What is the role of aggressive blood pressure management before conception?
- Should anti-hypertensive therapy be used in women with mild hypertension in pregnancy? If so, what drug should be used?
- If a woman with hypertension, who is already well controlled with a particular agent, becomes pregnant, should another agent be used?
- African-American women with hypertension before and during pregnancy have higher maternal and fetal complications than white women with hypertension. Racial disparities in management approaches and pregnancy outcome need to be studied.
- There is little information about the pharmacokinetics, pharmacodynamics, and fetal effects of anti-hypertensive drugs in pregnancy.

Research Goals and Opportunities

- Understand pathophysiologic abnormalities leading to adverse pregnancy outcome in these women.
- Identify risk factors for adverse outcomes (e.g., preeclampsia, abruption, preterm birth) in these women and design preventive strategies based on these risk factors.
- Understand the genetic diversity that could lead to a role for pharmacogenetic research; and identify a subset of women at risk for preeclampsia or cardiovascular complications in the future.
- Develop long-term follow-up of these women from preconception to 10-years postpartum similar to methods used in non-pregnant hypertensive individuals; identify risk factors for cardiovascular complications and their modification.
- Develop career development programs should be developed to enhance research capabilities of scientists interested in hypertension in pregnancy.

New Directions and Approaches to Address Gaps

Investigations in chronic hypertension and gestational hypertension should take into consideration the need for medications, as well as the effects of these medications on utero-placental and feto-placental circulations, fetal growth, and long-term outcomes. The research

should also focus on pregestational control of maternal blood pressure, as well as on the long-term cardiovascular morbidities and mortality. Such a study should include a group of women who never had a pregnancy beyond 20 weeks' gestation, and a group of age-matched women who had a normotensive pregnancy. In addition, the effects of subsequent pregnancies and the role of weight gain, lifestyle changes, cigarette smoking, presence of gestational diabetes, or subsequent diabetes can be assessed longitudinally. Finally, some of these women have acute morbidity in the form of stroke, heart failure, renal, and liver failure; there is urgent need to study the long-term outcomes for these women.

THROMBOPHILIAS

Thrombophilic conditions have been associated with an increased risk of a variety of adverse pregnancy outcomes, including: severe, preterm preeclampsia; abruption; IUGR; late first trimester or second and third trimester fetal loss; and rare conditions, such as *in utero* fetal stroke. Collectively, these conditions complicate 8 percent of pregnancies and have tremendous personal, familial, societal, and economic impact in the United States. As in the case of the importance of thrombophilic conditions and maternal thromboembolic disease, controversy exists regarding thrombophilias and adverse pregnancy outcomes. For example, Infante-Rivard (NEJM 2002) did not find an association between thrombophilic conditions and IUGR; in fact, the authors of this large Canadian case-control study found that one of the mutations, MTHFR was protective of IUGR in the newborn. On the other hand, Kupferminc (NEJM 1999) found that the three most-common inherited conditions (FVL, MTHFR, Prothrombin gene mutation 20210A) were responsible for one half of the cases of IUGR in the Israeli population.

Research Gaps

There is a tremendous research gap between the presence of these conditions and their association with maternal and fetal pathology; the pathways linking circulating maternal prothrombotic and proinflammatory markers to placental pathology must be defined. Future research should focus on these key areas: pathogenesis of disease in patients with these thrombophilic conditions; detailed epidemiologic studies to assess the magnitude of the risk to women of childbearing age; screening strategies, if appropriate; and surrogate circulating blood markers indicative of the presence of a thrombophilic condition or a marker of increased risk of maternal, fetal, or neonatal risk. Levels of circulating coagulation activation markers increase with the number of prothrombotic conditions (Arkel 2002).

Research Goals and Opportunities

- Understand the fundamental pathologic processes involved patients harboring these 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; and
  - Base prevention and treatment strategies based upon risk assessment.
- With the natural history of the individual thrombophilic mutations and pathologic mechanisms elucidated, focus on specific prevention and treatment strategies.

- Develop a comprehensive database with epidemiologic information, tissue, biologic fluids, and biophysical components available for future investigations.
- Establish regional centers of excellence composed of scientists, researchers, and clinicians with special interest in these areas to optimize resources, patient care, and, most importantly, strengthen research.

New Directions and Approaches to Address Gaps

Basic research efforts should be directed toward understanding relevant physiologic changes that occur in pregnancy, in non-thrombophilic and thrombophilic conditions, such as the Protein C system and its derangements. The regulation of angiogenesis and thrombogenesis early in pregnancy must be defined in order to explain common antenatal events such as utero-placental thrombosis and hemorrhage, which have significant implications for the remainder of pregnancy. New relevant biologic markers that improve upon existing screens for thrombin generation will aid in monitoring disease progress and prognostication of undesired events. More efficient genetic screening strategies, using current and future genetic technologies such as gene-chip array and SNPs, will provide an initial step at identifying patients who may benefit from intervention.

Priority of Area for PPB

- Who should undergo thrombophilia evaluation and the components of such screening?
- What are the appropriate treatment/ prevention strategy(ies) that are currently available to practitioners?
- What other evaluation is appropriate for patients identified with thrombophilic conditions?
- Based upon current understanding, what is the appropriate counseling regarding the patient and her offspring?

AREA OF OPPORTUNITY: NEONATOLOGY (SPECIFICALLY INTENSIVE-CARE ISSUES)

Advances in the field of neonatal perinatal medicine include: care and diagnosis of fetal conditions; better understanding, application, and access to neonatal intensive care; the effect of prenatal steroids on lung and brain maturation; improved delivery-room care for the neonate; improved respiratory function and decreased mortality and morbidity with surfactant replacement therapy; and increased survival for smaller preterm infants <28 weeks' gestation and < 1000 g birth weight. There has also been increased short-term and long-term morbidity such as BPD, cerebral palsy, mental developmental delay, and limitation in intellectual potential. The best outcomes for the newborn arise from successful collaboration among many subspecialties (e.g., genetics, pediatric/fetal surgery, cardiology, pediatric cardiovascular surgery, and others) and maternal fetal medicine in particular. In large part the neonatal-perinatal research effort has been directed to neonatal intensive care issues (e.g., modes of ventilation, the biology of lung surfactant deficiency) and acute problems (e.g., respiratory distress syndrome [RDS], meconium aspiration syndrome, persistent pulmonary hypertension of the newborn). Although follow-up studies, an important component of the NRN, have been done, the data are limited due to cost and the lack of availability of infants and families for later follow up at school ages.

The incidence of preterm newborn births is increasing in the United States, in part, due to later maternity, more common multiple gestation pregnancies, and advances in and increased use of assisted reproductive technologies and methods. Infants born with complex anomalies and perinatal cardiorespiratory problems can respond to intensive care, which may include Extracorporeal Membrane Oxygenation (ECMO), renal dialysis, and experimental therapies. The field is evolving from addressing primarily acute developmental and intensive care issues, to addressing the longer-range implications of preterm birth and neonatal diseases, which require neonatal intensive care for later health and function.

RESEARCH GAPS AND OPPORTUNITIES

Long-term childhood morbidity (e.g., blindness, deafness, cerebral palsy, mental delay and limitation, and physical handicaps) are all sufficiently common; for instance, the incidence of cerebral palsy is less than 15 percent for preterm infants $\leq$ 1250 g birth weight. At the present time, we are limited in determining whether the morbidity occurs prenatal, intrapartum or postpartum. *Research regarding cause, prevention, and treatment would lead to improvement in the neurological outcome for the infant. Basic research in neuroscience and translational research should be priorities. Early identification of infants at high risk for long-term neurodevelopmental impairment is needed (See Area of Opportunity: Fetal/neonatal brain development and damage, including prenatal, perinatal, neonatal, infant periods).*

In general, the effect of stress and demand for more mature function from immature organ systems, often associated with neonatal intensive care, must also be studied to determine if the ultimate level of function and maintenance of function over time is comparable to control infants and children. If not comparable, can it be modified or improved? The effectiveness of neonatal intensive care over the last three decades has improved survival rates; it is now appropriate and

timely to raise questions about lifetime health issues. *Basic and translational research on organ development, the effect of intensive care interventions, and the effect of prenatal and postnatal influences on development and long term potential for function should be a priority.*

Many low birth weight (< 1,500 g) preterm infants who are appropriate size for gestational age or small for gestational age at birth are growth retarded at the time of discharge. *Basic and translational research in fetal nutrition and gastrointestinal development should be a priority to prevent extrauterine growth retardation, and malnutrition, and to address developmental issues in organ development during a critical window of development.*

AREA OF OPPORTUNITY: PRENATAL SCREENING, DIAGNOSIS, AND FETAL THERAPY

RATIONALE

The primary goal of the PPB is to support research that improves pregnancy outcome and infant health. An important aspect of this goal is to develop tools for prenatal diagnosis and screening that help to identify pregnancies at risk. Historically, prenatal diagnosis research has been funded through the through the Intellectual and Developmental Disabilities (IDD) Branch, formerly the Mental Retardation and Developmental Disabilities (MRDD) Branch, of the NICHD. Some examples of this research include: the U.S. Amniocentesis Trial (*circa* 1976); the U.S. Chorionic Villus Sampling (CVS) Trial (*circa* 1983); the Early Amniocentesis vs. - Transabdominal CVS Trial (*circa* 1999); Fetal Cells in Maternal Blood or NIFTY Trial (1994 2002); and the First and Second Trimester Evaluation of Risk for Aneuploidy (FASTER) Trial (1999-2004).

PRIORITY OF AREA OF OPPORTUNITY WITHIN PPB

To date, the NICHD has supported research in prenatal diagnosis and screening, but this work has been primarily performed under the aegis of the MRDD Branch. One could argue that this area might belong under the category of Maternal/Clinical research. One example is the FASTER trial, in which ultrasound and biochemical markers are being analyzed to detect pregnancies at risk for both Down syndrome, and congenital heart disease, although congenital heart disease is not necessarily associated with mental retardation. There will undoubtedly be new markers of fetal well-being developed over the next decade that could be applied to broad populations of pregnant women. Prenatal diagnosis is a huge clinical area in which clinical obstetric practice is altered on the basis of the published literature, but not necessarily through careful evaluation or through randomized prospective clinical trials.

AREAS OF INQUIRY

Prenatal screening and diagnosis can be grouped into three broad areas of inquiry: 1) Imaging studies of the fetus and/or placenta; 2) Biochemical testing of the blood or urine in a pregnant woman, to identify products of the fetus and/or placenta; and 3) Genetic studies through analysis of fetal material obtained invasively and non-invasively.

The ultimate goal of prenatal diagnosis is to be able to treat the underlying abnormality *in utero* to minimize symptoms or even correct the underlying disorder. Thus, fetal therapy (e.g., medical, surgical, and minimally invasive) could also arguably fit into this category.

RESEARCH GAPS AND OPPORTUNITIES

Sonography and Fetal Imaging

- Some major limitations of current approaches include the need for specialized training and quality assurance with regard to sonographic markers of fetal anomalies. Who should perform sonography, and what should they be studying in the fetus at each trimester? Should sonographic studies be performed only (or primarily) in centers of expertise, as suggested by the RADIUS trial? What can be done to assess fetal well-being in the primary care obstetric setting? What is appropriate quality assurance?
- What additional fetal anatomic markers can be seen on ultrasound examinations that correlate with fetal well-being? What role will 3-D (or 4-D) ultrasound studies have in routine prenatal care? What novel indications exist for fetal MRI or fetal functional MRI? What other imaging technologies is on the horizon that merit assessment by the PPB?

A relatively large number of fetuses are found to have "soft markers" for aneuploidy (i.e., nuchal thickening, pyelectasis, echogenic cardiac focus, and short limbs). The management of these patients has not been well defined. This issue currently generates significant patient anxiety and potentially unnecessary testing and interventions, with all the accompanying morbidity and cost. Studies are needed to accurately determine the likelihood ratios of these findings in a large and nationally representative population. Methods and mechanisms are needed to use this information clinically in counseling and management of these patients, in a process similar to what is in place for serum markers.

The appropriate method of delivery for some fetal structural defects (i.e., abdominal wall, neural tube) remains controversial. Randomized studies are not available and may only be possible if a large multicenter trial is funded.

Noninvasive Markers in Maternal Serum and Urine

Maternal serum screening approaches to the detection of fetal Down syndrome are limited by a sensitivity of detection of about 70 percent and a calculated false-positive rate of 5 percent. How can the false-positive rate be minimized, while assuring adequate sensitivity of detection of Down syndrome? What new aspects of the underlying biology of pregnancy can be learned from the study of placental and fetal biochemical markers?

What can non-invasive markers tell us about complications of pregnancy besides aneuploidy? Fetal cell-free DNA is elevated in the blood of pregnant women who will develop preeclampsia, unstoppable preterm labor, hyperemesis gravidarum, or placenta accreta, and in women who carry a fetus with Down syndrome or trisomy 13. Furthermore, cell-free fetal DNA is useful in the diagnosis of single-gene disorders such as Rhesus D incompatibility and congenital adrenal hyperplasia. Insight regarding the trafficking of nucleic acids (including RNA) between fetus and mother may lead to a new understanding of perinatal biology, while providing novel clinical applications.

- Novel technologies to increase the amount of information obtained from standard obstetric procedures are needed.

- Novel technologies are in development that could be used to study fetal material acquired through conventional methods of prenatal diagnosis, CVS, and amniocentesis. Fetal gene expression and an expanded karyotype using cDNA and genomic DNA-based microarrays are available on a research basis. These technologies could expand prenatal diagnosis from primarily a study of aneuploidy to an assessment of fetal developmental biology.

With the return to first trimester diagnosis, chorionic villi could serve as a source of novel biochemical data that could improve our understanding of early fetal metabolism.

The traditional metaphase karyotype may eventually be replaced with molecular analysis of the entire genome using bacterial artificial chromosomes (BACS) and a competitive genomic hybridization (CGH) approach. This analysis will present new opportunities to study the effect of genetic microdeletions and/or duplications on the developing fetus.

Similarly, as microarray technology becomes routinely applied to the fetus and placenta, there will be additional clinical and biological information available that will presumably improve perinatal care.

Preimplantation Genetic Diagnosis (PGD)
PGD presents an opportunity to "prevent" genetic disease by transferring only unaffected embryos for implantation. To date, research in this important, cutting-edge area does not have a formal "home" in a branch of the NICHD.

With the increase in the use of assisted reproductive technologies, many in older gravidas, aneuploidy screening in multiple gestations is becoming relatively common. Investigations into methods for screening in established pregnancies are needed. In addition, advances in molecular analysis of the entire genome may provide a way for PGD.

PGD presents an opportunity to improve selection of embryos for transfer in assisted reproductive technology. Currently, embryos are selected based upon morphologic criteria, which does not accurately identify aneuploidy. Microarray, cytogenetic, and biochemical data could be combined with morphology to better predict the embryos that are likely to successfully implant, leading to a clinical pregnancy. Furthermore, this technology presents an outstanding opportunity to study the early developing human embryo.

Fetal Therapy
A broad-based approach to fetal treatment should be encouraged and explored. This approach should encompass a systematic evaluation of fetal medical treatment, minimally invasive treatment (i.e., endoscopy, laser ablation), and open surgical clinical trials with outcome assessment.

In the next decade, it is reasonable to expect that *in utero* gene therapy will become feasible via the administration of stem cells. The PPB would allow an ideal collaboration between perinatologists, who would administer the cells, and the neonatologists, who would study the effects of the therapy upon the developing infant.

Infrastructure Resources Needed

- Research funding
- Data-analysis resources
- Tissue and specimen banks with corresponding clinical data
- Linkage of medical records between fetus, newborn, and child

Health Disparity

It is well known that socio-economic disparity exists in the utilization of prenatal screening and diagnostic services. How can this disparity be minimized?

Research Risk/Ethical Aspects of Research

- As in other areas of obstetric research, there are two patients whose well-being needs to be considered.
- In particular, in areas of fetal therapy, there are risks to the fetus and to the pregnant woman.
- Genetic screening studies may identify issues that do not directly impact fetal well-being, but may "label" the fetus in unintended ways. For example, newborn screening for cystic fibrosis in Massachusetts has the intended goal of detecting newborns with cystic fibrosis to maximize therapeutic options, but the screening may also identify newborns who are carriers of a single cystic fibrosis mutation. Sonographic studies that identify subtle fetal anomalies with little or no clinical significance may have an unintended impact on the long-term care of the child.
- The impact of the Health Insurance Portability and Privacy Act on clinical perinatal and neonatal research needs to be explored.

AREA OF OPPORTUNITY: FETAL/NEONATAL BRAIN DEVELOPMENT AND DAMAGE (INCLUDING THE PRENATAL, PERINATAL, NEONATAL, AND INFANT PERIODS)

During the past five decades, marked clinical research has led to major advances in fetal monitoring and diagnosis, and in perinatal intensive care; simultaneously, basic research has provided an ever-broadening understanding of cerebral development from the molecular to the behavioral plane. The Workshop participants believe that the most vexing issues for PPB are in the implementation of translational research that targets problems common to the developing brain. Almost 1 percent of all live births weigh <1000 g at birth; 0.2 percent to 0.4 percent of term infants born each year suffer hypoxic ischemic encephalopathy; the incidence of fetal stroke, xenobiotic exposure, and other conditions that impact neurobehavioral outcome remains largely unknown. Nonetheless, all of these children are at high-, and potentially preventable risk for neurodevelopmental handicap.

RESEARCH GAPS AND OPPORTUNITIES

I. Interaction of the environment and the genome in developing brain (i.e., molecular, cellular, animal models of injury and repair):

- Broaden understanding of unique features of the immature brain that impact vulnerability and response to stress; understand the normal developmental pattern and function of expression and activity of neurotransmitters, growth factors, metabolic capacity, cell death/apoptotic activity, etc.
- Identify common pathways of injury to developing brain (i.e., metabolic, infectious, and xenobiotic agents).
- Determine genomic factors that render the developing brain resistant and/or susceptible to injury.
- Identify environmental factors that promote plasticity or enhance defect.
- Develop strategies to prevent injury and promote neural repair.

Examples: Growth factors are known to promote angiogenesis and neurogenesis both *in vitro* and *in vivo* in animal models of disease. The chronic hypoxemia and nutritional deficits associated with IUGR and with postnatal conditions such as premature birth, BPD, etc., result in elevated levels of these growth factors and, thus, merit study in the developing brain. The association of environmental intervention with alterations in neurogenesis and in enhanced learning and neurobehavioral outcomes in animal models warrants further research.

II. Translation of the basic science data to the newborn unit and beyond

- Broaden collaborative use of the MFMU Network and the NRN to validate animal models of injury and repair.
- Develop intervention and prevention trials for these populations.

Example: Collaboration in translational research is exemplified by the ongoing Beneficial Effects of Antenatal Magnesium Sulfate in the Prevention of Cerebral Palsy (BEAM) trial. In

this extraordinary study, the MFMU Network and the NRN work together to test hypotheses derived from animal studies that examine strategies for prevention of injury to the brains of preterm infants.

III. Improved methodologies for assessment of normal neurobehavioral development, for diagnosis of injury, for documentation of efficacy of therapies, and for repair of developmental injury applicable in the clinical situation

- Implement comprehensive infant follow-up studies as projected for the National Children's Study.
- Develop behavioral methodologies and probes to evaluate continuities and trajectories relevant to long-term outcomes.
- Develop improved fetal-imaging strategies (i.e., fetal MRI, DWI, fMRI, volumetric studies).
- Develop improved neonatal-imaging strategies (i.e., MRI, DWI, MRS, DTI).
- Develop standardized strategies to assess early language abilities.

Examples: Neuroimaging in the immediate perinatal period is now the standard of care for fetuses and infants with encephalopathy; numerous recent studies have documented the importance of MRI, DWI, and MRS for the diagnosis of hypoxic ischemic encephalopathy, and for prognostication and monitoring clinical interventions/treatment strategies. Further, DWI shows promise for preterm infants, in whom abnormal early DWI studies may reflect an increased risk for cystic periventricular leukomalacia (PVL), at a time when intervention therapies may be considered. Similarly, fMRI studies may be able to document plasticity in the injured developing brain. Finally, fetal MRI and fMRI provide a window into the structure and function of the developing brain, yet these techniques are not widely employed.

AREA OF OPPORTUNITY: TRAINING

This section is structured to answer three questions, which are important in training, both for physician and non-physician scientists: (1) How do we attract potential trainees in the field? (2) How do we maintain the involvement of trainees over the course of training? (3) How do we assure success of the process through generation of independent investigators?

The statement of each question is followed by a series of suggested changes that might be implemented by PPB to address the problem. There are a series of training problems for which the solutions rely primarily on bodies other than NIH. This section discusses all such problems; however, the proposed solutions are divided into those that have relevance for the PPB, and those that will necessitate action by other organizations.

These questions are based on the premise that existing training structure and funding have failed to develop an adequate cadre of scientists in perinatal medicine who can perform the basic, translational, and clinical research required to answer the most pressing questions and to advance the field.

PHYSICIAN-SCIENTIST

How to attract them?

The field does not provide sufficient exposure, generate interest, or excite students/clinical trainees at a sufficiently early stage to generate a pool of talented individuals committing to research careers in the field. These individuals need to get an understanding of the field, its problems, its complexities, and its intellectual challenges. The field does not provide opportunities for them to experience various aspects of perinatal medicine, as these aspects occur in the real world; the field does not enable them to follow through on possible career paths, neither by exploring clinical and research perinatology, nor by providing guides, mentors, or role models. Given this problem, discussants were in agreement that a variety of methods could provide a greater initial pool of trainees.

Action Steps for PPB

Increase research exposure, involvement, and interest among medical students through support of perinatal research programs in:

- Summer research
- Research electives
- Year-out programs

Programs such as these should be developed by first identifying a pool of mentors who are willing to participate, and then matching the most appropriate mentor for the student interest. Similarly, for residents, increased research exposure should be sought through support of:

- Resident research educational programs
- Year-out programs

Action Steps for Other Resources

- Evaluate the model used by Five School Program.
- Assist interested medical students in matching for residency in perinatal research-oriented departments.

How to maintain involvement?

The pathway to a research career in perinatal medicine can be daunting, and the end-point is often seen as unattractive. The length of time required for specialist/subspecialist clinical and research training by standard pathways often exceeds seven to 10 years, after medical school. Clinical training time is encumbered by the non-educational service element. Competing residency training requirements preclude substantive research experience. Research training time in subspecialty fellowship is insufficient to produce independent physician scientists.

Action Steps for PPB

Maintain interest in research by:

- Providing funding to reduce clinical service demands in exchange for greater research training time
- Developing programs that will facilitate continuing research by MD, PhD, and other trainees who have already been involved in, and wish to continue in the perinatal research track

Action Steps for Other Resources

- Utilize flexibility in residency training for research training.
- Incorporate and fund PhD, MPH, MSCE tracks in training.
- Assist finishing residents in identifying appropriate post-residency training programs.
- Consider a new model for training in research. Perhaps the best time for training is after the fellowship training in a subspecialty; however, for this plan to succeed, this training period be made more attractive, both in terms of ease of obtaining support (K awards) and of reducing the monetary burden (loan payments). In addition, an easier way to make the period more attractive may be to allow supplemental awards to all R01s, which would allow interested individuals to obtain excellent mentored training from established scientists, independent of a formal training program.

How to assure success?

- Salary levels for continuing a research-oriented career are low, when compared to private or academic clinical practice. This disincentive is further exaggerated by rising medical school debt, rising medical liability costs, and salary caps for research components of effort.
- Changing environment after clinical training, but before completing independent research training may result in disruption of research and mentorship. Research training frequently consists of 18 to 24 months in fellowship, with limited research goals and training. Trainees often do not have the support mechanisms necessary to succeed. Often, departments cannot or will not provide adequate support for protected research time for new faculty. Faculty require clinical involvement to maintain and refine skills, as well as to generate research questions and materials, but new faculty are buried under clinical demands.
- Current research funding levels are insufficient to assure protection from competing clinical demands. There is a lack of financial support from departments for new faculty that would allow them to pursue research goals in the early part of their careers. These faculty never get

as far as the R03; they need a bridging grant, seed money to start them off, based on the presence of experienced, funded faculty mentors, not based on a project. Seed money should come with a protected time requirement.

- The follow through in the latter part of training or after training is frequently inadequate. Many new clinical research faculty have had wholly inadequate training to prepare them for the role of independent investigator. One of the most important elements is the presence of basic scientists with whom they can collaborate, and through whose expertise they can continue to learn. These researchers frequently have no mentors within their new departments, neither clinically, nor for their research. Often there is little or no oversight of their progress in the first crucial years.

Action Steps for PPB

Maintain interest in research by:

- Expanding loan forgiveness programs
- Increasing levels of funding for research training to compete with clinical compensation
- Implementing rigorous oversight and quality control of training programs
- Providing increased flexibility of programs, such as Women's Reproductive Health Research (WRHR) awards and programs

Action Steps for Other Resources

- Ensure that liability costs do not necessitate a volume of clinical practice that precludes substantive research time.
- Assure consistent and capable mentoring.

NON-PHYSICIAN SCIENTISTS

How to attract them?

There is little or no appeal to basic scientists to enter the field. There is also a dearth of good scientists at the graduate student and postdoctoral levels who are interested in the field. Finding candidates for postdoctoral positions is extremely difficult, even when considering including foreign scientists. This situation is made all the more difficult given the restrictions on the recruitment of non-U.S. citizens to various positions, such as National Research Service Award postdoctoral fellowships. There are no short-term training programs designed to give potential trainees some understanding of the field. There are very few programs that offer graduate studies designed to emphasize or to appeal to those interested in reproductive biology.

Action Steps for PPB

Increase research exposure, involvement, and interest amongst undergraduate and graduate students through support of perinatal research programs in:

- Summer research
- Laboratory rotations
- Year-out programs

Action Steps for Other Resources

- Encourage interdisciplinary programs that include reproductive biology.
- Develop graduate studies programs in reproductive biology.

How to maintain interest/involvement?

The process by which training is funded is currently cumbersome and lengthy. The time between establishing contact and the start of a training grant can be 18 months or more, with no guarantees that funding will ensue. The small number of training programs, usually associated with major university centers, limits the number of positions available. Substantial resources are required to establish and maintain additional institutional training programs. The WRHR and Building Interdisciplinary Research Careers in Women's Health (BIRCWH) programs have been developed without an understanding of the needs for training of non-physician scientists. It is assumed that postdoctoral positions will be found from research grant funding. In this way, much of the emphasis on training is lost, since the trainee is required produce research results to justify the research grant funding, whether or not this provides training for independent investigator status. Training stipends need to be continually updated to avoid industry recruiting the most promising trainees.

Action Steps for PPB

- Simplify methods for obtaining funding for pre-doctoral and postdoctoral positions.
- Allow principal investigators to apply for a pre-doctoral or postdoctoral award without having a named candidate.
- Remove U.S. citizen/permanent resident requirement.
- Allow a supplement to R01 grants to allow addition of a training position.
- Establish WRHR-type programs for non-physician scientists in reproductive biology.
- Establish loan-forgiveness program for non-physician scientists.

How to assure success?

Developing independent basic scientists is problematic because of continued dependence on poorly funded postdoctoral positions, the lengthy time required to obtain necessary experience, and the need to publish sufficiently to attain R01 funding. Although there is some non-NIH postdoctoral funding, usually it is for specified topics, and only includes salary support. Preference is usually given to physician-scientists by industry and private foundations. Establishing a track record of funding is commonly restricted to those who are already have faculty appointments. Yet, obtaining a faculty position without extant funding is difficult. Current funding mechanisms for new/junior faculty are inadequate. The R03 does not provide sufficient funding for salary and technical assistance. The R01 "new investigator" designation is insufficient to allow a new/junior faculty member to compete against established investigators, the result being that the new/junior faculty member must often spend years accumulating enough data and support to submit a competitive R01.

Action Steps for PPB

- Provide postdoctoral grants for salary, supplies, and technical support for which trainees can apply during the postdoctoral training period.
- Fund a bridge grant to include salary, supplies, and technical support for which a postdoctoral applicant can apply. Evaluate bridge grant applications on credentials,

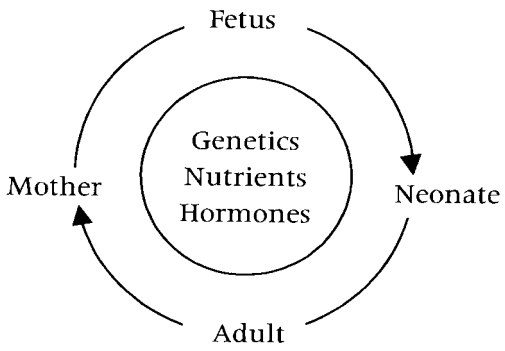
postdoctoral research, and research plan, such that grant can be taken up at a suitable institution once the trainee has accepted a new faculty position.

- Re-establish a starter grant mechanism similar to R29 to foster development of new/junior faculty.

AREA OF OPPORTUNITY: OBSTETRICAL, FETAL AND NEONATAL INTERVENTIONS AND INFANT/CHILD OUTCOMES

Recent evidence from epidemiological studies in humans located in several different parts of the world, and from studies in animals provides strong support for the concept of imprinting and programming during development and early childhood. In this context, the fetus, neonate, and child represent a continuum, influenced by genetics and environment at every stage of development. At each of these stages, growth and development is determined by genetics and is influenced by the environment (i.e., metabolism, endocrine, nutrition, infections).

The consequence is a change in patterning or imprinting that not only has an impact on the health of the individual during adulthood, but also may be transmitted to the future generation (epigenetic).



FETAL GROWTH AND ITS LONG-TERM CONSEQUENCES

The data from human studies strongly suggests that "thinness" at birth is associated with chronic diseases in adulthood, such as type II diabetes, coronary artery disease, etc. However, a number of inconsistencies in the reported data, conflicting data, selection bias, and ecological trends have raised some concern regarding this hypothesis and will need to be addressed in the future. Additionally, the mechanism(s) of IUGR and the mechanism of development of chronic disease have not been addressed. These topics are particularly important because identification of various mechanisms will allow development of intervention strategies and examination of their effectiveness.

While a large body of data has accumulated to relate small size at birth with various diseases in adults, the relationship between large-for-gestational-age infants and adult disease has not been carefully examined. In human studies, maternal diabetes, both type I and gestational diabetes, has been used as the major paradigm for examining the impact of maternal metabolic environment on fetal growth. However, the impact of other metabolic/nutritional perturbations during pregnancy on fetal growth and on the neonate remains to be examined. In this context, the influence of maternal obesity, energy, and protein intake on metabolic imprinting of the developing fetus requires detailed evaluation.

This topic is particularly important because obesity in adolescents and adults is rapidly reaching epidemic proportions. Obesity could have its origins during fetal life as a consequence of the intrauterine environment. Data from a number of studies have shown that obese mothers, even those who do not develop glucose intolerance during pregnancy, give birth to macrosomic babies. The mechanism of macrosomia and its long-term consequences are not known. Only

carefully performed studies examining the molecular and environmental mechanisms involved in these pattern formations will help in the development of intervention strategies.

INTERVENTIONS IN THE NEONATE

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. Studies in animals (rats) provide strong evidence that nutritional experiences during the newborn period can have consequences in the adult. The data of Patel and colleagues have clearly demonstrated that newborn rats, exposed to a high carbohydrate diet until weaning develop hyperinsulinemia as adults, become obese, and develop resistance to insulin action. Of significance, the pups of these obese mothers, although of normal size at birth, become obese as adults. Such animal models provide unique opportunities for the study of nutritional/hormonal and other factors that influence the phenotype, perhaps via epigenetic mechanisms.

Research Gaps

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. It should be underscored that, by influencing the expression of multiple genes at appropriate times in development, the intrauterine environment during pregnancy may have a major impact on both physical and functional phenotypes.

In order to accomplish such goals, the development of new, innovative, non-invasive, and safe methodologies (i.e., isotopic tracers, NMR, PET scan, and molecular biology method) will be required, which will allow physiological and functional assessments of whole body and organ systems, such as the placenta and fetus *in utero*.

A major emphasis should be placed on developing sophisticated techniques for animal models. Recent research using animal models has primarily focused on genetic influences, but not on physiological phenotypes. This situation has resulted from the small size of the commonly used animals, mice and rats. The development of newer, non-invasive methods should allow easy access to important physiological data.

Health Disparity

Multiple studies have demonstrated an association between experiences of socioeconomic disadvantage (disparity) and health during reproductive life, childhood, and adulthood. The physiological mechanisms remain to be elucidated. The influence of health disparity on neurodevelopment has also been suggested.

Evaluation of Interventions

A number of intervention strategies, including nutritional and pharmaceutical, have been used in the care of pregnant mothers and newborn infants. Many of these strategies have not been carefully evaluated for their effectiveness and long-term impact. Future studies should be directed at examining the biological basis of these interventions, and the impact of timing of the

intervention (i.e., early or late in pregnancy, intrapartum, or the neonatal period). The latter is particularly important for the prematurely born infant.

Outcome Measures

There is now a recognized need for the development of new algorithms to examine outcome. This development will require new, sensitive techniques to address functions, including functional imaging methods (MRI), anthropometric studies (body composition measurements), and other methods to assess neurodevelopment early in life.

OTHER AREAS OF FUTURE EMPHASIS

- Evaluation of intrauterine genetic environment, including fetal polymorphism, and its relation to IUGR, preeclampsia, hypertension, and stroke
- Examination of congenital anomalies, including fetal therapy
- Identification of infections not related to prematurity that continue to result in significant fetal and neonatal morbidity, such as hepatitis C, HIV, CMV, etc.

APPENDIX C: PPB STAFF AND PPB PLANNING WORKSHOP PARTICIPANTS

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