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.