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PPB MAJOR MILESTONES AND ADVANCES: 2000-2004

(+ denotes highlighted manuscript)

2000

- 2000 (March) Consensus Development Conference: Antenatal Corticosteroids Revisited: Repeat Courses
- 2000 (June) From Bronchopulmonary Dysplasia to Chronic Lung Disease Workshop
- 2000 (July) Maternal-Fetal Surgery Conference
- 2000 (September) Nausea and Vomiting During Pregnancy Workshop
- 2000 (November) SIDS Pathogenesis in the New Millennium
- 2000 Elevated mid-trimester vaginal fetal FFN levels predict spontaneous preterm birth; *AJOG* 183:469,2000+
- 2000 Treatment of asymptomatic trichomoniasis increases risk of preterm birth; *NEJM* 345:487, 2001+
- 2000 Thrombin initiates uterine contractions in pregnancies complicated by hemorrhage; *AJOG* 183: 674-81 and 183: 799-804+

2001

- 2001 (March) Setting a Research Agenda for Stillbirth Workshop
- 2001 (May) Role of Genetics in the Health Disparity of Preterm Birth and Low Birth Weight Workshop
- 2001 (August) Prenatal Alcohol Exposure and Risk for Adverse Pregnancy Outcomes and SIDS Workshop
- 2001 A novel X chromosome-linked genetic cause of recurrent miscarriage; *AJOG* 185:563-68 +
- 2001 Maternal protein restriction in pregnancy programs subsequent adult hypertension; *Pediatr Res* 49:1-8+
- 2001 Mid-trimester sonographic cervical length predicts preterm birth; *JAMA* 286:1340-1348+

2002

- 2002 (February) *Seminars in Perinatology*: Stillbirth > 20 Weeks' Gestation
- 2002 (June) Defining the Content of Follow Up Care Workshop
- 2002 (December) Pregnancy and Perinatology Branch Planning Workshop
- 2002 (December) Fetal and Neonatal Growth and Development Workshop
- 2002 Temporal response of fetal erythropoietin to hemorrhage; *J Soc Gynecol Invest* 9:75-79+
- 2002 Home uterine activity monitors not useful for predicting preterm birth; *NEJM* 346:250-255+
- 2002 Adaptation of ovine pancreatic insulin secretion to chronic hypoglycemia—implications for adult onset diabetes; *J Physiol* 15:95-105+
- 2002 Prenatal cocaine exposure affects behavior at one month of age and fetal growth deceleration; *Pediatrics* 110:1182-92; and *Obstet Gynecol* 100: 916-24+
- 2002 Varicella in pregnancy increases risk of pneumonia; *J Inf Dis* 185:422-427+
- 2002 Risk factors for SIDS among Northern Plains Indians; *JAMA* 288:2717-2723+
- 2002 Changes in pathogens causing early onset sepsis in very low birth weight infants; *NEJM* 347:240-7+
- 2002 Causes of late onset sepsis in very low birth weight neonates; *Pediatrics* 110:285-91+
- 2002 Mechanisms of how estrogen protects from arteriosclerosis; *Endocr Rev* 21: 655-686+

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- 2003 (April) Investigation of Fetal Origins of Adult Health in Twin Cohorts Workshop
- 2003 (May) Role of Genomic Imprinting, Confined Placental Mosaicism, and Uniparental Disomy in Fetal Growth and Beyond Workshop
- 2003 (June) First Steering Committee Meeting of the Community Child Health Research Network
- 2003 (June) *Seminars in Perinatology*: Highlights from the NICHD's Maternal-Fetal Medicine Units Network
- 2003 (July) From Bench to Bedside: Preventing Bilirubin-Induced Brain Injury (BIBI) in the Newborn and Kernicterus in the 21st Century Workshop
- 2003 Progesterone prevents recurrent preterm birth; *NEJM* 348:2379-85+
- 2003 Mechanism of pulmonary hypertension in newborns; *Am J Physiol Heart Circ Physiol* 285:H204-211+
- 2003 Maternal autoantibodies linked to preeclampsia; *J Soc Gynecol Invest* 10:82-3+
- 2003 American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 291: Progesterone and Preterm Birth; *Obstet Gynecol* 102:1115-6+
- 2003 Antibiotics not useful to prevent preterm birth in FFN-positive women; *Obstet Gynecol* 101:847-855+
- 2003 Asthma severity predicts morbidity in pregnancy; *J All Clin Immunol* 112: 283-288+
- 2003 (November) First Steering Committee Meeting of the Stillbirth Collaborative Research Network
- 2003 (December) First Steering Committee Meeting of the Prenatal Alcohol in SIDS and Stillbirth Network

2004

- 2004 Optimal treatment of moderate asthma in pregnancy; *AJOG* in press +
- 2004 (January) NICHD-American Academy of Pediatrics (AAP) Research and Training in Neonatology Workshop
- 2004 (January) NICHD-USAID Periconceptual Nutrition and Pregnancy Outcome Workshop
- 2004 (January) PPB Strategic Plan distributed to NACHHD Council
- 2004 (January) Fetal growth restriction RFA presented to Council+

EXECUTIVE SUMMARY

The mission of the Pregnancy and Perinatology Branch (PPB), within the Center for Developmental Biology and Perinatal Medicine (CDBPN), National Institute of Child Health and Human Development (NICHD), is to improve the health of mothers and children with a focus on maternal health, pregnancy, fetal well being, labor and delivery, and the developing child. The Branch seeks to acquire scientific information that supports the mission through basic and clinical research, including: determining basic mechanisms that underlie normal and disease processes; identifying new treatments, methodologies, and preventive strategies that arise from translational and evidence-based research; assessing the dissemination and impact of therapeutic and preventive interventions; and increasing scientific resources through recruitment and training of investigators.

Since its last report to the National Advisory Child health and Human Development (NACHHD) Council, Branch funding in current dollars has increased from $70 million to $93.4 million. The PPB utilizes many existing National Institutes of Health (NIH) funding mechanisms to support its activities, which extend from basic research to clinical trials (see Figure 1).

Over the past four years, the Branch has expanded significantly, making considerable strides in incorporating the obstetrical, neonatal, and basic science fields. The Branch's long-term Networks, the Neonatal Research Network (NRN) and Maternal-Fetal Medicine Units (MFMU) Network, continue to be very successful. Each year, the Networks have each given more than 20 national presentations. In addition, through the success of a number of initiatives, the Branch has expanded its portfolio to incorporate fetal surgery, stillbirth, perinatal alcohol exposure, health disparity of preterm birth, and perinatal genetics.

In fiscal year 2002, the PPB launched a Maternal-Fetal Surgery Network, involving three sites and a data center, to perform a randomized trial on *in utero* versus postnatal repair of spina bifida, a devastating neurological condition that results from failure of the fetal spine to close.

In fiscal year 2003, the PPB established three collaborative networks:

- The Branch, in collaboration with the NICHD's Center for Population Research (CPR), initiated a Community Child Health Network (CCHN) to support community-research institution partnerships that study how community, family, and individual level influences interact with biological influences and result in health disparities in pregnancy outcome and infant and early childhood mortality and morbidity.
- The Stillbirth Collaborative Research Network (SCRN), with five clinical research sites and a data center, was established to develop and implement common research protocols to study stillbirths (defined as fetal death at 20 weeks' gestation or later) in the United States.
- The PPB, in collaboration with National Institute on Alcohol Abuse and Alcoholism (NIAAA), started the Prenatal Alcohol in SIDS and Stillbirth (PASS) Network to develop community-linked studies that investigate the role prenatal alcohol exposure in high-risk populations plays in the risk for Sudden Infant Death Syndrome (SIDS) and adverse pregnancy outcomes, such as stillbirth and fetal alcohol syndrome, and how they may be interrelated.

In fiscal year 2004, the Branch funded a new portfolio on mechanisms of fetal growth restriction. In addition, many members of the Branch are involved in planning the National Children's Study,

a longitudinal study of environmental influences on the health and development of more than 100,000 children across the United States.

In addition to its work with the CPR and the NIAAA, the Branch has also had significant interaction and partnership with other Institutes and agencies, including (but not limited to):

- U.S. Department of Health and Human Services (DHHS)—the Interagency Coordinating Council on Low Birth Weight and Preterm Birth
- DHHS and the Centers for Disease Control and Prevention (CDC)—the Healthy Motherhood Initiative
- DHHS, U.S. Food and Drug Administration (FDA), and the NIH Office or Research on Women's Health (ORWH)—the Best Pharmaceuticals for Children Act, the obstetrical and neonatal pharmacology initiative, and the breastfeeding survey
- FDA (in collaboration with the MFMU Network and NRN)—the development and testing of equipment and investigational drugs.
- National Institute of Mental health (NIMH)—co-sponsoring the program announcement (PA) on Women's Mental Health in Pregnancy and the Postpartum Period
- National Institute on Neurological Disorders and Stroke (NINDS), National Heart, Lung, and Blood Institute (NHLBI), and ORWH—co-sponsoring MFMU Network studies

The Branch members also serve as liaisons to major societies in their respective fields, including the American Academy of Pediatrics (AAP), the Committee on Fetus and Newborn, the Society for Maternal Fetal Medicine, the American College of Obstetricians and Gynecologists (ACOG), and the Liaison Committee for Obstetricians and Gynecologists.

PPB Areas of Interest

Branch activities are organized around five maternal-fetal emphasis area, which complement each other and build a comprehensive approach to research during the pre-, peri-, and postnatal periods:

High-Risk Pregnancy is concerned with those factors, both normal and abnormal, that influence the course and outcome of pregnancy, including maternal physiology, environmental variables, conditions, and treatments that occur during pregnancy, all of which contribute to adverse outcomes (e.g., low birth weight). Studies in this area include (but are not limited to): elucidating the mechanisms involved in the pathophysiological states of pregnancy; the health impact of pregnancy-related disorders on mother and infant; pathogenesis of symptomatic and asymptomatic maternal infections and their effects on fetal development, with the aim of improving treatment and prevention; the effect of maternal medications and mother's use and abuse of drugs on fetal development; and adolescent pregnancy.

Fetal Pathophysiology includes studies of the physiologic, metabolic, endocrine, and pharmacologic events related to abnormal development of the fetus, such as the morphology, function, and metabolism of the placenta and uterine blood flow. Studies in this area are encouraged to improve existing methodologies for antenatal diagnosis regarding fetal status, growth, position, maturity, and well being.

Premature Labor and Birth promotes studies of the factors that affect the initiation and completion of labor, as well as the physiology, endocrinology, and pharmacology of parturition. Of special concern are causes and prevention of premature labor, threatened and habitual pregnancy loss (miscarriage), prolonged and dysfunctional labor, and dystocia.

Disorders of the Newborn includes basic and clinical studies concerned with the etiology, pathophysiology, therapy, and follow-up of conditions associated with the perinatal and neonatal period, such as adaptation to extrauterine life, hyperbilirubinemia, and sequelae of prematurity (i.e., asphyxia, respiratory distress, bronchopulmonary dysplasia, hypoglycemia, anemia, and infection).

SIDS encompasses studies to elucidate underlying mechanisms of SIDS and its probable cause(s). Additional research strives to identify infants at risk for SIDS and to develop preventive approaches.

Findings from Branch initiatives and studies have also resulted in policy and practice changes. For instance, in 2000, the PPB convened an NIH Consensus Development Conference on repeat courses of antenatal corticosteroids in pregnancy and their effectiveness and safety in enhancing fetal maturation. After reviewing the research evidence, the panel concluded that, although a single course was beneficial and safe, the data were inadequate to support using repeated courses outside of ongoing clinical trials. As a result,

providers now administer only a single dose (for more information on this finding, go to *http://consensus.nih.gov/cons/112/112_intro.htm*).

Similarly, a recently completed study from the MFMU Network identified, for the first time, a treatment for recurrent preterm birth that has changed obstetric practice. This trial was highlighted in the national news, including CNN and the front page of the *New York Times* (for more information on this finding, go to page 24).

The PPB is convinced that investing efforts and funds in basic and clinical research for mothers' and infants' health problems will result in significant savings of later expenses for the care of patients who develop preventable disabilities and/or diseases. Most importantly, these investments will help promote the birth of healthy infants, able to achieve their full potential for healthy and productive lives.

BRANCH ACTIVITIES: RESEARCH PROJECT GRANTS AND CONTRACTS

The Branch classifies grants and contracts in five categories: Maternal, Fetal, Newborn, Placental, and SIDS; each has basic and clinical components. The following section highlights a few of the advances in each category; due to space limitations, all the advances could not be included in this report. Highlights from a number of clinical studies are summarized in the Cooperative Agreements section.

MATERNAL RESEARCH

This portfolio includes basic, translational, and clinical research studies that address a myriad of issues in pregnancy to understand normal and abnormal physiological events and the effects of maternal, acute, or chronic diseases on pregnancy and fetal development.

Birth Weight and Cardiovascular Disease

It is well recognized that the causes of adult diseases involve a combination of a "lifestyle" (environmental) component and a genetic component. Accumulating research over the last decade has provided evidence of a third component: *in utero* environment. Barker and colleagues reported on the role of the *in utero* environment by demonstrating an inverse relationship between birth weight and death from cardiovascular disease in adulthood. Subsequently, a number of epidemiological studies have suggested that maternal malnutrition impacts the fetus and results in the onset of other major adult diseases, such as diabetes, obesity, hypertension, and cardiovascular disease, a theory known as the "fetal origins of adult disease" or the Barker hypothesis. Although this hypothesis remains controversial, accumulating research has provided increasingly strong support for this theory. This research indicates that factors in the perinatal environment, probably related to maternal nutrition, can program the fetus for increased disease risk in later life.

The precise physiologic and molecular mechanisms by which this programming occurs are unknown. One PPB-supported researcher has demonstrated that moderate protein restriction to pregnant rats results in pups born with reduced weight and decreased renal development that

persist into adulthood. The resulting decrease in renal function and increased arterial pressure leads to hypertension and an increased risk of cardiovascular disease. This investigator also demonstrated the mechanism by which this occurs: suppression of the intrarenal renin-angiotensin system (RAS) during fetal life. This hormonal system is known to be important in regulating blood pressure and volume in adults. Based on these findings, it is likely that the RAS plays other critical roles during fetal development, such as setting the total nephron endowment of the kidney and programming the set point for adult blood pressure. These findings support a possible mechanism by which the fetal environment could "program" an individual for hypertension, and for increased cardiovascular risk in adulthood (*Pediatr Res* 2001; 49:1-8).

Gestational Diabetes Mellitus (GDM)

The adverse maternal and fetal effects of GDM have long been an important research area for the PPB. The maternal hormonal and metabolic alterations associated with GDM profoundly modify the *in utero* environment, which can lead to an abnormal pattern of fetal growth. Impaired fetal development has severe metabolic consequences, including increased risk of developing glucose intolerance and obesity in adolescence and adulthood. The molecular basis for the imbalance that leads to fetal, neonatal, and adult metabolic compromises has not been well understood. An NICHD grantee's study has provided the first explanation of the molecular basis of this imbalance. This work linked GDM to changes in expression of specific placental genes, including interleukin 1 (IL-1), leptin, and tumor necrosis-alpha (TNF-α). These changes result in adverse fetal programming, which leads to an increased risk of glucose intolerance and obesity in adolescence and adulthood (*Diabetes* 2003; 52:2951-58).

Preeclampsia

Preeclampsia is a major and potentially serious disorder of pregnancy. This hypertensive disease affects approximately 7 percent of first pregnancies and 3 percent of all pregnancies. Preeclampsia contributes significantly to premature deliveries in the United States and, in its severest form, eclampsia, is a leading cause of maternal morbidity and mortality.

Although its exact mechanism is unknown, preeclampsia is widely believed to result from poor vascular development between the placenta and the uterus. In a normal pregnancy, trophoblastic cells, the main cell type of the placenta, invade deep within the uterus and remodel the small uterine arteries into large diameter vessels. In preeclampsia, the trophoblastic cells fail to invade the uterus adequately, which prevents the normal remodeling process of the uterine vessels. In turn, the poorly perfused placenta releases factors into the maternal circulation that result in the systemic symptoms of the disease.

In pursuit of one of these placental factors, one PPB-supported grantee compared plasma from women with severe preeclampsia to plasma of normal women, specifically looking at interleukin-6 (IL-6). This research demonstrated that severe preeclampsia results in the production of endothelial cell IL-6. The administration of vitamin E inhibits the production of IL-6. These findings provide a potential cellular mechanism for preeclampsia and suggest beneficial effects of antioxidant therapy for the condition (*Am J Obstet Gynecol* 2003; 188:740-4).

Other pathophysiologic mechanisms involved in preeclampsia and potential targets for prevention and therapy are under active pursuit by PPB-funded investigators. Earlier work indicated that a majority of preeclamptic women experience an abnormal immune response, called autoimmunity, in which they produce antibodies against one of their own proteins; these antibodies are called

autoantibodies. Autoantibodies target a receptor, designated AT-1, which is involved in mediating the effects of angiotensin II, a potent protein hormone involved in the contraction of blood vessels. In contrast to most antibodies that neutralize their target, autoantibodies actually activate the AT-1 receptor. Researchers speculate that these autoantibodies are responsible for the hypertension associated with preeclampsia because of their ability to contract blood vessels.

Because trophoblastic cells also express AT-1 receptors, efforts are under way to understand how these cells are affected by the presence of autoantibodies. One PPB-funded investigator has shown that the autoantibodies can inhibit the invasiveness of trophoblastic cells through increased production of PAI-1, a regulatory protein that inhibits the conversion of plasminogen to plasmin, a key enzyme important in cellular invasion and involved in blood clot degradation. These results are consistent with those of other investigators that show elevated blood levels of PAI-1 and increased clot formation in preeclamptic women. Autoantibodies to the AT-1 receptor appear to be linked to many of the symptoms associated with preeclampsia, suggesting that they may be the cause of the disease. If causality can be substantiated, it may be possible to develop effective therapeutic interventions for preeclampsia (*J Soc Gynecol Investig* 2003; 10:82-83).

Other Maternal Research Topics

Regular physical activity during pregnancy and its potential to reduce the redistribution of blood flow away from the viscera is another area of study for PPB-funded investigators. One research group compared the infants of women who were randomly assigned to a high volume of physical activity (defined as moderate-intensity, weight-bearing exercise in mid- and late pregnancy) with infants of women who were randomly assigned to reduce their exercise volume after the 20th week. They found that infants in the first group were significantly lighter and thinner than their counterparts (3.39 kg versus 3.81 kg, and 8.3 percent fat versus 12.1 percent fat, respectively). These data suggest that a high volume of moderate-intensity, weight-bearing exercise during mid- and late pregnancy symmetrically reduces fetoplacental growth, whereas reduction in exercise enhances fetoplacental growth with a proportionally greater increase in fat mass than in lean body mass (*Am J Obstet Gynecol* 2002; 186:142-7). This group of investigators also demonstrated that portal vein flow rises significantly during pregnancy, and that exercise training reduces the normal flow redistribution away from the splanchnic and uterine circulations in response to severe hemodynamic stress in mid- and late pregnancy. Regular exercise during pregnancy confers maternal and fetal protective effects by allowing maintenance of adequate uterine blood flow during times of severe hemodynamic stress (*Am J Obstet Gynecol* 2000; 183:167-72).

During pregnancy, a decrease in the motility of the gastrointestinal tract (GIT) can result in significant discomfort because of esophageal reflux, bloating, and constipation. Release of nitric oxide (NO) by neuronal NO synthase (nNOS) found in nonadrenerergic, noncholinergic (NANC) neurons in the GIT has been shown to be responsible for reducing GIT mobility. Little is known, however, about the factors responsible for regulating NO release by NANC neurons during pregnancy. A PPB-supported researcher investigated the role of the prominent sex steroids, estradiol and progesterone, produced during pregnancy, as likely candidates involved in this regulation. Using a rat model, the researcher demonstrated that estradiol, but not progesterone, was involved in decreasing GIT mobility. Estradiol enhanced NO levels via an increase in nNOS that was mediated by an increase of nNOS mRNA. This finding has broader implications in that it suggests that sex steroids may be involved in the regulation of the NO component of NANC nerves in other systems, including the central nervous system, urogenital system, and other organs innervated by the NANC (*Am J Physiol Regul Integr Comp Physiol* 2001; 280:R1546-54).

Medication use during pregnancy is another understudied research area. A team of researchers jointly funded by the NICHD, NIMH, and the National Center for Research Resources is studying birth outcomes after maternal use of antidepressant medication during pregnancy. They found that prenatal use of selective serotonin reuptake inhibitor medications was not associated with an increase in neonatal complications or in congenital anomalies above that for the general population. However, maternal use of high doses of fluoxetine throughout pregnancy was associated with an increase rate of low birth weight (LBW) infants (*Am J Obstet Gynecol* 2003; 188:812-5).

Recurrent miscarriage affects one out of 100 couples who attempt to have children. Numerous reasons for this malady have been identified, including anatomic, immunologic, infectious, endocrine, and genetic causes; however, approximately half of all recurrent miscarriages are unexplained. A team of researchers supported by the PPB has identified a novel genetic cause that accounts for 25 percent of previously unexplained cases of recurrent miscarriages (*Am J Obstet Gynecol* 2001; 185:563-68). This research showed that the genetic flaw resides in one of the mother's two X chromosomes, only affects male fetuses, and results in miscarriage. Because male fetuses receive only one copy of the mothers' X chromosome, the chances of receiving the abnormal chromosome are 50 percent. Female fetuses, who receive an additional normal X chromosome from their fathers, preferentially use the paternal chromosome over the flawed maternal X chromosome (normal female fetuses randomly use one or the other of the parental X chromosomes). However, females with one flawed X chromosome are at high risk for future recurrent miscarriages, with a probability of 25 percent of all their conceptions resulting in miscarriage. The identification of this genetic defect may allow researchers to develop a blood test to assess the risk of miscarriage due to this defect in future pregnancies, as well as to provide an explanation and hope to the women who are carriers of this malady.

FETAL RESEARCH

Intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity, death, and long-term complications, such as diabetes and hypertension in adulthood. IUGR is associated with a reduced rate of net protein accretion. One PPB-funded research group is focused on increasing the rate of fetal growth by altering maternal amino-acid concentrations. This group already demonstrated that, in normal human pregnancies, maternal infusion of a commercial amino-acid solution elevates maternal amino-acid concentrations, which leads to significantly higher umbilical uptake of most amino acids. Their current research project has demonstrated that, in pregnancies complicated by IUGR, increasing the maternal concentration of amino acids leads to an increased fetal uptake of some amino acids. PPB researchers are continuing their studies of the development of IUGR (*Am J Obstet Gynecol* 2002; 187:741-6).

Locally expressed, vascular mediators that are of a paracrine nature regulate the uteroplacental vasculature. By studying these mediators, diseases related to inadequate uteroplacental perfusion, including IUGR and preeclampsia, can be better understood. One PPB-funded researcher has concentrated on endothelins, a family of potent, long-acting vasoconstrictors, and their role in perfusion. Specifically, this work explores endothelin-1 (ET-1), the most physiologically significant isoform in mammals that is produced by the vascular endothelium. This research has studied the role of ET-1 in the pathophysiology of hypoxia-induced IUGR in the rat model. By

administering an endothelin-A receptor agonist to prevent hypoxia-induced IUGR, the grantee has elucidated the primary role of ET-1 in the development of growth restriction. An ET-1-mediated increase in vascular resistance in the uteroplacental vascular bed leads to decreased placental perfusion, which then leads to hypoxia and IUGR. A better understanding of the mechanisms that regulate placental perfusion and function may allow for treatment strategies in pregnancies complicated by IUGR or preeclampsia at early gestational ages when delivery is not an option (*J Soc Gynecol Investig* 2004; 11:16-21).

Another PPB-funded investigator has studied the complications associated with nuchal cord, in which the umbilical cord loops around the fetal neck. This common condition is observed in 16 percent to 35 percent of neonates at birth. The researcher found that antenatal nuchal cords usually occur randomly, with increased frequency in late gestation, and appear to be a normal part of intrauterine life that does not significantly increase the risk of acute- or labor-associated fetal hypoxia.

Investigators have also been exploring why neonates born to mothers who smoke have altered lung mechanics. In one study, rhesus monkeys exposed to nicotine in early and mid-gestation had increased thickness and increased collagen gene expression in their airway walls. The collagen production occurred in cells containing nicotine and acetylcholine, which suggests that nicotine can cross the placenta and directly affect lung development.

PLACENTAL RESEARCH

The placenta is essential for the maintenance of pregnancy. The prominent function of the placenta is in the transfer of nutrients, gases, and waste products between the mother and fetus; it is effectively the lung, gut, and kidney of the fetus. The placenta is also involved in the production of hormones that are involved in the maintenance of pregnancy and the initiation of labor. Another important function of the placenta is to act as a selective immunological barrier, so that the mother's immune system does not attack the fetal allograft. Thus, perturbations in one of its many functions can have dire consequences for the fetus, ranging from IUGR to fetal death. This section highlights some findings from PPB-supported grants in placental research over the last five years and illustrates the multifaceted nature of this research.

Trophoblast cells are essential components of the placenta. Early in pregnancy, one type of trophoblast, cytotrophoblast cells, are involved in uterine invasion, grafting the embryo onto the mother and establishing a blood supply. During placental development, these cells differentiate into syncytiotrophoblast cells, which form the continuous surface of the placental villous that bathes in the maternal blood. The syncytiotrophoblast cells are primarily involved in nutrient, gas, and waste product exchange transport between the maternal and fetal circulation. Because of the essential roles both these cell types play in the maintenance of pregnancy, it is essential to understand the mechanisms involved in trophoblast lineage determination. One PPB-supported investigator, taking advantage of powerful RNA-expression microarray technology, characterized the process of cell differentiation using a cell culture model system (*Recent Prog Horm Res* 2003; 58:263-81). After analyzing approximately 7,000 genes for RNA expression levels, the researcher found a total of 397 genes that changed during the differentiation process; 141 genes were up-regulated, while 256 were down-regulated. These genes were grouped into functional categories that were either strongly induced or repressed during the differentiation process and were found to

be tightly coupled to key morphological changes. Thus, trophoblast differentiation comprises a highly dynamic process that affects the expression of classes of genes based on their functionality.

As mentioned earlier, preeclampsia is a leading cause of maternal morbidity and mortality. It is widely speculated that factors emanating from the placenta are responsible for the disease by damaging the vascular endothelium. One group of investigators has been studying the possible role of oxidative stress in the etiology of preeclampsia (*Am J Pathol* 2000; 156:321-31). These researchers believed that post-ischemic reperfusion of the placenta results in excess levels of reactive oxygen species and their metabolites, which, in turn, cause these factors to enter the maternal circulation and result in systemic vascular endothelial damage. To learn more, the researchers explored whether xanthine oxidase, a key enzyme involved in the production of reactive oxygen species, mediates oxidative stress in placentas from women with preeclampsia. They found that a subpopulation of cytotrophoblasts in preeclamptic women had increased xanthine oxidase levels. In addition, the expression level of superoxide dismutase, another enzyme involved in degrading reactive oxygen species that is generated by xanthine oxidase, was reduced in the same cells. Furthermore, immunostaining for nitrotyrosine, an indicator of oxidative damage, showed a high level of damage in these cells and in the villous vessels. These results indicate that placental cells have an increased capacity to generate reactive oxygen species in preeclampsia, supporting a role for oxidative stress in the disorder.

Placenta growth factors (PlGFs), a family of proteins produced in the placenta by trophoblast cells, are primarily involved in regulating placental angiogenesis in the placenta, and trophoblast function and survival. PlGFs can act either in a paracrine fashion to influence vascularity, or in an autocrine fashion to influence trophoblast function. Recent studies have demonstrated that PlGFs may have divergent functions. For example, angiogenesis may be promoted or inhibited depending on the particular PlGF isoform under study. Until recently, there had been only three known PlGF isoforms (PlGFl-3). A PPB-funded investigator discovered a fourth isoform, called PlGF4 (*J Reprod Immunol* 2003; 60:53-60). Like PlGF2, PlGF4 contains a heparin-binding domain, which suggests that it remains bound to the plasma membrane and probably acts in an autocrine manner. Further functional studies of the PlGF4 protein isoform and its expression during gestation will help to clarify its role in mediating placental vascularity and trophoblast function.

As a result of trophoblast differentiation, the syncytiotrophoblast produces pregnancy-specific peptides, such as chorionic somatomammotropin (CS), also known as placental lactogen. CS is a member of the growth hormone family and has significant effects on both mother and fetus. It plays a role in regulating fetal growth, mammary development, and lactogenesis, and in maternal intermediary metabolism. The regulation of placental CS production, however, is not well understood. Using the baboon as a nonhuman primate model, a team of PPB-supported investigators previously showed that estrogen accelerated the morphological differentiation of cytotrophoblast during the first half of pregnancy, and stimulated the functional maturation of the syncytiotrophoblast in the second half of pregnancy with regard to steroidogenesis. This team is now investigating whether estrogen also regulates CS production by the syncytiotrophoblast (*J Clin Endocr Metab* 2003; 88:4316-4323). This research found that estrogen suppressed CS production during the first trimester, but had no effect on key steroidogenic enzymes. Together, these results indicate that estrogen has very different and specific actions on steroid and peptide hormone biosynthesis within the placental trophoblast. This differential effect may be important in regulating placental function and promoting fetal-placental during the course of pregnancy.

Natural killer (NK) cells are the predominant immune cells present in rodent and human placental implantation sites. Phenotypically, uterine NK cells undergo a gestational-dependent transformation during the course of pregnancy. NK cells expand in number and differentiate, but do not acquire a classic activation of cell killing. In the rodent, trophoblast cells produce a large number of protein hormones that belong to the prolactin family, one of which, called PLP-A, has been shown to specifically interact with rodent uterine-NK cells within the uteroplacental compartment, inhibiting NK-cell killing activity. A PPB-funded investigator studied the role of PLP-A as a potential modulator of NK cells at the maternal-fetal interface (*Mol Cell Endocrinol* 2003; 204:65-74). He found that PLP-A interactions with NK cells are not mediated by receptors known to be utilized by modulators of NK activity, such as IL-2, IL-7, IL-12, or IL-15. In contrast, PLP-A suppresses the ability of NK cells to produce interferon-gamma, a key mediator of NK-cell function. This latter finding may be especially important because it has been reported that interferon-gamma also inhibits trophoblast cell outgrowth. Consequently, the inhibition of interferon-gamma production by PLP-A in NK cells may be important in permitting continued placental development.

The Branch also supports efforts in other areas of placental research as they relate to both normal and disease processes, including:

- The role of vasodilators, vasoconstrictors, and factors that are produced by the placenta in relation to preeclampsia and IUGR
- Hormonal interactions between the fetus and placenta
- The autocrine, paracrine, and endocrine roles of PlGFs and cytokines, including studies to determine the effects of these proteins on placental growth, differentiation, and function
- Signal transduction mechanisms at the cellular level

Additional studies are currently supported by the Branch in the following areas: angiogenesis, infectious agents, gene regulation, metabolism, growth and differentiation, morphology, growth factors and cytokines, nutrients, hormone production and regulation, transport, immunology, and vascular function. Undoubtedly, new areas of research will arise in the future and the emphasis in particular areas will shift, depending on future discoveries and developing technologies.

LABOR AND DELIVERY RESEARCH

Labor is a complex and interwoven physiological process involving fetal, placental, and maternal signals. A number of stimulatory and inhibitory mechanisms have been identified that play a role in uterine contractility, fetal membrane integrity, and cervical maturation. The Branch promotes studies of the physiology, endocrinology, and management of preterm, term, and post-term deliveries.

An understanding of the normal physiological and biochemical events that occur during parturition is essential for the successful intervention and prevention of preterm labor. Preterm births are increasing in the United States and occur in more than 10 percent of all births, accounting for more than 75 percent of all perinatal morbidity and mortality. The PPB and the NICHD have made a significant research investment in understanding the causes and mechanisms that underlie preterm

labor and delivery. The brief descriptions below highlight some findings from PPB-funded efforts related to labor and delivery, including preterm labor and delivery.

In most mammalian species, a drop in the blood level of progesterone, a hormone produced in large quantities by the placenta during pregnancy and necessary for maintaining the uterus in a quiescent state. Withdrawal of this hormone results in uterine contractions and labor. In contrast to other mammalian species, neither human nor nonhuman primates exhibit a detectable drop in progesterone prior to the onset of labor; the initiating signal for primates remains unknown. An NICHD-supported investigator has identified a possible mechanism that may rectify this apparent conundrum between mammalian species (*J Soc Gynecol Invest* 2002; 9:125-36). Because the effect of progesterone is mediated by the hormone binding to receptors in target tissues, the researcher hypothesized that there may be changes at the progesterone receptor level, rather than in the hormone itself that may be responsible for initiating labor.

Prior research indicated that there were two types of progesterone receptors (A and B); type A antagonized the effects of type B, which mediated the relaxation effects progesterone had on the uterus. Investigators measured the levels of these receptors in the myometrium and fetal membranes of the nonhuman primate uterus during the course of pregnancy. Consistent with their hypothesis, at term, there was a shift in progesterone receptors from type B to type A in the myometrium and a loss of both receptors in the fetal membranes. These data provide evidence for a functional progesterone withdrawal mechanism in nonhuman primates, similar to that seen in other species. If substantiated in the human, this finding would not only have important implications in understanding normal labor, but would also be highly relevant to understanding the possible mechanism(s) involved in preterm labor.

Normally, pregnancy is accompanied by increased fetal growth and a concomitant increase in uterine growth to accommodate the fetus; near the end of pregnancy, uterine growth subsides and the uterus becomes appreciably distended. Pregnancies in which uterine distention is abnormally increased, such as in multi-fetal pregnancies or in situations of abnormal intrauterine fluid volume (polyhydramnios), have an increased incidence of preterm labor; however, little is known about the effect of uterine distention or stretch in pregnancy. One PPB-funded investigator has made significant progress in understanding the biochemical events associated with uterine stretch and its role in the initiation of labor (*Am J Physiol Cell Physiol* 2002; 283:1530-9). Using a rat model, he has shown that mechanical stretch of the uterus can lead to biochemical changes, which cause the activation of proteins critically involved in stimulating uterine contractions and labor. These data indicate that mechanical distention of the uterus plays a role in labor, in addition to the known role of the endocrine or hormonal pathway in the process. These findings may help develop strategies to prevent preterm labor due to abnormal uterine distention.

The neuropeptide corticotrophin-releasing hormone (CRH) plays a central role in regulating the physiological response to stress. Although normally produced in the brain, CRH is also produced in the placenta. During the course of pregnancy, the developing placenta produces increasing amounts of the hormone, which can be measured in the blood; the placental-derived CRH is believed to play a role in regulating the length of pregnancy. For example, abnormally high blood levels of CRH are associated with preterm delivery, while abnormally low levels are associated with post-term delivery. A Branch-supported investigator has provided further support for this so-called “placental clock” and has identified an additional role for placental CRH in fetal growth (*Am J Obstet Gynecol*, In press). The research showed that women with elevated CRH levels at 33

weeks of pregnancy were approximately three times more likely to deliver preterm than women whose CRH levels were normal at the same point in pregnancy. Notably, the investigator also showed that women with elevated CRH levels were also approximately four times more likely to deliver an IUGR infant. In fact, the highest CRH levels were associated with both IUGR and preterm delivery. These findings support the notion that placental CRH is involved in the timing of birth (the "placental clock") and expands on the role of placental CRH in fetal growth. It also suggests that CRH blood measurements may be diagnostic in predicting an adverse birth outcomes and may allow for the development of interventions.

Placental abruption, or *abruptio placentae*, is the premature separation of the placenta from the uterus, initiated by intrauterine hemorrhage. This life-threatening complication for mother and fetus occurs in one in 75 to 90 pregnancies. Although maternal mortality is rare, the perinatal mortality rate is approximately 35 percent, and the condition accounts for 15 percent of all third-trimester stillbirths. Moreover, 15 percent of infants born live after placental abruption suffer a significant rate of neurological impairment. Typically, women with an abruption progress through labor and deliver rapidly due to potent uterine contractions; the mechanism by which the contractions occur is unknown. In research supported by the Branch, the investigator discovered that the blood-derived protein thrombin may initiate these potent uterine contractions (*Am J Obstet Gynecol* 2000; 183:674-81 and 799-804). The research showed that thrombin itself can stimulate potent uterine muscle contractions. Furthermore, an investigator showed that the molecular mechanism by which this stimulation occurs is similar to known, classical, physiological mediators of uterine contractions. Thus, thrombin appears to be the physiological component responsible for the stimulation of uterine contractions in the presence of intrauterine hemorrhage. These findings also indicate the likely possibility that thrombin-stimulated uterine contractions may be part of the pathophysiological process leading to the hyperstimulated uterine contractions observed with placental abruption. Thrombin may also play an important role in other complications of pregnancy associated with uterine bleeding, such as first-trimester miscarriages and preterm deliveries in the third trimester. This work may provide important insight into these complications of pregnancy that would allow researchers to develop various preventive therapeutic strategies targeting thrombin.

Currently, obstetrical care providers monitor cervical changes by manual, visual, or ultrasonographic inspection, but these tests have high false-positive results. A more accurate method would be valuable for the diagnosis of preterm cervical ripening, and for the determination of cervical status before induction of labor. One Branch-funded investigator has developed a novel diagnosis method based on the breakdown of cross-linked collagen that occurs during cervical ripening (*Am J Obstet Gynecol* 2003; 188:537-41). This method employs an instrument placed in the vagina that measures the light-induced fluorescence (LIF) of cross-linked cervical collagen. Preliminary studies showed that LIF correlated inversely with gestational age, positively with the time-to-deliver, and was predictive of delivery within 24 hours. Further refinement of this method may provide an accurate and quantitative measure of cervical ripening that can aid clinicians in determining the status of the cervix in relation to delivery.

In addition, the Branch is currently funding a diverse portfolio of projects that use physiological, biochemical, and molecular approaches to elucidating the various mechanisms involved in parturition, including: the role of the hypothalamic-pituitary-adrenal axis in both preterm and term labor; the involvement of hormones such as CRH, adrenocorticotrophic hormone, cortisol, and androgens in parturition; mechanisms involved in the premature rupture of fetal membranes, such

as infection, cytokine production, and extracellular matrix biology; and uterine relaxation and contraction factors, such as NO, oxytocin, relaxin, steroids, and prostaglandins, and their mechanisms of action. This research will provide a better understanding of the mechanisms responsible for parturition to help promote successful deliveries.

NEONATAL RESEARCH

The Branch supports basic and clinical studies concerned with the etiology, pathophysiology, therapy, and follow-up of conditions associated with the perinatal and neonatal period, including adaptation to extrauterine life, hyperbilirubinemia, and sequelae of prematurity, such as asphyxia, respiratory distress, bronchopulmonary dysplasia, hypoglycemia, anemia, and infection. In addition to the PPB, other NICHD Branches and NIH Institutes support neonatal research. Funded projects share the common aim of clarifying neonatal physiology and pathology to permit further developments in the care of these infants.

Cochrane Neonatal Review Group (CNRG)

The NICHD has funded the contract with CNRG since 1995, to provide systematic reviews of randomized controlled trials in neonatal medicine. The reviews are posted on the NICHD Web site (*http://www.nichd.nih.gov/cochrane/cochrane.htm*). The latest Cochrane Library Volume (V1, 2004) contains 169 completed reviews, the same number as in the main Cochrane Library. All reviews are performed by experts who are identified by four international editors at no cost to the NICHD. The CNRG ranks second in the total number of reviews produced for the prestigious Cochrane Collaboration. The Neonatal Cochrane Reviews have played an important role in developing policies of professional academic societies. It is a popular site for health care professionals; in fact, it is one of the most frequently visited pages on the NICHD Web site.

THE COCHRANE COLLABORATION®

Bilirubin, Jaundice, and Brain Injury

Many pathological states in the fetus and newborn lead to jaundice, a condition often seen even in healthy infants because of transient developmental immaturity of liver. Branch-supported studies have helped to understand the basic biochemistry and photobiology of bilirubin, decipher the mechanism of cell injury with elevated bilirubin, and explore the value of new and evolving treatments for jaundice, such as heme oxygenase inhibitors. Among the latter, PPB-supported studies have shown that tin-mesoporphyrin is safe and effective in reducing bilirubin load in experimental animals and human infants. This avenue of therapy is currently being explored in large-scale clinical studies (*J Perinatol* 2003; 23:123-7; and *J Mol Med* 2002; 80:655-64).

Hypoxia and the Fetus

Blood vessels in the developing fetal brain respond to hypoxia (low oxygen levels) differently than do adult blood vessels. Defining the pathological mechanisms of hypoxia is crucial to understanding certain conditions in the fetus and the infant, such as intracranial hemorrhage seen in hypoxia and other brain injuries. NICHD-supported investigators have developed a unique model system of fetal hypoxia that relies on high altitude to test its effects on the development of fetal brain and cardiovascular systems.

By using the innovative "patch-clamping" technique, in which electric current changes in single-ionic channels of biologic membranes can be studied under experimental conditions, researchers showed that blood vessels in different parts of the body respond differently to the same levels of hypoxia. Furthermore, the research indicated that a variety of nutritional factors, extracellular chemical signals, and molecular signals control and modulate hypoxic responses. By understanding the underlying mechanisms of certain disease conditions in newborns, researchers may be able to mediate their effects and determine how they impact the developmental origin of adult diseases.

Neonatal Pain and Pain Control

The Branch funded a large, multicenter, controlled trial of prophylactic, preemptive analgesia to reduce or control pain in high-risk newborn infants (24 to 32 weeks' gestation) who were receiving mechanical ventilation support. The findings of this study show that preemptive analgesia markedly reduced pain experience, but also increased the incidence of adverse side effects (*Lancet* 2004, 363:1673-1682). Researchers found a strong correlation between the need for any analgesic support and poor outcome. The study also concluded that continuous infusion of opioid analgesic was associated with more systemic side effects than intermittent use of the same, as clinically needed. These findings will have a significant impact on clinical practice.

Fetal Erythropoeisis

Many pathological conditions, including fetal anemia and hypoxia (low oxygen concentrations), may lead to low oxygen levels or anemia in the developing fetus; in response, both the fetus and placenta produce erythropoietin (EPO) to restore fetal red blood cells. To understand the mechanisms of these physiological adjustments, a group of researchers supported by the PPB examined how and to what extent the genes producing EPO were expressed in the fetal tissue of sheep. Their work showed that, during hypoxia, the fetal kidneys increased the secretion of EPO by seven-fold and the placenta by 15-fold; at the same time, both the amnion and chorion actively participated in producing EPO, but this response was not sustained if the hypoxia was prolonged. In addition to augmenting knowledge of the mechanisms of homeostatic adjustments and fetal and placental regulation of overall well-being, these studies have implications for potential treatment of anemic fetuses (*J Soc Investig* 2002; 9:75-79; and *Am J Obstet Gynecol*, In press).

Fetal Insulin Adaptation Responses

Accumulating evidence supports the hypothesis that adult-onset coronary artery disease, diabetes, and hypertension may have developmental origins. For instance, it is known that when the fetal supply of glucose and other nutrients is deficient, the fetus does not grow adequately. Thus, abnormal fetal metabolism of glucose may be related not just to poor fetal growth, but also to adult onset of diabetes. A number of Branch-supported investigators are studying fetal endocrine functions and their relationships to glucose homeostasis, specifically those related to fetal insulin production, the size of the pancreatic islet cells, and factors affecting fetal growth. One group of researchers studying how pancreatic cells respond to changing blood glucose levels in fetal sheep found that exposure to hypoglycemia for 14 days, with subsequent recovery to normal blood glucose levels, led to a weaker insulin response in subsequent challenges or hypoglycemia as compared to adult controls. The sheep fetuses subjected to chronic starvation were not able to respond to glucose infusion by producing insulin. This lack of insulin response may underlie the origin of diabetes in later life. These findings strongly indicate that programming of pancreatic insulin-secretion responsiveness can occur in fetal life, predisposing to type 2 diabetes in adult life. (*Placenta* 2004; 25:70-7; and *J Physiol* 2003; 15:95-105).

Normal and Abnormal Development of Brain Blood Vessels in the Fetus and Newborn
It is known that the cerebral arteries receive a large fraction of cardiac output because of high brain metabolism; however, the mechanisms that control metabolic rate and blood flow are not well understood. Many chemical messengers are involved in mediating such responses. Using a variety of developmental animal models, PPB-supported researchers have shown that endothelium-dependent relaxation is depressed in immature cerebral arteries. Such depression, they found, involved attenuation of endothelial sensitivity to shear-stress (the force of blood circulating in arteries) in the neonate, resulting from a decrease in the specific activity of endothelial NO synthase (eNOS) in fetal arteries, a situation not present in adult arteries (*Arch Physiol Biochem* 2003; 111:36-44; *J Physiol* 2003; 549:625-33; *High Alt Med Biol* 2003; 4:203-13; and *J App Physiol* 2003; 94:724-32).

These results suggest that maturation has a dramatic influence on the relative balance of different components of the endothelium-dependent vasodilator pathway. Understanding the molecular mechanisms through which postnatal maturation of blood vessels occurs is crucial to deciphering the complexities of growth and maturation. Further, elucidation of the key roles played by hormones and growth factors are critical to understanding the fundamental biology of growth and development. This line of work provides a glimpse into how such regulations evolve and offers an avenue to test new strategies for clinical management of neonatal vascular pathologies. Such knowledge will also enhance understanding of fetal origins of adult cardiovascular disorders (*High Alt Med Biol* 2003; 4:203-213).

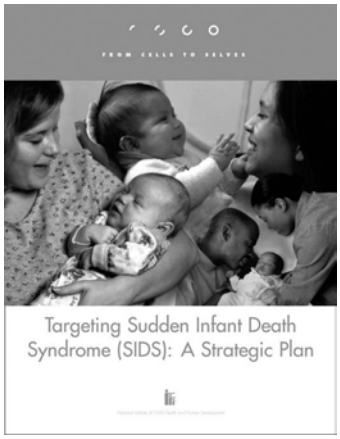
Blood Vessels in the Lungs of Newborn Infants
Normal functioning of the blood vessels in the lungs of newborn infants is critical for healthy transition from the fetal to neonatal period and beyond. Infants who have persistent pulmonary hypertension (PPHN) experience poor outcomes and are at risk for problems later in life. Research by NICHD-supported scientists is helping explain the mechanisms of PPHN in newborns as a way to improve the infants' outcomes. The research showed that the increase in pulmonary blood flow normally occurring at birth is related to an increase in synthesis and release of adenosine triphosphate (ATP), which is made in response to increasing levels of oxygen in the blood of normal infants. ATP released into the plasma not only acts as a signal to increase the pulmonary blood flow, but also interacts with NO synthase (NOS) to stimulate NO release into the pulmonary circulation; researchers found that, in models of PPHN, this mechanism was altered. Instead of replying on NOS, in PPHN, other enzymes were involved in the release of superoxide, a vasoconstrictor. These findings may uncover possible therapeutic agents that can help correct the imbalance in NOS function that occurs in PPHN (*Am J Physiol Heart Circ Physiol* 2003; 285:H204-11).

Neonatal Lung Injury
PPB-funded investigators are working to understand factors that enhance fetal and neonatal lung injury from inflammatory mediators in premature animals and to develop treatment strategies that will reduce the development of bronchopulmonary dysplasia, a chronic lung disease seen in a large proportion of surviving, extremely premature infants. Researchers induced amniotic fluid inflammation in pregnant sheep using endotoxin and delivered the lambs on the 130th day of gestation (equivalent to 34 weeks of human pregnancy); the fetal lambs were delivered and were supported by various ventilatory strategies. The results showed that endotoxin-exposed lungs required higher ventilation pressures, although ventilation, per se, did not increase lung injury.

However, the trachea and lungs of the ventilated and antenatal endotoxin-exposed animals contained six-to-12 times more inflammatory cells, indicating that fetal lung inflammation had a very serious effect on the developing immature lungs (*Am J Physiol Lung Cell Mol Physiol* 2004; 286; 3:L573-9).

The same group of investigators is trying to determine whether continuous positive airway pressure (CPAP) can reduce the need for mechanical ventilation in preterm infants as a strategy to minimize lung injury. They studied premature lambs randomized to: no ventilation, conventional mechanical ventilation, or CPAP. The CPAP lambs breathed without distress and maintained normal blood carbon dioxide levels; their lungs also held more air compared to the ventilated lambs. Lung washing revealed about seven times more neutrophils (inflammatory cells) in ventilated lambs when compared to unventilated and CPAP lambs. These findings suggest that early CPAP may be a safe strategy to support infants with lung disease, rather than implementing early positive pressure ventilation (*Pediatr Res* 2002; 52; 3:387-92).

SIDS RESEARCH



In 1999, PPB staff initiated a planning process for the Institute's third, five-year strategic plan on SIDS research. A working group composed of distinguished scientists and health care professionals from around the country, in collaboration with staff from the PPB and other NICHD Branches, identified research objectives and strategies designed to achieve these objectives. The group drew on previous and ongoing planning efforts, conferences, workshops, and research findings to develop *Targeting Sudden Infant Death Syndrome (SIDS): A Strategic Plan*, a public health agenda that would guide the Institute's research over the next five years. Like all NICHD strategic plans, the draft plan was placed on the NICHD Web site for public comment. The final plan was published in the summer of 2001, and is available on the NICHD Web site at: *http://www.nichd.nih.gov/strategicplan/cells/SIDS_Syndrome.pdf*.

The plan is divided into four topics: Etiology and Pathogenesis, Prognostics and Diagnostics, Health Disparities, and Prevention/Intervention. Each topic contains a statement of the problem, background information, and specific recommendations designed to address gaps in the current knowledge and intervention activities and to correct deficiencies in basic scientific infrastructure. The following sections outline some of the Branch's accomplishments within three of these topic areas since 1999.

Etiology and Pathogenesis

Understanding the pathogenic mechanisms of SIDS requires a multidisciplinary approach and involves the analysis of postmortem tissue and death recordings, as well as modeling potential environmental and physiological pathways in animals and infants. Over the past four years, research has significantly expanded knowledge about autonomic nervous system abnormalities in infants who succumb to SIDS.

In earlier work, researchers had observed decreased binding of acetylcholine and kainate to receptors in the arcuate nucleus of SIDS infants, suggesting that the number of these neurotransmitter receptors was decreased. The arcuate nucleus region, on the ventral brainstem, is believed to control chemoreception and cardiorespiratory and cardiovascular responses and is linked to other brain regions that control arousal from sleep. It has been hypothesized that SIDS infants lack the ability to respond to life-threatening hypercapnic, hypoxic, hyperthermic, and/or cardiovascular episodes that occur during sleep. Researchers have now observed deficiencies in the serotinergic receptors in the arcuate nucleus, as well as in the n. raphe obscurus, inferior olive, n. paragigantocellularis, and the n. gigantocellularis regions of the brain *(J Neuropathol Expt Neurol* 2000; 59:372-384). The deficits were not observed in brainstems of infants who died from other causes. These results suggest that the scope of the neurochemical abnormalities in SIDS infants is greater than previously expected and that these abnormalities involve several functionally related nuclei derived from the rhombic lip. These regions develop from the rhombic lip in early gestation. Further studies have shown that they are connected by a communicating neuronal pathway that is present by mid-gestation. A special tract-tracing dye was injected into one of the fetal brainstem regions in the rostral ventral medulla (RVM) and later appeared in all six areas that were observed to have deficits in serotonin receptors in the SIDS infants (*Autonomic Neurosci* 2001; 89:110-124). This information supports the theory that the development of a life-sustaining brainstem pathway may be altered during gestation in infants who later succumb to SIDS.

Another PPB-supported program project has developed a piglet model to study the role of ventral brainstem regions in cardiorespiratory and cardiovascular responses to potentially life-threatening environmental stimuli that occur during sleep. The investigative team has been focusing on arcuate nucleus homologues in the RVM. Using muscimol to inhibit the RVM and stimulate gamma-aminobutyric acid receptors, researchers found that the breathing response to elevated carbon dioxide was inhibited while the animals were awake and asleep; the effect was greatest during sleep (*JAP* 2001; 90:971-980). These data provide evidence that the RVM contains neurons critical to the piglet's response to elevated carbon dioxide.

In addition, the investigators obtained the first evidence that the RVM contains neurons that are involved in the regulation of sleep architecture (*Sleep* 2001; 24:514-527). When the RVM was exposed to muscimol, sleep cycling was abolished in some experimental animals; in others, there was a decrease in low-frequency electroencephalogram (EEG) activity and delta power, reflecting a decrease in the depth of quiet sleep. Resting respiration, blood pressure, heart rate or ventilation, and their modulation by state were unaffected. These investigators have also developed a sensitive, automated method to score sleep arousals (*Sleep* 2001; 24:499-513) that is being applied to analyses of infant polysomnograms collected in the Collaborative Home Infant Monitoring Evaluation (CHIME) Study (see page 28 for more details on this study).

Sleeping on the stomach increases the risk of SIDS, but the exact reason for this increase is unknown. One theory on the hazard of stomach sleep position relates to an inability to respond to elevated carbon dioxide and low oxygen levels during sleep. Laboratory studies show that infants who sleep on their stomachs bury their faces or heads in bedding, which causes them to re-breathe inspired air low in oxygen (*JAP* 2001; 91:2537-2545). Under these conditions, infants experience an increased frequency of oxygen desaturation in the blood. Some infant responses did not successfully get them fresh air; these infants experienced greater desaturations that required intervention (*Pediatrics* 2002; 111:e328-e332).

Studies of animals that were deprived of oxygen have shown that the low blood oxygen concentration results in a rapid decrease of oxidative metabolism in tissues, which leads to bradycardia, apnea, and hypoxic coma. To alleviate this decrease, the animals initiate a gasping (large breaths) response; if the gasp provides enough oxygen to the heart and lungs, the cardiovascular function rapidly improves, resulting in "autoresuscitation" and rapid recovery. Analyses of home monitor recordings from infants who died of SIDS and from other causes showed that hypoxic gasping takes place immediately before death; but, the infants who succumbed to SIDS were distinct in that they had more double and triple gasps. Most of the non-SIDS cases showed evidence of return of cardiovascular function and partial or complete autoresuscitation prior to death. Among the SIDS cases, only one infant showed a transient increase in heart rate following a gasp, and none of the infants had evidence of complete resuscitation. These results suggest that infants who die of SIDS may have a deficit in the circulatory or other components of the autoresuscitation mechanism (*Pediatr Pulmon* 2003; 36:113-122).

Another theory about the potential risk of the stomach sleep position relates to sleep state. Infants who sleep on their stomachs spend more time in quiet sleep (deep sleep characterized by fewer awakenings and an increased arousal threshold) and less time in active sleep compared with those who sleep on their backs. PPB-supported researchers at Columbia University have found that, after a feeding (the post-prandial period), infants enter a period of quiet sleep. In infants who sleep on their stomachs, the duration of this quiet sleep period increases with the level of carbohydrates in the diet (*Pediatr Res* 2002; 52:399-404); the growing infant expends a lot of energy to absorb these nutrients during the post-prandial period. The energy expenditure that results from absorption and from being in a stomach sleep position may put too much demand on thermoregulation and cardiovascular regulation, resulting in SIDS.

Although the risk for SIDS does not appear to have a large genetic component, some deaths diagnosed as SIDS may have defined causes that are genetic in origin. For instance, genetic defects in fatty acid oxidation may account for 1 percent to 2 percent of SIDS cases. A recent finding also observed that 2 percent of a prospective population of SIDS cases had an identifiable genetic defect in the cardiac sodium-channel gene SCN5A that disturbed channel function. Follow-up studies supported by the PPB are investigating all sodium- and potassium-channel genes implicated in long Q-T syndrome, a set of abnormalities that predispose a person for heart arrhythmia, and their relationship to SIDS. Analysis of one mutation in SCN5A, detected in an infant with long Q-T syndrome who died suddenly, showed that the loss of sodium-channel function was due to a trafficking defect, which prevented the channel protein from reaching the plasma membrane within the cell. The investigators also identified polymorphisms within the gene that restore the loss of function due to the mutation (*Physiol Genomics* 2003; 12:187-193).

Prevention/Intervention

In 1994, the NICHD formed a partnership with the AAP, the SIDS Alliance, the Association of SIDS and Infant Mortality Programs, the Maternal and Child Health Bureau at the Health Resources and Services Administration, and other organizations to launch a public health education campaign that would educate caregivers about reducing the risks of SIDS—the *Back to Sleep* campaign. The campaign's main message at the time was that healthy babies should be placed on their backs or sides to sleep to help reduce the risk of SIDS. In 1996, the AAP revised its sleep position statement to recommend the back sleep position as preferred over the side position. Epidemiological studies have shown that side sleeping confers about twice the risk for SIDS relative to back sleeping, in part because babies are likely to roll from their sides to their stomachs. The *Back to Sleep* campaign materials were revised to reflect this change.

In order to evaluate changes in infant care practices in response to the AAP recommendation and the *Back to Sleep* campaign, the NICHD has supported two surveys. The first, the National Infant Sleep Position (NISP) Study, initiated in 1992, is annual telephone survey of nighttime caregivers in households with infants younger than eight months of age. Since the study began, NISP has documented a decline in the number of infants placed to sleep on their stomachs that correlates with the decline in SIDS rates. Furthermore, analyses of the nighttime caregiver surveys between 1994 and 1998 (*JAMA* 2000; 283:2135-2142) showed that physician recommendation was the single strongest influence on caregiver choice of sleep position, independent of sociodemographic characteristics of the mother. However, the analyses also showed the strongest probability of back sleep position when the caregivers reported exposure to the recommendation from multiple sources, including the hospital nurse, the baby's physician, magazines and newspapers, and radio and television. By the spring of 2000, 66 percent of nighttime caregivers surveyed placed babies on their backs to sleep, while 14 percent placed them on their stomachs to sleep. Correspondingly, the SIDS rate in the United States dropped from 1.2 deaths per 1,000 live births in 1992, to 0.6 deaths per 1,000 live births in 2000.

The NISP study is also providing important information about other infant care practices. For instance, if an infant sleeps on an adult bed alone or with anther person, the practice is hazardous because it can lead to entrapment, overlay, and suffocation. Bed sharing with other children is known to increase SIDS risk, but controversy remains regarding the risk associated with sharing a bed with a parent. On average, almost half of infants in the survey population spent at least some time at night on an adult bed within two weeks of being surveyed. Between 1993 and 2000, the proportion of infants usually sharing an adult bed at night increased from 5.5 percent to 12.8 percent. Factors that independently increased the probability of usual bed sharing included young maternal age, maternal race reported as African American or as Asian/other, household income of less than $20,000 annually, and infant age younger than eight weeks. NISP data also showed that bed-sharing infants were almost twice as likely to be covered by a quilt or comforter than infants who did not share an adult bed; research shows that a quilt or comforter in the bed-sharing environment is a potential hazard for SIDS if the baby's face or head gets covered (*Arch Pediatr Adolesc Med* 2003; 157:43-49). More research is needed to understand the range of bed-sharing practices, motivations, and potential benefits or hazards.

When the AAP recommendation about back and side sleeping was first issued in 1992, one of the concerns was that infants placed on their backs or sides to sleep may be at risk for adverse health effects other than SIDS, particularly those due to aspiration or choking. To investigate these risks, the NICHD initiated the second of its evaluation studies, the Infant Care Practices Study (ICPS), a longitudinal, prospective study of more than 15,000 mother-infant dyads enrolled at birth between 1995 and 1998 in Massachusetts and Ohio. The ICPS has provided valuable information to allay concerns about choking. When infants were one month, three months, and six months of age, the researchers questioned their mothers about sleep position and whether they had symptoms such as fever, cough, wheezing, stuffy nose, trouble breathing, trouble sleeping, and/or vomiting. Mothers of 3,733 infants reported that their infants were always placed to sleep in the same position; among these infants, researchers found that those who slept on their backs were less likely to have fevers than were infants who slept on their stomachs at one month of age. At six months old, back sleepers were less likely to develop a stuffy nose than were stomach sleepers. At three and six months old, back sleepers needed to visit the doctor less often for ear infections than did stomach sleepers. Moreover, at six months, the mothers of back sleepers reported fewer instances of infant sleeping trouble than did the mothers of stomach sleepers. None of the infants in the study were reported to have choked on their vomit (*Arch Pediatr Adolesc Med* 2003; 157:469-74).

In countries that have experienced successful risk reduction campaigns, there is a change in the contribution of risk factors to SIDS between the pre- and post-intervention periods. Between May 1997 and April 2000, the NICHD conducted a population-based, case-controlled study in 11 counties in California to evaluate SIDS risk since the initiation of the *Back to Sleep* campaign. This study provided critical evidence to support the recommendation that "back is best" for all sleep periods, and that the position should be used consistently by all caregivers. The researchers found that infants who were last placed on their sides to sleep were twice as likely to die of SIDS as infants who were last placed on their backs to sleep. In addition, the risk of SIDS was significantly increased if the infants turned from their sides to their stomachs during sleep. While the reason isn't clear, the researchers believe that the instability of the side position makes it more likely for babies to roll over onto their stomachs during sleep. When the researchers looked specifically at the position in which an infant was last placed to sleep, a pattern emerged when compared to the usual sleeping position; if an infant who was usually placed to sleep on the back was then placed to sleep on the stomach or side, his or her SIDS risk was seven to eight times greater than that of an infant who was always placed to sleep on his or her back (*AJE* 2003; 157:446-455).

Since the NICHD-led *Back to Sleep* campaign began, the rate of SIDS has declined steadily and significantly. According to preliminary figures from the National Center for Health Statistics, the SIDS rate for 2001 was about 0.5 deaths per 1,000 live births, a decline of more than 50 percent since the campaign began.

Health Disparities

Although SIDS rates have declined in all segments of the population, a significant disparity still exists between majority and minority populations. In particular, SIDS rates are two to three times higher among African Americans and American Indians compared with whites. The PPB has supported two case-controlled studies to specifically shed light on this racial disparity by examining the pattern of SIDS risk factors.

Northern Plain Indians have the highest rates of SIDS in the nation. To understand the reasons for this high SIDS rate, the PPB, in collaboration with Aberdeen Area Tribal Chairman's Health Board, the Indian Health Service, and the CDC conducted the Aberdeen Area Infant Mortality Study (AAIMS). The AAIMS identified risk factors in this population that had not previously been reported. For instance, despite reports that mothers in the study reduced their alcohol consumption significantly by their second trimester, binge drinking during the mothers' first trimester of pregnancy increased the risk for SIDS eight-fold. Any maternal alcohol use during the periconceptual period (three months before pregnancy or during the first trimester) was associated with a six-fold increase in the risk of SIDS. The study also found that infants were more likely to die of SIDS if they wore two or more layers of clothing during sleep. More positively, though, infants whose mothers were visited by public health nurses before and after giving birth were only one-fifth as likely to succumb to SIDS as those whose mothers were not visited. These data highlight the importance of health outreach to this population (*JAMA* 2002; 288:2717-2723).

The AAIMS was the first study to link epidemiological findings with neurochemical deficits in the developing human brain. The binding abnormalities in serotinergic receptors of the medullary regions of AAIMS infants were similar to those observed in SIDS cases from other populations. In addition, the serotinergic abnormalities in the arcuate nucleus in these infants were associated with exposure to adverse prenatal exposures, such as cigarette smoking ($p=0.011$) and alcohol use ($p=0.075$), during the periconceptual period or throughout pregnancy. These results suggest that these prenatal exposures may contribute to abnormal development of the fetal medullary serotinergic system in infants who die from SIDS (*J Neuropathol Expt Neurol* 2003; 62:1166-1177).

From 1993 through 1996, the NICHD and the CDC supported a case-controlled study of infant deaths in Cook County that employed standardized death scene investigation and autopsy protocols to elucidate the unique factors of SIDS deaths. In this primarily African American, urban sample, prone sleeping was found to be a significant risk factor for SIDS, after adjusting for potential confounding variables and other sleep environment factors (OR 4.0, 95% CI 1.8-8.8); approximately one-third of the SIDS deaths could be attributed to prone sleep position. Fewer case mothers of SIDS infants (46 percent) than control mothers of living infants (64 percent) reported being advised about sleep position in the hospital following delivery ($P<0.001$). Of those advised, a similar proportion of case mothers as control mothers were told to use the incorrect (stomach) position, but a higher proportion of African American mothers (cases and controls combined) were advised to use that position compared with non-black mothers (*Pediatrics* 2002; 110:772-780). Further analysis showed that, in addition to prone sleep position, a soft sleep surface, pillow use, and bed sharing in combinations other than with parent(s) alone significantly increased SIDS risk. Pacifier use significantly decreased risk (*Pediatrics* 2003; 111:1207-1214). Pacifier use has been found to be protective for SIDS in several studies worldwide, but the mechanism is unknown.

In 1999, the Institute's *Back to Sleep* campaign began a partnership with several African American organizations to develop focused, community-centered information materials and outreach to help reduce the risk of SIDS in African American communities. The NICHD, in partnership with the National Black Child Development Institute, enlisted the National Coalition of 100 Black Women, the Women in the National Association for the Advancement of Colored People, and the Alpha Kappa Alpha Sorority, Inc., to help design materials and develop an outreach plan. One of the focal events of this outreach was a series of national summit meetings hosted by each partner

organization and the NICHD, held in Tuskegee, Los Angeles, and Detroit, respectively. These summits focused the attention of the organizations' members on ways to reduce the risk of SIDS and how to effectively get safe sleep messages into their communities.

Building on the community-centered framework that was used for the African American outreach, the *Back to Sleep* campaign coordinators are designing a similar outreach component for American Indians/Alaska Natives. Planning for this outreach is still in the early phases.

BRANCH ACTIVITIES: COOPERATIVE AGREEMENTS

To respond to the need for well-designed clinical trials in maternal-fetal medicine and neonatology, the NICHD established two large-scale Networks—the NRN and the MFMU Network—as administrative frameworks in which to conduct multicenter, randomized clinical trials and other prospective clinical studies in obstetrics and neonatology. Each Network is guided by a Steering Committee, which consists of representatives from each clinical site, from the PPB, and from the data-coordinating center. These Networks allow for a timely response to urgent clinical questions in a cost-effective manner. Currently, the NRN has 16 sites, and the MFMU Network has 14 sites. Sites are selected every five years following an open competition. Typically each Network has two to three randomized controlled trials and two to three observational studies ongoing at any given time. Network investigators agree to use common protocols, definitions, and data forms and are linked by their common data centers and common data-entry computer systems. Investigators, together with the PPB and the data-center staff, develop protocols that are reviewed by Advisory Boards, external reviewers, and Data Safety and Monitoring Committees (DSMCs). The DSMCs, which are established for each Network, ensure that the trials are safe and scientifically significant.

There are several advantages to doing clinical trials within the Networks. First, the Networks provide large populations with which to conduct studies, with adequate statistical power to resolve many research questions; inadequate sample size is a common limitation of many published clinical trials. Approximately 120,000 births occur per year in the MFMU Network, and 100,000 infants are born per year in the NRN. Second, because the study population is diverse, a therapy or management strategy shown to be effective across an array of ethnic and socioeconomic backgrounds and health care settings is more likely to prove effective in real-world clinical practice. Third, the data-coordinating centers attached to the Networks have sufficient resources to assure excellent study management and data quality. Finally, the administrative systems of the Network are efficient and cost-effective. To ensure their cost-effectiveness, the Networks are funded through a combination of a minimum base budget and capitated funds for enrollment in specific protocols. New trials can be brought online relatively rapidly because the infrastructure is already in place. The Networks address the need for clinical trials in neonatology and obstetrics, especially those relating to the prevention of LBW infants (<1,500 grams) and their management. The Networks build upon contributions to the clinical trial field and are unique in that they rely, to a greater extent, on shared responsibility and commitment. The following section describes the PPB-supported Networks and other efforts funded through cooperative agreements.

NEONATAL RESEARCH NETWORK (NRN)

In 1986, the NICHD convened the first NRN, consisting of seven sites; after four competitive recompetitions, the NRN currently includes 16 sites. This scientific partnership between the PPB, the funded neonatal-perinatal divisions, and the data-coordinating center has become a strong force in neonatal research. NRN representatives present regularly at national and international scientific meetings.

Randomized Controlled Trials

Since 1999, the PPB-supported NRN has conducted a number of clinical trials.

- In 1999, the NRN conducted an innovative, factorial-design trial to evaluate whether an early 10-day period of permissive hypercapnia and/or an early 10-day stress dose of corticosteroid would reduce the incidence of death caused by chronic lung disease in extremely LBW (ELBW) infants (< 1,000 grams birth weight). The trial was halted because of safety concerns when 220 infants of the projected 1,200 required were enrolled. Early dexamethasone was found to have no effect on death or chronic lung disease and was associated with gastrointestinal perforation and decreased growth (*N Engl J Med* 2001; 344:95). Long-term outcome information is currently under review.
- The Network is conducting a trial of whole-body hypothermia for reducing death or disability in term infants with acute perinatal asphyxia at 18 months of age (n=208). Recruitment is complete, and long-term follow up of infants 18- to 22-months old is under way. Outcome information is anticipated in the next year.
- The Network recently completed a trial to evaluate the effect of parenteral glutamine supplementation on the risk of death or late-onset sepsis of ELBW infants (n=1433). Results indicate that such supplementation has no effect on death or sepsis (*Pediatrics* 2004; 113). Many secondary studies are now utilizing this important dataset to evaluate nutritional information for ELBW infants. Nutrition management remains a significant problem for this population.
- A cytokines study was conducted concurrently with the previous trial. Such measurements of cytokine values in ELBW infants may give insight into short- and long-term complications of prematurity.
- The NRN recently completed a CPAP delivery room pilot study in ELBW infants (n=103). The Network is planning a large-scale, factorial design CPAP and oxygen saturation level trial scheduled to begin later in 2004.
- The Network's first benchmark protocol to increase survival of very LBW (VLBW) infants (<1,250 grams) is ongoing.
- The Network is currently evaluating data from a trial utilizing inhaled NO in sick, preterm infants.
- A randomized trial of phototherapy for hyperbilirubinemia in ELBW infants is ongoing.

Observational Studies

In addition to clinical trials, the Network has completed a number of observational studies.

The NRN has a detailed registry, generic database, and follow-up program for infants born at ELBW. One of the most important Network efforts using these resources has been the development and implementation of a standardized follow-up protocol for evaluating outcomes of

ELBW infants at 18- to 22-month corrected age. The follow-up protocol provides the largest standardized follow-up assessment of ELBW infants to date. Highlights of published information from this study include:

- Changing pathogens from gram positive to more resistant gram negative organisms in sepsis in VLBW infants (*Pediatrics* 2002; 110:285; and *N Engl J Med* 2002; 347:240)
- Significant neurodevelopmental impairment in survivors despite significant strides in the care and management of these vulnerable infants

The Network has recently completed an observational trial of necrotizing enterocolitis (NEC) and results should be forthcoming. In addition, the NRN is about to embark on an observational trial of Candida and an observational trial of a pneumococcal vaccine conjugate.

The NRN will undergo competitive review in 2006; information on the Network is available at *http://neonatal.rti.org*.

MATERNAL LIFESTYLES STUDY (MLS)

Prenatal substance abuse continues to be a major public health problem that affects millions of children and places both financial and social burdens on society. The most recent report from the National Household Survey on Drug Abuse estimated that, in 1999, the rate of drug use among pregnant women was 3.4 percent for illicit drugs, 17.6 percent for tobacco, and 13.8 percent for alcohol.

The MLS, another PPB-supported effort, began in the early 1990s as an interagency, longitudinal study against a backdrop of debate and controversy about the effects of prenatal cocaine exposure on child outcomes. Through the NRN, researchers could access a large, multisite population of newborn infants and their mothers, allowing an in-depth, prospective study of mothers and children *in utero* exposed to cocaine. The collaborative nature of the NRN provided access to a multicultural, multiethnic, socioeconomically and demographically varied population in which widespread use of drugs was previously demonstrated.

Now in its eleventh year, the MLS is the largest clinical, prospective, longitudinal study of prenatal drug exposure and child outcomes to date. It is conducted at four NRN sites at the University of Miami, the University of Tennessee at Memphis, Wayne State University, and Brown University. The cohort includes 658 exposed and 730 comparison mother/child dyads. In addition to PPB support, the National Institute on Drug Abuse has consistently co-funded the MLS effort since it began.

In Phase I of the MLS, 19,079 pregnant mothers were recruited just before or immediately after they gave birth. Of these, 16,988 (89 percent) met basic eligibility criteria, and 11,811 (70 percent) of these agreed to participate in the study. Drug use was confirmed by an interview with the mother and by gas chromatography/mass spectroscopy for cocaine/opiate metabolites in the meconium of the infant. Based on this information, 1,185 infants (10 percent) were exposed to either cocaine or opiates during pregnancy. A total of 7,442 infants (63 percent) were confirmed as not having been exposed to either cocaine or opiates; the exposure status of 3,184 infants

(27 percent) was not confirmed. The use of alcohol, tobacco, and/or marijuana by the mother occurred in all three of these groups.

Phase II of the study tracked the development of infants who had been exposed to illicit drugs, comparing the results to infants whose mothers had not used illicit drugs. A total of 1,388 subjects were recruited for this phase of the MLS. Of these, 658 infants were exposed to cocaine, opiates, or both *in utero*, while 730 infants had been exposed to neither. All of these infants were initially assessed at one month of age; mothers or caretakers were encouraged to participate in visits at four, eight, 10, 12, 18, 24, 30, and 36 months of age. During these visits, the children participated in a variety of assessments that noted both their medical and developmental outcomes over time. Researchers also asked mothers and caretakers questions about the infant and the environment.

Mother/child dyads have continued their involvement in the MLS through subsequent phases. Phase III assessed children during visits that occurred when they were ages four through seven. Phase IV, which is now under way, includes children between the ages of eight and 11.

MATERNAL-FETAL MEDICINE UNITS (MFMU) NETWORK

In 1986, the NICHD convened the first MFMU Network, consisting of seven sites; after four competitive recompetitions, the Network currently funds 14 sites. Like the NRN, the scientific partnership between the PPB, the funded maternal-fetal medicine divisions, and the data-coordinating center has also become a strong force in the obstetric research community; Network staff present regularly at national and international scientific meetings.

Evaluations of Common Medical Practices

The MFMU Network continues to rise to the challenge of designing programs and treatments for the prevention of preterm births using evidence-based medical practices. Based on the scientific literature and the rapidly growing practice in the obstetric community of using prophylactic antibiotics during pregnancy for the prevention of poor birth outcomes, the MFMU Network designed a randomized, double-blind clinical trial to evaluate this practice. The hypothesis for this study was derived from earlier randomized studies that showed a benefit to treating asymptomatic bacterial vaginosis in women with a history of prior preterm birth, as well as studies that correlated bacterial vaginosis in pregnancy with LBW babies. This study evaluated whether treatment of asymptomatic bacterial vaginosis in low-risk women reduced the risk of preterm delivery. Almost 2,000 women in the Network were assigned to receive either an antibiotic or a placebo at 16 to 23 weeks' gestation, and again at 24 to 29 weeks' gestation. The primary outcome was delivery before 37 weeks' gestation. Surprisingly, there was no difference in the rate of preterm birth between the two groups; preterm delivery occurred in about 12 percent of pregnancies in each group (*N Engl J Med* 2000; 342:534-40). Although the results of the study were negative, the findings were important for the obstetric community in that mass screening for bacterial vaginosis in pregnancy could not be recommended. These findings also support the growing body of evidence that preterm birth is a multifactorial problem.

A study of mid-trimester endovaginal sonography in women at high risk for spontaneous preterm delivery further examined this multifactorial basis by evaluating the contribution of cervical length, as measured by ultrasound in the second trimester, to preterm labor. The study concluded

that cervical length at 16 to 18 weeks' gestation predicted spontaneous preterm delivery at less than 35 weeks' gestation in women with a prior early spontaneous delivery (*JAMA* 2001; 286:1340-1348). Thus, sonographic evaluation of the cervix identifies women at increased risk for preterm birth and may identify a subgroup of patients eligible for an intervention.

The MFMU Network also builds upon information obtained from its own studies. For example, an MFMU Network study designed to identify predictive factors for spontaneous preterm birth found that fetal fibronectin (FFN) was a promising biological marker. To elucidate this relationship, 13 Network sites conducted a randomized trial of antibiotic treatment in women who were FFN-positive (n=700) for reducing preterm births. Treatment of asymptomatic women with a positive cervical/vaginal FFN test between 21 and 25 weeks' gestational age with metronidazole plus erythromycin did not decrease the risk of spontaneous preterm delivery (*Am J Obstet Gynecol* 2000; 183:469-75).

In part due to an ongoing trial in the MFMU Network that was evaluating repeat courses of antenatal corticosteroids, in March 2000, the NIH convened a consensus development conference *Antenatal Corticosteroid Revisited: Repeat Courses*. Its purpose was to review research on repeat courses of antenatal corticosteroid therapy. The panel concluded that the available data was inadequate to recommend the repeated use of antenatal corticosteroid therapy for women at risk of preterm birth (*http://consensus.nih.gov/cons/112/112_intro.htm*). This consensus conference changed the practice patterns of many obstetricians regarding the use of antenatal corticosteroids. Further, the conclusion supported the continuation of the Network's ongoing, randomized, placebo-controlled trial of women at less than 32 weeks' gestation who were at risk for spontaneous preterm delivery (n=2,400) and remained pregnant more than one week following initial corticosteroid therapy. Following the recommendation of the DSMC, the NICHD halted the trial after enrollment of approximately 450 patients due to safety concerns suggesting lower birth weight in the treatment group, slow recruitment, and no evidence of efficacy. The findings indicate that routine weekly repetition of antenatal steroids to women at high risk for preterm birth, in order to assure maximum exposure to all preterm neonates, cannot be justified. Furthermore, exposure to weekly courses of steroids decreased birth weight and increased the risk of small-for-gestational-age neonates.

In addition, Network researchers recently released findings from a groundbreaking trial that identified a therapy for the prevention of recurrent preterm birth. They studied 463 women who had a previous preterm delivery and were, therefore, considered at high risk for recurrent preterm delivery. This randomized, double-masked, clinical trial compared the effects of weekly treatment of 17 Alpha-hydroxyprogesterone caproate (17P) versus placebo injections on preventing preterm birth in women at high risk for preterm birth. Importantly, the trial showed that showed that 17P treatment reduced preterm birth by 34 percent in this population. Women who received weekly 17P injections starting at 16 to 20 weeks' gestation had a significantly reduced risk of preterm delivery before 37, 35, or 32 weeks' gestation when compared to women who received placebo injections. Further, among those who did deliver preterm, infants of women treated with 17P had significantly lower rates of severe complications. Treatment was equally effective in African American and non-African American subjects (an important consideration because the preterm birth rate is two-fold higher in African Americans) and showed benefit in preventing spontaneous and indicated preterm births. 17P is the first successful treatment demonstrated to reduce the risk of recurrent preterm delivery in a subset of high-risk women and to improve neonatal outcomes for

infants born to these women (*N Engl J Med* 2003; 348:2379-85). Further studies to determine whether this treatment can be used for other populations of pregnant women at high risk for preterm delivery, such as those with multiple gestations and women with short cervical length, are currently being planned.

The rate of cesarean delivery has risen dramatically over the past two decades; in fact, cesarean delivery currently ranks as the most commonly performed surgical procedure. A substantial portion of women who undergo a cesarean delivery have a history of a previous cesarean delivery, but some women who have had a previous cesarean deliver their infants vaginally. Evidence about the risks and benefits of vaginal birth after cesarean (VBAC) that would assist the obstetrician in counseling women with a history of a prior cesarean delivery is not current and is generally derived from small studies. The MFMU Network thus chose to use its large patient population to study the outcomes of VBAC, including information on complications, fetal injury, and contributing factors. The MFMU Cesarean Registry, completed in December 2002, includes observational data on more than 52,000 primary and repeat cesarean deliveries and more than 18,000 VBAC deliveries. This landmark study provided the largest resource of information on cesarean deliveries collected in a standardized, prospective fashion by trained study personnel. The study found that women who attempted trial labor had significantly higher rates of maternal morbidity (i.e., uterine rupture, endometritis, and transfusion) and neonatal complications (i.e., hypoxic-ischemic encephalopathy) compared with women undergoing an elective repeat cesarean delivery.

In another study, the Fetal Pulse Oximetry (FOX) trial, the Network is studying the utility of fetal pulse oximeter during labor under an Investigational Device Exemption through the FDA. The goal of this randomized, controlled trial is to determine if fetal pulse oximetry during labor affects the overall cesarean delivery rate, or the rate of cesarean delivery for fetal distress, in women with a singleton gestation who experience labor at more than 36 weeks' gestation. Current recruitment is approximately 3,000 patients; researchers anticipate that the sample size of 10,000 will be enrolled prior to the start of the next Network cycle (April 2006).

To address the question of the benefit of screening and treatment for GDM, the MFMU Network is conducting a randomized clinical trial to test the hypothesis that daily self blood glucose monitoring and diet therapy reduces neonatal morbidity in women with mild GDM. The primary outcome composite includes hypoglycemia, hyperinsulinemia, hyperbilirubinemia, birth trauma, death, or stillbirth.

A Spirit of Trans-NIH Collaboration

As the PPB-supported MFMU Network has grown and developed, additional expertise and funding for large studies has come from other NIH Institutes. The first of these trans-NIH collaborations, with the NHLBI, set out to address the growing numbers of pregnant women with asthma and the lack of evidence-based information about how best to treat them. This observational study of 3,000 pregnant women with mild and moderate asthma was completed in March 2000. The study found that, except for an increased incidence of discharge diagnoses of neonatal sepsis, asthma and its contemporary management were not associated with adverse perinatal outcomes (*Obstet Gynecol* 2004; 103:5-12).

Nested within this observational study, the MFMU Network conducted a randomized trial of theophylline versus inhaled steroids to treat moderate asthma during pregnancy. The objective was to determine if prolonged anti-inflammatory therapy with inhaled corticosteroids would result in better control of moderate asthma during pregnancy. Despite its greater anti-inflammatory effects, beclomethasone treatment of persistent asthma resulted in similar rates of asthma exacerbations requiring intervention and similar pregnancy outcomes as treatment with theophylline (*Am J Obstet Gynecol* 2004; 190:737-44).

The NHBLI also provided funding to the MFMU Network to conduct the Combined Antioxidant and Preeclampsia Prediction Study (CAPPS) for the prediction and prevention of preeclampsia. This randomized, controlled trial is designed to determine if antioxidants (vitamins C and E) can prevent preeclampsia in low-risk women (n=10,000). In addition, the observational component of the trial is designed to identify markers that may predict preeclampsia. Initiated in 2003, CAPPS is just getting under way.

The MFMU Network is collaborating with the NINDS on a randomized trial of the beneficial effects of antenatal exposure to magnesium sulfate for the prevention of cerebral palsy. This trial is based on case-control studies that identified magnesium sulfate as protective against the development of cerebral palsy. This double-blind, randomized trial involves more than 2,000 women at high risk of delivering very preterm (less than 32 weeks of gestation, a major risk factor for cerebral palsy). All of the children will be followed for two years with the primary outcome of developmental tests at age two correlating with the diagnosis of cerebral palsy. Recruitment into the trial is expected to end in May 2004, with data expected by fall of 2006.

The NIH ORWH has also supported the MFMU Network, specifically in funding studies of pharmacokinetics in recognition of the widespread use of medications during pregnancy that are not studied for such use. Pregnant women are often excluded from clinical trials, resulting in product labeling that does not address pregnancy dosage, safety, or efficacy; as a result, providers often prescribe drugs off-label. These funds were an attempt to address the common clinical practice of off-label drug administration. ORWH support was distributed to MFMU Network sites that submitted proposals for pharmacokinetic studies of certain drugs in pregnancy.

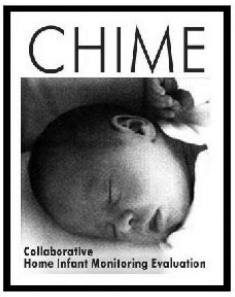
In addition, the ORWH supported the MFMU Network's Factor V Leiden study, conducted to determine the incidence of pregnancy-related thromboembolism in women carrying the Factor V Leiden mutation, a genetic factor that has been associated with an increased risk for thromboembolic events. Initially, this study was proposed as an interventional trial of heparin versus placebo in women with the Factor V Leiden mutation, but Network researchers felt that baseline data for the mutation's effect on risk for a thromboembolic event in pregnancy was needed before an interventional trial was undertaken. In this prospective, observational, multicenter study, 5,188 low-risk nulliparous pregnant women were enrolled and tested for the mutation. The trial showed that the Factor V Leiden mutation did not increase risk of thromboembolic events or adverse pregnancy outcomes. The interventional trial was not undertaken, then, and this population of low-risk nulliparous women with the Factor V Leiden mutation does not require prophylactic treatment in pregnancy.

The June 2003 issue (Volume 27) of *Seminars in Perinatalogy* was devoted exclusively to the MFMU Network, highlighting its history, trials, findings, and impact in the field in the following articles:

- Meis P, Spong C, and Thom EA (Eds). Introduction. (183-4)
- Goldenberg RL, Iams JD, Mercer BM, Meis, P, Moawad A, Das A, Copper R, and Johnson F for the NICHD MFMU Network. What we have learned about the predictors of preterm birth. (185-193)
- Iams JD and Owen J for the NICHD MFMU Network. What we have learned about cervical ultrasound. (194-203)
- Iams JD for the NICHD MFMU Network. What we have learned about uterine contractions and preterm birth. The HUAM Prediction Study. (204-211)
- Carey JC and Klebanoff MD for the NICHD MFMU Network. What we have learned about vaginal infections and preterm birth. (212-216)
- Mercer BM, Goldenberg RL, Das AF, Thurnau GR, Bendon RW, Miodovnik M, Ramsey RD, and Rabello YA for the NICHD MFMU Network. What we have learned regarding antibiotic therapy for the reduction of infant morbidity after preterm premature rupture of the membranes. (217-230)
- Andrews WW and Goldenberg RL for the NICHD MFMU Network. What we have learned from an antibiotic trial in fetal fibronectin positive women. (231-238)
- Sibai BM, Caritis S, and Hauth J for the NICHD MFMU Network. What we have learned about preeclampsia. (239-246)
- Iams JD and Mercer BM for the NICHD MFMU Network. What we have learned about antenatal prediction of neonatal morbidity and mortality. (247-252)
- Thom E and Rouse D for the NICHD MFMU Network. What we have learned about conducting randomized controlled trials in the NICHD MFMU Network. (253-260)

The MFMU Network will be recompeted in 2006; more information on the MFMU Network is available at *http://www.bsc.gwu.edu/mfmu/*.

THE COLLABORATIVE HOME INFANT MONITORING AND EVALUATION (CHIME) STUDY



The CHIME Study, now complete, was a multicenter, cooperative study of home monitoring of high-risk infants. Almost 1,200 infants were enrolled in the following subject groups: healthy term infants; preterm infants weighing less than 1,750 grams; and siblings babies who died of SIDS or experienced an idiopathic apparent life-threatening event. The objectives of the study were to:

- Determine whether home apnea monitors that employed event recordings were effective in identifying episodes dangerous to infant health
- Determine the conditions that optimized the use of apnea monitors in high-risk infants
- Correlate physiological markers, health status, and behavior with the propensity for life-threatening events
- Provide important information on the maturation of heart and respiratory functions in sleeping infants

The PPB, CHIME investigators, and industry collaborated in the development of a new monitoring technology, which was being tested for its potential to detect and record life-threatening cardiorespiratory episodes. The technology incorporated new, advanced computer capabilities, inductance plethysmography, electrocardiogram (ECG), pulse oximetry, and an accelerometer to detect motion and infant position. In addition to event recording, which captured the physiology for a period before, during, and post-event, monitors were programmed to store continuous R-R intervals from the ECG, continuous breath-breath intervals, and normative three-minute epochs at hourly intervals.

One analysis of these data showed that 80 percent of the apneas that the CHIME monitor identified as obstructed were supported by either nasal end-tidal carbon dioxide measurements, or nasal/oral thermistor measurements (*American Journal of Respiratory and Critical Care Medicine* 2000; 162:471-480). Therefore, with the new home-monitoring technology to measure obstructed breaths, the longitudinal monitoring records collected during sleep periods in the CHIME study provide an opportunity to analyze physiological events not previously recorded in the home.

A major analysis of CHIME data showed that cardiorespiratory events (i.e., apnea and bradycardia) that met conventional alarm thresholds were quite common, even in healthy term infants (*JAMA* 2001; 285:2199-2207). More severe events were common only in preterm infants, and their timing suggested that they were not likely immediate precursors to SIDS. In addition, the data suggested that conventional monitoring techniques would likely miss most of the cardiorespiratory events detected in the study subjects because the events had a high frequency of obstructed breathing. The AAP Committee on Fetus and Newborn used this information in drafting its policy statement, *Apnea, Sudden Infant Death Syndrome, and Home Monitoring* (*Pediatrics* 2003; 111:914-917). In addition, analyses of the CHIME Study data have been used to develop scoring algorithms for cardiorespiratory recordings and polysomnograms. An *Atlas of Infant Polysomnography* was published by CHIME Study investigators and is a valuable resource for researchers and clinicians.

The CHIME database, which includes all raw physiological records and study forms was recently transferred to CD-ROM; in January 2004, the entire database became accessible to researchers at *http://dccwww.bumc.bu.edu/ChimeNisp/*.

NEW PPB-SUPPORTED NETWORKS

In addition to the aforementioned Networks and studies, the PPB initiated four new networks since its last report to the NACHHD Council. These new projects are highlighted below.

Maternal Fetal Surgery Network

In 2001, the PPB created the Maternal Fetal Surgery Network to evaluate *in utero* surgery as a treatment for antenatally diagnosed spina bifida in a randomized clinical trial. The Management of Meningomyelocele Study (MOMS) trial includes three sites: the Children's Hospital of Philadelphia, the Vanderbilt University Medical Center, and the University of California at San Francisco. The PPB provides additional oversight and guidance, and the George Washington Biostatistics Center serves as the data center for the

Network. This collaborative, five-year, multicenter trial is comparing the safety and efficacy of fetal surgical repair and traditional postnatal repair of open neural tube defects. For more information on the MOMS trial or on the Network, visit *http://www.spinabifidamoms.com/english/index.html*.

Community Child Health Research Network (CCHN)

The CCHN represents Phase I of a community-linked research effort on maternal and child health. Through cooperative agreements, the community-linked Network will work over a three-year span to plan a multisite, multilevel study that examines how community, family, and individual-level influences interact with biological influences to result in health disparities in pregnancy outcomes and in infant and early childhood mortality and morbidity. The goal of the Phase I research program is to blend substantive theory, measurement regimes, and study designs found in the biomedical, social, and behavioral sciences into a study of infant mortality and child health. Findings garnered from this study will improve understanding of the complicated interplay of environmental and genetic factors that produces biological outcomes in high-risk minority populations.

The current products of Phase I include a plan of action that describes the hypotheses, design, and content of a multisite, multilevel study, as well as preliminary work at each site that will provide a foundation upon which to build such a Network. The CCHN includes five collaborating sites, each one a partnership between an academic institution and community institutions, and staff from the PPB, from the NICHD Demographic and Behavioral Sciences Branch, and from the National Institute on Nursing Research. The CCHN has made progress toward its core hypotheses, methods development, and study design. One of the foci of the research enterprise will be to improve family heath in the interconceptional period as a means to improve the outcomes of future pregnancies.

Prenatal Alcohol in SIDS and Stillbirth (PASS) Network

In 2003, the NICHD and NIAAA began funding four cooperative agreements to create a Network that would develop 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, and how they may be interrelated. The PASS Network is composed of two comprehensive clinical sites, a developmental biology and pathology center, and a data coordinating and analysis center. Investigators will work collaboratively with the PPB and the 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 comprehensive clinical sites will be working with Northern Plains Indian communities and with populations in the Western Cape of South Africa. In the long term, this initiative aims to decrease fetal and infant mortality and to improve child health in these communities.

Stillbirth Collaborative Research Network (SCRN)

Stillbirth, defined as death at 20 weeks' gestation or greater, account for a large proportion of perinatal mortality. According to annual national vital statistics, the number of fetal deaths at 20 weeks or more gestation, including stillbirths, is similar in magnitude to the total number of infant deaths in the United States. In 2001, there were 27,568 infant deaths, and 26,373 fetal deaths. More than half of the fetal deaths occurred at 28

weeks' gestation or more, and 20 percent, or about 5,000 cases, were at term gestation. In addition, the cause of about half of all stillbirths is undetermined.

On March 26, 2001, the PPB convened a workshop with experts in the field to set a national agenda for stillbirth research. Participants identified gaps in current knowledge that hamper progress in this field, as well as problems associated with current data on stillbirths in the United States, including:

- Fetal death reports are voluntary, and under-reporting of stillbirths may be as high as 10 percent to 15 percent;
- Variability exists in the quality and completeness of fetal death certificates, including identification of the cause of death;
- No standard protocol is available for postmortem investigation of stillbirths, including serologic, toxicologic, and genetic tests;
- Although placental pathology is common, fetal autopsy rates are low; and
- Few geographic, population-based, detailed investigations of reproductive and fetal risks associated with stillbirth are available.

To begin to address these gaps, the PPB issued *Research on the Scope and Causes of Stillbirth in the United States* (RFA-HD-02-025), to create a Network of clinical research sites with a central data collection and analysis resource for developing and implementing common research protocols to study stillbirth (defined as fetal death at 20 weeks' gestation or more). The objectives of the initiative are to:

- Develop a standard stillbirth postmortem protocol that includes review of clinical history, protocols for autopsies, pathologic examinations of the fetus and placenta, and other postmortem tests to illuminate genetic, maternal, and other environmental influences.
- Obtain a geographic, population-based determination of the incidence of stillbirth, its causes, and risk factors via a geographic, population-based study of stillbirths enrolled at the time of demise and a sub-cohort, case-controlled study.

The awards for the SCRN were made in September 2003, to the following clinical investigators and research sites: Dr. Marshall Carpenter, Women and Infants Hospital of Rhode Island, Providence; Dr. Donald Dudley, University of Texas Health Sciences Center, San Antonio; Dr. George Saade, University of Texas Medical Branch, Galveston; Dr. Robert Silver, University of Utah, Salt Lake City; Dr. Barbara Stoll, Emory University, Atlanta; and Dr. Corette Parker, Statistical Center at Research Triangle Institute, Raleigh. Investigators have made progress made toward the development of a standard postmortem protocol, as well as of protocols for surveillance and investigations into the associated risks and mechanisms of death.

BRANCH ACTIVITIES: TRAINING AND CAREER DEVELOPMENT PROGRAMS

The Branch supports research training and career development through various award mechanisms. The success rate for training and career awards has been very favorable, ranging from 40 percent to 70 percent. The number of applications received and awarded, and the corresponding success rate for each type of mechanism during fiscal years 2000 through 2003 is outlined in Table 2. In general, PPB training and career development awards for this period include:

- Four new National Research Service Award Predoctoral Fellowship for Minority Students and Students with Disabilities (F31)
- Six new and three continued National Research Service Award for Individual Postdoctoral Fellowship (F32)
- Eight new and four continued Mentored Clinical Scientist Development Award (K08)
- Seven new and one continued Mentored Patient-Oriented Research Career Development Award (K23
- Five new and one continued Mid-Career Investigator Award in Patient-Oriented Research Award (K24)
- Seven new and one continued National Research Service Award Institutional Research Training Grants (T32); six of these programs have been active for 10 years, and five of these have been active for 20 years or more

OTHER BRANCH ACTIVITIES

NATIONAL CHILDREN'S STUDY

The National Children's Study is a large, long-term study of environmental influences on children's health and development. For this effort, environment is broadly defined to include chemical, physical, social, and behavioral influences on children that will help researchers better understand the roles 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, which directed the NICHD to conduct the study with a consortium of federal agencies, including the Environmental Protection Agency, the CDC, and the National Institute of Environmental Health Sciences.

Researchers will follow about 100,000 U.S. children from conception, through birth and childhood, into adulthood. By examining participants over a span of 21 years, 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 well under way; working groups for the study are considering issues, such as hypotheses and study design, ethics, development and behavior, chemical and physical exposures, injuries, emerging technologies to measure exposures and outcomes, privacy, and community outreach/participation.

The PPB is active in this planning process. For example, Drs. Marian Willinger and Cathy Spong are the federal co-chairs of the Pregnancy and the Infant Working Group, which was charged to focus on events, outcomes and measurements of pregnancy and infancy and to develop findings on information to be collected about pregnant women, fetuses, and infants in the context of this large, long-term study. The Working Group will also develop findings regarding potential core study hypotheses in those areas relevant to its expertise. Drs. Willinger and Spong have sponsored a number of workshops to help define issues relevant to the Working Group and have led in the development of overarching study hypotheses and pilot studies.

BEST PHARMACEUTICALS FOR CHILDREN ACT (BPCA)

The congressional mandates of the BPCA provide an opportunity to address the challenges of clinical trials of drugs in children, for the purpose of labeling drugs for use in pediatric populations. Branch staff, especially Drs. Tonse Raju and Rosemary Higgins, are actively involved in this important initiative, in collaboration with other NICHD and NIH staff. Drs. Raju and Higgins have also helped to organize an NICHD/FDA Newborn Drug Development Initiative to foster the development of safe and effective drug therapies for term and preterm infants.

DHHS INTERAGENCY COORDINATING COUNCIL ON LBW AND PRETERM BIRTH AND DISPARITIES SUBCOMMITTEE

The purpose of this Interagency Coordinating Council is to galvanize multidisciplinary research, scientific exchange, policy initiatives, and collaboration among DHHS agencies, including the NIH, and to assist the Department in focusing efforts to achieve the greatest advances toward the national goal of reducing infant mortality. The challenges faced by the Council include assuring adequacy of data, uncovering new knowledge through research, and promoting the best possible delivery and financing of relevant health care. In particular, the DHHS Secretary asked the council to develop a Department-wide research agenda on combating LBW and its associated outcomes.

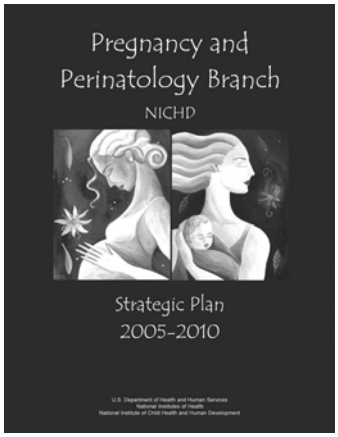
On August 4, 2003, the Deputy Secretary of DHHS charged a subgroup of the council with developing an agenda focused on the disparity that exists in the rates of infant mortality among African American and American Indian/Alaska Native populations. Specifically, the Deputy Secretary asked the subcommittee to identify appropriate best practices from research outcomes and to develop a set of recommendations for DHHS on research, interventions, and policy actions that will help reduce infant mortality (especially LBW and SIDS) among African American and American Indian/Alaska Native infants. Dr. Higgins, Dr. Willinger, and other PPB staff are actively involved in the Council and the subcommittee.

WEB SITE: COMMITTEE EXPERTISE IN OBSTETRICS AND GYNECOLOGY

To better provide study section and advisory groups with needed expertise, the PPB developed an internal, password-protected, NIH Web resource, http://extranet.nichd.nih.gov\comm\. The site provides a database of obstetric and gynecological expertise from scientists and physicians; those involved in the review process can use this expertise to inform their decisions about incoming applications. The database also increases the number of obstetrician/gynecologists involved in the review process. The Web site provides the experts' contact information, curricula vitae, and keywords. Dr. Uma Reddy is actively working on and supporting this project. Additional experts' names can be submitted electronically at *NICHDObGynExpertise@exchange.nih.gov*.

FUTURE DIRECTIONS FOR THE PPB

On December 5-6 2002, the Branch convened a two-day workshop to develop a research agenda that would help guide activities and priorities for the years 2005 through 2010. Participants were experts in the field and included individuals nominated by professional societies/groups related to PPB constituents. These 14 eminent scientists identified scientific areas and issues that offered the greatest opportunities and needs of the community served by the Branch.



The findings from this two-day workshop were used to develop the *Pregnancy and Perinatology Branch Strategic Plan: 2005-2010*. The plan outlines ongoing areas of PPB-supported research and outlined some steps for expanding these initiatives. In addition, the plan identifies new areas of emphasis that are crucial to the PPB mission.

New areas of emphasis in the plan included research in:

- Prematurity
- Fetal development, including maturation of individual organ systems and the impact of interventions on long-term function
- Maternal morbidities
- Neonatology, specifically intensive care and long-term outcomes
- Fetal/neonatal brain development and damage, including prenatal, perinatal, neonatal, and infant periods
- Training of scientists and physician-scientists
- Defining and improving the link between fetal, obstetric, and neonatal interventions and infant/child outcomes

Based on discussions from the workshop, PPB staff outlined action steps within each new area of emphasis that would help to achieve PPB goals for the next five years. The full report is available at: *http://www.nichd.nih.gov/publications/pubs/ppb/ppb_strategic_plan.htm*.

FIGURES AND TABLES

TABLE 1: PPB PROJECTS BY PROGRAM AREA IN FISCAL YEAR 2000 AND FISCAL YEAR 2003

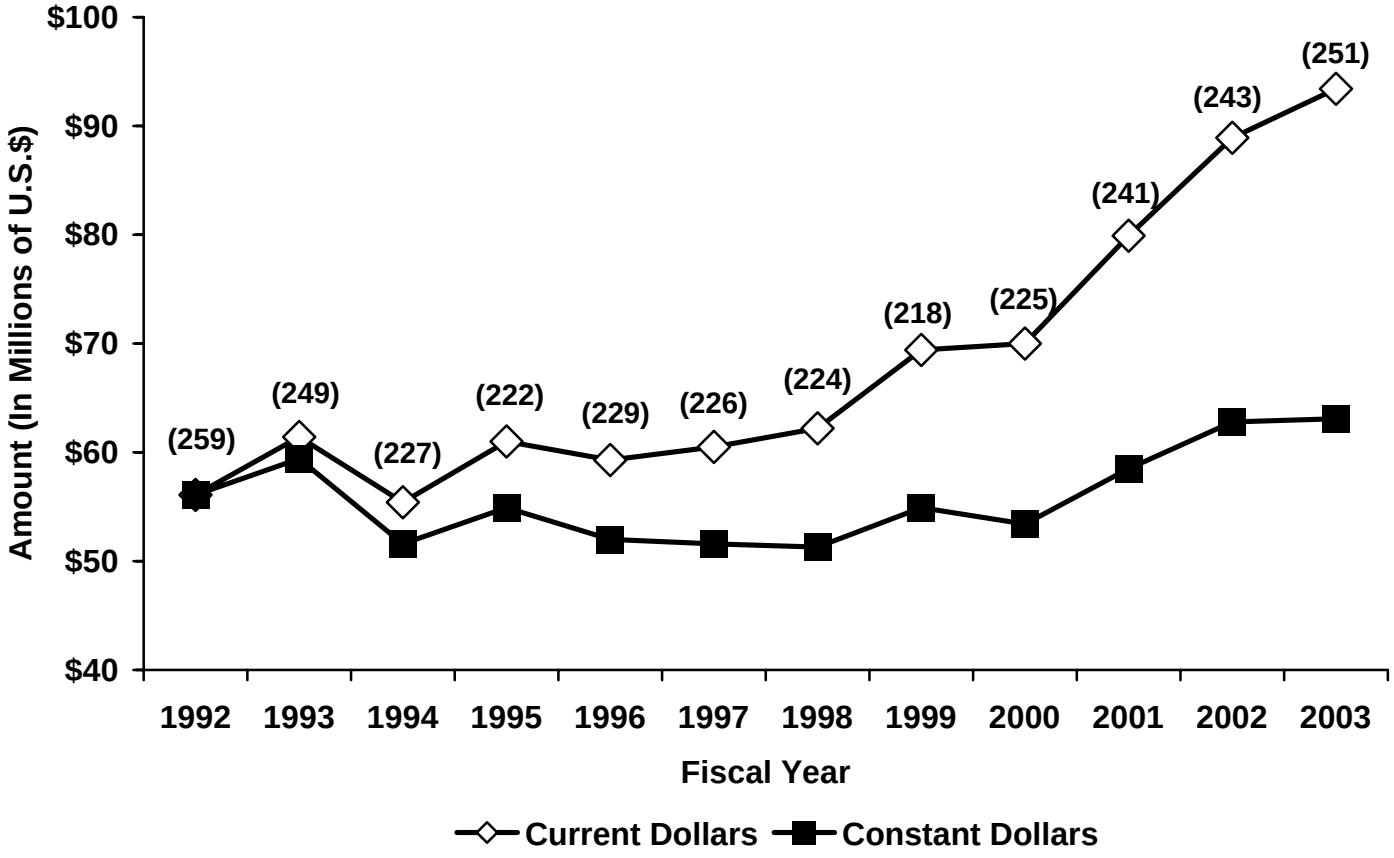
	Fiscal Year 2000		Fiscal Year 2003	
	Projects	Funds	Projects	Funds
Maternal				
Basic	13	$2,866,387	7	$1,638,891
Clinical	44	$17,069,455	33	$16,916,727
Fetal				
Basic	33	$7,392,339	28	$7,414,627
Clinical	4	$841,115	12	$4,592,060
Placental	30	$5,833,037	38	$10,134,258
Labor and Delivery	51	$13,264,197	53	$14,777,817
Neonatal				
Basic	12	$1,921,424	11	$2,354,008
Clinical	23	$9,927,268	40	$20,460,847
SIDS				
Basic	16	$3,839,299	18	$4,325,465
Clinical	15	$3,033,301	10	$3,300,173
SUBTOTAL	241	$65,987,822	250	$85,914,873
Training				
F31	—	—	4	$111,119
F32	3	$116,988	4	$198,150
T32	9	$1,254,514	11	$2,175,188
K (01,02,08,12,23,24,25)	11	$2,615,354	26	$5,042,460
SUBTOTAL	23	$3,986,856	45	$7,526,917
TOTAL	264	$69,974,678	295	$93,441,790

Note: Cooperative Agreements are included under Maternal, Neonatal, and SIDS categories.

TABLE 2: NUMBER OF APPLICATIONS PPB RECEIVED AND SUCCESS RATE OF EACH MECHANISM, FISCAL YEAR 2000 TO FISCAL YEAR 2003

Mechanism	Total No. Received	No. Funded	Success Rate (%)	No. Supported 2000-2003
F31	8	4	50.0	4
F32	14	6	42.9	9
K08	13	8	61.5	12
K23	17	7	41.2	8
K24	7	5	71.4	6
T32	14	7	50.0	11
F31	8	4	50.0	4

FIGURE 1: PPB GRANTS/CONTRACTS IN CURRENT AND CONSTANT DOLLARS, FISCAL YEAR 1992 TO FISCAL YEAR 2003



(Includes total grant and contract extramural funding; numbers in parentheses represent the number of projects.)

FIGURE 2: PPB FUNDS BY PROGRAM CATEGORY, SELECT FISCAL YEARS

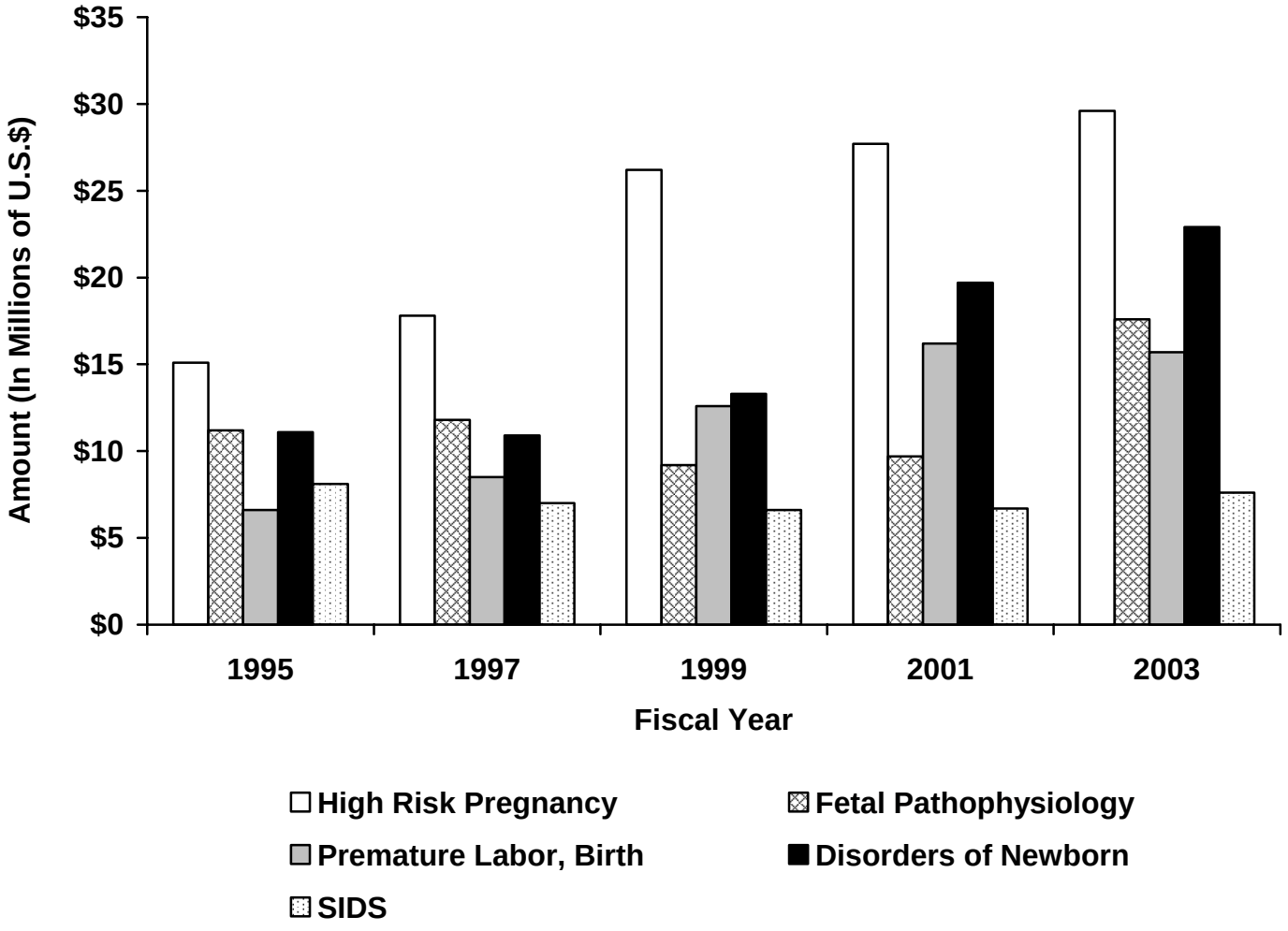


FIGURE 3: PPB-SUPPORTED RESEARCH BY DEPARTMENT, SELECT FISCAL YEARS

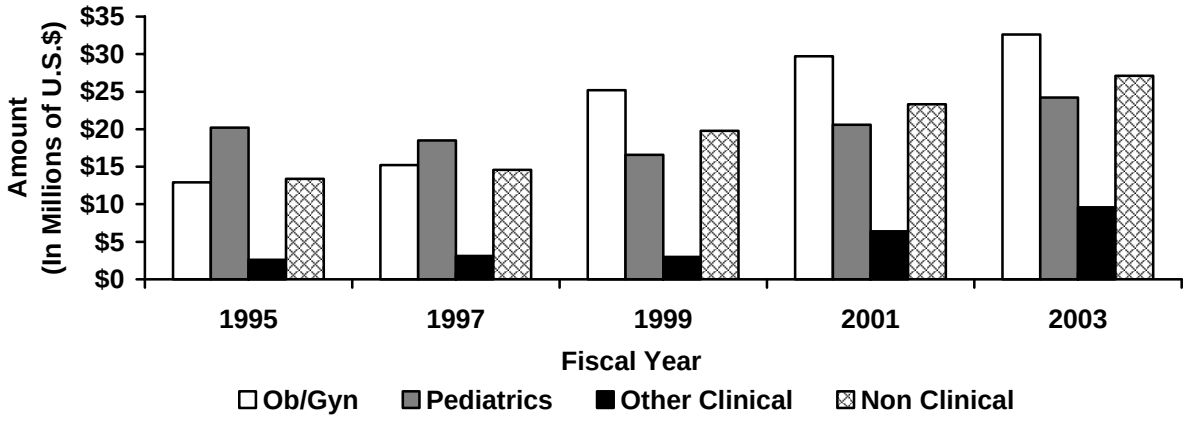


FIGURE 4: PPB-SUPPORTED RESEARCH BY INVESTIGATOR'S DEGREE, SELECT FISCAL YEARS

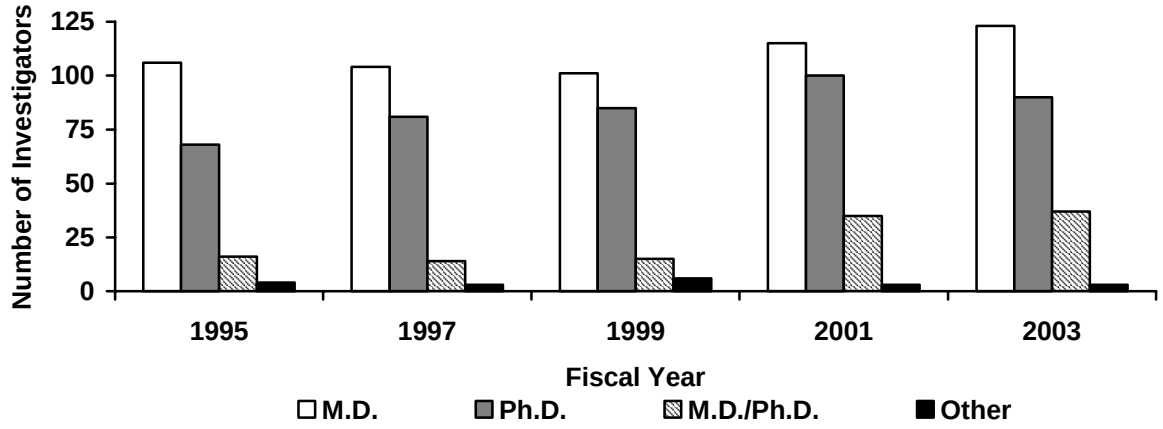
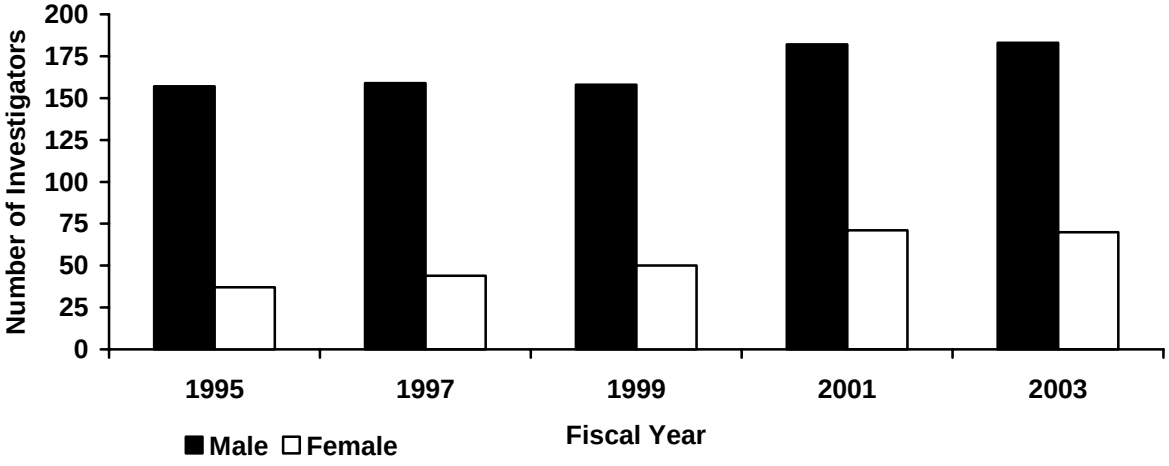


FIGURE 5: PPB-SUPPORTED RESEARCH BY INVESTIGATOR GENDER, SELECT FISCAL YEARS



APPENDIX A: PPB-SUPPORTED CONFERENCES AND WORKSHOPS, 2000-2004

- *Long Term Follow-up of Prenatal Drug Exposure: Advances, Challenges, and Opportunities* (sponsored by NIDA, NICHD, ORWH), March 23-24, 2004; Rockville, Maryland
- *MLS Advisory Board Meeting*, March 25, 2004; Rockville, Maryland
- *Workshop on the Border of Viability*, March 4-5, 2004; Rockville, Maryland
- NICHD-USAID Working Group to Plan the Stakeholders' Meeting: *Improving Maternal And Infant Nutrition: Development of a Research Plan*, January 26-27, 2004; Rockville, Maryland
- NICHD-AAP Workshop on *Research in Neonatology*, January 15-16, 2004; Bethesda, Maryland
- *The Role of Psychosocial Stress in Pregnancy on Pregnancy and Infant and Childhood Outcomes*, November 12-13, 2003; Bethesda, Maryland
- *Placental Measurements Workshop*, November 3-4, 2003; Bethesda, Maryland
- *From Bench to Bedside: Preventing Bilirubin-Induced Brain Injury (BIBI) in the Newborn and Kernicterus in the 21st Century*, July 21-22, 2003; Bethesda, Maryland
- *Role of Genomic Imprinting, Confined Placental Mosaicism, and Uniparental Disomy in Fetal Growth and Beyond*, May 15-16, 2003; Potomac, Maryland
- *Investigation of Fetal Origins of Adult Health in Twin Cohorts*, April 14-15, 2003; Bethesda, Maryland
- *MFMU Advisory Board Meeting*, March 9, 2003; Rockville, Maryland
- *Fetal and Neonatal Growth and Development*, December 15-16, 2002; Baltimore, Maryland
- *PPB Planning Workshop*, December 5-6, 2002; Potomac, Maryland
- The NIH Workshop on *Defining the Content of Follow Up Care*, June 19-20, 2002; Bethesda, 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 LBW Infants*, May 4, 2001; Rockville, Maryland
- *Setting a Research Agenda for Stillbirth*, March 26, 2001; Rockville, Maryland
- *SIDS Pathogenesis in the New Millennium*, November 29-30, 2000; 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 Disease (BPD) to Chronic Lung Disease (CLD): The Evolution of a New Disease*, Chronic Lung Disease Workshop, May 31-June 2, 2000; Rockville, Maryland

APPENDIX B: BRANCH SOLICITATIONS, 2000-2004

REQUESTS FOR APPLICATIONS

- HD-03-018: *Research into Mechanisms of Fetal Growth Restriction*
- HD-03-017: *Obstetrical-Fetal Pharmacology Research Units*
- HD-03-004: *Prenatal Alcohol Exposure Among High-Risk Populations: Relationship to SIDS*
- HD-02-025: *Research on the Scope and Causes of Stillbirth in the United States*
- HD-02-008: *Development of Community Child Health Research*
- HD-01-005: *Health Disparity in Preterm Birth: The Role of Infectious and Inflammatory Processes*
- HD-00-010: *Cooperative Multicenter NRN*
- HD-00-009: *Cooperative Multicenter MFMU Network*

PROGRAM ANNOUNCEMENTS

- PA-02-102: *The Role of Gene-Environmental Interactions Underlying the Health Disparity of Premature Birth* (sponsored by the NICHD, NIEHS, and NINR); expiration date: January 1, 2005, unless reissued
- PA-03-135: *Women's Mental Health in Pregnancy and the Postpartum Period* (sponsored by the NIMH, NIDA, and NICHD); expiration date: May 2006, unless reissued
- PA-04-027: *Reducing Preterm and LBW in Minority Families;* expiration date: December 5, 2006, unless reissued

APPENDIX C: PUBLICATIONS FROM PPB STAFF AND PPB-SUPPORTED NETWORKS, 1999-2004

(PPB staff names appear in **bold**.)

SELECTED PPB PORTFOLIO PUBLICATIONS

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Please note that Don McNellis, Susie meikle, and Linda Wright (names in bold above) are no longer PPB personnel, but were part of the Branch when the above papers were published.

APPENDIX D: PPB PERSONNEL

Nancy Chescheir, M.D., is board certified in maternal-fetal medicine and an obstetrician/gynecologist. She joined the Branch in January 2003 on an interpersonal agreement with the University of North Carolina to be the program scientist for the MOMS trial. Dr. Chescheir is a professor of obstetrics and gynecology and the director of the Fetal Therapy and Surgery Program at the University of North Carolina. She is nationally recognized in the area of fetal surgery.

Rosemary D. Higgins, M.D., is a board-certified neonatologist, who joined the Branch in January 2003. She is the program scientist for the NICHD NRN and MLS. Prior to joining the Branch, she held faculty positions at New York University Medical Center and at Georgetown University. Dr. Higgins is a member of the Society for Pediatric Research, is the NICHD liaison for the DHHS Interagency Coordinating Council on LBW and Preterm Birth and Disparities Subcommittee, and is a fellow of the AAP. Dr. Higgins' area of expertise is retinopathy of prematurity.

John V. Ilekis Ph.D., joined the Branch in June 1999. He holds a Ph.D. in biology with specialization in molecular biology. Prior to joining the PPB, Dr. Ilekis was a research assistant professor in the department of obstetrics and gynecology at the University of Illinois, Chicago. Dr. Ilekis' area of research focuses on understanding the molecular regulation of growth-factor receptors in reproductive tissues. His scientific responsibilities include managing basic research grants on: the physiology and biochemistry of the placenta, uterus, and cervix; preeclampsia and preterm birth; and psychosocial stressors and their physiological effects on pregnancy.

Susan Pagliaro joined the Branch in November 2001. She previously worked as program coordinator in the private sector in the area of adolescent health care. Ms. Pagliaro earned her bachelor's degree in public health from the University of Massachusetts. Her organizational skills and interest in clinical trials led her to the NIH, where she serves as the network coordinator of the MFMU Network and the Maternal-Fetal Surgery Network. In 2003, Ms. Pagliaro received an NIH Merit Award for "Superior commitment, dedication, and accomplishment to the NICHD's MFMU Network."

Tonse Raju M.D., D.C.H., F.A.A.P., is a board-certified neonatologist, who joined the PPB in June 2002. Prior to joining the Branch, he was professor of pediatrics and associate director of the Neonatal Intensive Care Unit at the University of Illinois, Chicago. His research background includes neonatal intensive care topics, pulmonary surfactant, bilirubin, non-invasive monitoring, neurological problems, neuronal protection, long-term learning and memory functions, and meta-analysis and systematic reviews. He is the program scientist and medical officer for a portfolio of neonatal research grants (R01, R03, R21); training grants (T32, K, and F); and Small Business Innovative Research/Small Business Technology Transfer programs administered through the Branch; he is also the project officer for the CNRG contract. Dr. Raju is the NICHD liaison for the AAP Committee on Fetus and Newborn, is a fellow of the AAP, and holds membership in the American Pediatric Society, the Society for Pediatric Research, the American Osler Society,

and the American Association for the History of Medicine. He also serves as the associate editor for the *Journal of Investigative Medicine*.

Uma M. Reddy, M.D., M.P.H., joined the Branch in September 2003. Board certified in obstetrics and gynecology and maternal-fetal medicine, she was a Robert Wood Johnson Clinical Scholar and received her master's in public health from Johns Hopkins University. Dr. Reddy manages translational and clinical research grants in obstetrics and maternal-fetal medicine and serves as program scientist for the SCRN. Prior to joining the Branch, Dr. Reddy was on the faculty at the University of Maryland School of Medicine and in the maternal-fetal medicine division at York Hospital, Pennsylvania. Dr. Reddy has published in peer-reviewed journals on clinical and laboratory obstetrics.

Diane Scholl joined the Branch in 1999, after a leave of absence from NICHD. Previously, Ms. Scholl worked at the NICHD as a program assistant for the director of the Centers for Research for Mothers and Children, and as a budget assistant in the Office of Financial Management. She began her career in 1978, at the Office of the Assistant Secretary for Health of the U.S. Public Health Service. Ms. Scholl's illustration appeared on the cover of the Branch's last report to the NACHHD Council in 2000.

Catherine Spong, M.D., joined the Branch in January 2000 and is board certified in maternal-fetal medicine and obstetrics and gynecology. Dr. Spong is the program scientist for the MFMU Network and has been Branch chief since January 2001. She is an associate professor of obstetrics and gynecology at Georgetown University and associate editor of *Obstetrics & Gynecology* and *William's Obstetrics*. Dr. Spong is the NICHD liaison for the ACOG Committee on Obstetric Practice, the Society for Maternal-Fetal Medicine Executive Board, and the Liaison Committee of Obstetrician/Gynecologists. She is a fellow of ACOG and a member of the Society for Maternal-Fetal Medicine, the Society for Gynecologic Investigation, the Society for Neuroscience, and the Perinatal Research Society. Dr. Spong is also the federal co-chair of the Pregnancy and the Infant Working Group for the National Children's Study.

Marian Willinger, Ph.D., is the NICHD special assistant for SIDS, responsible for the direction of the Institute's SIDS research program, which has included the development of the third, five-year research plan. She also serves as an expert on SIDS within the U.S. Public Health Service. Dr. Willinger is a program scientist for the CHIME Study, the PASS Network, the CCHN Network, and the SCRN. She also recently completed contracts to support SIDS epidemiological studies. Dr. Willinger has been involved in the development, implementation, and evaluation of the *Back to Sleep* campaign and serves as a consultant to the AAP Task Force on Infant Positioning and SIDS. Over the last five years, Dr. Willinger has participated in NIH- and government-wide activities, including the Advisory Board of the National Center on Sleep Disorders Research and the Interdisciplinary Research Workgroup of the NIH Roadmap. She is also federal co-chair of the Pregnancy and the Infant Working Group for the National Children's Study.