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PREFACE

The Pregnancy and Perinatology Branch (PPB) staff presents this summary of activities and accomplishments to the National Advisory Child Health and Human Development Council (NACHHD). The Branch supports basic and clinical research directed toward improving the outcome of pregnancy, reducing infant mortality, and minimizing maternal and infant morbidities. To advance to the ultimate goal of uncomplicated pregnancies and the birth of healthy, thriving infants, there is a need to expand the basic understanding of what constitutes maternal well being and to clarify the scope of maturational processes of fetuses and newborn babies. Acquisition of new knowledge leads to further questions and, therefore, more research. Most important is to determine how to use the new information to benefit patients, specifically applying it to safe and efficacious interventions. For this purpose, clinical trials are a major component of the Branch portfolio.

This report covers the period from the last presentation to the NACHHD at its meeting in September 1995 to 1999. It is not possible to provide a comprehensive overview of accomplishments and ongoing research for the wide area of responsibility of the Branch, but the report highlights some of the most salient aspects of the program.

The Branch wishes to acknowledge the support and encouragement of Dr. Duane Alexander, Director of the National Institute of Child Health and Human Development (NICHD); Dr. Yvonne Maddox, Deputy Director, NICHD; Dr. Sumner J. Yaffe, Director of the Center for Research for Mothers and Children (CRMC); colleagues of the other branches of the CRMC; the other extramural centers of the NICHD; as well as the coworkers of the Office of Grants and Contracts, the Office of Science Policy, Analysis, and Communication, the Public Information and Communications Branch, and the Office of Administrative Management. In addition, the Branch wishes to recognize effective and satisfying interactions with colleagues of other Institutes at NIH and of other agencies addressing issues of mutual interest and responsibility.

The staff is cognizant of and thankful for the support from, and positive interactions with, the NACHHD Council and hopes that this association will continue, providing the impetus to reach the goals established for the Branch.

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Report to the NACHHD Council

January 24, 2000

EXECUTIVE SUMMARY

The goal of the Pregnancy and Perinatology Branch (PPB) is to support research that improves pregnancy outcome and infant health. An important aspect of this aim is the reduction of preterm birth, infant mortality, and maternal and infant morbidity.

Activities of the Branch were organized around five maternal-fetal emphasis areas, which complemented each other and were viewed as a comprehensive approach to research during the pre-, peri- and postnatal periods. Although the Branch has re-grouped and renamed the emphasis areas (as seen in Table 1), it continues to provide the same comprehensive approach. The Branch utilizes a great number of available NIH funding mechanisms to support a program extending from basic research to clinical trials.

Activities of the PPB examine maternal adaptation during gestation, the sequence of events that guarantee a quiescent uterus, and complications that lead to negative birth outcomes. In the fetal area, there are studies at the molecular, tissue, organ, and whole organism levels to unravel the factors influencing normal and abnormal growth and maturation. Fetal life is recognized as an interval when a great many potential and relatively common problems occur that can have long-term repercussions. Therefore, study is focused on understanding maternal-fetal communications. Under scrutiny are the mechanisms responsible for intrauterine growth retardation (IUGR) which is associated with a striking increase in neonatal mortality and morbidity. The Branch supports exciting research on ways to augment fetal maturation through maternal therapy.

Placenta, labor, and birth are other components of the PPB portfolio with special emphasis on preterm birth - the single greatest cause of newborn and infant mortality - with potential lifelong sequelae in surviving infants. Furthermore, the high prematurity rate explains the relatively high infant mortality of the U.S. compared to other countries. Studies continue to clarify the normal onset of labor, the etiology of premature labor, and how labor might be stopped without detrimental effects.

A significant number of deaths are caused by disorders of the newborn, and many survivors suffer long-term disabilities. For the newborn, the continuous process of growth and maturation extends from the intrauterine milieu to the external environment where the infant must adapt to new conditions. Remarkable advances in the care of small infants have taken place, but many problems remain. An overlapping goal in this area of research and in that of preterm labor and birth is to reduce the risk of being born immaturely and not being able to adapt successfully as a newborn.

Finally, efforts in Sudden Infant Death Syndrome (SIDS) are moving in two major directions. The public health campaign "Back to Sleep" continues its success and, since its inception, has

resulted in a 38 percent relative decrease in the rate of SIDS. This campaign is directed at families and mothers of young infants, the professionals responsible for their care, and the public in general. While the advances in prevention are moving rapidly, research is continuing to slowly fill in the gaps in the etiology and pathogenesis of this devastating disorder.

Opportunities in the emphasis areas are recognized and investigators encouraged through existing NIH funding mechanisms. The progress realized in the years since the last report is indicative of what can be achieved in the years to come. Staff of the PPB is convinced that investment of efforts and allocation of funds for 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, the investment would guarantee the birth of healthy infants, able to achieve their full potential and contributions to our society.

ACTIVITIES OF THE PREGNANCY AND PERINATOLOGY BRANCH

TRAINING AND CAREER DEVELOPMENT PROGRAMS

The Branch continues to support research training through the use of Individual Postdoctoral Fellowships (F32) and Institutional Research Training Grants (T32). In FY 1995, the report stated that the Branch supported five F32s and nine T32s grants. These numbers have not changed. In 1999, four F32s are active and address issues in pregnancy and perinatal medicine. Of the nine T32s, eight have been active for a minimum of six years, and half of the eight have been supported for more than 20 years. The unchanged numbers of programs does not represent a lack of interest from U.S. institutions, as many have applied for such awards over the last four years. The limited availability of training funds has maintained successful programs, but has not allowed expansion.

The Branch supports clinically trained individuals through the Mentored Clinical Scientist Development Award (MCSD) (K08) to develop skills that will allow these individuals to pursue independent research careers. Five K08s are currently active. In addition, two special K08 awards per year are awarded to individuals located at one unit for both cooperative agreements in maternal-fetal medicine and neonatology to develop skills in clinical trials.

The following new K programs began in 1998 in response to the NIH stated special interest in increasing the number of scientists trained to conduct high-quality clinical research. In FY99, the first year that applications were accepted for these awards, the Branch supported one K23, one K24, and one K30.

The K23, a mentored, patient-oriented research career development award, is directed at candidates who have completed their clinical training and are committed to becoming independent clinical investigators. Candidates must identify a mentor with extensive research experience, and they must spend a minimum of 75 percent of effort in this endeavor.

The K24, a mid-career investigator award in patient-oriented research, provides support for clinicians to allow time for research and to act as mentors for beginning clinical investigators. Candidates must be conducting patient-oriented research, have independent research support, and devote between 25 percent to 50 percent effort to these activities in addition to mentoring.

The K30, a clinical research curriculum award, is awarded to institutions who have a highly trained faculty active in clinical research and show a commitment and capability to provide the core curriculum for individuals to develop a clinical research career.

The Branch continues to support the Pediatric Scientist Development Program or K12 in collaboration with the Association of Medical School Pediatric Department Chairmen (AMSPDC). Five years of training are involved: Phase I, consisting of two years of training in basic research funded by the NICHD and/or by other private agencies, and Phase II, consisting of three years funded by the sponsoring institution. Trainees hold junior faculty positions and are guaranteed 75 percent protected time to conduct research under an identified preceptor. A task force representing the AMSPDC, NICHD, and participating private agencies administers the program. Since 1987, 85

trainees have participated in this program. Of the first 68 graduates, 25 have competed successfully for NIH grants.

RESEARCH PROJECT GRANTS AND CONTRACTS

For many years, the Branch classified the grants and contracts in the following five categories: High-Risk Pregnancy, Fetal Pathophysiology, Premature Labor and Birth, Disorders of the Newborn, and Sudden Infant Death Syndrome. Recently, these categories were regrouped under Maternal, Clinical and Basic; Fetal, Clinical and Basic; Newborn, Clinical and Basic; Placental; Labor and Delivery; and Sudden Infant Death Syndrome.

A brief summary of some advances are presented for each category, although they are not subdivided into basic or clinical because many studies address both aspects and cannot be divided accurately. A significant number of clinical studies are summarized under the heading of Cooperative Agreements for both Maternal and Neonatal areas.

Maternal

The portfolio includes basic and clinical studies addressing a myriad of issues in pregnancy. The objective is to understand normal and abnormal physiological events and clarify the effects of maternal, acute, or chronic diseases on pregnancy and fetal development.

Preterm birth complicates 11 percent of all pregnancies in the U.S. and remains the leading cause of infant morbidity and mortality. One of the best predictors of poor outcome in an ongoing pregnancy is a history of poor outcome in a previous pregnancy. The mechanisms responsible for spontaneous pregnancy loss and a high rate of repeat preterm birth in some women are not known, but strong evidence supports the hypothesis that upper genital tract microbial infection and/or inflammation during the inter-pregnancy interval may have an important etiologic role. Such colonization or inflammation may contribute directly to adverse maternal and neonatal outcomes including an increased gestational age-specific risk for neurological injury. Indeed preliminary results of an ongoing study indicate that microbial colonization of the endometrium between pregnancies is an event more common than previously recognized.

Studies of adolescent pregnancies have demonstrated that although mothers who are still undergoing adolescent growth have greater weight gain and increased fat stores, their infants weigh significantly less at birth when compared with infants of non-growing adolescents or mature women. Studies showed a reduction in the transmission of nutrients between mother and fetus in growing adolescent pregnancies, suggesting that the metabolic demands of the still-growing adolescent take precedence over fetal needs. Also, these adolescent mothers retain more of their weight gain, thereby increasing the risk of obesity in the postpartum period. During adolescent pregnancy, growth appears to be associated with hyperinsulinemia. Black adolescent women show increased insulin levels compared to white adolescent women, which may explain the higher number of low birth weight (LBW) infants for that group. The investigator speculates that an additional side effect of hyperinsulinemia in this population may be long-term maternal overweight and obesity.

Ongoing studies are assessing the role of regular exercise training during pregnancy and its potential to reduce the redistribution of blood flow away from the viscera. With ultrasound technique, preliminary results show that fasting portal vein flow increases at rest, and the fall in flow associated with the upright posture becomes minimal after mid-pregnancy. However, the fall in flow in early pregnancy appears to be blunted in women who exercise regularly. Concurrent with the fall in portal vein flow, an equivalent rise in fetal heart rate occurs, suggesting that changes in splanchnic circulation reflect similar changes within the uterine circulation. In addition, data show that in response to maternal exercise the fetus increases the blood flow in the middle cerebral artery and decreases renal blood flow. These findings might indicate that flow redistribution is part of the fetal sympathetic response. Researchers assessing the impact of exercise on feto-placental growth have shown that a very moderate exercise program throughout pregnancy produces a larger baby (200-300 grams increase in lean body mass and a proportionate increase in fat mass). Offspring of women assigned to a high volume of exercise in early pregnancy, followed by a reduction later, showed similar changes.

An epidemiological study of Cytomegalovirus (CMV) infection carried out in several childcare facilities examined the factors, especially hygiene behavior, that contribute to the transmission of the virus. The risk to seroconvert for the staff and children at these facilities has been documented. In addition, prior investigations have shown that mothers of infants who seroconverted were themselves at risk to become infected. The investigators instituted protocols for teaching hygiene at these facilities and introduced the use of rubber gloves by personnel while changing the infants. With these simple measures they reduced the annual rate of CMV acquisition among children by 2.6 percent. Although this percentage seems small, it is statistically significant and highlights the fact that continuous hygienic practices influence the rate of CMV transmission.

Exciting new data has been obtained by a team of investigators using a new non-invasive technique (ultrasound and doppler) to measure umbilical blood flow in pregnant women. The technique was validated in an animal model (sheep) by comparing results from the new technique to those obtained by a classical invasive method (steady-state diffusion). Human measurements of vein diameter, mean velocity, and absolute umbilical venous blood were obtained by two independent observers, who followed established rigid criteria to assess intra- and inter- observer variabilities. Results showed that umbilical blood flow increases exponentially during gestation and that the major determinant for the increase is the growth of the vasculature as a consequence of an increase in umbilical vein diameter, not primarily by an increase in mean velocity. In pregnancies complicated by fetal growth restriction, there was a significant reduction in umbilical blood flow, not just velocimetry, as well as a reduction in amino acid transport from the maternal to the fetal circulation.

A recently initiated study addresses the issue of violence and spontaneous abortion in inner city women. The aim of this research is to characterize the prevalence and type of violence experienced by women early in pregnancy. In the first three months, investigators enrolled 119 eligible subjects who were seen in a very busy, inner city emergency medicine department. They will be followed according to a specific protocol.

Fetal

Studies address the physiologic, metabolic, endocrinologic, and pharmacologic events related to the growth and maturation of the fetus. New laboratory tools have widened research possibilities and increased our understanding of normal and abnormal development during intrauterine life.

Corticosteroid (CS) administration antenatally and postnatally enhances organ maturation and may decrease perinatal brain injury. A team of investigators studied the effect of CS on the development of the N-methyl-D-aspartate (NMDA) receptor, a mediator of perinatal hypoxic-ischemic brain injury. Results showed that the receptor's function was altered in an immature brain and that the effect depended on the degree of brain development at the time of CS administration. An apparent decrease in NMDA receptor numbers was noted in newborn lambs after CS treatment, which could be the consequence of non-specific effects on cell membrane structure in altering receptor configuration and binding characteristics. Concurrent studies showed that antenatal CS administration reduces blood-brain-barrier permeability, early but not late, in ovine fetal development, suggesting a progressive increase in the integrity of intercellular endothelial tight junctions.

Several researchers are examining the molecular mechanisms responsible for lung development in the perinatal period. Neonatal respiratory function depends on the prenatal development of a pulmonary capillary bed adequate to allow efficient diffusion of oxygen from the air-liquid interface of the alveoli to the pulmonary vasculature. Studies have clarified the histologic changes that occurs during the development of the air-blood barrier in the lung, and further experiments are examining the factors that may regulate this process. One factor being studied is vascular endothelial growth factor (VEGF), a potent cell mitogen, which is recognized as a regulator of angiogenesis in many developing systems. An investigator has found that VEGF mRNA and protein are produced in the distal airway epithelial cells of midtrimester human fetal lungs and that levels increase (in an in-vitro system of fetal lung explants) with the differentiation of those cells into alveolar type II cells. Further significant increases occur by cyclic adenosine monophosphate (cAMP) and by low oxygen environments, which exist in the distal airway epithelial cells. These cells have a VEGF specific receptor (KDR) which may signify a possible autocrine role for this factor in epithelial cell function. These findings imply that VEGF may be important in regulating type II cell proliferation, differentiation, and synthesis of surfactant proteins in the developing human lung.

Pulmonary vasodilation during cardiopulmonary transition at birth is mediated by endothelial-derived nitric oxide (NO), which is generated by the endothelial NO synthase (eNOS). It has been determined that NO production is high at birth and that pulmonary eNOS expression increases during late gestation. Concurrently, there is an increase in fetal estrogen levels, which may indicate that estrogen up-regulates NOS gene expression in pulmonary endothelium through the activation of pulmonary artery endothelial cells (PAECs). These events optimize the capacity for NO-mediated pulmonary vasodilation at birth. It can be hypothesized that pregnancies complicated by placental dysfunction may have a decreased estrogen synthesis, which may lead to diminished fetal pulmonary eNOS expression and contribute to the pathogenesis of persistent pulmonary hypertension of the newborn. Studies in fetal lambs have shown that decreased eNOS expression may contribute to both abnormal vasoreactivity and excessive muscularization of the pulmonary circulation in fetal pulmonary hypertension.

Fetal development progresses through a series of maturational steps that culminate in a successful transition to the extrauterine environment. A team of investigators is studying beta adrenergic receptors (BAR), a G-protein-coupled receptor family, which are vital for the successful adaptation to postnatal life and are regulated by corticosteroids and thyroid hormones. Although these receptors share structural and functional similarities, their gene structure and regulatory characteristics are varied. The first receptor to be cloned and sequenced is the B2AR, and the gene has been studied extensively. B1AR gene characterization is currently underway. It has been determined that the fetal ovine B1AR is not responsive to hormone induction, but undergoes up-regulation by steroids in newborns and adults. This effect might represent a unique transcription mechanism and/or novel interactions with hormone receptors. Ongoing research has identified the promotor region, conferring glucorticoid responsiveness and narrowing its possible location on the DNA, upstream from the transcription start site. Studies are starting to characterize the thyroid response element in the proximal promoter of the B1AR gene.

The fetal origin of adult disease or Barker's hypothesis is being examined in studies supported by both the maternal and the fetal portfolios. One investigation supports the hypothesis that factors present or absent from the maternal diet cause suppression of the fetal/newborn renin-angiotensin system (RAS) setting the stage for long-term control of blood pressure by altering renal development. In the rat, perinatal blockage of angiotensin IIAT1 (ANGIIAT1) receptors resulted in fewer, but enlarged glomeruli, reduced renal function, and an increased arterial pressure in adulthood. Perinatal suppression of the RAS in offspring of protein-restricted mothers leads to a reduced number of nephrons as well as hypertension in adulthood. Experimentally, the surgical removal of 50 percent of the nephrons during development caused reduced renal function and salt-sensitive hypertension in the adult. A very complex, but not well understood, picture is emerging from studies in piglets. These studies show a great number of renal AT2 receptors found in fetal kidneys, with a striking excess in female over male fetal kidneys, which suggests a potential gender-specific difference in that females appear to lack detectable renal AT1 receptors.

The RAS is also being studied in fetal sheep, specifically in regard to the developmental aspects of renin gene responsiveness. RAS appears to play multiple roles ranging from the regulation of fetal blood pressure to the control of angiogenesis in the kidney. During kidney growth, RAS also participates in the regulation of extracellular fluid composition and blood volume. One investigator observed a remarkable increase in renin expression during the prenatal period which could be attributed to a greater renin gene responsiveness to stimulation and to an augmented renin message stability within the fetal kidney. The increase could also indicate a reduction in the ability of angiotension II to inhibit RAS close to term. Studies suggest that the post-transcriptional processing of renin is an important point of regulation in RAS during development. Renal denervation has been shown to blunt the rise in plasma renin activity and renin gene expression during the transition from fetal to newborn. Experiments with dispersed renal cortical cells from lamb fetuses with intact innervation showed an increase in renin mRNA in response to isoproterenol stimulation, whereas the response to isoproterenol was lost in cells from fetuses that had undergone renal denervation. Thus, renal neural innervation is needed to maintain renin gene responsiveness to adrenergic stimulation in late gestation.

Intensive studies of the mechanisms underlying placental and fetal development are needed to understand and prevent low birth weight (LBW) and prematurity. Current studies in baboons show a close association between the levels of estrogen and estrogen mRNA and the specific activity of the P-450 cholesterol side-chain cleavage (P-450 SCC) enzyme, which is expressed in the placenta during the second half of pregnancy. Based on these results, the investigators propose that the P-450 SCC enzyme that catalyzes the conversion of substrate cholesterol to pregnenolone is regulated mainly by estrogen in the primate placenta. Investigators also suggest that it signals functional/biochemical differentiation of syncytiotrophoblasts during primate pregnancy. In-vitro studies with human syncytiotrophoblast demonstrated that the estrogen receptor is present in the nuclei of these cells and, consequently, this organ is an estrogen-responsive tissue. These researchers have shown (in the baboon) that the placenta, via metabolism of maternal cortisol and cortisone by the 11 β-hydroxysteroid dehydrogenase (11β-HSD) enzymes types 1 and 2 in the syncytiotrophoblast, regulates the maturation of the fetal pituitary-adrenocortical axis. Because of similarities in human adrenal development, studies were done in parallel with baboons and results showed that both types of the enzyme were expressed in placental syncytiotrophoblasts. Based on the experimental data, it was concluded that the human placenta has the ability to convert cortisone to cortisol and also contains the means for the transport of the latter; therefore, it could regulate the fetal pituitary-adrenocortical axis.

Several aspects of the hormonal control of fetal growth are addressed by different investigators. One group is centering their efforts on insulin-like growth factor 1 (IGF-1), belonging to the insulin superfamily, which plays a role in the growth and development of the central nervous system (CNS). IGF-1, its cognate receptor, and selected IGF binding proteins (IGFBPs) are expressed in many regions of the CNS during early development. IGF-1 is known to stimulate neuron progenitors and increase the survival of neurons and oligodendrocytes in culture systems. Using transgenic mice that express IGFBP-1 ectopically in the brain, brain growth retardation was noted from an apparent inhibition of IGF-stimulated growth and development. In transgenic mice that are overexpressing IGF-1 during early postnatal development, brain size and weight are increased significantly due to an increase in neuron number, total brain myelin, and density of myelinated axons. The increase in neuron number appears to result from the inhibition of IGF-1 on programmed cell death. Concurrent studies indicate that IGF-1 can ameliorate the brain growth retardation caused by undernutrition imposed during development. Studies examining the regulation of growth of glial cells indicate that a coordinated interaction between IGFs, IGFBPs, and specific properties of the latter are required to determine the growth of these cells.

Studies concerning the interaction of endocrine modifications, changes in placental angiogenesis with early placental development, and later nutrient transfer capacity are clarifying important aspects of fetal growth. Using two groups of sheep that were heat treated during pregnancy for 15 and 55 days, respectively, it was shown that chronic heat exposure lowers circulating placental hormone concentrations. Placental lactogen mRNA and protein contents are similar in both groups, suggesting that the decrease may result from impaired trophoblast cell migration. The impact of heat exposure during maximal placental growth restricts early fetal development. Therefore, intrauterine growth retardation (IUGR) may result primarily from placental trophoblast cell dysfunction and secondarily from later reduced placental size. Investigators determined that there was a lack of hypothermia effect on the expression of ovine vascular endothelial growth factor, ovine placental growth factor, and their interactions with placental growth factor receptors. These findings

suggest that alterations in IUGR placental vasculature occur early in placentation. In the same laboratory, research is underway to determine cellular adaptations to fetal hyper- and hypoglycemia. Glucose is transported into cells by a family of structurally related membrane-spanning glycoproteins. The predominant fetal glucose transporter isoform (GLUT-1) that mediates transport into rapidly growing cells was found in high concentration in all fetal tissues examined. In contrast, tissue-specific glucose transporter isoforms such as GLUT-3 (in brain and neurons) and GLUT-4 (in insulin-responsive tissues) are higher in the adult. Through a series of maternal glucose infusions that caused hyperglycemia and insulin infusions that lead to hypoglycemia, a picture emerged showing cellular adaptations of GLUT-1 and GLUT-3 geared toward protecting the fetus from perturbations in substrate availability and adaptations of GLUT-4 geared toward development of fetal insulin resistance.

A team of researchers has evaluated the longitudinal changes during gestation in maternal body composition, resting metabolic rate, and serum leptin concentrations. Leptin, the product of the ob gene, is expressed in adipose tissue, and may function in signaling pathways that underlie the regulation of body weight. In rodents, circulating leptin binds to a hypothalamic form of its receptor and exhibits profound effects on satiety and energy expenditure. In humans, the evidence showed that leptin increases significantly during early pregnancy before any major changes in body fat and resting metabolic rate occur, suggesting that pregnancy may represent a leptin-resistant state. Another objective of these studies is to understand the underlying mechanisms that provoke gestational diabetes mellitus (GDM) and lead to fetal macrosomia and obesity. In a mouse model of spontaneous GDM, studies suggest that a single mutant allelle for the leptin receptor confers a dominant effect on susceptibility to GDM through abnormalities in insulin receptor signaling, defective insulin secretion and greater nutrient availability.

Perinatal asphyxia occurs in 0.2-0.4 percent of full-term births, of these 20 percent suffer mortal hypoxic-ischemic encephalopathy; of the survivors, 25 percent exhibit permanent neuropsychological deficits. A team of investigators are studying the mechanisms responsible for fibrin formation and the role of polymorphonuclear cells in the observed hypoxic injury. Studies of neutrophils in hypoxia-induced thrombosis showed that neutrophils were called into hypoxic vascular microenvironments by the up-regulation of intercellular adhesion molecule-I (ICAM-I) in vascular endothelial cells and by the translocation of P-selectin from storage vesicles (Weibel-Palade bodies). Packaged alongside P-selectin is the Von Willebrand factor, which shows increased secretion. This might explain the development of the prothrombotic phenotype of the vascular wall in hypoxia. Ischemia-induced P-selectin expression was shown to recruit polymorphonuclear leukocytes (PMNs) and exacerbate tissue damage. Nevertheless, PMNs were found to be minor players in hypoxia-induced thrombosis, while recruited mononuclear phagocyctes (MPs) also played a critical role. Studies showed that immunodepletion of PMNs prior to hypoxia had little effect on fibrin deposition, whereas depletion of MPs attenuated hypoxia-induced thrombosis.

A team of researchers is exploring the basic physiologic and biochemical mechanisms of acclimatization to high altitude as a model for long-term hypoxia. These studies are carried out in pregnant and non-pregnant ewes that are maintained at high altitude to examine the adaptations of cerebral blood vessels and the cardiovascular system in both adults and fetuses. In the cardiovascular system, researchers found major alterations in the contractile responses of coronary arteries from long-term hypoxemic fetuses and hypothesized that these changes may result from alterations in

intracellular calcium sensitivity. It was concluded that long-term hypoxemia did not alter fetal cardiac morphologic parameters and that the fetus relies only on elevated coronary blood flow and/or other physiologic adaptations for adequate tissue oxygenation during long-term hypoxemia. Studies of the cerebral blood vessels showed that long-term hypoxemia is associated with a markedly altered contraction response in both fetus and adult. These changes are related, in part, to altered α2-adrenergic receptor (α2-AR) density and/or cyclic adenosine monophosphate (cAMP) levels. Indeed, α2-AR density in the main branch of cerebral arteries was decreased significantly in both fetus and adult; in contrast, basal cAMP values were much higher than in normoxic animals which suggest a cellular basis for changes in cerebrovascular contractility in response to long-term hypoxia. In another set of experiments, using a neonatal rat brain model of hypoxia-ischemia (HI), it was demonstrated that there is a differential expression of several genes in ipsi- and contralateral midbrain after HI injury. Further studies regarding the temporal up- and down-regulation pattern of these genes may provide clues as to their role in injury, repair, or regenerative processes.

Studies to determine the endocrine control of fetal cardiovascular dynamics focus on a specific hormone: atrial natriuretic factor (ANF). This hormone is important for regulating blood pressure and fluid balance in the fetus under both normal and stressful conditions, such as hypoxia. It has vasodilating properties at the peripheral arteries as well as diuretic and natriuretic effects at the renal tubules. The fetal atria appears to be the primary site of ANF synthesis, but it is also produced in the ventricles, seemingly having a developmental pattern as atrial expression is induced while the ventricular one is suppressed with fetal maturation. In the near-term fetus, vascular volume expansion, hyperosmolatlity, and hypoxia are effective stimuli for ANF production.

Placental

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 intrauterine growth retardation to fetal death. This report highlights some findings of supported grants from the last five years in placental research. It is hoped that these selected grants will illustrate the multifaceted nature of the research.

Preeclampsia is a severe form of hypertension induced by pregnancy. It is associated with inadequate development of utero-placental circulation. Progress by supported investigators has uncovered basic mechanisms involved in the formation of the normal utero-placental vasculature, and has shown that certain of these mechanisms are aberrant in preeclampsia. These findings indicate that specialized placental cells called cytotrophoblasts, which are involved in grafting the embryo onto the mother and establishing a blood supply, change their cell surface adhesion receptors from epithelial to endothelial during the process of uterine invasion and vascularization. This process does not fully occur in preeclampsia. In addition, the investigators have also shown that cytotrophoblasts from preeclamptic placentaes that are in direct contact with uterine cells undergo a high rate of apoptosis, or "cellular suicide", without a compensatory increase in mitosis when compared to normal placentaes. Consequently, the maternal-fetal interface is compromised.

Ethanol consumption during pregnancy is associated with decreased birth weights. The effect of ethanol toxicity within the placenta is poorly understood. One new investigator studied the effect of ethanol on a factor that is involved in placental blood flow, which could lead to intrauterine growth retardation, one of the clinical features seen in fetal alcohol syndrome. Nitric oxide (NO) production in the placenta is involved in maintaining low basal vascular tone in fetoplacental circulation that helps to maximize blood flow. It is known that ethanol induces oxidative stress by generating free radicals. Since NO can react with free radicals, the grantee hypothesized that ethanol exposure reduces the level of NO. The investigator demonstrated that placentaes perfused with physiological levels of ethanol resulted in lower levels of NO. The investigator then concluded that the decreased level of NO was a result of its destruction by reacting with free radicals as induced by ethanol. In turn, reduced NO levels could adversely affect placental blood flow, leading to fetal growth restriction.

In most women who experience recurrent spontaneous miscarriages, no cause can be identified. It is speculated that rejection of the fetus by the maternal immune system is responsible for some or all of these losses. A number of mechanisms have been identified in the placenta that may be involved in maintaining immunotolerance of the fetus. One grantee recently identified an additional mechanism. Previous studies of immunoprivileged sites, such as the eye and testis, have shown that immunotolerance is achieved by the production of a peptide, FasL, that binds to its cognate receptor (Fas) on activated immune cells. The binding results in the apoptotic death of the activated immune cells. The grantee investigated whether such a mechanism may also be taking place in the placenta. The investigator showed that the trophoblast cells of the placenta produced FasL. Importantly, a functional assay demonstrated that isolated trophoblast cells that are cocultured with activated immune cells (lymphocytes) induced the lymphocytes to undergo substantial apoptosis. Thus, the investigator revealed another possible mechanism for immunotolerance of the fetus. Future research is required to determine whether a redundancy of mechanisms exists as a fail-safe system to ensure survival of the fetus, whether certain of the identified mechanisms are essential, or whether an unidentified mechanism(s) is crucial for immunotolerance.

The mechanisms involved in the maternal transfer of nutrients through the placenta to the fetus are also poorly understood. Two critical nutrients are amino acids and glucose. One grantee identified three types of amino acid transporters using recombinant DNA methodology. These transporters are expressed in the trophoblast and are involved in cationic amino acid transport. The cloning of these specialized transporters will facilitate further studies to increase our understanding of the mechanism of transplacental amino acid transfer. Another grantee identified that a specific type of glucose transporter (GLUT1) in the trophoblast is up-regulated in mothers with gestational diabetes. The researcher demonstrated that the number, as well as the activity of this transporter is increased in the basal membranes of the syncytiotrophoblast. The up-regulation of this transporter may be responsible for abnormal glucose availability to the fetus and could contribute to fetal macrosomia, a condition in which the fetus is excessively large. This condition is commonly associated with gestational diabetes and results in a higher rate of perinatal mortality and morbidity from birth trauma.

A broad-grant portfolio in other areas of placental research as they relate to both normal and disease processes is currently supported by the Branch. A number of grantees are studying the role of

vasodilators (i.e., NO, prostacyclins), vasoconstrictors (i.e., thromoxanes), and lipid peroxides that are produced by the placenta in relation to preeclampsia and IUGR. Other grantees are investigating hormonal interactions between the fetus and placenta. It is speculated that hormonal communication between the placenta and fetus is essential in the maintenance of pregnancy and in the induction of labor. A number of investigators are studying the autocrine, paracrine, and endocrine roles of placental growth factors and cytokines. These studies include determining the effects of these compounds on placental growth, differentiation, and function. Research is also underway to elucidate signal transduction mechanisms at the cellular level.

Currently supported areas of research are tabulated below. 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.

Angiogenesis	Infectious Agents
Gene Regulation	Metabolism
Growth & Differentiation	Morphology
Growth Factors & Cytokines	Nutrients
Hormone Production & Regulation	Transport
Immunology	Vascular Function

Labor and Delivery

The Branch promotes studies of the physiology, endocrinology, and management of preterm, term, and post-term deliveries.

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. An understanding of the normal physiological and biochemical events occurring during parturition is essential for the successful intervention and prevention of premature labor. Although premature labor occurs in only 7-10 percent of all births, it accounts for more than 75 percent of all perinatal morbidity and mortality. Premature rupture of fetal membranes (PROM) is the leading cause of preterm deliveries, representing 30-40 percent of preterm births. An additional 30 percent of preterm labors are thought to result from intraamniotic infection. A significant research investment is being made to understanding the underlying causes and mechanisms of premature labor. The brief descriptions below highlight some of the findings of several of our grantees in premature labor and various aspects of paturition during the last five years.

One grantee studied the genes up-regulated in fetal membranes by infection or labor. Subtractive hybridization was used to identify differentially expressed genes in fetal membranes obtained either from women with preterm PROM, undergoing preterm cesarean, or during normal vaginal delivery. Two genes, F-actin capping protein and chitinase precursor, were up-regulated in infected tissue from preterm PROM women. These two genes were not previously known to be expressed in response to infection. A regulatory G-protein, signaling protein and interleukin-8 gene expression were upregulated during labor. In addition, the expression level of the complement factor-B gene directly correlated to the duration of membrane rupture. The identification of these genes will help

in elucidating the molecular events involved in both normal and premature rupture of fetal membranes.

Relaxin is a protein hormone that originates primarily from the ovary and plays a role in cervical ripening during pregnancy. This hormone is also synthesized in the decidua and placenta, where it is believed to play an autocrine/paracrine role in collagen remodeling of the amnion and chorion during parturition. One investigator has hypothesized that relaxin may also be involved in the premature rupture of fetal membranes. This researcher found higher levels of relaxin in the decidua and placenta of women with PROM, irrespective of infection. This result suggests the possibility of a relaxin-mediated pathway for PROM, independent of infection.

A number of psychological and social studies have proposed that maternal stress can influence pregnancy outcome. In particular, some investigations show that maternal stress is associated with a higher incidence of premature labor. Numerous animal studies support this observation, and various physiological mechanisms underlying this effect in non-humans have been identified. Little is known of the physiological processes that mediate this effect in humans. Studies by a grantee show that the levels of certain endocrine hormones (ACTH, cortisol, CRH) that are produced by the hypothalamic-pituitary-adrenal-placental axis (HPAP) are significantly altered during maternal stress. Therefore, the level of specific hormones may be linked to certain pregnancy outcomes. Specifically, the grantee documented maternal stress during the third trimester as being associated with increased maternal plasma levels of ACTH and cortisol. Since maternal ACTH and cortisol can increase the placental release of CRH, a hormone implicated in the labor initiation, this increase may represent a mechanism by which maternal stress may induce premature labor. This hypothesis is consistent with the finding by the same investigator that maternal CRH levels predict the length of gestation and that preterm labor was associated with higher levels of CRH.

Uterine contractions are dependent on the level of intracellular calcium, the presence of which is necessary for the activation of the myosin-actin contractile unit. Oxytocin stimulates uterine contractions by increasing intracellular calcium. The increase of calcium is due to increased excess extracellular entry and release from intracellular stores. The entry of extracellular calcium is called noncapacitative calcium entry. However, replenishment of depleted intracellular stores from the extracellular environment is necessary for continued uterine contractions. This process is called capacitative calcium entry. One grantee determined that the action of oxytocin also involves the stimulation of capacitative calcium entry.

Tobacco smoking is a risk factor for PROM. Collaborating grantees investigated a possible mechanism by which tobacco smoke may contribute to this risk. Tobacco smoke is known to contain the heavy metal cadmium. Cadmium is known to induce the heavy metal scavenger metallothionein, which also binds and sequesters copper. Since copper is required for the activity of lysyl oxidase, an enzyme involved in generating tensile strength in the fetal membranes, the investigators hypothesized that cadmium may stimulate induction of metallothionein in the amnion. The investigators found that amnion epithelial and mesenchymal cells were highly sensitive to cadmium. Cadmium, at the concentrations found in the amniotic fluid of smokers, increased metallothionein gene expression levels 1000-fold in epithelial cells and 10-fold in mesenchymal cells. Thus, the cadmium component in tobacco smoke may contribute to reducing the tensile strength of fetal membranes via the induction of metallothionein.

The fetus is central to the initiation of labor in non-primate species. In sheep, which is the classical model of parturition, the activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis is the critical component initiating labor. In this model, fetal pituitary ACTH stimulates the production of cortisol from the fetal adrenal. In turn, cortisol initiates a cascade of biochemical events associated with labor, including the induction of a key placental enzyme involved in estrogen production. This enzyme is not expressed in the placentae of humans or primates; consequently both of these species depend on C19 steroids secreted from the fetal adrenal for the production of estrogens by the placenta. The importance of the fetal HPA axis in the initiation of labor in primates and humans, however, remains controversial. Recent work by a number of grantees suggests that in the primate, the fetal HPA access may also play a key role in the initiation of labor. In the rhesus monkey, the level of androstenedione, a C19 steroid produced by the fetal adrenal in response to release of ACTH by the fetal pituitary, dramatically increases in the fetal circulation near-term. Peripheral infusion of androstenedione during late gestation resulted in all the normal temporal biochemical and endocrine changes associated with spontaneous-term labor. Interestingly, the concurrent infusion of an aromatase inhibited the induction of labor by androstenedione. This indicated that the action of androstenedione was mediated through its conversion to estrogen. Paradoxically, although the infusion of estrogen stimulated myometrial activity, it did not produce preterm labor or fetal membrane changes. Since the effect of androstenedione was mediated by its conversion to estrogen, these results implied that estrogen acted at its site of production in a paracrine, rather than endocrine, manner. Although significant differences exist between species, it appears, as in sheep, that the activation of the fetal HPA axis may be central to the initiation of labor in primates.

A number of grantees have made progress in learning the mechanisms by which uterine contractility is regulated. A paradigm for the study of the mechanism involved in uterine contractility of many uterotonic agents is oxytocin. Oxytocin is an important uterine contractant and plays a role in the progression of parturition and labor. The molecular events by which oxytocin elicits its effect is currently under considerable investigation. Oxytocin stimulates uterine contractions through a phosphatidylinositide (PI) turnover mechanism. Binding of oxytocin to its receptor results in the activation of phospholipase-C (PLC) beta-isoforms, which generate the second intracellular messenger IP-3. IP-3 stimulates the release of calcium from intracellular stores and leads to uterine contractions. One grantee demonstrated that the agents that activates protein kinase A, a cAMP-dependent regulatory protein, could inhibit oxytocin-stimulated PI turnover. This inhibition could be reversed by a specific PKA inhibitor. Since the G-protein isoform (alpha-q), involved in activation of PLC beta-2 isoform, was a suggested target of PKA, the possibility that the oxytocin receptor was coupled to this same G-protein was implicated. Thus, the G-alpha-q protein may represent a common regulatory point of convergence between contraction and relaxation pathways in the myometrium.

Magnesium sulfate is the first-line treatment for premature labor. One grantee investigated the cellular mechanisms by which magnesium suppresses uterine contractility. In-vitro contraction studies were performed on myometrial smooth muscle using oxytocin and other uterotonic agonists, both with and without the addition of magnesium, in the presence and absence of extracellular calcium. The investigator found that magnesium inhibited extracellular calcium entry, intracellular calcium release, cytosolic calcium oscillations, and phasic contractions of myometrial smooth muscle stimulated by these agents.

A number of uterine-associated neuropeptides as known to induce uterine quiescence during pregnancy. One of these is a peptide released by uterine nerve fibers called calcitonin gene-related peptide (CGRP). One grantee investigated the effects of CGRP on myometrial contractions and the changes in CGRP receptors during pregnancy. The investigator demonstrated that CGRP induced dose-dependent relaxation in spontaneously contracting myometria from pregnant women. The effect of CGRP could be inhibited by both a guanylate cyclase and NO inhibitor, suggesting that its effect is mediated through an NO-cGMP-type mechanism. The relaxation effect, however, is diminished in myometria obtained from women during labor. Immunohistochemical studies revealed that CGRP receptors are abundant in the myometria of pregnant women who are not in labor, but are substantially lower in the myometria during labor. Thus, the diminished activity of CGRP to inhibit uterine contractions may be attributed to a decreased number of CGRP receptors at the time of labor.

Prostaglandins (PGs) are important factors involved in parturition. The level of PGs are increased at the onset of both term and preterm labor. PGs are synthesized within the fetal membranes and decidua and act to ripen the cervix, change fetal membrane structure, and contract the myometrium. Each type of PG species has a specific receptor isoform linked to a distinct signal transduction pathway that leads to contraction or relaxation responses. One researcher investigated the expression of PGH-synthase isoforms (1 & 2), key enzymes involved in PG formation, in human myometrium at parturition. The investigator showed that both isoforms are expressed in pregnant human myometrium. The level of isoform 2 was higher than isoform 1, but their levels did not change with gestation or labor. Other grantees studied the regional variations in contractile responses to prostaglandins and prostanoid receptors in the pregnant baboon uterus. These investigators demonstrated that PGE2 contracted the myometrium from the fundus but had no significant effect on the myometrium from the lower uterine segment. In contrast, PGF2 alpha contracted myometrium from both regions equally. The distribution of prostanoid receptor isoforms for PGE2 indicated that the lesser contractile response of the lower uterine segment to PGE2 might result from the greater expression of the inhibitory-contractile and less-contractile receptors, EP2 and EP3, respectively. These results suggest that drugs designed for selective activity on different PG receptor isoforms are likely to allow safer and more effective control of the uterus than native PGs.

A polymorphism within the promoter region of the gene for tumor necrosis factor (TNF) alpha at position -308 is associated with enhanced gene transcription. One group of investigators postulated that this polymorphism might be associated with a higher incidence of spontaneous preterm labor. The study was restricted to African American women. The investigators found no significant difference in the incidence of the polymorphism between women with idiopathic preterm labor (44 percent) or term labor (30 percent). However, a significantly higher incidence (58 percent) of the polymorphism was found in women with preterm labor following premature rupture of membranes. The results suggest a possible genetic predisposition to PROM in this ethnic group due to hyper-responsiveness of the TNF alpha gene, which may be triggered by environmental factors such as genital tract infections.

One group of investigators challenged the notion that the measurement of inflammatory-associated cytokines in the amniotic fluid during labor is indicative of infection induced preterm labor. It was

hypothesized that the accumulation of microorganisms and inflammatory mediators in the amniotic fluid that occurs after labor is in progress may be the consequence, not the cause, of labor both at term and preterm. The investigators measured the concentrations of interleukin (IL)-1 beta and IL-6 in amniotic fluids that were collected before and during premature labor (< 34 weeks gestation) and in amniotic fluid of those at term. The incidence of IL-1 beta and IL-6 accumulation increased similarly during the first 18 hours of preterm and term labor. The investigators concluded that the accumulation of these cytokines in the amniotic fluid could not be taken as evidence for the role of infection in the pathogenesis of preterm labor.

The Branch is currently funding a diverse portfolio of grants using physiological, biochemical, and molecular approaches to elucidate the various mechanisms involved in parturition. A number of grantees are studying the role of the HPAP axis in both term and term labor. The involvement of hormones such as CRH, ACTH, cortisol, and androgens are some of the active areas of research. Some grantees are studying mechanisms involved in the premature rupture of fetal membranes. These include studies involving infection, cytokine production, and extracellular matrix biology. Other grantees are investigating uterine relaxation and contraction factors and their mechanisms of action. Some of the factors under investigation are NO, oxytocin, relaxin, steroids and PGs. The current research will provide a better understanding of the mechanisms responsible for parturition. In turn, this knowledge will help to ensure a successful pregnancy.

Neonatal

Neonatal research is not supported exclusively by the PPB. Specific areas are funded by other programs at NICHD and by other NIH Institutes. These projects share the aim of clarifying neonatal physiology and pathology. The acquired knowledge will permit further developments in the care of these infants.

The Cochrane Neonatal Review Group is the only NIH-funded Cochrane group. It has been funded by contract with the PPB to do meta-analyses of randomized controlled trials in neonatal medicine, since 1995. The contract supports the infrastructure, including salaries for an Editorial Board, coordinator, and data analyst, as well as funds for software updates, international training workshops, and travel. Another NICHD branch funds individual Cochrane reviews. All reviews are done by experts at no cost to the NICHD. The Neonatal Review Group ranks second in the total number of reviews produced for the Cochrane Library (182 assignments, 81 completed reviews, 39 review updates, and 24 protocols). All completed reviews are posted at www.nichd.nih.gov/cochraneneonatal/ (The NICHD Cochrane Web Site).

A team of researchers conducted studies in human infants born prematurely that focus on the short-term maturational effects (on growth, physiology, and behavior) of variation in the content and quantity of diet. The aim was to determine whether diet-induced differences might account for short-term variations in morbidity and mortality and perhaps the longer-term differences in neurodevelopment and susceptibility to cardiovascular and metabolic pathology. An intriguing observation showed that despite attentive nutritional support (both parenteral and enteral), very low birth weight (VLBW) infants (<1250 grams) grow differently than their larger cohorts. At comparable discharge weights from the nursery they are shorter, their heads are smaller and several indices of protein metabolism suggest that they suffered from relative protein deficiency, which

could account for short-term variations in morbidity and mortality. These findings have important clinical ramifications for the standard of nutritional care of these infants while in the nursery.

The Branch also supports investigation on extracorporeal life support in neonates with severe respiratory failure, placing a major emphasis on improving the methods used. A double-lumen venovenous system cannula was developed for infants weighing more than 3 kg. which allows adequate gas exchange while preserving the carotid artery. Current efforts are directed toward developing and evaluating a cannula with a non-thrombotic surface, which would eliminate the need for systemic anti-coagulation for prolonged extracorporeal circulation.

The Branch is also supporting a series of trials investigating heme oxygenase inhibitors in the management of hyperbilirubinemia in newborns. Randomized, controlled trials are underway in Athens, Greece and Buenos-Aires, Argentina. The initial work established the safety, efficacy, and the appropriate dosage of tin-mesoporphyrin (SnMP) in preterm babies. SnMP was more effective in preterm infants than phototherapy for the management of hyperbilirubinemia. No adverse side effects were reported in infants followed up to age three. Similar studies were conducted in Greece in neonates with hyperbilirubinemia that resulted from a direct Coombs positive ABO incompatibility, and in those with (G6-PD) deficiency. In Argentina, studies randomized healthy, full-term, breast-fed infants (> 2500 grams) with elevated bilirubin levels to either an SnMP or a standard therapy. SnMP prevented bilirubin levels from increasing, whereas 21 percent of infants in the standard therapy group required phototherapy. Follow-up examinations of these infants reveal no adverse outcomes.

This Branch also supported one of the major success stories in neonatal medicine - the use of antenatal steroids (ANS) for fetal maturation and the development of surfactant for respiratory distress syndrome (RDS). Subsequent research, based on the observation that preterm infants born to women who have clinical chorioamnionitis may have a decreased incidence of RDS, demonstrated that the lungs of preterm lambs exposed to an inflammatory stimulus were more mature than those of control lambs. The observed changes in structure and lung function were similar to those induced by maternal betamethasone treatment. The effect of the route of fetal exposure to glucocorticoids was an unanticipated aspect of the response in sheep. When directly compared, using the same dose of 0.5 mg/kg/betamethasone (based on maternal weight or fetal weight), maternal administration of betamethasone resulted in a larger maturational response of the fetal lungs, characterized by better compliance, improved gas exchange, large lung volumes, and larger increases in saturated phosphatidylcholine following multiple doses given at seven-day intervals. Single or repetitive maternal betamethasone treatment resulted in proportionate fetal growth retardation following preterm and term delivery. In contrast, single or repetitive fetal treatment did not cause growth retardation, even though fetal betamethasone treatment resulted in plasma levels about three-fold higher than those achieved after maternal treatments. In this model, the acute physiologic lung maturational responses and the delayed increases in surfactant occurred without fetal growth retardation, dissociating these two glucocorticoid effects on the fetal sheep.

Finally, the Branch is funding a large, multicenter, controlled trial of prophylactic analgesia on outcomes (death or severe neurologic injury) in ventilated, preterm infants (24-32 weeks gestation). Use of prophylactic analgesia in intubated premature infants is not the current standard of care, although its use is standard treatment for adults who are intubated. A pilot study of such premature

infants demonstrated reduced behavioral responses to pain and decreased incidence of death or neurologic injury in the treated group compared to the controls.

Sudden Infant Death Syndrome (SIDS)

Between FY 1995 and FY 1999, the NICHD SIDS research program followed the objectives of the active five-year research plan. The objectives are to: understand the etiology and pathogenesis of SIDS, develop strategies to identify and monitor infants at risk for sudden death, and develop and implement strategies to prevent SIDS. To reach these objectives, the program supports a combination of cellular, molecular, and physiologic studies in animal models, anatomic and neurochemical studies in pathologic specimens, physiologic studies in clinical settings, and case-control studies and surveys in the community. Many studies are multidisciplinary and address more than one of the objectives listed above. The by-products of SIDS research have been an increased knowledge in infant development and improvements in infant health.

Etiology and Pathogenesis

Researchers hypothesize that SIDS infants lack the ability to respond to life-threatening hypercapnic or hypoxic episodes during sleep or to changes in blood pressure. Investigations of tissue specimens from SIDS infants focused on the brain regions involved in cardiorespiratory and cardiovascular control and arousal. NICHD-supported researchers have observed decreased binding of acetylcholine and kainate to receptors in the arcuate nuclei of SIDS infants. The arcuate nucleus is a region on the ventral brainstem that is believed to control chemoreception as well as cardiorespiratory and cardiovascular responses. It is linked to regions that are active in arousal from sleep. These results, unique to SIDS infants, suggest a specific neuronal deficit in the brainstem of more than half of these infants. Studies are now underway to determine whether this abnormality originates in utero and to map the pathways that might be affected.

In FY 1998, a program project grant was awarded for the development of a piglet model to study the role of the various brainstem regions in cardiorespiratory and cardiovascular responses to potentially life-threatening environmental stimuli. This investigative team is studying arcuate nucleus homologues in the ventral medulla, as well as regions involved in "gasping"- an exaggerated sigh that terminates severe hypoxia. This project will permit physiological, neurochemical, and neural mapping studies that are not possible in infants or in postmortem tissue.

Another program project grant is focusing on the cellular and molecular consequences of hypoxia and glucose deprivation and on the mechanisms of injury, repair, and adaptation in the developing organism. It was found that during tissue hypoxia, the loading of sodium into neurons places an energy demand on the neuron at a time when substrates are low. The loading of sodium occurs primarily via activation of the Na^+/H^+ exchanger (NHE), which alters intracellular pH. One of the protective mechanisms during hypoxia is to shut down the sodium channel in an attempt to reduce the entry of sodium into the cell. Studies are underway in developing neurons and glia cells to elucidate the role of the NHE and acid-base transporters in cell injury and survival.

Maternal smoking during pregnancy increases the risk for SIDS about three-fold. Among pathologic specimens from control infants with a history of maternal smoking, nicotinic receptors were observed

to be up-regulated in all brainstem nuclei examined when compared to control infants without a history of smoke exposure. This up-regulation reached statistical significance in three nuclei involved in cardiorespiratory control and arousal. Up-regulation of nicotinic receptors is the expected response to nicotine exposure. In SIDS cases with a history of maternal smoking, up-regulation of nicotinic receptors was not observed. The meaning of this deficit is unclear but points to abnormalities in the development of these brainstem nuclei in SIDS infants exposed to cigarette smoke in utero.

Brain imaging studies in humans have revealed that other brain regions, in addition to the ventral medullary surface, are involved in ventilatory responses to hypercapnea and hypoxia during sleep. Functional magnetic resonance imaging of children shows that both forebrain regions and the cerebellum become activated in response to hypercapnia. These regions are also activated in the controls in response to hypoxia. However, children with congenital central hypoventilation syndrome (CCHS) have reduced activation in forebrain and cerebellar sites in response to hypercapnia and fail to activate the cerebellum in response to hypoxia. These sites will be investigated further in animal models and in postmortem tissues of SIDS infants.

Other studies in living infants are trying to identify potential pathways that could be impaired in infants at risk for SIDS. Sleeping on the stomach is a major risk factor for SIDS. In all countries where campaigns advocating non-prone sleep position have been successful in changing behavior, SIDS rates have dropped. Infants sleeping on their stomachs spend time with their faces in the bedding and re-breathe expired carbon dixoide. Infants sleeping on their backs may have their faces covered by bedding. Researchers have now established there is a specific arousal sequence that protects infants from hypercapnic or hypoxic environments. The reflex sequence proceeds as follows: sigh, startle, thrashing, activation of brain wave activity, and awakening. In many cases, the arousals do not proceed beyond the startle. The sigh and startle are sufficient to terminate hypoxia or hypercapnia because they are associated with neck extension and relieve obstruction of the lower and upper airways. If the external airways are still blocked, then the thrashing movements follow. The sigh and startle intensity peaks at three months of age (within the peak age range for SIDS). As the baby matures, the startle and symmetrical movements are replaced with specific, exploratory, asymmetrical movements that are more effective to remove the obstruction. This sequence suggests that both an intact neural substrate and the opportunity to learn the protective behaviors over time may be necessary for infant survival.

Studies also reveal differences in autonomic control of preterm LBW infants in the prone and supine position. These infants exhibit higher heart rates, lower heart rate variability, and higher respiratory rate in the prone position than in the supine position, in both active and quiet sleep. With advancing postconceptional age, the differences in autonomic function between the prone and supine position increase. The observed variations in autonomic control for the prone position are similar to those recorded in term newborns who later died of SIDS. The more rigid autonomic control, and the observation by investigators that infants sleeping prone spend more time in quiet (deep) sleep than do supine infants, may lead to a compromised response to cardiorespiratory or cardiovascular challenges.

The sleep environment plays an important role in the health outcome of infants. It is likely that sleep environment plays an important role in the development of life-sustaining physiology as well. For

most of human history, infants presumably did not sleep alone, but slept with their caretakers. Thus, the evolution of sleep in hominids occurred with the interactive sensory input of babies and mothers. In our present-day culture, many babies spend some part of the night in bed with their parents. One possibility is that the sensory input present in the shared sleeping environment may have profound effects on the development of sleep physiology, which may be beneficial to the infant. The NICHD has supported the first study of mother and infant behavior and physiology when they are sharing a bed for the night's sleep. By comparing various measures on the bed-sharing night with the solitary sleeping night, the scientists observed that regardless of how they routinely slept, infants were never placed to sleep on their stomach on the bed-sharing night. On these nights, infants spent the majority of the time sleeping face to face with their mothers, at very close distances, less than 10 inches apart, where carbon dioxide levels are elevated due to the mother's respiration. The investigators also observed that, on the bed-sharing night, the infant experiences significantly more arousals and less time in stage 3-4 sleep compared with the solitary sleep night.

There are concerns that bed sharing increases the risk that an infant will die from being overlain by the mother. In the study above, maternal arousals increased and, on many occasions, overlapped with the infant's on the bed sharing night. However, total maternal sleep time did not decrease because the arousals were of short duration. This study provides evidence that the mother appears to be responsive to the infant's arousals, and the risk of overlay due to maternal exhaustion from sleep deprivation may not be a real threat. The maternal responses appear to be intrinsically programmed, as they were observed in routine solitary sleepers on the bed sharing night. However, there is no evidence to suggest that fathers or siblings have similar responses. Data from other studies suggest that it is hazardous to have multiple family members in bed with the infant.

Identifying and Monitoring Infants at Risk

In the last five years, the PPB has supported epidemiological studies to identify modifiable social, behavioral, medical, and environmental risk factors, and physiological studies to identify functional abnormalities in the fetal and newborn period that increase the risk for life-threatening events or SIDS. These studies provide information that may aid in the development of screening tools and therapeutic strategies for infants at risk, as well as improving our understanding of the mechanisms of SIDS.

Two epidemiological studies, the Aberdeen Area Infant Mortality Study and the Chicago Infant Mortality Study, focus on minority populations with high rates of SIDS. The Aberdeen Area Infant Mortality Study is a collaboration between the NICHD, the Indian Health Service (IHS), the Centers for Disease Control and Prevention (CDC), and the Aberdeen Area Tribal Chairman's Health Board. The Northern Plains Region has the highest infant mortality rates (IMR) of all IHS areas, with a SIDS rate about five times the national average. As most babies in this area sleep on their backs, infant sleep position is not a major risk factor. This case-control study provides a unique opportunity to identify other major risk factors, particularly those that can be modified. The NICHD is also supporting the analysis of deficits in the central nervous system in study cases and their correlation with medical, environmental, and behavioral risk factors. Enrollment of cases is complete, and preliminary findings were presented at a meeting of representatives of the tribal communities that participated in the study. These findings, as well as recommendations for public health action, were published in a special report to the tribes. The study confirmed that Northern Plains Indians suffer

from a high rate of SIDS. In this population, it was observed that drinking rates in case mothers were higher than in control mothers before and during pregnancy. Infants who died from any cause were more likely to have mothers who binge drank in the second half of pregnancy than did control mothers. Smoking rates for case mothers were also higher than for control mothers before, during, and after pregnancy. SIDS mothers also reported fewer home visits by public health nurses or other health care workers during pregnancy or after the baby was born.

The Chicago Infant Mortality Study, conducted in collaboration with the CDC, examined social, environmental, behavioral, and medical risk factors for sudden infant death in a primarily African American inner-city community. Autopsy and death scene investigation protocols were standardized. Preliminary analyses showed that the major modifiable, independent risk factors for SIDS in this population include prone sleep position, soft mattress under the baby, maternal smoking and illicit drug use during pregnancy.

There are several studies in progress to identify physiologic markers of risk for life-threatening cardiorespiratory events and SIDS. One prospective longitudinal study correlates cardiovascular, respiratory and arousal function in the fetus and infant with maternal medical and behavioral risks, SIDS, and poor developmental outcome. The study involves a low-risk population in New York City and a high-risk population in the Aberdeen Area of the IHS. Since it has been shown that SIDS infants have reduced heart rate variability in the first few weeks of life when compared to normal infants, investigators have developed a test for the baroreceptor reflex, which controls heart rate in response to changes in blood pressure. Studies of newborn infants show that the reflex is already present in the first few days of life during deep sleep. In addition, the magnitude of the heart rate response is proportional to the baseline heart rate variability of the infant. In longitudinal studies, a change is observed at two-four months of age, the peak age range for SIDS. The heart rate response to a head-up tilt, while present a birth, is absent by this time and indicates a vulnerability to compensate for decreases in blood pressure. Studies are in progress to longitudinally investigate cardiovascular and respiratory control from fetal life in the low- and high-risk groups and to correlate the responses with toxic exposures in utero, such as tobacco smoke and alcohol.

Prevention and Public Health

The "Back to Sleep" National Public Health Education Campaign

Based on growing epidemiological evidence that sleeping on the stomach increases the risk for SIDS, the American Academy of Pediatrics (AAP) recommended in the spring of 1992 that healthy infants be placed on their sides or backs to sleep to reduce the risk of SIDS. In the spring of 1994, the "Back to Sleep" coalition was formed between the U.S. Public Health Service, the AAP, the Association of SIDS Program Professionals, and the SIDS Alliance for the planning, development, and implementation of the "Back to Sleep" national public education campaign. The campaign was launched in June of 1994. In 1996, the AAP revised the sleep position statement to recommend that the back sleep position is preferred over the side and sleeping position. The "Back to Sleep" campaign materials were revised to reflect this change.

The PPB has been evaluating the implementation and health impact of the AAP recommendation and the "Back to Sleep" campaign since 1992. In collaboration with Boston University, three methods of

evaluation were initiated in the U.S.: (1) annual telephone surveys of nighttime caregivers of infants less than eight months of age in the 48 coterminous states to assess infant care practices and dissemination of the AAP recommendation; (2) periodic surveys of samples of the membership of the AAP, the American Academy of Family Practitioners, pediatric health providers in the National Association of Community Health Centers, and nurses in newborn nurseries to assess provider beliefs and practices regarding the AAP recommendation; and (3) a longitudinal survey of over 15,000 mother-infant pairs in the metropolitan Boston and Toledo areas to assess the effect of the recommendation on infant care practices and health outcomes.

Between 1992 and 1997, the U.S. SIDS rate declined 38 percent from 1.2 deaths per 1,000 live births to 0.77 deaths per 1,000 live births. The decline in SIDS rate correlates with a decline in the proportion of infants who are placed to sleep on their stomachs and also with an increase in the proportion of infants placed on their backs to sleep. The prevalence of infants placed prone to sleep declined at a steady rate between 1992 and 1997, from 70 percent to 21 percent. Since the initiation of "Back to Sleep" there has been a substantial increase in infants being placed to sleep on their back from 27 percent in 1994, to 53 percent in 1997. Multiple logistic regression analyses of the cross-sectional and longitudinal surveys show that African Americans are twice as likely to place infants on their stomachs to sleep as other ethnic groups. This may partially explain why the SIDS rate among blacks, while declining, remains about 2.2 times that of whites. It is likely that the routes of message dissemination and the cultural context in which they are received influence behavioral change among African Americans. The Branch is currently supporting a contract to obtain information on baseline knowledge of SIDS risk factors, how knowledge was obtained, perception of SIDS risk, cultural influences affecting infant care practices related to SIDS risk, and perception of a variety of SIDS educational materials within African American communities across the country.

Another aspect of the evaluation of the "Back to Sleep" message is to examine whether the health of infants is affected by sleeping on their sides or backs. The PPB supported studies in Tasmania and England, where investigators followed birth cohorts in existence before and after interventions to promote non-prone sleeping. These studies showed that there were no discernible adverse health effects of side or back sleeping, such as increases in visits to the doctor or in respiratory problems. The analysis of a U.S. prospective cohort is underway and preliminary results support the findings overseas.

Public Health Guidelines

PPB staff has been instrumental in formulating guidelines to improve SIDS diagnosis and reduce SIDS risk in the infant sleep environment.

In July 1993, the process began to develop guidelines for an adequate, national standard death scene investigation protocol for sudden infant deaths. NICHD and the CDC sponsored a workshop to define the objectives and the necessary data elements for a standard protocol, and provide recommendations for format and strategies for implementation. Using the information obtained at the workshop, the CDC and NICHD developed and published a short protocol form and instructions for its use (*MMWR* 1996;45: RR-10). The protocol ensures that information pertinent to determining the cause, manner, and circumstances of an infant death is considered in each investigation. The form is computerized, can be used for research purposes, and is employed in many jurisdictions across the country.

Based on another workshop convened by the NICHD, the AAP Task Force on Infant Positioning and SIDS and PPB staff developed a statement clarifying the relationship between bed-sharing and risk for SIDS (*Pediatrics* 1997; 100:272). In addition, the statement informed caregivers of the potential hazards of a bed-sharing environment and provided guidelines to reduce the risk of entrapment or overlay of the infant.

COOPERATIVE AGREEMENTS

In 1986, the NICHD established cooperative agreements as administrative frameworks to conduct multicenter randomized clinical trials and other prospective clinical studies in obstetrics and neonatology, in the Maternal-Fetal Medicine Units and the Neonatal Research Networks.

The increase in the rate of LBW infants during the last 20 years was a critical factor in the decision to develop these Networks. In 1985, a total of 255,718 LBW infants (≤2500 grams) were born in the U.S., of which 45,502 were very low birth weight (VLBW) infants (≤1500 grams). The corresponding numbers for 1997 were 292,069 LBW and 55,659 VLBW infants. VLBW infants account for a disproportionately large share of infant morbidity and mortality as well as subsequent developmental problems such as cerebral palsy. Although U.S. infant survival rates improved significantly in the early 1980s, this improvement was largely attributable to regionalization and increasingly effective neonatal intensive care of LBW and VLBW infants. It was clear that further progress in perinatal health would depend on the prevention of preterm delivery and on the continued development of better therapeutic regimens in preterm infant care.

Problems included the pace of change, the number of therapies that were considered standard practice without proper evaluation, and the large sample sizes required to detect statistically significant, clinically important differences. In the highly technical environment of the neonatal intensive care nurseries, principles of management and innovative methodologies were changing within months, before rigorously controlled studies of their safety and efficacy could be initiated, much less completed. The specific aim of the NICHD Perinatal Networks was to provide a format for the conduct of large, multi-center clinical trials and observational studies in maternal-fetal medicine and neonatal medicine.

There are several advantages of clinical trials done within the Networks. First, the Networks provide large populations (approximately 90,000 births per year in the Maternal-Fetal Medicine Units Network and 100,000 inborn infants per year in the Neonatal Research Network, of which 3,600 are VLBW) in 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. Second, since the study population is diverse, a therapy or management strategy shown to be effective across an array of ethnic and socio-economic backgrounds as well as 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. Thus, new trials can be brought online relatively rapidly. In order 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.

The Networks address the need for clinical trials in neonatology and obstetrics, especially those relating to the prevention of LBW infants and their management. They build upon contributions to the clinical trial field, but are unique in that they rely to a greater extent on shared responsibility and commitment.

Investigators in both Networks agree to use common protocols, definitions, and data forms and are linked by a common data center and data entry computer system. Investigators, together with the NICHD 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.

Neonatal Research Network

The original Neonatal Research Network was composed of seven participating centers; in 1991 membership was expanded to include 12 centers. Capitation funding for trials and studies was also introduced at that time. In 1996 membership was expanded to 14 centers. A special Network training fellowship (SCIDA) was introduced in 1995 to support training in clinical research for fellows and junior faculty from Network centers.

The Neonatal Research Network has addressed a variety of issues in neonatology including trials of therapies for sepsis, intraventricular hemorrhage, chronic lung disease, pulmonary hypertension, anemia, acute perinatal asphyxia, and nutrition. The Network has also explored the following major areas of newborn pathophysiology: cerebral function, pulmonary physiology, gastrointestinal function, immunology, the rapid transfer of new technologies to neonatal medicine, and strategies to reduce the cost and preserve the quality of neonatal care.

Randomized Controlled Trials

The first protocol initiated by the original Network was a large, randomized trial of intravenous gamma globulin (IVIG) to prevent sepsis in infants $\leq$1500 grams. IVIG was not effective in decreasing the incidence of nosocomial infection in VLBW infants. Subsequent to the publication of the trial results, use of this expensive therapy decreased dramatically. The original Network also demonstrated that two major forms of exogenous surfactant replacement therapy for the treatment of RDS were equally effective in preventing death and chronic lung disease in VLBW infants.

The second Neonatal Research Network completed randomized, controlled trials of "early" versus "late" steroids to decrease the time to successful extubation of VLBW infants (n=371). Early steroid treatment was no more effective than late steroid treatment, and both were associated with significant growth restriction. A trial of antenatal phenobarbital to prevent intracranial hemorrhage and early death in preterm infants, < 33 weeks gestation (n=668) documented that the substance was not effective in preventing brain injury in preterm infants, although previous smaller trials had suggested that the therapy was protective.

The Neonatal Research Network has participated in a number of international collaborations. In 1997, the Neonatal Inhaled Nitric Oxide Study (NINOS) trial involving 11 Network centers and 10

Canadian centers, tested the efficacy of inhaled nitric oxide (iNO) in decreasing the risk of death or extracorporeal membrane oxygenation (ECMO) in term infants with hypoxemic respiratory failure. This exciting new therapy significantly reduced the use of ECMO, but did not reduce mortality in critically ill infants with hypoxic respiratory failure. Data from this trial will be presented to the Food and Drug Administration to support the application for approval of iNO therapy in newborns. The Network is currently participating in a second trial ("Early iNO") with the NINOS group to evaluate whether the use of iNO in term infants with less severe respiratory failure will decrease the risk of ECMO or death before discharge (n=400). The Neonatal Network also participated in a third international collaboration, the Trial of Indomethacin Prophylaxis (TIPP), to determine whether prophylactic administration of low-dose indomethacin to preterm infants 500–999 grams at birth improves survival without neurosensory impairment at 18 months (n=880). The follow-up of TIPP will be completed by early 2000.

The Neonatal Research Network has also participated in a number of collaborative efforts with other ICs, including a 23-center, randomized trial co-sponsored by NICHD, the National Eye Institute, and the Nursing Institute to test the efficacy of supplementary oxygen in preventing the progression of pre-threshold retinopathy of prematurity. The trial was halted at 660 infants of the 880 sample size anticipated. Currently the data is being analyzed in preparation for publication.

The third Neonatal Research Network conducted a pilot study of vitamin A (n=90) to establish appropriate dosing regimens, followed by a randomized controlled trial of supplementary vitamin A (n=780) to prevent chronic lung disease and nosocomial infection in extremely low birth weight (ELBW) infants. The trial concluded that the vitamin A regimen tested is a safe and inexpensive intervention that reduced evidence of vitamin A deficiency and resulted in one additional infant without chronic lung disease for every 14-15 infants treated.

Two trials to evaluate the efficacy of early erythropoietin (EPO) and supplementary iron administration found that the combination did not reduce transfusion requirements, despite stimulating erythropoiesis in preterm infants <1250 grams.

In 1998-1999, the Neonatal Research Network 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 (CLD) in ELBW infants. The trial was halted at 220 infants enrolled of the 1,200 required because of safety concerns; the conclusions are under review.

Currently, the Neonatal Research Network is conducting a trial of hypothermia in term infants with acute perinatal asphyxia in reducing the incidence of death or disability at 18 months of age (n=200). The Network recently initiated another trial to evaluate whether early parenteral glutamine supplementation of ELBW infants decreases the risk of death or late-onset sepsis (n=1300). Trials of surfactant with immediate extubation and sedation for pain control during ventilation are planned for early 2000. The Network's first benchmark protocol to increase survival without CLD of VLBW inborn Network infants will also be initiated in early 2000. This important project will identify the two Network centers with the lowest rates of CLD as "role models," randomize the other Network centers to a benchmark intervention or control, and facilitate the implementation of center-specific programs designed to reduce the incidence of chronic lung disease.

Observational Studies

In addition to clinical trials, the Network has completed a number of observational studies. Early in the existence of the Network, a detailed registry, called the generic data base (GDB), of all infants born at ≤1500 grams was designed to provide data on the consequences of neonatal disease and therapy and to generate hypotheses for future studies. The GDB now has detailed data on more than 31,500 infants who were ≤1500 grams. Several summary papers on the status of newborn care have been published by the Network, the most recent of which includes inborn VLBW infants cared for between January 1995 and December 1996 (under review *American Journal of Obstetetrics Gynecology*).

A study of the effectiveness of antenatal steroid (ANS) treatment on pregnant women to enhance fetal maturity in 9,949 VLBW infants revealed that ANS use was associated with a decreased risk for mortality, intracranial hemorrhage (ICH), RDS, and CLD among 28-day survivors, even after artificial surfactants were introduced. Among protective factors against severe ICH in VLBW infants, ANS was the only effective therapeutic intervention; other protective factors included ANS treatment, African-American ethnicity, female gender, maternal hypertension, increased gestational age, and increased birth weight. The results of Network studies on ANS treatment and those of three other data bases (total n = 35,000) were presented at the NIH Consensus Development Conference on Enhancing the Maturity of Preterm Infants. ANS treatment of VLBW infants increased from approximately 18 percent before the conference to more than 70 percent 18 months later. Network studies indicate that the increase in ANS use was associated with a decrease in the incidence and severity of severe ICH in VLBW infants.

Additional observational studies, completed prior to randomized clinical trials, documented the impact of therapy on outcome. The introduction of artificial surfactant treatment for 2,780 infants who were 601-1300 grams at birth was associated with a sharp reduction in mortality (27.8 percent to 19.9 percent), suggesting that adoption of surfactant as part of routine clinical care would be widely effective. This conclusion was subsequently verified with a one-year decrease in the infant mortality rate of 6.2 percent.

Adequate nutrition and growth represents another critical issue in the outcome of VLBW infants. Studies to generate new growth curves for VLBW infants (2172 screened) and to determine the accuracy of the new Ballard score to date the gestation of infants < 28 weeks (4420 screened) were recently published. Other manuscripts examined the impact of multiple gestation and gender on VLBW outcome. A study of a bedside method to predict jaundice in healthy term infants (tested by measuring end-tidal carbon monoxide in the exhaled breath) concluded that end-tidal carbon monoxide levels help to explain the mechanisms of jaundice in these infants.

The Neonatal Research Network has undertaken several studies to predict outcome of care, resource utilization, and quality of care in VLBW infants at the threshold of viability. Among an entire birth weight cohort of 501-1500 grams inborn infants (n=3,603), African-American ethnicity was associated with a decreased risk of mortality; however, among the tiniest infants (501-800 grams, n=1,087), ethnicity had no discernable effect on survival, but female gender had a survival advantage equivalent to a 112 grams increase in birth weight. Center differences were striking, with survival

ranging from 10 to 82 percent and total hospital days from 95 to 202 per survivor. Center differences in outcome will be the focus of future efforts.

One of the most important Network efforts has been the development and implementation of a standardized follow-up protocol for evaluating outcome of infants of ELBW born ≤1000 grams at 18- to 22-month corrected age. The follow-up protocol provides the largest standardized follow-up assessment of ELBW infants to date. The first follow-up publication of the outcome of 1,037 infants (mean BW 796 grams ±35 grams), born between 1993 and 1994, demonstrated that 25 percent had an abnormal neurological exam; 37 percent had a Mental Development Index (MDI) of 2 or more standard deviations below the mean (<70); and 29 percent had a Psychomotor Development Index (PDI) of 2 or more standard deviations below the mean (<70). The protective and risk factors for normal neurodevelopmental outcome were explored in the manuscript (in press). A number of additional follow-up studies focus on growth, site differences in outcome, resource utilization after discharge, and family coping skills. The standardized follow-up protocol also evaluates the outcome of the Network's randomized trials; intact neurodevelopmental outcome is assuming an increasingly important role as an outcome of the randomized trials of both Networks.

The Maternal Lifestyle Study (MLS) was developed against the backdrop of debate about the effects of prenatal cocaine exposure in the early 1990s. The MLS is an interagency, collaborative effort involving the NICHD, the National Institute on Drug Abuse (NIDA), the Administration on Children, Youth and Families (ACYF), and the Center for Substance Abuse Treatment (CSAT). The MLS is the largest clinical prospective longitudinal study of acute neonatal events and long-term health and developmental outcomes relative to drug use (cocaine and/or opiates) during pregnancy to date. The MLS addresses methodological issues, including inadequate sample sizes, methods of drug detection, polydrug use, the role of the caretaking environment, the inclusion of preterm infants, and a neurodevelopmental assessment battery sensitive to putative drug effects.

MLS is based on a developmental model that examines prenatal cocaine exposure in relation to child outcome in the context of other developmental influences. Cocaine is included as part of the configuration of risk. Risk factors include other drugs (opiates, alcohol, marijuana, and tobacco), medical factors (LBW, poor health), parenting factors (depression, parenting style), environmental factors (poverty, home environment), and factors in the child (temperament). The cumulative effects of cocaine and other risk factors on child outcome and resilience factors are examined. The study will determine how cocaine and other risk factors impact on development, as well as how the effects of risk factors are modified by resilience factors and pathways to adaptation for drug exposed children.

The MLS study is divided into three phases: Phase I, through hospital discharge; Phase II, a longitudinal follow-up of a subsample of 1,400 exposed and comparison children between one month and three years of age; and Phase III, from 3 years to school performance at 7 years of age. Families were evaluated during 16 visits over a seven-year period with pediatric developmental follow-up and a neurodevelopmental assessment battery, which looks at infant physiologic state, attention, and temperament, maternal-child interaction and attachment, maternal stress and depression, the neighborhood exposure to drugs and violence, etc.

The study, conducted at the University of Miami, the University of Tennessee at Memphis, Wayne State University and Brown University, screened more than 19,000 mothers for enrollment (1993–1995). Of the eligible mothers, 11,800 gave consent to participate in the acute phase of the study.

The Neonatal Research Network will be recompeted in 2001; information on the Neonatal Research Network can be obtained at the Network website: http://neonatal.rti.org.

Maternal-Fetal Medicine Units (MFMU) Network

Overview

The first MFMU Network, consisting of seven sites, was convened in 1986 and has since grown to 13 funded sites. Since its inception, almost 20,000 women have participated in Network studies during their pregnancies. This scientific partnership between NICHD, the funded Maternal-Fetal Medicine divisions, and a data coordinating center has become a strong force in the obstetric literature, and presents regularly at multiple scientific meetings each year. In addition, the Network has extended its research goals to include collaboration with other NIH centers. The MFMU Network's growth and development has furthered the goals of evaluating "real world" practices in obstetric management.

***"Real World" Evaluations of common medical practices*: The treatment of asymptomatic bacterial vaginosis with antibiotics early in pregnancy to prevent premature delivery.**

Based on the scientific literature and the rapidly growing use of prophylactic antibiotics during pregnancy for the prevention of poor birth outcomes in the obstetric community, the MFMU Network designed a randomized double-blind clinical trial to evaluate this "real world" 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. There have also been studies that correlate bacterial vaginosis in pregnancy with LBW babies. Almost 2,000 low-risk and high-risk women were assigned to receive either an antibiotic or a placebo at 16-23 weeks gestation and again at 24-29 weeks gestation. The primary outcome measure was delivery before 37 weeks gestation. Surprisingly, there was no difference in premature birth between the two study groups; premature birth occurred in about 12 percent of pregnancies in each study group. Although the results of the study were negative, these were important findings for the obstetric community. First, mass screening for bacterial vaginosis in pregnancy could not be recommended. Second, although this regimen did not produce the desired improvement in pregnancy outcomes, there may be other treatment regimens that will have an effect. Further research is needed to clarify this situation. Finally, the growing body of evidence indicates that premature birth is a multi-factorial problem.

The MFMU Network continues to rise to the challenge of designing programs and treatments for the prevention of premature births with evidence-based medical practices. Other studies that are currently underway to further examine the multi-factorial basis for premature birth include an evaluation of the contribution of cervical length as measured by ultrasound in the second trimester,

as well as a randomized trial of the use of 17 alpha-hydroxyprogesterone caproate for the prevention of preterm birth in high risk women.

The MFMU Network has also built upon information obtained from its own studies. For example, in the study designed to identify predictive factors for spontaneous preterm birth, fetal fibronectin was found to be a promising biological marker. Consequently, a randomized trial of the treatment of fetal fibronectin positive women with antibiotics to reduce preterm births is currently underway.

Vaginal birth after cesarean section is another real-world evaluation that the MFMU Network has undertaken. The rate of cesarean section has risen dramatically over the past two decades. It is currently the most commonly performed surgical procedure. A substantial proportion of women who undergo a cesarean section have a history of a previous cesarean section. The evidence for the risks and benefits that would assist the obstetrician in counseling women with a history of a prior cesarean section when they become pregnant again 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 vaginal births after cesarean section and to include, along with the study, information on complications, fetal injury, and contributing factors. Records from 13,000 women have been reviewed thus far. This study will be completed in the next one to two years.

***A spirit of trans-NIH collaboration*: The Asthma in pregnancy and BEAM (Beneficial Effects of Antenatal Magnesium) studies.**

As the 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 was a series of three studies, which were co-funded by the National Heart, Lung, and Blood Institute (NHLBI). The need for these studies came from recognition of the growing numbers of pregnant women with asthma and the lack of evidence-based information about how best to treat them. An observational study of mild and moderate asthma in pregnancy, involving 3,000 women was recently completed. Nested within the observational study, the MFMU Network conducted a randomized trial of theophylline versus inhaled steroids to treat moderate asthma during pregnancy. This randomized trial is nearing completion, and the NICHD expects that it will set the standard for asthma care during pregnancy.

The second trans-NIH collaboration is ongoing between the MFMU Network and the National Institute of Neurological Disorders and Stroke (NINDS). This collaboration lead to a randomized study of the effectiveness of antenatal magnesium in the prevention of cerebral palsy. This is a complicated protocol involving the evaluation of intravenous magnesium during labor in more than 2,000 infants of <32 weeks gestation. These infants are at high risk for complications of prematurity. This study is currently underway and over 600 infants have been recruited.

Finally, funding for a study of pharmacokinetics was provided by the NIH Office of Research on Women's Health (ORWH) in recognition of the widespread use of medications in pregnancy that are not well studied for use during pregnancy. Pregnant women are often excluded from clinical trials, resulting in product labeling that does not address pregnancy. It is the intent of these funds to attempt to address the common clinical practice of off-label drug administration. These funds will be distributed to MFMU Network centers that submitted proposals in the area of pharmacokinetic studies of certain drugs in pregnancy.

As the MFMU Network has become established, the possibilities for productive collaboration have increased and now seem limitless. Without the investigative spirit to examine practices that may be difficult to study or controversial, these collaborations and difficult study questions would not be possible. Teamwork is an important element in the Network studies. This investigative spirit must extend from the principle investigator, to the nurse coordinator, to the rest of the staff at each MFMU Network center. The staff of the MFMU Network looks forward to another successful grant period and to the future of improving care in pregnancy and childbirth.

SIDS - The Collaborative Home Infant Monitoring and Evaluation Study (CHIME)

The Collaborative Home Infant Monitoring Evaluation (CHIME) Study, a multicenter, cooperative study of home monitoring high-risk infants is now complete and analyses are in progress. Almost 1,200 infants were enrolled in the following subject groups: healthy term infants, preterm infants <1750 grams, siblings of SIDS infants and babies experiencing an idiopathic apparent life-threatening event. The objectives of the study were to: determine whether home-apnea monitors that employ event recordings are effective in identifying episodes that are dangerous to the infant's health; determine the conditions that optimize the use of apnea monitors in high-risk infants; correlate physiological markers, health status, and behavior with the propensity for life-threatening events; and provide important information on the maturation of heart and respiratory function in sleeping infants. Infants were followed in their home environments for six months.

The CHIME study has made several advances in the interface between clinical research and technology development. The NICHD, CHIME investigators, and industry collaborated in the development of new monitoring technology, which is being tested for its potential to detect and record life-threatening cardiorespiratory episodes. The technology incorporates 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 captures the physiology for a period before, during and post-event, the monitor is programmed to store continuous R-R intervals from the ECG, continuous breath-breath intervals, and normative three-minute epochs at hourly intervals. A data archive will be placed on CD-ROM for future dissemination to the scientific community. This wealth of data will aid in the investigation of developmental and physiologic processes leading to severe cardiorespiratory events and of the mechanisms of recovery from these events.

CHIME investigators have developed special protocols for scoring the cardiac and respiratory tracings recorded by the monitor and for scoring sleep state from the polysomnographic studies. These scoring protocols result in high agreement and consistency between the observers, which are important requirements for clinical diagnosis and research. Comparative analysis of simultaneous recordings of thermistor and flow signals from polysomnography, with the CHIME monitor recordings, shows that the CHIME monitor detects cardiorespiratory events that include obstructed breaths. This is an important advance for a home monitor. The cessation of airflow in the presence of continued respiratory effort is believed to be a significant stress for infants and is more common in infants who die of SIDS.

The CHIME study is already providing valuable information regarding the developmental physiology of term and preterm infants. Preliminary analyses of the recordings of preterm infants reveal that they experienced prolonged apnea after reaching a postconceptional age equivalent to term. The apneas include more than one obstructed breath. Over 40 percent of the prolonged apneas were associated with desaturations, but less than 10 percent with bradycardia. Investigators concluded that respiratory control remains immature past term in preterm infants. A study of oxygen saturation in healthy term infants showed that they generally have baseline levels at >95 percent saturation, but transient acute desaturations do occur. These decreases were correlated with younger age, periodic breathing, and apnea. They appear to be part of normal breathing and oxygenation behavior.

CONFERENCES AND WORKSHOPS, 1995-1999

Since the last report to Council, staff has organized several meetings and participated in national and international workshops.

The Branch supports a yearly **Trophoblast Workshop**, held in conjunction with the meeting of the Society for Gynecological Investigation.

Every two years the Branch convenes a **Perinatal Emphasis Research Center (PERC) Meeting**, held at one of the support center or program project doing research in perinatology.

- **Pregnant Women in the Workplace: Sound and Vibration Exposure, February 22-23, 1996, Gainesville, FL**

- **4th SIDS International Conference, June 23-26, 1996, Bethesda, MD**
  Co-sponsored with the SIDS Alliance.

- **Placenta and Child's Brain, July 18-19, 1996, Bethesda, MD.**
  Co-sponsored with NINDS.

- **Infant Sleep Environment and SIDS Risk, January 9-10, 1997, Bethesda, MD.**

- **"Mi in a kin towani ewaktonji kte ni", "I will never forget my child", September 17-19, 1997, Rapid City, SD.**
  Co-sponsored with CDC and the Indian Health Service.

- **Postpartum Hemorrhage and Placenta Accreta Conference, February 11-12, 1998, Detroit, MI.**
  Co-sponsored with the Perinatal Research Branch, NICHD.

- **SIDS pathogenesis- Approaches to Identifying High Risk Infants, September 13, 1998, Lake Arrowhead, CA.**

- **Colloquium Perinatal Endocrinology, September 20-22, 1998, Nancy, France.**
  Co-sponsored with Universite Henri Poincare, Nancy, France.

- **Bed Coverings for Infants: What is safe? December 8, 1998, Bethesda, MD.**
  Co-sponsored by Consumer Product Safety Commission (CPSC).

- **Epidural Conference, February 19-20, 1999, Bethesda, MD**
  Co-sponsored with the Perinatal Research Branch, NICHD.

- **Endothelial Derived Vasoactive Substances and Free Radicals in Perinatal Biology, May 6-8, 1999, Alexandria, VA.**

- **Workshop of Sleep Needs, Patterns, and Difficulties of Adolescents, Forum on Adolescence, Board on Children, Youth, and Families, National Academy of Sciences, September 22, 1999, Washington, DC**

- **Fetal Origins of Adult Disease, September 2-3, 1999, Bethesda, MD.**

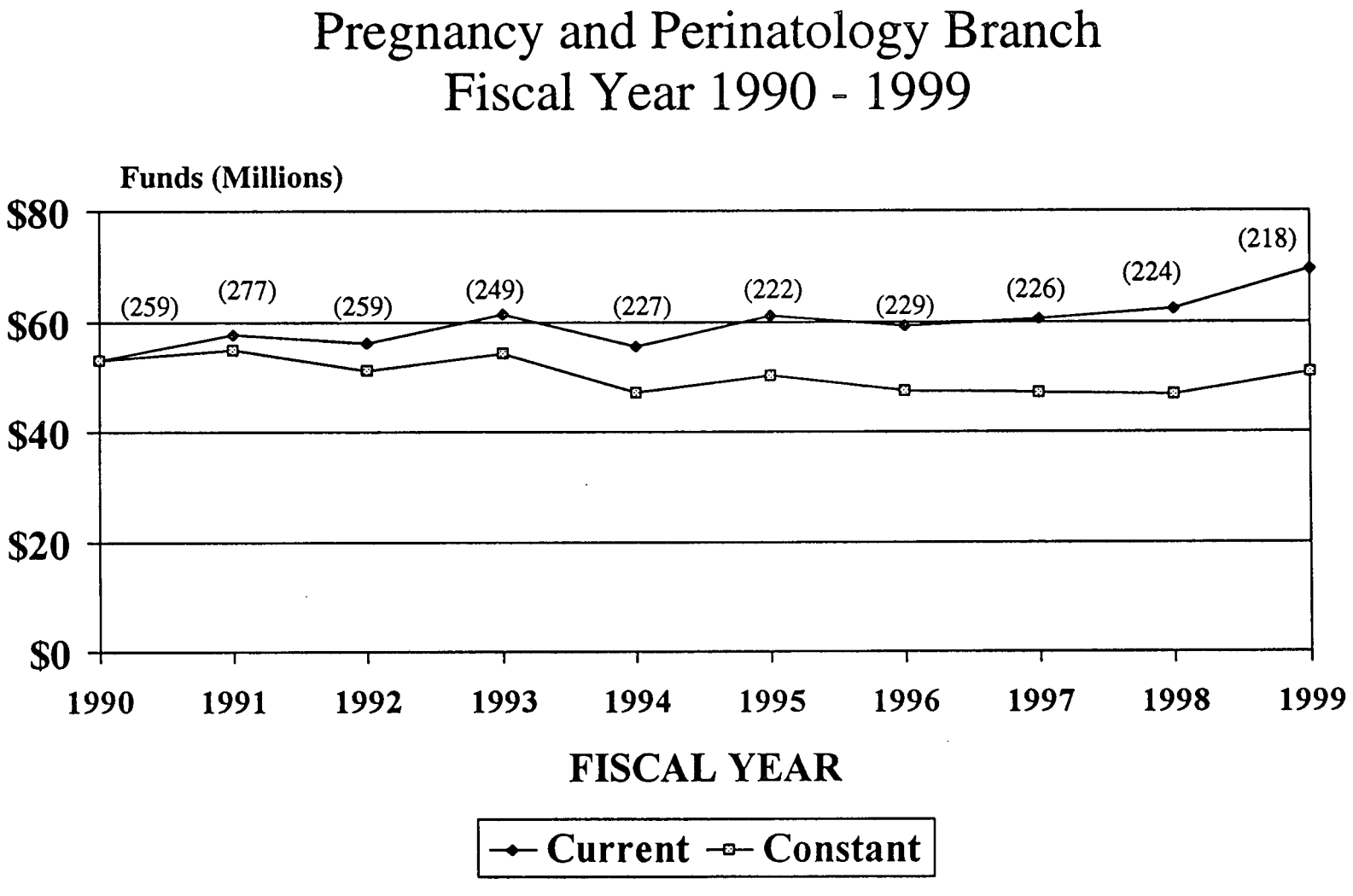
  Co-sponsored by NHLBI, NIDDK, Office of Research on Women's Health and NICHD (ENG Branch and PP Branch).

TABLE I

PPB PROJECTS BY PROGRAM AREAS, FY 1999	#	FUNDS
Maternal		
Basic	7	$ 1,393,879
Clinical	45	$16,307,590
Fetal		
Basic	35	$ 7,932,414
Clinical	4	$ 714,093
Placental	25	$ 5,260,596
Labor and Delivery	52	$12,449,376
Neonatal		
Basic	9	$ 2,122,923
Clinical	24	$ 9,856,527
SIDS		
Basic	15	$ 3,746,804
Clinical	18	$ 3,475,805
SUBTOTAL	234	$63,260,007
TRAINING		
F32	4	$ 148,672
T32	9	$ 1,266,248
K's (01-04-08-12-23-24)	10	$ 1,797,277
SUBTOTAL	23	$ 3,212,197
TOTAL	257	$66,472,204

The Cooperative Agreements are included under Maternal, Neonatal, and SIDS categories in the above table.

FIGURE I, Grants/Contracts, Current and Constant Dollars, 1990-1999



* BASE YEAR (1990=100)
Numbers in parentheses represent the number of projects.

FIGURE II, Branch by Program Category, 1995-1997-1999

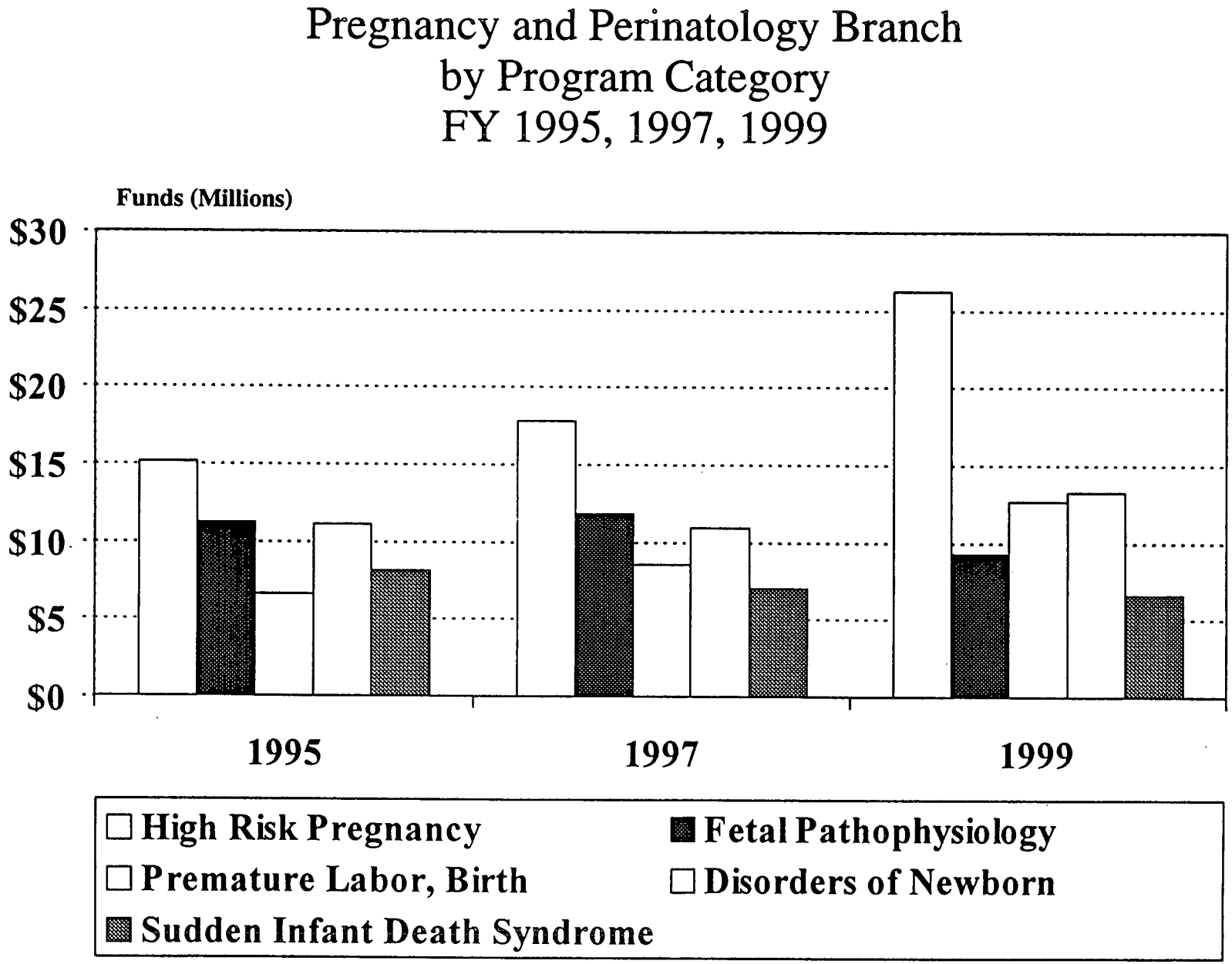
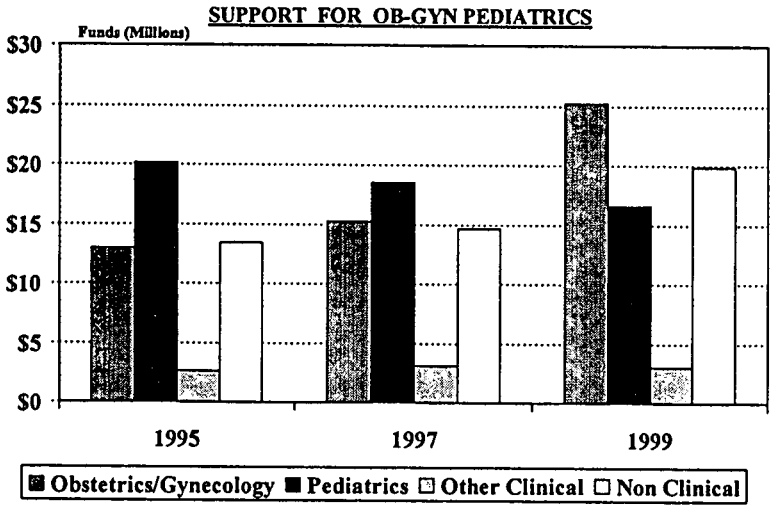
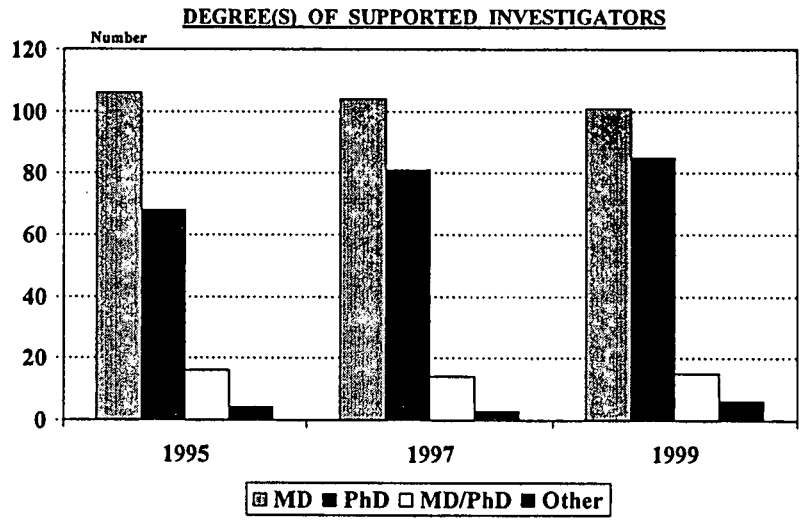
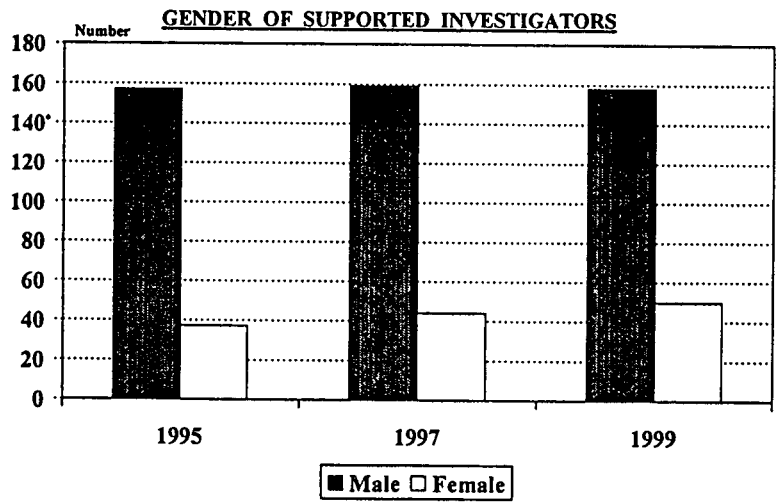


FIGURE III, IV, V, Supported Research by Departments, Investigator's Degree, and Gender, 1995-1997-1999

Pregnancy and Perinatology Branch
FY 1995, 1997, 1999







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BIOGRAPHICAL SKETCHES

Charlotte Catz, M.D., a board-certified pediatrician, is the Pregnancy an Perinatology Branch Chief and for the last two years is the Acting Deputy Director of the Center for Research for Mothers and Children. She is an ex-officio member of the Maternal and Child Health Research Grants Review Committee of the Health Resources and Services Administration; member of the Trans-NIH Sleep Research Committee; member of the Pediatric Scientist Development Program Steering Committee and of the Reproductive Scientist Development Program Executive Committee. She represents NICHD on the NIH Committee overseeing the activities of the K30 program. She is a faculty member of NICHD's Annual Aspen Perinatal Training Program. She serves on the Data Safety and Monitoring Committees for the three Networks supported by the Branch.

Kimberly Howell joined NICHD in April, 1999. She formerly worked on large epidemiological multi-center trials at the George Washington University Biostatistics Center. Kimberly attained her Masters Degree in Organizational Psychology at Columbia University. Her organizational skills combined with her interest in clinical trials led her to NIH, where she serves as the Network Coordinator of the MFMU Network.

John V. Ilekis has recently joined our branch, and holds a Ph.D. in biology. Dr. Ilekis is responsible for managing grants dealing with the physiology and biochemistry of the placenta, myometrium and cervix. Prior to joining our branch, he was a Research Assistant Professor in the Department of Obstetrics and Gynecology at the University of Illinois at Chicago. Dr. Ilekis' area of research was the study of growth factor receptors in reproductive tissues.

Elizabeth M. McClure, M.Ed., is the Network Coordinator for the NICHD Neonatal Research Network. In conjunction with the Network Program Official, she plans and coordinates the activities of the NICH Neonatal Research Network and prepares the capitation budgets for protocols.

Susan Meikle, M.D., M.S.P.H. is board-certified in obstetrics and gynecology and preventive medicine. She recently joined NIH from the Centers for Disease Control and Prevention where she worked in the areas of HIV in women, refugee reproductive health, and assisted reproductive technology. Dr. Meikle has co-authored an obstetrics book chapter on evidence-based medicine and a surveillance chapter in a refugee reproductive health manual in addition to peer-review articles on infertility, length of hospital stay after vaginal delivery, and laparoscopic-assisted vaginal hysterectomy. She has been active clinically, most recently as a clinical assistant professor at Grady Hospital in Atlanta and previously as a locum tenens with the Indian Health Service.

Dr. Jonelle C. Rowe is a board-certified Neonatologist and Professor of Pediatrics at the University of Connecticut School of Medicine. Prior to coming to NICHD in 1998, she was Chief of the Division of Neonatology at the University of Connecticut Health Center. Rowe is currently a Health Scientist whose responsibilities include project management of a multi-centered trial on pain prevention in premature infants and other NICHD funded projects. She is a member of the Society for Pediatric Research; her area of clinical research at Connecticut was neonatal nutrition.

Marian Willinger, Ph.D is the Special Assistant for Sudden Infant Death Syndrome. She is responsible for the direction of the SIDS research program for the NICHD, which has included the development of two five year research plans, and serves as the expert for SIDS within the U.S. Public Health Service. She is the Program Officer for the Collaborative Home Infant Monitoring Evaluation Study as well as for contracts designed to elucidate SIDS risk factors. She has been involved in the development, implementation, and evaluation of the "Back to Sleep campaign, and serves as a consultant to the Task Force on Infant Positioning and SIDS of the American Academy of Pediatrics. Within the last five years, Dr. Willinger has participated in number of NIH and government-wide activities including: the Advisory Board of the National Center on Sleep Disorders Research, the NIH Working Group on Archiving and Sharing Data, the Health Committee of the Gore-Primakov (Chernomyrdin) Commission, and the Interagency Work Group on Child Abuse and Neglect.

Linda L. Wright, MD, is a board-certified neonatologist and the Program Official for the NICHD Neonatal Research Network. She serves as the NICHD liaison to the Committee on Fetus and Newborn of the American Academy of Pediatrics. She is a faculty member of NICHD's annual Aspen Perinatal Training Program and has participated in a number of NIH-wide activities, including membership on the NIH Director's Working Committee on Clinical Trials (as Chairman of the Data Access and Data Center Monitoring Subcommittee). She has consulted on the development of several NIH Cooperative Agreements and served on a number of Data Safety and Monitoring Committees for large randomized controlled trials. Dr. Wright is the Project Officer for the contract that supports the Cochrane Neonatal Collaboration meta-analyses. She has recently coordinated the development of the NICHD clinical trials web site.