

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

AREA OF OPPORTUNITY: PREMATURITY

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

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

RESEARCH GAPS AND OPPORTUNITIES

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

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

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

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

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

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

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

NEW DIRECTIONS AND APPROACHES TO ADDRESS GAPS

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

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

PRIORITY OF AREA OF OPPORTUNITY WITHIN THE PPB

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

INFRASTRUCTURE RESOURCES NEEDED

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

Environmental and Genetic Influences

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

Health Disparity

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

Technology Development

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

Research Risk and Ethical Aspects of Research

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

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

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

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

RESEARCH GAPS AND OPPORTUNITIES

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

1. Tools for Defining Fetal Growth

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

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

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

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

Examples of stressors include:

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

3. Epidemiological Associations of Specific Intrauterine Stressors and Later Outcomes

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

Examples of needed studies include:

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

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

4. Biological Integration of Effects during Intrauterine Stress

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

Examples include:

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

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

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

6. Intergenerational Programming

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

7. Post-Fertilization Biology

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

8. Maternal Stress during Pre- and Postnatal Life

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

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

9. The Role of the Placenta in Programming

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

10. Structured Repository of Developmental Information

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

AREA OF OPPORTUNITY: MATERNAL MORBIDITIES— HYPERTENSION AND THROMBOPHILIAS

HYPERTENSION

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

Research Gaps

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

Research Goals and Opportunities

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

New Directions and Approaches to Address Gaps

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

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

THROMBOPHILIAS

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

Research Gaps

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

Research Goals and Opportunities

- Understand the fundamental pathologic processes involved patients harboring these conditions, in order to:
 - o Enable accurate counseling regarding personal, fetal, and neonatal risk assessment surrounding pregnancy;
 - o Stratify the at-risk patient population to assess risk for thromboembolic events and adverse pregnancy outcomes; and
 - o Base prevention and treatment strategies based upon risk assessment.
- With the natural history of the individual thrombophilic mutations and pathologic mechanisms elucidated, focus on specific prevention and treatment strategies.

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

New Directions and Approaches to Address Gaps

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

Priority of Area for PPB

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

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

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

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

RESEARCH GAPS AND OPPORTUNITIES

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

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

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

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

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

RATIONALE

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

PRIORITY OF AREA OF OPPORTUNITY WITHIN PPB

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

AREAS OF INQUIRY

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

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

RESEARCH GAPS AND OPPORTUNITIES

Sonography and Fetal Imaging

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

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

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

Noninvasive Markers in Maternal Serum and Urine

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

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

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

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

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

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

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

Preimplantation Genetic Diagnosis (PGD)

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

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

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

Fetal Therapy

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

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

Infrastructure Resources Needed

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

Health Disparity

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

Research Risk/Ethical Aspects of Research

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

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

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

RESEARCH GAPS AND OPPORTUNITIES

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

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

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

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

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

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

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

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

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

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

AREA OF OPPORTUNITY: TRAINING

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

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

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

PHYSICIAN-SCIENTIST

How to attract them?

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

Action Steps for PPB

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

- Summer research
- Research electives
- Year-out programs

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

- Resident research educational programs
- Year-out programs

Action Steps for Other Resources

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

How to maintain involvement?

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

Action Steps for PPB

Maintain interest in research by:

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

Action Steps for Other Resources

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

How to assure success?

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

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

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

Action Steps for PPB

Maintain interest in research by:

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

Action Steps for Other Resources

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

NON-PHYSICIAN SCIENTISTS

How to attract them?

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

Action Steps for PPB

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

- Summer research
- Laboratory rotations
- Year-out programs

Action Steps for Other Resources

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

How to maintain interest/involvement?

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

Action Steps for PPB

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

How to assure success?

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

Action Steps for PPB

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

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

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

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

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

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

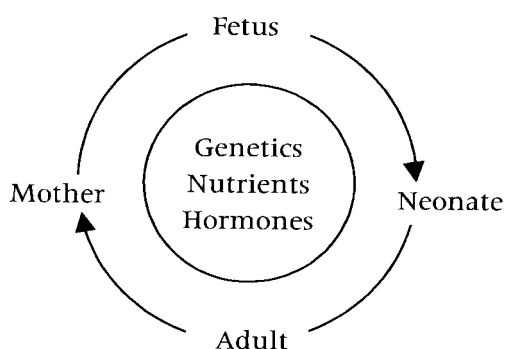
FETAL GROWTH AND ITS LONG-TERM CONSEQUENCES

The data from human studies strongly suggests that “thinness” at birth is associated with chronic diseases in adulthood, such as type II diabetes, coronary artery disease, etc.

However, a number of inconsistencies in the reported data, conflicting data, selection bias, and ecological trends have raised some concern regarding this hypothesis and will need to be addressed in the future. Additionally, the mechanism(s) of IUGR and the mechanism of development of chronic disease have not been addressed. These topics are particularly important because identification of various mechanisms will allow development of intervention strategies and examination of their effectiveness.

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

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



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

INTERVENTIONS IN THE NEONATE

Although short-term impact of nutritional and other interventions in the neonate are well known, their impact on health during adolescence and adulthood is not known. Studies in animals (rats) provide strong evidence that nutritional experiences during the newborn period can have consequences in the adult. The data of Patel and colleagues have clearly demonstrated that newborn rats, exposed to a high carbohydrate diet until weaning develop hyperinsulinemia as adults, become obese, and develop resistance to insulin action. Of significance, the pups of these obese mothers, although of normal size at birth, become obese as adults. Such animal models provide unique opportunities for the study of nutritional/hormonal and other factors that influence the phenotype, perhaps via epigenetic mechanisms.

Research Gaps

Prospective studies in humans, using state-of-the-art methods in a carefully identified contemporary cohort are required to distinguish the genetic, nutritional, metabolic, and hormonal influences during pregnancy that impact fetal growth, and to examine the relationship between size at birth and adolescent and adult health. It should be underscored that, by influencing the expression of multiple genes at appropriate times in development, the intrauterine environment during pregnancy may have a major impact on both physical and functional phenotypes.

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

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

Health Disparity

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

Evaluation of Interventions

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

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

Outcome Measures

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

OTHER AREAS OF FUTURE EMPHASIS

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