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From Cells to Selves

National Institute of Child Health and Human Development
From Cells to Selves
FROM CELLS TO SELVES:
NICHD CHARTING A FUTURE COURSE

FOREWORD

The National Institute of Child Health and Human Development (NICHD) is setting forth its strategic ideas that will guide many, but not all, of its major research initiatives over the next several years. This plan is useful for Institute staff, the scientific community, and the public, all of whom have had a role in its preparation by providing a set of priority research areas that will serve as the framework for Institute initiatives and enhanced funding.

Establishing such a strategic framework is a challenge for all Institutes, but is especially so for the NICHD due to the enormous diversity of its mission and to the areas of science that it actively pursues. But, it is an extremely important effort because so much of the health and well-being of the world’s population depends on the success of our research. To us falls the task not of curing a single disease or group of diseases but of solving the fundamental question in biology and all that derives from it: how does a single fertilized egg develop into a fully functional adult human being, and how do a multitude of genetic and environmental factors influence that process for good or for ill. Thus the title of this plan: “From Cells to Selves.”

Solving this fundamental question is the key to the Institute achieving its mission: helping parents to have the children they want at the times they want them, helping every child be born healthy and every mother suffer no adverse consequences of the pregnancy, helping every child reach adulthood free of disease and disability and able to achieve his or her full potential; and ameliorating the consequences of physical or mental disability to enable all individuals to function as fully as possible in society. To the extent that we succeed, we will solve many of the world’s most significant problems: ending unchecked population growth, minimizing mortality and morbidity of children, establishing a healthy physical and social environment, maximizing learning ability, preventing adult disease that originates prenatally or in childhood, and developing healthy behavioral and social skills that are essential for success as well as for avoiding hostile interpersonal actions in a complex and diverse society.

The research efforts required to address these issues are as extensive and diverse as the scientific topics they encompass. These topics involve many disciplines, skills, and techniques, so that a “strategic framework” cannot possibly address them all. Consequently, this plan highlights some current areas for major emphasis due to their importance and the emergence of scientific opportunities to address them. Future planning efforts will address additional areas.

It is our hope that this framework will guide our research in significant directions, and advance our gain in scientific knowledge so that we will forward the mission of the NICHD to the benefit of all those who depend on our success.

Duane Alexander, M.D.
Director
National Institute of Child Health and Human Development
The NICHD Today

Bearings

Our Unique Mission...

In 1962, a task force report to President Kennedy called for establishing an Institute at the National Institutes of Health (NIH) that could “launch a concentrated attack against a range of disorders inherent in human development, and help coordinate the research into the physical, intellectual and emotional growth of children.” Thus, the NICHD was born, the first national agency to concentrate research on the normal processes of growth and development upon which the health of both children and adults universally depends.

Important additions to our mission came when President Johnson directed the Institute to address questions concerning population and human reproduction, as the Nation and the world recognized the increasing burdens posed by unrestrained population growth. This research was to include basic biomedical, contraceptive, and behavioral studies. Finally, recognizing the need to improve the health and care of persons with disabilities, Congress established the National Center for Medical Rehabilitation Research in the NICHD to help restore, replace, enhance, and prevent decline in function.

Over time, the Institute has remained dedicated to its mission. Researchers need to know what makes healthy development happen: what are the factors and processes involved, how do they work, how can they be encouraged to evolve properly and how can they be corrected when mechanisms go wrong? It starts with trying to understand what leads to the production and union of healthy cells needed for reproduction—what can go wrong with the process, what can pose obstacles, and what is the cascade of finely choreographed steps that must occur to transform these individual cells into fully functioning individuals. The science starts early and involves understanding every biological and behavioral factor governing the long-term growth and development upon which the health of infants, children, youth, and families depends. No NIH Institute directly addresses this broad array of scientific issues except for the NICHD.

... In a Changing World

As the Institute has evolved, so has the science that its supports and the challenges that it faces. Although science has produced more answers, it has given us more questions and revealed a world far more complex than we imagined. When the NICHD started as an Institute, scientists searched for the one gene, the one protein for one disease; but this “singular” concept is no longer valid. Researchers now know that it is far more complicated than this. For example, for cystic fibrosis, researchers have documented at least 800 different abnormalities or variations in the gene associated with the condition; some may influence the severity of the disease, others may not.

There are also multigene diseases, involving the interaction of several different genes, which can influence whether one develops a disease or not. Add to this the idea of having many different “environmental” or “outside” factors that help determine if or how a gene gets expressed, and the number of possible answers and the potential for new questions only increases.
Thus, over the decades, science has demonstrated that no simple or single answer exists. Even when no genetic factors are implicated, scientists now know that the complex interaction between many different biological and external factors, starting as early as the prenatal period, can influence developmental and long-term outcomes—physically, cognitively, emotionally, behaviorally, and socially. This, in turn, has led to vast differences in health outcomes between and among various population groups, across the Nation and the world. The NICHD mission is dedicated to solving human issues in the face of emerging knowledge and changing needs.

**Strategic Forces**

Our Strategic and Scientific Strengths

**Multidisciplinary and Creative Solutions**— For the NICHD, a great strength lies in the breadth and the diversity of its science. To answer the varied and complex questions implied by our mission requires the insights of many disciplines. This includes experts in molecular and developmental biology, genetics, neurology, obstetrics, gynecology, pediatrics, psychology, psychiatry, orthopedics, physiatry, immunology, endocrinology, sociology, demography, anthropology, primatology, and epidemiology, just to name a few. The exchange of ideas from vastly different domains can lead to novel collaborations and creative solutions.

**Home to Vast Array of Scientific Opportunities**— The science embodied in the Institute’s mission encompasses some of today’s most exciting research opportunities. Starting with genetics and its potential applications, it also involves understanding the basic science of germ cells (the sperm, the egg); the amazing power of some of the earliest human cells (stem cells) before they transform into recognizable tissue; the potential to discern how events in utero may dictate significant health consequences decades in the future; and the potential to answer the nature versus nurture question in shaping human behavior.

**Key to Prevention and Cures**— Inherently, advancing NICHD’s mission can lead to one of the most elusive yet prized goals of medical science and public health—prevention and cures. Understanding human development provides essential knowledge for actually preventing and treating a range of diseases, conditions, or undesirable outcomes. Inherently, understanding how and why biological and behavioral processes evolve over time, and what “goes right,” highlights ways to prevent these same events from “going wrong.” Conversely, understanding why processes go wrong provides clues as to how to encourage them to “go right.” Because prevention and the potential for treatment may start well before birth, NICHD research holds promise for a range of conditions that have early roots but may be manifest anytime starting before birth to later in life. For instance, this includes:

- before conception (unintended pregnancy, inherited diseases, infertility)
- in utero (miscarriage, birth defects)
- at birth (prematurity, low birth weight)
- as a toddler/preschooler (autism, mental retardation)
- as a child (learning disabilities, trauma/injuries)
- as a teenager (eating disorders, violent and risky behaviors)
- as an adult (obesity, heart disease, Type 2 diabetes, gynecologic conditions, sexually transmitted diseases)
- in later years (osteoporosis).
Translating Science to Meet the Needs of Special Populations and Eliminate Health Disparities— The NICHD mission requires that knowledge be transformed into practice for all of the special populations that the Institute serves: women, infants, children, adolescents, families, and persons with disabilities. This “translational” research is all the more important because of the health disparities that result from the many forces influencing early human development. Because its mission targets all of the factors that may lead to disparate paths and health outcomes, the key to understanding, if not eliminating, “health disparities” lies in much of the basic and applied science that the NICHD supports.

Our Strategic and Scientific Challenges

Establishing scientific priorities, in the face of naturally limited resources, is perhaps one of the Institute’s greatest challenges— especially in view of the breadth of its mission and the diversity of disciplines and range of patient groups that have a stake in NICHD’s progress. This is combined with the challenges of:

• Taking advantage of rapidly emerging and some of the most “explosive” technological advances in science today. This entails not just initiating research, but doing so efficiently and collaboratively, while meeting shared, as well as unique, goals across the NICHD and the NIH. This may mean selectively and strategically approaching scientific, financial, and administrative opportunities, as well as identifying and creating research opportunities where they are critically needed.

• Ensuring that the Institute’s clinical research keeps pace with basic research, and that our basic science leads to clinically relevant outcomes. This includes outcomes for all populations, including those with special or unmet needs. Ultimately, NICHD’s research success will be evident in the enhanced health of future generations of parents, infants, children, adolescents, and young adults.

• Providing unique resources, training, and infrastructure to bring the Institute’s diverse disciplines together to accomplish our goals.

• Acknowledging the ethical challenges inherent in our research and working with scientists, policymakers, and the public to share a common and correct understanding of the issues. This understanding, in turn, should lead to judicious priorities and shared goals.
Future Goals

For the NICHD, the future promises a substantial range of achievements, guided by a series of goals. This includes a vision:

• To create and apply the knowledge to understand the developmental origins of health disparities. This would allow scientists, clinicians, and policymakers to reduce or eliminate disparities, starting with differences in infant mortality rates and extending to all developmental outcomes as children develop into functional and healthy adults.

• To create and apply the knowledge to ensure that global well-being is no longer threatened by unchecked population growth.

• To create and apply the knowledge to better address reproductive health with its far-ranging sequelae and lifelong impact, particularly on women’s health and well-being.

• To create and apply the knowledge to increase the likelihood that all birth outcomes are predictable and good. This would include eliminating perinatal transmission of infections (including HIV) and delivering full-term babies—no matter the race or ethnicity of the mother.

• To create and apply the knowledge to prevent birth defects, inherited disorders, mental retardation, and developmental disabilities. Where this is impossible, the NICHD will create and apply the knowledge to treat children and youth based on their unique needs, rather than what we know about adults. This treatment would also apply to children’s experiences with injury and trauma.

• To create and apply the knowledge, as well as effectively harness the newest technologies, to rehabilitate, persons with disabilities and to enhance their functional capabilities and productivity, based upon scientific facts rather than on myths.

• To create and apply the knowledge to better understand the developmental and biological processes dictating the physical well-being and growth of infants, children, and adolescents.

• To create and apply the knowledge concerning the developmental and biological bases of behavior, including cognition, language, learning, memory, emotions, and motor and social functions. This knowledge would be used to address some of the most serious health problems facing youth today.
A Global and Compelling “Burden of Disease”

The NICHD’s goals are far-reaching because there is no one set or type of diseases or conditions that accurately captures the breadth of our mission. Unlike many other Institutes that can quantify a specific disease burden, the vast numbers affected by our mission go beyond counting the number of premature babies, infants who die, children with mental retardation or a specific set of developmental disabilities, women suffering with a range of gynecological-related conditions, couples unable to have children, youth who adopt risky behaviors, or children with a range of inherited disorders and birth defects. The totality of the human and economic impact is virtually impossible to quantify.

The impact of the Institute’s research should be counted in terms of every couple hoping to become parents, every couple wanting to avoid an unintended pregnancy, every woman dealing with the biological consequences of her reproductive capacity, every infant born, every child meant to thrive, every person with a disability seeking full functioning, and every adult wishing to avoid major chronic health conditions that start early in youth. Much of the health and well-being of the world’s population depends on the success of our research.

Operational Planning

Reflecting the complex nature of our mission, the NICHD has long supported a planning process that occurs at many levels.

• Every extramural branch is responsible for conducting a review of its scientific accomplishments, opportunities, and needs, while addressing future plans. This is consolidated into a branch report that is presented to the Institute’s National Advisory Child Health and Human Development Council, once every 4 years, in a process that is open to outside review and comment. All branches complete reviews on a rotating basis.

• The Board of Scientific Counselors (BSC) also reviews the research of every laboratory and branch in the Division of Intramural Research on a rotating basis, once every 4 years. In addition to commenting on current activities, the BSC evaluates plans for and makes suggestions concerning future research directions. These comments and reviews are also shared with the NICHD Council.

• Twice a year, every extramural and intramural Center and Division develops a plan for its individual, as well as collaborative, trans-Institute and trans-NIH scientific conferences and workshops. These conferences and workshops constitute reviews of emerging scientific opportunities, public health concerns, or state-of-the-science assessments, many of which outline specific areas of research that should be the target of future initiatives or activities. Consensus development conferences also may be held. Besides yielding clinical recommendations, future research directions are outlined.

Representatives from an array of scientific institutions and organizations, other Federal agencies, industry, advocacy groups, and other non-profit groups participate actively in these proceedings.
• Annually, staff are asked to translate these activities and recommendations into research initiatives that can be implemented starting within 18 months. Staff are urged to develop collaborative efforts, where possible, that build on the expertise or cosponsorship of other branches, Centers, Institutes, agencies, industry, and public groups supporting similar research. While priorities are first suggested by the Centers, ultimate approval for initiatives is linked with strategic concerns and priorities, such as those outlined in this document.

• Every 2 years, the NICHD outlines “scientific emphasis areas” (SEAs) that guide the Institute in deciding which investigator-initiated projects, of those that fall just beyond the certain funding range, should be supported. Staff initially suggest these areas based on portfolio reviews and many of the above activities. Once outlined, the areas are discussed in public forums, which include scientific experts and the NICHD Council, where the concepts are further refined before being published.

Strategic Planning

Criteria

For the NICHD, strategic planning involves charting future research activities within a longer horizon—3 to 5 years. This entails amassing knowledge from ongoing planning activities and highlighting those areas that:

• Are critical to our mission and represent topics in which significant gaps in knowledge remain, or where concentrated efforts are required to take research quickly to the next level

• Capitalize upon emerging scientific and technological advances, which demand concentrating resources and encouraging collaborations to yield significant returns on investment

• Represent important public health concerns that require new strategic, coordinated, and multidisciplinary efforts.

Because of the breadth of our mission and the natural limit of resources, the NICHD decided to identify a few major strategic areas that, when outlined, could provide a “framework” for targeted activities over the next 3 to 5 years. The strategic goals and emphasis areas so outlined would suggest areas for immediate attention and, as presented here, would be further developed into detailed research agendas suggesting specific research initiatives and resource needs.

Identifying Strategic Topics

To identify initial research topics, staff members drew upon their many ongoing planning efforts, and suggested research agenda items, previous emphasis areas, and issues emanating from many NICHD-sponsored forums, workshops, and conferences. Simultaneously, a group of nine scientists from across the nation were identified (their names are included in the Appendix, marked with an asterisk [*]). They are all members of the Institute of Medicine or the National Academy of Sciences and were selected for their objectivity and broad understanding of future science, across the spectrum of basic to clinical research that is core to our mission. These advisors were invited to join the Director and Deputy Director to review and discuss the mission and current activities of the
Institute, as well as the initial strategic areas outlined by staff. Ultimately, they were asked to offer their own suggestions for future research, identifying emerging science, urgent needs, unusual opportunities, and new directions that could be topic areas for a strategic research agenda.

Seven broad areas emerged from these discussions:

- Developmental Biology/Understanding Normal and Abnormal Human Development, including basic developmental and behavioral biology
- Management of Fertility and Improving Reproductive Health, including overcoming infertility, contraceptive development, and research into gynecologic conditions
- Genetics of Susceptibility to Diseases and Disorders, including gene therapy
- Understanding the Mechanisms that Lead to Racial, Ethnic, and Social Disparities, covering a wide range of science inherent in our research mission
- Preventing Adverse Maternal-Fetal Events
- Preventing HIV/AIDS and Adverse Consequences of HIV Therapy
- Disability Prevention and Intervention.

The first three major topics, one of which was later divided into two areas, were chosen for immediate review and development. An inclusive process was followed to develop these themes:

- Four separate panels were formed, composed of 30 scientists and public representatives (see Appendix) to review the scientific issues in each strategic topic area, and discuss what research the NICHD should highlight as major goals and emphasis areas. Initial teleconferences and electronic discussions yielded a first set of outlines.

- The resulting definitions and outlines were posted on the NICHD Web site to make them available for comment to a broader public. This material was shared with our Council members and the Friends of the NICHD, a coalition of more than 100 professional and patient organizations committed to the Institute’s broad scientific mission. Notice of the Web site posting was shared with additional organizations, which were not members of the Friends, that staff members believed would have a special interest in the research.

- The public comments, which ranged from those from private citizens to national organizations, were shared with each panel. Panel members and staff were asked to review these comments and incorporate them as would best serve the science being discussed.
• After the panels refined their work, the scientific outlines were shared with the NICHD Director and executive staff for final review and approval. The outlines, which are presented below, provide a flexible scientific framework for establishing research priorities, developing Institute initiatives, and enhancing funding.

Areas for Immediate Strategic Review

The areas chosen for immediate strategic review encompass some of today’s most exciting and important science.

**Developmental Biology: Understanding Normal and Abnormal Development**—This topic includes the basic biological science necessary to understand early development in utero, and through the time when many organ systems form. Once the human genome is mapped, the advances will be expansive. Even within a couple of years, the mapping will provide scientists with the “bricks and mortar” they need to understand the intricate programs for turning genes on and off—just at the right moment, in the right sequence, and triggering “back-up circuitry.” Given the intricacies of the process, it is amazing that so much goes right when so much can go wrong: it is those instances where things go wrong that lead to birth defects and inherited disorders. With concerted efforts, NICHD science is poised not only to understand but to correct and prevent these conditions.

**Biobehavioral Development**—Originally, issues regarding “biobehavioral development” were to be considered within the framework of developmental biology. However, the “Decade of the Brain” with its expanded knowledge of the brain’s structure, function, and relationship to other biological systems, coupled with emerging technologies, has created a separate and new frontier for developmental scientists. Enormous potential exists for scientists to better understand the developmental processes involved in forming cognitive, learning, emotional, social, and physical behaviors. Research is now possible to identify the biological and environmental factors that make infants, children, and adolescents more susceptible to behavioral disorders or to adopt risk-taking and violent behaviors. As with developmental biology, targeted efforts may soon unlock the mechanisms that will enable clinicians to repair things that go wrong, neurologically and in the brain, replacing or fully compensating for damaged functions. The overall promise of this area is exciting for clinicians, parents, educators, and society where the future depends upon the positive cognitive, emotional, and social development of all children, no matter what their personal circumstances may suggest, and no matter what their disability. Furthermore, the rehabilitation of persons with physical disabilities, adults and children alike, will be enhanced by these strategic efforts.

**Reproductive Health for the 21st Century**—Scientists now have access to the technologies they need to better understand the very early events that can lead to infertility and to determine how to overcome these problems, whether they involve the genetics of sperm motility or early fetal loss, or improving assisted reproductive techniques. In addition, as millions of women approach the end of their reproductive years, a significant percentage will face an array of conditions that clinicians currently have difficulty treating effectively without a solid research base. Now is the time to develop this scientific foundation.

1Other topics are to be developed at a later time, using processes relevant to the nature of the science, extent of current commitments, and existence of simultaneous or near-term program reviews. For example, current or planned internal and external reviews are underway or are planned concerning HIV/AIDS, medical rehabilitation, and health disparities.

2Because of the individual nature of the panels and the science that they address, each framework has its own style, which is maintained for this report.
But the more compelling issue is one of the most pressing public health challenges facing the world today, uncontrolled fertility. By 2050, the world’s population could reach a staggering 10.7 billion, with 99 percent of the growth in developing countries. The world is unprepared for dealing with these numbers and their public health, economic, and environmental impact. No country, including the United States, will be immune from the consequences of such population growth, as resulting problems will honor no boundary. One answer lies in the science and research supported almost entirely by the NICHD, which will mount a concerted and multifaceted effort to develop novel contraceptive leads. This will involve creating more effective, easy-to-use, longer-lasting, contraceptive options for both men and women. However, no scientifically effective option will work unless researchers also understand the social, cultural, and behavioral factors needed to encourage individual use.

**Genetics of Disease Susceptibility**—Science and technologies are on the horizon that will enable researchers to predict, essentially at or before birth, the diseases to which we are particularly susceptible, what environmental contaminants pose a particular threat, and what factors we should avoid to prevent lifelong problems such as obesity, diabetes, and heart disease. NICHD research has helped develop some of these technologies, and now the Institute will lead efforts to ensure that these technologies are refined, used ethically, and used to enhance the treatment and care of infants—before and after birth—and children as they develop into young adults.

In addition to the scientific goals captured above, this plan addresses resource- and training-related issues. To more completely unravel the complex biological and behavioral processes that characterize development, the Institute must capitalize on and further develop essential biotechnologies such as those emerging from structural, functional, and comparative genomics and proteomics and from increasingly sophisticated imaging and computer technologies. To complement these efforts, the NICHD must also target infrastructure development and specialized training. The basic, clinical, and translational activities that are outlined will require new ways of collaborating, thinking, and problem solving. Combining expertise and resources should provide the foundation for enhancing human development and for preventing, ameliorating, and treating a range of conditions that start at or before birth.
AREAS OF MAJOR SCIENTIFIC OPPORTUNITIES

DEVELOPMENTAL BIOLOGY: UNDERSTANDING NORMAL AND ABNORMAL DEVELOPMENT

This strategic planning area focuses on human birth defects, primarily those resulting in structural malformations and abnormal development of the immune system. While great progress has been made in preventing infant deaths resulting from low birth weight, prematurity, respiratory distress syndrome, and Sudden Infant Death Syndrome (SIDS), birth defects remain the leading cause of deaths in infants under 1 year of age, accounting for one in five infant deaths. It is estimated that more than 150,000 babies in the United States (about 4 percent of all live births) are born each year with significant birth defects. Families of babies born with severe, non-fatal, birth defects, many of them accompanied by mental retardation, are burdened financially by expensive special medical treatment, education, rehabilitation, and other supportive services to care for childhood and adult disabilities. While there are thousands of different types of birth defects with varying degrees of severity, the lifetime costs to the U.S. economy of children born each year with any of 17 major birth defects is estimated to be nearly $6 billion a year. Consequently, the full economic impact for all birth defects would be much greater and the emotional costs to families incalculable.

With the development of this special emphasis area, the NICHD will be expanding its leadership role in clarifying the causes of, and in coordinating multidisciplinary efforts for, reducing birth defects. While our ultimate goal is to prevent birth defects, effective prevention measures and strategies can be developed only with a thorough and in-depth knowledge and understanding of the epidemiology, etiology, and pathogenesis of birth defects—where tremendous gaps exist. This will require both a better understanding of clinical phenotypes, human syndrome delineation, epidemiology and natural history of birth defects, as well as a better understanding of the basic mechanisms underlying normal developmental processes through the use of important animal models and appropriate use of stem cell research. Of necessity, this will require a joint effort by clinicians and basic scientists to approach birth defects research from their respective strengths and to build on each other’s progress to fill the gaps in our knowledge of how both genetic and environmental perturbations of normal processes cause developmental abnormalities.

In the context of this strategic area, the time frame of development ranges from the earliest stages of embryonic development, including blastocyst and trophoblast formation, gastrulation, neurulation, and the establishment of the basic body plan, through organogenesis. A common theme in the emphasis areas described below is the two-way flow of information from research endeavors. It is anticipated that findings from clinical studies will provide insight and direction to basic scientists studying developmental processes. Similarly, the translation of findings from the use of animal models and stem cell research to clinically relevant conditions will increase our understanding of human embryonic development and the formation of birth defects.

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3 Any research initiative supported by the NICHD involving fetal or embryonic stem cells will meet the “National Institutes of Health Guidelines for Research Involving Human Pluripotent Stem Cells,” which are under development and likely to be finalized in early 2000. This applies to all relevant initiatives in this strategic planning document.
I. SCIENTIFIC GOALS

A. Birth Defects and Developmental Biology: Clarify the Underlying Mechanisms of Normal and Abnormal Developmental Processes as a Means of Understanding the Formation of Birth Defects

As previously indicated, the approach being taken investigates birth defects from both clinical and basic science points of view. Clinical studies are important to address the genetics, phenotyping, and classification of birth defects. Basic studies using experimentally manipulable systems are essential for clarifying the underlying mechanisms of both normal and abnormal development. Finally, there will be a continuing need to create models to test the hypotheses derived from both scientific approaches.

The multidisciplinary approaches mentioned in this section require cutting-edge technologies, such as those associated with structural, functional, and comparative genomics and proteomics and with imaging, to efficiently accomplish these goals. These areas are addressed in the next section on "Research Technologies and Resources."

• Genetic Studies of Birth Defects: This emphasis area works from the patient orientation towards determining the genes involved in and the underlying mechanisms leading to birth defects. Mapping and sequencing data generated by the human genome project will be useful to help study the genes associated with human hereditary conditions. Linkage analysis of pedigrees and mapping studies are a mainstay of clinical genetics studies. However, the complexity of congenital anomalies, especially those associated with syndromes having multiple phenotypes, argues for additional classification/phenotyping research and genetic epidemiological studies, as noted below:

◆ Phenotype Delineation: A better understanding of human disease can be improved by phenotyping or characterizing the entire physical, biochemical, and physiological makeup of individuals with a specific condition. This will provide extremely useful information when compared to and correlated with the genotype of these individuals. Consequently, there is a need to develop improved methods for phenotypic analysis, including syndrome delineation, and natural history of disease. It also will be important to develop registries for collecting cases and networks to provide data on phenotype and families for linkage analysis and, ultimately, for mapping the genes responsible for specific birth defects.

◆ Genetic Epidemiology: This comparatively new field of research has recently emerged from the integration of genetics into traditional epidemiological research and focuses on the contribution of genetic and environmental factors, identified at the molecular level, to the etiology, distribution and prevention of disease within families and across populations. Collaborative and interdisciplinary studies on human malformations, which integrate the latest advances in developmental and molecular genetics with new and innovative analysis of epidemiological data, are important. These efforts will lay the foundation for developing hypotheses concerning molecular genetics and the developmental biology of structural birth defects.
Basic Mechanisms of Normal and Abnormal Development: In this emphasis area, focus is on the use of model systems to clarify the mechanistic causes of birth defects. Through basic research, we are now revealing the many factors regulating genetic networks that trigger and control developmental processes. Of particular interest to the NICHD are studies relevant to defects of gastrulation, generalized body patterning, and the formation of organs, such as the nervous, skeletal, and visceral systems. All of these major developmental events require precisely integrating many developmental processes such as morphogenetic movements, cell-cell and cell-matrix interactions, signal transduction, cell proliferation, and apoptosis, to name a few. While we envision the extensive use of animal models, an essential goal is the translation of research findings to clinically significant congenital structural malformations. Major areas of emphasis include:

- Early embryonic events and processes: The elaborate early embryonic events, such as body axes formation, gastrulation, and neurulation, are crucial for normal embryogenesis and influence the formation of the basic body plan and cell fate. Significant defects in these processes are frequently lethal to the embryo. Understanding the genetic events underlying these dynamic processes is critical.

- Organogenesis: The formation of organ systems requires precisely integrating many developmental processes that involve the coordination of complex genetic and developmental networks. The field of developmental biology is now reaching the level of sophistication to study the formation of organs. Clarifying the gene expression patterns, defining the genetic networks, and characterizing biochemical interactions are crucial for our understanding of structural birth defects.

Development of Model Systems: The next approach is the creation or development of models to test hypotheses generated as a result of clinical and basic studies. For many years, animal models have been used to clarify and understand developmental processes. More recently, the importance and potential applications of embryonic stem cells have been established. As noted below, both of these important models will be essential components of this emphasis area.

- Animal Models: Multidisciplinary studies using appropriate animal model systems are essential to clarify the molecular, biochemical, and morphological aspects of such crucial, basic processes as cell proliferation, cell differentiation, and cell interactions as well as the complex processes of gastrulation, patterning, neurulation, and organogenesis. Such investigations will improve our insight into the mechanisms of development, facilitate the identification of critical developmental periods, and enable us to verify the genetic and environmental miscues that give rise to such conditions as neural tube and skeletal defects. The conservation of genes, genetic networks and developmental pathways across the animal kingdom has provided credence to the use of such diverse models as C. elegans, Drosophila, Xenopus, the zebrafish and the mouse to study developmental processes. Consequently, the increased understanding provided by work on model systems will also provide the basis for translational studies of human congenital defects. Such understanding will ultimately lead to improving early diagnostic procedures and developing gene therapies that can ameliorate or prevent birth defects. Continued support for the use of animal models to study development cannot be overemphasized, and to accomplish this goal, we would need to: a) Enhance the use of all animal models including natural mutants, targeted/induced mutants, and transgenic animals, and b) Develop new methods to target gene expression (e.g., selective spatial or temporal) in model systems.
Embryonic Stem Cells: Embryonic and other stem cells for differentiated tissues are important models for understanding basic processes associated with development and differentiation. While research on embryonic stem cell biology using animal models is still in its early stages, it is a very promising approach to understanding developmental processes. Once the processes and factors that govern proliferation and differentiation of embryonic stem cells are better understood, this approach offers the potential for therapeutic interventions in birth defects and abnormal immunological development, particularly those involving cell and tissue replacement. To accomplish this, we will need to: a) Characterize and define embryonic and postnatally derived stem cells from different species; and b) Foster the use of stem cells as a tool for studying the processes of differentiation and cell lineage determination.

In addition we will need to identify the factors that stimulate and trigger the proliferation and differentiation of stem cells towards various cell lineages.

B. Developmental Immunobiology: Normal and Abnormal Development of the Human Immune System

Understanding normal and abnormal development of the human fetal and neonatal immune system and its interactions with maternal immunity has enormous clinical implications. Basic studies will provide the essential fundamental knowledge, understanding, and insights that can be translated into effective diagnostic procedures, safe and efficacious prophylactic and therapeutic modalities, and useful prevention strategies to reduce infant morbidity and mortality. The health of neonates and infants will benefit significantly from the synergistic impact of basic, clinical, and applied approaches. Currently, large gaps still exist in our knowledge of the developing human immune system. While insights can be obtained from animal models, particularly the mouse, differences in the timing of T and B cell generation and their population of lymphoid organs argues for the importance of parallel studies of immune cells from human and mouse at different developmental and functional stages. Studies in this area will cover a broad range and involve basic, applied, and clinical studies on the ontogeny of immunity, the development of immune responsiveness, and reproductive immunology. Targeted areas of research include:

- Ontogeny of the Normal Immune System and Host Defense Mechanisms
- Genetic Programs Governing Normal and Abnormal Development of Immunity
- Cellular and Molecular Mechanisms of Immune Tolerance and Transfer of Immunity During Pregnancy.
II. RESEARCH TECHNOLOGIES AND RESOURCES

For innovative and creative scientific projects to succeed, the appropriate infrastructure, resources, and technologies need to be available. Some of the technology and resource areas listed below overlap since their integration is necessary to achieve a scientific end (e.g., imaging, genomics, and computational/bioinformatics are all involved in the development of atlases/gene expression databases). A major consideration of these endeavors is cost: the establishment of databases or genomic/proteomic resources is one thing; continuing to maintain them in perpetuity is extremely expensive. Consequently, while the NICHD understands the importance of and is committed to developing important human and animal databases and resources, their maintenance will require the coordinated support of several Institutes, particularly those that are more technology-driven, as well as private organizations with similar goals.

A. Functional Genomics and Proteomics

The research areas of functional genomics and proteomics deal with the analysis of gene activity and the processes leading to the expression of proteins and their relationship to cell function. The combination of these two powerful approaches provides a means of analyzing regulation at many levels. Genomics and proteomics represent important scientific strategies to address questions raised in both the developmental biology/birth defects and immunobiology emphasis areas. The importance of these approaches as a means of capitalizing on genome sequence cannot be over emphasized. In addition to their important role in addressing important scientific questions in development, they are also extremely important, when used with imaging technologies, for cataloging gene expression in databases and atlases. Targeted areas of research will include efforts to:

- Determine patterns of gene expression during development of specific cell types, complex tissues and organs
- Examine the protein expression profiles and structural/functional relationship of key developmental proteins
- Advocate comparative genomics and proteomics
- Support mutagenesis and phenotyping strategies to identify and characterize genes involved in normal and abnormal development
- Develop new methods for spatial or temporal inactivation of genes in specific cell types in model systems
- Support the development and distribution of gene arrays and microchips to identify species similarities and differences or to facilitate identification of genes associated with birth defects
- Promote the use of proteomics to study normal and abnormal development
- Develop techniques to isolate specific cell types from tissues so that cell-type gene expression can be accurately assayed
• Promote the use of computational biology and bioinformatics to address issues of normal and abnormal development

• Develop and maintain gene expression databases and digital atlases of development and ensure that resources from developmental human and model systems are linked to facilitate comparisons between species.

B. Imaging Technology and Visualization of Development Processes

This area of technology development has implications both for basic and clinical research. Advanced imaging technologies can be used to develop models showing morphogenetic movements in the temporal development of organ systems and for capturing gene expression data for inclusion in a database. Emerging technologies will enable scientists to visualize developmental processes and to monitor cellular and molecular changes at a level of resolution not previously possible. Additionally, advanced imaging techniques can be used for diagnosing abnormal development in utero. Support for the following areas is essential for the future of integrated research in basic and clinical developmental biology:

• Establishing high quality developmental atlases of commonly used vertebrate models with a variety of imaging techniques and making them broadly accessible electronically to the community

• Establishing and maintaining morphological databases of developmental gene expression patterns

• Establishing similar atlases and databases for human development

• Promoting the development of noninvasive imaging methodologies to study developmental events in animal models

• Translating high-resolution technology, used for analyzing developmental defects in animal models, to humans for early gestational and fetal assessment

• Developing more sophisticated techniques for 3-D rendering allowing for “fly through” analysis of fetal structures

• Developing safe contrast agents or molecular probes to enhance imaging of the fetus to assess anatomic or genetic abnormalities.
C. Birth Defects Research Networks

An overriding, important issue in the birth defects initiative is to provide understanding of normal developmental processes and clarify how these processes are perturbed to cause birth defects. Much of what we know about development has come from the use of animal models. There is a need to take this one step further in order to understand the implications of what has been learned in animal models and apply them to human congenital abnormalities. This brings us to the last infrastructural emphasis area:

- Support multidisciplinary birth defects centers or networks combining basic researchers and clinicians to enhance translation of basic findings to clinical applications.

III. EDUCATION AND TRAINING

As technological advances continue at a rapid rate, the sophistication of methodologies will require specialization of scientists in these new approaches. This will heighten the need for multidisciplinary collaborations to address research issues. It also will require scientists to be conversant in new methodologies and approaches used by their collaborators in order to strengthen interactions so that they become productive, successful, enduring collaborations. In addition, although there is an increasing need for a diverse and well-trained workforce for birth defects research, the need is broader than that for trained laboratory investigators. The clinical and epidemiological workforce studying birth defects is small and should be expanded since they can be valuable collaborators for basic scientists interested in studying human birth defects. Emphasis will be placed on:

- Cross-training of biomedical researchers and computational/bioinformatics biologists
- Fostering interactions between basic, epidemiological, and clinical investigators
- Fostering training in phenotyping of human birth defects and in comparative phenotyping in animal models down to the level of the cell
- Developing support mechanisms that will promote interdisciplinary training opportunities for young investigators.
If we truly wish to understand the human being in terms of health and behavior—and devise effective, practical ways to apply what we learn from basic science—we must understand the human being as a whole organism that results from a complex interplay between external, biological, and behavioral factors. These interactions, and all related functions, processes, and outcomes, also must be understood in the context of developmental changes that occur over time. Without understanding such fundamental biological factors as brain structure and function, changing hormone effects, or genetic contributions, it will be difficult to develop more effective ways to treat, let alone prevent, such complex developmental conditions as mental retardation, autism, attention deficit disorder, or learning disabilities. Nor will we be able to truly understand how one learns to read or communicate, or how best to teach and parent our children. However, interventions that only address developmental problems, without addressing the simultaneous impact of external factors on biological and behavioral functioning, could waste not only funds, but critical time and the fragile hopes of affected individuals and their families.

By targeting the biobehavioral approaches outlined in this strategic area, the NICHD plans to expand its leadership role in addressing significant developmental health problems ranging from chromosome abnormalities associated with cognitive deficits to childhood violence. The Institute’s effort also can unravel the scientific mysteries of how children learn, think, plan, feel emotions, decide, and act in ways that not only support their well-being but contribute to society. This is no small effort and one that requires targeting existing knowledge gaps, integrating multidisciplinary approaches, and encouraging collaborations to translate basic science to practical solutions.

In terms of knowledge gaps, amazingly little scientific information exists to tell us exactly which aspects of behavioral experience are essential to human development, or how experience and behavior relate to the biological functioning of the developing organism. Thus, the main goals of the following strategic research areas are to expand our knowledge of 1) how the developmental processes associated with behavior and experience are incorporated into biological structures and mechanisms, 2) how biological processes shape behavioral development, and 3) how this new scientific information can be used to devise relevant and effective interventions to improve the lives of children. These goals require an unprecedented integration of several scientific disciplines involving behavioral, social, and basic biological sciences. In turn, this multidisciplinary, integrative approach promises to greatly stimulate interest in and scientific advances concerning human behavioral development. More importantly, this effort offers an important new opportunity for the scientific community to address pressing yet complex child health and development issues.

The following definitions are implied when discussing the strategic research goals and emphasis areas:

- Biobehavioral development research targets the study of the development of behavioral processes—along with their interrelations with molecular, genetic, cellular, and neural systems, whole organ processes, and environmental factors—to understand how these interrelations contribute to typical and atypical development in humans and animal models.

- By “behavior” we mean both internal and external actions or responses originating from factors such as cognition, language, learning, memory, academic skill acquisition, emotion, cognitive-based social interactions, and planned motor function.
By “environment” we mean external factors such as nutrition, health care, environmental toxins, schooling, and the full range of experiences of children in the family, community, and broader society.

I. SCIENTIFIC GOALS

Although the following strategic research areas are diverse and wide-ranging, they all require an integrated, multidisciplinary approach. These areas were identified on the basis of our most recent breakthroughs in developmental research, and represent areas where gaps in our current understanding of development still exist, as well as where the integration of biological with behavioral science can best be applied to the developmental problems faced by children in our society today.

A. Biobehavioral Bases of Developmental Continuities and Discontinuities: From Birth Through Parenthood

An emphasis on development is an important approach to biobehavioral research, which is unique to NICHD research. For our purposes, it is critical to apply biobehavioral research paradigms to questions that are relevant to specific developmental periods, developmental transitions across periods, or commonly experienced developmental episodes. Much more needs to be learned about the biobehavioral bases of development, and the continuities and discontinuities that occur as children mature from birth until they themselves reach parenthood. The behaviors of interest include cognition, perception, attention, memory, speech, language, emotional and social developmental behaviors, as well as the ability to regulate behaviors (e.g., behavioral inhibition, sleep regulation, and feeding). The processes here are also bidirectional—biobehavioral studies should be able to address not only how behavioral/environmental processes influence biological development but also how biological factors influence behavioral/environmental interactions. Many of the emphasis areas below target areas where critical knowledge gaps exist.

• Influences of Sex/Gender Throughout the Developmental Process: There are few studies on why differences exist between males and females in the occurrence of behaviors and related diseases. To better understand this aspect of human development, it is important to clarify the interaction of biological factors with environmental, social, and cultural influences and to examine how these mechanisms lead to differential outcomes between the sexes.

• Fetal Behavior: We know little as to what fetal and early postnatal behaviors, and their interactions with biological and environmental factors, tell us about the developing fetus or neonate and how such behavior is related to physical and neurological status and perinatal outcome.

• Understanding and Facilitating Learning in Typically Developing Populations: Much more science-based evidence needs to be gathered to help us understand how best to aid the learning process for all children across a variety of domains (e.g., reading, mathematics, reasoning, and critical thinking). This research requires a truly integrated, biobehavioral approach. Such research needs to relate our understanding of neuroanatomical development, developing brain processes, neurochemical and neuroendocrine effects with learning behaviors and environmental influences (e.g., curriculum, mode of presentation of content, home
environment influences, peer influences). Particular attention needs to be paid to disparities in learning acquisition and outcomes as functions of biological as well as environmental factors.

• **Development of Children With Disabilities and Chronic Diseases:** There is a paucity of research examining the interactive factors associated with processes of biological, neurocognitive, and behavioral development specific to and characteristic of individuals with mental retardation or other developmental disabilities or chronic diseases over time. Such research is particularly important for predicting the developmental course and risk/protective factors associated with a particular disability or chronic disease as well as for developing effective, developmentally sensitive interventions for these children.

• **Adolescence:** There is little comprehensive research on adolescence, despite the many important neurobiological, hormonal, and social behavior interactions to be addressed during transitions into, from, and throughout this developmental period. Research is needed to understand both typical adolescent development as well as adolescent development in atypical populations. Such research should examine the factors leading to increased vulnerability during adolescence, in terms of emotional, behavioral, conduct, and social developmental difficulties, and the subsequent effects of these difficulties upon adulthood.

• **Health Behavior and Risk Factors in Childhood:** Although information about health behaviors in adulthood (e.g., smoking, diet, exercise) and their effects has grown dramatically in the last decade, researchers need to learn much more about health-related behaviors during childhood and how they influence developmental as well as lifelong health outcomes. The biobehavioral approach to this type of research will examine not only the biological disease or injury processes themselves but the behavioral and external factors preceding, maintaining, aggravating, or interacting with these processes. Identification of biobehavioral risk factors in childhood, which predispose the child to injury, illness, eating disorders, obesity, chronic disease, and unplanned pregnancy, are a high priority. Biobehavioral intervention studies, including biofeedback, behavior modification, and other developmental, behavioral pharmacologic studies, are needed that include evaluating the biological systems affected by the intervention being studied. It will also be important to include variables that will help capture differences that occur across populations groups and to extend these studies to community-based applications.

• **Developmental Neurobiology Underlying the Emergence of Prosocial Behaviors Versus Violent and Aggressive Social Behaviors:** Several lines of animal-model and human evidence indicate the important roles that hormones, neurotransmitters, neuroendocrine factors, neurocircuitry, and neuroreceptors play in the development of complex social behaviors, including the formation of social affiliations, parental care, and social aggression. Much more needs to be learned, however, about how these biological factors, interacting with brain development, cognition, and environmental and situational influences, result in prosocial, empathetic behaviors or, alternatively, in social aggression and violent behaviors, particularly over time. Understanding how biological and developmental factors modulate aggressive responses to environmental and situational stimuli in humans will aid our ability to predict and prevent human violence, while facilitating our ability to construct effective interventions for preventing human aggression and violence.
B. Therapeutic Interventions for Developmental Disabilities and Related Conditions
(Including Mental Retardation and Other Atypical Development)

This emphasis area refers to exploiting basic scientific advances to further the development of innovative therapies (including new pharmaceuticals), as well as to refine and enhance the use of interventions, based on the effective dissemination of these advances, for specific developmental problems. Studies are needed to clarify the mechanisms and processes concerning a specific disease, or disability and efficacy of related therapeutics. This would include pharmacological, educational, and psychological mechanisms and interventions. Researchers also must examine why some interventions are effective for one individual and not for another. Such efficacy assessments should include measures relevant to independent and adaptive functioning. Long-term followup studies also are needed to better understand the impact of, or outcomes associated with, the use of specific interventions over time. Both animal models and human applications are pertinent. Some specific examples of areas to target include:

• **Clinical Trials of Existing Pharmacotherapies in Specific Disabilities or Disease Groups in Children:** There is a paucity of research addressing the efficacy, long-term side effects, and outcomes of a wide range of commonly used pharmacological agents in children. Such research requires both cross-sectional and longitudinal approaches. This emphasis area is particularly relevant for children with multiple disorders, dual-diagnosis disabilities, or mental retardation and for guiding practitioners to use more effective pharmacological interventions for children with developmental disabilities.

• **Innovation and Translations of Interventions for Specific Learning and Other Developmental Disabilities:** A pressing need exists to develop effective interventions for children with developmental disabilities involving learning deficits or behavior deficits (e.g., stereotyped, aggressive, self-injurious behaviors) that interfere with optimal development. This would include developing both new pharmaceuticals and other biological or behavioral strategies based on emerging scientific advances. This intervention research will require identifying and clarifying the neurobiological, behavioral, and environmental mechanisms and processes underlying efficacy. Therapeutic research also needs to address the optimal timing of intervention throughout development. In addition, a great need exists to develop innovative interventions that address deficits in reading, mathematics, written communication skills, language usage, communication strategies, and learning ability or retention. The development of intervention strategies and devices should be emphasized for both typical and atypical developmental populations.

C. Interactions Between Individual Biological Processes and Environment Affecting or Facilitating Development

• Genetic and Environment Interactions: Clarifying and better understanding the interplay among genetic and environmental influences on neurobehavioral development in populations with typical development, learning disabilities, developmental disabilities, or other developmental disorders is a major research target. To pursue this research, investigators will need to develop age-appropriate instruments to help them understand and explain genetic variation and gene/environment effects on behavioral variability, efficiently and inexpensively, across populations.
• **Interaction of Neuroendocrine and Environmental Influences:** Because the endocrine system plays an important role in stimulating neurobiological activity, it is important to better understand the interaction of neuroendocrine and environmental factors on typical and atypical development and behavior, particularly in response to internal and external stressors.

• **Interaction of Neurotoxic or Infectious Agents With Development:** Prenatal and perinatal exposure to infectious agents and toxins has been linked to pathogenesis of developmental disabilities and neuropsychiatric disorders. Researchers need to learn more about the possible connections and identify the mechanisms by which such outcomes may occur, how such effects can be treated, and any related long-term outcomes.

• **Biobehavioral Effects of the Interaction Between the Individual, Technology, and Multimedia Sensory Experiences Throughout Development:** We know very little about the impact of computers and other technologies on the development of children—including physiological, neural, social, and emotional development. Computers and other new technologies also hold the promise of useful, individualized, and specific interventions for children with developmental and learning disabilities.

**D. Neuroplasticity in Development, Learning, and Memory**

It is critical to understand the interactive effects of behavior, environment, and neuronal cell motility as part of the developmental process. This research needs to include investigating the factors that control axonal growth and targeting as well as an understanding of how learning and experience influence neuronal “pruning.” Related emphasis areas could include the following topics:

• **Neuroplasticity and Learning:** Hormones and stimulants (such as caffeine) have pronounced effects on dendritic spine shape and motility, potentially affecting the efficiency of associative learning networks. Research is needed to better understand how these events occur and influence outcomes throughout development. In addition, recent studies demonstrate that neurons within the temporal lobe may be regenerated, opening several important avenues of research on human learning and development.

• **Dendritic Networks:** Recent progress in the microphysics of dendritic networks in processing sound also opens up new possibilities for understanding differences in extracting auditory information in various social or learning contexts. Further studies could enhance our knowledge of the biologic factors influencing human learning and behavior in a variety of different situations.
II. RESEARCH TECHNOLOGIES AND RESOURCES

The following technical development areas are relevant for all the biobehavioral research areas targeted above, and are highlighted because of their importance for studies specifically addressing developmental issues.

A. Data Collection and Analysis Related to Neural Networks and Dynamic Systems for Analysis of Development

Investigations in the emphasis areas should incorporate innovative methods of statistical or mathematical analysis to better understand developmental trajectories, developmental growth curves, dynamic systems for representing multiple influences, and developmental transitions. These improved analytic techniques also are necessary to better understand the complexity of neurobehavioral action or response. Investigators also require tools to represent “fluid behaviors” such as skilled performance or the change in this “fluidity” with maturation in a skilled motor performance. A great need also exists to develop new statistical techniques that will permit the analyses of multiple variables in situations where there may be relatively few subjects. Current statistical techniques that insist on 10:1 ratios between subjects and variables do not apply to the data produced by more advanced imaging techniques such as fMRI, PET, and multichannel ERP and EEG studies involving 64 or more electrodes.

B. Animal Models

Some of the most fundamental, mechanistic aspects of biobehavioral research will have to be examined in animal models. Emphasis should be placed on developing parallel behavioral models in animal models (including the mouse and monkey), as well as in humans. In addition, it is critical to develop and use animal models of particular syndromes associated with developmental disability to investigate biobehavioral influences on development, from conception through young adulthood.

C. Functional Genomic and Proteomic Approaches

Functional genomic and proteomic approaches to identifying cellular abnormalities during development, or for indicating presence of disease, can aid researchers in better understanding the biological mechanisms associated with developmental disability and disease. For example, c-DNA chip techniques have recently enabled investigators to zero in on all cDNA (messenger RNA) from large regions on chromosomes suspected of carrying a disease-causing gene. This has allowed scientists to isolate, rapidly and efficiently, a group of suspect genes for further testing. Other techniques include single cell PCR (laser capture micromanipulation of cells), homology modeling of receptor classes, and modeling of signal transaction networks. Development and application of this technology, when applied to exploring the biological bases of behavior, will help researchers clarify gene-cell-brain-behavior relations.
D. Functional Neuroimaging

The ability to use new functional neuroimaging modalities (e.g., EEG, ERP, fMRI, DTI, MEG, MRS) to link physical parameters in the brain with specific behaviors, and to do so over the course of development, presents investigators with an unprecedented opportunity. These tools allow earlier diagnosis and enable researchers to examine the effects of interventions. The use of such techniques will be important for addressing many of the questions relevant to many of the above strategic emphasis areas in biobehavioral development. However, it is impossible to conduct functional neuroimaging studies without specifying functional tasks to be studied. Functional genomic and functional imaging research require accurate analyses of the phenotype and the development of age-specific activation tasks likely to target specific brain areas involved in emotional and cognitive functioning. Thus, the development of age-specific model tasks also is emphasized in this research area. Priority also needs to be placed upon work that uses multiple techniques on the same subjects, for example co-registration of subjects involved in both fMRI and ERP procedures. One technique yields more information about spatial resolution (fMRI) while the other yields good temporal information (ERP). When combined, data from both techniques will tell a more interesting story and provide complementary information to enhance research insights.

E. Brain Tissue Banks

Although the Human Genome Project will reveal which proteins (e.g., transcription factors, enzymes, receptors) are implicated in various developmental disorders, the individual biochemical states of cells in different regions of the brain can only be determined with tissue from autopsies. Recruiting families of individuals with such conditions (e.g., with autism, fragile-X, or Down syndrome) to donate tissue in the event of death is an important undertaking. Behavioral profiling of individuals whose brains have been donated is necessary, and the sharing of brain tissue among researchers is important in standardizing brain sectioning or brain preservation among investigators. Given these needs, it is essential to create a network of brain tissue banks and to improve the way that investigators communicate the results of neuropathological examination targeting different syndromes.

III. EDUCATION AND TRAINING

A tremendous need exists for predoctoral and postgraduate training programs that integrate experiences across the disciplines that address the many issues and questions relevant to biobehavioral development research, in general—and to the strategic emphasis areas listed above, in particular. It also is imperative to integrate advanced training in the behavioral and basic biological sciences to enhance and create new opportunities for effective and productive, multidisciplinary, research endeavors.
The ability to have children is one of the most basic human values. It encompasses not only the desire to have children but also to have them at a time and in a manner that their future health, both physical and mental, is best assured. Reproductive health significantly influences the overall health of individuals and society and has been the subject of increased attention from a health and economic viewpoint. The economic burden imposed on infertile couples attempting to achieve pregnancy is difficult to estimate accurately since the cost of treatment is not always reported as infertility-related. The projected direct cost of assisted reproductive technologies together with the cost of multiple-gestation pregnancies is estimated to be $1.1 billion for the year 2000. The costs of unintended adolescent pregnancies alone is more than $1.5 billion. Thus, the overall costs of infertility treatment and those of all unintended pregnancies would substantially exceed $3 billion annually. These costs are in addition to the considerable indirect costs associated with the immediate and long-term psychological and other consequences that accompany both conditions. In addition, the direct and indirect costs associated with uncontrolled population growth, worldwide, are difficult to comprehend and calculate. Consequently, addressing these problems from the broadest possible perspective is of paramount importance.

During the past decade, major advances have been made in both biomedical and behavioral sciences that can be applied to the important issues of assisted reproductive technologies, development of improved methods of family planning, and behavioral factors that impact on both fertility and infertility. It must be recognized that this strategic framework builds on a solid research base developed with funding from the NICHD and other sources. By focusing on the goals listed below, the Institute plans to advance the technologies that are indispensable to achieving reproductive health without neglecting other research areas that are the focus of the Institute’s broad mandate. We emphasize the need for close collaboration between biomedical and behavioral sciences as the basis for successfully accomplishing our goals.

To explore new opportunities in reproductive health, the NICHD proposes to address the following goals:

I. SCIENTIFIC GOALS

A. Pursue Research Leading to Improved Outcomes in Assisted Reproductive Technologies (ART)

The term ART encompasses any method beyond natural intercourse intended to help produce a child. These methods range from the simple and well-tested to the complex and controversial. ART practices have grown faster than the science needed to make evidence-based decisions in patient care, leading to empirical choice of treatment, often with loss of time, significant cost, and in some cases, morbidity. Many questions can be addressed that will yield important information concerning improved outcomes of ART. The main theme is how to improve pregnancy and delivery rates and to reduce multiple pregnancies. Research should focus on:

- The “quality” of eggs and sperm
- Detection of abnormalities in preimplantation embryos
• What constitutes a receptive uterine environment and how it can be enhanced

• Improvement of culturing immature sperm and ova

• The side effects of fertility treatments

• The underlying causes of infertility and ways to treat them

• Age-related fertility factors.

B. Use of Genetic Advances to Identify Factors Leading to Infertility

As the power of human genetic analysis has increased, the evaluation of infertile couples has begun to uncover mutations involving essential factors or processes in reproductive health. For example, when a mutation occurs in a critical hormone receptor, individuals may become infertile because the effect of relevant hormones is decreased, even though adequate amounts of the chemical substances are produced. When the mutation occurs in the machinery of sperm tail movement, these sperm cannot normally fertilize eggs, leaving men infertile. This and similar knowledge must be applied to achieve healthy pregnancies. In addition, the availability of new models to researchers must be assured. Research should focus on:

• Use of genetically-engineered animals to study the pathophysiology of infertility

• Development of new animal models

• Identification of familial gene deletions resulting in infertility.

C. Use of Genetic Advances To Identify Novel Contraceptive Leads

Many steps are involved in normal human reproduction including production and maturation of gametes; cell proliferation and programmed cell death; synthesis, secretion, and action of hormones; fertilization; preimplantation embryonic development; implantation; and sex determination. Genetic research involving reproductive processes, such as meiosis, could reveal molecular targets that could be the focus of new interventions to regulate fertility. These molecular loci would be especially valuable if they effectively target reproductive factors and processes without consequence to somatic systems. This could include such molecular structures as coding sequences for proteins or receptors, or regulatory sites that control gene expression. As a result, it is important to understand the genetic regulation of essential reproductive processes to identify new targets for developing novel contraceptive leads for both sexes. In particular, research should focus on:

• Applying techniques of gene targeting and of gene array technology to define networks of gene expression in various parts of the female and male reproductive tracts that can be explored for fertility regulation

• Targeting interventions with minimal side effects.
D. Increase Efforts to Develop Acceptable Male Contraceptives

Basic and applied research during the past decade has uncovered a number of steps in the gametogenic process in the testes, as well as steps in epididymal sperm maturation, that may be amenable to therapeutic intervention. Studies have shown that suppressing the hypothalamic-pituitary axis with a variety of hormonal agents yields azoospermia and severe oligozoospermia. Both of these conditions result in effective contraceptive regimens. Much of this research, however, was conducted on a small number of volunteers making it very difficult to select the more effective regimens. In addition, several recent studies point to the fact that men will utilize effective, reversible male contraceptive methods when they become available. Based on these facts and that the 1994 Cairo Population Conference has identified the development of contraceptives for men as a component of its women’s health agenda, research should focus on:

• Identifying more specific hormonal agents and target their delivery
• Developing new approaches that are based on molecular biology of the epididymis and testis, especially the epithelial cells in sperm maturation; signal transduction pathways in seminiferous tubules, especially Sertoli-germ cell interactions; and germ cell survival signals that affect differentiation.

E. Identify New Treatments for Common Reproductive Problems

Benign gynecological conditions result in considerable morbidity, lowered fertility, and substantial economic burden. These reproductive problems span the reproductive life of women and can be observed in postmenopausal women on hormone replacement therapy. Treatments, however, are frequently empirical and not based on solid scientific evidence. Consequently, additional research must be conducted to identify the etiology and proper treatment for conditions such as dysfunctional uterine bleeding, endometriosis, leiomyoma, and polycystic ovary syndrome. Research should focus on:

• Exploring gynecological issues that are important to women in their later reproductive years
• The effects of new specific estrogen receptor modulators (SERMs) on reproductive tissues
• Dysfunctional bleeding, particularly emphasized because of its health and economic impact
• Developing databases to examine demographic and biobehavioral information about women’s decisions regarding the management of reproductive diseases and disorders.

F. Conduct Research on Male Reproductive Behaviors

Understanding how men choose to become fathers and the circumstances in which they do so is critical to improving the well-being of families and children. Opportunities to improve knowledge about men’s access to, attitudes towards, and use of contraceptive methods will pave the way for developing new male methods that respond to men’s needs. Research should focus on:
• Studying men and couples with regard to perspectives on gender roles, sexual access and function, fertility management, and parenting responsibilities to advance our understanding of fathers and fathering.

G. Identify New Strategies for Improving Contraceptive Use

Changes in the delivery of health services and the increasing diversity of our population have prompted the need for re-examining individual, institutional, and cultural barriers to accessing and effectively using contraceptive methods. To reduce the high prevalence of unintended pregnancies and unwanted births in this country, research should focus on:

• How experience with contraception over the reproductive life span is affected by individual risk-taking, partner relationships, STD risk, and male involvement in pregnancy prevention

• Service delivery factors as they relate to contraception.

H. Study the Behavioral Factors Leading to Infertility, The Use of Infertility Services, and the Ethics of Infertility Treatment, as Well as the Effect of ART on Child Outcomes

Demand for infertility services has risen dramatically in our country. To gain important knowledge about the prevalence of infertility and its antecedent risk factors, decisions of infertile individuals and couples about the use of infertility services, the impact of economic and other barriers to services, and the health and development of children born as a result of ART, research should focus on:

• Behavioral, population-based, and clinical research coupled with biological measures of reproductive function and child outcomes

• Decisionmaking of patients and of providers in seeking and using infertility services.
Effective strategies for the 21st century to prevent and treat disease must include studies of the underlying factors contributing to human morbidity and mortality. Studies must investigate not only biological factors but also socioeconomic, environmental, and psychological factors that contribute to the pathophysiology of human diseases, and that account for health disparities among different groups. Research on “fetal programming,” on the in utero environment, and on factors that perturb fetal development is necessary to document effects on health from childhood to adulthood. From conception through fetal development, infancy, childhood, and adolescence, individual patterns are established that determine disease susceptibility. These traits, under genetic control but often modified by the environment, determine disease patterns that frequently manifest themselves during fetal and neonatal life, childhood, or in later life. The interaction of genotype with the fetal and postnatal environment may result in disease manifestations not only in childhood but also in adult-onset diseases including hypertension, diabetes mellitus, and atherosclerosis. Factors that regulate fetal growth may also influence the later susceptibility to autoimmune diseases, infectious diseases, and cancer.

Genetic and epigenetic influences on cellular replication and growth by mechanisms such as imprinting and the post-translational modification of various transcription and growth factors are but one component of these complex processes. In addition, other molecules may “imprint” the fetus so that later gene-gene or gene-environment interactions may result in disease and pathological responses to the environment.

A basic understanding of the biological and adaptive mechanisms operative during intrauterine life and early childhood will certainly lead to new insights to the diagnosis, pathophysiology, and treatment of a wide spectrum of human diseases from affective disorders to autoimmune conditions. In the post-genomic era it is appropriate that NICHD initiate a rigorous program of research to address the following topics.

I. SCIENTIFIC GOALS

A. Study of Disease Susceptibility

Heritable diseases may become clinically manifest as early in life as intrauterine development and infancy (such as Tay-Sachs disease or phenylketonuria) or later in adulthood (such as Huntington disease, hypertension, and coronary artery disease). Even antecedents to the process of aging clearly occur during fetal development and childhood. Some genetically-determined disorders are absolute and develop inevitably whatever the environment (e.g., Tay-Sachs disease). Others exist genetically but their expression and manifestation is modifiable by environmental change (e.g., phenylketonuria). It is highly likely that there are other disorders in which interactions between intrauterine development of the fetus, genotype, and the environment will determine normal versus pathological development. Investigations of the role of gene function and gene expression, both in utero and in early childhood development, as predeterminants of the incidence and course of pediatric and adult-onset disease should lead to new understanding of disease origin and susceptibility and possibly new therapeutic interventions. Research should focus on the following issues:
• **Pathogenesis:** Epidemiological studies have documented the consequences of maternal malnutrition during the second and third trimester of pregnancy on birth weight, perinatal mortality, childhood morbidity, and adult-onset disease. Studies of the mechanisms whereby fetal nutrition, altered growth and “re-programming” lead to altered homeostasis and adult-onset disease can provide new insights into their pathogenesis.

• **Transgenerational Effects:** Some of these consequences appear to be re-transmitted transgenerationally. It is important to determine whether they are caused by action of the environment on germ cells of the parent or by creating a parental uterine environment for development that recapitulates the circumstances in which the parent developed. Investigations of transgenerational characteristics that are affected by environmental influences and “epimutations” (mutations that do not affect the DNA sequence itself) are needed to enhance our understanding of these phenomena.

**B. Fundamental Biological Investigations**

Biological studies should focus on developmental genomics, fetal growth, the functional role of cellular receptors, fetal/placental interactions, and the fetal neuro-endocrine axis:

• **Fetal Gene Expression:** Relationships have been documented demonstrating the temporal and organ-specific action of transcription and growth factors in the development of the central nervous system and viscera. Investigations of the functional anatomy of fetal gene expression are central to an understanding of “fetal programming.”

• **Genetic-Environmental Interactions:** Investigations of family history and genotype such as those defining the risk of Type 1 diabetes, or the relationship of vitamin D receptor genotype and osteoporosis, provide clues into the pathogenesis of complex diseases. Research on complex diseases (e.g., diabetes mellitus, obesity, hypertension, and coronary artery disease), their heritability, and fetal and postnatal environmental influences will offer new clues on the pathogenesis of these diseases.

• **Linkage Studies:** Investigation of “complex diseases” requires expansion and development of linkage studies, longitudinal investigations, and large-scale mutagenesis studies to define disease pathophysiology.

**C. Development of Diagnostic Products**

Recognition of the pathophysiology of heritable diseases requires careful assessment of the relationship between genotype and phenotype so as to define the pathogenesis of clinical manifestations. Diagnostic products that examine genetic and epigenetic factors involved in disease susceptibility are pivotal requirements. Research on model (animal) systems is essential, as is the development of human fetal tissue banks and libraries of embryonic and fetal tissues. Research should attempt to identify the following factors:

• **Biomarkers of Altered Fetal Growth:** Molecular biomarkers of fetal gene expression should be defined in model and human systems. This will permit identification of molecular biomarkers of altered fetal growth as a prelude for studying the mechanisms of “fetal programming.”
Biomarkers of Adult-Onset Disease: The identification of prenatal and postnatal factors that moderate the natural history of adult-onset diseases requires a search for molecular biomarkers of adult-onset diseases such as diabetes, obesity, and coronary artery disease.

D. Development of Therapeutic Approaches

These efforts should attempt to correct altered basic gene functions and recognize the potential role of genetic or environmental modifiers to disease susceptibility. Nutrition during fetal development and childhood, metabolic responses to nutrient deprivation, and environmental regulation of epigenetic modification of gene expression provide new avenues for disease prevention and treatment. Collaboration with industry and the “high tech community” are integral components for success in this area. Research should focus on novel therapies such as the following:

- Pharmacology: Pharmacologic agents that alter receptor expression and function may modify disease susceptibility.
- Gene Therapy: Gene therapy and modification of gene expression may result in correction of the underlying gene defect.
- Growth Mimetics: Growth “mimetic” agents may correct altered fetal growth during fetal development and thus possibly modify disease susceptibility.
- Stem Cells: Studies of stem cell biology in general and fetal stem cell transplantation therapy in particular are important for the development of new therapeutic approaches.
- Genetic Modifiers: Investigations of the role of genetic modifiers—agents which enhance or suppress cellular phenotype and differentiation—may permit identification of fetal programming factors.
- Pharmacogenomics: Pharmacogenomics, the identification of the genetic basis of idiosyncratic reactions to pharmacological agents, is central for the beneficial application of new and old drug treatments.

II. RESEARCH TECHNOLOGIES AND RESOURCES

Investigations of the genetics of disease susceptibility, the natural history of the origin of adult-onset disease, the role of environment and its interaction with the genotype of the individual, and fetal programming will require the development and application of technologies which will permit studies of regulation and control of fetal growth, studies of cellular death (apoptosis), and studies of stem cell biology. These technologies include:

- “Integrative markers”: This would include the analysis of proteins and metabolites.
- Animal models: Such models are needed to study “fetal programming.”
• **Gene therapy:** This would include gene replacement therapy, gene regulation therapy, and studies of gene delivery and expression.

• **Computational genetics:** This would include development of genetic, epidemiologic, and drug databases in addition to related bioinformation systems.

• **Gene imaging techniques:** These technologies will permit in vivo tracking of fetal and infant gene expression in animal models.

### III. EDUCATION AND TRAINING

Applying knowledge of disease susceptibility requires clinician-scientists. These individuals who have been trained to appreciate the complexity of human diseases are versed in scientific fundamentals, and are sensitive to the needs of the patient. Thus, a critical element for the movement from “bench to bedside” is the need to train physician scientists who are grounded in the principles of ethics and humanism in genetics and clinical science. To enhance these efforts, the development of specialized programs is important. These should include the following components:

- **Infrastructure:** Core facilities with capacity for biocomputation, development of animal models, and proteomics are essential.

- **Centers:** Centers for the training of clinician-scientists need to emphasize the “cross-training” of clinical, behavioral, and basic scientists.
Next Steps

With the completion of our strategic planning framework, the NICHD has concluded the first phase of its strategic planning process. This document will be presented formally to the National Advisory Child Health and Human Development Council in January 2000. In its public session, the Council will have the opportunity to provide the NICHD with feedback, preliminary to the next phase of the planning process.

We have benefited from the thoughtful comments of members of the scientific and lay communities who have helped us refine our strategic directions. The next step is to take each strategic area and develop individual research agendas. Once again we will call upon NICHD’s constituents—both non-scientific and scientific—to assist us. In the early months of 2000, we will be convening workshops to develop targeted research plans that expand upon the four strategic areas described in this document. In the draft stage, each plan will be placed on the NICHD’s Internet site for public comment, with broad notification to interested groups and individuals. Our Council will continue to provide input. All comments will be considered by the NICHD and our advisors and integrated into the strategic plans for each research area.

These “research agendas” will be published in mid-2000 and form the basis for the NICHD’s fiscal year (FY) 2002 operational plans. These operational plans consist of targeted biomedical research initiatives to be announced by the NICHD including Requests for Applications (RFAs), Program Announcements (PAs), and Requests for Contracts (RFCs). For the FY 2002 budget planning process, the highest funding priority will be given to those initiatives that derive from the NICHD’s strategic plans.

Sustaining Momentum

Funding Options

In addition to implementation through operational planning, we have identified other ways to build and sustain the momentum of the NICHD’s strategic research agendas. One strategy that the NICHD has used with success is the “discretionary zone” (DZ), through which a percentage of the research project grant budget is targeted to “scientific emphasis areas,” noted earlier. Based on a multiyear cycle, the NICHD’s DZ emphasis areas are due for revision in 2000. The revised SEAs will be derived from the strategic directions outlined in the four strategic plans the Institute will release in mid-2000.

Another potential strategy is to employ “differential paylines” for the highest priority areas. Similar to the DZ, it would allow grants that address the NICHD’s strategic areas to be paid to a different priority score than other applications, to preferentially build the targeted grant portfolios.

The NICHD also plans to carefully consider the “infrastructure needs” that accompany deployment of funds into our strategic directions. Such issues as training, facilities, instrumentation, resources, innovative mechanisms to foster interdisciplinary collaborations, and creating partnerships across the NIH will be carefully considered and tailored to the subject, to help ensure the success of implementing the strategic plans.
With finite resources, strategically emphasizing certain scientific areas will necessitate de-emphasizing others. The NICHD will develop a process to decide what we should be doing less of to help fund our strategic agenda.

Future Scientific Areas

The NICHD will continue to strategically pursue a range of scientific topics that are critical to our mission, developing research agendas and initiatives through means that are most appropriate to the topic and complement existing activities. For example, the NICHD will revise its existing strategic plan for medical rehabilitation research over the next couple of years, relying upon the advice of the Institute’s National Advisory Board on Medical Rehabilitation Research. Plans for future HIV/AIDS activities are being shaped by the NICHD’s internal AIDS Coordinating Committee, in concert with ongoing trans-NIH reviews by scientific boards, public advisory groups, and activities targeting the evaluation and review of existing and planned research in such areas as pediatric AIDS.

Strategic planning efforts in the Institute are also targeting a wide range of issues involving health disparities. The Institute has established a trans-NICHD Working Group on Health Disparities to develop several comprehensive and coordinated research agendas particularly targeting the concerns of racial and ethnic populations. The effort will build on the fact that each of the four topics identified in this document targets scientific research that is pertinent to health disparities. The Working Group will then focus its attention on developing a series of collaborative initiatives that can complement these efforts and that will specifically address such areas as disparities in infant mortality, reproductive health, medical rehabilitation, and child and adolescent health. Topics of interest could range from those pertaining to normative development in racial and ethnic populations, factors leading to the development of health-conducive rather than health-risk behaviors, unintentional and intentional injuries, violence, developmental or learning disabilities, and obesity. The Institute’s unique strength in understanding the biological, social, behavioral, and population forces inherent in immigration and acculturation will aid these efforts. Ideas are also being developed to encourage strong collaboration between community-based groups and academic institutions to uncover the most important community factors, which when combined with biological and behavioral mechanisms may lead to significant health disparities that start in early pregnancy and childhood. Finally, to implement these far-reaching initiatives, the NICHD is dedicated to creating training opportunities that will increase the number of basic and clinical investigators who are sensitive to and trained in the issues concerning racial and ethnic populations, particularly targeting researchers at minority institutions.
Our Destination

To be successful, strategic planning must be a dynamic process. Whether informal or formal, strategic planning is ongoing. Evaluation points need to be built into plans and research agendas, to see “how we’re doing” in meeting goals and objectives along the way and adjustments must be made. Among other activities, this requires obtaining and integrating feedback from within and outside the NICHD as an essential part of the process. Prior to reaching the approximately three-year horizon of our strategic plans, the NICHD will need to renew the cycle of requesting formal advice from scientists and the public, evaluating impact on the relevant fields and deciding what needs to be modified. As the research agendas are developed in early 2000, the advisory groups will be asked for ideas to build evaluation into the implementation process, both in terms of methodology and of data collection, to ensure that the NICHD can measure success in achieving our goals.

Even while implementing its research agendas, the NICHD will consider additional candidate areas to develop strategically. Once again, we will consult with our Council, the scientific community, and the public in developing new strategic directions for the future.
Appendix – Roster of Advisors

Although this planning document has benefited from the input of the public and of many scientists within and outside the NICHD, we wish to particularly note the advice of the following advisors:

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