FROM CELLS TO SELVES

Genetics and Fetal Antecedents of Disease Susceptibility

National Institute of Child Health and Human Development

Contents

The NICHD Mission

The National Institute of Child Health and Human Development (NICHD) seeks to ensure that every individual is born healthy, is born wanted, and has the opportunity to fulfill his or her potential for a productive life unhampered by disease or disability. The Institute further strives to help parents have the children they want, at the times they want them, and to ensure that every mother experiences a pregnancy free of adverse complications. Key to the success of this mission is answering the fundamental questions of how a single fertilized cell eventually develops into a fully functional adult human being and how a multitude of genetic and environmental factors influence that process for good or ill.

Programs at the NICHD are based on the concepts that adult health and well-being are determined in large part by episodes early in life, sometimes before birth; that human development is continuous throughout life; and that optimal outcomes of development are important not only to the individual but to society. NICHD research is also directed toward restoring or maximizing individual potential and functional capacity when disease, injury, or a chronic disorder intervenes in the developmental process. Thus, the NICHD mission truly spans the life cycle, and much of the health and well-being of our population depends on the success of the Institute's research.

The Strategic Planning Process

During 1998 and 1999, the NICHD staff engaged the scientific community in jointly developing a strategic plan to facilitate achieving its mission. The initial framework document for this plan, *From Cells to Selves*, highlighted four areas for immediate strategic development and described a series of scientific goals under each area. These four areas were as follows:

- *Genetics and Fetal Antecedents of Disease Susceptibility* includes the interaction of the genotype with socioeconomic, environmental, and psychological factors in the fetal and postnatal environment that contribute to health or the pathophysiology of diseases.

- *Reproductive Health for the 21st Century* comprises the biological and behavioral factors that allow couples to have healthy children when they want them and the reproduction-related conditions that may affect women during and after their reproductive years.

- *Developmental Biology: Understanding Normal and Abnormal Development* consists of the basic biological science necessary to understand early development *in utero* and through the time when many organ systems form.

- *Biobehavioral Development* includes research to better understand the developmental processes involved in forming cognitive, learning, emotional, social, and physical behaviors, and the biological and environmental factors that make infants, children, and adolescents more susceptible to behavioral disorders or to adopting risk-taking and violent behaviors.

This document refines the goals and objectives outlined under the area titled "Genetics and Fetal Antecedents of Disease Susceptibility."

To help establish the more detailed research agenda that follows, the NICHD convened a working group comprising distinguished scientists (see Appendix) from around the country and asked them to collaborate with Institute staff to identify and prioritize research goals and to suggest appropriate strategies to meet those goals. The working group drew upon ongoing planning efforts, previous emphasis areas, recent forums, workshops, conferences, and research findings to develop a draft of the strategic plan that would guide the Institute's research agenda in genetics and fetal antecedents of disease susceptibility for the next 5 years.

The draft plan was posted on the NICHD Web site to allow members of advocacy groups, nonprofit organizations, the scientific community, and the general public to comment. In addition, the Institute shared the plan with members of the National Advisory Child Health and Human Development Council and with the Friends of the NICHD, a coalition of more than 100 professional and patient organizations committed to the Institute's scientific mission. After consolidating and reviewing all comments, the NICHD revised and finalized the plan. This document is intended as a targeted, but flexible, blueprint that can be modified as new scientific findings, research opportunities, or resources become available.

Introduction

From conception through fetal development, childhood, and adolescence, patterns are established that determine individual susceptibility to disease. Although genetics and related biological factors provide the initial blueprints, environmental, developmental, and social traits, beginning in the womb, interact with and modify this "imprinting." How and when these factors interact may determine whether individuals start life on a healthy and fully functional path or experience disease manifestations not only in childhood but throughout life. Furthermore, as scientists now believe, the cumulative effects of these events can be passed down to future generations.

Overall Goals and Objectives

Research in this arena will provide insight into the pathogenesis of disease by defining pathways from mutant genes that lead to disease phenotypes or by identifying the role of "modifiers" in the disease process. These modifiers include gene-gene interactions, epigenetic factors (i.e., factors that can affect the phenotype of an organism without affecting the genotype), or environmental influences. The identification of the human genome sequence, as well as the application of new technologies such as expression microarrays and proteomics, will lead to new prevention and treatment strategies and to public health programs. This strategic plan identifies high-priority research areas and opportunities, research resources, and strategies necessary to accomplish the goals and objectives outlined below.

Basic understanding of the biological and adaptive mechanisms operative during both very early fetal and intrauterine life and early childhood will lead to new insights into the diagnosis, pathophysiology, and treatment of a wide spectrum of human diseases, ranging from affective disorders to autoimmune conditions. A broad array of basic, clinical, and translational studies will build a better understanding of fetal and genetic antecedents of disease. Basic scientific studies will provide information about biological and regulatory processes involved in human development and will identify critical pathways in which genetic changes result in disease. Information will come not only from human studies but also from vertebrate and invertebrate models that can provide insights about key homologue genes operative in more complex systems, such as the mouse and human. Clinically based studies on populations and families will help define genetic

and environmental influences on disease risk and pathogenesis. Finally, translational studies will apply this knowledge to develop prevention and treatment strategies.

Scope of the Plan

The study of genetics and fetal antecedents of disease susceptibility focuses on investigating the many factors contributing to human morbidity and mortality. Such studies must investigate not only biological but also socioeconomic, environmental, and psychological factors that contribute to the pathophysiology of human diseases and that account for health disparities among different groups. The interaction of the genotype with the fetal and postnatal environments may result in disease manifestations not only in childhood but also in adulthood, including hypertension, diabetes mellitus, and atherosclerosis. Factors that regulate fetal growth may influence later susceptibility to autoimmune diseases, infectious diseases, and cancer.

Scientific Context and Opportunities

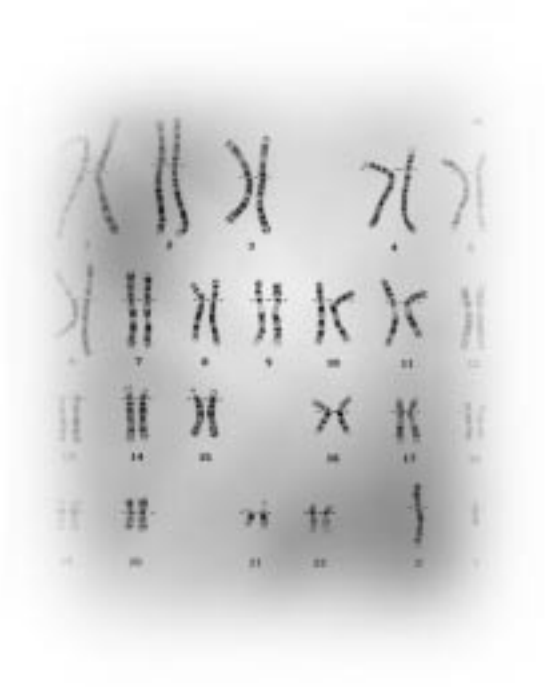
Genetic Diversity and Complex Diseases

Studies of complex genetic diseases need great care in design and implementation. The selection of the study group (whether families or populations), the definition of the disease (phenotype), and the choice of technologies are critical in determining the quality and reproducibility of the research outcomes. Each susceptible allele (mutation in a gene) may exist in a human population in a relatively high frequency (10 to 15 percent) but with low penetrance; thus, its presence does not lead to disease. In addition, environmental and cellular factors in individuals play an important role in determining whether the person develops the disease. Although some human diseases and syndromes are explained by mutations in single genes or alterations of single chromosomes, most human diseases are complex and have more complicated genetic origins, often involving multiple genes. Hirschsprung disease (congenital megacolon) is an example of a complex genetic disease in which careful application of genetic methods led to the identification of five genes associated with this malformation. Although changes in one gene, *RET*, appear to play a predominant role, the five genes identified appear to account for less than 50 percent of cases. Clearly, more research is needed to identify the cause of the other half of cases. All of the involved genes have a logical biological function that relates to the disease phenotype; four of these genes are two pairs of receptors and their ligands (*GDNF* and *RET*; *EDN3* and *EDNRB*), and one gene (*SOX10*) regulates endothelial expression. Such complex genetic diseases present scientific challenges and opportunities for important future research.

Genomics, Development, and Disease

The sequence of the human genome provides the catalog for all possibilities of gene expression. When these genes are expressed, the roles they play during human development and their ultimate function are the result of a systematic plan for gene expression in different cell types, at different physiological and developmental stages. Each cell type within the body has a unique profile of expressed proteins. As body organs develop, a defined pattern of changes occurs in various cell types.

It is possible to use DNA microarray technology, accompanied by computer analysis, to systematically evaluate gene expression. The findings can be used to



develop molecular portraits of disease and profiles of development. For example, comparing the pattern of expression of unknown genes with that of known genes during different stages of development, in different types of cells, or in different diseases can provide important insights about the regulatory pathway in which an unknown gene may function.

Applicable technology is becoming more user friendly and less expensive. For instance, a protein-based system, analogous to the DNA system, is being developed to further detail the molecular basis of development and disease. Such knowledge can then be expanded to assess disease prognoses or to devise patient-specific treatment strategies. For example, in a retrospective analysis of breast cancer tissue from patients treated with chemotherapy, scientists discovered, in a small set of patients, that survival and responsiveness to a particular chemotherapy corresponded to the molecular profile of the tumor tissue.

Growth Factors and Development

Neurotropic growth factors provide an example of a family of diverse factors involved in the proliferation, survival, differentiation, maintenance, and plasticity of one of the major physiological systems of the body. For example, nerve growth factor (NGF) plays an important role in maintaining the basal forebrain cholinergic neurons, which are lost in Alzheimer's disease. Effective therapeutic strategies for using various growth factors may be developed through research that can determine the specific growth factor for various neurons, appropriately match the growth factors with various diseases and disorders, and determine how to deliver growth factors at the appropriate time to the relevant neuron type. The mouse model of Down syndrome, for instance, has several analogies to Alzheimer's disease. These animals show developmental delay and cognitive decline and have increases in several proteins and pathological changes in their brains, comparable to human dementia.

Collectively, there are a number of diverse factors, functioning through a variety of biochemical and physiological mechanisms, that act on different levels of the nervous system. To understand the development and function of the nervous system in normal and disease states, these factors need to be studied at the molecular level. Specifically, research is needed into their role in signaling, into their interaction with various receptors, and into their role at the organ level, including their anatomic and temporal patterns of expression.

Genetics of Arteriosclerosis and Unexplored Areas of Genetic Disease

Arteriosclerosis is a disease with some known predisposing genetic risk factors in which behavioral and medical interventions can influence disease development. It is known that good diet, avoidance of smoking, and exercise have beneficial effects. Drugs such as aspirin, statins, folate, and niacin also have positive effects in preventing disease. In addition, imaging technologies can further assess persons at higher risk for disease. Thus, it is possible to combine genetic and imaging assessment, with lifestyle modifications and medications, to greatly control this illness. However, in addition to the known risk factors for atherosclerosis, other genetic or fetal antecedents may be predisposing factors yet to be discovered, such as birth weight.

Many hypotheses that deserve exploration suggest other factors that may generally influence disease susceptibility. For example, diseases of the placenta or abnormal maternal or fetal genes may be found to affect placental development. Also, maternal or fetal deficiencies in genes may be expressed only in the uterine interface with the placenta, and these deficiencies

may ultimately result in developmental problems such as mental retardation.

In addition, a complex set of gene methylations and demethylations takes place during development and requires further study. The roles of environmental (e.g., dietary) factors and genetic factors that affect these biochemical processes must also be explored. An example of the latter is the agouti allele in mice. Mice with this allele are diabetic, obese, and yellow in color. However, by varying the mother's diet, the expression of the phenotype in the offspring can be diminished. The fact that this beneficial effect appears to persist into the second generation (grandchildren) of these mice is an intriguing finding and requires exploration.

A broad range of epigenetic mechanisms exist that must be explored to fully understand how disease develops in humans. For example, administration of Diethylstilbestrol (DES) to pregnant women to prevent premature delivery and miscarriages resulted in an increased incidence of vaginal cancer in their daughters. In addition, investigators studying mammalian genetics may obtain important insights into potential explanations and mechanisms for complex human diseases by considering whether some of the epigenetic effects observed in microorganisms and plants, such as bacteria, may also be operative in mammalian species.

Genetic/Fetal Antecedents of Type 1 Diabetes

Type 1 diabetes is an example of an autoimmune disease in which genetic, environmental, and immunologic factors contribute to disease development. Autoantibodies to beta-cells and to beta-cell markers may herald disease; however, not all persons with beta-cell autoantibodies develop the condition. Studies of twins and families suggest genetic factors play a role in the development of type 1 diabetes. However, if one monozygotic (identical) twin develops the disease, there is only a 30 to 50 percent chance that the twin sibling will. The HLA markers DR3 and DR4 are present in more than 95 percent of persons who have type 1 diabetes; however, not all persons with these haplotypes develop disease. Conversely, the DR2 and DR15 haplotypes appear protective. Clearly, in addition to genetics, other factors affect disease development.

For example, changes in environmental factors may play a role in the development of type 1 diabetes, the incidence of which has been increasing about 3 percent a year over the past 40 years. The largest increase has been observed in children younger than 5 years of age. This suggests that environmental factors may play a role *in utero* or early in life. Further evidence of the role of environmental factors is seen in the worldwide country-to-country variation in disease prevalence and in the observation that Asian immigrants coming to San Francisco from countries with low incidence of type 1 diabetes develop diabetes at the higher U.S. rate. Environmental factors such as viral infections and diet also have been suggested for initiating or promoting disease. Epidemiological data and animal model

observations provide some support for the hypotheses that both rubella and Coxsackie virus infections trigger onset of the disease *in utero*, and decreased periods of breast feeding, early introduction of cow's milk, and maternal coffee consumption have been postulated to play roles in the perinatal and intrauterine periods. However, to date, studies have not yielded definitive findings because of differences in their design, low statistical power, and lack of measurement of genetic factors. Research focusing on genetic factors has been difficult to conduct because of genetic heterogeneity; the large number of loci, each of which has a weak effect; and lack of gene expression analysis. This situation presents an opportunity for well-designed studies that take advantage of emerging technologies.

Research conducted in a strain of rats with genetic susceptibility to diabetes offers hope for prevention of type 1 diabetes in some high-risk children. Administration of glucose and arginine early in life resulted either in lower incidence of diabetes or later onset of disease for those animals that developed the disease. It may be possible to identify high-risk children for potential intervention by screening for their HLA haplotype and monitoring them for development of autoantibodies. Such screening would identify potential subjects for prevention trials, allow for a better understanding of the natural history of type 1 diabetes, and provide for early diagnosis. In addition, the use of microarrays may allow for the delineation of the molecular susceptibility genes and the identification of the molecular markers for disease progression. Clinically, this information could be used to classify disease and potentially provide markers for therapeutic clinical trials. Clearly, the study of genetic and epigenetic antecedents of disease is complex and challenging but holds great promise for improving public health.

Pharmacogenomics, Development, and Therapeutics

Assessing the role of genetics in health, disease, and response to therapy is difficult from both the clinical and technical perspective. A significant understanding of the effects of genetic and environmental factors on disease susceptibility could be achieved by instituting a prospective longitudinal study in which quantitative measures are incorporated and data are collected on genetic and environmental factors. Study participants would be followed from preconception (that is, by studying their parents), through fetal development and the postnatal and childhood periods, to adulthood.

An example of a long-term prospective longitudinal study that has provided important information about heart disease is the Framingham Heart Study. A key feature of the study was the quantification of traits; for example, the actual blood pressure of study participants, rather than a descriptor such as "high blood pressure," was recorded and analyzed. The Framingham study also helped researchers identify heritable factors that affect drug action. The association of these genetic factors is very strong, in the 90-percent range (as compared with 40 to 46 percent for other heritable diseases), and appears to be linked to the P450 genes.

Thus, understanding the genetics of responsiveness to drug classes has extraordinary potential for improving drug efficacy and reducing drug toxicity and should have high priority for exploration. Genetic assessment could identify persons who are not responsive to certain drug classes and/or are at higher risk for drug toxicities. An example is the variance in thiopurine methyltransferase that predicts the toxicity of 6-mercaptopurine, a drug used to treat cancer patients. As with all drugs, dosages are based on efficacy and

cytotoxicity for the patient population as a whole, without knowledge of the genetic background of individual patients. About 1 percent of individuals are not responsive to this drug. At the same time, it is estimated that about 90 percent of patients could receive higher doses without increased toxicity, possibly with a better clinical outcome. In addition, where different drug classes are available for treatment of a disease, the patient and drug could be properly matched to achieve maximum efficacy with minimum cytotoxicity if research can reveal how to make this match.

Human genomics presents many technical challenges. For example, the currently available techniques and methods are relatively expensive and do not measure haplotypes. New technologies under development and potentially available in the next few years may be more accurate and less expensive. In addition, investigations of mutations must go beyond single base changes and consider multiple variances and the structural consequences of the mutational changes and haplotypes. At best, molecular studies measure prevalence and predisposition, but many factors may affect progression to disease. Methods must be developed to analyze and structure the vast amount of information that will be obtained by microarray analysis. Finally, clinical studies are hampered by many factors, including the reproducibility of tests, the objectivity of data interpretation, the delineation and adequacy of the case group and spectrum and of the comparison group, and the quantitative summary of the results. The development of necessary research tools and novel study designs are essential elements of this strategic plan.

Contribution of Model Systems to Birth Defects Research in a Postgenomic World

Simple model systems have enabled researchers to understand many aspects of human gene regulation and human development, and these topics deserve further investigation. *Drosophila*, the fruit fly, is an example of a model system in which a number of key signaling pathways have been identified and human homologues are being sought. For example, the fruit fly has been used as a model for dorsal closure because of its analogies to neural tube closure in humans. Among its other advantages are its low genetic redundancy, the array of genetic analysis techniques and methods available to study it, and the extraordinary conservation of the organism at the tissue, cell, and molecular level. In addition, the simplicity of the organism and the availability of imaging techniques allow the fruit fly to be visualized under normal conditions and after genetic or environmental changes. The study of second-site noncomplementation with a set of mapped genes has also permitted investigators to readily identify genes that interacted with the principal gene involved in dorsal closure; such *a priori* identifications in mammalian systems are more technically and genetically complex. Furthermore, the availability of the sequences of both the human and *Drosophila* genomes will allow investigators to identify potential human homologues, enormously simplifying the task of studying both the genes and processes involved in key developmental steps.

Another model organism that has had tremendous impact on studies in humans is the jellyfish, in which green fluorescent protein (GFP) was identified. GFP is an autonomously folding protein fluorophore. In the past, an investigator wishing to study a biological process with a fluorescent protein had to chemically label the protein after it was made in the cell. The protein under study had to be purified in some manner either before or after labeling. Now investigators can link the GFP coding sequences to the gene they wish to study and have the cell form a specifically labeled protein. They can then assess the protein's function directly in the cell without other purification and modification steps. Thus, simple nonvertebrate systems have the potential to offer insights into mammalian systems and to facilitate the study of human disease. The further development of these systems should be a research priority.

Research Priorities

The scientific opportunities described in the previous section highlight many important areas for future efforts. Scientists have found very early fetal development to be a major determinant of future disease susceptibility. The development of the placenta and its function in fetal growth and development through the interplay of genetic, nutritional, and metabolic hormones and growth factors have thus assumed increasing importance as an area of investigation. Nutritional interventions and other environmental factors, which influence developmental processes such as neural tube closure and the hard-wiring of the central nervous system through the development of synaptic connections, also represent important areas for further study. The completion of the human genome will make it possible to better understand the genetic basis of human development and to sort out the varied constellations of disease-producing alleles that undoubtedly underlie a variety of degenerative and metabolic disorders, such as diabetes, arteriosclerosis, and mental retardation.

The following proposed areas for future emphasis require a balance of individual projects, centers of excellence for the study of human development and disease susceptibility, and interdisciplinary and interinstitutional collaborative program project grants. Attention should also be given to the development of mechanisms for attracting younger scientists and/or mentoring awards in these areas. These "infrastructure" requirements are discussed in the next section.

- Research the maternal-fetal aspects of human development, including genetics, implantation, placenta, fetal growth, nutrition, environment, and epigenetic effects.

- Conduct a longitudinal assessment of the effects of placental factors on future outcomes, following a population from preconception through fetal development, childhood, and adulthood, to assess genetic and environmental factors that impact on health and disease susceptibility. Biological specimens, such as samples of the placenta, would be saved as part of this project. The psychological impact of participating in this study and identification of factors that influence participation should also be measured.

- Apply genomic and proteomic approaches to the analysis of normal and abnormal development.

- Develop mechanisms for support of microarray technology, perhaps in core facilities of program project grants.

- Study developmental neurobiology in relation to diseases and disorders, e.g., behavioral disorders, mental retardation, autism, dyslexia, and defective neural tube closure.

- Elucidate the role of fetal/developmental antecedents in chronic adulthood diseases and conditions, including cancer, diabetes, and arteriosclerosis.

- Better understand the development of the immunological system, including the role of abnormalities and genetic factors in autoimmune diseases and allergic disorders (e.g., type 1 diabetes and asthma).

- Study the genetics of specific developmental abnormality syndromes.

- Better understand the biology of plasticity as it involves neurocircuits, including basic studies about the mechanisms of signaling and the biology of synapses

that underlie plasticity, as well as its applications to reading, learning, and cognition.

- Study the biology of the placenta, fetal and maternal factors affecting the placenta, and outcomes associated with placental problems.

- Study the potential relationship of P450 genes to drug responsiveness and/or toxicity, with a goal of identifying the most effective and least toxic treatment modality for individual patients.

- Better understand the role of epigenetic effects in human development and malformation. Mechanisms observed in *Drosophila* and yeast can be applied in mouse systems as a model for human disease.

- Study the interactions between genes, the environment, and the immune system. This should include how the major histocompatibility complex (MHC) system may act early in life.

- Study how the intrauterine environment may affect genetic mutations and outcomes related to the function of these genes.

- Develop a trans-NIH Human Biology Project to determine gene expression through the various phases of development and across multiple diseases.

- Better understand the ontogeny of gene expression in normal developing systems, including studies of the ontogeny of the immune system.

- Study the behavioral genetics of specific genetic disorders, applying the finding that certain behaviors are associated with particular chromosomal changes.

- Collaborate with systems neuroscientists to better understand brain activation pathways in various disorders and pave the way for developing prevention and treatment strategies.

Infrastructure Priorities

Research like that highlighted in the previous section requires a strong infrastructure of trained scientists and dedicated institutional resources.

Train Scientists

There is a need to develop a cadre of young clinicians who would design and conduct clinical trials. Currently, there is little interest among candidates to pursue such training, and there is a scarcity of available mentors. This is due, at least in part, to the current financial climate in medicine that tends to force institutions, and the clinicians who work there, to focus exclusively on patient care. Incentive programs, such as medical school loan repayment, should be adopted to encourage more young physicians to train for and participate in clinical research. Similar incentive programs to encourage more experienced researchers to serve as mentors should also be explored.

Additional training mechanisms should be developed or modified to increase the time for interdisciplinary training of Ph.D. scientists. For example, a physicist or mathematician who would like to contribute to biological research will need additional time, beyond the traditional 1- to 2-year training grants, to learn the basics of a new discipline. Thus, interdisciplinary training mechanisms might allow for up to 5 years of training. Trainees who already have completed a postdoctoral fellowship should be allowed additional time to study a new discipline under this training mechanism. Any program should provide two mentors, representing both academic areas of interest. The mentors could be located in different institutions, and the trainee would be allowed to spend time with both mentors. Finally, efforts are needed to encourage Ph.D. trainees to receive additional exposure to human biology, particularly to human physiology.

Build Centers of Excellence

Centers of excellence should be established to focus on topics of broad public health importance and to foster basic and clinical expertise. Staff of these centers would train clinical researchers and practicing physicians, and would disseminate their research findings to the public and to policymakers.

While several mechanisms could be used to implement such an effort, it is important that these centers have core facilities for technologies such as microarrays. They may also need some internal, simple funding process for pilot projects to allow investigators to be creative and to rapidly test their ideas. To ensure the range of scientific expertise and sophisticated technology required, several institutions could be a part of one center.

Facilitate and Build Interdisciplinary Collaborations To Address Complex Diseases

There is a need to build interdisciplinary collaborations of basic and clinical researchers, as well as collaborations involving experts in fields such as health policy, law, and ethics.

Facilitate the Development of Animal Models of Human Genetic Disorders

Establish mouse genetic facilities and core laboratories for generating mutant mouse strains via transgenic and site-specific recombinational strategies, and for evaluating the phenotypes generated in terms of their physiological, morphological, behavioral, and pathological aspects.

Build an Infrastructure That Helps Individual Scientists

Build on the success of research institutions that have been successful at obtaining new technologies by having them serve as models for other institutions also interested in obtaining that technology.

Provide Databases and Biological Resources To Test Hypotheses

Significant progress in understanding the impact of genetic and environmental factors on disease susceptibility may be achieved by establishing a large-scale longitudinal population study. The longitudinal study described in the previous section would prospectively follow populations from preconception (by studying the parents) and gestation, to the postnatal period and childhood, and through adulthood. Although the study itself would not be entirely hypothesis based, it would provide a vast source of information and data for investigators to use in designing and conducting research projects. Access to data and materials from this study would be readily available to the scientific community; therefore, this study is also included under "infrastructure."

Priority Methodology and Policy Issues

New methodologies and policies also need to be developed for solving certain scientific problems. High-priority needs are described below.

Microarrays

This methodology has the potential to provide knowledge about normal development, genetic function, and the molecular basis of disease. Systematic approaches are needed to develop institutional capacity to implement this technology and analyze resultant data.

Application of Model System Information to Human Disease

Increased attention should be devoted to developing and utilizing simple nonvertebrate systems, which have the potential to offer insights into mammalian systems and to facilitate the study of human disease. Model systems should be chosen by individual investigators on the basis of the best model to address the questions posed by the research.

Database/Bioinformatics Issues

There is a need to provide guidelines and information about establishing, maintaining, and sharing databases to avoid duplication and to make data readily available for use by the entire research community. Furthermore, the NICHD needs to better advertise the existence and content of the databases it maintains and to facilitate their use by the research community.

Improved Definition of Disease Phenotypes

Studying complex diseases in an effort to determine the genetic and molecular basis of the disease or disorder has been hampered by difficulties in clearly defining and measuring disease phenotypes. Efforts should be made to devise criteria and methodological approaches to define and measure phenotypes.

Research Policy Issues

The current debate about collecting personal data on individuals can adversely affect the implementation of important human genetic studies. Health policy and ethics experts need to work with researchers to devise ways to educate the public about the importance of collecting and analyzing genetic data to solve public health problems, while also addressing privacy concerns.

Creation of a Study Section To Review High-Risk Projects

Highly innovative or high-risk applications often do not compete well in standard peer review. A study section should be established that targets this type of project. Investigators could designate their applications as highly innovative and request review by that study section, thus assuring that such projects would compete with one another rather than with other more conventional applications.

Appendix—Roster of Advisors

Although this document has benefited from the input of many scientists within and outside the NICHD, and from the general public, we wish to particularly note the advice of the following members of the strategic plan working group:

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