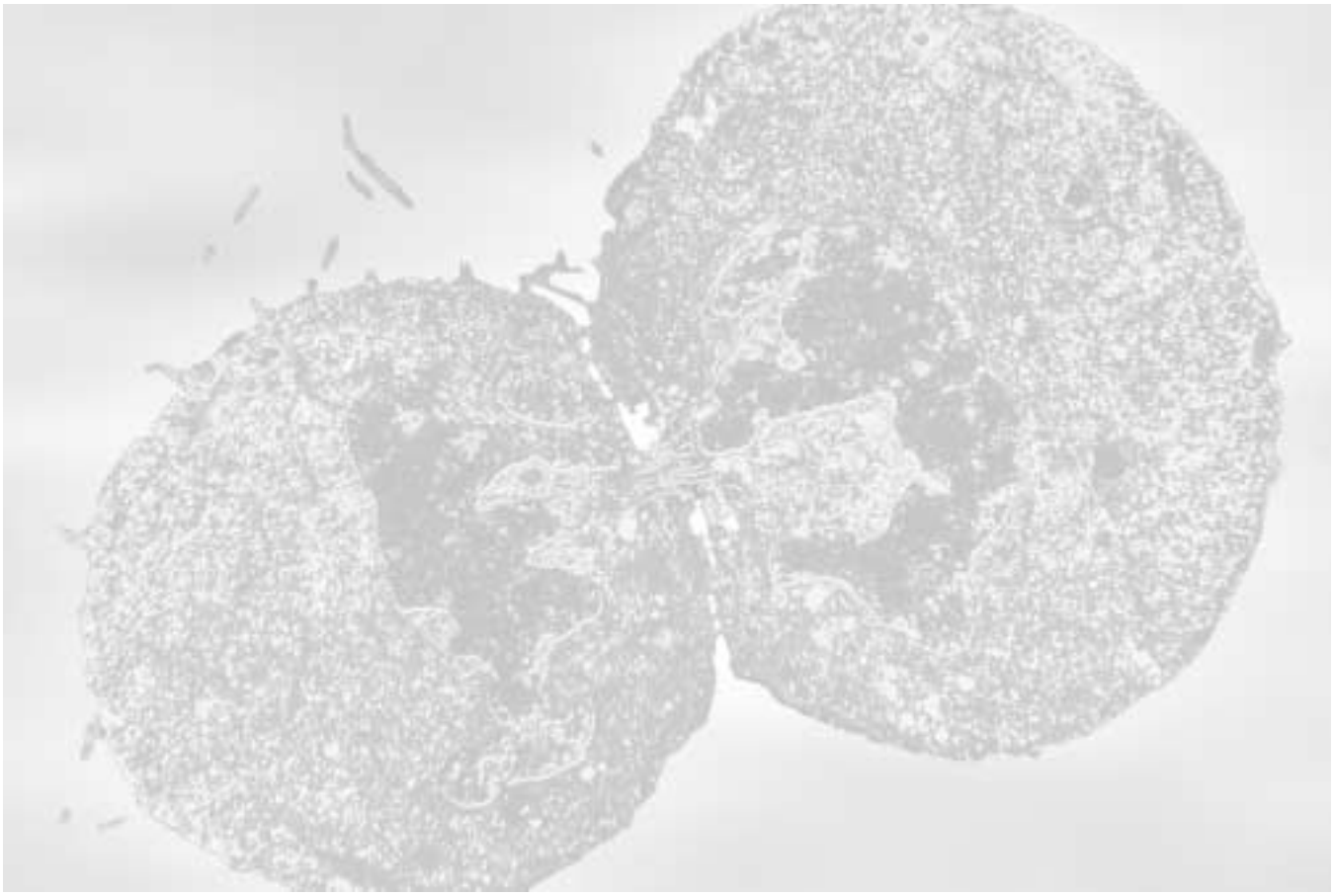
FROM CELLS TO SELVES



# Developmental Biology

## Understanding Normal and Abnormal Development

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 "Developmental Biology: Understanding Normal and Abnormal Development."

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 developmental biology 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

Although the Institute has made great progress 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 younger than 1 year of age, accounting for one of five infant deaths. Estimates indicate that more than 150,000 babies in the United States are born each year with significant birth defects (about 4 percent of all live births). Families with babies born with severe, nonfatal birth defects, often accompanied by mental retardation, are burdened financially by expensive special medical treatment, education, rehabilitation, and other supportive services to care for their disabled children from childhood into adulthood. 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 with any of 17 major structural birth defects are estimated to be more than $6 billion a year. Consequently, the full economic impact for all birth defects is much greater. The emotional costs to families are incalculable.

Developing effective strategies to prevent birth defects is possible only with a thorough understanding of the epidemiology, etiology, and pathogenesis of birth defects–areas where tremendous gaps in knowledge still

exist. Progress in these areas requires a better understanding of clinical phenotypes, human syndrome delineation, teratogens, epidemiology, and the natural history of birth defects. Also essential is gaining an in-depth understanding of the basic mechanisms that underlie normal developmental processes, through the appropriate use of animal models and stem cell* research. Accomplishing these goals will require a joint effort by clinicians and basic scientists to approach birth defects research from their respective strengths and build on each other's progress. Thus, a common theme in the emphasis areas outlined in this strategic plan is the need for a two-way flow of information between scientists with different types of research interests and endeavors. Such collaboration will help to fill the gaps in knowledge about how both genetic and environmental perturbations of normal processes cause developmental abnormalities.

Findings from clinical studies will also provide insight and direction to basic scientists studying developmental processes. Similarly, translating basic findings from the use of animal models and stem cell research to relevant clinical research will increase our understanding of human embryonic development and the formation of structural birth defects.

The scientific goals delineated in the following section of this strategic plan take advantage of the most recent technological and scientific advances and provide a schema for the NICHD to continue its efforts to clarify the patterns and processes involved in the genetic program of human development. In the context of this strategic plan, the timeframe 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. In certain cases, such as research dealing with the immune and nervous systems, studying later stages of development may help scientists to better understand how these systems respond to the environment during the postnatal period.

The sections on Research Technologies and Resources and Training and Education address resource and training requirements, which the NICHD views to be as vital to the advancement of these research areas as is support of basic research itself. The section on Research Technologies and Resources also capitalizes on and further develops the essential biotechnology from the emerging areas of structural, functional, and comparative genomics and proteomics, to unravel the complex processes of developmental biology at higher levels of resolution. Both the application of this expanding technology and the expected data from the Human Genome Project increase the need for support of infrastructure, bioinformatics, and data presentation. The section on Training and Education highlights the need for basic/clinical integrative training, as well as support for training in some targeted areas, such as clinical phenotyping, dysmorphology, teratology, genetic epidemiology, and informatics and data management.

* 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 was released in August 2000. The guidelines apply to all relevant initiatives in this strategic planning document.

# Scientific Goals of the Strategic Plan

The goal of this strategic plan is to clarify the underlying mechanisms of normal and abnormal developmental processes to provide the basis for understanding the formation of birth defects. In pursuit of this goal, the Institute will investigate birth defects from both clinical and basic science perspectives. Clinical studies are important to address the genetics, phenotyping, and classification of human birth defects. Basic studies that use experimentally manipulable systems are essential to clarify the underlying mechanisms of both normal and abnormal development. Science also has a continuing need to create models that test hypotheses derived from both scientific approaches.

Multidisciplinary approaches mentioned in this section require cutting-edge technologies, such as those associated with structural, functional, and comparative genomics, proteomics, and imaging. The approaches addressed in the section on Research Technologies and Resources are expected to include (1) determining patterns of gene expression during development of specific cell types, complex tissues, and organs and (2) examining protein expression profiles and structural/functional relationships of key developmental proteins.

## Genetic Studies of Birth Defects

The research in this emphasis area begins with describing the physical traits, or phenotype, of a patient and then works toward determining the genes involved in that defect and its underlying mechanisms with a birth defect. Mapping and sequencing data generated by the Human Genome Project will help scientists study the genes associated with human hereditary conditions. Linkage analyses of pedigrees and mapping studies are a mainstay of clinical genetics studies. Additional classification/phenotyping research and genetic epidemiological studies are needed to address the complexity of congenital anomalies, especially those associated with syndromes that have multiple clinical features.

- **Phenotype delineation.** Once scientists phenotype or characterize the entire physical, biochemical, and physiological makeup of individuals with a specific condition, they will have a better understanding of the human disease process. Beginning *in utero*, the full-spectrum characterization will provide extremely useful information when compared with and correlated with the genotype of these individuals. Consequently, there is also a need to develop improved methods for phenotypic analysis, including syndrome delineation and natural history of disease. Developing registries to collect cases and networks to provide data on phenotype and families will prove vital for linkage analyses and, ultimately, for mapping the genes responsible for specific birth defects. For these reasons, the NICHD encourages research that links phenotyping to well-defined research projects; such efforts will also include clear and delineated plans for the eventual analysis of these data at the molecular level. These programs will focus on a tractable scientific problem and will include impact analyses on birth prevalence and innovative and novel approaches for, and technology development relevant to, phenotype delineation. The efforts will also strive to increase throughput/efficiency, while making the resulting data/specimens widely available. In addition, the programs will integrate basic science activities to ensure that collected clinical data and specimens are productively channeled to the laboratory.

- **Genetic epidemiology.** This comparatively new field of research emerged from the integration of

molecular genetics into traditional epidemiological research. Generally, genetic epidemiology focuses on the contribution of genetic, teratogenic, and environmental factors identified at the molecular level to the etiology, distribution, and prevention of disease within families and across populations. For example, the causes of ethnic and racial disparities in the incidence of certain birth defects are relevant to this area of research, as are collaborative and interdisciplinary studies of human malformations that integrate the latest advances in developmental and molecular genetics with new and innovative analyses of epidemiological data. Such investigations will provide a foundation for developing hypotheses concerning molecular genetics and the developmental biology of structural birth defects.

## Basic Mechanisms of Normal and Abnormal Development

The NICHD continues to recognize research into the basic mechanisms of normal and abnormal development as a high priority area. Further, the enormous success and fast pace of advances in this field merit additional future support. This research focuses on using model systems to clarify the mechanistic causes of birth defects. Through basic research, scientists are beginning to identify the many factors that regulate the genetic networks triggering and controlling developmental processes. Coupled with the advances from the Human Genome Project, the NICHD expects that opportunities to foster interaction between the laboratory and the clinic will continue to increase. Of particular interest to the Institute are studies examining defects of gastrulation, generalized body patterning, and the formation of organs, such as those of the nervous, skeletal, and visceral systems. All of these major developmental events require the precise integration of many developmental processes, including morphogenetic movements, cell-cell and cell-matrix interactions, signal transduction, cell proliferation, and apoptosis, to name a few. Understanding the normal choreography of these developmental processes, as well as gaining insight into the results of genetic abnormalities or teratogenic insults, are essential if scientists are to make the leap from basic knowledge to therapeutic intervention or prevention of structural birth defects. Without overlooking more standard methodologies and physiological approaches to these questions, the inclusion of state-of-the-art genomics and proteomics technologies is inherent to these studies. This work will allow scientists to determine the patterns of gene expression during the development of specific cell types and complex tissues and organs, and to examine protein expression profiles and structural/functional relationships of key developmental proteins. Although it is likely that this work will rely heavily on animal models, translating the basic research findings to congenital structural malformations that are clinically significant is also important. Major areas of emphasis within basic mechanisms of normal and abnormal development include the following:

- **Early embryonic events and processes.** The elaborate and early embryonic events, such as body axes formation, gastrulation, and neurulation, are crucial for normal embryogenesis and greatly influence both the formation of the basic body plan and cell fate. Because significant defects in these processes are frequently lethal to the embryo, understanding the genetic events that underlie these dynamic processes is critical.

- **Organogenesis.** The formation of organ systems requires a precise integration of many developmental processes that involve the coordination of complex

genetic and developmental networks. Advances in the field of developmental biology now allow scientists the level of sophistication to study the formation of organs. Clarifying gene expression patterns, defining genetic networks, understanding matrix biology, and characterizing biochemical interactions are crucial for our understanding of structural birth defects.

- **Unique opportunities in developmental immunobiology and neurobiology—intriguing systems associated with "learning" and "memory."** Although this strategic plan focuses on anatomically evident structural defects, the functional ramifications of more subtly aberrant developmental processes also deserve attention. In this respect, two important areas of research are developmental immunobiology and developmental neurobiology, with each associated with memory and learning in slightly different contexts, resulting from interactions with the environment. The analogy is most apparent with the learning and memory processes of the central nervous system (CNS), such as when a child goes to school and learns to read. Similarly, in the immune system, the mature cells that form the body's defenses against assaults from foreign antigens must "learn" and "memorize" the identities of invaders to protect the body from disease. In both the immune and nervous systems, even abnormalities in developmental processes that are not readily detected as structural defects have devastating functional implications, such as the occurrence of primary immunodeficiency diseases or mental retardation and learning disabilities. The NICHD plans to incorporate studies on the following topics:

  ➢ ***Developmental immunobiology.*** Large gaps still exist in our knowledge of the developing human immune system. Understanding both the normal and abnormal development of the human fetal and neonatal immune system and the interactions of this immune system with maternal immunity has enormous clinical implications. Basic studies will provide the essential fundamental knowledge, understanding, and insights that researchers can translate into effective diagnostic procedures, safe and efficacious prophylactic and therapeutic modalities, and useful prevention strategies to reduce infant morbidity and mortality. Animal models, particularly those of mice, provide valuable insights into human immunobiology. Because of differences in the timing of T- and B-cell generation and the population of lymphoid organs, parallel studies of human and mouse immune cells at different developmental and functional stages are also important. Studies of developmental immunobiology will involve basic, applied, and clinical research on the ontogeny of immunity, the development of immune responsiveness, postnatal responses to the environment, and reproductive immunology. Other, more focused, research includes ontogeny of the normal immune system and host defense mechanisms, genetic programs governing normal and abnormal development of immunity and response to infection and immunization, and cellular and molecular mechanisms of immune tolerance and transfer of immunity during pregnancy.

  ➢ ***Developmental neurobiology.*** Like all developing systems, the CNS is shaped by the developmental and genetic programs of the organism, as well as by numerous gene-environmental interactions. In its initial phases, the developing CNS has many processes in common with the formation of other organ systems. However, minor flaws in subsequent, complex processes, such as those associated with synapse formation and higher levels of integration, can result in subtle structural defects that have devastating functional implications. Consequently, in addition to supporting basic research in classical areas such as axonal guidance, tissue differentiation, and gene discovery in the developing CNS, the NICHD will also place an emphasis on studies that develop criteria for and collect descriptive data on various

neurological syndromes. These endeavors represent a prime example of the need for a merger of detailed phenotyping and gene expression analyses. The proactive development and inclusion of these data in comprehensive databases for neurological disorders will prove invaluable for analyses of both structural defects and abnormal brain function, which would benefit behavioral scientists searching for a genetic cause for a specific syndrome or functional deficit. The NICHD will coordinate efforts to support research and database development, both between its own branches involved with different aspects of neurobiology research and with other Institutes, research institutions, and organizations from the private sector with shared interests in developmental neurobiology.

## Development of Model Systems

The discovery of the highly conserved nature of developmental processes across species, from worms (*C. elegans*), flies (*Drosophila*), zebrafish (*D. rerio*), frogs (*Xenopus*), and mice to humans, has been an important conceptual advance. For many years, scientists have used animal models to clarify and understand developmental processes and identify many genes involved in human development. The next step in this development is to create or identify models for testing hypotheses that are generated as a result of clinical and basic studies. Recently, scientists also established the significance and potential applications of embryonic stem cells. Thus, both animal and stem cell models are essential components of research in this emphasis area.

- **Animal models.** Multidisciplinary studies using appropriate animal model systems are essential to clarify the molecular, biochemical, and morphological aspects of crucial, basic processes such as cell proliferation, cell differentiation, and cell interactions, as well as the complex processes of gastrulation, patterning, neurulation, and organogenesis. Such investigations will improve scientific insight into mechanisms of development, facilitate the identification of critical developmental periods, and enable researchers to verify the genetic and environmental miscues that give rise to conditions like neural tube and skeletal defects. The conservation of genes, genetic networks, and developmental pathways across the animal kingdom provides credence for using diverse models, such as *C. elegans*, *Drosophila*, *Xenopus*, the zebrafish, and mice to study human developmental processes. Consequently, the knowledge provided by work on model systems will also provide the basis for translational studies of human congenital defects. This knowledge will lead to the improvement of early diagnostic procedures and the development of gene therapies that can ameliorate or prevent birth defects. The NICHD cannot overemphasize the importance of continued support for the use of animal models to study development. To accomplish its goal, the Institute will support the use of all animal models, including natural mutants, targeted/induced mutants, and transgenic animals, and the development of new methods to target gene expression (e.g., selective spatial or temporal expression and genetically controlled cell ablation to study the function of specific cell populations) in model systems. These efforts will also incorporate a critically needed mechanism by which information about animal models can be quickly disseminated and advertised to the research community.

Curly tail mouse photo provided by Stanton K. Short, The Jackson Laboratory, Bar Harbor, Maine

- **Embryonic stem cells.** Embryonic and other stem cells of differentiated tissues provide important models for understanding basic processes associated with development and differentiation. Although research on embryonic stem cell biology using animal models is still in its early stages, it is a very promising approach to unraveling 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 goal, the Institute will support studies to characterize and define embryonic and postnatally derived stem cells from different species, identify factors that stimulate and trigger the proliferation and differentiation of stem cells toward various cell lineages, and foster the use of stem cells as a tool for studying the processes of differentiation and cell lineage determination.

# Research Technologies and Resources

For innovative and creative scientific projects to succeed, the appropriate infrastructure, resources, and technologies must be available. Some of the technologies and resources listed below overlap because their integration is necessary to achieve a scientific end; for instance, imaging, genomics, and computational/bioinformatics are all involved in developing atlases/gene expression databases. Cost is a major consideration in these endeavors. Establishing databases or genomic/proteomic resources is costly enough; however, maintaining them in perpetuity is extremely expensive. Consequently, while the NICHD understands the importance of developing human and animal databases and resources and remains committed to the task, maintaining these databases requires the coordinated support of several Institutes, particularly those that are more technology-driven, in addition to private organizations with similar goals.

## Functional Genomics and Proteomics

Genomics and proteomics represent important scientific strategies for capitalizing on genome sequencing to address questions raised in the developmental biology and birth defects emphasis areas. The research areas of functional genomics and proteomics deal with the analysis of gene activity and the processes that lead to the expression of proteins, as well as the integrated, systematic view of protein interactions and their relationships to cell function. The combination of these powerful approaches provides a means of analyzing regulation at many levels. These strategies are also extremely important when used in conjunction with imaging technologies to catalog gene expression in databases and atlases. Indeed, the use of these new methodologies is embedded in the very fiber of the studies recommended in the section on Scientific Goals of the Strategic Plan. At the same time, as new fields, functional genomics and proteomics have provided immense amounts of data and will continue to do so well into the future. Because researchers anticipate that one-half to three-fourths of all human genes will prove important in developmental processes, generating efficient and uniform data, cataloging the data, and presenting them in a form that is useful to scientists pose complex challenges to genomic and proteomic research strategies. Possible solutions to these challenges include the following:

- Promoting the use of computational biology and bioinformatics to address issues of normal and abnormal development.
- Developing new strategies to support mutagenesis and phenotyping to identify and characterize genes involved in normal and abnormal development.
- Identifying new methods of spatial/temporal inactivation of genes in specific cell types in model systems.
- Developing new techniques for using proteomics to study normal and abnormal development.
- Developing techniques to isolate specific cell types from tissues to accurately and systematically assess cell-type gene expression.

## Imaging Technology and Visualization of Development Processes

Developing these technologies has implications both for basic and clinical research. Advanced imaging technologies allow researchers to develop models showing morphogenetic movements in the temporal development of organ systems and to capture 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 previously not possible. In addition, advanced imaging techniques can be used for diagnosing abnormal development *in utero*. The NICHD recognizes that support for the following areas is essential for the future of integrated research in basic and clinical developmental biology:

- Promoting the development of noninvasive imaging methodologies to study developmental events in animal models.
- Translating high-resolution technology, currently used for analyzing developmental defects in animal models, to humans for prenatal and postnatal assessment.
- Developing more sophisticated techniques for three-dimensional rendering to allow for "fly through" analysis of fetal structures.
- Developing safe contrast agents or molecular probes to enhance imaging of prenatal and postnatal subjects to assess anatomic or genetic abnormalities.

## Developmental Databases

Although a number of high-quality developmental databases currently exist, information regarding what is available requires better dissemination. In addition, although the creation of new databases will increase resources, the content of these databases needs careful consideration and focus to provide the maximum benefit and cost-effectiveness. Both new and existing registries need to adopt a uniform collection process so that data are comparable. The NICHD is interested in developing such an infrastructure and intends to collaborate with parties who have successfully developed such databases and registries. Creating a database to which researchers could submit their mutants before publishing their research findings could foster and expedite contributions to that database by other investigators. Maintaining such databases could be shared among a variety of public and private organizations. Major areas of interest include the following:

- Establishing and maintaining databases of developmental mutations in vertebrate animal models. This effort would entail fostering registries of widely useful mutants, such as "effector" mice for work with knockout mutants, mice with conditional or time-specific knockouts, or those with genetically controlled cell ablation, to study function of a particular cell population.
- Developing high-quality developmental atlases of commonly used vertebrate models using a variety of imaging techniques and making the atlases broadly accessible to the community (i.e., electronically).
- Establishing and maintaining morphological databases of patterns of developmental gene expression.
- Creating similar atlases and databases related to other aspects of human development.
- Establishing and maintaining gene expression databases and digital atlases of development and ensuring that resources from developmental human and model systems are linked to facilitate comparisons between species.

## Programs for the Study of the Developmental Biology of Birth Defects

An overriding and important issue in studying birth defects is understanding the normal developmental processes and determining how these processes are perturbed to cause birth defects. As mentioned, much of what we know about development has come from using animal models. The Institute must take advantage of the knowledge that results from animal models and apply this to human congenital abnormalities by supporting multidisciplinary birth defects research programs or networks that bring together basic and clinical researchers to enhance translation of basic findings to clinical applications.

# Training and Education

As scientific and technological advances continue at a rapid rate, the increasing sophistication of methodologies will require scientists to specialize their knowledge in these new approaches, which will heighten the need for multidisciplinary collaborations to address research issues. Scientists must also be conversant in new methodologies and approaches used by their collaborators to strengthen these interactions into becoming productive, successful, and enduring collaborations. In addition, while there is an increasing need for a diverse and well-trained work force for birth defects research, that need extends beyond trained laboratory investigators. The NICHD will expand the small clinical and epidemiological work force studying birth defects to ensure the availability of valuable collaborators for basic scientists interested in studying human birth defects. The Institute emphasizes the following areas:

- Encouraging interdisciplinary training of biomedical researchers and computational/bioinformatics biologists.
- Promoting training of and interaction between basic, epidemiological, and clinical investigators.

- Fostering targeted training support for areas in critical need, such as phenotyping human birth defects, comparative phenotyping in animal models down to the level of the cell, genetic epidemiology, and bioinformatics.
- Developing support mechanisms that will promote interdisciplinary training opportunities for young investigators.
- Supporting programs to train clinical investigators in birth defects and developmental biology research.
- Encouraging efforts to help senior investigators move into new research areas with new model systems.
- Promoting training for investigators in more than one model system.
- Examining the potential for providing high school and undergraduate students with training in needed areas, particularly bioinformatics.
- Creating a graduate student technical program.
- Fostering reliable outsourcing of now routine tasks, such as cloning, making transgenic mice, and some chip-based technologies, as laboratories become burdened with these tasks. However, since these techniques must also be readily available for training purposes, the Institute will consider providing for additional core facilities at other research institutions. For example, http://www.geneclinics.com and http://www.genetests.org, currently funded by the National Institutes of Health, provide Web pages that list laboratory tests for various genetic diseases as well as investigators who will perform these services. These sites could serve as models for other developmental biology sites. Again, given the cost of maintaining such a site, the NICHD will need to make its choice of areas carefully.

# 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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