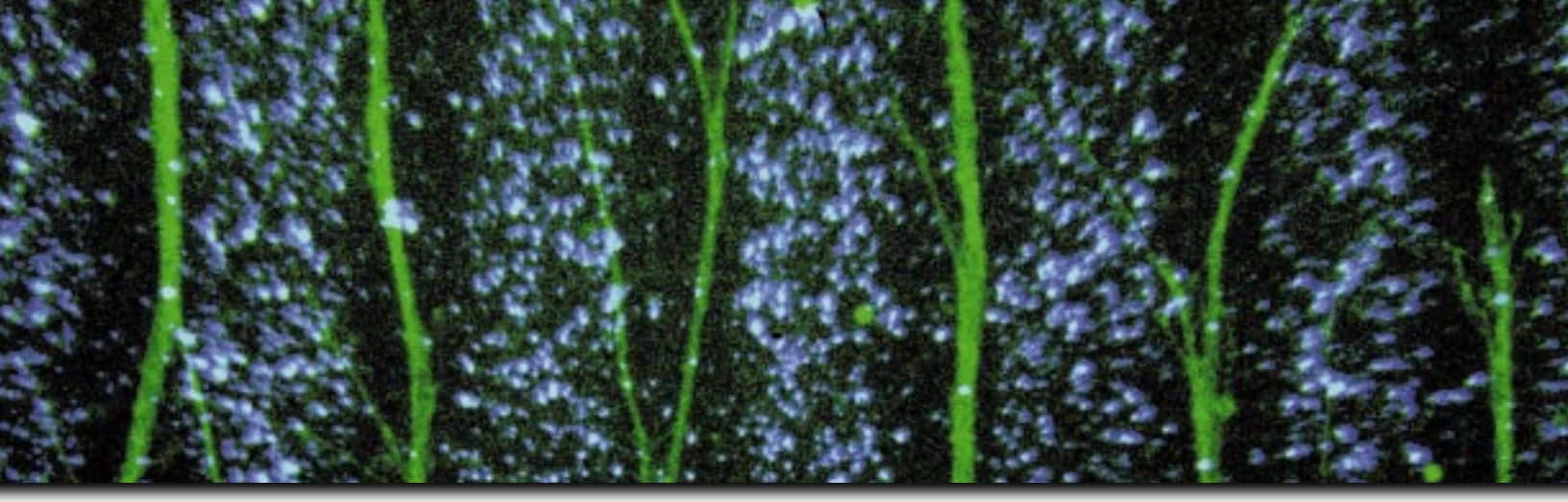


# Neuroscience at the New Millennium

Priorities and Plans for the National Institute of Neurological Disorders and Stroke
Fiscal Years 2000–2001

August 1999

# A message from the Director

It is my pleasure to share with you this first strategic research plan for the National Institute of Neurological Disorders and Stroke. My experience at NINDS over the past year has reinforced what I have learned in 30 years as a research scientist, teacher, and academic administrator: scientific opportunities are abundant, the task of preventing and treating nervous system diseases has never been more urgent, and the confidence of the public in biomedical research has never been stronger.

The subject of priority setting has been prominent in discussions of research funding policy. We welcome these discussions, because we are convinced that the best way to use our resources wisely and honor the confidence placed in us is to seek the views of all concerned with research aimed at reducing the burden of neurological disease—the neuroscience research community, patients and families, and our own staff.

Because some fundamental questions remain unanswered, it is impossible to plan each major breakthrough. We will, therefore, continue to rely on the initiative of basic and clinical neuroscientists throughout the country. Without a strong base of investigator-initiated projects, the rate of advance would slow, and all planning efforts would, eventually, fall short.

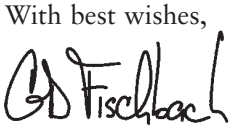
The process of planning and setting priorities was undertaken in close collaboration with the National Advisory Neurological Disorders and Stroke Council. Following a discussion at the Council's meeting in September 1998, we asked leaders in the neuroscience community to address several critical cross-cutting scientific topics that hold the greatest promise for advancing knowledge and for leading to effective ways to prevent neurological diseases, delay their onset, design effective treatments, or restore function after illness or injury.

Each group was asked to review the state of research in its area and describe opportunities for investment in the next two to three years. Representatives of patient groups were invited to a meeting in early 1999 to discuss the findings, to raise other issues that should be considered in setting research priorities, and to recommend how the Institute might seek public input on an ongoing basis. The results of all these deliberations were shared with Council and discussed at length at its meeting in February 1999.

A preliminary report, reflecting those discussions, was widely circulated for comment to representatives of the public, especially patients and advocacy groups and members of professional societies concerned with neurology and neuroscience research. This document reflects most of the input received from these groups. As other major issues arise they will be considered and incorporated into our research planning and implementation.

At the May 1999 Council meeting, advisory board members discussed the plan and agreed that it captures both the breadth of the challenges we face and the enthusiasm of the scientists who will address these challenges. We look forward to working with the research community and the public as we continually refine our research plan in the years ahead.

With best wishes,



Gerald D. Fischbach, M.D.
Director, NINDS

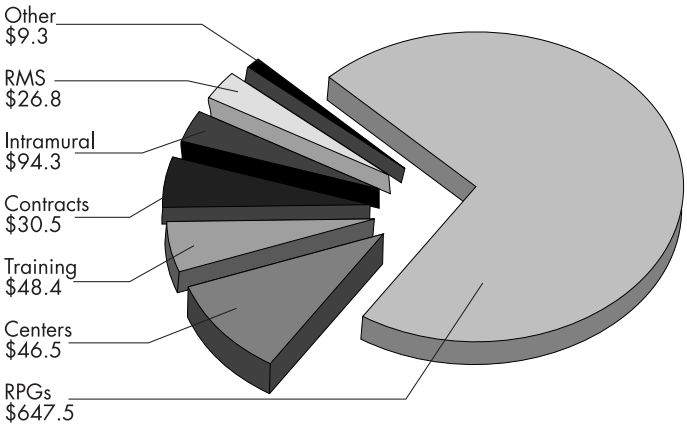
# Report Summary

## NINDS TODAY

One of 25 Institutes and Centers (ICs) comprising the National Institutes of Health, NINDS has occupied a central position in the world of neuroscience for nearly 50 years. Its extramural program supports 2,240 research project grants and 85 research contracts. Institutional training grants and individual fellowships support 585 scientists in training; another 246 "career awards" provide a range of research experience and support for faculty members at various levels. Scientists in the Institute's laboratories and clinics conduct research in most of the major areas of neuroscience and many of the most important and challenging neurological disorders. Currently, 644 staff support the Institute's efforts.

This overview of planned expenditures in Fiscal Year 1999 shows that research project grants (RPGs) are the Institute's highest priority; these are primarily investigator-initiated.

**National Institute of Neurological Disorders and Stroke**
**FY 1999 Budget of $903 Million**




The Neurology Institute's interests, broad as they are, are not limited to NINDS programs. The Institute collaborates widely with other NIH components, almost all of which support neuroscience research in areas of mutual interest. Even broader interest is focused on topics such as genomic analysis and selected research resources. Many collaborations are already in place, and it is our hope that the planning process will inspire more. The Institute has a history of productive collaborations with other agencies such as the Department of Defense, the Department of Veterans Affairs, the National Aeronautics and Space Administration, the Centers for Disease Control and Prevention, and the Food and Drug Administration, as well as industry. We shall strive to maintain and expand these relationships.

# CHALLENGES

The mission of NINDS is ***to reduce the burden of neurological disease***—a burden borne by every age group, by every segment of society, by people all over the world. To this end, the Institute supports and conducts research on the healthy and diseased brain, spinal cord, and peripheral nerves. Hundreds of disorders afflict the nervous system. Common killers and disablers such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke, epilepsy, and autism are well known. Other disorders we study may be known only to the patients and families affected, their doctors, and scientists who look to rare disorders for help in understanding the brain as well as treating more common diseases.

This is a time of accelerating progress and increasing hope in the battle against brain disease. Advances in understanding the nervous system are beginning to pay off in the form of treatments for previously intractable problems—spinal cord injury, acute stroke, multiple sclerosis, and Parkinson's disease, to name a few. We are fortunate that scientific progress is matched by unprecedented public commitment to research, and we are aware that increased public support and funding require visionary leadership and effective stewardship of the resources entrusted to us.

With our mission in mind, the strategic planning effort has identified the following overall goals. In the coming years NINDS will:

- **attack neurodegenerative disorders over the entire life span from birth to the last years of life.**
- **harness the power of molecular genetics to understand neurological disorders, to define healthy function, and to develop better treatments.**
- **unravel the complexities of information transfer within the brain and how the central nervous system communicates with all other major organ systems.**
- **gain a greater understanding of brain mechanisms underlying higher mental functions and complex behaviors.**
- **use remarkable new discoveries about early development to enhance repair and regeneration in the mature nervous system.**
- **exploit new methods for studying how non-neuronal cells in the nervous system maintain the delicately balanced neural environment.**
- **enhance our program in clinical research and epidemiology to develop more effective therapies and prevention strategies.**
- **build the foundations for the neuroscience enterprise of the future.**
- **exploit the unique environment of the NIH intramural program to create a model collaborative neuroscience community.**

# PLANS

Hundreds of different disorders affect the brain and nervous system, complicating efforts to prevent and treat them. Fortunately, there is increasing evidence for similar mechanisms of disease that operate in disorders as diverse as acute stroke, trauma, multiple sclerosis, developmental disorders, and chronic neurodegenerative conditions. In neurodegenerative disorders, we know that several specific responses to stress, injury, or genetic mutations damage nerve cells. Disorders as diverse as autism, epilepsy, and the dysmyelinating disorders are influenced to some extent by perturbations in the mechanisms that guide neuronal development in specific target areas of the brain. Even hereditary diseases, which can involve the malfunction of hundreds of genes, show patterns that suggest common mechanisms may be at work. Understanding how to manipulate these mechanisms in one disorder will certainly lead to methods for prevention and treatment of many other disorders as well. To meet these challenges, we have begun an intensive planning process focused on the following cross-cutting topics:

- Neurodegeneration
- Neurogenetics
- Channels, Synapses, and Circuits
- Cognition and Behavior
- Neurodevelopment, Plasticity, and Repair
- Glia and Other Non-neuronal Cells
- Experimental Therapeutics and Clinical Trials

We asked leading scientists to review recent advances and immediate opportunities in each of these fields. Each group provided NINDS with a report. What follows is a distillation of their reports.

An earlier draft of this document was circulated for comment to disease advocacy groups and scientific societies, with most of the comments received being incorporated into this document. Discussions with the research and patient communities will continue, and will be integrated with the budget development process. This document is the first step in what will become an ongoing process of identifying opportunities and setting research priorities.

## Neurodegeneration

Cells in the brain die following stroke, trauma, and in chronic neurodegenerative disease. Since the mature brain cannot normally replace lost nerve cells, an important goal of treatment and prevention is to minimize nerve cell death. Nerve cells degenerate by one of two mechanisms. *Necrosis* occurs when cells swell, burst, and discharge toxic products that damage neighboring cells. *Apoptosis,* or "cell suicide," is a more controlled form of cell death in which cells shrivel rather than swell, with only minimal damage to surrounding cells. It is now clear that apoptosis is pervasive following acute stroke and trauma as well as during chronic neurodegenerative disorders. A more complete understanding of the agents that damage cells and trigger cell death and the metabolic steps that carry out the process will certainly lead to new therapeutic strategies for many neurological disorders.

Therefore, NINDS will vigorously pursue:

▶ **a clearer understanding of brain cell death.**
Brain cell death occurs at all stages of life, in early development (Batten disease, spinal muscular atrophy) and in the mature nervous system (Lou Gehrig's disease, Huntington's disease, multiple sclerosis, muscular dystrophy, ataxias, and Alzheimer's disease), as well as following stroke, trauma, and invasion by various infectious organisms.

▶ **how protein aggregation damages neurons.**
Protein aggregation, the formation of abnormal clumps of proteins, is emerging as a common mechanism in several neurological diseases. Examples include the Lewy bodies of Parkinson's disease, amyloid plaques of Alzheimer's disease, and prion protein aggregates in Creutzfeldt-Jakob disease.

▶ **how genes and the environment interact to cause neurodegenerative disease.**
Much of the recent progress in understanding neurodegenerative disease has come from neurogenetics. Some genes cause disease directly, while others influence susceptibility and disease progression. Understanding the complex interplay between genes and the environment is crucial for prevention and treatment of all diseases, but is especially so in neurodegenerative disorders because this interaction plays out over the course of many years.

## Neurogenetics

Genetic analysis is a unifying force in the study of the nervous system. Almost half of all human genes are expressed in the brain. Genetic approaches are helping to elucidate the critical roles of proteins such as ion channels that control electrical activity, trophic factors that sustain survival and growth of nerve cells, guidance substances that direct wiring of the developing brain, transporters that carry essential substances into cells, and receptors that detect signaling molecules. These proteins are keys to understanding the nervous system and its diseases and present the targets for most of the drugs that treat nervous system disorders.

About a third of all known genetic defects affect the nervous system. To date more than 200 genes have been identified that can cause or contribute to neurological disease. Among these are genes associated with Alzheimer's disease, Parkinson's disease, and genes known to cause Duchenne muscular dystrophy, Huntington's disease, Friedreich's ataxia, Batten disease, neurofibromatosis, spinal muscular atrophy, a familial form of amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) and several forms of epilepsy. While many of the less common neurological disorders are due to defects in single genes, it is now becoming clear that combinations of multiple genes interact to influence disease susceptibility, progression, and severity in the more common disorders. A better understanding of these multigenic influences is essential for preventing and treating these disorders.

It is imperative that neuroscience exploit the power of modern genetics and the information now available from sequencing the human genome. In order to do so, NINDS will:

- **gather family data on a worldwide basis to identify new disease genes.**

The identification of families with inherited diseases is the limiting factor in the discovery of "disease genes." Specific populations in various parts of the world provide unique advantages for identifying these genes.

- **pursue mechanisms by which disease genes contribute to neurological disorders.**

Once "disease genes" are identified, the challenge becomes to determine how these mutations give rise to disease. More appropriate animal models are needed, from the simplest organisms to complex mammals, including models that mimic progressive neurodegeneration.

- **expand our efforts to understand where and when genes are expressed in the nervous system.**

Location and timing are everything in the brain. The temporal and spatial patterns of gene expression will provide crucial clues about how nerve cells develop and function, react to insult, and respond to treatment. The power of new DNA and protein array technologies will make this ambitious effort a realistic goal.

- **overcome barriers to effective gene therapy in the nervous system.**

The nervous system presents unique problems for gene therapy, in which nonfunctioning genes are replaced with healthy genes. Three of the most pressing are: bypassing the blood-brain barrier; targeting genes to specific brain regions; and sustaining the expression of foreign genes.

## Neural Circuits

Information in the nervous system is carried by brief electrical impulses that are conducted away from the nerve cell body along thin extensions of the nerve cell called axons. The electrical charges are carried by ions such as sodium, potassium, and calcium that flow across the nerve cell membrane through "holes" in certain membrane proteins called ion channels. Successful conduction depends on the exquisite timing of opening and closing of these channels. When impulses reach the tips of axons, information is transmitted to the next nerve cell in line, or in the periphery, to a muscle or gland. At the specialized point of contact, called a synapse, the information is carried across the tiny gap between cells by chemicals called neurotransmitters. Collections of nerve cells that are connected by synapses form neural circuits that are called into play as an ensemble.

Channels, synapses, and circuits offer the most promising opportunities for therapeutic breakthroughs in the near future. Many drugs currently used to treat neurological disorders affect the conduction of impulses or the action of neurotransmitters. Recent progress in identifying new ion channels and neurotransmitter receptors and in characterizing their structure at the atomic level have

revolutionized the ways we will seek new drugs. The opportunities for new discoveries are far greater today than they have been in recent years, and will certainly lead to better therapeutic targets for treating epilepsy, pain, movement disorders, and neuromuscular disorders.

In the immediate future, NINDS will:

▶ **promote further study of ion channel structure and function.**
Recent breakthroughs in determining the detailed structure of ion channels in bacteria must be extended to ion channels, neurotransmitter receptors, and transport molecules in more complex organisms. With the structures of these molecules in hand, scientists can rationally design drugs to modify these molecules rather than relying on serendipity.

▶ **emphasize the molecular bases of synaptic transmission.**
We must now understand how the many proteins that make up synapses act together to orchestrate the release of and response to neurotransmitters. Understanding this molecular machinery will lead to therapeutic agents that may act by novel mechanisms and with unprecedented specificity.

▶ **encourage new approaches to circuit analysis.**
New methods are needed to study groups of neurons that may number in the hundreds or thousands. Simultaneous recording of groups of neurons using multi-electrode arrays and improved methods for optical detection of electrical signals are powerful techniques that require further development. It will also be important to perturb neuronal circuits to test critical hypotheses. New computational approaches are also needed to handle the massive amounts of information that will surely be generated.

▶ **focus attention on particular circuits of immediate medical relevance.**
Further analysis of spinal cord circuits that coordinate locomotion is essential for all studies of repair or recovery of function. Other networks of great importance for neurological disorders include thalamic circuits that regulate sleep and contribute to epilepsy, spinal and supraspinal circuits activated by pain, circuits critical for the initiation and coordination of movements that malfunction in Parkinson's disease and other movement disorders, and cortical circuits involved in learning, memory, and motivation.

## Neural Systems and Behavior

Higher brain functions that give rise to language, cognition, and emotion depend on the proper functioning of neural circuits. In recent years, remarkable progress has been made in correlating mental events with brain activity in specific areas. New brain imaging methods measure not just structure but also activity and function of the brain. The development of these non-invasive functional imaging technologies such as PET (positron emission tomography) and fMRI (functional magnetic resonance imaging) has revolutionized the study of cognition and behavior. They will certainly provide valuable surrogate markers that mark early changes in brain function during development, early stages of disease, treatment, and recovery.

To accelerate progress in correlating brain function and behavior, NINDS will:

▶ **seek more precise descriptions of patterns of behavior in developmental disorders.**
We need a more precise definition of the behavioral deficits seen in developmental disorders. For example, in searching for the mechanisms underlying autism, it is necessary to better define the behavioral characteristics of the disorder. Equally important is the need to develop powerful non-invasive functional brain imaging methods suitable for the special needs of infants and children.

▶ **promote understanding of the neural bases of cognition, emotion, and their interaction.**
Cognition and emotion affect all neurological disorders. One cannot study one area and ignore the other. On the contrary, it has become essential to link patterns of brain activity that underlie thought, language, and emotions. New psychological paradigms must be brought together with new methods for analyzing brain activity.

▶ **encourage a broad analysis of the experience of pain.**
To fully understand the experience of pain, an integrated approach is needed combining anatomical, physiological, and psychological approaches, as well as molecular aspects. This will lead to new modalities of treatment to supplement traditional analgesics.

▶ **develop better methods for assessing behavior and other neurological functions in the mouse.**
Due to the extensive knowledge of mouse genetics, this species has emerged as the preferred model organism for understanding the mammalian genome. This makes it essential that in the next few years we gain a better understanding of mouse behavior, neuroanatomy, and neurophysiology, and that standardized assays be developed for measuring the effects of genetic manipulations on these systems.

## Neural Development, Plasticity, and Repair

We must understand how the nervous system develops and continues to change throughout life. This information has profound implications for the treatment of nervous system diseases. In infants and children many disorders disrupt the development of the brain with lasting consequences. These include epilepsy, cerebral palsy, Friedreich's ataxia, meningitis, spinal muscular atrophy, and the muscular dystrophies, to name just a few. In adults, harnessing the capacity of the nervous system to adapt by reactivating developmental mechanisms offers great hope for restoring function in the injured or diseased brain. Beyond disease, a more complete understanding of the plasticity of the brain, that is, how it can change, might contribute to methods for educating children and preserving cognitive function throughout life.

In this area of research, our immediate goals are to:

▶ **elucidate mechanisms of synapse formation and plasticity.**
The important new information about molecules that guide axon growth and formation of nerve cell connections in invertebrate species must be applied to understanding development in higher vertebrates. Most importantly, these insights must be applied to encouraging regeneration in the human nervous system. Likewise, neurotrophic factors (natural chemical signals that promote growth and survival) important in development are also likely to influence synaptic plasticity in adults. An important challenge in coming years will be to identify new trophic factors and guidance molecules and to understand how they interact to orchestrate synapse formation and plasticity.

▶ **restore function in neurologically disabled individuals.**
New knowledge about circuit function and formation must be brought to bear on the urgent need to repair the injured nervous system. This is particularly important for spinal cord injury and stroke. We must harness the plasticity of the brain for recovery through a variety of means, including chemicals such as neurotrophic factors that stimulate and direct nerve fiber growth, chronic brain stimulation, behavioral techniques such as virtual environments and novel training methods beyond traditional rehabilitation. Neural prostheses, electronic and mechanical devices that connect with the nervous system to restore lost function, will remain an important part of this effort.

▶ **encourage development of stem cell biology to repair the injured nervous system.**
Stem cells are immature cells that have the ability to multiply and specialize into almost any cell or tissue in the body. In no area of medicine is the potential for harnessing human stem cells greater than in diseases of the nervous system. Enormous scientific and ethical considerations must be addressed, but recent advances in stem cell biology offer great hope for repair and recovery of function for Parkinson's disease, multiple sclerosis, and many other neurological disorders.

## Neural Environment

The nervous system contains many types of cells other than nerve cells. Non-neuronal cells, including glia and the endothelial cells of the brain's capillaries, maintain the health of the nervous system and play crucial roles in disease. Glial cells, which outnumber nerve cells in the brain by 10 to 1, regulate the brain's milieu, divide metabolic duties with nerve cells, react to infection and injury, guide migrating nerve cells in development, ensheathe nerve fibers with critical electrical insulation, and interact with nerve cells through chemical signals in complex and poorly understood ways.

Neurological disorders may result when non-neuronal cells are compromised, as in demyelinating disease, or non-neuronal cells may themselves become aggressors, as in most brain tumors, human immunodeficiency virus infection, autoimmune disorders such as multiple sclerosis, and possibly in some neurodegenerative diseases. Neurological disorders may also occur as the result of

infection. The accumulated information about non-neuronal cells is much less than that for neurons, and critical molecular and immunological reagents are not easy to obtain.

To facilitate research in this area, NINDS will:

▶ **encourage research on the functions of glia and other non-neuronal cells.**
We must understand the normal functions of glia and other non-neuronal cells so we can elucidate their roles in disorders such as perinatal injury, multiple sclerosis, tumors, infections like AIDS, and in inhibiting neuronal regeneration following injury. In addition to their traditional roles in maintaining the neuronal milieu, possible new roles of glia in information processing demand investigation.

▶ **intensify efforts to understand the blood-brain barrier.**
Both glial cells and endothelial cells of the brain's blood vessels make up the blood-brain barrier that restricts entry of potentially harmful substances from the general circulation, but also limits access of therapeutic agents. Understanding how to manipulate its selective permeability is essential for all efforts at drug therapy.

▶ **expand ongoing molecular analysis of brain tumors.**
Glial cells are responsible for the most aggressive type of brain tumor, the glioblastoma. A goal is to sequence all genes activated when this tumor arises in order to understand what causes uncontrolled tumor cell proliferation and invasion of surrounding brain tissue.

## Experimental Therapeutics and Clinical Trials

The great challenge of modern neuroscience is to translate the remarkable findings of basic science into useful therapies. NINDS has responded by making organizational changes that will strengthen our capacity to support clinical research. We will use every funding mechanism available to expand this effort, including our new pilot and planning grants. Throughout, we will strive to establish new collaborations and expand existing ones with biotechnology and pharmaceutical companies, with other governmental agencies, including NIH Institutes, the Department of Veterans Affairs, the Food and Drug Administration, the Centers for Disease Control and Prevention, and the National Aeronautics and Space Administration, with patient advocacy groups, and with industry.

Given rapid advances and technological breakthroughs, new issues concerning privacy, informed consent, and sharing of information will surely arise. In all that follows, we are committed to exploring the ethical dimensions of our research.

In this area, NINDS will:

▶ **expand our Clinical Trials Program.**

- We plan to study a wider spectrum of disorders and a greater diversity of patients. A successful program will require support for a sequential series of studies ranging from initial translational efforts through early investigations of safety and efficacy to the final definitive trials. In addition, the increased incidence of nervous system disorders seen in certain ethnic and geographic groups in this country must be addressed.

- We will extend recent discoveries of the causes and mechanisms of disease to a better understanding of the epidemiology and natural history of disease. This is essential for developing better treatment strategies.

- The development of better surrogate markers – biological tests that are used to track disease progression and determine the effectiveness of treatment – will enhance the efficiency of clinical trials. In addition, better measures of treatment outcome and economic benefits are needed.

- We will emphasize development of novel therapies and technologies for clinical research, including stem cell implants and gene transfer. Better access to functional imaging technology is necessary for monitoring normal nervous system function, disease progression and treatment outcomes. One effort now underway is an evaluation of chronic brain stimulation for treating refractory Parkinson's disease.

- Given the complexity of neurological disease, new therapies based on combinations of drugs must be evaluated. This is particularly important because combination therapies are not being pursued by the pharmaceutical industry.

- Important methodological issues must be addressed in clinical trials involving brain disorders. These include methods for improving quality and productivity of trials through better selection of patients and monitoring of effectiveness. In addition, we will enhance the biostatistical and trial design expertise of the Clinical Trials Program, so that NINDS can serve as a catalyst and resource for the extramural community.

One particularly challenging yet rewarding effort will be to initiate a national epidemiological study that would define normal cognitive health and impairment. This effort, ranging from childhood to old age, could be undertaken in collaboration with other NIH Institutes.

▶ **promote discovery of new drugs and effective delivery of useful agents to specific locations within the central nervous system.**

Rational drug design will be based on knowledge of the three dimensional structure and function of crucial receptor molecules. Other aspects of drug design that will be explored include combinatorial chemistry, which generates large numbers of potentially useful chemical compounds, and better quantitative measures of synaptic transmission and neural circuit function to screen candidate drugs. Methods should be explored for managing the permeability of the blood-brain barrier or bypassing it with novel drug delivery systems.

## Infrastructure: Foundations for the Future

In addition to pursuing specific opportunities, NINDS is committed to laying the foundations for neuroscience in the years ahead. The discoveries and technologies that are allowing us to conquer disease have also changed the way research is carried out. A plan for the future would be incomplete if it did not address the physical resources needed for modern neuroscience, the funding mechanisms needed to support new approaches to doing research, and the training of a new generation of neuroscientists. NINDS will:

▶ **Commit a portion of new funds to shared resources.**

Science is increasingly becoming a communal endeavor, and a major part of the cost of doing science is the cost of shared resources. Resource sharing ultimately benefits patients. The NINDS will play a major role in the creation and distribution of research resources by setting aside a percentage of yearly increases for the support of resources and infrastructure, even at the possible expense of other important programs or initiatives.

To accomplish this, NINDS will aggressively pursue opportunities for partnership with voluntary, professional, and commercial organizations.

High priority resources include the following:

- distribution of critical research chemicals and tools, including genetic resources (in particular full length cDNAs), new organic chemicals useful in imaging, antibodies, and genetically altered animals.

- investment in computational neuroscience and bioinformatics technologies.

- access to emerging cDNA and protein array technology.

- expanded participation in trans-NIH genetic initiatives, including the Human Genome Project (HGP), the Brain Molecular Anatomy Project (BMAP), and the Brain Tumor Gene Anatomy Project (BTGAP). For example, one resource to come out of BMAP would be a novel interactive gene expression atlas of the mouse brain.

- access to and continued development of the most advanced imaging technology, including techniques suitable for monitoring brain activity in adults, children, and experimental animals, and methods for exploring the internal working of cells and circuits in the nervous system.

- methods for dissemination of information about all aspects of neuroscience suitable for scientists, physicians, and patients.

- development of more appropriate *in vitro* cell culture models for nervous system studies from both normal and diseased human brain tissue.

▶ **Utilize new funding mechanisms.**

For many of the exciting scientific opportunities described above, the current culture of individual investigators carrying out all phases of a project must be complemented by one in which collaboration among laboratories with

different expertise is the norm. NINDS will develop means to facilitate these collaborations. Possible mechanisms include:

- core grants to support required common facilities and resources of groups of funded investigators at a single institution, including technical staff to operate such facilities.

- small grants to support the planning and conduct of collaborations by funded investigators at separate institutions, including temporary exchange of postdoctoral fellows to acquire specialized techniques needed for the collaboration.

- regional facilities for large-scale resources not fully justified at a single institution (e.g., high intensity imaging facilities).

- grants to support the organization and functioning of consortia formed to attack a specific problem.

Given the rapid pace of scientific discovery, it will be important to streamline the review and funding process for grant applications as much as possible.

▶ **Develop new training initiatives.**
As science becomes more interdisciplinary, it is essential that scientists receive training in multiple areas. Recognizing that the transition from basic to clinical research is particularly difficult, we will explore novel training mechanisms to develop scientists capable of conducting the translational research that will bridge the gap. We will also continue our efforts to increase the number of scientists from groups currently underrepresented in the neurological sciences. Possible initiatives include:

- masters program in clinical investigation for physicians that goes beyond biostatistics and clinical trial design to include bioethics and cooperative aspects of large-scale clinical research.

- programs to encourage a renewed emphasis on systems physiology as it relates to clinical neuroscience.

- training in clinical investigation for Ph.D.s so that they can appreciate pathophysiology and become more effective partners in neurological research.

- extended apprenticeship training in electrophysiological and cognitive neuroscience techniques, including multi-electrode recording and bioinformatic approaches.

- short courses for both junior and senior investigators to facilitate their moving into new areas.

- new training programs to develop physician scientists who are experts in clinical translational research and epidemiology.

## An Integrated Neuroscience Community at the NIH

The NIH intramural research program should house one of the best interdisciplinary neuroscience communities in the world. Its research program provides unique opportunities for collaborations across institute and disciplinary lines, for long-term studies, and for rapid response to problems of special urgency. The NIH Clinical Center also provides special opportunities for patient oriented studies, especially in today's competitive health care environment. NINDS can serve as a resource for the broader neuroscience research community.

Scientific opportunities and our research setting make it possible to integrate brain sciences in a manner that has not been accomplished before. Virtually all areas of modern neuroscience would benefit by removing artificial barriers between neurologists, neurosurgeons, psychiatrists, neuroscientists, developmental neurobiologists, and behavioral scientists, and bringing together investigators focused on fundamental research, translational issues, and clinical research.

NINDS will work with other institutes to develop a superb integrated neuroscience community. It is time to consider an intramural neuroscience program with no institute boundaries. We will also promote fruitful collaborations with our extramural colleagues.

# PUBLIC COMMENTS

An early discussion draft of this document was mailed to 240 patient advocacy organizations and a dozen scientific and professional societies for comment. Panel members and Institute staff were also provided an opportunity to review and comment on the draft. Most of these comments have been incorporated into the document. Others will require more deliberate evaluation in the next stages of planning and implementation.

We are pleased to see that the initial response has been positive and supportive of the Institute's goals and approach to strategic planning. Most organizations, while concerned with specific diseases, supported the concept of attacking the research questions necessary for further progress. Several helpful suggestions for collaborations within government and with the private sector were included in the comments. Particularly encouraging was the strong support for efforts to reduce health disparities both by targeting disease problems more common in some population groups and by seeking to increase the diversity of the research environment.

These comments are helpful, both in crafting the plan and in taking the next steps to implement it. The eagerness of many organizations, some of them relatively new to the NINDS environment, to work collaboratively with the Institute has been especially gratifying. Their willingness to work with us will be enormously helpful as NINDS develops an expanded public liaison program in the months ahead.

## Planning for the Future

NINDS views strategic planning as critical to future success. The next steps of critical evaluation and implementation will follow several paths. The planning panels will continue to meet periodically, with some panels being asked to pursue specific topics that were raised but not fully explored in their initial meeting. NINDS staff will participate in these activities and also in a review of currently supported research to determine what specific initiatives are needed to carry out the most important recommendations. NINDS will assess future directions in terms of scientific opportunities identified in the planning process, in public comment, and in Congressional and Administration guidance.

The process we envision is a dynamic one, so much so that it is difficult to capture it in a single document. NINDS hopes this document will serve as a reference and guide to those directly engaged in our mission and as a source of information for anyone interested in research on the brain and nervous system. Information on the planning process will be maintained on the NINDS website: http://www.ninds.nih.gov/neuro2000/

# Appendix A

## An Overview of Neurological Diseases and Disorders

Hundreds of disorders affect the nervous system. Some, like stroke, the epilepsies, and Alzheimer's disease, affect millions of Americans. Others are rare. All are important. As we learn more about the nervous system and about mechanisms of disease, classification schemes are in a state of flux. The following presents one brief and admittedly incomplete listing of nervous system disorders by categories. A few examples are included.

- ***Stroke and vascular diseases***
- ***Epilepsies***
- ***Demyelinating disorders,*** such as multiple sclerosis.
- ***Tumors,*** such as glioblastoma, meningioma, and neurofibromas.
- ***Pain,*** acute, paroxysmal, and chronic, including migraine, trigeminal neuralgia, reflex sympathetic dystrophy, back pain, and fibromyalgia.
- ***Traumatic injury of brain, spinal cord, and nerves***
- ***Degenerative disorders of the mature nervous system,*** including Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Friedreich's ataxia, and the spinocerebellar ataxias.
- ***Movement disorders,*** including the dystonias, supranuclear palsy, and essential tremor.
- ***Developmental disorders of the nervous system,*** such as autism, Rett syndrome, Tourette syndrome, cerebral palsy, Down syndrome, and malformations of the brain and spinal cord.
- ***Infections,*** such as meningitis, poliomyelitis and its sequelae, neuro-AIDS, and Lyme disease.
- ***Sleep disorders,*** such as narcolepsy and restless legs syndrome.
- ***Myasthenias, muscular dystrophies, and other myopathies,*** including myasthenia gravis; Duchenne, facioscapulohumeral, and myotonic muscular dystrophies; and the mitochondrial myopathies.
- ***Neuropathies,*** both genetic and acquired, such as Charcot-Marie-Tooth disease and diabetic neuropathy.
- ***Autoimmune disorders,*** including multiple sclerosis, paraneoplastic syndromes, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), and polymyositis.
- ***Metabolic disorders,*** genetic and acquired, including Tay-Sachs disease, Fabry's disease, Batten disease, Gaucher's disease, and other storage diseases, aminoacidurias, and Reye's syndrome.
- ***Other genetic disorders,*** such as tuberous sclerosis, Sturge-Weber syndrome, von Hippel-Lindau disease, neurofibromatosis, adrenoleukodystrophy, ataxia-telangiectasia, and many rare disorders.

# Appendix B – Rosters

## Planning Panel Chairs

**Neurodegeneration**
Allan J. Tobin, Ph.D.
University of California
at Los Angeles

**Neurogenetics**
Kenneth Fischbeck, M.D.
National Institute of Neurological
Disorders and Stroke, NIH

**Channels, Synapses, and Circuits**
David A. McCormick, Ph.D.
Yale University

**Cognition and Behavior**
John H. R. Maunsell, Ph.D.
Howard Hughes Medical Institute
Baylor College of Medicine

**Neurodevelopment, Plasticity, and Repair**
Luis R. Parada, Ph.D.
University of Texas Southwestern
Medical Center

**Glial and Other Non-Neuronal Cells**
Francisco A. Gonzalez-Scarano, M.D.
University of Pennsylvania Medical
Center

**Experimental Therapeutics and Clinical Trials**
Henry F. McFarland, M.D.
National Institute of Neurological
Disorders and Stroke, NIH

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The Johns Hopkins University

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Stanford University

Julian T. Hoff, M.D.
University of Michigan

Ms. Anne Kathleen Hunter
International Rett Syndrome
Association

Ms. Martha E. Keys
Keys Consulting

Mr. Morton Kondracke
Executive Editor and Columnist,
*Roll Call*

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University of California
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Arent Fox Kintner Plotkin & Kahn

George A. Ojemann, M.D.
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Jerome B. Posner, M.D.
Memorial Sloan-Kettering Cancer
Center

Carla J. Shatz, Ph.D.
University of California at Berkeley

Richard W. Tsien, D.Ph.
Stanford University, School of
Medicine

*Ex Officio Members*

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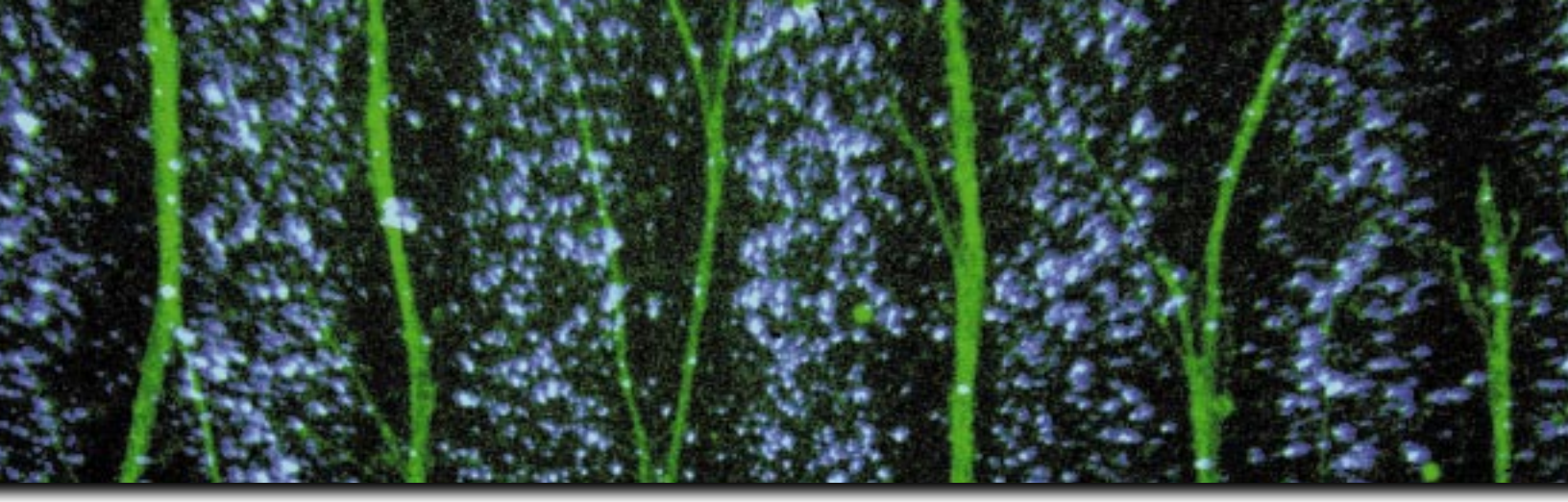
Veterans Administration Medical Center

Andrew Dutka, M.D.
National Naval Medical Center

Constance W. Atwell, Ph.D.
Executive Secretary
Associate Director for Extramural Research, National Institute of Neurological Disorders and Stroke, NIH



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