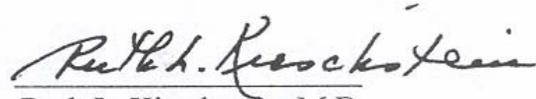


DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

PARKINSON'S DISEASE RESEARCH AGENDA



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June 2001

Parkinson's Disease Research Agenda

INTRODUCTION

In its report on the Fiscal Year 2001 budget for the Department of Health and Human Services, the Senate Committee on Appropriations stated:

“Parkinson’s disease research agenda – The Committee is very pleased that a credible, thoughtful plan to effectively maximize the chances of a near-term cure has been developed. The plan is the NIH’s 5-year “Parkinson’s Disease Research Agenda”.... In response to that request the NIH held a meeting of seven Institutes to discuss Parkinson’s disease research, then formed a steering committee of external scientists, NIH staff and Parkinson’s advocates to engage in an intense planning process. This culminated in a very successful 2-day interdisciplinary workshop involving leading Parkinson’s researchers, prominent scientists from related fields, industry representatives, and Parkinson’s advocates. Out of this workshop came a specific 5-year research agenda—with professional judgements as to the costs that would be entailed—to advance dramatically our understanding and treatment of Parkinson’s disease and pave the way to its cure.

....Some of the research identified as needed is broadly applicable to other neurodegenerative diseases, indicating that Parkinson’s disease research may well lead the way to finding the cause and cure of these other conditions. To carry out the plan, the professional judgement budget estimates call for increases over existing Parkinson’s research of \$71,400,000 in year 1 (fiscal year 2001) and larger increases in subsequent years....The Committee strongly supports overall implementation of the plan. This will require both clarity in the lines of responsibility within the NIH and sufficiency in the level of additional funding. The Director should be responsible for coordinating the overall implementation of the Agenda within the NIH. The Committee requests that the NIH develop mechanisms for monitoring its implementation of the plan, and to **report on its progress in implementing the agenda by March 1, 2001**. NIH is also requested to report on its progress in deploying innovative and accelerated funding mechanisms. The Committee believes that this plan represents a new paradigm for helping manage the Federal research effort on Parkinson’s disease and merits both sustained support and careful monitoring.” Pgs. 181/2

The conferees further stated:

"The NIH has developed a five-year Parkinson's Disease Research Agenda. To carry out the plan, the professional judgement budget estimates call for increases over existing Parkinson's research of \$71,400,000 in year one (fiscal year 2001). The conferees strongly urge the [NIH] Director to work toward implementation of the research agenda and oversee coordination of all relevant Institutes, including NINDS, NIEHS, NIA, and others conducting Parkinson's research. The Director is requested to report by March 1, 2001 on the progress towards implementation of the research agenda and to submit updated professional judgement funding projections for

subsequent years." (Conference Report, P.142)

The following report has been prepared by the National Institutes of Health of the Department of Health and Human Services in response to this request.

BACKGROUND

Congress, in FY 2000 Conference Report language, directed NIH to develop a Parkinson's disease research agenda for the next five years, with professional judgement funding projections. In November 1999, the NIH Parkinson's Disease Coordinating Committee (PDCC), working together with patient advocates, initiated a planning process to develop a research agenda. The PDCC includes the directors and staff of all components of NIH that conduct research on Parkinson's disease. At a January 4-6, 2000 workshop, intramural, extramural, and industry scientists, representatives from several Parkinson's disease advocacy groups, and ethicists held intensive discussions which formed the basis of the "NIH Parkinson's Disease Research Agenda." The Acting NIH Director submitted the Agenda to Congress in March 2000. Since then the document has been widely disseminated to the scientific community and is available on the NINDS home page (http://www.ninds.nih.gov/about_ninds/nihparkinsons_agenda.htm) .

The Agenda outlines a comprehensive five year plan for research against Parkinson's disease. The professional judgment estimates included in the plan are just that. These projections indicate what funds NIH estimates could be productively spent but do not take into account budgetary constraints, competing priorities, or other pressing commitments. Congress, through legislation, report language, hearings, and direct communications from members, has reminded NIH of the urgency for accelerating progress against not only Parkinson's disease, but also many other neurological disorders. Formal research planning efforts are underway or in implementation phase for brain tumors, stroke, epilepsy, and health disparities, with expanding activities in childhood disorders, such as autism and Duchenne muscular dystrophy, and intensified emphasis on critical public health issues such as Creutzfeldt-Jakob disease and "mad cow disease." We are encouraged that needs for research on different disorders overlap extensively. However, each disease has its own special research requirements, and funds for NIH, while generous, are not unlimited. Despite these real constraints, NIH, led by the National Institute of Neurological Disorders and Stroke (NINDS), is working with unprecedented aggressiveness to carry out the Parkinson's Agenda.

Ultimately success in implementing the Agenda must be judged by results—finding ways to cure or prevent Parkinson's disease. This document, however, focuses on actions NIH is taking to implement the Agenda, not on results in Parkinson's research. Although there have been notable scientific findings since the Agenda was developed, it is too early to disentangle which progress should be attributed to the Agenda rather than to ongoing NIH research programs.

NIH has widely disseminated the Agenda among researchers and encouraged proposals that address all aspects of the plan. Total NIH funding for Parkinson's disease research in FY00 was

\$155,934,000, including more than 50 new grants and contracts. NIH has made extensive use of grant supplements, which can be made rapidly, to expedite early stages of Agenda implementation, but supplements are limited to projects that fall within specific aims of active grants. More generally, before targeted programs to address Agenda objectives produce results, NIH and researchers must complete several steps, many mandated by law or policy. A common sequence might include, for example: NIH program directors convene a workshop of outside experts to shape specific goals, then write a grant or contract solicitation targeting those goals, obtain Institute and NIH approvals, publish the solicitation and encourage potential applicants to respond; researchers prepare proposals, gather appropriate animal and human subjects assurances, and submit applications; NIH organizes peer review of proposals; Institute advisory councils approve funding decisions; Institutes disburse funds; researchers buy equipment, hire personnel, carry out the research, and submit results for publication; and, finally, journals peer review and publish results. NIH has increased staff resources directed toward Parkinson's disease, but there are limits to how much this process can be accelerated. The following discussion can provide only a snapshot of rapidly evolving activities at many stages of this process.

ORGANIZATION, TRACKING, AND MONITORING OF IMPLEMENTATION

The NIH Parkinson's Disease Coordinating Committee (PDCC) spearheaded the development of the Parkinson's Disease Research Agenda and continues to play an active role in its implementation. Led by the NINDS, the PDCC consists of institutes and centers that support research on Parkinson's disease, including the National Institute on Aging (NIA), the National Institute of Mental Health (NIMH), the National Institute of Environmental Health Sciences (NIEHS), the National Human Genome Research Institute (NHGRI), the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Nursing Research (NINR), and the National Center for Research Resources (NCRR). Parkinson's disease is a multifaceted disease. Each of these organizations brings valuable perspectives to confront the biological complexities of the disorder, to pursue the diverse therapeutic strategies showing promise, and to provide the resources necessary to carry out a research agenda of this breadth.

In order to achieve the goals of the Agenda as quickly and effectively as possible the NINDS also created the Parkinson's Disease Implementation Committee (PDIC). The PDIC is a smaller working group that meets more frequently to advise on priorities, make suggestions on implementation, and consider the implications of new research findings for the directions of Agenda efforts. The PDIC includes outside scientists and representatives of the advocacy community as well as key NIH staff. The PDIC held its first meeting on July 31, 2000 and most recent meeting March 12, 2001.

NINDS is developing a website that will help the public and NIH staff track progress of the Agenda. The Institute will make the site available this spring, after modifying the prototype to take into account suggestions offered by Parkinson's advocates and the comments NIH staff gave at a meeting in February 2001. The website will provide information on funded research projects and on solicitations for new research. The site will also provide resources for scientists,

people with Parkinson's disease, and the advocacy community, such as funding opportunities, services and resource sharing for researchers, clinical trials information, links to the eleven Morris K. Udall Centers of Excellence in Parkinson's Disease, patient caregiver information, links to Parkinson's advocacy groups, and a facility for automatically searching the National Library of Medicine's database of published research for the latest (and older) findings in specific areas of Parkinson's disease research. When fully implemented, the web site will provide the most complete information NIH has yet offered for tracking efforts against a particular disease.

UNDERSTANDING PARKINSON'S DISEASE

We know that the progressive death of nerve cells that normally release the neurotransmitter dopamine in a particular area of the brain leads to the cardinal symptoms of Parkinson's disease. However, we don't know what triggers these particular nerve cells to die, nor do we understand in detail how the loss of these, and cells in other parts of the brain, causes the many problems associated with this complex disorder. The Agenda emphasized the need for complementary approaches to advance our understanding, including the use of genetics and molecular biology, epidemiological studies to assess risk factors and provide clues to what triggers the disease, fundamental studies of the life and death of nerve cells in brain areas affected by Parkinson's disease, and efforts to unravel the nerve cell brain circuits whose ability to control movement and other aspects of behavior is undermined by the progress of the disorder.

A 1995 NIH Workshop led directly to an intramural-extramural collaboration that discovered the first gene defect that can cause Parkinson's, a mutation in the gene coding for the protein alpha-synuclein. Subsequent research demonstrated that alpha-synuclein is also involved in the more common, non-inherited form of Parkinson's disease. Research continues to follow that lead and to explore several other genes and proteins that have since been implicated in Parkinson's disease, including the parkin gene. NIH has undertaken several actions to further stimulate efforts on the molecular and cellular aspects of Parkinson's disease emphasized by the Agenda. These include the following solicitations for grant proposals:

- "The Function of Synaptic Proteins in Synapse Loss and Neurodegeneration." (NS-01-002, issued 3/9/00). This request for applications (RFA) targets research on synaptic proteins, such as synuclein, that are critical in neurodegeneration.
- "Mitochondrial Function and Neurodegeneration," (NS-01-003, issued by NINDS with NIEHS 3/9/00). This RFA focuses research on mitochondria and neurodegeneration. Mitochondria are the powerhouses of the cell which derive useful energy from sugars and oxygen. They have been implicated in Parkinson's disease and other neurodegenerative disorders as generators of damaging free radicals and, more recently, as gatekeepers of "cell suicide" programs.
- "The Role of Parkin and Related Proteins in Parkinson's Disease." (NS-01-005, issued 4/24/00). This RFA is designed to capitalize on recent genetic findings that implicate Parkin and other proteins in Parkinson's disease. The normal functions of these proteins

and their contribution to disease are poorly understood.

- "NINDS Administrative Supplements for DNA Microarray Analysis." (NS-00-007, issued 4/24/00) Microarrays, identified as a priority by the Agenda, allow scientists to monitor the activity of thousands of genes as disease progresses, in response to treatment and for many other purposes.

Because the first three requests for applications (RFAs) listed above elicited more high-quality proposals than anticipated, NIH increased the set-asides by 50% from the original levels of \$1 million each. The program of administrative supplements for DNA microarray analysis was not restricted to Parkinson's disease, but has awarded supplements to five Parkinson's disease research projects.

Other implementation efforts in advanced planning stages also relate to the genetic and molecular aspects of the Agenda. These include:

- NINDS is preparing an RFP (Request for Proposals) for a contract to develop a Parkinson's disease registry and repository for biological materials to facilitate research on Parkinson's disease. The development of this RFP has involved considerable background research to ensure that human subjects protections issues such as informed consent and privacy/confidentiality are thoroughly and appropriately addressed during the design and solicitation stages. A meeting will be held in 2001, after the RFP has been issued, to explore ways to encourage the participation of Parkinson's families in this central registry/repository, and to encourage researchers who have already collected families to participate as well.
- NINDS, NIA and NIMH have issued an RFA (request for applications) "Gene discovery for neurological and neurobehavioral disorders" (RFA-02-002, issued March 26, 2001). The RFA is targeted at finding genes that cause neurological disorders, including Parkinson's, or affect their severity or outcome. Complex genetic contributions, which are likely to play a role in susceptibility and progression of Parkinson's, are also a focus of this request. A condition of grant awards made under this program will require contribution of data to a repository for sharing among researchers.
- Synuclein was first implicated in an uncommon form of inherited Parkinson's, then linked to the common non-inherited form of Parkinson's. More recently, this protein has been implicated in other neurodegenerative disorders. NIA, together with NINDS, is planning for summer 2001, a workshop focused on the role of synuclein in neurodegenerative disorders tentatively entitled "Synuclein and Cortical Lewy Bodies Associated with Dementia in Alzheimer's Disease, Lewy Body Disease and Parkinson's Disease."

NIH has enhanced its activities relevant to epidemiological and environmental aspects of Parkinson's disease research. Some of these actions were begun prior to the Agenda but are ongoing and directly responsive to its goals. NIEHS-led efforts include:

- On September 19-20, 2000 NIEHS sponsored a “Parkinson’s Disease Epidemiology Workshop.” NIEHS is also sponsoring a session at the Annual Society of Toxicology Meeting, March 29, 2001 on “The Role of the Environment in Parkinson’s Disease” and a follow-up meeting to the previous workshop on March 30-31, 2001.
- NIEHS, with participation of NINDS, issued a request for applications "The Role of the Environment in Parkinson's Disease." (ES-00-002, issued 9/21/99). The total estimated funds available for support of the research project grant (R01, R21) award mechanisms in this RFA are \$4,000,000 per year.
- NIEHS, with participation of NINDS, issued a companion request for applications, "The Role of the Environment in Parkinson's Disease: Career Development Programs for Physician-Scientists." (ES-00-003, issued 9/21/99). This program is directed at training clinical investigators in this area. The specific total estimated funds available for support of the mentored clinical career development (K08, K23) award mechanisms in this RFA are \$520,000 per year.

It is also important to note that several components of NIH conduct research on other types of neurotoxic processes that may contribute to our understanding of Parkinson’s disease and other neurodegenerative disorders. NIDA, for example, has a significant research program on the neurodegenerative processes induced by drugs, such as methamphetamine, that cause degeneration within the nigrostriatal dopamine system, the same brain circuits affected by Parkinson’s disease. Similarly, research continues on the brain effects of nicotine, which has been associated with reduced risk for Parkinson’s disease in some epidemiological studies.

DEVELOPING NEW TREATMENTS FOR PARKINSON’S DISEASE

One of the most encouraging aspects of Parkinson’s disease research is the variety of therapeutic strategies that are under development. The Agenda emphasized the importance of pursuing several different approaches to treatment, including drugs, deep brain stimulation and other surgical approaches, cell implantation, gene therapy, rehabilitation, and outcomes research and evidence based medicine. NIH actively carries out research in all of these areas and is taking steps to enhance its efforts.

Drug therapies: Existing drug therapies for Parkinson’s disease can compensate for some of the symptoms, at least early in the disease, but do not slow the underlying death of nerve cells. Most current drug therapies aim to replenish or compensate for the dwindling supplies of dopamine. Ultimately drugs fail as too many dopamine nerve cells die and the drugs themselves produce troublesome side-effects at higher doses needed in advanced Parkinson’s disease. We need not just better symptomatic therapy, but also drugs to slow down or stop damage to the brain. The Agenda noted that efforts are required at several levels, from early laboratory studies to develop new lead compounds for drug development, through phase III clinical trials that prove the safety and efficacy of drug candidates.

NIH is taking several steps to develop a program of clinical trials of drugs for Parkinson's disease. The primary focus is on drugs that slow the course of Parkinson's disease, rather than just masking symptoms. The design of this collaborative research effort will enable several potentially therapeutic compounds to be efficiently evaluated during a single trial, and it will allow a large number of patients to be involved. Prior to the trial, NINDS will seek suggestions broadly for possible drugs to test in the trial, from NIH investigators, the Parkinson's research community, Parkinson's patients and advocates, and pharmaceutical companies. The following describes the steps taken so far:

- Following a suggestion at the Agenda workshop, on October 10, 2000 NINDS hosted a "Workshop on therapeutic opportunities in Parkinson's disease." The meeting took inventory of the state of clinical trials for Parkinson's disease and identified the highest priority areas in which to focus new efforts, including efforts to develop "neuroprotective" strategies that target the disease process itself. The discussion helped shape approaches to encourage clinical trials involving drugs and also strategies to evaluate deep brain stimulation (DBS).
- Following up on the recommendations of the October meeting in March 2001, NINDS released a request for applications (RFA) "Parkinson's disease neuroprotection clinical trial: coordinating and statistical centers" (NS-01-012). This RFA solicits applications for coordinating and statistical centers to collaborate in large, randomized, double-blind trials of potential neuroprotective agents in people who are in the early stages of Parkinson's disease.
- Another RFA seeking to fund more than 40 clinical centers to recruit patients for large neuroprotection trials and pilot studies will be released shortly.

NIH is also directing efforts to finding lead compounds for drug development or potential drug candidates, especially by taking advantage of increasing understanding of Parkinson's disease at the molecular level. These efforts include:

- A supplement awarded to a Udall center to apply high throughput drug screening technology to finding lead candidates for drug development in Parkinson's disease. High-throughput screening (HTS) is an approach to speeding drug development through the use of robotics and miniaturized assays (tests) to find lead compounds for further study. Although the drug industry now uses HTS extensively, developing drugs for Parkinson's disease has not been a focus of these efforts and the technology is not readily available to academic researchers.
- In January 2001, NINDS issued "High throughput drug screening facility for neurodegenerative disease" (NS-01-005). The encouraging responses to this RFI (request for information) will help shape a request for contract proposals (RFP) to establish a facility to provide more general access for investigators working in neurodegenerative diseases to high throughput drug screening technology. An RFA will

be issued in conjunction with the RFP to stimulate the development of assays (tests) for screening purposes.

- NINDS is preparing an administrative supplement program for investigators to screen a library of FDA-approved compounds for activity against Parkinson's and other neurodegenerative disorders. Assays developed for this program might be adapted for high-throughput screening of more extensive libraries of chemicals that can serve as starting points for drug development. Any promising drugs might also be candidates for the neuroprotection clinical trials initiative.

The Agenda highlighted the importance of non-motor symptoms on the quality of life of Parkinson's disease and the dearth of research in this area. A working group including staff from NIMH, NINDS and other Institutes with relevant missions, has formed to address non-motor symptoms in Parkinson's disease, such as the cognitive and behavioral problems. The group has undertaken the following actions:

- In January 2001, NIH sponsored a two-day workshop focused on the cognitive and emotional aspects of Parkinson's disease. Among other issues, the workshop emphasized the need for clinical trials in this area and the opportunities for studying the relationship of Parkinson's disease pathophysiology to non-motor problems in animal models. NIMH, NINDS, and other members of the PDCC are preparing a solicitation for grants targeting high priority areas identified at that meeting.
- A symposium focusing on the cognitive and emotional problems associated with Parkinson's disease is planned for the 2001 meeting of the Society for Neuroscience, the largest meeting of neuroscience researchers in the world. More research in this area is needed, and education is also important because many physicians are not aware of the extent to which these problems can affect treatment of people with Parkinson's.
- The NIH Intramural research program has recently taken an active role in studying non-motor symptoms of Parkinson's disease, such as cardiovascular effects, while continuing efforts in other areas such as early phase clinical trials in neurotrophic factors and glutamate pharmacology.

Deep Brain Stimulation: Deep brain stimulation (DBS) is a promising approach to treating Parkinson's disease and many other brain disorders. This strategy uses chronically implanted devices to electrically stimulate particular areas of the brain and builds upon increased understanding of the brain circuits that control movement and go awry in Parkinson's disease. The immediate goal of DBS is to compensate for the disruption of brain circuits caused by disease, but there are also tantalizing suggestions that DBS may somehow slow the death of nerve cells in Parkinson's disease. NIH is extending its ongoing efforts to encourage exploration of deep brain stimulation (DBS).

- The RFA "Consortium on deep brain stimulation for the treatment of Parkinson's disease and other neurological disorders," (NS-99-006, issued just prior to the Agenda), yielded

13 new research projects on several aspects of DBS, including clinical issues, mechanisms of action, device development and ethics. Through this program the NIA and NINDS, in addition to funding individual projects, established a consortium of research programs in DBS to serve as a focal point for collaborations and expansion of the field. Annual meetings are planned to facilitate interaction and data sharing among the investigators. Future membership of the consortium will include researchers responding to NIH initiatives in this field, scientists presently doing relevant work, and lay advocates.

- The October Therapeutic Opportunities Workshop discussed what further research is needed in the DBS area. In response NIH staff are preparing two new solicitations. One is directed toward improving technology and safety of DBS. The other targets better understanding of the mechanisms of DBS effects, which are poorly understood. Efforts are also continuing to foster clinical trials in this area and to solicit industry cooperation with these efforts.
- The Veterans Administration has initiated planning for a clinical trial in deep brain stimulation. NIH is working with the VA to help design that effort in light of recent progress in the field.

Gene Therapy: Gene therapy is another frontier of medicine that holds promise for treating Parkinson's disease. As the Agenda emphasized, gene therapy may be useful even for Parkinson's patients who have non-inherited forms of the disease. Gene therapy might, for example, deliver natural growth and survival signals into the brain to slow the death of nerve cells or deliver enzymes that regulate the production of dopamine.

- On October 23-24, 2000 NINDS held a workshop on "Gene therapy for Neurological Disorders" which focused on Parkinson's disease and on lysosomal storage disorders. The goal was to evaluate the current state of preclinical research and to facilitate its translation to the clinic. Scientific, clinical, and regulatory issues were discussed by a diverse group which included extramural and intramural scientists, patient advocates, and representatives of the FDA. An article has been published summarize the results (*Molecular Therapy* 3:3-7 2001). This Workshop, in turn, catalyzed a subsequent meeting organized by workshop participants themselves to further discuss ways to work together to apply gene therapy in Parkinson's disease. A solicitation is in preparation along lines the workshop suggested to expedite research on gene therapy for Parkinson's and other diseases.

CREATING NEW RESEARCH CAPABILITIES

The Agenda noted that NIH could facilitate efforts against Parkinson's disease by providing resources and tools that are not readily available to researchers.

- As noted above, NIH is addressing recommendations for new research technologies in

the area of high-throughput drug screening, microarrays, gene therapy and registries/repositories.

- With the growing understanding of Parkinson's disease, and the creation of unique reagents for study of the disease, resource sharing has become important for progress in the field. NINDS has awarded a supplement to one of the Udall Centers to support a website to facilitate sharing of biological reagents critical for Parkinson's disease research.
- NIA and NINDS are also exploring opportunities to foster closer interaction among the Udall centers and the NIA funded network of Alzheimer's Disease Centers, so as to better utilize the Parkinson's disease and related tissue collection and research being carried out by the network of Alzheimer's Centers. There is increasing recognition of the ties between these two neurodegenerative disorders.

ENHANCING THE RESEARCH PROCESS

Beyond the specific scientific concerns, the Agenda emphasized that NIH should enhance the research process itself with regard to funding mechanisms, consideration of ethics, and partnerships with private groups. Mechanisms that bring researchers together in cooperative efforts, stimulate innovative approaches, recruit new investigators, and rapidly fund new research as opportunities arise are critical. NIH has taken several steps to accomplish these aims.

- In the year prior to the Agenda, NINDS funded eleven Morris K. Udall Parkinson's Disease Centers of Excellence. Each center encourages interaction of researchers from different disciplines, and the eleven centers come together regularly to foster cooperation and stimulate new ideas. The centers represent a core of expertise relevant to many aspects of the Agenda. NINDS has encouraged single centers or groups of centers to apply for supplements to undertake research projects that address specific aspects of the Agenda. Noted above were supplements to Centers for high throughput drug screening (HTS) and a reagent sharing web resource. Other supplements awarded to these centers target efforts to identify Parkinson's genes through investigation of genetically isolated populations (Icelandic and Amish) and investigations of Parkinson's disease in minority racial and ethnic groups (African Americans in Mississippi; members of the Navaho Nation).
- Supplement programs not restricted to Parkinson's disease have helped accelerate research toward goals of the Agenda. The Microarrays supplement program was noted above. The NINDS Infrastructure Supplement Program, supplying funds for equipment purchases up to \$50,000, made fifteen awards for work specifically focused on Parkinson's disease.
- On November 16, 2000 NINDS issued a notice for "NINDS administrative supplements for research on Parkinson's disease" (NS-002-01). This program sets aside up to \$3

million in supplements to foster additional research on Parkinson's disease. The intent is to allow NINDS funded investigators to generate preliminary data that will allow them to apply for new grants on Parkinson's disease. This program has produced a very strong response, with more than 90 proposals that are now being evaluated. This supplement program is directly responsive to recommendations in the Agenda.

- As noted above, several working groups will help encourage interactions among researchers and among NIH staff focused on issues critical to Parkinson's disease research. The request for applications on deep brain stimulation formed the nucleus of a consortium of investigators working in this field. Funds to encourage exchange of investigators among laboratories, share materials, and undertake cooperative projects are part of the consortium. Following the workshop on gene therapy, investigators in Parkinson's met to form a working group in that area, and a working on non-motor aspects of Parkinson's disease is also underway, and the NINDS clinical trials group has placed strong emphasis on Parkinson's disease as a model for future efforts in other areas.
- NINDS has implemented a grant mechanism (R21) that the Institute has not used previously to support innovative, potentially high impact research projects for neurological disorders, including but not restricted to Parkinson's disease. Such projects generate pilot data to assess the feasibility of novel avenues for investigation, undertake high-risk experiments that could lead to a breakthrough in a particular field, or demonstrate new and potentially valuable technologies. We hope to encourage proposals from both new and established investigators.
- This year the NINDS-sponsored teaching workshop on the neurobiology of disease at the Society for Neuroscience Annual meeting focused on Parkinson's disease. The meeting is the largest convocation in the world of scientists studying the brain. The purpose of this workshop was also to educate and attract new investigators to the field, and the day long presentation attracted intense interest.
- NIH is engaging the expertise of the private sector through SBIR grants, when appropriate, to accomplish goals of the Agenda. New SBIR efforts include, for example, developing a device to facilitate implantation of gene therapy vectors or cells, testing the safety and efficacy a dopamine cell based therapy, and improving technology for neurosurgical treatments.

Ethics: Vigilance and forethought with regard to ethics is important for all areas of research. This is especially so for Parkinson's disease for several reasons, including the promise of interventions now at the frontier of biology, such as gene therapy and deep brain stimulation. NINDS and other members of the PDCC are active participants in ongoing NIH efforts to ensure ethics receives due consideration. These include, for example, the groundbreaking Ethical Legal and Social Issues program of the Human Genome Project. NINDS has recently awarded a grant to specifically investigate the unique ethical and policy challenges deep brain stimulation (DBS)

presents, and together with the NIH Office on Research Integrity in August 2000 posted a request for applications NS-01-008 “Research on Research Integrity.”

Public Private cooperation: The process of developing the Agenda, and its subsequent implementation, itself represents a sea change in the relationship between the NIH and private Parkinson’s disease groups. Representatives of private advocacy and industry organizations participated actively in the development of the Agenda, and advocates are members of the Parkinson’s Disease Implementation Committee (PDIC). The Parkinson’s advocacy community and representatives from industry have also participated in many of the specific issue workshops that are helping to guide implementation of the plan, as well as advising the NIH in the development of resources such as the website and registry. The web site, described above, will provide extensive information to allow the public and researchers to track progress of the plan, as well as providing useful information about other aspects of Parkinson’s disease. NIH has greatly expanded its formal and informal communication with the Parkinson’s community and is committed to further enhancing these interactions in the future.

Staff resources: Implementing the Agenda places intensive demands on program directors, review, and other professional staff. NIH has expanded the staff resources directed to carrying out the activities described in this document. This includes new program directors, including professionals hired specifically for their expertise in areas such as brain banking and patient registries. When necessary NIH is using flexible personnel options such as the Intergovernmental Personnel Act (IPA) to fill these needs.

FUNDING ESTIMATES

In its report on H. R. 4577, the Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, the Conferees requested updated professional judgement funding projections for subsequent years. As documented in this report, NIH has committed resources and energy to the development of solicitations, workshops, and other activities to implement the Parkinson’s Disease Research Agenda. Weekly meetings of the neurodegeneration program cluster include an assessment of progress and discussion of future plans. The Parkinson’s Disease Coordination Committee and the Parkinson’s Disease Implementation Committee provide regular opportunities for interaction among NIH components and with external advisors. The establishment of a new unit focusing on clinical trials and the development of collaborative relationships with the Department of Veterans Affairs has set the stage for vigorous efforts in clinical research. Together, all of these actions have raised the consciousness of the research community about research opportunities and NIH commitment to fostering progress against Parkinson’s disease.

FY 2001 marks the first year of this agenda. While there has been much activity in Parkinson’s research, and some important advances, the overall scientific landscape has not changed dramatically. As noted in the introduction, sufficient time has not yet elapsed to gauge the effectiveness of the initiatives already undertaken. Therefore, we respectfully conclude that the original estimates, shown in the appendix to this document, should stand.

CONCLUSION

NIH is vigorously implementing the Parkinson's Disease Research Agenda. In the first year of the five year plan NIH held several workshops focused on specific aspects of Parkinson's disease research, and is planning several more meetings for the near term. Including solicitations issued shortly prior to the Agenda or nearing release, NIH has developed more than a dozen programs of requests for grants or contracts that target specific Agenda priorities. Supplement programs have been used extensively to expedite the Agenda in the first year. Working groups or consortia have formed in several critical areas. NIH has worked with Parkinson's advocates throughout the process, and is nearing completion of a website that will set the standard for informing the public about progress in implementing a disease specific research plan. As noted in the Agenda, the best prospects for curing Parkinson's often arise from areas of research not focused on the disease, such as bioengineering, gene therapy, and neurotrophic factor research. Success against Parkinson's disease thus relies heavily upon maintaining the broad front of scientific progress. At the urging of Congress increased efforts are underway against other neurological disorders, such as stroke, epilepsy, brain tumors, autism, and muscular dystrophy. What is most encouraging is the degree to which the research needs overlap and the promise that progress against each disorder will help the fight against others. The Parkinson's Agenda represents a new approach to confronting neurological disorders, combining a commitment to cure a particular disease with a broad perspective on the necessary scientific context. Thus the Agenda is leading the way for progress against many neurological disorders, and NIH is committed to carrying out the Agenda the fullest extent possible in light of scientific opportunities, competing responsibilities, and available funding.

APPENDIX
National Institutes of Health
PARKINSON'S DISEASE RESEARCH AGENDA
PROFESSIONAL JUDGMENT ESTIMATES

(Dollars in thousands)

	Year 1	Year 2	Year 3	Year 4	Year 5	Subtotal, 5 years
RESEARCH:						
Understanding PD:						
Genetics.....	5,000	10,200	10,600	11,000	11,400	48,200
Epidemiology.....	5,000	15,200	25,800	26,800	27,800	100,600
Life & Death of Neurons in PD.....	10,000	26,400	33,500	41,600	43,400	154,900
Circuits.....	2,000	4,100	6,300	8,800	9,200	30,400
Subtotal, Understanding PD.....	22,000	55,900	76,200	88,200	91,800	334,100
Treating PD:						
Pharmacological Approaches:						
Phase I/Pilot Studies.....	4,000	4,100	4,200	4,400	4,600	21,300
Large Clinical Trials.....	8,000	12,300	16,700	17,200	17,800	72,000
Complications & Non-Motor Symptoms.....	2,000	2,100	2,200	2,300	2,400	11,000
Prevention Trials.....	1,000	1,000	1,000	1,000	1,000	5,000
Subtotal, Pharmacological Approaches.....	15,000	19,500	24,100	24,900	25,800	109,300
Other Approaches:						
Deep Brain Stimulation and other Surgical.....	10,000	15,400	21,000	21,800	22,600	90,800
Cell Implantation.....	2,000	4,100	6,300	12,600	13,700	38,700
Gene Therapy.....	2,000	3,100	5,200	7,400	9,300	27,000
Rehabilitation.....	1,000	1,000	1,000	1,000	1,100	5,100
Outcomes Research.....	1,000	2,000	2,000	2,000	3,000	10,000
Subtotal, Other Approaches.....	16,000	25,600	35,500	44,800	49,700	171,600
Subtotal, Treating PD.....	31,000	45,100	59,600	69,700	75,500	280,900
Creating New Research Capabilities.....	15,000	35,500	51,800	78,600	106,500	287,400
Enhancing the Research Process - Ethics.....	1,000	2,000	3,000	3,000	3,000	12,000
SUBTOTAL, RESEARCH.....	69,000	138,500	190,600	239,500	276,800	914,400
PROGRAM MANAGEMENT & DIRECTION	2,400	5,000	6,800	8,600	9,900	32,700
GRAND TOTAL.....	71,400	143,500	197,400	248,100	286,700	947,100