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PARKINSON'S DISEASE RESEARCH AGENDA

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Executive Summary

In Senate report No. 107-84 (pages 184-185), the Senate Committee on Appropriations requests the National Institute of Health (NIH) to convene a series of consortium meetings, in order to re-evaluate the Parkinson's Disease Research Agenda and identify emerging scientific opportunities in Parkinson's disease (PD) research.

In order to respond to this request, NIH held the initial Consortium meeting on January 9-10, 2002. Participants included scientists, clinicians, representatives of PD advocacy groups, and NIH staff involved the implementation of the Agenda. The primary charge to the participants was to evaluate the implementation efforts of the NIH, and to identify both emerging scientific opportunities and areas of research identified in the original Agenda that need additional resources. The meeting focused on the scientific opportunities in the field of PD research, and the participants identified a number of research priorities. While explicit budget recommendations were not provided by the participants, clear goals within the scope of the original PD Research Agenda emerged from discussions about the basic science of PD, and about therapeutic opportunities. These priorities include:

- Facilitating translational approaches to PD research
- Increasing our understanding of how PD affects the dopamine systems of the brain
- Broadening studies of the effects of PD on cells and circuits other than dopamine systems, including treatment of non-motor complications
- Improving and validating biomarkers and assessment tools
- Supporting the necessary preclinical studies of gene therapy and facilitating translation into clinical trials
- Supporting improvements in models for PD in invertebrates, small mammals and non-human primates

NIH will use these priorities, as well as the suggestions that emerged from the individual breakout sessions, as a guide for allocating its resources in PD research for the coming years. NIH anticipates that participants in future gatherings – such as at the Udall Center meetings, and Consortium meetings being planned on deep brain stimulation, drug screening for neurodegenerative disorders, gene therapy, and gene-environment interactions in PD – will continue to identify additional priorities as they emerge during the implementation of the PD Agenda.

Introduction

In its report on the Fiscal Year 2002 budget for the Department of Health and Human Services (DHHS), the Senate Committee on Appropriations stated:

> "Last year, the Congress strongly urged the NIH to work toward implementing Year 1 of the research agenda, which cited the need for a $71,400,000 increase in Parkinson's research funding. The Committee is concerned that the NIH did not meet that goal. As a consequence, much of the agenda remains to be undertaken, and this highly promising field of research is not moving ahead as speedily as the Congress intended.
>
> An estimated $143,500,000 increase over the baseline year would be needed to implement Year 2 of the research agenda, and the Committee has provided additional funds for that purpose. In order to ensure full implementation and funding, the Committee directs the NIH to host a series of consortia in collaboration with the Parkinson's research-related Institutes and the extramural research community by February 15, 2002. The consortia shall identify, to the full extent of available scientific opportunity, the research needed to implement the Research Agenda and the funding mechanism and dollars necessary for each area. **The Committee requests the Director to report by March 15, 2002, that the consortia have been held, and on the specific steps the NIH will take to implement the Research Agenda.** " (Senate report No. 107-84, pages 184-185)

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

In FY2000, Congressional report language directed the NIH to develop a PD research agenda for the subsequent five years, including professional judgment funding projections. As requested, NIH developed a comprehensive Agenda, with input from leading researchers in the field, and several PD advocacy groups. This Agenda included professional budget estimates, based on feedback from the extramural community as to the research opportunities addressing Agenda issues that could be supported if both the funds and the workforce were available. Since the appropriations for NIH are not known far enough in advance, the five-year

Agenda budget was developed without taking into account future appropriation levels, Congressional research mandates, or the scientific opportunities that other disease areas might offer. Both the Agenda, and the budget projections that accompanied it, provided a strategic framework for NIH to use in planning its Parkinson's programs and identifying areas of research that may necessitate greater financial support.

NIH has been actively involved in implementing the PD Agenda for nearly two years, and its actions have built upon past commitments to this area of research and initiatives that were already in the planning stages at the time the Agenda was developed. In the context of neurological disease, this effort has been unprecedented in the history of NIH, and has led to the development of multiple centers of excellence, new grant applications on important topics, targeted contracts, consortia in several research areas, and research workshops (please see Appendix for more details). With regard to absolute budget expenditures on PD, the NIH has made every effort to commit as much funding as possible to this area of research, given that it is also responsible for supporting research on hundreds of other disorders. This commitment has led to significant progress since the start of the Agenda: numerous scientific advances have been made, the best new ideas have been funded, junior investigators and researchers from other disciplines have been encouraged to apply for grants on PD, and dozens of new studies – including important clinical trials – have been initiated, that will lead to an improved understanding of PD, strategies for prevention, and opportunities for therapy, in the near future.

In response to FY2002 Congressional report language, NIH convened a special Consortium meeting, including key representatives of the research and advocacy communities, and the staff of the NIH Institutes involved in Parkinson's disease research. This meeting, held January 9-10, 2002, provided an opportunity for participants to discuss the original Agenda, to document the progress made thus far, and to identify the emerging scientific opportunities and areas of research that would be likely to require additional investments in the future. NIH provided a background document to participants that outlined all of the activities initiated by the NIH as part of its Agenda implementation, a complete list of grants currently funded by NIH in the area of PD research, and a budget report detailing expenditures in PD through FY2001. These documents served as the basis upon which the participants evaluated the NIH efforts to expand and encourage areas of research that were targeted in the original Agenda. Participants attended plenary opening and closing sessions, while the group divided to attend breakout sessions focused on "Understanding Parkinson's Disease" and "Treating Parkinson's Disease." Attendees in both breakout sessions were asked to consider issues

related to "Creation of New Research Capabilities" and "Enhancing the Research Process." These four topics formed the structure of the original PD Research Agenda.

The scientific attendees were also asked to consider budget planning issues. The group's responsibility with respect to the professional judgment budget was discussed extensively at the opening session with the result that the group elected to restrict its efforts to identifying and prioritizing scientific and clinical issues in PD. Therefore, the scientific priorities and goals that were identified at this meeting will be interpreted by the NIH as a guide to prioritizing expenditures in PD over the remaining years of the Agenda and beyond.

Results of the Consortium Meeting: Evaluation of Agenda Implementation and Identification of New Priorities

The January 2002 Consortium meeting differed from the January 2000 Parkinson's disease meeting in several important ways. While the initial meeting – held to develop the Agenda – encouraged broad discussions, the 2002 meeting allowed researchers to address more specific issues in the context of the original Agenda. In many areas of research, the participants agreed that NIH had taken an appropriate course of action and should continue its efforts. These activities included:

- Major advances in the initial identification of genes that contribute to parkinsonism
- An understanding of environmental factors that may contribute to PD
- A better characterization of the cellular processes that link genetic mutations and environmental factors to nerve cell degeneration
- Support of research on the normal circuitry of the brain areas that are involved in PD
- Major advances in stem cell biology
- Initiation of the first large clinical trial of deep brain stimulation
- Initiation of large scale clinical trials of pharmacological approaches for neuroprotection

As expected, the attendees at the Consortium meeting also outlined emerging areas of research that could require additional resources, as well as areas of research that were identified in the first Agenda meeting but still have not received enough attention. These priority areas will be identified below within the framework of the original Agenda. Common themes that emerged independently from both

breakout sessions will be highlighted at the end of the report, and will serve as a guide for NIH to prioritize its future resources in Parkinson's disease. Participants in the individual breakout sessions also identified a number of other research priorities that were specific to these sessions; these research topics are discussed in the body of the report.

Understanding Parkinson's Disease

Genetics of Parkinson's Disease

The genetics of PD is a field that extends from epidemiological studies of families with hereditary parkinsonism and related disorders, to the study of gene mutations that contribute to neurodegeneration at a cellular level. Although the same group of genes may be targeted using both approaches, each field of study contributes to a better understanding of how genetics influences the development of disease.

Since the discovery that mutations in the alpha-synuclein gene contribute to rare forms of inherited parkinsonism, the chromosomal locations of as many as eight other genes involved in parkinsonism have now been identified. The participants at the Consortium meeting were supportive of the ongoing efforts at NIH to fund the sequencing and characterization of these genes, but it was noted by several participants that there is a clear gap in our understanding of how mutations in these genes lead to the cellular and biochemical alterations that are a hallmark of this disorder. Altered protein processing and folding – which is also seen in other neurodegenerative disorders like Alzheimer's disease – is likely to be one link, but there are probably other mechanisms which remain unidentified.

Although the inherited forms of parkinsonism characterized in the initial genetic studies are very rare, gene mutations might also contribute – along with many other factors – to the forms of PD seen in the majority of affected individuals. The complex interaction of genes, the environment, and other influences makes the untangling of these factors extremely difficult. However, continued investments in both basic science and clinical research and large scale studies of populations (and their risk factors) are critical to ensuring that these relationships will ultimately be understood, and that we will have a better understanding of how the rare familial forms of parkinsonism are related to the cases of PD that arise with no known cause.

In addition to genetic mutations that may contribute to neurodegeneration, other

genes/proteins can help to protect neurons from damage. For example, the heat shock proteins are one of several families of molecules that may help neurons survive in several different neurodegenerative disease states, including PD. These types of genes/proteins may be induced to perform beneficial cellular functions that counteract neurodegenerative processes. Future efforts of NIH, therefore, will need to be focused on a wide range of molecules, including those that contribute to degeneration, those that protect cells from damage, and those that serve a common role in many different neurodegenerative disorders.

Risk Factors for Parkinson's Disease and Epidemiological Studies

Like genetics, risk factor research is a broad field that encompasses studies ranging from large-scale analyses of epidemiological trends in PD to the development of animal models of PD using environmental toxicants. In terms of epidemiological approaches, the study of risk factors has focused more on families with hereditary PD. However, as in the field of genetics, it will be important for future studies to include more individuals who do not have a family history of the disorder. This is particularly important as familial parkinsonism appears to represent a fairly small fraction of the known cases of PD. Identifying risk/susceptibility factors for typical PD requires different approaches, including population studies combined with laboratory investigations. These investigations will need to consider the combined effects of many different influences, including genetics, the environment, race, etc.. This research will be essential in preventing the development of PD in healthy populations.

Large-scale studies among other approaches may also yield information helpful to the development and validation of biomarkers - biological indicators/tests of disease risk, progression, or response to treatment - which was a clear need identified by the participants. A high-risk/high-payoff grant program was suggested to jumpstart this area of research. Improvements in preclinical diagnoses could also benefit from large-scale studies, and it was suggested that NIH continue to promote collaborations among currently funded centers (where multiple aging populations are studied). These longitudinal studies may enable clinicians to identify strategies that would allow individuals at risk to be recognized well before the clinical onset of PD. New, prospective, longitudinal studies on healthy individuals may also help identify clues for improving preclinical diagnoses. However, the participants were also mindful that the ethics of bringing healthy participants into such a study would need to be considered and addressed.

Like the relationship of genetics to the cellular pathology of PD, the relationship of environmental influences on the cellular pathology in PD also requires renewed

focus. Recent research has informed the community about a number of environmental agents – pesticides in particular – that can lead to the symptoms of PD in animals, but there are gaps in our understanding of how these signals (particularly in combination with genetic risk factors) lead to neurodegeneration. Continued investments in both basic science research, as well as large-scale studies in this area will be needed. An important step in the planning for this area of research will be made in the next year, with the development of a National Institute of Environmental Health Sciences Consortium devoted to the study of gene-environment interactions in the etiology of Parkinson's Disease. Regular meetings of these Consortium investigators, along with associated scientific workshops, will focus attention on emerging areas of research in this field.

Life and Death of Neurons in Parkinson's Disease

An important point of agreement in the discussion about neurodegeneration in PD focused on the emergence of a "conceptual framework" based on our growing understanding of the role of dopamine, genetic mutations, and environmental influences in the development of PD. The convergence point of these three influences is now believed to involve alterations in protein processing and clearance, and more research needs to be devoted to exploring the link between protein processing/breakdown and neuronal degeneration. However, some participants noted that many such "central" mechanisms have been identified over the years – including the effects of free radicals, mitochondrial dysfunction, and over-excitation of neurons. All of these may play some role in the degenerative process, and all probably offer important possibilities for therapeutic intervention based on rational drug design, or perhaps gene therapy.

Although NIH has made substantial investments in this area of research, the Consortium participants indicated that these efforts need to be expanded to include more studies on the effects of PD on neurons outside of the central area of dopamine loss (the substantia nigra and related brain regions). For example, very little is understood about how other parts of the nervous system (both in the brain, and in other parts of the body – such as the gut) are affected in PD. Clearly, these neurons are altered, since individuals with PD experience abnormalities in cognition, sleep, emotions, digestive function, etc. However, little is known about whether these neurons undergo the same types of cellular changes that are observed in the dopamine systems of the brain, and whether these changes can be prevented or reversed.

Neural Circuits in Parkinson's Disease

Meeting attendees expressed enthusiasm about the extent to which NIH has supported basic studies of dopamine brain circuitry since the start of the Agenda. However, it was noted that more work is needed on the study of the circuitry outside the dopaminergic systems of the brain. How do these systems adapt to the loss of dopamine in PD? Do genetics play a role in these circuitry changes? When clinicians treat PD, they are typically treating the dopaminergic abnormalities, with the hope that the rest of the brain will respond normally. However, this may not be the case, since dopaminergic drugs do very little to treat (and may actually worsen) some of the non-motor effects of PD, like cognitive changes and/or psychosis. However, it is possible that a better understanding of how these circuits are altered in PD will enable the rapid development of new therapies, or a re-evaluation of currently-used therapies, such that motor and non-motor deficits can be improved in individuals currently affected by PD.

Developing New Treatments for Parkinson's Disease

Pharmacological Approaches

For many years, NIH has supported clinical research designed to improve treatment options for individuals with PD. This work continues today with a large trial of neuroprotective therapies, recently initiated by the National Institute of Neurological Disorders and Stroke (NINDS). While this study was welcomed by the Consortium participants, several other priorities were also identified with respect to clinical trials. Participants agreed that in addition to trials of neuroprotective agents, an important research goal for the PD community should be the development of clinical trials that address the many debilitating non-motor complications of PD and the side effects of Parkinson's medications. These include sleep problems, depression, cognitive impairment, and dyskinesias (uncontrolled movements); they are often the most discouraging effects of PD from the patient's perspective. Dyskinesias in particular were identified as a problem that is poorly understood, and can be a limiting complication in the medical management of patients. Although surgical approaches can offer some degree of relief from this condition, more needs to be known about its underlying causes. Animal models, particularly those developed using non-human primates, may be extremely valuable in this research. With additional knowledge about the mechanisms of dykinsesias, both prevention and treatment of this side effect might

become an option. Non-motor complications of PD that markedly affect quality of life, such as depression and sleep disturbances might also be ameliorated, or at least treated more consistently by practitioners, if well-designed trials addressing the effects of currently marketed drugs were conducted on individuals with PD.

Deep Brain Stimulation and Other Surgical Approaches

The use of deep brain stimulation (DBS) to treat PD has been approved by the Food and Drug Administration (FDA) since the Consortium meeting was held, however NIH has been committed to expanding this field of research for several years. During this time, NIH has issued several requests for applications in an effort to increase the number of basic and clinical studies, and to develop a Consortium of researchers involved in this approach. To a degree, these efforts have been very successful – Consortium development is moving forward, a number of researchers have already been funded, and a meeting of these researchers is being planned. In addition, NINDS is collaborating with the Department of Veterans Affairs (VA) to conduct the largest trial of DBS in PD to date. The goal of this trial is to compare DBS to best medical management, and then to evaluate DBS in two different brain regions if it proves to be more effective than medical treatment. During the development of this trial, NINDS has worked with the FDA to ensure that the results of the study will have broad benefits to individuals with PD.

At the Consortium meeting, attendees emphasized the importance of understanding the mechanisms of action of DBS, as well as further developing the required medical technology to move this field forward. Participants further suggested that future DBS clinical trials be designed to explore aspects of this therapy such as non-motor effects, its effects on dyskinesias, and/or its possible neuroprotective action. While it is hoped that studies that investigate the mechanisms of action of DBS will be funded in the very near future (in response to an NINDS/National Institute of Mental Health request for applications), neuroprotection trials will require additional data on the long-term safety of DBS. The collaborative trial with the VA will not only help to establish these safety data, but it will also provide long-term data on the safety and effectiveness of DBS in treating both motor and non-motor symptoms of PD.

Delivery of treatment agents to specific brain regions was also identified as an area that needs further exploration and support from NIH. Both intramural and extramural researchers at NIH are already pursuing this goal, and expect to identify and test techniques within the near future that will help improve treatment delivery for individuals with PD as well as other brain disorders.

Cell Implantation

The field of cell and tissue implantation has made great strides in the past few years, and although unexpected adverse events occurred during a recent clinical trial of tissue transplantation in PD, it is clear that this approach to treatment is still supported by the research community. However, attendees acknowledged that important gaps exist, that need to be addressed as the implementation of the PD Agenda continues. First, from a clinical perspective, more needs to be known about what caused the unanticipated dyskinesias in the first tissue transplantation trial. The surgical approach used and level of dopamine released by the transplanted cells could have been contributing factors; future studies should address surgical strategies, regulation of transplant growth, and possible side effects of these procedures. The results of a second NINDS-funded clinical trial on tissue transplantation in PD are expected within the next year, and may help to address some of the questions raised during the Consortium meeting.

In addition to these research issues, it is clear that replacement of dopamine-producing cells will probably not address many abnormalities of brain circuitry in PD. Thus, a number of complications of PD will not be resolved even if dopamine replacement is achieved through cell or tissue transplants. More research will be needed to determine how transplantation approaches either alone or in combination with other therapies can address these non-dopaminergic complications. For all of these issues, participants acknowledged that more pre-clinical work (possibly involving non-human primates) is needed before researchers initiate any additional clinical trials.

From a basic science perspective, remarkable developments have been made in the study of stem cells over the past several years. These advances have given researchers and the public hope that replacement cells may someday be available for treating disorders like PD. However, Consortium participants agreed that more basic research is needed, particularly studies that are directed toward the development of a homogeneous and self-replicating cell line (or lines) of dopamine-producing neurons. Participants indicated that the availability of such cells would have dramatic effects on the field of PD research, not only for use in transplantation experiments, but also for conducting effective preclinical screening of therapeutic drugs and/or genes. NIH is already invested in the development of these cell lines and the study of stem cells (consistent with the President's August 9, 2001 stem cell policy), through both its intramural and extramural research programs, and will continue to support and expand these efforts within the existing policy guidelines.

Gene Therapy

Gene therapy is another therapeutic approach that is already a priority of NIH, but will require further investments over the next several years. Several issues within this field of research were identified as critical areas of scientific focus, as investigators move closer to gene therapy trials in PD. The primary need identified was the development of animal models that would allow better preclinical evaluation of the safety of different viral vectors (the "delivery" vehicles), mechanisms to control the expression of the vector, methods to non-invasively monitor gene expression, and the responses of both the nervous and immune systems to the release of foreign proteins into the brain. In addition to these scientific issues, questions about informed consent, intellectual property rights, and sharing of gene therapy technology, were also raised. Informed consent issues are not new, and will likely be addressed by NIH in collaboration with the PD Gene Therapy Study Group, as its members make progress towards clinical trials. However, intellectual property rights and sharing of research materials and technologies are emerging as more significant roadblocks for researchers in this field than might have been predicted several years ago. Institutions have responded to the development of new technology by moving to protect the investigator's rights, however in some cases, this is counterproductive to the sharing of reagents that is necessary for productive collaborations. Although NIH is acutely aware of sharing concerns in general, special attention may be needed in future years to address any issues that are specific to gene therapy and essential for its successful implementation.

Rehabilitation

NIH has long recognized the importance of rehabilitation in all areas of neurological disease, and has provided support for this area of PD research over the past two years. However, it was clear from the discussion at the Consortium meeting that many new opportunities for rehabilitation have emerged since the original Agenda was developed, that may require an increased commitment from the NIH. Participants offered behavioral interventions as a prime example of how complications of PD that are normally resistant to drug therapies – such as swallowing and speech disorders – may be effectively and non-invasively treated. Targeted behavioral interventions may be needed to treat some of these complications, while other more general forms of therapy – such as exercise – may help with symptoms ranging from postural problems to depression. Further follow-up on recent experimental data suggesting that exercise may actually be

neuroprotective may warrant further study as well. Participants identified the development of new clinical trials to test behavioral interventions in PD as an important need in this field.

Outcomes Research and Evidence-based Medicine

Outcomes research and evidence-based medicine use two somewhat different approaches to establish the best medical practices for treating PD. Outcomes research focuses on the development and refinement of a variety of outcomes that can be used to evaluate the safety and effectiveness of therapeutic or preventative interventions. Evidence-based medicine is the development of best practices in medical treatment, such that health practitioners are using therapeutic approaches that have the most sound basis in scientific and clinical evidence. With regard to outcomes research, participants identified several priority areas, including the development of better clinical assessment tools and reliable markers of disease progression, particularly in treated patients where symptoms are masked. It was suggested that a workshop might help to cement future goals for NIH in this area. In the area of evidence-based medicine, the participants acknowledged that several groups, such as the American Academy of Neurology and the Agency for Healthcare Research and Quality, are already developing guidelines for treatment in individuals with PD. Any role for NIH would likely be identified after such reports have been made public. However, one possible outcome of these findings might be the development of additional clinical trials to compare treatment strategies and approaches to therapy.

<u>Creating New Research Capabilities</u>

Participants in both the "Understanding PD" and "Treating PD" breakout sessions were urged to consider how new and evolving research capabilities could aid in the progress in these areas. Many of the research tools identified in the original Agenda were also discussed at this meeting. High throughput drug screens and genetic microarrays, two areas identified in the original Agenda, have been the focus of extensive NIH activity over the past two years and accordingly, were not addressed at length. By contrast, areas of research that participants identified as future priorities include the development of models of Parkinson's disease – both in the intact animal, and at the level of cell culture – and the development of better biomarkers and imaging tools that can be used both to identify individuals at risk for PD, and for assessing both disease progress and treatment success.

Consortium participants encouraged NIH to support the development of new animal models of PD, and to improve the availability of these models to the research community. With regard to new models, the generation of animals that more accurately reproduce the clinical pathology seen in PD was encouraged. Models that are currently available are good, but not every species reproduces all of the pathological and clinical features of human PD, and there is still much room for improvement in this area. In addition, new models might help to address an immediate need of the field – the testing of therapies for non-motor symptoms of PD. Model development will probably require several different species, depending upon the type of study and disease features that are needed in the animal. Mammalian models are an obvious need, but participants also suggested that continued investments be placed in invertebrate models of the disease, since it is often much easier to manipulate genes in a species such as the fruit fly and basic information on the cell biology of disease can be gained in these studies. Additional non-human primate models may also be needed for studies of dyskinesias and other complications of PD, and for the translation of therapies into clinical trials. However, participants noted that in some cases, appropriate small animal models can help the translation of therapies to clinical trials without the need for testing in non-human primates. Alzheimer's researchers have used this approach in recent years, but it is not clear at present whether comparable rodent models could be developed for PD.

As was discussed in an earlier section, better cell culture models of PD are also needed. Specifically, homogeneous cultures of dopaminergic neurons would help researchers to understand the normal function of the substantia nigra and to evaluate and screen treatments.

Participants also identified the development and validation of biomarkers as one of the most critical areas to need additional resources. Some biomarkers are currently available, but it would be helpful to have a battery of validated tests that could be used to assess susceptibility to the disease, document progression of the disease in affected individuals, and assess the effectiveness of therapies. Imaging is one tool currently in use, but it is possible to conceive of many different types of screening that could be developed – in particular, if they are based on known mechanisms of disease (for example, testing for abnormal proteins in the blood plasma or cerebrospinal fluid). NIH staff noted that grant submissions in this area were not forthcoming in the first two years of the Agenda, but participants believed that the use of a high-risk/high-payoff grant mechanism might stimulate applications.

Enhancing the Research Process

Ethical Issues

Without question, ethical issues have emerged as a topic of concern in many areas of clinical research, including PD. The clinical use of DBS, for example, has raised numerous issues over the years – related to the routine use of DBS for PD before full-scale clinical trials have been conducted, and the proposed use of DBS as a neuroprotectant in individuals who have not first exhausted the possibility of medically managing their disease. Unfortunately, there is no simple solution, or even an identifiable goal, for managing this problem. In the case of DBS, NIH believes that the information gained from its collaborative trial with the VA will provide additional safety and efficacy information that will prove invaluable in planning subsequent clinical trials of DBS. NIH will continue to give individual attention to the ethics of this approach as individual grant proposals are submitted, and the DBS Consortium will have at least one ethicist as a participant, so that these issues can be addressed as they arise within this group.

Informed consent is a broad issue affecting many fields of PD research. Obtaining appropriate informed consent from healthy subjects for prospective longitudinal studies, and from human subjects trials of new approaches such as gene therapy, as well as protecting participants' identities as research materials are exchanged and studied are just a few of the issues that need to be addressed by the research community, with the support and guidance of the NIH.

Innovative Funding Mechanisms

Following the recent completion of a very successful high-risk/high-payoff grant program in PD by several NIH Institutes in collaboration with a number of private research organizations, there is renewed interest in the scientific community in these types of small, innovative grants. Many areas might benefit from this type of program – and Consortium participants suggested a solicitation on biomarkers, and a general solicitation for innovative approaches to PD research as possible mechanisms to pursue.

Public-private Partnerships

As described above, the recent grant program on PD that was successfully co-funded by NIH and private research agencies serves as a model for productive collaboration between these groups. Additional opportunities for co-funding proposals may present themselves in the future. However, Consortium participants also identified several other ways in which private advocacy groups can help the NIH implement the PD Agenda, including:

- Helping to inform the PD community about ongoing clinical trials, which will aid in participant recruitment
- Participating in discussions about informed consent, and other ethics issues
- Helping NIH improve its educational outreach to PD groups (via the NINDS Parkinson's Disease Research Web)
- Continuing to engage in dialogue with the research community and NIH about areas of research interest to individuals with PD

Intellectual Property and Data Sharing

The subject of intellectual property (IP) and sharing of data also cuts across many research areas. Consortium attendees expressed concerns about IP restrictions in both gene therapy and stem cell research. With gene therapy, the concerns focused on the availability of vectors and other reagents, as universities seek to restrict use of gene therapy tools such that patents and licensing agreements can be protected. One suggestion was to require investigators to contribute resources to a central repository, such as the National Gene Vector Laboratories. Model development is also subject to resource sharing issues, and participants questioned the enforcement of sharing obligations that are required of NIH grantees. To respond to this issue, NIH hopes to improve the sharing of models among PD

researchers through the development of an NINDS web resource, and NIH staff will continue to engage in discussions about how sharing can be encouraged though specific language in grant awards. The Office of Technology Transfer at NIH is already engaged in many broad IP issues, however they can be more actively engaged in issues relevant to PD as these needs arise.

Research Centers of Excellence

NIH has provided several years of support for the eleven Morris K. Udall Centers for Excellence for Parkinson's Disease Research, and although the success of these centers was acknowledged by the participants, several suggestions were made about needs for future centers. Some of these needs might be incorporated into future solicitations for Udall Centers, while other needs might require additional approaches:

Inclusion of outside participants in the Udall Center meetings. NIH indicated at the Consortium meeting that the first three Udall Center meetings were limited to researchers from these Centers in order to allow the Udall researchers to develop a feeling of mutual trust – which was designed to enhance the sharing of data that would otherwise not have been publicly available. Some participants at the Consortium meeting expressed a desire to include researchers from outside the Udall Centers in future meetings, and it was agreed that this suggestion would be considered for the next Udall gathering.

Expand opportunities for new/junior investigators at Udall Center meetings. Although previous Udall center meetings have included poster sessions, with the hope that this forum would benefit junior investigators, more such opportunities are needed. Greater inclusion of these investigators, perhaps through breakout sessions, was encouraged.

Better integration of basic and clinical research at centers of excellence. This point was raised in reference to the Udall Centers, which in many but not all cases have optimized both their basic and clinical research efforts. NIH staff will evaluate the balance at these Centers as they identify grant mechanisms for continuing their support.

Inclusion of translational research at centers. This point was raised in the context of translational research, however Udall centers could also respond to this suggestion. Participants felt that opportunities for moving research from the lab to the clinic could be facilitated if specific support were given to centers either located within a single institution, or "virtual" centers that would offer researchers at

multiple institutions an opportunity to collaborate on a central translational project in PD research. Such support would allow the development of true "comprehensive centers" that would have all elements (from bench to bedside) included in a tightly integrated program that would greatly facilitate translation of basic research findings to the clinic, and clinical findings back to the laboratory for investigation.

Scientific and Budget Priorities

Given the focus of the Consortium attendees on the scientific opportunities available to the PD research community, it would be appropriate to consider the top scientific needs and opportunities identified by Consortium participants as guidelines for future expenditures in PD research. These needs were identified independently by participants in both breakout sessions at the Consortium meeting, and include:

- Facilitating translational approaches to PD research – NIH was encouraged to support approaches to the study of PD that help move research findings from basic science research into clinical trials. Translational research studies are often not hypothesis-driven, and may involve several different questions that do not easily fall into the framework of a typical investigator-initiated grant. Thus, consideration of these differences by NIH in the review process is one possible goal for the immediate future. Further, researchers should consider that translational research is often a two-way street, and clinicians should have the opportunity to suggest basic science approaches based on clinical observations in the same way that basic scientists propose clinical studies that are based on their findings in the laboratory. NIH could facilitate this exchange as much as possible within the scientific community, including the development of real or "virtual" centers of translational research.

- Increasing our understanding of how PD affects the dopamine systems of the brain – Even with the identification of genetic mutations and external factors that may lead to degeneration of dopamine neurons, we still do not understand the mechanisms underlying the selective vulnerability of these cells. How do gene mutations alter processes inside the cell? What mechanisms exist to protect cells? A better understanding of how the dopaminergic system breaks down in PD should provide multiple options for developing therapies.

- Broadening studies of the effects of PD on cells and circuits outside of the dopamine systems – Attention has already been given to the normal function of

the dopamine circuits in the brain, including the substantia nigra and related structures. It will be important for the NIH to devote a comparable level of effort in the future to understanding how cells other than those in the dopaminergic systems respond to both the effects of Parkinson's disease, and the to the treatments that are currently used. Non-motor symptoms are among the most debilitating effects of PD, and additional studies designed to understand the biological mechanisms of these effects, and to treat them effectively, are needed. Importantly, data from both types of studies may lead to immediate improvements in the way individuals with PD are currently treated.

- Improving biomarkers and assessment tools – Healthcare practitioners are in great need of imaging and screening tools to help identify individuals at risk for PD, to provide accurate staging information for those with the disease, and to assess outcomes for individuals as they embark on different forms of therapy. Biomarkers based on the mechanisms of disease would be particularly helpful. Participants agreed that large-scale studies would assist in developing these tools, but some of these studies – particularly those involving healthy participants - raise important ethical concerns. A more reasonable, and cost-effective strategy could involve the collaboration of research centers that are already following aging or at-risk populations, along with a separate grant solicitation for the development of biomarkers.

- Supporting the necessary preclinical studies of gene therapy and facilitating translation into clinical trials – The field of gene therapy is moving steadily toward clinical trials, although many researchers agree that substantial preclinical studies of vector safety, tolerability, and efficacy are necessary before clinical trials can be considered. NIH support of these studies could ensure that clinical trials can be initiated at a time when appropriate levels of preclinical data are available.

- Supporting improvements in models for PD in invertebrates, small mammals and non-human primates – Model development was identified as a critical area for continued NIH investment. Fruit flies, and other invertebrates, can contribute valuable information about the genetics of PD, while small animal and non-human primate models offer unique advantages for studying different aspects of the human disorder. In particular, new models need be developed that will help researchers understand and identify treatments for dyskinesias, and non-motor complications of PD.

In addition to the six goals described above, many other important issues were raised in the individual breakout sessions. These recommendations were highlighted within the body of this report, and will also be considered as high priorities of NIH as it plans its programs in PD research.

Conclusions

From the perspective of the NIH, and by all accounts from the scientific and advocacy participants, the January 2002 Consortium meeting was a success. Participants engaged in highly specific discussions about the successes of the original Agenda, and about emerging and existing areas of research that will require more attention. Although researchers will never come to a complete consensus on what they feel are the most important areas of science to pursue, it was striking at this meeting how common themes clearly emerged from the participants in the two breakout sessions. This clarity will enable NIH to move forward, in the remaining years of the Agenda and beyond, to allocate its resources in PD to the most pressing questions identified by the research community.

As the implementation of the PD Agenda continues, NIH will continue to hold regular meetings of both the Parkinson's Disease Implementation Committee and the Parkinson's Disease Coordinating Committee, to foster additional discussion. New research priorities may emerge from these meetings, and from the anticipated Consortium meetings on deep brain stimulation, gene therapy, gene-environment interactions in PD, and drug screening in neurodegenerative assays, as well as upcoming meetings of the Udall Center investigators. All of these meetings will include both junior and senior investigators, and will involve a wide range of researchers from many different disciplines. These recurring, relatively broad-based meetings will also be complemented by many other workshops and scientific events convened by the NIH on specific topics identified in the original Agenda. With so many forums for discussion planned and projects and program activities underway, NIH expects that the implementation of the PD Research Agenda will continue on an aggressive and positive course.

APPENDIX

PARKINSON'S DISEASE RESEARCH AT THE NATIONAL INSTITUTES OF HEALTH: Update on Agenda Implementation

Background and Current Status

In FY2000, Congressional report language directed the National Institutes of Health (NIH) to develop a Parkinson's disease (PD) research agenda for the subsequent five years, including professional judgment funding projections. This language states:

> "NIH is expected to consult closely with the research community, clinicians, patient advocates, and the Congress regarding Parkinson's research and fulfillment of the goals of the Morris K. Udall Parkinson's Research Act. NIH is requested to develop a report to Congress by March 1, 2000 outlining a research agenda for Parkinson's focused research for the next five years, along with professional judgment funding projections. The NIH Director should be prepared to discuss Parkinson's focused research planning and implementation for fiscal year 2000 and fiscal year 2001." (Conference Report No. 106-479, page 607.)

As requested, NIH developed a comprehensive Agenda, with input from leading researchers in the field, and several PD advocacy groups. This Agenda included professional budget estimates, based on feedback from the extramural community as to the level of meritorious research addressing Agenda issues that could be supported if completely unlimited funds were available. These estimates were made without taking into consideration either the anticipated or actual level of appropriations, or competing scientific priorities in other disease areas. The Agenda itself provided a framework for NIH to use in planning its Parkinson's programs, and to identify areas of research that necessitate greater financial support.

For many years, NIH placed considerable emphasis on the study of PD. In fact, one of the most significant investments made by NIH in this area of research was the funding of eleven centers dedicated to the study of PD. This program was initiated in response to a 1997 Senate authorization, with NINDS funding a total of eleven Morris K. Udall Centers of Excellence for Parkinson's Disease Research. These Centers serve as the centerpiece to the Institute's ongoing efforts in PD, as their work impacts every major area of research highlighted in the PD Agenda. Their research is designed to improve diagnosis and treatment of patients with PD and related neurodegenerative disorders, and to gain a better understanding of the fundamental cause(s) of the disease. The Centers have also been successful in serving as a model for centers to establish research collaborations, while carrying out their own independent research programs.

General areas of each Center's interests are described below.

Brigham and Women's Hospital Center for Neurological Diseases in Boston: Evaluation of structure and function of PD proteins; development of animal models of PD; screening of potential therapies.

Neurological Institute at Columbia University: Cell death mechanisms in animal models and cell culture; genes that regulate degeneration; imaging studies; gender and ethnic differences in people with PD.

University of Virginia: Mitochondrial mutations in PD, including the role of mitochondria in cell death, oxidative stress, and other changes in PD.

Mayo Clinic in Jacksonville, Florida: Genetics of PD, including cloning of disease genes and studies of families with hereditary PD; development of animal models of PD.

University of Kentucky: Behavioral, functional, and anatomical effects of growth factors in PD, including effects of stopping and starting growth factor therapy.

Duke University: Genetics of PD, including studies of families with inherited PD.

University of California at Los Angeles: Brain circuitry involved in PD; effects of PD therapies on animal models of the disease, and comparison to human postmortem tissue.

Harvard University Medical School and McLean Hospital in Belmont, Massachusetts: Novel treatments for PD in animal models, including neuroprotective agents, and cell/tissue implantation.

The Johns Hopkins University School of Medicine: Mechanisms of neuronal injury and protection in cellular and animal models of PD; gene expression in brain regions affected by PD.

Massachusetts General Hospital/MIT: Relationship of proteins linked to movement dysfunction; genetics of movement disorders.

Emory University in Atlanta, Georgia: Animal models of PD; cellular studies of neurodegeneration; neuronal circuitry in PD and surgical approaches to treatment.

The Udall Centers have made, and continue to make some of the most significant discoveries in the field of PD research. They have also participated in exchanges of preliminary and unpublished data with one another, most recently at the Third Annual Udall Centers meeting (held in August, 2001), where sharing of information was the theme of the discussions. All eleven Principal Investigators presented data, contributed to the discussion, and participated in three breakout sessions on high-throughput drug screening, resource sharing, and gene discovery – all focused on the sharing of information and the coordination of research activities.

In addition to the investments in the Udall Centers, recent scientific discoveries – some made by Udall Center researchers – also help to illustrate how far this research has come in the past decade. A few of these developments are described below:

- In 1995, a collaboration facilitated by the National Institute of Neurological Disorders and Stroke (NINDS) between intramural researchers at the National Human Genome Research Institute (NHGRI) and extramural researchers in New Jersey, Italy, and Greece led to the initial discovery that genetic mutations could play a role in PD. This finding linked the protein alpha-synuclein with familial forms of Parkinson's, and literally paved the way for the tremendous progress that has been made in understanding the role of genes in this disorder. Recent NINDS-funded work that has built on this earlier discovery indicates that the nerve cell damage caused by accumulation of alpha-synuclein may be enhanced by mutations in other Parkinson's-related genes. Since the discovery of alpha-synuclein, seven more genes of major impact in PD have been discovered, and other genes have been found to increase the risk of developing PD. This work has been pioneering, in terms of discovering the real cause of Lewy body formation in the nerve cell and cell loss, and it should reveal targets for therapeutics. Both extramural and intramural researchers continue to explore these findings.

- The motor system declines with age both in terms of muscle mass and function, and the central nervous system regulation of motor function declines as well. In a 1996 community-based study supported by the National Institute on Aging (NIA), several components of motor function that characterize both PD and normal aging of the nervous system were found to be associated with a twofold increase in risk of death. Understanding the differences (and relationship) between normal aging of the motor system and PD will be important to the development of new therapeutic approaches, such as surgery,

and neurotrophic factor or other drug treatment.

- In 1999, National Institute of Environmental Health Sciences (NIEHS)-supported researchers examined groups of people occupationally exposed to heavy metals and found that exposures to combinations, rather than single compounds, were associated with increased risk of developing PD. A recent report in the literature that certain heavy metals may directly accelerate alpha synuclein fibrillation leading to aggregation provides a possible link between the epidemiological findings of increased risk of PD from occupational exposure to heavy metals and the cellular events implicated in PD.

- In 2000, NINDS-funded researchers demonstrated that the application of specific growth factors to the nervous system through the use of gene therapy can reverse the behavioral changes and neuronal degeneration observed in a primate model of PD.

- Numerous recent findings in the field of stem cell research have strongly suggested that some types of animal stem cells may be useful in replacing damaged neurons in a wide variety of neurological disorders, including PD.

- In 2000, intramural researchers at NINDS demonstrated that individuals with PD exhibit a reduction in the number of norepinephrine-producing nerve endings in the heart. These findings suggest a more widespread effect of PD on the nervous system than was previously thought, and may help researchers to diagnose and treat the orthostatic hypotension (a drop in blood pressure upon standing) that often accompanies the disorder.

- In 2000 and 2001, a number of significant discoveries have been made that link environmental agents to PD on both a macro and a micro scale. In 2000, NINDS and NIA-funded researchers demonstrated that administration of the pesticide rotenone to rats leads to the development of anatomic and behavioral changes that mimic those seen in PD. The similarities of this model to the human illness suggest that it will be of tremendous value to PD researchers. Two more recent studies supported by NIEHS have compared the cellular effects of agricultural compounds to the effects of PD on cells. In one study, the compound paraquat was shown to alter the formation of alpha synuclein fibrils, producing a dramatic acceleration in the rate of fibrillation. Administration of paraquat to mice produced an increase of alpha synuclein and changes inside the neurons that reflected alpha synuclein fibrillation.

Another NIEHS-funded study found that a mix of paraquat and maneb in mice decreased motor activity, increased dopamine turnover, and reduced other measures of dopamine effects at levels far greater than when the same chemicals were administered singly. Both the data from single agent exposures, and combined exposures that may more accurately simulate "real-world" applications, provide strong support for an environmental link to this disorder.

- In 2001, a group of researchers funded by NINDS, the National Institute of Mental Health (NIMH), and the National Institute on Drug Abuse (NIDA), developed a mouse model of PD by altering a neurotransmitter receptor that is activated by the chemical nicotine. This manipulation led to degenerative changes in neurons similar to those seen in the human disorder.

- Two recent studies supported by NIA have examined the relationship between normal aging of the brain and the development of PD. Research in rodents has shown that growth factors protective in neurotoxin models of Parkinson's can have a similar beneficial effect in animals that have undergone normal aging, although this effect diminishes in the oldest groups of animals. Studies in primates have used novel imaging techniques to map age-related responses to dopamine stimulation in areas of the brain implicated in PD. Results from these studies have contributed to our understanding of the circuits of the aging brain that may be responsible for specific motor features of aging that are similar to features of Parkinson's.

- A recent study supported by NINDS has provided important insights into the pathological processes that lead to the degeneration of neurons in PD. This work tested a key hypothesis in this field of research: that the alpha synuclein fibrils which accumulate in the brains of individuals with PD are the cause of the neuronal destruction. It involved the screening of a number of drugs to detect effects on the formation of protofibrils, an intermediate structure in the process, or on the conversion of protofibrils to fibrils. Surprisingly, the researchers found that both dopamine and L-dopa seemed to stabilize the protofibrillar form of alpha synuclein, in a way that could promote the development of PD. This finding may not only help researchers design more effective treatments for PD, but it may also help them to understand why long term dopamine therapy can cause severe side effects.

These highlights illustrate how far this research has come in the past decade, and confirm that the NIH investments were made in important areas of PD research.

It is also important to acknowledge that numerous significant findings in other fields have also contributed to our understanding of PD, and in fact, every promising treatment now being considered for PD has had its origins in very basic research. This includes new drug therapies, deep brain stimulation, gene therapy, growth and trophic factors, and cell replacement therapies. Two recent examples of how basic research, and research unrelated to Parkinson's, have contributed to the study of PD are illustrated below:

- Long-time NIH grantee Dr. Paul Greengard, along with fellow NIH grantee Dr. Eric Kandel, and Dr. Arvid Carlsson, were awarded the 2000 Nobel Prize in Physiology or Medicine for their discoveries in signal transduction in the nervous system. Dr. Greengard's work, which found that dopamine and a number of other transmitters can alter the functional state of neuronal proteins, made a significant impact on our understanding of how neurons signal one another in both the short and long term. He also found that such changes could be reversed by subsequent environmental signals. Along with the contributions of Dr. Carlsson, this work advanced our understanding of the brain's dopaminergic system, and diseases of that system, such as Parkinson's. Their discovery of multifunctional signaling molecules in dopaminergic neurons raises the prospect developing of new drug therapies.

- Dr. Stanley Prusiner, a 1997 Nobel Prize winner and recipient of numerous NIH grants, has recently demonstrated that cell culture models of neurological disease can be used effectively to generate candidate compounds for evaluation in clinical trials. In an August 2001 publication, Dr. Prusiner and his colleagues described the results from a screening study, using scrapie-infected cells as a model for human prion diseases (such as "mad cow disease"). In this study, two drugs – quinacrine and chlorpromazine – with a history of clinical use, were identified for their ability to inhibit the formation of abnormal prions. Because these drugs had previously been used in the clinical setting, the discovery that they might be used to treat prion diseases provided two immediate candidates for clinical trials. This work establishes the "proof of principle" for the type of work NINDS is supporting in neurodegenerative diseases, such as Parkinson's. An ongoing NINDS supplement program, which will be discussed in detail below, is using the same approach to identify candidate therapies for neurodegenerative disorders.

These two examples illustrate how many areas of research can contribute to

progress in Parkinson's. NIH continues this investment today through the support of hundreds of individual and collaborative research projects, some that are directly relevant to Parkinson's, and others that are more basic in nature. Although the scope of these awards is too broad to discuss in this background document, information on the current NIH PD grant portfolio will be discussed at the January meeting. The purpose of this overview is to highlight the NIH efforts to enhance and expand its ongoing support of PD research, as outlined in the PD Research Agenda. Not all areas of the Agenda have been targeted with specific solicitations in the first 18 months of the Agenda, however other areas, such as "Non-motor Complications of Parkinson's Disease" have been added. The solicitations, contracts, and workshops described below should be evaluated along with the existing grant portfolio to determine where additional efforts needed.

MECHANISMS USED TO IMPLEMENT THE AGENDA

NIH has multiple means at its disposal of stimulating research in specific disease areas, or in research areas that span multiple disorders. One of the central roles of NIH program staff is to establish open lines of communication with researchers in specific fields. This involves personal communications, and discussions with researchers at scientific meetings and site visits. Another mechanism that NIH often uses to stimulate interest in a particular research topic is the sponsorship of conferences. Some conferences are planned by the research community, and NIH helps to sponsor these meetings by awarding grants to the conference organizers. Other conferences and workshops are initiated by NIH staff, based on a recognized need in the research community. Several extremely productive workshops on issues of interest to PD researchers have been organized by the NIH since the Agenda was released, and are described in more detail below.

Through these channels, staff can educate researchers about each Institute's priorities, and researchers can obtain assistance in navigating through the grant system. It is a mutually beneficial relationship, and one that has served and will continue to serve as the most basic means for stimulating research in areas of interest. However, in some areas of research, further encouragement and support by the NIH is often helpful to enhance the submission of grant applications. In these cases, NIH can utilize several methods to solicit grants in areas of high priority to individual Institutes or groups of Institutes:

Program announcements (PAs) are used to announce an Institute's or multiple Institutes' interest in building or enhancing their research program in a particular

area. The PA typically is an ongoing solicitation, encouraging applications for multiple receipt dates, for up to three years. The PA specifies the scope and objectives of the research of interest, application requirements and procedures, and review criteria to be applied. Funds may or may not be specifically set aside to support applications submitted in response to PAs.

Requests for Applications (RFAs) are solicitations for grant applications addressing a defined research topic. Each RFA specifies the scope and objectives of the research to be proposed, application requirements and procedures, and the review criteria to be applied in the evaluation of applications submitted in response to the RFA. Specific levels of funds are typically set aside by an Institute to support proposals submitted in response to an RFA, and the levels of individual grants are usually comparable to those of unsolicited awards approved during the same fiscal year.

Contracts are be used for all acquisition, i.e., when NIH intends primarily to obtain goods, services, research studies, surveys, systems, or property for the direct benefit or use of NIH or other Government agencies; these agencies may, in turn, intend to provide the end-products or results to non-Government parities, including the general public.

Notices are announcements published in the NIH Guide that provide policy or other information relevant to funding. The availability of supplemental funding for current grantees is sometimes announced through a notice. Grant supplements are smaller, more flexible awards, that enhance research in labs already supported by NIH, and they can serve to expand a laboratory's scope of interest and bring new investigators into the field.

ORGANIZATION, TRACKING, AND MONITORING OF IMPLEMENTATION

Parkinson's Disease Coordinating Committee

The NIH Parkinson's Disease Coordinating Committee (PDCC) spearheaded the development of the PD 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 PD, including NIA, NIMH, NIEHS, 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 is a multifaceted disease, and each of these Institutes brings a valuable perspective to confronting the biological complexities of the disorder, to pursuing the diverse therapeutic strategies showing promise, and to providing the resources necessary to carry out a research agenda of this breadth.

Parkinson's Disease Implementation Committee

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, makes suggestions on implementation, and considers 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 has held three meetings since the inception of the Agenda, in July 2000, November 2000, and March 2001. The agenda for these meetings has included discussions of the upcoming neuroprotection trial, the initiative to screen FDA-approved drugs, recent workshops, and user testing of a prototype of the NINDS PD website.

Parkinson's Disease Research Web

NINDS has also developed a website that will help the public and NIH staff track progress of the Agenda. Designed by Institute Staff with input from both extramural scientists and advocacy representatives and released in May 2001, the site tracks agenda activities, provides information on funded research projects, solicitations for new research, and resources for scientists, people with PD, 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 PD, patient caregiver information, links to Parkinson's advocacy groups, and a tool for automatically searching the National Library of Medicine's database of published research for the latest findings in specific areas of PD research. NINDS staff anticipate that the Parkinson's Web will both assist in the rapid dissemination of Parkinson's information and facilitate research.

Progress in Agenda Implementation

UNDERSTANDING PARKINSON'S DISEASE

Using Genetics to Understand Parkinson's Disease

Grant Solicitations

"Role of Parkin and Related Proteins in Parkinson's Disease" (April 2000, NINDS) - This RFA was specifically targeted to encourage applications on the role of the protein parkin in the development of PD. Five applications have been funded in response to this solicitation, for a total of $1.3 million.

"Gene Discovery for Neurological and Neurobehavioral Disorders" (March 2001, NINDS, NIA, NIMH) The goal of this RFA was to accelerate the identification of genes that cause or contribute to the development of neurological diseases, in particular disorders such as PD that are probably influenced by a complex array of genes along with environmental factors. Grant applications received in response to this solicitation are currently under review. The participating Institutes expect to commit approximately $4 million to this solicitation, and anticipate that 10-14 new grants will be funded.

An administrative supplement was awarded by NINDS to accelerate the study of PD in genetically isolated populations, and in racial minority and ethnic groups

Contracts

During the last decade, many genes that cause single-gene Parkinsonism have been identified. For most cases of PD, however, complex genetics play a role, and discovering the genetic risk factors in these diseases requires a large sample and a clinical database. To facilitate this, sharing of biological samples and subject information is critical. The "DNA Repository for Human Genetics" contract (funded by NINDS) will support the development of a repository of data, cell lines, and DNA samples, for the study of the genetic factors contributing to neurological diseases. This repository will allow sharing of resources, thus encouraging work by junior investigators, investigators with novel approaches, and others not included in current collaborations, without excluding those who are established in their fields. The mission of this NINDS Repository is to develop a sample resource that can be shared by the research community, while protecting the rights of subjects, in order to expedite discoveries into the causes and treatments of neurological diseases. Although the repository will not be limited to the study of PD, PD will be one of the diseases to be included in the "ground floor" development of this resource.

Meetings and Workshops

In July 2001, NIA and NINDS co-sponsored a small meeting entitled "Synuclein and Cortical Lewy Bodies Associated with Dementia in AD, LBD, and PD," which brought together investigators from several different areas of neurodegeneration research. Researchers are continually identifying pathways and mechanisms common to many neurodegenerative disorders; for this reason, it is critical to foster communications between individuals who may ultimately be working on similar cellular processes in different disease models. Exciting new data were presented for discussion at this meeting, and at the urging of the attendees, it will reconvene in the fall of next year.

Intramural Research

NHGRI has been actively involved in studying the genetics of PD for several years. Collaborations with researchers in New Jersey and Italy led to the discovery that mutations in alpha synuclein could cause familial PD. Further studies carried out at NHGRI revealed that alpha synuclein was a major component of Lewy body plaques seen in the brains of many individuals with Parkinson's. Fewer than a half dozen papers had been written on alpha-synuclein before this discovery and now there are well over 500 publications exploring this protein's role in PD.

After discovering the importance of this protein in the development of PD, researchers began to examine the function of alpha synuclein. A great deal of effort at NHGRI has focused on the creation of a genetic mouse model of PD, as this would offer exciting new ways to study PD in terms of both etiology and treatment. In this model, the alpha synuclein gene is removed and replaced with a mutated form of the human gene. In one case a mouse homozygous for the human mutation appeared to have "Lewy body-like lesions" in a brain region affected by Parkinson's but there was no clinical phenotype consistent with PD. Thus, research is continuing toward this goal.

The function of proteins that are important in the development of PD is also being explored intramurally through comparisons of normal mice and mice with mutations engineered in genes that may contribute to PD. In addition, studies that evaluate the contribution of protein modifications, protein-protein interactions, and factors that can affect the expression of proteins are also underway.

In other projects, NHGRI continues to enroll families in its protocols in order to identify other mutations in existing genes or attempt to identify other genes that may cause inherited PD. As some families do not have a sufficient number of individuals to include in linkage studies, NHGRI has collaborated with researchers from NINDS, NIMH and the NIH Clinical Center to perform PET scans on certain family members. It is hoped that individuals with equivocal signs of the condition will be classified based on the results of these tests, and can be appropriately included in the linkage studies.

In addition, intramural researchers at NINDS are currently collaborating with NIA in gene discovery efforts in PD. These studies are focused on the contribution of known genes to PD in different ethnic populations. In addition, these investigators are working towards discovering genetic risk factors of common influence in the general population.

Risk Factors for Parkinson's Disease, including Environmental Factors

Grant Solicitations

"Collaborative Centers for Parkinson's Disease Environmental Research," (December 2001, NIEHS) The purpose of this RFA is to more fully explore and accelerate research on the role of gene-environment interactions in the development of PD through the creation of the Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) Consortium Program. The individual Centers funded under this program will be required to foster multidisciplinary research approaches to elucidate gene-environment interactions in PD by augmenting and enhancing already funded research projects in this area and infusing them with new projects and technologies. The NIEHS CCPDER Consortium Program will consist of a highly interactive national network formed from the individual CCPDERs that will function to share data and resources, engage in the planning and conduct of collaborative studies to understand the joint contribution of genes and environment in the etiology of PD and, most importantly, to translate the findings into the public health arena.

Meetings and Workshops

"Parkinson's Disease Epidemiology Workshop," (September, 2000, NIEHS) In September 2000 over a dozen epidemiologists who were currently conducting population studies of PD came together at NIEHS to discuss methods and

scientific results focusing on environmental exposures and the risk of PD. Similarities and differences in cohort, case-control and clinical studies of PD, funded by NIEHS and NINDS, were compared as the investigators discussed issues related to exposure assessment, case definitions and clinical symptomatology, and genetics. Current studies are being conducted in populations across the country, and include an analysis of numerous risk factors. Genetic studies have focused on gene discovery for major PD genes and susceptibility genes which may increase one's risk of developing disease after specific environmental exposures.
In April 2001 these investigators met again with toxicologists to discuss laboratory and epidemiologic research that focused specifically on pesticides as a possible risk factor for PD. Novel animal model systems have been developed in which rodents dosed with high levels of pesticides have developed parkinsonian symptoms. The expert scientists discussed the possible mechanisms of these effects in animals and humans. Sessions on exposure assessment of pesticides in human populations were especially informative, cataloguing the difficulties with this type of research, and providing valuable instructions to the epidemiologists interested in considering the effects of these types of exposures in their ongoing studies.

"The Role of the Environment in Parkinson's Disease" (March 2001, NIEHS) This symposium, sponsored by NIEHS at the Society of Toxicology meeting in San Francisco, involved reports from four researchers on their findings from both animal and human-based studies. There is provocative evidence that environmental exposures to certain chemicals such as pesticides and fungicides may play a role in the development of PD. This symposium cited work that described mechanisms by which these exposures could affect the brain systems involved in PD and how subtle genetic differences can also contribute to the development of the disease.

NIEHS was a major sponsor of the "19th International Neurotoxicology Conference: Parkinson's Disease, Environment and Genes" (August 2001, co-sponsored by NINDS). This meeting brought together internationally known scientists in the field of PD. Clinicians, epidemiologists and basic researchers described their research and collectively identified research gaps that would be most fruitful to pursue.

"NIEHS Brainstorming Session on Parkinson's Disease" (August 2001) in conjunction with the 19th International Neurotoxicology Meeting. The NIEHS convened this brainstorming session to seek the advice of experts in the field of

PD regarding the most promising research opportunities that could benefit from a multidisciplinary collaborative research program. A number of areas were identified, including fundamental cellular mechanisms of the disease, promising animal models, biomarker development and identification of specific environmental factors that may trigger or protect in PD.

Life and Death of Neurons involved in Parkinson's Disease

Grant Solicitations

"Function of Synaptic Proteins in Synaptic Loss and Neurodegeneration" (March 2000, NINDS) This RFA was designed to encourage applications that would examine the involvement of synaptic proteins - molecules like synuclein, that are localized to the connection points between neurons - in the disease-related degeneration of these cells. PD is one of several disorders that will benefit from the research funded by this program. Five grants have been funded in response to this RFA, for a total of approximately $1.47 million.

"Mitochondrial Function and Neurodegeneration" (March 2000, NINDS, NIEHS) - The cellular energy centers called mitochondria have long been implicated in neurodegenerative disorders, including PD. This RFA, released in March of 2000, was developed to encourage investigators to submit applications that would explore this area further. Six grants have been funded in response to this solicitation, for a total of $1.5 million.

Because the applications received in response to these two RFAs were of such high merit, NIH increased the set-asides by 50% from the original levels of $1 million each.

Meetings and Workshops

NINDS supported a teaching workshop on the neurobiology of Parkinson's disease at the Society for Neuroscience meeting in November of 2000. This workshop attracted 175 participants at this meeting, the largest annual gathering of researchers in the neuroscience community.

Non-motor Complications of Parkinson's Disease

Meetings and Workshops

NINDS, along with NIA and NIMH, held a "Cognitive and Emotional Aspects of Parkinson's Disease" workshop in January of 2001. This meeting brought together a working group of researchers in order to identify unmet scientific needs in the study of the cognitive and emotional effects of PD. Participants engaged in discussions on a wide range of issues, including: circuitry, epidemiology, assessment, treatment strategies, potential clinical trials, and innovative research approaches to this area of research. In addition to the scientific presentations, the meeting also featured two extensive breakout sessions that provided ample opportunity for discussion and planning, which resulted in a number of specific recommendations from the participants.

In March 2001, NIMH held an open mental health forum, entitled "Depression: The Unwanted Cotraveler - A Day for the Public." Designed to capture public interest and input, the meeting provided an opportunity for mental health advocates and the public to contribute to the NIMH planning efforts in several different mental health disorders, including PD. PD advocates presented their views of the difficulty involved in treating depression as a comorbid symptom of the disease. Although depression can be a frequent side effect of Parkinson's, other effects of Parkinson's on facial expressions and posture can lead to an erroneous diagnosis of depression. An additional breakout session on Parkinson's Disease and other Neurological Disorders offered a more extensive opportunity for discussion and planning, with a number of recommendations developed by the attendees.

Intramural Research

Intramural neuro-cardiology researchers at NINDS are currently conducting studies to expand on their finding that sympathetic nerve terminals in the heart are lost in individuals with PD, to determine if this loss is restricted to the heart or if it also affects other organs of the body. The researchers also hope to determine why dopamine- and norepinephrine-producing nerve terminals in the heart and in only a particular part of the brain are lost in PD. One theory they are evaluating is that a toxic breakdown product builds up in dopamine- and norepinephrine-producing nerves due to lack of a necessary enzyme in those nerves. This information contributes to our understanding of the systemic effects of Parkinson's, and may help in identifying therapeutic approaches for complications of Parkinson's such as orthostatic hypotension.

Other Activities

Grant Solicitations

"Self-Management Strategies Across Chronic Diseases" (June 2000, NINR, NHLBI, NIA, NIAMS, NICHD, NIDDK, NIMH, NINDS) The purpose of this PA is to solicit applications to expand research on established self-management interventions to multiple chronic diseases, such as PD, across the life-course. Many interventions aimed at chronic disease self-management are well-described in the literature, but are often presented as specific to a particular chronic disease. This PA encourages applicants to investigate the applicability of effective self-management interventions to a broader spectrum of chronic diseases. Chronic disease, for this announcement, is defined as illnesses that are prolonged, are rarely cured completely, and require self-management behaviors by affected individuals and/or their caretakers.

DEVELOPING NEW TREATMENTS FOR PARKINSON'S DISEASE

Pharmacological Approaches

Grant Solicitations

"Parkinson's Disease Neuroprotection Trial - Coordinating And Statistical Centers," (March 2001, NINDS) and "Parkinson's Disease Neuroprotection Trial - Clinical Centers," (July 2001, NINDS) NINDS has recently released these two RFAs to solicit applications for a coordinating center, a statistical center, and numerous clinical centers to participate in a large, randomized, double-blind trial of potential neuroprotective agents in individuals who are in the early stages of PD. This collaborative research effort will enable several potentially therapeutic compounds to be evaluated during the trial, and it will permit several thousand patients to be involved in the study. The coordinating and statistical centers were recently selected, and approximately $1.47 million have been committed from FY01 funds to develop the infrastructure for this trial. Applications for the participating clinical centers are currently under review.

"NINDS Administrative Supplements: FDA-approved Compound Screens for

Neurodegeneration," (May 2001, NINDS) These administrative supplements were provided to help laboratories screen for drugs already approved by the FDA, in a variety of neurodegeneration assays. The goal is to identify drug compounds with clinical promise. Twenty-seven supplements have been funded through a $1 million NINDS set-aside and an additional $450,000 in funds from several private funding organizations. In addition, this screening consortium includes NINDS intramural researchers. Initial results from the screening are expected in the spring of 2002, and the more than 30 investigators participating in this program will meet as a Consortium at that time to evaluate their collective results and identify candidates for clinical trials.

"Neurodegeneration Disease Assays for High Throughput Drug Screening and Chemical Genetics," (December, 2001, NINDS) The goal of this RFA is to encourage the development of in vitro assays for high throughput drug screening. High throughput screening is a new approach for PD research, using powerful techniques developed in industry to identify candidate drugs. This approach will also provide novel research tools to identify disease mechanisms through a process known as chemical genetics. This program has a set aside of $1.5 million for R21 awards specifically focused on assay development. Assays developed under this program may be screened at the NINDS High Throughput Drug Screening Facility, which will be established via an NINDS contract in 2002.

Contracts

The "High Throughput Drug Screening Facility for Neurodegenerative Disease" (October 2001, NINDS) contract will improve the access of academic researchers to the same type of high-throughput screening assays that are currently being used in industry to accelerate drug development. The cellular changes that occur in PD will likely be reproduced in many of these assays. The facility will screen neurodegeneration assays against many thousands of compounds to identify those that can block the disease process modeled in the assays. These compounds will serve as leads for further drug development and will also be useful research tools to help investigators understand the disease mechanisms.

Meetings and Workshops

The "Workshop on Therapeutic Opportunities in PD" (October 2000, NINDS) offered an opportunity for both researchers and Institute staff to review the current status of drug therapy, deep brain stimulation, and other therapies in treating PD. Discussions initiated at this meeting led directly to the development

of the clinical trial of neuroprotective agents described above.

Intramural Research

Intramural researchers at NINDS are engaged in the development of better-targeted and more effective medications for PD. Data collected in these laboratories suggest that the side effects of some PD medications may result from an abnormal stimulation of dopamine receptors in specific areas of the brain - first, when the disease itself damages and kills nerve cells, and later when standard dopamine-enhancing treatments activate the receptors intermittently. Adaptive changes inside nerve cells may also cause or contribute to dyskinesia, and other common side effects of PD therapy. Investigators at NINDS are exploring ways in which new therapies can be developed that do not trigger these changes. Other lines of intramural research include the evaluation of neuroprotective compounds and growth factors, as potential treatments for PD.

Deep Brain Stimulation and Other Surgical Approaches

Grant Solicitations

"Technology Development for Safe and Effective Deep Brain Stimulation" (July 2001, NINDS) Chronic activation of specific brain regions with deep brain stimulation (DBS) has shown a great deal of promise in treating movement disorders such as PD, although the field is still at an early stage. Released in July 2001, this announcement encourages research in several areas of technology that are directly related to the success of DBS as a therapy for neurological disorders. These areas include: research on electrode positioning, electrode stability and reliability, electrodes with multiple uses, improvements in stimulators, and enhancement of system safety. Applications in response to this RFA were due in November, 2001. NINDS hopes to fund approximately 2-5 new applications under this RFA, for an estimated total of $1.5 million.

"Mechanisms of Action of Deep Brain Stimulation" (July 2001, NINDS, NIMH) This complementary request for proposals was designed to encourage researchers to explore how DBS works, both in an immediate time frame, as well in the chronically-stimulated patient. Applications in response to this RFA were also due in November, 2001. Approximately 5-7 new projects, for an estimated total of $2.9 million, are expected to be funded by NINDS and NIMH under this solicitation.

DBS Consortium

Importantly, the investigators funded through both of these RFAs will become part of a DBS Consortium, which is being organized by NINDS and NIA staff to coordinate the ongoing research in this field. Annual meetings of the Consortium investigators are planned to provide them with an opportunity to share their results, plan collaborations, and contribute patient data to a central database, critical for the assessment of the efficacy of DBS. The first such meeting is being planned for Winter 2002. Other experts who are not currently funded by NIH as well as representatives from private industry will also be included in this meeting, to speak on clinical trials for PD, advances in technology for DBS, and current findings on brain circuitry.

Intramural Research

Advances in basic biological science in the past two decades have led to the discovery and development of many new molecules with therapeutic potential for PD, such as agents that prevent cell death and/or promote cell survival, and delivery systems that can introduce new genes into nerve cells. Therapies have also been developed that can selectively eliminate certain subsets of neurons associated with the abnormal activity in the neural circuit affected by PD and agents with protective or regenerative potential for PD. However, because of the blood-brain barrier, which excludes large molecules from the brain, it has been difficult to use many of the newly discovered or developed molecules successfully for treatment. NINDS intramural researchers are currently exploring techniques that can be used for the targeted delivery of either large or small therapeutic molecules to specific brain regions. This biological approach to neurosurgery would have applicability in both the treatment of PD and a variety of other disorders of the nervous system.

Other Activities

NINDS has signed a Memorandum of Understanding with the Department of Veterans Affairs (VA) to collaborate on the largest trial to date of DBS in individuals with PD. The trial will be conducted in two phases - the first to compare DBS and best medical management, and the second to evaluate the effects of DBS in two different brain locations. NINDS will provide over $7 million in support for this trial over a 4-year period, which will permit the recruitment of 150 of over 300 total participants in the trial. Because NINDS participation allows recruitment of participants through the Universities affiliated

with the six VA sites, involvement of women and minorities in this study is expected to be enhanced as a result of this collaborative effort.

Cell Implantation

Grant Solicitations

"Stem Cell Plasticity in Hematopoetic and Non-hematopoetic Tissue," (November 2000, NHLBI, NIDDK, NINDS) The objective of this RFA is to promote the thorough exploration and characterization of stem cell plasticity in hematopoietic and non-hematopoietic tissue. Studies that evaluate the ability of stem cells from non-neuronal tissues to develop along neuronal and glial lineages were identified as being of special interest.

"The Biology of Non-Human Stem Cells in the Environment of the Nervous System," (April 2001, NINDS, NIMH, NIDCD, NIA, NICHD); "Plasticity of Human Stem Cells in the Nervous System," (December 2001, NINDS, NIA, NIMH, NHLBI) The goal of these two complementary PAs is to encourage investigators to submit applications for studies on the plasticity and behavior of non-human and human stem cells, respectively, and the regulation of their replication, development and function in the nervous system.

NINDS is also planning a supplement program to enhance basic and applied research on human embryonic stem cells, and encourage investigators to join this field. In addition, a number of other grant solicitations in the area of stem cell research have been issued by the NIH, some of which may ultimately be relevant to PD.

Intramural Research

PD patients have already received cell therapy where cells of the fetal midbrain have been grafted into the striatum, and there is compelling evidence that this approach has clinical benefit. The controversy surrounding the recent clinical trial emphasizes the importance of developing new techniques for generating dopamine neurons that can be tested first in animal models of PD. It is also clear that improved access to human dopamine neurons will have significant impact on other therapeutic approaches including gene delivery and drug discovery. Stem cell research in the NINDS intramural program is based on data showing that mouse embryonic stem (ES) cells can efficiently develop into neurons with

characteristics of midbrain dopamine cells. These neurons function in an animal model of PD. These results suggest that ES cells may provide access to unlimited numbers of useful dopamine neurons. Researchers anticipate that the development of a technology based on ES cells will be rapid and have a major impact on the development of new therapies for PD.

Other Activities

NINDS has also formed a working group with the Center for Biologics Evaluation and Research branch of the Food and Drug Administration to discuss issues on stem cells, gene therapy and other biological therapies; the goal of this collaboration is to foster communications that will facilitate the translation of preclinical studies on these areas to clinical trials.

Stem Cell Policy

On August 9, 2001, the President announced his decision to allow Federal funds to be used for research on existing human embryonic stem cell lines as long as prior to his announcement (1) the derivation process (which commences with the removal of the inner cell mass from the blastocyst) had already been initiated and (2) the embryo from which the stem cell line was derived no longer had the possibility of development as a human being. The President also outlined four criteria that must be met for any cell lines to be studied with Federal funds. In order to facilitate research using human embryonic stem cells, the NIH has created a Human Embryonic Stem Cell Registry that lists the human embryonic stem cell lines -- at varying stages of development -- that meet the eligibility criteria. The Registry was opened on November 7, 2001, and grant applications may currently be submitted that propose the use of the cells listed.

NINDS has taken a special interest in grant applications related to PD that employ stem cells. A database devoted to PD stem cell grants is currently being developed to track this new portfolio of research and to effectively manage this program.

The following websites provide further information about the use of human and non-human stem cells in NIH-funded research:

Stem cell registry: http://escr.nih.gov/

Stem cell information index (NIH): http://www.nih.gov/news/stemcell/index.htm

Stem cell information page (NINDS):
http://www.ninds.nih.gov/funding/repair_and_plasticity/stem_cell_research.htm
or www.ninds.nih.gov/stemcells

Gene Therapy

Grant Solicitations

"Gene Therapy for Neurological Disorders" (July 2001, NINDS, NICHD, NIA, NIDDK, NIDCD) - At an October 2000 Gene Therapy workshop, researchers indicated the need for additional studies in several areas of gene therapy, including PD, before the field moves forward with clinical trials. The goal of this solicitation is to accelerate the translation of gene transfer technology into the clinic, and scientific, technological, and safety issues were identified as priorities in the announcement. Proposals submitted in response to this RFA were due in November, 2001. NINDS, and the other Institutes involved in this RFA, expect to commit approximately $5 million to these awards, with the hope that 8-12 projects can ultimately be funded.

Meetings and Workshops

Held in October 2000, the "Gene Therapy for Neurological Disorders" (NINDS, ORD) meeting focused on PD and lysosomal storage disorders as two conditions with clear potential to benefit from gene therapy approaches. Discussions among PD researchers at this meeting led directly to the formation of a Gene Therapy Consortium; the investigators involved have already held one meeting on their own since the October workshop, supported with a supplement from NINDS.
CREATING NEW RESEARCH CAPABILITIES

High-throughput Drug Screening

The following efforts are described in more detail under "Pharmacological Approaches":

The "High Throughput Drug Screening Facility for Neurodegenerative Disease" (October 2001, NINDS) This contract will provide a service facility for neurodegeneration researchers to screen many thousands of drugs against assays for PD and other neurodegenerative diseases.

Administrative supplements (May 2001, NINDS) have been provided to researchers to develop neurodegeneration assays and use these to test over a thousand FDA-approved compounds. In addition to identifying new candidates for neuroprotection clinical trials, this program has identified assays that can be screened at the NINDS High Throughput Drug Screening Facility.

The "Neurodegenerative Disease Assays for High Throughput Drug Screening and Chemical Genetics" RFA (December, 2001, NINDS) will encourage the design and development of new assays for future testing at the High Throughput Drug Screening Facility.

Array Technology

NINDS administrative supplements have been provided to make microarray technology more readily available to researchers. Six investigators in the field of PD research, including three Udall Center investigators, received these supplements.

Models of Parkinson's Disease

The NINDS staff is currently engaged in the development of a web resource for PD researchers. This site would permit researchers to post extensive information about animal models of PD that they are currently using in their laboratories, in order to inform other investigators and facilitate the sharing of models.
To facilitate greater discussion on developing models of PD, the NINDS Parkinson's web features a copy of the recent publication detailing the development of an animal model of Parkinson's using the pesticide rotenone (described at the beginning of report). This feature is a first-time enterprise between the NIH and the scientific journal *Nature* in presenting research articles across the web (free of charge to the public). Future articles will also be featured that are timely and found to stimulate the research field.

Brain Banks and Other Repositories

The "DNA Repository for Human Genetics" contract is described in a section above, and will help support the collection of tissues from individuals with PD,

among others.

An administrative supplement has also been awarded to a Udall Center to start a brain-banking initiative. As a follow-up, the recipient of this supplement will chair a special session on PD at an NIH-wide brain banking meeting this spring, also sponsored by NINDS.

ENHANCING THE RESEARCH PROCESS

Ethical Issues

NINDS and other ICs at the NIH are actively engaged in the analysis of ethical issues in a number of different ways, many of which have an impact on research in PD. Ethicists have been included as invited participants in NIH meetings on PD, deep brain stimulation, and gene therapy. NINDS is also funding a study on the ethics of DBS, a key area of interest in the PD community. In addition, Parkinson's researchers, as well as investigators in other disease areas, have benefited from discussions with NINDS staff as part of the new clinical trials application process at the Institute. This process enables clinical trial investigators to meet with staff prior to submission of their application, to gather feedback on their proposal, ranging from the relevance of the study to the mission of NINDS, to ethical issues such as informed consent.

Other NIH programs are focused on more broad-based ethical issues, or those that affect multiple disease areas. The following RFA is an example of this type of activity:

"Research on Research Integrity," (August 2000, re-released May 2001, Department of Health and Human Services (DHHS) Office of Research Integrity (ORI), NINDS) The integrity of research is a vital component of both the trustworthiness of the research record and of the trust that underlies public support for research. This RFA was designed to foster empirical research on the institutions, processes, and values that positively and/or negatively influence integrity in research. It is hoped that these projects will help the development of DHHS and NIH policies that will foster an appropriate level of attention to this issue. Seven grants in areas of research ranging from research integrity and data quality in clinical trials to financial conflicts of interest were awarded from the first RFA.

Innovative Funding Mechanisms

Fast-track Grant Program

"R21 Fast Track Grants for Parkinson's Disease Research" - (May 2001, NINDS, NIDCD, NIEHS, NIMH, Fox Foundation, Parkinson's Disease Foundation/National Parkinson's Foundation, Parkinson's Alliance) The goal of this RFA was to stimulate novel, innovative, or high impact approaches to the field of PD research. Funding decisions on this group of applications have been made recently, with 30 awards selected for support. NIH Institutes are planning to commit approximately $2.8 million for grants awarded under this RFA, with an additional $2.2 million provided by several private funding organizations, for a total of $5 million.

Supplement Programs

In addition to the grant solicitations described above, grant supplements have been awarded by NINDS to investigators to make progress toward a number of goals. A number of these awards, such as the awards to help investigators screen FDA-approved drug compounds, purchase DNA microarrays, and develop high-throughput assays, have already been described above. In addition to these, several other types of supplements have been awarded to investigators, for the following purposes:

- To develop and maintain a website devoted to sharing of biological reagents relevant to PD

- To permit laboratories with ongoing Parkinson's research grants to purchase equipment that will enhance their research programs

In addition to these awards, NINDS has also funded a large number of administrative supplements through a separate program, for a total of nearly $3 million. Investigators with current NINDS grants, who were interested in applying their expertise to additional Parkinson's-related questions, were eligible for these awards. Investigators in the field of PD research, and in particular, those investigators not already in the field who could expand their research to include projects relevant to PD, were encouraged to apply. A total of 53 investigators received supplements through this mechanism, and their projects ranged from the

development of vectors for gene therapy, to a study of the epidemiology of PD in China. A full list of these supplements is currently available on the NINDS Parkinson's Disease Web. At the end of the award period, a follow-up summary will also be provided on the website.

Public-private Partnerships

FY01 was a landmark year for the Agenda in terms of coordinating the efforts of NIH with the private funding and advocacy organizations who represent the PD community. As described in an earlier section, the establishment of the NINDS PD website opened up numerous possibilities for communicating progress on the Agenda to private organizations, the public, and to the research community. Moreover, a listserv has been added to the functionality of the web site by notifying users of new advances, funding opportunities, clinical trials, and research services as they become available. NINDS hopes that the use of this website will increase, making the implementation of the PD Agenda more transparent, and feedback on the site from all of its users continues to be encouraged.

NINDS has always placed significant emphasis on coordinating its activities with other NIH Institutes, government funding agencies, including the Department of Defense, VA, and private funding organizations. The collaboration with the VA on the upcoming DBS trial is an example of the NIH efforts in this area.

To keep the NIH and advocacy communities informed, PDIC and PDCC meetings have been held on a regular basis. These meetings have helped NIH to coordinate with and inform other federal agencies that support PD research, as well as the PD advocacy community, and to streamline efforts among its own Institutes.

OTHER INVESTMENTS IN PARKINSON'S DISEASE RESEARCH

Alzheimer's Disease Centers

The NIA-funded Alzheimer's Disease Centers (ADCs) are also actively involved in PD research. Several Centers have expanded their brain-banking activities to include tissue from Parkinson's patients, and have studied the Parkinsonian signs in patient populations partially supported with NIA funds. Additional research at

the ADCs is designed to improve the diagnosis of Parkinson's in these populations, and to better understand their cognitive deficits. At some level, the overlap in symptoms that is observed in individuals with Parkinson's and Alzheimer's diseases may be due in part to common molecular mechanisms in the two disorders. Researchers within the ADCs are exploring these commonalities, in the hope of understanding the underlying causes of motor dysfunction, memory impairment, and dementia.

Conclusion

Parkinson's disease is a significant burden to the health of our Nation, and NIH has long been invested in understanding this disorder and developing more effective treatments. The PD Research Agenda has helped all of the participating NIH Institutes build on the solid research foundation that was laid many years earlier. NINDS has taken the lead in these activities, moving forward with an unprecedented commitment of effort and resources. Many other NIH Institutes are aggressively pursuing specific areas of PD research that fall within their own scope of expertise. The fruits of current grant solicitations, clinical trials, and consortium development will likely be several years away. However, NIH feels confident that it is making every possible effort, given its broad responsibilities to many neurological disorders, to implement the Agenda and move the field of PD research forward with energy and determination.