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Parkinson's Disease: The Case for Novel Treatment Strategies

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Over the past 30 years, significant strides have been made toward improving symptomatic therapy of patients with Parkinson's disease. However, limitations persist, and the incremental improvement each new drug offers a patient yields only a minimal advantage therapeutically. Therefore, to alter meaningfully the natural course of this debilitating disorder, which becomes more prevalent each year in our society, significant novel therapeutic approaches must be tested. Genetic intervention in Parkinson's disease may offer an entirely different method for treating this disease in the future, based not only on symptomatic therapy, but also on neuroprotective and/or neuroregenerative therapy which would alter the natural history of relentless progression. © 1997 Academic Press

Effective symptomatic treatment of Parkinson's disease (PD) began with levodopa in the late 1960s (1). The past 30 years of clinical research in PD have led to improvements in pharmacological management and, more recently, novel therapeutic concepts such as regenerative and neuroprotective therapies. Despite the potential to slow PD progression or restore lost neuronal functions, the clinician treating PD is predominantly concerned with finding the most effective drug combination to enhance dopaminergic transmission in the brain. Dopamine replacement therapy remains a cornerstone in PD treatment, yet its limitations have become a catalyst for finding the cause of PD and more effective ways of combating its inexorable progression.

Levodopa preparations remain most effective in alleviating PD symptoms, but are frequently associated with long-term complications, such as motor fluctuations and dyskinesias (3). The wearing-off effect of levodopa usually becomes noticeable within a few years of treatment. The long-duration response is replaced by a progressively shorter duration levodopa response, and a once-smooth pattern of motor function is gradually replaced with a frustrating pattern of motor responses closely linked to the ingestion of levodopa (4). As a result, the goal of pharmacological management is to achieve satisfactory symptomatic benefit without adverse effects. The use of adjunctive medications, such as dopamine agonists, has allowed more judicious dosing of levodopa and contributed to more effective physiologic management. The use of combination drug therapy (levodopa and a dopamine receptor agonist) relatively early in the course of PD has become an accepted strategy to avoid long-term, levodopa-related complications (8). Pharmacological management has been further refined by the use of controlled-release levodopa preparations, new dopamine agonists, catechol-*O*-methyl transferase (COMT) inhibitors, monoamine oxidase (MAO) inhibitors, and other compounds in development that will enhance dopaminergic transmission.

The pharmacological management of PD is aimed at symptomatic control by approximating the natural physiology of the nigrostriatal dopamine system. While secondary medications, such as amantidine and anticholinergics, may be useful for some patients, particularly in tremor-predominant PD, the majority of patients require dopaminergic drugs early in the course of disease. Initiating therapy with a long-acting levodopa preparation has become accepted practice, supplemented by either standard levodopa compounds or dopamine agonists, as symptoms warrant. The use of levodopa preparations in combination with dopamine agonists provides both the substrate for dopamine production in presynaptic neurons and postsynaptic receptor stimulation—a strategy thought to better mimic normal physiology than high-dose levodopa alone. While this approach may indeed delay the onset of troubling fluctuations and dyskinesias, there is little reason to believe that these common problems of drug therapy can be avoided entirely. Even MAO-B inhibitors, which delay the need for levodopa in early PD (5), show no evidence of prolonging the latency from levodopa initiation to onset of fluctuations and dyskinesias (6). One hopes that the introduction of new dopamine agonists (ropinerole, pramipexole, cabergoline, etc.) with slightly different receptor profiles will provide alternatives to patients no longer responding well to existing drugs. Similarly, inhibiting the metabolism of dopamine with COMT inhibitors may prolong the clinical effect of a levodopa dose (7). Unfortunately, it is

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unlikely that these additions to our therapeutic arsenal will substantially improve upon our current standard of care.

With an ever-increasing array of drugs to combat the motor symptoms of PD, one wonders to what greater extent we can alter the natural history of PD. Clinicians treating PD patients are still facing the ravages of PD and complications of drug therapy in the majority of their treated patients. Moreover, enhancing dopaminergic transmission may do little for some of the most disabling PD symptoms—postural instability, freezing, and dementia. A substantial impact on PD will therefore require both improvements in dopamine delivery to the striatum and therapies directed at the actual underlying disease process.

The concept of protecting neurons from the degenerative process began with antioxidants and, in particular, MAO inhibitors. While somewhat controversial, MAO inhibitors (such as deprenyl and selegiline) are used frequently in early PD. More importantly, other avenues of neuroprotection are showing promise in assuming a role in the management of PD. Restorative therapies using fetal cells or other cell types which are genetically engineered to produce dopamine and/or neurotrophic factors are under active investigation to attempt to alter the natural history of PD. Genetic intervention may prove to be particularly appealing. Advances in the basic science of gene transfer have placed us on the threshold of human trials. For application to PD, this approach may be multifaceted, based on either *in vivo* gene therapy directly into the patient's brain or *ex vivo* gene therapy based on genetically altering cell lines or tissues which are then grafted into the host brain (2). Numerous gene transfer systems and cell types have been tested in preclinical studies with many yielding encouraging results. Although no gene transfer approach has overcome all the obstacles of cytotoxicity, immune rejection, long-term expression, and delivery, there is tremendous excitement based on the dramatic principle of targeting novel therapies directly to the brain in patients ravaged by PD.

The science of gene therapy has evolved considerably over the past several years, prompting us to organize a symposium focused on the prospects of gene therapy for PD. Investigators from a variety of clinical and scientific disciplines gathered in Washington, DC, on April 11–13, 1996, for the first meeting of the Parkinson's Disease Gene Therapy Consortium. We hope that this early assembly of clinicians and scientists in an organized consortium will provide the foundation for the responsible, sound, and effective development of this promising field, and that future meetings will be expanded to include all basic scientists and clinicians interested in the development of novel therapeutic approaches to PD, without attendant media hype.

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EDITORIAL

Recently, the development of genetic intervention in human diseases has received a great deal of media attention, obscuring the steady progression and historical context of this field. In the 1940s Avery, MacLeod, and McCarthy discovered that nucleic acids constitute genes, and speculation about the possibility of gene transfer for human disease soon began. However, it was several years after Watson and Crick's discovery of the structure of DNA that experiments focusing on gene transfer as a potential therapeutic tool began in earnest in the 1960s. Since then, enormous progress has occurred, but significant obstacles and ethical considerations persist. Perhaps the opportunity for gene therapy of diseases affecting the central nervous system is the greatest, since cell turnover is low and the immune system is restricted. Yet perhaps the potential risk of gene therapy for these same diseases is the greatest, with the possibility of altering the function of the mind or destroying vital areas of the brain.

Of all diseases affecting the brain, Parkinson's disease has been the subject of most investigations focused on genetic intervention, using a variety of approaches and techniques. Parkinson's disease is a natural choice, given its prevalence, the limitations of existing pharmacotherapy, the established neurochemical alterations in the disease, the knowledge of reasonable anatomic and genetic targets, and the availability of tested animal models.

This special issue of *Experimental Neurology* focuses on gene therapy for Parkinson's disease, examining the rationale, prospects, and limitations of current approaches. The senior authors of all of the papers in this issue are members of the Parkinson's Disease Gene Therapy Consortium and participated in a closed meeting held in Washington, DC from April 11 to 13, 1996, and sponsored by the National Parkinson Foundation and the National Foundation for Brain Research. Initially, this small consortium was established to reflect expertise in a variety of fields relevant to the development of gene therapy approaches to Parkinson's disease, but, as often happens with such organizations, its membership continues to grow, and the next meeting is likely to be expanded significantly.

This special issue is divided broadly into two sections: (i) the examination of existing pharmacological and surgical approaches to Parkinson's disease, which, because of their significant limitations, provide the rationale for the development of genetic intervention; and (ii) the evaluation of gene therapy approaches to Parkinson's disease (some of which have been tested already in preclinical animal trials) and the consideration of the limitations and ethical issues surrounding the initiation of clinical trials in patients within the next several years.

It is an explicit tenet of the consortium that open discourse prior to initiating clinical trials is the best approach to avoid a disastrous outcome and to provide the best opportunity for improving therapy for patients burdened by this common and terrible disease. I thank the members of the consortium, particularly Matthew Stern and Matthew During, who were cofounders with me; Michael O'Connor, who provided a supportive environment for its development; Larry Hoffheimer of the National Foundation for Brain Research; and John Sladek, who has offered the unique opportunity to publish the many important issues discussed at this meeting in *Experimental Neurology.* I dedicate this issue to Mimi Wolle, who knows all too well the limitations of current therapy for Parkinson's disease.

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