Clinical Trial for Parkinson's Disease?

Recent discoveries give reason to believe that certain drug therapies may one day slow down the steady deterioration of Parkinson's disease

A small, informal group of biomedical researchers and clinicians met in Chicago on 5 October to consider ways in which the neurological and behavioral deterioration normally seen in Parkinson's disease may be slowed, if not halted altogether. The group will seek approval and financial support for a prospective clinical trial to test the effect of Deprenyl, a monoamine oxidase B inhibitor, and vitamin E, a general antioxidant, on the progression of the disease. The multicenter project would probably span at least 3 years and involve some 400 patients.

If the nationwide collaborative trial produces significant positive results, it may eventually prove possible to prevent, or at least significantly delay, the onset of the disease in individuals who are at risk but have not yet manifested any symptoms. This more distant prospect depends on the ability to identify the preclinical condition, which a recent study for the first time indicates might well be possible (*1*).

Although there is a high level of enthusiasm for this initiative among clinical neurologists, there is also a healthy degree of caution too, and for good reasons. One such reason is that Deprenyl is already prescribed for Parkinson's patients in some European countries, and there is no obvious, *dramatic* disparity in general prognoses on the two sides of the Atlantic. In addition, there have been limited trials in the United States that tested the ability of Deprenyl to control the irregular response that some patients develop to L-dopa therapy. The results here have been disappointing.

In spite of these somewhat discouraging data, neurologists agree that a controlled, double-blind trial must be done. For instance, one of the organizers, Stanley Fahn of Columbia University, says that although he judges a positive outcome from the trial to be unlikely, he considers it to be based on a reasonable hypothesis that must be tested. There is, he says, too much at stake for the patients for the idea to be ignored. Roger Duvoisin, who is taking part in discussions on the design of protocol but will not participate in the trial itself, concurs. Duvoisin, who is at Rutgers University, says that, as the idea has been raised as a serious issue, it is incumbent on Parkinson's clinicians to evaluate it.

The Chicago proposal is in part a consequence of the revolution that has swept through research on parkinsonism during the past 3 years. This revolution was sparked by the discovery that *N*-methyl, 4-phenyl, 1,2,5,6-tetrahydropyridine (MPTP), which is a contaminant of a certain "synthetic heroin," causes neurological and clinical symptoms that are virtually identical with naturally occurring parkinsonism. Some observers consider that the natural disease may indeed be caused by chronic exposure to environmental chemicals that are similar to MPTP in structure, of which there are many examples.

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MPTP appears to be harmless in itself, but is converted to a toxic derivative, MPP+, by monoamine oxidase B enzymes in the brain. For some as yet poorly understood reason, MPP+ is selectively toxic to virtually the same set of neurons that degenerate in natural parkinsonism: these are the neurons of the substantia nigra in the midbrain. The enzymic conversion of MPTP to MPP+ can be blocked by monoamine oxidase B inhibitors, which is one reason why researchers are interested in the possible therapeutic potential of such drugs.

Parkinson's disease is clearly the result of some kind of defect in the brain's dopaminergic system, and involves highly specific degeneration of neurons in the substantia nigra and related areas. These cells manufacture dopamine for use in higher brain centers and, as they die, those remaining appear to be pushed to higher and higher levels of productivity in order to compensate for the potential deficit. Some observers believe that the breakdown products of dopamine, which include peroxides that eventually generate cytotoxic free radicals, might in fact be the root cause of nigral degeneration in Parkinson's disease. If this is so, then the higher levels of dopamine manufacture that are thrust upon surviving cells in the nigra might be responsible for an acceleration of neuronal degeneration. The supposition that free radicals might be involved in cytotoxicity in parkinsonism is the rationale for suggesting antioxidant therapy, of which vitamin E is an example. In addition, monoamine oxidase might be involved in the generation of free radicals, hence a second rationale for testing the effect of inhibiting these enzymes to some degree.

Knowledge of the underlying pathology has led to two basic types of treatments. In the United States patients are given L-dopa, which boosts declining dopamine reserves: the symptoms are relieved, but the progressive degeneration continues. In Europe, L-dopa therapy is often supplemented with Deprenyl treatment, which also helps to maintain dopamine levels and, some observers argue, improves prognosis (*2*).

This European study is based on a cohort of more than 300 patients in several age groups. The patients are said to derive greater functional benefit from the combined drug regime, and, for those in the 80+ year age group, to enjoy a prolonged life span. These conclusions are questioned by many clinicians in this country, not least because the clinical data adduced to support the claim are retrospective and involve multiple treatment regimes.

The problems with retrospective clinical studies are well known: the principal issue is the absence of control and information on the history of subjects involved. The question of uncertainties arising from a mixed drug regime is more problematical, not least because of the frankly empirical nature of L-dopa therapy: administer L-dopa to a parkinsonian individual and his symptoms will disappear, that is, until degeneration proceeds beyond a certain point. Now, while some clinicians believe that L-dopa simply addresses the symptoms of the disease, and has no impact on the overall prognosis,

others fear that it might actually accelerate degeneration of neurons in the substantia nigra. Such uncertainties make for a difficult assessment of the true efficacy of Deprenyl in a mixed drug regime with L-dopa.

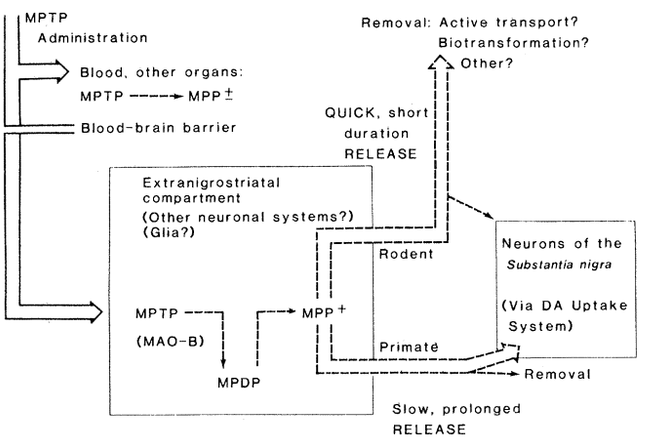
Nevertheless, the various threads from normal and MPTP-related conditions were promising enough to spur Ira Shoulson of the University of Rochester to convene informal discussions on the potential benefits of antioxidants and monoamine oxidase inhibitors at the American Academy of Neurology meetings held in Dallas this spring. Fahn joined in the deliberations, and a more formal gathering was held in Rochester at the end of June, at which more than a dozen medical centers from around the nation and Canada were represented. The Chicago meeting has now brought into sharper focus the manner in which the group considers it best to proceed.

If a prospective study is eventually begun it will be carried out with patients with early-stage Parkinson's disease, at which point progress can most readily be monitored. Patients will receive either Deprenyl, vitamin E, a Deprenyl/vitamin E mixture, or a placebo, and their performance on a series of neurological and behavioral tests will be measured over a period of years. Some observers believe that if the effects of the drugs are significant beneficial signs will be detectable within a year or so.

The development of a battery of highly sensitive, standardized measures of motor function is vital for the success of the project. One possibility here is that a semi-independent investigation already planned by William Langston and his colleagues at Stanford University Medical School may well address these issues, somewhat in the manner of a pilot study. Their project is the first in this country to receive Food and Drug Administration approval for use of Deprenyl as a possible means of slowing the progression of Parkinson's disease.

Looking further to the future, and depending on the outcome of the proposed clinical trials with Deprenyl and vitamin E, there lies the tantalizing prospect of preventing the development of overt Parkinson's disease in people who are particularly at risk. The disease is, of course, a disease of aging, except in the MPTP-induced condition, and so those at risk will normally be in the sixth or seventh decade.

Everyone progressively loses neurons throughout life, but this loss appears to be particularly acute in the substantia nigra. As the degeneration of cells in this region progresses the level of dopamine declines, producing the onset of parkinsonian symptoms when the deficit reaches 70 percent or so. Clearly, if it were possible routinely to monitor people's nigral dopamine levels, a pre-parkinsonian condition should be detectable, if, for instance, the dopamine level approaches 70 percent depletion.



On the trail of a neurotoxin

MPTP is converted to MPP+ by the enzyme monoamine oxidase B in nonneural (glial) cells in the brain. This metabolite, which is toxic to nerve cells, is then avidly taken up by neurons of the substantia nigra. Inhibiters of MAO-B prevent nerve cell destruction.

The rash of young individuals exposed to MPTP in northern California during 1982 (*3*) offered the potential of examining subjects whose substantia nigra might well be at least partially damaged. Langston, in collaboration with Donald Calne, Wayne Martin, and their colleagues at the University of British Columbia, Canada, used positron emission tomography (PET) to visualize dopamine and its metabolites in the nigrostriatal regions of four young individuals who had used MPTP but manifested no clinical symptoms (*1*). The readings for these people fell midway between those for normal and parkinsonian subjects.

Because of these subjects' history of exposure to MPTP, the investigators infer that their low dopamine levels represent a true, pre-parkinsonian state. No such preclinical condition has been previously demonstrated.

There is a long path between the detection of a pre-parkinsonian state in four clearly identified, at-risk individuals and the application of any kind of general screening program, not least because of the expense and limited availability of PET scanning. It is possible, however, that the job could be done using the much cheaper and now under-used brain scanners, which are generally considered virtually obsolete because of their limited field of scanning compared with the PET machines. But this relatively small scanning field might well be adequate for focusing on the area of the brain in question here, the substantia nigra.

One of the debating points that has arisen from the MPTP-inspired revolution in research into Parkinson's disease is, of course, how concordant the MPTP-induced and natural conditions are. By contrast with MPTP-induced parkinsonism, in which brain lesions reported so far are very sharply focused on the substantia nigra, neuropathology in the natural disease is more extensive. Does this mean that MPTP inflicts a parkinsonian-like condition simply by chance, and is in fact an incomplete model of the disease? Alternatively, the parkinsonian syndrome may derive almost exclusively from the nigral degeneration, and the other neuropathology may be rather secondary.

Two observations bear upon these questions. The first is the noting in one MPTP user of the progressive deterioration of handwriting: specifically, this was progressive micrographia, in which the handwriting becomes smaller and smaller, which is a typical, progressive parkinsonian symptom (*1*). The fact that progressive symptoms are seen in the drug-induced condition is, to some observers at least, suggestive.

The second observation is the very close matching of intellectual impairment between MPTP users and natural Parkinson's patients, as recently reported by Langston and Yaakov Stern of the Neurological Institute, New York (*4*). There has long been a debate about the source of these progressive defects in Parkinson's patients: are they dopaminergic or cholinergic in origin? The fact that they are observed in individuals whose neuropathology is probably restricted to the dopaminergic system of the substantia nigra appears to answer that question.—**ROGER LEWIN**

References

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