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MPTP-INDUCED PARKINSONISM

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CONTENTS

1. INTRODUCTION

In 1979, the publication of a little noticed article presaged a major advance in the knowledge of and research approaches to Parkinson's disease (PD) (Davis *et al.*, 1979). The paper reported the case history of a 23-year-old man who, in 1973, developed parkinsonian symptoms including bradykinesia, rigidity and tremor which progressed to mutism and virtual paralysis over a period of days. His physicians determined that he had been preparing and self-injecting a potent meperedine analogue 1-methyl-4-phenyl-propionoxypiperidine (MPPP), apparently as a substitute for demerol. He had taken some short cuts in the preparation of the compound, resulting in the presence of a by-product, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which was apparently responsible for the parkinsonian syndrome. The patient responded to the standard dopamine replacement therapy used in PD. Following his untimely death, post-mortem examination revealed depletion of cells in the pars compacta of the substantia nigra, the characteristic pathologic change of PD. These observations suggested for the first time that exposure to a toxin might produce a disease that has no known cause.

In 1982, Langston and his colleagues deduced that a group of drug addicts referred to several medical and psychiatric institutions in Northern California with severe symptoms including catatonia and mutism were all suffering from symptoms of PD. It was eventually determined that they had all injected a new form of "synthetic heroin" and, with the help of the previous paper, the presence of MPTP in samples of the illicit drug was established. These observations sparked an interest in this compound and a renaissance in Parkinson's disease research.

This paper will review some of the developments in the investigation of MPTP-induced parkinsonism. It will then focus on how the MPTP syndrome has allowed us to better delineate the nature and causes of the cognitive changes of PD.

2. PARKINSON'S DISEASE

Parkinson's disease is a slowly progressive neurological illness that typically begins around age 58–62 (Martilla, 1987). It is identified by its cardinal motor signs: resting tremor; rigidity, or resistance of the joints to passive movements; bradykinesia, paucity or slowness of movement; and postural instability. Other motor difficulties, including speech disorders, micrographia, or small handwriting, gait disturbance, and facial masking also occur.

The primary neuropathologic changes in Parkinson's disease are loss of cells in the pars compacta of the substantia nigra and the presence of Lewy bodies. The pars compacta of the substantia nigra sends dopamine via the nigrostriatal projections to the

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striatum. Presumably the disease process begins prior to its clinical manifestations, since depletion of approximately 80% of the dopaminergic stores in the striatum is required before clinical signs become evident (Riederer and Wuketich, 1976).

There is also loss of cells in the locus coeruleus in PD, with resulting depletion of the noradrenergic system (Scatton *et al.*, 1983). Depletion of raphe neurons with concomitant reduction in serotonin levels also occurs (D'Amato *et al.*, 1987).

While reports of up to 40% prevalence of dementia in PD have been made, best current estimates are at 10% (Brown and Marsden, 1984; Mayeux *et al.*, 1988). There is a great degree of overlap between dementia in PD and Alzheimer's disease (AD): dementia in PD has been related to reduced choline acetyltransferase (Perry *et al.*, 1983) and depleted cholinergic neuron counts in the basal forebrain (Whitehouse *et al.*, 1983), and typically has associated neuritic plaques and neurofibrillary tangles (Boller *et al.*, 1980). Depletion of serotonergic neurons occurs in both AD and PD (D'Amato *et al.*, 1987) as does degeneration of raphe neurons which are responsible for serotonin synthesis (Yamamoto and Hirano, 1985). In addition, some patients with AD display extrapyramidal motor signs similar to those of PD (Pearce, 1974) and these are associated with the neuropathologic changes of idiopathic PD (Ditter and Mirra, 1986).

Treatment of PD focuses primarily on the replacement of dopamine. Standard medication is levodopa, which crosses the blood–brain barrier and is converted to dopamine. Carbidopa is typically administered simultaneously to inhibit peripheral decarboxylation of levodopa.

The etiology of idiopathic Parkinson's disease has never been established, and opinion has vacillated between a genetic and endogenous or environmental toxic origins. Consequently, while the neuropathology and neurochemistry of the disease have been well understood much basic research had focused on improving treatment.

3. MPTP-INDUCED PARKINSONISM

3.1. INDEX CASES

Case histories of the seven individuals discovered in 1982 to have MPTP-induced parkinsonism have been reviewed by Ballard *et al.* (1985). All had used a "new synthetic heroin", most probably intended by the illicit laboratory that synthesized it to be MPPP. In 4 of the 7 cases, samples of the drug they had been injecting were analyzed and contained a high proportion of MPTP. The other addicts were presumed to have taken the same drug based on identifying features in their history including specific reactions to the injection, particularly a burning sensation at the site of injection. In addition, the patients used the drug during the time it was known to be available and purchased it in a location where it was known that it was being sold.

The acute reactions included the burning sensation mentioned above, and a distinctive heroin-like euphoria. Initial motor symptoms included intermittent jerking of the limbs, increasing slowness, or both. In a few days motor symptoms evolved into slowing and stiffness, difficulty speaking and swallowing, and in some cases tremor. This progressed over several days to 3 weeks. By the time they reached the chronic stage of the disease, patients displayed all of the cardinal symptoms of PD. Based on standard staging scales for the severity of PD, the patients were comparable to those who had had PD for several years and had features of the disease which are typically seen only in the more advanced patient. In addition, while patients were responsive to levodopa/carbidopa therapy, most encountered treatment complications that are typically seen later in the disease after several years of drug therapy. Also notable was that these patients had no neurological signs other than those expected in PD, suggesting that drug exposure resulted in a neurological syndrome that replicated all features of idiopathic PD.

3.2. OTHER MPTP-EXPOSED CASES

In addition to the 7 index cases first reported, approximately 400 other drug addicts were identified that, based on the historical criteria described above, might have been exposed to this toxin. Ruttenber *et al.* (1986) described the results of interviews and physical examinations of 83 such individuals. Eighty percent had at least one of the following clinical signs and 60% had two or more: lack of facial expression, en bloc turning, action tremor, bradykinesia, decreased ability to produce alternating finger movement, seborrhea, or resting tremor. In addition, 49% had increased tone or rigidity in at least one extremity. The acute and chronic symptoms of these patients were markedly less severe than those for the index cases. These findings suggest that there was a range of exposure and of consequent MPTP-induced symptomatology. Some exposed individuals remain asymptomatic and others have subtle symptoms while the index cases have a full blown parkinsonian syndrome.

Tetrud *et al.* (in press) compared 22 individuals with mild parkinsonism resulting from MPTP exposure to 130 patients with early, untreated parkinsonism and 51 intravenous narcotics users not exposed to MPTP. The MPTP-exposed group was highly comparable to patients with early PD, except for a lower prevalence of resting tremor. Control subjects had virtually no signs or symptoms of parkinsonism, suggesting that drug abuse alone does not produce these neurological manifestations. They concluded that MPTP can produce a full spectrum of disease stages similar to those seen as idiopathic PD develops.

Six MPTP-exposed, relatively asymptomatic patients underwent PET scan utilizing labelled 6-[^{18}F]fluoro-L-dopa, which is converted centrally to dopamine (Martin *et al.*, 1986). Dopamine uptake to the striatum was compared to a control group of 7 normal subjects without a history of narcotic use, and to 13 patients with idiopathic PD. Data were expressed as the ratio of regional to cerebellar activity. There was a progressive decrease in mean striatal activity from normals, to the MPTP-exposed individuals, to the patients with PD. The mean

caudate/cerebellum activity ratio in the MPTP-exposed individuals was similar to that seen in idiopathic PD and significantly lower than that in the controls. Mean putamen values did not differ from normals but were higher than those in patients with PD. These findings documented that a reduction in striatal stores of dopamine occurs with MPTP-exposure.

Calne *et al.* (1985) reported the results of the PET scans on a subset of these individuals, stressing that a large percentage of dopamine uptake to the striatum was depleted in these individuals although the signs and symptoms of PD were minimal. They suggested that these findings were compatible with subclinical damage to the nigrostriatal pathway, suggesting that dopaminergic impairment can exist without motor deficits. They felt that this finding lent support to the hypothesis that Parkinson's disease may stem from clinically silent damage to the substantia nigra, followed by slow attrition of neurons in this region because of its particular vulnerability to cell loss as a normal consequence of aging.

3.3. MPTP-Induced Parkinsonism in Animals

After the identification of the initial case of MPTP-induced parkinsonism, there was some effort to replicate this observation in several rodent species, mainly rats, but the parkinsonian syndrome was not elicited (Kopin, 1986). Following the newly published observations of the effects of MPTP in 1983, efforts to develop an animal model were renewed, and MPTP-induced parkinsonism was elicited in primates, including rhesus and squirrel monkeys (Burns *et al.*, 1983; Langston *et al.*, 1984) and dogs, among other species. Rats (Boyce *et al.*, 1984), guinea pigs (Chiueh *et al.*, 1984) and gerbils (Heikkila *et al.*, 1984a) are relatively resistent to MPTP's toxic effects, but repeated administration of high doses to mice does result in persistent dopaminergic depletion in the striatum (Hallman *et al.*, 1984). Some investigators have suggested that there is a relationship between the presence of neuromelanin in the substantia nigra, such that most animals susceptible to MPTP accumulate neuromelanin, whereas rats and other relatively immune animals do not (Burn *et al.*, 1984; Kopin, 1986). The advent of an animal model for Parkinson's disease has facilitated basic research into treatment and etiology.

3.4. Neurochemical and Neuropathological Changes

The acute effects of MPTP administration have been best described in animals, while chronic changes have been assessed in humans as well. Acutely, there are reductions in the major neurotransmitter systems including dopamine, norepinephrine and serotonin. However, as the chronic syndrome emerges, only the dopaminergic system remains impacted (Burns *et al.*, 1983). In both humans and animals this is detected by the persistent depletion in the concentration of HVA, the primary metabolite of dopamine (Burns *et al.*, 1985). Spinal fluid analyses in the index cases showed normal or elevated levels of MHPG, the principal metabolite of norepinephrine (Burns *et al.*, 1985). To date no neurochemical studies have shown neurotransmitters other than dopamine to be affected in chronic MPTP-induced parkinsonism.

There has been one case of probable MPTP-induced parkinsonism that has come to autopsy (Davis *et al.*, 1979). Pathologic data is also available from animal models. In both cases, the primary neuropathologic change consists of cell loss in the zona compacta of the substantia nigra, comparable to the primary pathologic change of PD. Two reports in primate models demonstrated occasional lesions in the locus coeruleus, suggesting that other neurotransmitter systems, particularly the noradrenergic system, may be affected (Mitchell *et al.*, 1985). Eosinophilic intraneuronal lesions have also been observed in very old primates treated with MPTP (Forno *et al.*, 1986). However, these lesions were typically found in the older primates, and no biochemical correlates to this change have been reported (Ricaurte *et al.*, 1987).

3.5. Comparability of Idiopathic PD and MPTP-Induced Parkinsonism

The striking comparability of neurologic signs and symptoms in idiopathic PD and MPTP-induced parkinsonism suggests that the latter is an excellent model for idiopathic PD. Further, it establishes that all of the primary motor signs of PD can result from disruption of the nigrostriatal system. However, there are at least two important differences between the two entities.

First, as described above, PD typically involves more widespread neuropathologic and neurochemical changes than MPTP-induced parkinsonism. While the pathology of PD consists primarily of degeneration of dopaminergic input to the basal ganglia, other neuropathologic changes including degeneration in the locus coeruleus and Lewy bodies typically occur. In the demented patient, senile plaques and neurofibrillary tangles in the neocortex can be present. Neurochemical depletions in serotonin and norepinephrine, and in the demented patient in acetylcholine, are present. Therefore, MPTP-induced parkinsonism better represents a pure hypodopaminergic condition, with well defined and restricted neuropathology, while PD is a more complex entity involving multiple neuropathologic and neurochemical alterations.

Second, PD is a progressive disease. Whether MPTP exposure results in a progressive syndrome has not yet been established. Kopin (1986) reports that the originally described individual did not show progression of symptoms over several years. However, Langston (1986) speculates that the histories provided by relatively asymptomatic patients suggest that there has been some progression of their symptoms. The definitive answer to this question awaits careful follow-up of the exposed cohort.

4. MODE OF ACTION OF MPTP

MPTP itself is not the toxic agent that causes parkinsonism. MPTP is oxidized to 1-methyl-4-phenylpyridinium (MPP^+) via monoamine oxidase B (MAO-B) (Markey *et al.*, 1984), and it is this

compound which is taken up into the presynaptic dopaminergic neurons and causes their destruction by means yet to be determined (Javitch and Snyder, 1985). It has been demonstrated both *in vitro* and *in vivo* that the administration of MAO-B inhibitors blocks the effects of MPTP (Chiba *et al.*, 1984; Heikkila *et al.*, 1984b). Currently a large scale clinical trial of the ability of deprenyl, a MAO-B inhibitor, to slow the progression of PD is in progress (Parkinson Study Group, 1989). This is based, in part, on the hypothesis that there is some endogenous destructive agent oxidized in a fashion similar to MPTP that is responsible for the progression and/or inception of PD.

The mode in which MPP^+ contributes to the destruction of dopaminergic neurons is unclear. One hypothesis is that MPP^+ operates in a mechanism similar to that proposed for paraquat (Bus *et al.*, 1976) and increases cytotoxic free radicals (Castagnoli *et al.*, 1985). Sensitivity to MPP^+ might be related to the presence of neuromelanin: the presence of melanin may reflect decreased ability of the cell to cope with free radicals, or the malanin itself in the presence of MPP^+, may be a source of free radicals (Kopin, 1986). The leading hypothesis is that MPP^+ may inhibit mitochondrial respiration within the dopaminergic neuron, which would lead to cell death (Nicklas *et al.*, 1985).

5. INTELLECTUAL CHANGES IN PD AND MPTP-INDUCED PARKINSONISM

5.1. Role of MPTP in the Study of Intellectual Change

The great majority of patients with PD do not become demented. Neuropsychological investigation of the nondemented patients has focused on defining the nature of any cognitive change in these patients with the goal of relating it to the neurochemical and neuropathological changes of the disease. As in all neuropsychological investigation, determining these relationships would aid in understanding the role of these neuronal systems in normal cognition. Parkinson's disease has often been used as a model for investigating the role of the basal ganglia in cognition. However, in attempting to determine the actual neuroanatomic basis for any cognitive deficits, the potential participation of the multitude of neurochemical and neuroanatomic changes which occur in PD must be considered.

Specific aspects of cognitive change in PD have been related to dopaminergic depletion and the consequent disruption of a system comprising complementary projections between the frontal lobes and the basal ganglia (Stern, 1983). This level of localization has relied on observations in PD, findings in other diseases affecting the basal ganglia, such as Huntington's disease, as well as on animal lesion studies. Other cognitive changes, such as disruptions in attention, have been related to the noradrenergic system (Stern *et al.*, 1984b; Mayeux *et al.*, 1987). Since MPTP exposure appears to result in a pure hypodopaminergic condition, it affords the unique opportunity to investigate the relationship between dopamine and cognitive change.

Another issue that has impeded the interpretation of the cognitive changes in PD has been the contribution of motor signs such as slowness and tremor to the observed performance on tests. This is particularly important since several tests on which patients do poorly can have a motor component. This issue has been addressed by developing tests that require no motor input (e.g. Boller *et al.*, 1984). Still, the identification of individuals who were exposed to MPTP have PET documented depletion of dopaminergic stores and are relatively asymptomatic allows the opportunity to determine the relative contribution of the motor change.

Finally, the existence of patients with varying ranges of exposure to MPTP allows us to investigate possible relationships between the extent of dopaminergic depletion and the magnitude of cognitive change. There are two possibilities: there might be a dose–response relation such that cognitive changes might worsen as depletion becomes more extensive. Alternatively, depletion below some critical point might result in cognitive deficit.

5.2. Intellectual Change in the Index Cases

Stern and Langston (1985) evaluated 6 of the 7 index cases of MPTP-induced parkinsonism and compared their performance on a selected battery of neuropsychological tests to that of demographically comparable drug-addict controls. Areas assessed included memory, attention, language and verbal fluency, digit span, visuospatial ability or construction, and executive ability. A brief mental status examination was also included. There was a slight but significant difference between the MPTP-induced parkinsonism and control groups on the mental status examination, suggesting a subtle change in intellectual function. Patients performed significantly worse than controls on tests of construction (the Rosen Drawing Test), verbal fluency (category naming), and executive function (Stroop Color-Word Test). Performance on attentional tests (reaction time and continuous performance tests), memory, digit span, and language (other than verbal fluency), was comparable in the two groups.

The types of tasks on which patients performed worse than controls are comparable to the pattern of neuropsychological deficits seen in idiopathic PD. One class of tasks frequently reported to be affected in PD is executive tasks, which involve the planning and modulation of ongoing behavior (Stern, 1987). The Stroop Color-Word Test is one example of tasks of this type on which performance is affected (Heitanen and Teravanien, 1988). The Stroop is administered in three sections. First, the subject is asked to read a list of color names as rapidly as possible. Next, the subject names a series of color patches. Finally, the subject is presented with word names printed in contrasting colors (for example, the word "green" might be printed in red ink) and the subject is asked to name the ink color. Since the subject must repress an overlearned response set (reading printed words without regard to the color of the type) in favor of a novel one, the final task is completed more slowly than the first two. The difference between performance on the final and either of

the first two yields a score that controls for motor speed and reflects the executive components of the task. Another executive task that has often been reported defective in PD is the Wisconsin Card Sort, in which the subjects must infer changing sorting rules from feedback about the accuracy of their performance (Bowen, 1975; Lees and Smith, 1983).

Performance on visuospatial or perceptual motor tasks has also often been reported affected in PD. Parkinsonians' poor performance on this class of tests has been demonstrated using puzzle assembly (Botez and Barbeau, 1975), digit symbol (Pirozzolo *et al.*, 1982), line orientation (Boller *et al.*, 1984) and drawing (Mayeux and Stern, 1983) tests.

Matison *et al.* (1982) described difficulties with naming words in particular categories in PD. Difficulties on memory tasks have also been reported in PD, although not as consistently as some of the other areas of cognition (Pirozzolo *et al.*, 1982; Tweedy *et al.*, 1982). These difficulties were not seen in the MPTP patients. Performance difficulties on reaction time and other attentional tests have also been reported in PD. Stern *et al.* (1984b) associated attentional difficulties in PD with altered concentrations of MHPG in the cerebrospinal fluid. Since the noradrenergic system is probably not affected by MPTP, attentional deficits would not be expected.

The delineation of a set of neuropsychological performance deficits stemming from a discrete lesion to the pars compacta of the substantia nigra and the subsequent depletion of dopaminergic projection to the striatum is a powerful demonstration of the role of the dopaminergic system in mediating these cognitive functions. Further, these findings strongly suggest that just as dopaminergic depletion is responsible for the majority of the motor signs of PD, it may also underlie many of the cognitive changes that have been described in the nondemented patient with PD.

5.3. Intellectual Change in Mildly Affected Cases

Stern *et al.* (in press) later assessed 6 of the individuals described above who had PET scans documenting reduced uptake of dopamine in the striatum. All had subtle signs of parkinsonism. However, none would have been diagnosed with PD because of the subtlety of the signs. Based on self-report, these individuals had self-injected significantly less of the illicit drug than had the index cases. The same battery of tests that had previously been administered to the index cases and controls was used to test this group as well.

These patients performed comparably to the index cases and worse than controls on category naming and a construction task, the Rosen Drawing Test. Performance was midway between the two other groups on the Stroop Color-Word test. They performed more poorly than the controls and index patients on a simple but not a choice reaction time task.

There were no significant correlations between PET derived measures of dopamine uptake and any measure of PD severity. Similarly, PET scan summary values for dopamine uptake to the striatum did not correlate with any measures of neuropsychological performance.

These findings are striking in that two different groups of patients with varying exposure to MPTP exhibited a similar pattern of cognitive impairment, and that this pattern was similar to that seen in PD. They lend further support to the idea that depletion of cells in the pars compacts of the substantia nigra can result in this specific pattern of cognitive deficit. The relative sparing of other functions, including memory and attention, suggests that when these areas are affected in PD it is due to changes in other neuroanatomic systems.

While the relatively asymptomatic group had less exposure to MPTP, significantly fewer signs of parkinsonism, and presumably less depletion of dopaminergic stores in the striatum, they performed comparably to the index patients on most tests. This might suggest that there is not a relation between level of dopamine depletion and cognitive performance and depletion below some critical level results in impaired performance. However, a dose–response relationship was observed for performance on the Stroop Color-Word test such that the relatively asymptomatic individuals performed at a level between controls and the index cases. This test of executive function might be more directly mediated by the neural systems that MPTP affects and therefore more sensitive to variations in the stability of that system.

The MPTP-exposed individuals were not completely asymptomatic, but did not have sufficient neurological changes to be classified as having PD. Their test results suggest that cognitive changes may occur even before the motor signs of the disease become apparent. Assessment of MPTP-exposed individuals who are completely asymptomatic would be required to confirm this speculation.

5.4. The Role of the Dopaminergic System in Cognition

The previous two studies supply powerful evidence for the role of the dopaminergic system in cognition and for the role of dopaminergic changes in the cognitive deficits of PD. Further, they help us to understand the role of the basal ganglia in cognition.

Stern (1987) suggested that the basal ganglia are part of a corticostriatal system that monitors ongoing activity, allowing it to be modulated in the absence of external cues. This might involve the planning of activity as well as the modification of motor or cognitive plans when they are no longer effective. While somewhat broad, this formulation subsumes the types of tasks that have been shown to be defective in diseases of the basal ganglia, including PD, and now following MPTP exposure.

Both parkinsonians and patients with prefrontal cortical lesions perform poorly on executive tasks (Bowen and Yahr, 1975; Lees and Smith, 1983) as do patients with Huntington's disease (Oscar-Berman *et al.*, 1973). Further evidence implying the role of the basal ganglia in these processes is derived from analogous tasks used in animal studies. For example, lesions to the head of caudate or to prefrontal cortex affect performance on alternation tasks, in which the

animal must always choose the response that had been incorrect on the previous trial (Divac, 1972).

Parkinsonians also perform poorly on motor tracking or tracing tasks which demand that they generate sequences of motor output without external guidance. When a shift from one motor program to another is required, for example, a radical shift in direction in a tracking task, parkinsonians have difficulty making this shift if no external guidance is provided (Flowers, 1978; Bloxham *et al.*, 1984). Stern *et al.* (1983, 1984a) demonstrated that in PD performance on these tracing tasks is related to that on construction tasks. The connection between these two types of tasks, and executive tasks in turn, is that they all require generating programs of activity without external guidance. In construction tasks, for example, patients have difficulty planning the approach toward the constructive activity and monitoring the accuracy of that activity. Stern *et al.* (1985) demonstrated that specific remediation directed at these aspects of constructional performance increases patients' ability to perform well.

In summary, evidence from studies of patients with PD and other basal ganglia diseases suggest a set of interrelated cognitive deficits that are possibly related to basal ganglia in dysfunction. These include poor performance on executive, constructional and motor sequencing tasks. That these functions were affected in the MPTP-exposed population strongly supports the role of dopaminergic depletion and subsequent disruption of basal ganglia function in these cognitive processes.

Further, these data suggest that a toxic insult that specifically impacts on a particular neurotransmitter system can result in a consistent and specific syndrome of neuropsychological changes.

6. CONCLUSIONS

The identification of the consequences of MPTP-exposure has opened up several new avenues of research in Parkinson's disease. It has sparked a resurgence of interest and investigation into the etiology of this condition. The availability of an animal model for the disease has obvious implications for both basic and applied clinical research. Finally, the affected individuals themselves provide an important "natural experiment". Prospective studies of these patients may provide insight into the etiology and progression of PD. The specificity of their neuroanatomic insult allows us to more clearly understand the underpinnings of the neurological and cognitive changes in Parkinson's disease, and helps clarify the role of the dopaminergic system and the basal ganglia in behavior.

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