

Parkinsonism Induced By 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP): Implications for Treatment and the Pathogenesis of Parkinson's Disease

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ABSTRACT: Our experience in treating 7 patients with moderate to severe parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is reviewed. Virtually all of the problems typically encountered with dopamine precursor and agonist therapy in treating Parkinson's disease have been observed during a one and one half year follow-up period, including "end-of-dose" deterioration (or "wearing off"), "peak-dose" dyskinesias, "on-off" phenomena, and psychiatric complications. These have occurred much earlier than is typically seen when treating the idiopathic disease. This rapid evolution of therapeutic side-effects favors the view that at least some of the complications of dopamine precursor therapy may be related to severity of disease rather than the length of levodopa therapy. Finally, we suggest that the occurrence of this full array of therapeutic complications in patients with MPTP-induced parkinsonism furthers the analogy between this syndrome and Parkinson's disease.

RÉSUMÉ: Nous citons notre expérience dans le traitement de 7 patients atteints de Parkinsonisme modéré ou sévère à la suite de la prise de MPTP. Nous avons observé tous les problèmes habituels de la thérapie à la Lévodopa, et ce dans la courte période d'un an et demi: oscillations de fin de dose, "on-off", dyskinesies du sommet, complications psychiatriques. Ces complications sont apparues beaucoup plus tôt que d'habitude. Ces observations sont en faveur du rôle de la sévérité de la maladie plutôt que de la durée de la thérapie à la Lévodopa dans l'apparition de certaines complications. Ces observations ajoutent également aux similitudes entre ce modèle expérimental et la véritable maladie.

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In the original report suggesting that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is selectively neurotoxic to the substantia nigra (Langston et al., 1983a), emphasis was placed on the similarities between Parkinson's disease and the clinical syndrome induced by this substance. Seven patients with moderate to severe "MPTP-induced parkinsonism" have now been identified and followed clinically for almost one and a half years, providing an extended opportunity to evaluate their response to therapy over time. Because these patients were in an advanced state of relatively pure parkinsonism virtually from the onset of their illness (all seven would meet disability stages IV and V of Hoehn and Yahr, 1967), it has been possible to carefully document the short term effects of newly initiated levodopa therapy in a relatively severe disease state. Therefore, this material provides data which may be relevant to current controversies regarding the timing of initiation of levodopa therapy in Parkinson's disease. We will also show that our experience with dopamine precursor and agonist therapy in these patients provides additional similarities between MPTP-induced parkinsonism and the idiopathic disease.

CASE SUMMARIES

A brief summary of the clinical features of these patients is presented here. A more detailed report of their case histories will be published elsewhere. All patients self-administered MPTP intravenously under the impression that it was "synthetic heroin." The first four patients have been briefly reported previously (Langston et al., 1983a).

Patient 1: A 42 year old man injected MPTP over a four day period beginning July 1, 1982. When first seen by us 15 days later, he exhibited profound bradykinesia, aphonia, drooling, generalized cogwheel rigidity, and a short-stepped, shuffling gait. He maintained a flexed posture and could neither stand nor feed himself without assistance. A brief trial of benzotropine produced only mild improvement. Treatment with levodopa was initiated on July 27, 1982.

Patient 2: This 30 year old woman was living with patient 1 and used the substance in the same amounts and during the same time. Examination 17 days later revealed a complete loss of facial expression, marked reduction in blinking, continuous drooling, and marked hypophonia with difficulty initiating speech. All voluntary movements were performed extremely slowly. Tone was moderately increased in the neck and axial musculature, and cogwheel rigidity was present in all extremities. A rhythmic resting tremor was noted intermittently in the right hand and foot. A two day trial of amantadine was without effect, but three days after starting benzotropine, limited improvement was seen with some

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return of facial movements and diminution of bradykinesia. Treatment with levodopa was initiated on July 29, 1982.

Patient 3: This 26 year old man is the first of two brothers who began using MPTP intravenously on June 5, 1982. He became profoundly akinetic and completely unable to care for himself after running out of the substance on June 25, 1982. Benzotropine, initiated by his family physician, produced only transient improvement in his condition. He was first seen in neurologic consultation on July 21, 1982, at which time examination revealed profound bradykinesia. He could communicate only by using lateral eye movements for "yes" and "no". He was unable to stand, sit, or eat without assistance and exhibited generalized cogwheel rigidity. Treatment with levodopa was initiated on July 29, 1982. This patient was the most severely affected of the group.

Patient 4: This 29 year old man is the brother of patient 3, and used MPTP during the same time period and in the same amounts as did his brother. While he was severely affected at first, he improved somewhat two to three days after cessation of use of the substance. There was little if any further improvement after a trial of benzotropine however. He was at first seen in neurologic consultation on August 16, 1982, at which time examination revealed a loss of facial expression, difficulty swallowing, monotonous speech, mild cogwheel rigidity of the arms, a slow, shuffling gait, and a pill-rolling tremor at rest in the arms. This patient was less severely affected than his brother as he could then speak and walk. Treatment with levodopa was initiated in early September, 1982.

Patient 5: This 24 year old woman used MPTP during the third week of June, 1982. She subsequently became immobile and was hospitalized for two weeks on a psychiatric unit with diagnosis of "functional paralysis". She was first seen by us on August 2, 1982, at which time examination revealed a rigid, mute woman who drooled copiously. There was a fixed stare with minimal blinking, profound facial masking, and striking generalized cogwheel rigidity. Tremor at rest was present in all extremities which was most pronounced in the right arm. She was totally immobile and nonambulatory. This patient was nearly as severe in terms of involvement as patient 3. Levodopa therapy was initiated on August 3, 1982.

Patient 6: This 22 year old man first began using MPTP in mid-March of 1982. Shaking of the extremities was a prominent early feature. This eventually became so severe that it interfered with his ability to function. He stopped using the substance early in June, 1982. Amantadine and benzotropine produced little improvement. Levodopa therapy was initiated on August 17, 1982. When first examined by us on August 20, 1982, he exhibited a severe 4 to 5 per second rolling tremor of the arms which was seen primarily at rest. The tremor also involved the legs as well as the tongue, lips and jaw. He also exhibited a fixed stare and loss of facial expression. Mild cogwheel rigidity was noted in the extremities (arms greater than the legs). Bradykinesia was minimal. When walking he exhibited a slightly stooped posture.

Patient 7: This 31 year old woman injected MPTP daily for a total of three weeks in mid-April and early May, 1982. Her legs became rigid abruptly several days after she stopped injecting MPTP. She also experienced a resting tremor in her legs. Amantadine and trihexyphenidyl provided only moderate symptomatic relief. She was first seen by us on March 10, 1983, at which time examination revealed a slight loss of facial expression, moderately increased tone in the lower extremities and the neck, mild cogwheel rigidity at the wrists, elbows, ankles, knees, and neck, and a rhythmic 4-5 per second resting tremor of the legs. Gait was slowed with a loss of associated movements. This patient was the least affected of our patient group. Levodopa therapy was tried briefly two months after onset of symptoms but was not reinitiated until March 10, 1983.

METHODOLOGY AND TREATMENT RESULTS

All patients were given levodopa (LD) combined with carbidopa (CD) in the form of Sinemet 10/100 or 25/250 tablets (except for patient 7, who receives a 25/100 CD/LD preparation). Medications were spaced evenly throughout the day, divided into three to eight daily doses, depending on the total amount prescribed. Bromocriptine (Parlodel) was given as 2.5 mg. tablets or 5 mg. capsules divided into two or more evenly spaced doses daily.

All patients showed a response to levodopa therapy. In patients 1 and 2, this was dramatic as they were virtually asymptomatic within 3 to 5 days after initiating treatment. Patients 3 through 5 improved, though more slowly, and less satisfactorily (see discussion below). Our two least affected patients from the standpoint of rigidity and bradykinesia (patients 6 and 7) also responded promptly to dopamine precursor and agonist therapy, but some tremor remains in both. The time between exposure to MPTP and initiation of CD/LD therapy ranged from 26 to 150 days, with an average interval of 64 days. In all patients, the addition of bromocriptine followed initial levodopa therapy (range: three days to eight months).

We have now followed these patients for almost a year and a half. During this period we have observed many of the typical problems encountered with long-term levodopa therapy including "end-of-dose" deterioration (or "wearing-off"), "dopa dyskinesias", "on-off" effects, and psychiatric disorders. In the following discussion, we will attempt to outline the sequence of appearance of these therapeutic complications and their relationship to treatment and severity of disease in this group of patients. We have also provided a Table which summarizes these results.

"End-of-dose" deterioration was the first therapeutic problem to be encountered in these patients after initiation of CD/LD therapy. Patients 3 and 5 were observed to have "end-of-dose" deterioration virtually as soon as an acceptable therapeutic response was achieved. After initiation of treatment, patient 3 began to gradually improve. However, by day 12 (total daily dose of CD/LD: 60/600 mg.), he was experiencing good symptomatic relief only during the second hour on an every-three-hour schedule. Increases in dosage and decreasing the interval between doses failed to correct this problem (and in fact quickly led to the appearance of "peak-dose" dyskinesias). In patient 5 end-of-dose deterioration was so severe when initiating levodopa therapy that bromocriptine was added at the beginning of the second week (dosage 150/1500 mg. CD/LD) in an attempt to smooth out her therapeutic response which was only partially successful. In the remaining four patients, "end-of-dose" deterioration appeared between 14 weeks and 8 months after initiation of dopamine agonist therapy (see Table), and always preceded the appearance of dose-related dyskinesias.

"Dose-related" dyskinesias have occurred in five patients, and have become dose-limiting in four. These began as early as three to six weeks after initiation of levodopa therapy (patients 5 and 3 respectively), and as late as one year later (patient 1). Daily dosages of CD/LD ranged from 80/800 mg. to 125/1250 mg. at the time of onset of the dyskinesias. The maximum dose eventually reached in these patients ranged from 120/1200 to 245/2450 mg. of CD/LD. This contrasts with maximum daily doses of 100/1000 mg. and 150/600 mg. of CD/LD used to date in the two patients who have not experienced dyskinesias (patients 6 and 7). Dyskinesias usually began after the onset of "wearing-off" effects (see Table), and were typically preceded by increases in levodopa to overcome this effect.

Clear cut "on-off" effects (defined here as abrupt *random* swings from normal or dyskinetic to rigid or the reverse in relatively short periods of time) have been seen in patients 1 through 5. These were first seen six to ten months after initiation of therapy.

Patients 1 and 2 are of particular interest in terms of their initial response to therapy. These individuals were almost

Table

Patient Number	1	2	3	4	5	6	7
Date and years of age (y/o) when first exposed to MPTP	7/1/82 42 y/o	7/1/82 30 y/o	6/5/82 26 y/o	6/5/82 29 y/o	6/15/82 24 y/o	3/14/82* 22 y/o	4/13/82 31 y/o
Relative severity of symptoms**	++	++	+++	++	+++	+	+
Date of initiation of CD/LD and dosage	7/27/82 30/300	7/29/82 60/600	7/29/82 30/300	9/1/82* 40/400	8/3/82 30/300	8/17/82 60/600	7/82*** 30/300
Date of first "wearing off" and CD/LD dosage at onset	3/27/83 40/400****	11/12/82 80/800	8/12/82 60/600	2/11/83 125/1250	8/10/82 80/800	4/83 30/300	None
Date of first dyskinesias and CD/LD dosage at onset	7/22/83 120/1200	11/12/82 80/800	9/15/82 180/1800	2/18/83 125/1250	8/26/82 125/1250	None	None
Date of first "on-off" and dosage at onset	4/2/83 80/800	3/83* 80/800	3/83* 225/2250	6/83 125/1250	12/3/82 75/750	None	None
Date and amount of maximum dosage of CD/LD	6/17/83 120/1200	4/1/83 160/1600	4/20/83 245/2450	4/83 200/2000	8/26/83 150/1500	4/83 100/1000	5/17/83 150/600
Date of first psychiatric symptoms	8/82/82	9/24/83	None	7/83	3/4/83	None	None

* Approximate

** Within group of 7 patients (+ mildest, +++ severest-bradykinesia/rigidity)

*** CD/LD stopped after 1 week; reinitiated 9 months later

**** Off CD/LD from November 1982 through March 3, 1983

completely controlled on 30/300 to 40/400 mg. of CD/LD daily and low doses of bromocriptine (2.5 mg. twice daily). Patient 2 clearly developed an end of dose "wearing-off" after four months. This triggered an increase in the dose of CD/LD, which in turn almost immediately resulted in "peak-dose" dyskinesias which were ultimately to become dose-limiting. Patient 1 is more complicated because after three months of almost complete control on the same dosage schedule as patient 2, he received no medications for the next four months while incarcerated. When restarted on his original dosage schedule in March of 1983, he did moderately well for 3 to 4 weeks, and then rather abruptly began experiencing end of dose "wearing off". His dosage was increased from 30/300 mg. CD/LD to 60/600 mg. CD/LD, which promptly lead to the appearance of fairly dramatic "on-off" effects. On at least four occasions, these were mistaken as respiratory arrest, resulting in several resuscitation attempts.

Psychiatric symptoms which developed after the initiation of therapy include hallucinations, delusions, and sensory mis-perceptions. In regard to hallucinations, patient 1 is of particular interest. He was first discharged from the hospital on 30/300 mg. of CD/LD daily, at which time he was virtually asymptomatic. Through an error, he took twice this dose, and returned four days later, at which time his thought processes were disorganized. He was suspicious with ideas of reference, and he was experiencing visual hallucinations comprised almost exclusively of seeing insects on his hands and arms, and at times, the faces of others. These symptoms all resolved when levodopa was temporarily discontinued for two days. In April of 1983 (eight months later), his CD/LD dosage was again increased to 60/600 mg. per day because of a decreasing therapeutic response.

Hallucinations of insects coming out of his skin reoccurred almost immediately. These hallucinations now occur every time his dosage is adjusted above 40/400 to 50/500 mg. per day of CD/LD, often leading the patient to severely excoriate his arms. As unacceptable rigidity occurs when CD/LD is decreased below this level (in spite of relatively high accompanying doses of bromocriptine), this patient continues to be a serious management problem. Three other patients have developed auditory and visual hallucinations after 9 to 15 months of therapy (patients 2, 4, and 5 respectively), usually comprised of vague shadows or voices talking about them. They seem to be aware that these are hallucinations, and are not particularly frightened by them. At times, the hallucinations are quite well formed and usually consist of people that the patients know; they may persist for hours at a time. Patient 4 was first noted to have developed paranoid delusions at 11 months (usually consisting of fears that people, usually police, are out to kill him); more recently these are taking the form of well formed visual hallucinations. This patient is also experiencing "parasitosis" at times.

Depression has been seen in the three female patients, and has been present from early on in their illness, clearly preceding the initiation of treatment in at least one. Two of the women are requiring tricyclic antidepressant therapy.

Finally, all attempts to wean patients completely off levodopa have been fruitless, in spite of concomitantly increasing bromocriptine to daily doses as high as 100 mg. Bromocriptine has been effective in allowing most patients to reduce their total daily CD/LD requirement to at least some degree.

DISCUSSION

In many ways, these patients represent a microcosm of the long-term problems encountered in treating patients with Parkinson's disease. Virtually all of the troubling side effects which usually occur during the course of levodopa therapy have been encountered, but much earlier and in rapid sequence. This chronology is of particular interest because these treatment related complications are not typically seen in the first year or two of levodopa therapy in patients with Parkinson's disease (Barbeau, 1980).

The earliest therapeutic problem encountered in this patient group was the so-called "end of dose" deterioration or "wearing off". Typically in Parkinson's disease, three to five years usually pass before the majority of patients begin losing their responsiveness to therapy (Sweet and McDowell, 1975). Long duration response to levodopa (sustained therapeutic effect despite falling plasma levels after each dose) may be replaced after several years of therapy with medium duration response in which clinical benefit parallels the rise and fall in blood levels from individual doses (Fahn, 1982; Muentner and Tyce, 1971). End-of-dose clinical deterioration has been correlated with a fall of plasma levodopa (Shoulson et al., 1975) and continuous intravenous infusion of levodopa has been reported to abolish these effects as long as the patient is lying quietly. Marsden and Parks (1976) have suggested that, as additional dopamine terminals are lost with disease progression, there is a decrease in ability to synthesize and store dopamine so that the striatum becomes more dependent on circulating levodopa. If this theory is correct, when initiating levodopa therapy in severely affected patients, one would expect to see short duration responses almost immediately. This is precisely what was observed in our two most severely involved patients (patients 3 and 5). Neither patient experienced a long duration response to levodopa therapy. Both exhibited end-of-dose "wearing off" literally as soon as a therapeutic response was observed. In our opinion, the finding that short duration responses were present from the time of initiation of therapy in these two patients is most compatible with the view that severity of disease is indeed a prime determinant in the lack of longer duration responses. Presumably these patients have the fewest nigral neurons to take up levodopa, and to synthesize and store dopamine to provide smooth long-duration responses. At the very least, the observations in these two patients provide evidence that long term levodopa therapy is not a pre-requisite to the appearance of short duration responses.

Patients 1 and 2, who were somewhat less affected clinically, are interesting because they experienced a distinct "honeymoon" period during the first three months of levodopa therapy. During this time, they required relatively low doses of levodopa and were nearly asymptomatic. Presumably the severity of disease was similar in these two patients as they took exactly the same amounts of MPTP. Patient 2 began experiencing "wearing off" rather abruptly after three months of low dose therapy (60/600 CD/LD daily). Patient 1 is slightly more complicated because he was taken off all medications at this time (during a period of incarceration) and was not started on levodopa therapy again until five months later at which time "wearing off" effect was noticed almost immediately. In these instances, one could argue that prior levodopa therapy played a role in the evolution of "wearing off" effects as has been suggested by Fahn (1982). On the other hand, the time period is far shorter than that which is

usually seen in treating patients with Parkinson's disease, and the dose is rather low. The possibility that these patients had progression of their disease during that time period seems unlikely four months following a toxic insult, although we cannot absolutely rule this out at the present time. The longest interval between initiation of levodopa therapy and appearance of wearing-off effects in this group of patients was eight months (Patient 6).

"Peak-dose" dyskinesias have now been observed in five of our seven patients (patients 6 and 7 being exceptions) and have become dose limiting in four. Because of the rapid evolution of the appearance of side effects, a well defined sequence of events was fairly obvious in each of these patients. In all instances, "peak-dose" dyskinesias followed the onset of "wearing off" effects (although in patient 2 they were seen almost simultaneously). These inevitably followed attempts to provide or restore a long duration response by increasing the total daily medication dosage. All of these patients were on bromocriptine at this time, but the appearance of dyskinesias appeared to correlate best with the levels of levodopa therapy. The lowest dose at which dyskinesias were encountered at the onset was 80/800 mg. of CD/LD in one patient, but all other patients were taking 120/1200 mg. of CD/LD or more at the time of onset of dyskinesias (see Table). The two most severely affected patients (who experienced immediate "wearing off" effects) were the first to develop dyskinesias, the latter occurring at 16 days and four weeks after initiation of treatment (patients 5 and 3 respectively). Overall this represents a relatively high and early incidence of dyskinesias when compared to the reported experience in Parkinson's disease (Mones et al., 1971; Klawans et al., 1977). Further, there appears to be a correlation even within this small group of patients between the severity of disease and the appearance of dyskinesias.

Five of our patients developed fairly clear cut "on-off" phenomenon during the second six months of therapy. This contrasts rather sharply with the typical time of appearance of these oscillations in Parkinson's disease, which are quite unusual during the first year of treatment (Granerus, 1978). While the exact pathophysiology of the "on-off" effect is not clearly understood, Fahn (1982) has suggested that excessive chronic receptor bombardment by dopamine results in sudden desensitization blocks which could then explain the "on-off" effects; this explanation would also account for the long latency before "on-off" phenomenon typically occur. Again, patient 1 is of particular interest. As noted earlier, he experienced an excellent response to low doses of levodopa for three months and then was off all medication for an additional five months. After restarting levodopa (CD/LD 40/400 mg. daily), he was found to have significant "wearing off" effects. After three weeks, his dosage was doubled (80/800 mg. CD/LD). Within 24 hours, he experienced his first clear cut "on-off" effect. Hence, while this patient had received approximately three months of levodopa therapy earlier, he had been on a prolonged drug holiday of five months duration almost immediately preceding these symptoms. One might speculate that abrupt flooding of hypersensitive receptors either caused a sudden desensitization shift of dopamine receptors or perhaps an agonist receptor blockage much as is thought to occur in myasthenia gravis where patients become weak after excessive anti-cholinesterase therapy ("cholinergic crisis"). Animal experiments have shown that levodopa treatment can reverse dopamine receptor supersensitivity (Ezrin-Waters

and Seeman, 1978; Friedhoff et al., 1977). Whether or not receptor sensitization-desensitization changes are valid explanation for "on-off" fluctuations, it seems that prolonged levodopa (i.e., more than one year) is not necessary for these to occur. A recent report of two children with symptomatic parkinsonism treated with levodopa indicates that this phenomenon may be seen within weeks of onset of therapy (Lang et al., 1982). Thus, long-term treatment or progressive pathological changes do not appear critical to the appearance of "on-off" swings in Parkinson's disease, again suggesting that the underlying severity of the disease may be the more critical factor.

It could be argued that age may be a factor in determining the early onset of "on-off" effects of this group of patients. Younger age at disease onset and time of initiation of treatment have both been positively correlated with "on-off" phenomenon (Granerus, 1978; Lesser et al., 1979). Central metabolism of levodopa may be qualitatively or quantitatively different in younger patients. Alternatively, it may simply be that MPTP-induced parkinsonism is different in some critical way from the idiopathic disease that will eventually explain these earlier therapeutic complications. Certainly the onset of parkinsonism was abrupt in these patients. Further, based on our work in the squirrel monkey, and a review of the pathologically studied human case of MPTP-induced parkinsonism, we believe that the extent of nigral cell loss may be more severe than is typically seen in Parkinson's disease. Finally, as will be discussed later, the cellular damage is more restricted than is seen in Parkinson's disease, being limited to the substantia nigra. However, it is interesting to note that the sequence appearance of complications seen with levodopa therapy in these patients faithfully reproduces that seen with long-term treatment of the idiopathic disease. For example, the appearance of dyskinesias usually preceded and to a degree predicted the onset of "on-off" phenomena, and observation which applies equally well to Parkinson's disease (Granerus, 1979; Marsden and Parks, 1976).

Psychiatric complications of levodopa therapy are well described and in fact may be dose-limiting. Our cases are no exception to this observation. Again, patient 1 is of particular interest. His hallucinations have involved bugs crawling on the skin, a type of hallucination which is unusual in our experience with levodopa therapy. These hallucinations appear to be highly dose dependent (occurring every time the total daily dosage of levodopa exceeds 40/400 mg. CD/LD). Because these symptoms were seen within five days of initiation of treatment (when the patient accidentally took twice the prescribed dose), it is difficult to argue that they are the result of long term treatment. This is the only instance where psychiatric complications have become the major dose-limiting factor. Another worrisome observation is the late onset of visual and auditory hallucinations in three more of our patients. This delayed onset is puzzling, and raises the question of a more direct complication of long-term levodopa therapy. Perhaps chronic levodopa therapy is resulting in receptor hypersensitivity, a phenomenon which has been suggested by Klawans and colleagues (1977). However, this presumably would be occurring in the mesolimbic dopaminergic system, an area which we believe to be unaffected pathologically in these patients. It could be argued that a history of drug abuse is a complicating factor, but patient 5 had used drugs less than three months prior to exposure to MPTP and had no psychiatric history.

Of equal interest in terms of the foregoing discussion are the two patients who developed few or none of these complications

(patient 6 and 7). Patient 7 is the least affected clinically and has never been on a dosage of greater than 150/600 mg. of CD/LD per day (maximum dosage range in the other five patients is 125/1250 to 225/2250 mg. CD/LD daily). Patient 6 experienced severe tremor, but rigidity and bradykinesia were minimal components of his illness. While patient 7 was started on levodopa much later than the other patients (see Table), and has been on medication for seven months only, patient 6 was started on levodopa at the same time as our other five patients. In these two patients, the degree of nigral damage is presumably less severe, and to date they have experienced fewer complications of therapy. However, they require lower doses of levodopa therapy for an acceptable therapeutic response. Hence, the amount of total levodopa therapy daily becomes another variable in the equation, making it difficult to draw exact conclusions.

Finally, it seems reasonable to suggest that the full array of typical therapeutic complications which have now been observed in these patients broadens the analogy between MPTP-induced parkinsonism and Parkinson's disease. From a clinical standpoint, these patients have exhibited virtually all of the features of Parkinson's disease, and are now manifesting many of the treatment complications seen in patients with the idiopathic disease. Perhaps the only clear distinction now remaining between these two disease conditions is at the pathological level. The evidence is now quite strong that MPTP selectively destroys the cell of the zona compacta of the substantia nigra, sparing other areas of brain in the human (Davis et al., 1979) and other primates (Burns et al., 1983; Langston et al., 1983b). While this selectivity allows one to infer the neuroanatomical origin of many of the clinical signs seen in our patients, it suggests that this analogy with Parkinson's disease may break down somewhat at the neuropathological level, as the pathological changes seen in Parkinson's disease extend well beyond the substantia nigra (Forno, 1982). It does seem possible that with time there might be secondary degeneration in other areas of brain, but to date, there have been few opportunities to study the long term effects of MPTP in nervous system of primates (including man). Certainly it seems reasonable to suggest that observing these patients over the next few years may provide information which will be of value in broadening our understanding of the pathophysiology and perhaps etiology of Parkinson's disease.

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REFERENCES

- Barbeau A (1980) High-level levodopa therapy in severely akinetic parkinsonian patients: Twelve years later. *In: Parkinson's Disease: Current Progress, Problems, and Management*, Rinne UK, Klingler M, Stamm G (eds). Elsevier/North Holland Biomedical Press, Amsterdam, pp 229-239.
- Burns RS, Chiueh CC, Markey SP, Ebert MH, Jacobowitz DM, Kopin IJ (1983) A primate model of parkinsonism: Selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine. *Proc Natl Acad Sci* 80: 4546-4550.
- David GC, Williams AC, Markey SP, Ebert MH, Caine ED, Reichert CM, Kopin IJ (1979) Chronic parkinsonism secondary to intravenous injection of meperidine analogues. *Psychiatry Res* 1: 249-254.
- Ezrin-Waters C, Seeman P (1978) L-Dopa reversal of hyperdopaminergic behavior. *Life Sci* 22: 1027-1032.

- Fahn S (1982) Fluctuations of disability in Parkinson's Disease: Pathophysiology. In: Movement Disorders, Marsden CD, Fahn S (eds). Butterworth Scientific, London, pp 123-145.
- Forno LS (1982) Pathology of Parkinson's Disease. In: Movement Disorders, Marsden CD, Fahn S (eds). Butterworth Scientific, London, pp 25-40.
- Friedhoff AJ, Bonnett K, Rosengarten H (1977) Reversal of two manifestations of dopamine receptor supersensitivity by administration of L-dopa. *Res Commun Chem Pathol Pharmacol* 16: 411-423.
- Granerus AK (1978) Factors influencing the occurrence of "on-off" symptoms during long-term treatment with L-dopa. *Acta Med Scand* 203: 75-78.
- Hoehn MM, Yahr MD (1967) Parkinsonism: Onset, progression and mortality. *Neurology* 17: 427-442.
- Klawans HL, Goetz C, Nausidea PA, Weiner WJ (1977) Levodopa-induced dopamine receptor hypersensitivity. *Ann Neurol* 2: 125-129.
- Lang AE, Meadows JC, Parkes JO, Marsden CD (1982) Early onset of the "on-off" phenomenon in children with symptomatic Parkinsonism. *J Neurol, Neurosurg and Psychiat* 45: 823-825.
- Langston JW, Ballard P, Tetrud JW, Irwin I (1983a) Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 219: 979-980.
- Langston JW, Forno LS, Rebert CS, Irwin I (In press (b)) Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1, 2, 5, 6-tetrahydropyridine (MPTP) in the squirrel monkey. *Brain Research*.
- Lesser RP, Fahn S, Snider SR, Cote LJ, Isgreen WP, Barrett RE (1979) Analysis of the clinical problems in parkinsonism and the complications of long-term levodopa therapy. *Neurology* 29: 1253-1260.
- Marsden CD, Parkes JD (1976) "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy. *Lancet* 1: 292-296.
- Mones RJ, Elizan TS, Siegel, GJ (1971) Analysis of L-dopa induced dyskinesias in 51 patients with Parkinsonism. *J Neurol Neurosurg Psychiat* 34: 668-673.
- Muenter MD, Tyce GM (1971) L-dopa therapy of Parkinson's disease: Plasma L-dopa concentrations, therapeutic response, and side effects. *Mayo Clinic Proceedings* 46: 231-239.
- Shoulson I, Glaubiger GA, Chase TN (1975) On-off response: Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. *Neurology* 25: 1144-1148.
- Sweet RD, McDowell FH (1975) Five years' treatment of Parkinson's disease with levodopa: Therapeutic results and survival of 100 patients. *Ann Intern Med* 83: 456-463.