Parkinson's Syndrome, Depression and Imipramine

A Preliminary Report

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• Patients with Parkinson's syndrome whose major symptoms are akinesis, rigidity, inertia, depression, irritability and failure of adaptation rather than tremor appear to benefit in a global way from therapy with imipramine. Patients without much over-all functional impairment do not show this improvement. The hypothesis is offered that motivation to move and ability to move are perhaps neurologically as well as psychologically related functions.

OBSERVATION of the effects of imipramine (Tofranil®) on patients with involutional depression who were undergoing psychotherapy led to a trial of the drug in patients with Parkinson's syndrome.

As to the patients who were receiving the drug during psychotherapy, the symptoms that seemed to improve first and most dramatically were those of psychomotor retardation, inertia and problems in decision-making and action-taking. Changes in these functions appeared pertinent to Mettler's descriptions of 47 patients with Parkinson's disease in Greystone Hospital,[2] 34 of whom appeared to be rather uniform as to reasons for hospitalization: Problems in decision-making (which Mettler called "pseudorigidity" of personality functioning), depression, inaccessibility, somatomotor deficits of diffuse type resulting in inability to react to the environment and lack of motivation to behave adaptively. Mettler felt these people resembled animals that had striatal lesions and could not initiate and perform movements necessary to remove themselves from noxious stimuli, even though they had intact sensorium and functioning motor system. He called this a defect in "prohairesis." It was this rather loose but stimulating conceptual framework that led to our more or less empirical trial of imipramine for Parkinson's disease.

METHODS AND MATERIALS

Our experimental design has gone through three phases: The first, involving seven patients, consisted of just the use of the drug, starting with 100 mg. (four tablets) per day and graduating to 250 mg., without otherwise departing from the regimen the patients were following at the time. We observed the patients weekly for four or five weeks, and then at gradually lengthening intervals. The second phase, involving eight patients, consisted of the use of psychological tests before and after a month's trial of the drug, a three-page physical therapy check list before and after, and objective neurological examinations including timed, rapidly alternating movement of each hand for thirty seconds. The third phase, not yet completed, consists of the same methods as the second, but this time using a double blind technique and including 20 patients. Since this drug appears to have its most pronounced effect on certain kinds of patients with Parkinson's syndrome, this third phase is being carried out in an attempt to find a way to predict which patients will benefit. The double blind study is being done on patients unselectively, just as they come to our clinic.

The present report deals with a group of 15 patients made up of those who had been rejected for operation, those who had not been helped by other drugs and those who in general presented clinical management problems.

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RESULTS

Following treatment, the patients appeared to be divided into three groups.

Group 1

The first group of five showed mild neurologic improvement. They could perform rapidly alternating movements 10 to 30 per cent better than before treatment, could write better, sew better, get up and sit down with greater ease and walk more freely, and in general had moderate improvement in fine movements and manipulations. Tremor was infrequently and only slightly changed by this drug.

The mild improvement occurred in patients with minimal defect in over-all functioning level and in patients who appeared both in their tests and interview to be least psychologically disturbed. This moderate but definite change in akinesis and rigidity

perhaps is related to Himwich's[1] recent observation that imipramine reverses akinetic, staring states in animals induced by injections of reserpine. Biochemical studies thus far, however, have shown that this drug does not alter monoamine oxidase or serotonin metabolism in brain tissue.[3]

Group 2

The second group of five were those who failed to get any improvement; some actually got worse. These patients became somnolent, manifested an increase in rigidity, developed akinetic states, fell more often and in general functioned more poorly. Two of these five were postoperative thalamotomy patients (although one of our three postthalamotomy patients made the improvement described for Group 1), and two of them were of the postencephalitic type. Three of the patients in Group 2 looked in many respects like those in the group with dramatic, over-all improvement that are described below, but they did not improve. The psychological tests before and after treatment either showed no significant change or became more abnormal. Tremor was unchanged.

Group 3

The third group of five manifested a most dramatic, over-all improvement. Four of the five had been considered candidates for custodial hospital care by their relatives. The fifth was a man who was about to give up a thriving business because of his inability to talk, walk and function. Four of the five had to have care of a nursing type. They could not dress, cook or keep themselves clean. Two of the five needed someone else helping them on and off the toilet, feeding them and turning them in bed. Severe rigidity and akinesia rather than tremor characterized this group. They were quite depressed, and in general out of contact with their environment in an adaptive sense. They were irritable, could not make decisions and were a burden on their relatives. They had great difficulty in starting, stopping and turning, in performing repeated or fine movement, in rising from a chair; and occasionally they had trouble in swallowing and talking. These patients were not good subjects for operative treatment and all of them had received most of the anti-Parkinson disease drugs, singly and in combination, without significant improvement.

Following one to three weeks of imipramine in dosages up to 250 mg. per day, over-all function improved considerably. Relatives called the change a "miracle." The ability of the patients to do timed rapidly alternating movements improved from 100 to 700 per cent. They all began to care for themselves. Only one of the patients retained someone to help her, although she was able to feed and dress herself, walk and cook—things she had not done in three years. One patient had spent his days in bed, and his wife had had to feed and dress him, and clean him after defecation. Three weeks after treatment was started, he was gardening, helping around the house and looking for carpentry work. The businessman moved to a larger location and began addressing and sending out his own mail, which he had not been able to do for three to four years. His ability to rise, turn, start and stop was strikingly improved. In two cases, associative movement with walking returned after it had been absent for several years. Clinical evidence of depression was lifted in these five cases, and indecision, inertia and lack of motivation were reversed. Four patients were receiving imipramine alone and one was taking trihexiphenidyl (Artane®) and imipramine. Tremor became more predominant in two.

Psychological tests revealed that the changes in Group 3 were either one or the other of two orders. Either most of the disturbance seemed much less and depression was ameliorated, or the depression so far as the tests could determine remained unchanged (we speculated probably a long standing characterological one). The patients saw themselves, however, as much less sick, less needing help and as more dominant people.

DISCUSSION

Interpretation of the change in Group 3 is difficult. One must be aware of the placebo effect, especially of an investigational drug, on a disease that is evaluated on the basis of voluntary motor participation. We believe that some "control" of the placebo factor is supplied in the fact that there were many previous trials of other agents. Even so, this aspect will be examined more closely in the double blind part of our study.

Conjecture as to specific modes of action and effects leads to a tangle of neurological and psychiatric variables. One might say that these patients who have used activity as a way of fending off psychological disturbance and especially depression will become psychologically ill when faced with an activity-constricting neurological disease such as Parkinsonism. On the other hand, a depression will certainly make functioning to overcome physical handicaps less likely. Thus, perhaps in these patients, psychological illness (depression) combines synergistically with the akinetic and rigid features of Parkinson's disease.

The mild anti-Parkinson effect of this drug or alleviation of depression does not seem to account entirely for the changes we have observed. One might wonder if this drug works through a diffuse neuronal system (the extrapyramidal system) which, in its upward and downward extensions, influences rigidity, akinesia, motivation and mood conjointly.

Speculations aside, it appears that there is a group of patients with predominantly akinesis, rigidity, inertia, depression, irritability and severe functional impairment that are helped in a rather remarkable way by imipramine.

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