

marked deficiency of a chemical called dopamine in the brain, the cause of which is unknown in the majority of cases. Parkinson's disease mainly strikes the aged, with onset between the ages of 50 and 70 in two-thirds of the cases. However, a rare juvenile form also exists. The disease affects close to one million persons, and there are 50,000 new cases each year.

Following its clinical introduction, L-dopa quickly became the preferred treatment and remains so today in a number of derivative forms. Although it does not cure the disease, it retards progress toward complete debilitation so that patients remain functional for several additional years. Symptoms present at the initiation of L-dopa treatment are generally reduced dramatically but reappear gradually, along with other symptoms that may be associated with the therapy.

In a broader context, L-dopa represents a dramatic advance in the treatment of diseases of the brain. It has provided a rational approach to medical treatment based on brain biochemistry and has stimulated interest in research on neutral diseases based on similar biochemical principles.

History In the early 1950's, there was widespread interest in the biochemistry of trace metals, and the use of radiotracers was developing. Dr. George C. Cotzias of BNL was searching for a research area employing radioisotopes of trace metals to study the chemical effects of the metals in humans over long periods. Links between manganese poisoning and Parkinson's disease had been discussed in the literature. Dr. Cotzias investigated manganese-56 because it was easy to make and had an appropriate half-life.

Although it turned out that there was not a good connection between Parkinson's disease and manganese poisoning, several important new areas of research evolved from these studies. One stemmed from Dr. Cotzias's understanding, gained in his research, of how the chemical

Table 4. Life Expectancy for Pre-L-dopa and Post-L-dopa Treatment

Age at Onset of Disease (Years)	Normal Life Expectancy (Years)	Life Expectancy (Years)		
		Pre-L-dopa ^a	Post-L-dopa ^b	Post-L-dopa ^c
50	23	13	19	20
60	15	8	11	12

^aExcess mortality rates calculated from Hoen and Yahr, "Neurology 17, 427-42 (1967).

^bExcess mortality rates calculated by Macdowell, Papavasiliou and Sweet, 1979.

^cExcess mortality rates calculated by Diamond and Markham, 1979

balance in the body gradually changed when a new substance was introduced.

The deficiency of the amino acid dopamine in the brains of persons suffering from Parkinson's disease had recently been discovered. Although it was not possible to introduce dopamine directly into the brain, it had been postulated that intravenous introduction of its metabolic precursor, levodopamine, might correct the brain dopamine level. Short-term clinical trials were unsuccessful; however, they were inconclusive and produced adverse reactions.

Dr. Cotzias recognized the need for very gradual L-dopa administration over long periods. The research hospital at BNL provided the capability for the necessary clinical trials, which proved successful. The first report of long-term L-dopa treatment was published by Dr. Cotzias in *The New England Journal of Medicine* in 1968, and a follow-up report on the results of a 2-year clinical study was published in the same journal in 1969. A February 1969 editorial described his work as "the most important contribution to medical therapy of a neurological disease in the past 50 years." Dr. Cotzias received the Albert and Mary Lasker Award for Experimental Medicine in 1969.

Benefits The two major benefits associated with the use of L-dopa in the treatment of Parkinson's disease are extension of life expectancy and delay of disability.

1. **Extension of life expectancy.** Two studies provide a basis for measuring the effect of L-dopa treatment for increasing the life expectancy of a patient. The first study followed a group of 100 patients on L-dopa therapy for 10 years beginning in 1968. During that period, 56 died, leading to a calculated excess mortality ratio of 1.54 for untreated patients. The second study surveyed a random sample of 327 patients who were being treated with an L-dopa derivative over a 5-year period and found an excess mortality ratio of 1.42 for untreated patients. These figures can be translated into an individual life expectancy extension for treated patients with an assumed age of disease onset (see Table 4).

2. **Delay of disability.** L-dopa therapy has also been found to produce moderate to marked improvement in 50 to 75 percent of Parkinson's disease patient's ability to function. Two studies demonstrate the initial improvement and subsequent decay of independent performances of patients treated with L-dopa.

A disability index related to symptoms and ability to perform normal functions was calculated at various times during the 10-year period. For the 41 patients who remained in the study throughout the period, the average disability index improved initially, but at the end of 10 years, the index was the