Monkey Model of Parkinson's Disease

A contaminant of illicit drugs has caused Parkinson's disease in humans and monkeys

Scientists at the National Institute of Mental Health (NIMH) recently discovered a simple and highly effective way to produce Parkinson's disease in monkeys. Although there have been previous attempts to produce animal models of this disease, the other methods either fail to produce all the symptoms or are too short-lived.

The discovery of this new way to produce Parkinson's disease in animals arose from clinical investigations of young people taking illicit drugs who seemed to be suddenly developing a severe form of the disease. Normally, Parkinson's disease develops slowly in older people. It turned out that a contaminant of the drugs these young people were taking selectively destroys cells in the substantia nigra—the portion of the brain that produces dopamine and that deteriorates in Parkinson's disease.

The first of these young patients was a 23-year-old man, a chemistry graduate student, referred to the NIMH in 1977 for evaluation. He was mute, unable to move or swallow, and he had a tremor. His symptoms subsided when he was given L-dopa. The immediate question the NIMH neurologists asked was, what caused this man to get symptoms that looked like Parkinson's disease? They began to inquire about the drugs he had taken.

"Since the age of 13 or 14 he had taken drugs of various types," says Irwin Kopin, one of the NIMH researchers. "A cocaine-Demerol (meperidine) mixture was his current favorite but he was having difficulty getting the Demerol. He learned to synthesize a compound related to Demerol in a home laboratory he set up in his basement and he made several batches."

At first, Kopin recounts, all went well, but by the fifth batch the man got "sloppy" and tried to cut down the reaction times by doing the experiments at a higher temperature. He inadvertently produced a by-product, *N*-methyl-4-phenyl-1236 tetra-hydro-pyridene (NMPTP). It was this by-product, the NIMH scientists later learned, that produced his symptoms of Parkinson's disease.

This first patient with drug-induced Parkinson's disease persisted in abusing drugs, including the L-dopa used to treat him, and died of an overdose of cocaine in 1978. When NIMH scientists Kopin, Richard Burns, and Sanford Mackey examined his brain, they saw, says Kopin, "lesions in his brain that are typical of aged Parkinson's disease patients." The cells of his substantia nigra were largely destroyed and there was a Lewy body—a structure typically found in brains of Parkinson's patients.

The NIMH scientists, meanwhile, tried unsuccessfully to use NMPTP to produce Parkinson's disease in guinea pigs, rats, and cats. Then, last summer, several young heroin users in California suddenly developed severe parkinsonism. They were referred to J. William Langston of Stanford and, eventually, it was learned that their symptoms had been caused by the same by-product that the first patient took, only this time the by-product was present in a "new heroin" being sold on the street.

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Two of these California patients were brothers who were sent to the NIMH for care. They were so severely affected that, without L-dopa, they were completely immobile, able to move only their eyes. It became clear from these two cases and the others that the parkinsonism did not develop from a single dose of NMPTP. Instead, the drug was used repeatedly for days before symptoms developed. What the NIMH scientists fear, however, is that others who took only one or two doses of drugs contaminated with NMPTP may now have subclinical damage to the substantia nigra. When they get older and lose subtantia nigra cells as part of the normal aging process, they may be pushed over the edge to parkinsonism.

Following the rash of drug-induced Parkinson's disease in California, the NIMH scientists tried to produce Parkinson's disease in monkeys by giving them NMPTP. In the first week of November 1982 they succeeded.

Burns explained that the monkey model of Parkinson's disease is different from all previous models because the drug specifically knocks out the nigra-striatal dopamine system of the brain and because the monkeys "have all the major clinical features of Parkinson's disease in humans. They have all the major pathological changes, all the major chemical changes, and they respond similarly to the major categories of drugs used to treat parkinsonism."

One promising use of the monkeys is to test new drugs. Currently, it is very expensive to test anti-parkinsonism drugs because they must be tested in humans and the human studies require long hospitalizations and elaborate clinical tests. Other possibilities are that the monkeys may allow researchers to understand on-off effects and dyskinesia in Parkinson's disease patients.

Some patients taking L-dopa will suddenly become completely immobile for periods of 2 to 3 minutes. These on-off effects are thought to be related to the functioning of dopamine receptors, but no one knows for sure. If some monkeys develop these effects, it would be possible to compare their brains to those of monkeys that do not develop them and to look for differences in receptors.

Another adverse effect in patients with Parkinson's disease is hyperactivity, or dyskinesia. "One of our patients (with drug-induced parkinsonism) and some of the California patients developed dyskinesia. Our monkeys probably will develop it too," says Burns. Once again, the monkeys may make it possible to learn why this side effect develops and how to prevent it.

Mackey speculates that the drug-induced parkinsonism may also lead to an understanding of why this disease occurs naturally in older people. "We have found that a small, peripherally administered molecule causes specific damage. In all the possible causes of Parkinson's disease being investigated, that's one that hasn't been given much credence," he says. Instead, people have looked for immunological causes or infectious agents such as slow viruses. According to Mackey, it would be worthwhile to examine the possibility that NMPTP may be present in some people's diet or in the environment or that it is made within the body.—**GINA KOLATA**