to improving the mathematical techniques for extracting measurements from the raw data to developing new ways of incorporating satellite data into forecast models. A conceptually simple experiment has been to mount a radiometer called VAS on the geostationary GOES-5 satellite rather than a polar-orbiting satellite. That increased the horizontal resolution and provided nearly continuous rather than twice daily coverage.

John Le Marshall of the Cooperative Institute for Meteorological Satellite Studies in Madison, Wisconsin, and William Smith and Geary Callan of the National Oceanic and Atmospheric Administration in Madison found that the VAS data reduced the mean position error in two 12-hour forecasts of Hurricane Debby from 139 to 50 kilometers (*4*). Analysis results from 12 storms are still encouraging, says Smith, but still do not represent strong statistical evidence of a consistent positive effect.

Such evidence of a positive effect in the Northern Hemisphere is something that all satellite observing system experiments still lack. Pre-FGGE computer experiments had indicated that the effect of satellites would be far more evident, probably because of a flaw in experiments designed to run on simulated data in the absence of real observations. In part to acquire such statistically valid evidence, an international field experiment will be conducted over the North Atlantic beginning in 1986. The observing systems tested during FGGE—including satellites, aircraft, ships, and buoys—will operate for 1 year to produce a sufficient number of cases for observing system experiments.

—RICHARD A. KERR

References

1. R. A. Kerr, *Science* **228**, 704 (1985).
2. *Data Assimilation Systems and Observing System Experiments with Particular Emphasis on FGGE, Vol. 1*, proceedings of a seminar and workshop held 3–11 September 1984 in Reading, United Kingdom (European Center for Medium Range Weather Forecasts, Reading, England, 1985).
3. *Proceedings of the First National Workshop on the Global Weather Experiment*, held July 1984 at Woods Hole, Massachusetts (National Academy of Science, Washington, D.C., in press).
4. J. F. Le Marshall, W. L. Smith, G. M. Callan, *Bull. Am. Meteorol. Soc.* **66**, 258 (1985).

Parkinson's Disease: An Environmental Cause?

As the pace of research on drug-induced Parkinsonism increases, data are produced, and disputed, that identify pesticides as causative agents

It is little more than 2 years since researchers in several laboratories discovered that a relatively simple pyridine compound, 1-methyl-4-phenyl-1,2,3-tetrahydropyridine (MPTP), induces a parkinsonian-like state in humans and some animals (*1*). The discovery stemmed from an incident in which a "synthetic heroin" was contaminated with by-product MPTP that produced severe neuropathies in several dozen young people in southern California (*2*). As a consequence of this unfortunate episode, however, there has been a tremendous surge of research in the United States and throughout Europe on the mechanism of action of the chemical, which some consider might give insights into the etiology of the natural disease. Four separate conferences on the topic within the past several weeks attest to the intensity of research activity, especially as most of the data presented are yet to reach the printed page.

Parkinson's disease, which involves degeneration of certain dopaminergic neurons in the substantia nigra of the midbrain, typically develops late in life. Treatment with L-dopa usually relieves the neurological symptoms, which include tremor, partial or complete paralysis, and characteristic posture, but with time the condition usually deteriorates.

People who have been exposed to MPTP develop within a few days clinical symptoms that are virtually indistinguishable from those of the natural disease. On the neuropathological level, however, there are some differences. Although the neurons of the substantia nigra are affected in both conditions, some groups of cells that look pathological in the natural disease are apparently unaffected in the drug-induced state. Most significantly, characteristic inclusions derived from neurofilaments, known as Lewy bodies, are present in the natural disease but absent in the MPTP syndrome.

One argument offered to explain the differences at the cellular level is that the MPTP syndrome is an acute condition brought about by the acceleration of naturally occurring processes. The more diffuse pathology, including the Lewy bodies, of the natural disease might simply be the product of time, it is suggested.

The striking chemical similarity of MPTP and its metabolites with certain industrial chemicals, specifically the herbicide paraquat, is sufficient to persuade some observers that Parkinson's disease is environmentally caused and that the MPTP syndrome is therefore a very direct model of the natural disease. Opponents of this view say that the natural condition simply does not have the appearance of paraquat-like toxicity at the cellular level and that evidence on the involvement of environmental agents is negative. The balance of opinion at a recent meeting held at the National Institutes of Health (NIH)* supported the position that Parkinson's is not an environmental disease.

Therefore, evidence presented a few days later by Andre Barbeau and his colleagues at a subsequent meeting in New York came as something of a surprise.† Barbeau, who is at the Clinical Research Institute of Montreal, collected data on the incidence of Parkinson's disease in the nine hydrographic regions of Quebec Province and matched it with pesticide use. The Montreal team used four independent methods to track the disease incidence and came up with more than 5000 cases in all. The correlation between disease incidence and level of pesticide use was very strong—0.967.

An area southwest of Montreal, Quebec's "breadbasket," recorded the highest rural incidence, 0.89 per thousand of population compared with 0.13 per thousand in regions where pesticide use was low. In Montreal itself there was a similar disparity between the industrialized east of the island and the residential west. All comparisons were adjusted for age structure of the populations.

Barbeau and his colleagues stress that pesticides are just one class of potential environmental neurotoxin that might be important in the etiology of Parkinson's

*Symposium on MPTP, Uniformed Services University of the Health Sciences, Bethesda, Maryland, 6–7 June.
†The Eighth International Symposium on Parkinson's Disease, New York, 9–12 June.

disease. There are in fact scores of pyridine compounds in the environment, most of them products of the chemical industry. Barbeau notes that Parkinson's disease was unknown before the industrial revolution, and its incidence rose rapidly through the 19th century, apparently to plateau in the early decades of this century. He does, however, expect a further upsurge in incidence as a consequence of the relatively recent introduction of the paraquat-like pesticides.

The Montreal researchers further support their case by demonstrating that 67 percent of Parkinson's disease patients have a genetic deficiency in certain detoxifying enzymes of the liver, the P450 monoxygenases, which render harmless foreign chemicals such as paraquat. This compares with 18 percent in the normal population.

All these data contrast with the arguments presented at the NIH meeting by Roswell Eldridge, of the neuroepidemiology branch of the National Institute of Neurological and Communicative Disorders and Stroke. He noted that comparisons between nations of different degrees of industrialization reveal no significant difference in disease incidence, an observation that Barbeau disputes. An analysis of British data by Roger Duvoisin and R.C. Schweitzer, of Rutgers Medical School, has shown no increase in incidence since the 1940's, he said, which was paralleled by a study in Rochester, Minnesota. Eldridge also cited studies on 43 identical twin pairs from the United States, which showed only two sets to be concordant for the disease. Again, studies in the United Kingdom and Finland are in line with this result.

None of this makes a strong case for the involvement of either a heritable genetic defect or an environmental agent. Instead, Eldridge proposes developmental differences that might endow some people with lower numbers of dopaminergic neurons than others. Those with low numbers would be more likely to be at risk from the effects of the steady loss of neurons throughout life. This suggestion accords with the inference from the U.S. twin study that the disease sufferers were united by a more subdued, inward-looking personality compared with their sibling, a difference that could usually be identified from childhood. There is some indication from observations on animals that subdued behavior correlates with low levels of dopamine neurons.

The direct conflict between the data offered by Barbeau and the position argued by Eldridge is unresolvable as yet, but is clearly crucial to the development of further ideas.

One of the main messages of the NIH meeting was the consolidation of a finding reported earlier this year by Solomon Snyder and his group at the Johns Hopkins University School of Medicine (*3*), which relates to the site of metabolism of the MPTP once it has entered the brain.

One of the first major advances in the study of the mode of action of MPTP was the discovery that MPTP itself was not the toxin: toxicity depended on the metabolism by monoamine oxidase B to 1-methyl-4-phenyl-2,3-dihydropyridine (MPDP+), which is then transformed to the major stable metabolite 1-methyl-4-phenylpyridinium ion (MPP+). For instance, administration of monoamine oxidase B inhibitors protects an animal from subsequent treatment with MPTP. The question was, where was this taking place? And, more specifically, why were the dopaminergic cells of the substantia nigra so selectively destroyed?

In a Canadian study, the correlation between disease incidence and level of pesticide use was very strong—0.967.

The similarities between dopamine and MPTP were obvious and it was assumed that the subtantia nigra neurons selectively took in MPTP, which was then converted to the toxic MPP+. Being a charged species, it was further assumed that MPP+ would then be unable to escape from the nigral neuron, whose fate would then be sealed.

As Snyder demonstrated, however, and as several groups have since confirmed, the conversion of MPTP to MPP+ appears to go on in the supporting glial cells, the astrocytes, not in the neurons. The MPP+ is then highly selectively taken up by the dopamine uptake system of the nigral cell neurons. Block the dopamine uptake system, using any one of several amphetamine-like compounds, and the toxic effect of MPTP administration is prevented, at least in mice.

If this description is indeed correct, it must probably spell the end of one of the popular explanations of the mode of toxicity, which was proposed principally by Neal Castagnoli and Anthony Trevor of the University of California, San Francisco. They argued that the transformation of MPTP to MPP+ might generate many toxic species, perhaps involving interactions with dopamine, which would be lethal to the cell. If the astrocyte is the site of transformation, however, this argument in its basic form can no longer apply.

There was a lot of support at the NIH meeting for the notion that MPP+ is the toxic agent, which is perhaps not surprising in view of its similarity to paraquat. Several laboratories, including that of William Nicklas and Richard Heikkila at Rutgers Medical School, presented evidence that the species interferes with the first step of the electron transport chain of mitochondria, thus blocking respiration and killing the cell. The ion can also cause chemical havoc by generating oxidative stress, which results from the continuous formation of oxygen radicals, as Markey and co-workers have emphasized.

The general model as it stands at present, with MPTP conversion to MPP+ occurring in glia, followed by selective uptake by dopaminergic neurons, might explain the delayed onset of symptoms in patients exposed to MPTP, as noted by William Langston of Stanford University. MPP+ is known to remain in the brains of primates for some days after MPTP administration, so perhaps there is a slow shift from glia and subsequent concentration in striatal neurons. The scheme might also explain some of the species differences in susceptibility to MPTP. Rats and mice, for instance, are much less vulnerable than are primates, which might be related to a demonstrably much faster loss of MPP+ from the brain. And, in contrast with the results on mice, Langston and his colleagues have as yet been unable to demonstrate the protective effect of dopamine uptake blockers in monkeys dosed with MPTP. The meaning of this difference is as yet unclear.

For all its advances, the new scheme still does not explain adequately why the neurons of the substantia nigra suffer most while other dopaminergic neurons remain relatively unscathed. The answer may be simply quantitative: that the nigral cells accumulate much more MPP+ than do others. But that would seem be too simple a conclusion to what is turning out to be a very complex story.

—ROGER LEWIN

References

1. J. W. Langston, P. Ballard, J.W. Tetrud, I. Irwin, *Science* **219**, 979 (1983); R. S. Burns *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **80**, 4546 (1983).
2. R. Lewin, *Science* **224**, 1083 (1984).
3. J. A. Javitch *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **82**, 2173 (1985).