

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

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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 dis-

ease. 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 monooxygenases, 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 substantia 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 Fran-

cisco. 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 Heikkilä 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

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Pesticides, Parkinson Disease Linked

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MONTREAL (AFP) — Parkinson's disease, which leads to body spasms and muscle stiffness, is partly caused by excessive use of pesticides, according to a top Canadian researcher.

André Barbeau, head of neurobiology at the Clinical Research Institute in Montreal, said he found more victims of Parkinson's disease in agricultural areas sprayed with exceptionally high levels of pesticides. He noted that aging and genetics were other factors that caused the disease.

Neue Untersuchungen über Ursachen der Parkinsonschen Krankheit

Herbizide als Auslöser?

Um eine Standortbestimmung bei der Behandlung und den Erkenntnissen um die Entstehung der Parkinsonschen Krankheit ist es bei der diesjährigen Tagung der Schweizerischen Neurologischen Gesellschaft und der schweizerischen Gesellschaft der Neurochirurgen in St. Gallen gegangen. Bei der Tagung wurden ausserdem neueste Erkenntnisse über die Gefässerkrankungen des zentralen Nervensystems ausgetauscht.

AZ. St. Gallen. Wie der Leiter der Tagung, Professor Eberhard Ketz, ausführte, beschäftigte man sich mit neuen Ergebnissen der Forschung über die Parkinsonsche Krankheit. Bei dieser Erkrankung kommt es zu Bewegungserstarrung, aber auch zu einem Bewegungsüberschuss bei den Erkrankten. Letzteres führte zur Bezeichnung «Schüttellähmung» für die 1817 erstmals beschriebene Krankheit. Ausgelöst werde die Parkinsonsche Krankheit dadurch, dass sich der Farbstoff Melanin in verschiedenen Hirnzentren auflöse und dadurch die Bildung eines Stoffes gestoppt werde, der Informatio-

nen zwischen den Nerven übertrage (Dopamin). Bisher wisse man zwar, so Eberhard Ketz, dass die Krankheit durch langfristige und hohe Psychopharmak-Abgabe und durch andere Krankheiten ausgelöst werde. Allerdings seien die Ursprünge der Krankheit weiterhin unbekannt und so könne man auch heute noch die Krankheit lediglich in ihrem Verlauf verzögern, nicht aber heilen. Alle heute bekannten Medikamente verlören nach etwa zehn bis zwölf Jahren Einnahmedauer an Wirksamkeit.

Vor einigen Jahren seien nun Fälle aus den USA bekannt geworden, bei denen Hero-

insüchtige an Schüttellähmung erkrankten. Wie sich herausstellte war das Heroin, das die Süchtigen benutzten, mit einem bestimmten Pflanzenschutzmittel gestreckt worden. Dieses Mittel hatte nun im Gehirn der Betroffenen bestimmte Zentren ausfallen lassen.

Die Forschung beschäftige sich nun damit, «dass es nicht ausgeschlossen ist, dass ein Umweltfaktor z.B. in Zusammenhang mit einem Herbizid» krankheitsauslösend sein könnte. Bekannt sei beispielsweise schon seit langem, dass Kohlenmonoxidvergiftungen solche Wirkungen haben können. In Europa sei bisher allerdings noch kein entsprechender Fall bekannt geworden.

Auch in den USA seien die Forschungen noch nicht so weit gediehen, dass daraus gültige Schlussfolgerungen gezogen werden könnten. So habe man zwar einen weiteren Erkrankungsfall, der einen Laboranten betreffe; unbedingt nötig seien aber grossangelegte Untersuchungen.

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El mal de Parkinson, relacionado con un pesticida

Descrita por primera vez por el doctor James Parkinson en 1817, la enfermedad que lleva su nombre es un trastorno neurológico que afecta esencialmente a los núcleos de la base del cerebro.

Puede manifestarse a partir del octavo decenio de la vida del ser humano siendo sus manifestaciones clínicas características. Los síntomas incluyen temblores, parálisis total o parcial, posturas específicas, trastornos de la marcha y del habla, teniendo una progresión gradual y un curso prolongado. La alteración bioquímica consiste en la degeneración de ciertas neuronas que utilizan un compuesto denominado dopamina como neurotransmisor. Aunque en la actualidad existen tratamientos médicos que modifican favorablemente los síntomas, la enfermedad tiene origen desconocido. El tratamiento actual consiste esencialmente en proporcionar una serie de fármacos que aumentan la concentración del neurotransmisor dopamina del que estas células carecen o son deficitarias.

Las lesiones observadas en el cerebro de los pacientes son características y fácilmente identificables por un buen patólogo.

En los últimos años ciertos descubrimientos están ofreciendo clarificaciones con respecto a la causa desencadenante. Los nuevos conocimientos, aunque no resuelven completamente todas las incógnitas de la enfermedad, constituyen vías originales de investigación.

Como en tantas otras ocasiones, la casualidad sumada a la intuición científica proporcionaron hace un par de años una pista fundamental a los investigadores: el doctor J.V. Langston (del Medical



Adolf Hitler padeció la enfermedad de Parkinson

Center de Santa Clara, EE.UU.) observó la aparición de la enfermedad en pacientes jóvenes. Al profundizar en la investigación patológica de estos casos anormales en cuanto a la edad de los enfermos descubrió que todos ellos habían sido consumidores de un tipo de heroína sintética contaminada con un producto piridínico, el 1-metil 4-fenil 1,2,3-tetrahidropiridina (MPTP). Sorprendentemente, estos pacientes, al contrario de lo que ocurre en la evolución natural de la enfermedad, desarrollaban los síntomas clínicos característicos en pocos días.

Las lesiones observadas en las células nerviosas eran algo dife-

rentes a las habituales, aunque se arguyó que la diferencia radicaba en la agudeza en el desarrollo de la enfermedad. Esta relación directa entre un producto químico y la aparición de una enfermedad neurológica como el Parkinson orientaron las investigaciones hacia factores ambientales.

El estrecho parentesco químico entre el MPTP y sus metabolitos (productos de degradación) con ciertos pesticidas químicos como el "paraquat" orientó a determinados grupos de trabajo a tratar de buscar una relación epidemiológica ambiental entre la enfermedad y el contacto con este pesticida. En el VIII Simposio Interna-

Parkinson celebrado en Nueva York del 9 al 12 de junio pasado, el doctor Andre Barbeau y su equipo del Instituto de Investigación Clínica de Montreal presentaron los resultados de su investigación al respecto.

Barbeau recogió los datos de nueve regiones de la provincia de Quebec, estableciendo su relación con el uso del "paraquat". El estudio de más de cinco mil casos confirmó la existencia de una relación estadísticamente significativa entre el agente químico y la incidencia de la enfermedad. Barbeau hizo notar asimismo que la enfermedad era prácticamente desconocida antes de la era industrial y que su desarrollo ha aumentado a partir del siglo XIX. Como dato adicional, los investigadores de Montreal encontraron que el 67 por ciento de estos enfermos padecían una deficiencia genética de un enzima desintoxicante hepático (el P 450 monooxigenasa) que tiene como función la eliminación de agentes químicos extraños, carencia que es de tan sólo el 18 por ciento en la población normal. La suma de estos dos factores, el genético y el de exposición al pesticida, serían los determinantes de esta mayor incidencia de la enfermedad.

Aunque estas investigaciones son discutidas por otros neurólogos que consideran que esta tesis no explica todas las características de la enfermedad "natural", todos ellos admiten la evidencia de que un factor químico ambiental podría ser si no la causa fundamental un coadyuvante importante en el hasta ahora oscuro origen del mal de Parkinson.

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