Environmental Hypothesis for Brain Diseases Strengthened by New Data

A combination of dogged determination and inspired science appears to have solved the mystery of a brain disease on Guam and adds fuel to a controversial hypothesis in neurology

On page 517 of this issue of *Science* Peter S. Spencer and his colleagues at the Albert Einstein College of Medicine, New York, describe results on experimental monkeys that add weight to the increasingly popular notion that certain neurological conditions—such as Parkinson's disease, Alzheimer's disease, and motoneuron disease—may be caused by environmental toxins. "These results are extremely important," comments Donald Calne of the University of British Columbia. "The environmental hypothesis is still controversial, but it is looking more plausible everyday."

Spencer and his colleagues report that monkeys given repeated doses of the amino acid β-*N*-methylamino-L-alanine (BMAA) "developed corticomotoneuronal dysfunction, parkinsonian features, and behavioral anomalies, with chromatolytic and degenerative changes of motor neurons in cerebral cortex and spinal cord."

In short, the monkeys displayed many of the symptoms characteristic of a neurological complex that developed at extraordinarily high incidence among the Chamorro people of the island of Guam in the Marianas chain of Micronesia. Until recently, the Chamorro ate large quantities of seed of the false sago plant, *Cycas circinalis*, which is a natural source of BMAA: hence, the putative link between environmental toxin and disease.

The story of how the putative link was established is long and complex. It tells of a 30-year struggle by National Institutes of Health (NIH) researchers to understand the mysterious Guam disease. It shows that the cycad hypothesis has a long history, going back more than 25 years, but was widely dismissed until Spencer took up the challenge 7 years ago when he saw parallels between another neurological disorder, lathyrism, which is caused by a neurotoxin in the chickling pea. And the lessons of the Guam story go far beyond the shores of that remote Pacific island.

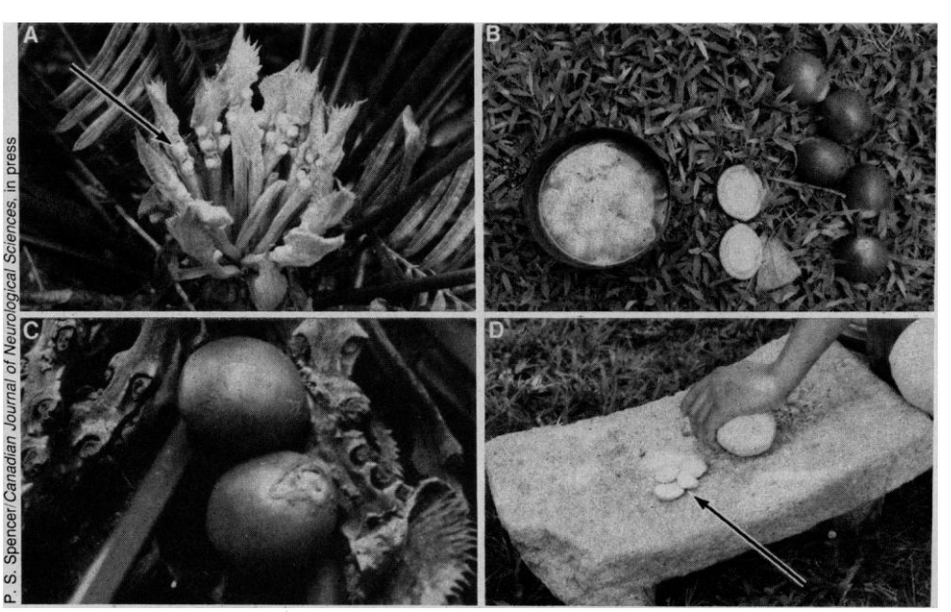
Guam first entered the neurological literature at the turn of the century when a high incidence of so-called "hereditary paralysis" was reported. Later it was realized that three apparently unlinked conditions occurred at extraordinarily high rates: motoneuron disease (or amyotrophic lateral sclerosis), Parkinson's disease, and Alzheimer's-like dementia. Genetic factors were implicated, as were slow viruses, but neither explanation has been borne out. Instead, the answer seems to lie with what Spencer calls a "slow toxin."

The cycad hypothesis was inspired partly as a result of a 1954 study of the Guamanian diet, which revealed heavy use of the seed, not only as food but also as medicine. As a result of food shortages during the Japanese occupation in World War II, many people lived almost exclusively on cycad flour, the production of which requires time-consuming pounding and soaking. A series of six NIH-sponsored "Cycad Conferences" were held between 1962 and 1972, primarily to explore the cycad hypothesis.

Leonard Kurland of the Mayo Clinic, who was a prime mover behind the conferences, had suspected a similarity of cause between the Guam disease and lathyrism, and several researchers in India and Britain pursued the idea. Four separate groups isolated the amino acid β-*N*-oxalylamino-L-alanine (BOAA) from the chickling pea, and fingered it as a cause of lathyrism. And, looking for something similar in the cycad, one of them came up with BMAA.

However, a report at the April 1972 cycad conference, which stated that rats given BMAA over a period of 78 days failed to develop any observable neurological changes, effectively killed the cycad hypothesis. No more conferences were held. An earlier report, at the third conference, of the case of a single monkey that developed behavioral and neuropathological symptoms after feeding on a diet of cycads, was forgotten.

But not by Kurland, who single-handedly kept the cycad hypothesis alive. In the late 1970s Kurland was serving on the National



P. S. Spencer/*Canadian Journal of Neurological Sciences*, in press

Cycad preparation. (*A*) *Immature seeds (arrow);* (*B*) *mature seeds split and showing the starchy white endosperm;* (*C*) *close-up of mature seed;* (*D*) *traditional method of grinding the washed and sun-dried cycad seed endosperm to produce flour used in tortillas and other local foodstuffs.*

Academy of Sciences toxicology section, where he met Spencer. "We got talking," says Kurland, "he about his interest in lathyrism and me about my obsession with getting to the bottom of the Guam mystery." That chance meeting stimulated Spencer to attack the two problems—lathyrism and the Guam disease—with the same approach.

"The first step," which began in 1981, says Spencer, "was to define the neurology of human lathyrism and to produce a satisfactory primate model in which the action of BOAA could be examined." This took 4 years and served as a guide to an attack on the Guam disease, the result of which is reported in the current paper. "It is not a total animal model of the human disease," admits Spencer, "but it is very close. I'm not trying to say that BMAA is the cause of this disease. I am trying to reawaken an interest in cycads." Spencer believes that there are probably other agents in the seeds that work in combination with BMAA.

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Spencer speculates that the three diseases that make up the neurological complex on Guam might be elicted by different "doses" of the cycad toxin. "A high level of intoxication leads to motoneuron disease, while Parkinson's and Alzheimer's develop after lower exposures."

So, perhaps the mystery of Guam is solved. But the story does not stop there. "There are wider lessons to be learned," says Spencer. For one thing, the fact that motoneuron disease, Parkinson's disease, and Alzheimer's-like dementia can each be triggered by the same neurotoxin implies that the three diseases might be linked at some fundamental level. Another is that just because a disease might occur at high frequency and affect individual families throughout generations does not necessarily mean it is genetically caused, as is often inferred. "This should influence our thinking about Alzheimer's disease, which has recently been linked with genetic causes," says Spencer.

But the key inference is the notion of early exposure to a neurotoxin whose effects are expressed clinically only many years later. For instance, many Guamanians who left the island at the age of 20 to live in the United States have developed the disease 30 years later: hence Spencer's term, slow toxin. The chemical assault on the brain, even if it is transient, is compounded by a steady loss of brain cells with advancing age. This is the core of the environmental-toxin model that Calne, Spencer and others have been developing for this group of neurological diseases.

For instance, Calne and William Langston, of the Institute for Medical Research, San Jose, suggested a little over 3 years ago that "in most cases of Parkinson's disease the cause may be an environmental factor, possibly toxic, superimposed on a background of slow, sustained neuronal loss due to advancing age." This suggestion was inspired by the discovery that a chemical that goes by the shorthand name MPTP causes parkinsonian-like symptoms in both humans and animals.

The notion is further strengthened by the results, soon to be published by Calne and his colleagues, of a survey of six families in which several members have Parkinson's disease. The patients often developed symptoms at more or less the same time, irrespective of their ages. "We construe this pattern of age separation within families as suggestive of an environmental rather than a genetic cause," they conclude.

Spreading the environmental hypothesis net yet wider, Calne and Spencer speculated at the end of last year that "Alzheimer's disease, Parkinson's disease, and motoneuron disease are due to environmental damage to specific regions of the central nervous system and that the damage remains subclinical for several decades but makes those affected especially prone to the consequences of age-related neuronal attrition."

Spencer's results on the Guam disease clearly support this position. "I'd be very disappointed if the link between toxin and motoneuron disease related only to the western Pacific form of the disease," adds Kurland. "Clinically, the motoneuron disease you see on Guam is identical to what you see in the United States. I'm optimistic that Spencer's results will set off a search for similar toxic agents to which people are exposed in the West." The culprits are not necessarily to be sought in food, says Spencer. "I expect our search will lead to a class of environmental chemicals that act as triggers for neuronal death. But at the moment we don't know what they are." ■

ROGER LEWIN

Artificial Intelligence Moves into Mainstream

For software developers, the most important result of this research may not be the AI programs at all, but the AI programming style

SITTING in one of the largest and busiest commercial exhibition booths at the 1987 annual meeting of the American Association for Artificial Intelligence (AAAI),* which was held recently in Seattle, and speaking in his capacity as a vice president of one of the most active corporate AI development groups in the country, Texas Instruments' W. Joe Watson made a very disconcerting statement: "Most of us think that AI per se will lose its identity within about 5 years."

Watson did not mean by this that the recent surge of interest in commercial AI applications is beginning to wane; if anything the AI industry is maturing and becoming better established. At this year's AAAI meeting, for example, Texas Instruments was sharing the exhibition hall with nearly 100 other vendors of AI software and hardware, up from 85 vendors last year. Some 5000 meeting participants were thronging the aisles and display booths. Half the companies in the hall seemed to be selling some kind of expert system software to run on ordinary personal computers. (Expert systems are programs that give expert-level advice in fields such as medical diagnosis or tax planning.) And there were so many high-powered, graphics-based workstations being offered for advanced AI development work that the exhibition floor looked like an upscale video arcade.

* The Sixth National Conference on Artificial Intelligence, Seattle, Washington, 13–17 July 1987.