Clues to the Cause of Senile Dementia

Patients with Alzheimer's disease seem to be deficient in a brain neurotransmitter

About 15 years ago a private donor approached David Drachman, a neurologist at the University of Massachusetts, offering to support research on senile dementias. Thinking the problem of understanding these dementias almost unsolvable, Drachman declined, saying, "Once we find a cure for baldness, maybe we can work on what goes on inside the head."

Baldness, of course, still has no cure, but in the past few years there have been signs that the senile dementias are not so unapproachable after all. As Drachman said at a recent conference* that focused on Alzheimer's disease, the major senile dementia, "We don't have a simple laboratory diagnostic test and we don't know how to treat the disease. But we do have clues and testable hypotheses. There are chinks in the armor."

The most promising discovery described at the NIH symposium on Alzheimer's disease was made by six independent groups of researchers. They found that the brains of patients with Alzheimer's disease have significantly decreased concentrations of choline acetyltransferase, the enzyme that makes the neurotransmitter acetylcholine. As Peter Davies of Albert Einstein College of Medicine points out, "To find confirmation by six different groups is quite striking in studies of dementia."

The magnitude of the problem of senile dementias is substantial. One out of every six persons over the age of 65—about 1½ million people—is at least moderately demented. Sixty to eighty percent of nursing home patients are demented. Although there are about 50 known causes of senility, half of all demented patients have Alzheimer's disease.

Patients with Alzheimer's disease gradually become forgetful, especially about recent events. As the disease progresses, they may become confused and irritable, may wander at night, and may become incontinent. In the most severe cases they eventually lose the ability to speak and require total care.

In some families, there seems to be an inherited predisposition to Alzheimer's disease. Leonard Heston of the University of Minnesota, who studied 125 families in which more than one member had the disease, estimates that one-third of all Alzheimer cases are familial in origin. The same families that have high incidences of Alzheimer's also tend to have high incidences of Down's syndrome and leukemia, Heston finds. The familial cases are frequently more severe than the isolated ones and occur in younger people—as young as age 40. The nonfamilial cases, Heston says, generally occur around age 70.

On autopsy, the brains of Alzheimer's disease patients are distinctive. According to Robert Terry of the Albert Einstein College of Medicine, there is a highly significant loss of large neurons in the midfrontal and superior temporal regions. In addition, the fibers in the nerve cells of the cerebral cortex are clumped and distorted, forming the neurofibrillary tangles first described in 1906 by Alois Alzheimer, a German neurologist. The brains also contain scattered plaques where nerve endings have degenerated. The number of plaques and tangles found in a patient's brain is indicative of the degree of dementia. Yet, says Terry, "Alzheimer's disease is a threshold phenomenon. All old people have a touch of it. But patients with the disease have a large loss of neurons, and a large number of tangles and plaques. Normal individuals have very few. And not many people are in between."

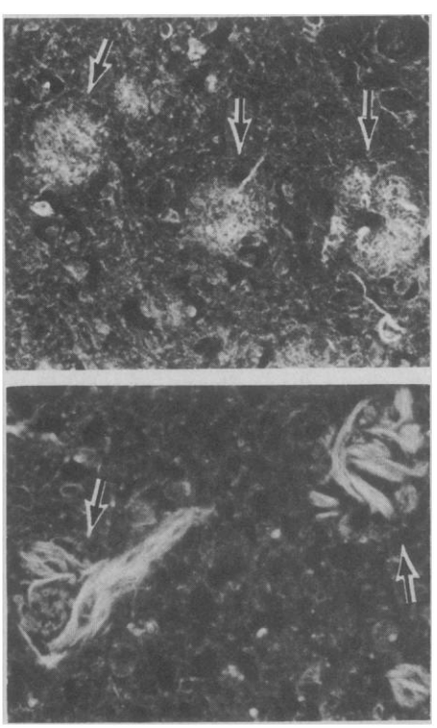
According to Davies, the more brain plaques patients have and the more demented they are, the lower the activity of choline acetyltransferase in the brain. Davies finds that the brain receptors for acetylcholine seem normal in these patients, however. So far, he and others have examined the brains of Alzheimer's disease patients for six other neurotransmitters: dopamine, norepinephrine, seratonin, γ-aminobutyric acid, vasoactive intestinal peptide, and somatostatin. There is general agreement that all of these substances except somatostatin are present in normal quantities.

Davies and, independently, Martin Rosser of the Medical Research Council in Cambridge, England, find that Alzheimer's disease patients have some loss of somatostatin-like activity in their cerebral cortexes. Somatostatin, says Davies, is present throughout the brain and is thought to inhibit the firing of nerve cells. "It is *possible* that choline acetyltransferase and somatostatin are present in the same neurons," he speculates.

The lack of acetycholine in Alzheimer's disease patients is the first consistent, marked biochemical abnormality to be found. What it means, says Davies, is that "if a neurological or psychiatric disorder is specific to a particular neurotransmitter system, we have a tool we can use to find its cause. In the case of dementias, we need to find agents that hit the acetylcholine system."

In both normal people and Alzheimer's disease patients, choline acetyltransferase does not work full blast. If it is supplied with more choline, it makes more acetylcholine. So the simplest way to treat Alzheimer patients might be to supply their brains with more choline. Unfortunately, this approach has not yet been successful.

John Growden of Tufts University School of Medicine reported at the conference on his attempts to use lecithin (phosphatidylcholine) to treat Alzheimer's disease patients. When people



Brains of Alzheimer patients

Plaques (top) and neurofibrillary tangles (bottom) in brains. [Source: Robert Terry]

*The conference on Alzheimer's disease and related disorders was held on 15 to 16 January 1981 at the National Institutes of Health (NIH). It was sponsored by the Alzheimer's Disease and Related Disorders Association in cooperation with the National Institute on Aging, the National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute of Mental Health.

0036-8075/81/0306-1032$00.50/0

consume lecithin, which Growden supplies in a milk shake, the amount of choline in the blood rises and more choline is delivered to the brain. In a double-blind crossover study, Growden and his associate Suzanne Corkin found that only 4 of 13 patients showed any improvement when given lecithin and even those patients improved on only one of a battery of psychological tests. "The cholinergic hypothesis remains persuasive," Growden says. "It may be that we have not found the right drugs. Perhaps we should combine drugs to simulate acetylcholine receptors and to increase acetylcholine synthesis. Perhaps we should also stimulate somatostatin."

Of course, the fact that Alzheimer's disease patients seem to make too little acetylcholine does not mean that there is a single cause of the disease. As Drachman points out, it could mean that the acetylcholine-producing neurons are the most vulnerable to a variety of insults. One such insult could be a lack of brain glucose, which itself could have numerous causes; another could be a slow virus infection. Another, suggested by James Austin of the University of Colorado, might be a change in brain microtubules which could produce the neurofibrillary tangles. Others include oxygen deprivation and exposure to toxic metals such as aluminum.

But even if Alzheimer's disease has multiple causes, it may have a single effective treatment. Consistent neurochemical findings are an important first step in devising a rational treatment, the conference participants agreed. "I want to stress my optimism in this area," Davies concluded.—GINA BARI KOLATA

Astronomers Look to the 1980's

Their latest 10-year plan should give them a united front for the coming budget wars

Now that the Reagan Administration has proposed its first round of budget cuts, it seems that funding for the physical sciences will emerge relatively unscathed. Still, the next few years promise to be stringent ones for all the sciences.

One discipline, however, astronomy, seems in a stronger position to defend its needs than most. With fortuitous timing the Astronomy Survey Committee of the National Academy of Sciences, under the leadership of George B. Field, director of the Harvard-Smithsonian Center for Astrophysics, has just finished hammering out the discipline's priorities for the decade ahead. Its report is due out this summer after academy review and approval.

The academy has sponsored 10-year reports in other fields, of course, but the astronomers and astrophysicists are especially excited about theirs. Between the 21-member Field committee itself and all its subsidiary panels and working groups, some 200 researchers were able to take part. That is a significant fraction of the 1000 or so active research astronomers and astrophysicists in the United States, one observer notes; thus the report will represent a wide consensus. This, in turn, should make it easier for NASA or NSF to sell a particular project on Capitol Hill: the agency can say that the whole community is behind it. Moreover, the report will rank each priority without regard to the federal agency that will manage it. "And that kind of list is something the Office of Management and Budget is very interested in," says Field.

This kind of thinking isn't really as wistful as it might seem. The 1970's were relatively good years for federally-funded astronomy; many astronomers attribute this largely to the influence of the Field committee's predecessor, the Greenstein committee of 1972.

Chaired by Jesse L. Greenstein of the California Institute of Technology, the committee produced a report that was short (about 150 pages), clearly written, and very specific in identifying and ranking its priorities. It, too, represented a community-wide consensus, and most of the projects it recommended have since been implemented. These include the Very Large Array near Socorro, New Mexico; the Multi-Mirror Telescope atop Mount Hopkins in Arizona; the three Earth-orbiting High Energy Astronomical Observatories; and the $750 million Space Telescope, to be launched in the mid-1980's. (Two other Greenstein proposals, however, the orbiting Gamma Ray Observatory and the 25-meter, millimeter-wave radio telescope, have been deferred by President Reagan.)

With memory of the Greenstein report still strong, the members of the Field committee have spent many long hours in arguments and negotiations over their own recommendations. The report will not be just a shopping list, says Field. The committee members were acutely aware that with money as tight as it is, listing an expensive project third instead of second might delay it for years, even kill it.

Field is reluctant to talk about specific projects and their rankings before the academy has approved and released the report. But it is no secret that advances in technology have placed astronomy on the verge of a new generation of instrumentation. Proposals having broad support within the community include an advanced x-ray orbital observatory for studying very high energy events; a ground-based telescope some 15 meters across for analyzing the spectra of very dim and distant objects; and a continent-spanning interferometer array, a system of radio telescopes that may be able to resolve structure in the interior of quasars.

Of course, no one report, however well-written, is going to have much of an impact by itself; Washington is full of reports. But astronomers have some other things going for them. One is the inherent appeal of their subject; people are turned on by black holes, quasars, and the Big Bang. Another is that astronomers and astrophysicists as a group have been notably articulate and energetic in making their needs known. Finally, as pointed out by Herbert Friedman, chairman of the academy's Assembly of Mathematical Research and Physical Sciences, the style of astronomical research is significant: "Optical, infrared, radio, x-ray—we need the full spectrum and all the methods of observing to figure out what is going on with a given object." Astronomers, he says, are used to working together.—M. MITCHELL WALDROP

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