# Senility
## THE ACETYLCHOLINE CONNECTION

**A significant neurochemical abnormality has been found to underlie senile dementia and may possibly lead to an effective treatment**

BY JOAN AREHART-TREICHEL

Two striking pathophysiological hallmarks of senility (also known as senile dementia in the elderly or Alzheimer's disease in somewhat younger persons) have been known for a few years now. They are cores of abnormal protein interspersed among nerve cells in the brain and twisted fibers in the bodies of nerve cells in the brain. These "senile plaques" and "neurofibrillary tangles," as they are called, are especially prominent in the cerebral cortex and hippocampus, areas of the brain involved in learning and memory, and may thus help explain why two of the major characteristics of senility are difficulty in learning and memory loss (SN: 10/1/77, p. 218).

But during the past five years, a significant neurochemical abnormality has been found to underlie senility as well. It's a deficiency in acetylcholine, a chemical that nerves in the brain use to signal one another and that is known to be involved in learning and memory. This finding suggests that an acetylcholine deficiency might contribute to the learning and memory deficits of senility and may lead to an effective treatment for senility, which is currently incurable.

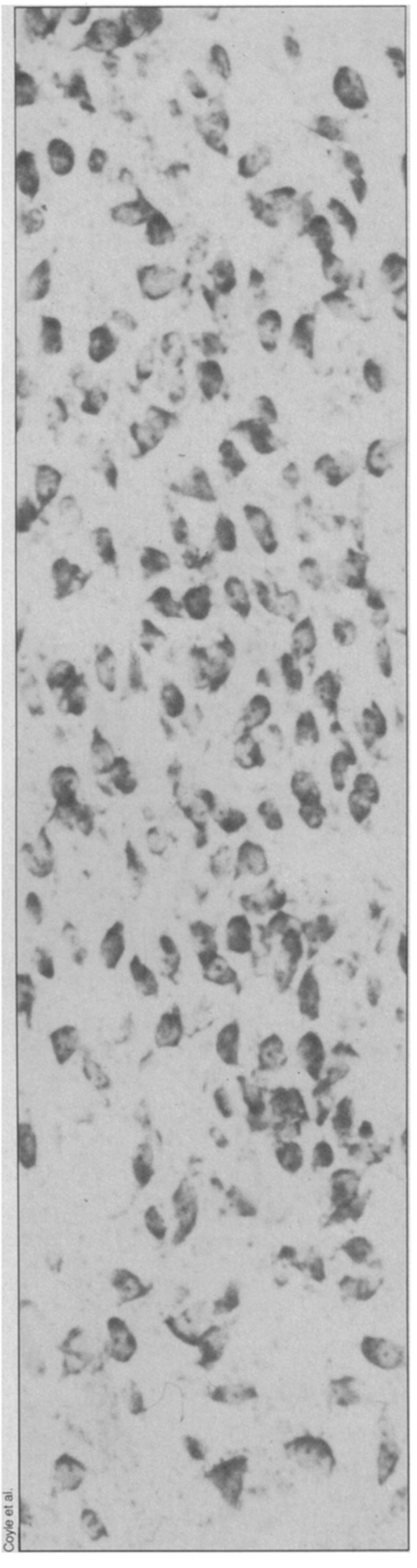
The first evidence that there is a deficiency of acetylcholine in the senile brain came in 1976 when the activity of choline acetyltransferase, the enzyme that helps convert choline into acetylcholine, was found to be much lower in the cerebral cortexes of senile patients than in those of healthy elderly subjects. The decrease in the activity of this enzyme was then found to be especially dramatic in the hippocampus as well, and especially in those areas of the cerebral cortex and hippocampus where senile plaques and neurofibrillary tangles are present, further implicating an acetylcholine deficiency in senility.

Then Joseph T. Coyle and colleagues at the Johns Hopkins Medical Institutions in Baltimore found that the nerves in the cerebral cortex that make the enzyme choline acetyltransferase do not originate in the cerebral cortex but at the base of the brain, in an area called the nucleus banalis. Coyle and Donald Price and his co-workers at Hopkins hypothesized that because there is an acetyltransferase reduction in the cerebral cortex of the senile brain, and because nerves that make acetyltransferase come from the base of the brain, acetyltransferase reduction in the cortex might be due in turn to a reduction in the number of these neurons. As they have found, that is the case. The paucity of these particular nerves may thus account for the deficiency of acetyltransferase in the senile cerebral cortex, which in turn may explain the inadequate amount of acetylcholine in it.

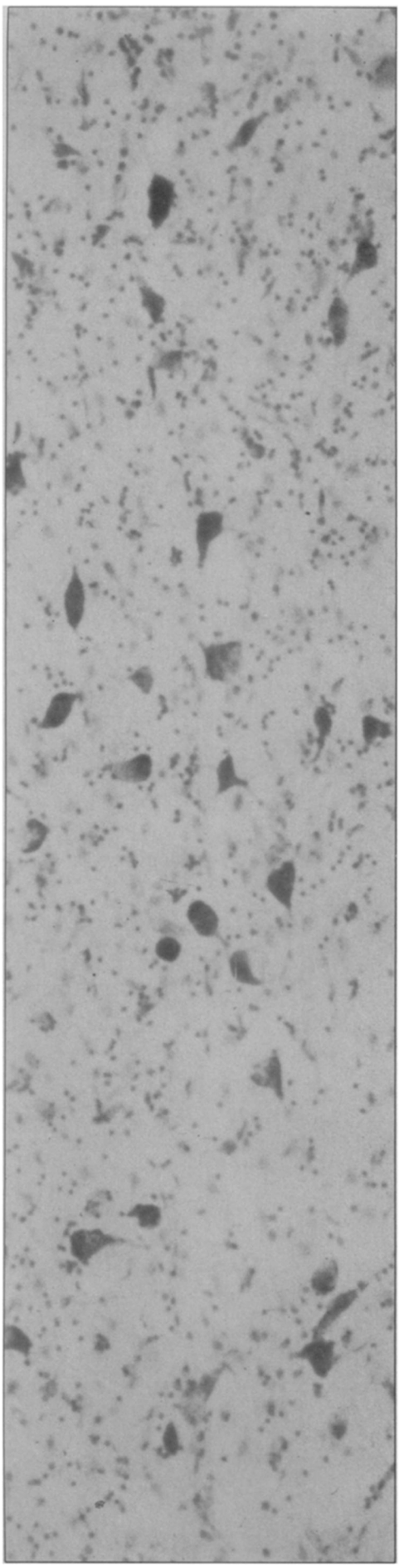
Coyle, Price and their colleagues are now trying to more precisely define which neurons in the nucleus banalis are responsible for this series of events. Mahlon DeLong of Hopkins is going even a step further — attempting to find out what the normal function of these nerves is and why they are reduced in the senile brain. Such insights could go a long way toward explaining the ultimate causes of the disease.

As evidence has grown that an acetylcholine deficiency may help bring about the learning and memory problems of senility, a number of scientists in the United States and abroad have decided to see whether cholinergic drugs (agents that increase acetylcholine or acetylcholine action in the brain) might improve senile patients' learning and memory, particularly as such drugs have improved learning and memory in animals, healthy subjects and patients with tardive dyskinesia (SN: 2/11/78, p. 85; 8/12/78, p. 102). Their studies have led to some improvement.

Two of the most interesting studies that have brought about some positive results come from Kenneth L. Davis and col-



Coyle et al.



leagues at the Bronx Veterans Administration Medical Center in the Bronx, N.Y., and from Bruce C. Peters and Harvey S. Levin of the University of Texas Medical Branch in Galveston.

Davis and his colleagues gave three different doses of physostigmine (a chemical that retards degradation of acetylcholine) as well as a placebo to each of 10 senile patients in a randomized order. The patients' memories were tested five minutes after receiving each of the physostigmine doses as well as the placebo. Memory improvement in all the patients was more marked after they received physostigmine than after they received a placebo. The test was then repeated, this time pitting the most effective dose of physostigmine for each patient against a placebo. Again, all of the patients' memories were better after getting physostigmine than after getting a placebo. These results, the scientists conclude in a paper that they have submitted for publication, "indicate that the acute augmentation of cholinergic activity in patients with Alzheimer's disease can partially reverse the memory deficit of that disorder and may provide an approach to the eventual therapy of this condition."

Peters and Levin measured the baseline memory of five mild to moderately senile patients, fed them lecithin (a dietary form of choline, which in turn is a precursor of acetylcholine), then measured their memory performances. The investigators repeated the test, this time giving the patients physostigmine injections rather than lecithin. The scientists repeated the test again, this time giving the patients physostigmine injections plus lecithin. Neither physostigmine nor lecithin alone improved the patients' memories, they found, but the combination of physostigmine with lecithin did. Finally, the researchers gave oral lecithin plus oral physostigmine daily to four senile patients over an 18-month period, and three of the patients experienced memory improvement as a result. "It may be that chronic use of medication of this or similar type could improve verbal memory in selected patients with Alzheimer's disease," the scientists reported before the International Study Group on the Pharmacology of Memory Disorders Associated with Aging, which met in Zurich, Switzerland earlier this year.

Still, cholinergic drugs have not benefited senile patients as much as researchers in the field had hoped. For instance, Jared Tinklenburg of Stanford University Medical Center and colleagues gave physostigmine or a placebo to senile patients and measured the patients' learning and memory abilities after each treatment. Physostigmine produced only moderate improvement in learning and memory compared to a placebo. Similarly, Herbert Weingartner and colleagues at the National Institute of Mental Health gave lecithin, physostigmine, arecholine (a chemical that stimulates the action of acetylcholine on the nerve that receives it) or lecithin plus tetrahydroaminoacredine (a chemical that prolongs the lifetime of acetylcholine at the nerve synapse) to 30 early-stage senile patients. While there was improvement in the patients' learning and memory abilities as a result of drug treatment, it was generally in patients who were the least impaired mentally. "This finding is consistent with what we get from other groups," Weingartner told SCIENCE NEWS. And as Suzanne Corkin of the Massachusetts Institute of Technology in Cambridge, Mass., points out, just as some studies have found that acetylcholine enhancement can help some senile patients, a number of other studies have not. Representative of the negative experiments is one carried out at MIT that Corkin helped conduct. In this investigation, 18 senile patients ranging from mildly to severely demented received lecithin and then a placebo and were given memory tests after each. Although some patients showed improvement on certain memory tests, no patient was more efficient on all measures during lecithin ingestion than during placebo ingestion, and no single test elicited better performance by all patients when they consumed lecithin as compared with placebo.

Nevertheless, as Davis points out, the fact that he and other scientists have achieved at least some learning and memory improvements in senile patients, and that these improvements were based on an attempt to alter a known abnormality underlying the disease, represents a "first step along a rational road toward treatment." "That is a much bigger step from where we were five years ago," he says, "when we were trying drugs that did diffuse things like increase energy metabolism or increase availability of cyclic nucleotides or dilate vessels, because these weren't problems that people with Alzheimer's disease had." Davis sees the results of this research leading to "drugs that are more potent, more efficacious, that increase cholinergic activity in a greater way, or to a combination of these drugs with other drugs that may also be shown in the future to reverse other abnormalities that at this point we could only guess could be there." For instance, Tinklenburg, Peters, Levin and some other scientists in the field are especially eager now to see whether combining cholinergic drugs with the pituitary hormone vasopressin might benefit senile patients more than cholinergic drugs alone do since vasopressin has brought about positive memory effects in some senile patients as well as in healthy subjects and in patients suffering memory loss from car accidents or alcoholism (SN: 2/11/78, p. 88). □

*The neurons that make up the nucleus basalis of the brain are plentiful in a healthy subject (left) but dramatically reduced in a senile patient (right).*