Clues to Alzheimer's Disease Emerge

Luck and basic neurobiology research combine to lead researchers on a new track

Deep in the brain is a tiny area that has been mostly ignored because no one had any idea what it did. But now this area, called the nucleus basalis of Maynert, appears to hold the key to understanding Alzheimer's disease, a relentlessly progressive senility that afflicts 5 to 10 percent of all people over age 65. The story of how scientists came to appreciate the nucleus basalis is one of coincidence and timing and of close interplay between basic research and clinical science. And, in the end, says Donald Price of Johns Hopkins University School of Medicine, "I think we've been very very lucky."

The nucleus basalis is in the basal forebrain, just above the optic chiasm, where the optic nerves meet and cross. "If you hold a gun to your temple and shoot, the bullet would go right through it," says Price. Neurologists knew it exists—it was, in fact, described in the 19th century by W. Maynert, but it was part of what neurologists aptly called the substantia innominata. "We knew there was this cell population called the nucleus basalis for a long time," Price confesses, "but no one knew what the cells connected to or what they did. We used to ignore it. We'd cut right through it when we sectioned the brain."

The neurologists studying Alzheimer's disease never thought to look at the nucleus basalis because the disease appeared to be so complex and involve so much of the brain. There were lesions, called neuritic plaques and tangles, all over the cortex. "We would look at the brain and see all these changes and say, 'Oh my God, is there any selectivity?' ", Price recalls.

The first hints of selectivity came in the mid-1970's when several groups of researchers virtually simultaneously reported that patients who die of Alzheimer's disease have 60 to 90 percent less choline acetyltransferase activity in their cortexes than age-matched controls. Choline acetyltransferase, which is an enzyme that synthesizes the neurotransmitter acetylcholine, is found only in cells that use acetylcholine. Thus the disease did seem selective for acetylcholine-using neurons.

At about the same time as this discovery was being made, scientists were learning about the neurophysiology of the basal forebrain. For example, they found that, in rats, cells in the basal forebrain stain intensively with acetylcholinesterase, indicating that they likely, but not definitely, are cholinergic. In addition, Mahlon De Long of Johns Hopkins recorded from these cells in monkeys and found that they have a very unusual firing pattern. The cells respond to rewards and higher order behavior. Consistent with De Long's finding, several groups of investigators showed, in 1975, that cells of the basal forebrain in monkeys project directly to the cortex. In 1978 and 1979, researchers at Johns Hopkins and elsewhere destroyed these cells in rats and showed that there is a reduction of cholinergic activity in the cortex, much like that which occurs in Alzheimer's disease.

> Price recalls that he picked up the slide. . . . "In two seconds, I knew we were onto something that would change the direction of our research."

The animal studies were tantalizing. "With all these lines of evidence as background, we began to suspect that a loss of neurons in the nucleus basalis may occur in Alzheimer's disease," says Price, "So we wanted to get an Alzheimer brain and look at these nerve cells."

About 2 years ago, they got an opportunity. The patient was a man who had developed Alzheimer's disease at age 60. As the disease progressed, he became profoundly demented, mute, incontinent, and bedridden. Finally, he died at age 74. His father, his father's brother, and his father's sister also had died of Alzheimer's disease and all of them had developed the disease at about age 60. Price and his associates Peter Whitehouse, Arthur Clark, Joseph Coyle, and De Long carefully cut up the man's brain. Price recalls that he picked up the slide containing the nucleus basalis cells. "In two seconds, I knew we were onto something that would change the direction of our research." The man had lost 90 percent of the cells from his nucleus basalis.

The next step was to look at other Alzheimer patients to see if the finding held up. It did. "We got brains from 5 additional Alzheimer patients and 5 controls. All the Alzheimer's disease patients had a loss of neurons from the nucleus basalis. All of the controls had the normal number of cells," Price says. They also looked at brains from a person with Down's syndrome who developed Alzheimer's disease when he was in his mid-30's—as nearly all Down's syndrome patients do. This man, too, had lost nucleus basalis cells.

After that, the Johns Hopkins group thought it might be important to see if the nucleus basalis is indeed cholinergic. Paul Salvaterra of City of Hope Hospital in Los Angeles and Bruce Wainer of the University of Chicago developed monoclonal antibodies to choline acetyltransferase. When the Johns Hopkins group exposed nucleus basalis cells to these antibodies they found that the antibodies bound tightly to the choline acetyltransferase in the cells. Next, Robert Struble, Susan Mitchell, and John Lehman of Johns Hopkins destroyed the nucleus basalis in monkeys with a neurotoxin, ibotenic acid, that destroys nerve cells at the site of injection, sparing their axons. As a result, the monkeys lost acetylcholine activity in their cortexes.

Alzheimer's patients are known to develop neuritic plaques and tangles. Moreover, the number of plaques correlates with the severity of the disease: Patients with many plaques are demented; patients who are demented have decreased choline acetyltransferase activity. And patients with decreased choline acetyltransferase activity in their cortexes have plaques. Is there any connection between the plaques and the loss of nucleus basalis cells?

Price suggests that as neurons of the nucleus basalis begin to fail, their cortical projections gradually begin to form plaques, "Maybe it starts as a few swollen axons," he says. "It is increasingly

apparent that the cells [of the nucleus basalis] don't suddenly die. They survive for long periods—months or years. And there is increasing evidence that plaques evolve."

One possible scenario is that the nucleus basalis cells begin to function abnormally and no longer make enough acetylcholine to allow the nerve terminals in the cortex to function properly. The axons start to turn into plaques as nerve transmission in the cortex falters.

Price believes there is a long period of time between when a nerve cell in the nucleus basalis is first affected by Alzheimer's disease and when it dies. "That's an important time to learn about," he says, "If we knew what is happening to the cells, the disease might be stopped or at least slowed."

But what causes the cells to die? A number of neurologists speculate that in diseases like Alzheimer's or Parkinson's or Huntington's, in which a specific population of nerve cells dies, the nerve deaths might be due to a loss of "trophic factors." The idea is that the target sites at the ends of the axons release some undefined factor that keep the cell bodies alive. If they stop making the factor for some reason, the cell bodies die.

This trophic factor theory, however, does not seem to hold in Alzheimer's disease. Price and his associates think it less likely now that they have examined the brain of a young woman who was admitted to Johns Hopkins hospital after trying to commit suicide by carbon monoxide poisoning. She failed to kill herself but she did destroy her cortex. After 10 months she died and, when the Hopkins neurologists looked at her brain, they saw that her nucleus basalis cells were relatively intact—despite the lack of any sort of trophic factors after her cortex was destroyed.

Price says that he and his colleagues are now looking more closely at the neuroanatomy and physiology of the nucleus basalis. "We still don't know what the basal forebrain does to the cortex, but we think it's an activator," Price says. "It might activate that part of the cortex that lets you attend to a person's face or attempt a complex action. It might also keep up the general tone of the cortex so you don't go to sleep."

In his clinical studies of Alzheimer's disease, Price wants to experiment with monkeys first, perhaps by selectively destroying nucleus basalis cells. Then he wants to go on to look at people with familial Alzheimer's disease—those in which Alzheimer's disease is inherited as an autosomal dominant trait—and persons with Down's syndrome.

Price warns, however, that the nucleus basalis is likely not to be the whole story in Alzheimer's disease. "There is increasing evidence that other transmitter systems are involved, although not so severely or so consistently as the cholinergic system. The cholinergic system may be the tip of an iceberg."

But whether or not it is the tip of an iceberg, the discovery of a specific group of cells that dies is an important beginning. "For perhaps the first time we can focus on a cell population that we know is affected in Alzheimer's disease," Price says.—**GINA KOLATA**

Deep-Sea Drilling Rescued by a New Option

Blocked in its drive to convert the Glomar Explorer, *the National Science Foundation has found a practical substitute*

The world oil glut has pulled the National Science Foundation (NSF) out of the tight corner that it found itself in when budgetary reality finally collided with NSF's ambitious plans for scientific deep-sea drilling. In the wake of glut-induced price cutting in the offshore drilling market, NSF finds that it can convert and lease a modern drill ship that is more capable than the planned stripped-down version of *Glomar Explorer*, yet no more expensive than an upgraded but less powerful *Glomar Challenger*. The ad hoc committee summoned to weigh this new prospect against other needs in crustal studies has given the new option its approval, even as it deep-sixed the *Explorer*. Next, NSF must convince Congress.

For 5 years, NSF has been pushing the *Explorer* as the only logical alternative to the aging and antiquated *Challenger*. Conversion of the one-time CIA retriever of submarines to scientific drilling would have made *Explorer* the most powerful, deepest-drilling vessel in the world. A long line of blue-ribbon committees and scientific study groups certified that the scientific return from *Explorer* would be well worth the added costs when compared to the limited capabilities of *Challenger*. *Explorer* maintained that approval even after budgetary constraints had indefinitely postponed development of one of its most attractive attributes, the ability to perform riser drilling on the continental margins (*Science*, 21 August 1981, p. 851). A riser and its blowout preventer are necessary to drill wherever oil or gas might be encountered.

Then, somewhere in the budget process for fiscal year 1984, the *Explorer* dream finally died. NSF did not ask for the $36 million for *Explorer* in the final budget request; the Administration would not have given NSF the money if it had asked. That left NSF with nothing but a *Challenger* drilling program, whose numerous deficiencies had been emphasized for years. Reluctantly, NSF asked for $26.3 million to continue *Challenger* drilling, something that it had told Congress in its fiscal year 1983 request it would not do. In the meantime, the new director of NSF, Edward Knapp, requested that some fiscally realistic priorities be assigned to ocean drilling and competing programs.

In the nick of time, industry offered NSF a third option—leasing a modern oil exploration drill ship. In early January, Sedco, Inc., the firm that would have operated the *Explorer*, approached NSF with the suggestion that one of its idled ships, such as the *Sedco 472*, might be leased at half the cost being paid for its services by industry only a few months earlier. That would be close to the $33,000-per-day rate now being paid for *Challenger*. The generous offer was spurred by the prospect of declining oil prices, the slackening pace of oil exploration, and rampant overconstruction of drilling platforms. The resulting glut of drilling vessels has severely depressed drill ship demand, especially for the half dozen ships that have been able to drill with a riser in more than 600 meters (2000 feet) of water while staying over the drill hole solely with the aid of positioning engines. *Challenger* pioneered such dynamic positioning, but she has been surpassed by newer ships.