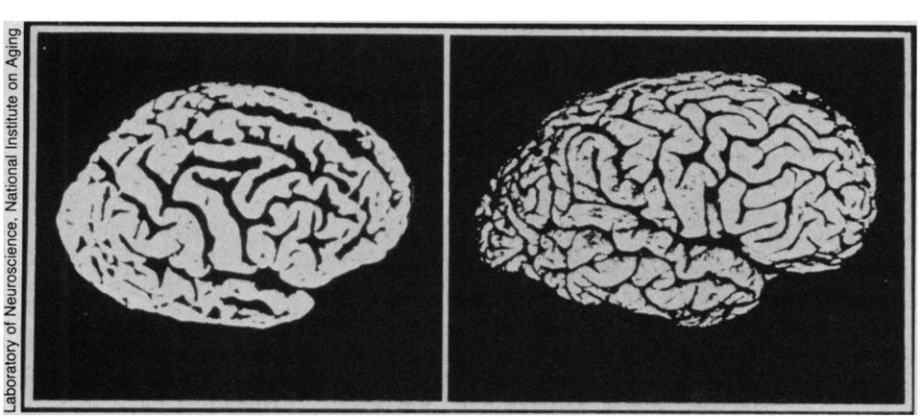
Researchers Hunt for Alzheimer's Disease Gene

At least some cases of Alzheimer's disease appear to be inherited as though there were a dominant gene, which leads researchers to believe that they can find a gene that causes the disease

ABOUT 10 years ago, a brother and two sisters traveled from their home in New Brunswick, Canada, to the National Institutes of Health to find out why they seemed to be losing their minds. The brother, who was 56 years old, was losing his memory, was confused, and was having trouble dressing himself. His 54-year old sister had similar symptoms, but her memory loss had become so severe that she was able to communicate only in phrases and was unaware of where she was or even what day it was. The youngest sister, age 52, was losing her memory and had difficulty doing simple additions.



Laboratory of Neuroscience, National Institute on Aging

Brain changes in Alzheimer's disease. *The brain on the left, from an Alzheimer's disease patient, is noticeably smaller compared to the normal brain on the right.*

The family knew that they were facing some sort of terrible progressive neurological disease, and they could trace the inheritance of the disease back for seven generations. But they were not sure just what the disease was nor did they know what to do about it. At various times, they had been told that it could be Huntington's disease or possibly schizophrenia.

The NIH scientists, led by Ronald Polinsky and Linda Nee, had an answer for the family—Alzheimer's disease. As devastating as that diagnosis was, it was at least a comfort to be told. "One of the things they found most valuable is that now they know what the disease is," Nee says.

The Canadian family remains in close contact with the NIH researchers who, says Nee, "give them a place to turn with their concerns and give them hope." The family, in turn, gives Polinsky and Nee hope. In this family and six other large "Alzheimer's families" that they are studying, they see a chance at last to get to the heart of the disease by finding a gene that causes it.

The Canadian family is a perfect example of the inheritance of Alzheimer's disease. It occurs in this family as an autosomal dominant; like Huntington's disease it seems to occur sooner or later in everyone who inherits the gene. If a parent has the gene, each child has a 50% chance of inheriting it.

At least two groups of investigators are now trying to find genetic markers near the gene for Alzheimer's disease and from there work their way down to the gene itself. These studies are just beginning, but James Gusella of Massachusetts General Hospital, who conducted a similar search for the Huntington's disease gene and found a marker for it (*Science*, 25 November 1983, p. 913), is optimistic. He is collaborating with the NIH group and estimates that, at worst, it might take 5 to 10 years to find genetic markers close to the Alzheimer's gene.

At the same time, other investigators are trying to find out just how frequent the autosomal dominant form of Alzheimer's disease is. Some say that most Alzheimer's is inherited this way. Others say it is nearly impossible to draw such conclusions from the data at hand and that it remains entirely possible that most Alzheimer's arises at random in families with no previous history of the disease.

The question of whether there is one or several forms of Alzheimer's disease is important. If there is only one form, the gene search should be fairly straightforward. But if there is more than one form, there may be more than one gene; it could be that many cases are not inherited at all. Some doctors speculate that Alzheimer's is caused by environmental factors or infectious agents such as slow viruses.

Nevertheless, researchers agree that Alzheimer's disease *can* be inherited. There have been numerous studies of families, like the Canadian one, in which the disease seems to be passed on through the generations. Consistently in these families, symptoms appear early. Family members get the disease before they are 70 years old, frequently when they are in their 50's or 60's. Yet most Alzheimer's disease occurs in people who are age 80 or older. Eleven percent of the population over age 85 has Alzheimer's, according to a survey by Marshal Folstein and his associates at Johns Hopkins University Medical School. This complicates all attempts to determine whether the disease is inherited; many people who may have been destined to get the disease die before they can develop symptoms. However, two recent studies lend support to the idea that, even in persons who develop Alzheimer's in their 80's, it is a genetic disease.

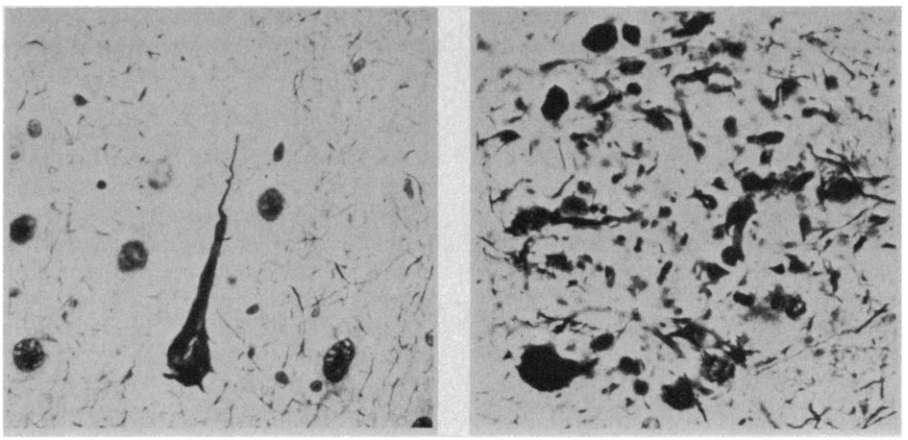
The first of these studies was directed by Folstein in collaboration with Diane Powell and John Breitner, who is now at the Bronx Veterans Administration Hospital. The three investigators began by asking, "If there is a genetic form of Alzheimer's disease, can we design a way to pick out the genetic cases?" They surveyed nursing home populations, looking for patients who had a loss of mental capabilities but no other conditions that could account for their dementia.

That meant that patients who had strokes or high blood pressure, heart disease, or diabetes were excluded.

"When we looked at our cases after we had thrown out everyone who could possibly have anything else, we were left with two groups," Folstein says. The first group, which constituted 78% of the patients with dementia, had classical symptoms of Alzheimer's disease. They had begun by becoming abnormally forgetful and within a few years had progressed to a point at which they forgot words and lost learned motor movements. They could not write, for example, and many could not use a telephone or dress themselves or use a knife and fork. Nor could they compose and write a sentence—which was Folstein's quick test for picking them out.

Patients from the second group did not have classical Alzheimer's symptoms. They were disoriented and could not pay attention, but they could compose and write a sentence. Yet, Folstein says, "they would have been called Alzheimer's patients by the usual criteria."

Folstein and Breitner compared the relatives of the first group of patients with those of the second group and with persons selected as controls, including other nursing-home patients and the spouses of their Alzheimer's patients. "We found big differences," Folstein says. "For this strictly selected group with classical symptoms, the relatives were much more likely to have dementias. Furthermore, when we analyzed just what the risk was and used modern methods of life-table analysis, we came up with a 50% probability that a first degree relative of an Alzheimer's patient—a mother, father, sibling, or child—will get the disease if they live to age 90."



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A microscopic view of an Alzheimer's brain. *The brains of Alzheimer's patients have large numbers of neurofibrillary tangles (left), which are strandlike clusters of filamentous proteins. The brains also contain senile plaques, which are areas in the gray matter of the brain in which nerve cell ends are deteriorating.*

Next, Folstein and Powell looked at patients from their neurology clinic. These patients, says Folstein, "are much more representative of the cases that neurologists see." Again, they found that the classical Alzheimer's cases were in the majority and that the disease seems to be inherited in these patients as though it were caused by a dominant gene.

But Folstein's work was subject to criticism for methodological reasons. Now, however, Breitner and his colleagues at the Bronx Veterans Administration Hospital have repeated the study with a larger population and a different methodology. For example, they adhered to the standard and exhaustive criteria recommended by the NIH to diagnose Alzheimer's disease by excluding every other possible cause of the dementia. Their results confirm those of Folstein.

Moreover, both Breitner and Folstein independently report that if they are not so strict about their definition of Alzheimer's disease and include demented patients who do not have classical symptoms of the disease, they get results just like those that are usually reported—about 25% of the first-degree relatives of Alzheimer's disease patients will develop the disease if they live to age 90.

Folstein concludes that, "in my opinion, this work provides a rationale for using molecular methods to look for an Alzheimer's disease gene." Still, not everyone is convinced by Folstein and Breitner's work. They do not question that some cases of Alzheimer's are inherited, but do question whether the vast majority are. Some researchers, including the NIH group, would like to see the diagnoses of Alzheimer's confirmed by autopsy. Others, including Leonard Heston of the University of Minnesota, distrust the life-table analysis that enables the two groups of researchers to say that the disease becomes manifest with a 50% probability in brothers and sisters of patients by the time these relatives reach age 90. Nonetheless, the search for a gene that causes at least the early onset form of the disease is under way.

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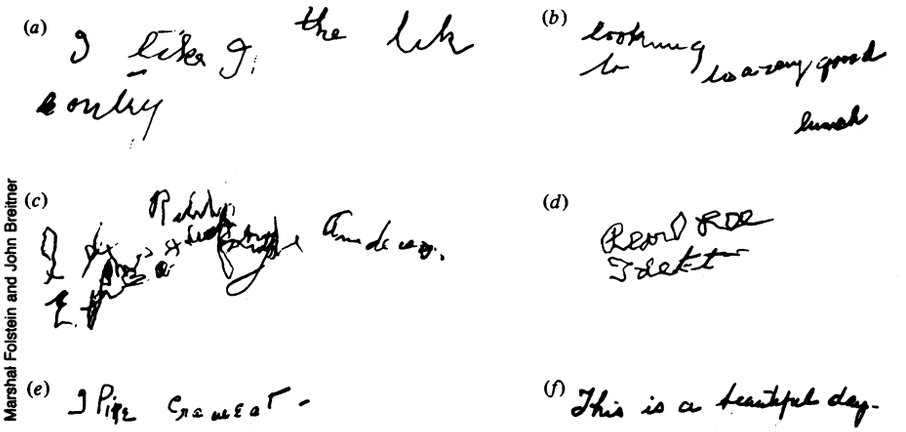


Marshal Folstein and John Breitner

Writing samples from Alzheimer's patients. *Marshal Folstein and John Breitner report that most Alzheimer's patients in nursing homes cannot compose and write a sentence. The relatives of this majority who cannot write a sentence are much more likely to be demented than the relatives of those who can write a sentence. Sentences* a, b, c, *and* d *are from Alzheimer's patients who cannot write a sentence. The woman who wrote sentence* a *was 92 years old and ill for 2 years with Alzheimer's disease. She said she was trying to write "I like the country." The woman who wrote sentence* b *was 81 years old, ill for 3 years, and trying to write "looking forward to a very good lunch." Sentence* c *was written by a 79-year-old woman, ill for 4 years, who could not explain what she was trying to write. Sentence* d *was by an 86-year-old woman, ill for 6 years, who was attempting to write her name. Sentences* e *and* f *are from Alzheimer's patients who could still write.*

dently, Harry Orr and Heston at the University of Minnesota are beginning to look at chromosome 21 for an Alzheimer's gene marker. Many people with Down's syndrome get Alzheimer's disease, and Down's syndrome is caused by an extra copy of chromosome 21. "We have blood samples from members of five high-risk families," says Heston. "We will just have to plug away." Gusella has cell samples from members of six large high-risk families that are being followed by Polinsky and Nee at NIH.

Investigators are now trying to find genetic markers near the gene for Alzheimer's disease.

If most cases of Alzheimer's disease are in fact inherited, what advice can researchers give to concerned family members? First of all, says Donald Price of Johns Hopkins University Medical School, it is no surprise to members of many families that the disease may be inherited. Price, who is collaborating with Polinsky and Nee, says, "as our work on Alzheimer's disease got publicity, people began to write to me. Over the years, I must have gotten thousands of inquiries. Some included really striking pedigrees. These people were saying, 'This disease seems to be in our family. What are the risks to me and my children?' "

Price advises these people that, even if they are at risk, they may not live long enough to get the disease. Folstein makes the same point. "Because the probability is low that people will live to be very old, the individual risk to a brother or sister or child of an Alzheimer's patient is still very low—in the realm of 17%."

All the researchers involved in this search for an Alzheimer's disease gene say that the basic message to relatives of Alzheimer's patients is a hopeful one. If a gene is found, it will most likely lead to a fundamental understanding of what causes the disease. From there, it is at least conceivable that researchers can devise treatments or even means of prevention. ■ GINA KOLATA

This is the second in a series of articles on the development of genetic tests to determine susceptibility to disease. The first article appeared in the 18 April issue.

ADDITIONAL READING

J. C. Breitner and M. F. Folstein, "Familial Alzheimer dementia: A prevalent disorder with specific clinical features," *Psychol. Med.* **14**, 63–80 (1984).

Briefing:

Mountain Goat Horn: A Clue to Extinction?

The precipitous collapse of the last glaciation, a little more than 10,000 years ago, coincided with the extinction of 57 species of large mammal in the Americas. The conclusion that the events were causally related is clearly very attractive, and has a good deal of support among paleobiologists. But the extinctions also coincided with the first thoroughly documented appearance of the so-called Clovis big game hunters. And this correlation encouraged other paleobiologists, Paul Martin of the University of Arizona most prominent among them, to suggest that the extinctions had been man-made. The debate has continued and developed over several decades.

Martin, together with seven colleagues from the University of Arizona and Northern Arizona University, has just produced a new set of data that, he contends, further strengthens the case in favor of man-made extinction. These data include new carbon-14 dating results on horn sheaths of Harrington's mountain goat, *Oreamnos harringtoni*, from several caves in the Grand Canyon.

The last of these goats apparently lived in the canyon a little more than 11,000 years ago, which makes their disappearance contemporaneous with that of the famous Shasta ground sloth, *Nothrotheriops shastensis*. Remains of these two very different animals—one an agile and gregarious grazer, the other a ponderous and nonsocial browser—are to be found in the same caves. In addition, the goat probably originated in holarctic latitudes while the sloth is a creature of the neotropics.

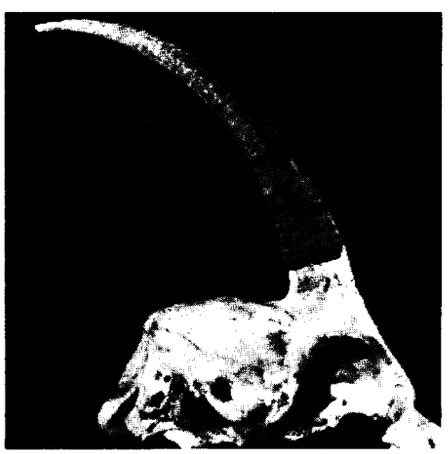
"Given these differences," note Martin and his colleagues, "one might expect that under natural stress, such as that imposed by severe climatic change, the two species would not disappear at the same time. A climatic change inimical to one might well favor the other, at least initially. Instead, our findings suggest concurrent loss."

Both the environmental and the human-impact hypotheses for the large mammal extinctions face problems of one sort or another. For Martin and his school there is the embarrassing fact that, although 57 species of mammal are supposed to have died at the hand of man, there are very few cases of remains of the putative victims in direct association with spear and arrow points of the Clovis hunters.

Martin argues that this is simply the result of the statistics of preservation under catastrophic conditions. The impact was so sudden that the chances of finding a "kill" are remote, he says. The argument is similar to the one over the absence of dinosaur remains at the very edge of the Cretaceous/Tertiary boundary. Some say this shows that the dinosaurs were extinct before the boundary event (comet impact?), while others suggest it is simply a matter of sampling statistics.

In the absence of a convincing smoking gun, Martin's only recourse is to produce more and more evidence of the contemporaneous disappearance of ecologically disparate creatures. The new data on the Harrington's mountain goat provide such evidence.

The dating was done using the tandem accelerator mass spectrometer, which has the disctinct advantage of requiring less than a gram of test material. Conventional carbon-14 dating techniques typically consume several grams of test material, which for many museum specimens represents too big a sacrifice. The Harrington's mountain goat material used in the recent tests was from the remarkably preserved horn sheaths, which are keratinous and ideally suitable for carbon dating. The dry conditions of many of the Grand Canyon caves has provided favorable conditions of preservation, so that in some cases the horn sheath is still attached to the skull (see photograph).



Horn sheath and skull

A leading proponent of the environmental hypothesis, Ernest Lundelius, of the University of Texas at Austin, considers this latest paper by Martin and his colleagues to be "significant and important," not because it solves the debate, but because it provides the kind of precision in dating that will be required if a resolution is ever to be reached. ■ ROGER LEWIN

ADDITIONAL READING

R. Lewin, "What killed the giant mammals?", *Science* **221**, 1036 (1983).

J. I. Mead *et al.*, "Extinction of Harrington's mountain goat," *Proc. Natl. Acad. Sci. U.S.A.* **83**, 836 (1986).