the alpha male's attention and encourages mating from the beta male.

It turns out that the degree of success a beta male has in mating with the female determines his willingness to help provision the offspring: in 80% of cases where the beta male mated with the female, it also helped provision, compared with only 9% of cases where no mating occurred. The beta males also adjust the amount of provisioning work they are prepared to give, increasing it in direct proportion to the amount of mating access they had achieved.

"The DNA fingerprinting data show that the beta males' measure of potential reproductive success is pretty accurate," says Davies. "But it is still a crude measure." It is accurate only inasmuch as most of the time a male has an offspring of his own in the nest—which Davis and his colleagues can determine with DNA fingerprinting—the male will help feed the offspring. However, the male does not discriminate between the offspring in the nest, usually feeding each of them at some point during rearing. "It is clear from this and other behavior that the males cannot recognize their offspring," concludes Davies. "They are therefore forced to use an indirect measure of paternity, one that works rather well, even though it is imperfect."

With the accurate measure of paternity provided by DNA fingerprinting, Davies and his colleagues were able to rationalize one intriguing behavioral vignette. This concerns polyandry, in which an alpha and a beta male share a female. From earlier work Davis knew that, *per nest*, polyandry had the highest reproductive success of any of the mating systems available to dunnocks, because of the greater provisioning that is available to the chicks. And yet alpha males object vigorously to the presence of the beta male, so what does this imply about the costs and benefits to all concerned?

"An alpha male would need at least 60 to 70% of the paternity in trio-fed broods for cooperative polyandry to bring greater reproductive success than monogamy," explain Davies and his colleagues. The DNA fingerprinting data show that the alpha male fails to achieve this, the mean split of paternity being 55% alpha and 45% beta. "This suggests that alpha males do not achieve the critical proportion above which it would pay them to share the female, and explains why, although females encourage the presence of males, alpha males attempt to drive them away." ■ **ROGER LEWIN**

ADDITIONAL READING

T. Burke *et al.*, "Parental care and mating behaviour of polyandrous dunnocks," *Nature* **338**, 249 (1989).

N. B. Davies, "Reproductive success of dunnocks in a variable mating system," *J. Anim. Ecol.* **55**, 123 (1986).

Brain Protein Yields Clues to Alzheimer's Disease

β-Amyloid, the principal protein component of Alzheimer's plaques, may be a key that will help unlock the mysteries of the degenerative brain disease

RESEARCHERS LOOKING FOR THE CAUSE of the devastating brain deterioration of Alzheimer's disease once had high hopes that they had found it in the gene encoding the protein β-amyloid, a prominent component of the abnormal plaques that stud the brains of Alzheimer's patients. By the end of 1987, however, it was clear that an amyloid gene defect was not the primary cause of Alzheimer's disease.

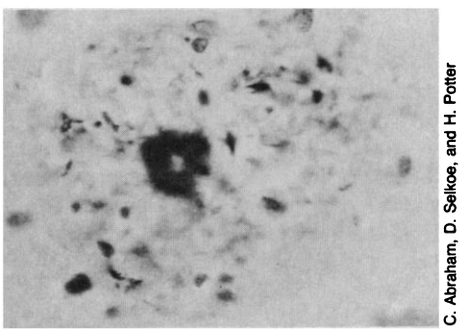
Nevertheless, the intervening year has not seen any diminution of interest in β-amyloid. Research during that time has, if anything, increased the likelihood that the protein contributes in a major way to the pathology of Alzheimer's disease, even though the abnormal deposition of β-amyloid in the brains of the patients may be secondary to some other, as yet unidentified, event. "It's getting more and more interesting all the time," says Dennis Selkoe of Harvard Medical School. "I'm getting even more convinced that it plays a role in the disease."

New evidence suggests, for example, that the protein that gives rise to the β-amyloid of Alzheimer's plaques has a normal function in the brain. This protein, called the β-amyloid precursor protein, may help to maintain nerve cell connections or survival. Anything that disrupts the precursor's ability to perform normally might therefore lead to the degeneration of brain neurons seen in Alzheimer's disease.

The current surge of research on β-amyloid began about 2 years ago with the cloning and sequencing of the gene encoding it. Although this opened the door to a molecular analysis of what goes wrong in Alzheimer's brains, the first outcome was a disappointment.

The β-amyloid gene had been mapped to chromosome 21, in or near a region that genetic studies had shown to contain a gene causing a hereditary form of Alzheimer's disease. Moreover, individuals with Down syndrome have an extra copy of chromosome 21 and therefore of the β-amyloid gene. They also begin developing plaques at an early age and often show dementia symptoms, similar to those of Alzheimer's disease, in their thirties or forties.

This suggested that Down's patients might develop the plaques because they make too much β-amyloid. Perhaps, the reasoning went, the β-amyloid gene was the "Alzheimer's gene." It might in some people have a defect that causes them to overproduce the protein, thereby leading to the plaque formation and brain degeneration of Alzheimer's disease. Researchers soon learned, however, that the β-amyloid gene could not be the Alzheimer's gene (*Science*, 4 December 1987, p. 1352).



C. Abraham, D. Selkoe, and H. Potter

Alzheimer's plaques *consist of a core of β-amyloid fibrils (dark circle) surrounded by a halo of degenerating nerve terminals and glial cells. [Reprinted with permission from* Cell **52**, *487 (1987) © Cell Press]*

Nevertheless, the sequencing of the β-amyloid gene had revealed that the material found in Alzheimer's plaques is synthesized as part of a larger precursor protein, the structure of which has changed little during the course of evolution. This implies that the precursor protein has a critical function in the normal brain. "This must be a very important gene and protein in that it has been so closely conserved in evolution," notes Donald Price of Johns Hopkins University School of Medicine.

Researchers do not know exactly what the β-amyloid precursor protein does, although there are two leading possibilities. One is that it helps to establish or maintain connections between nerve cells, possibly acting as an intercellular adhesion molecule that makes direct connections between neurons. Its structure and cellular location are consis-

tent with that role.

According to Konrad Beyreuther of the University of Heidelberg, Germany, Colin Masters of the University of Western Australia in Perth, and their colleagues, the precursor protein is inserted in nerve cell membranes with the carboxyl end projecting into the cell interior and the main portion of the protein sequence extending to the outside. About half of the β-amyloid segment, which contains a total of 42 or 43 amino acids, is in the membrane and the remainder is in the exterior segment.

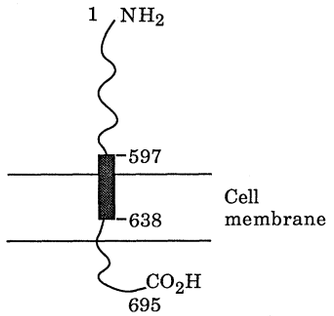
Several groups have verified that the precursor is made by nerve cells in the brain, and new findings suggest that its site of action may be the neuronal terminal, where one neuron makes contact with another. Price's group has shown, for example, that the precursor protein is rapidly transported down axons, a result that dovetails nicely with findings by the Beyreuther group that indicate that the precursor is located at the synapses where nerve terminals impinge on their target cells.

Moreover, a location at neuronal terminals fits with the structure of Alzheimer's plaques. These typically consist of a central core of β-amyloid filaments surrounded by glial cells and degenerating nerve terminals. "The protein is transported in the axons to the nerve terminals," Price says. "This puts it into immediate proximity to where amyloid plaques form."

Another function proposed for the physiological product of the β-amyloid precursor protein is the maintenance of neuronal growth or survival. Janet Whitson and Carl Cotman of the University of California at Irvine, with Selkoe, have found that a synthetic peptide encompassing the first 28 amino acids of β-amyloid enhances the survival of brain neurons maintained in laboratory cultures.

A recent development that may help to resolve the issue of what the β-amyloid precursor protein does comes from Kalpana White's laboratory at Brandeis University in Waltham, Massachusetts. She and her colleagues have isolated a gene that may be the fruit-fly equivalent of the mammalian gene encoding the precursor protein. The two genes are structurally similar. "It looks pretty convincingly like they have the same ancestor," White says.

White's results support the idea that the β-amyloid precursor protein participates in some way in the development or maintenance of the nervous system. The fruit-fly gene is needed for the normal development of the insect's nervous system. If it is equivalent to the mammalian gene, then the way is open to exploring the function of the precursor protein in an organism that is much more amenable to genetic and molecular analysis than are mammals.



Adapted from K. Beyreuther

The β-amyloid precursor protein *is inserted in the cell membrane with the β-amyloid peptide (heavy bar) partially buried in the membrane. The protease inhibitor segment, when present, is in the long exterior portion of the protein.*

The big question, of course, is what goes wrong in the brains of Alzheimer's patients to cause β-amyloid deposition in plaques. On one point at least there is general agreement. Alzheimer's disease develops slowly. Several groups have found that plaque formation begins years, and even decades, before symptoms of dementia become apparent. Researchers have diverse views, however, about what causes the plaque development.

Some think that the β-amyloid accumulation may cause the neuronal loss of Alzheimer's disease. "The scope and course of the disease is over decades," Selkoe says, "and the amyloid comes first."

In addition to having fully formed plaques, the brains of Alzheimer's and Down syndrome patients also contain diffuse β-amyloid deposits that are not accompanied by degenerating nerve cells and glial cells. These diffuse deposits may occur well before symptoms develop and can be found in brain areas, such as the cerebellum, that are not usually affected in Alzheimer's disease, as well as in those that are.

Selkoe suggests that β-amyloid deposition is a normal part of aging, but that for some reason the deposits are not cleared as they should be from the brain areas that degenerate in Alzheimer's patients. The growth-promoting activity of the β-amyloid peptide might then contribute to plaque formation by fostering the outgrowth of the neuronal projections (known as neurites) around the deposits. This may account for the profusion of degenerating terminals in the plaques.

β-Amyloid deposition may instead be the result of the neuronal degeneration in Alzheimer's brains. One possibility is that the brain neurons produce the β-amyloid precursor protein in an effort to compensate for neuronal loss by making an agent that stimulates nerve growth. This would be consistent with earlier work by Cotman and his colleagues who found indications of increased neuronal sprouting in Alzheimer's brains.

Still another possibility is a defect that results in a loss of connections between nerve cells. Neurons that fail to maintain their connections usually degenerate, and this could lead to the release of the β-amyloid peptide from their membranes. The β-amyloid–containing peptides, once they are free, can readily associate with one another to form insoluble deposits such as those in the plaque cores, according to Beyreuther and his colleagues.

However β-amyloid deposition occurs, the peptide must first be cut out of the precursor protein by the action of the protein-splitting enzymes known as proteases. Researchers are anxious to get their hands on the proteases that cut the β-amyloid precursor protein because of the key role they may play in forming Alzheimer's plaques.

The Beyreuther and Price groups may have identified the first step in the release of the β-amyloid peptide. They have found that the bulk of the external segment of the precursor is rapidly removed from cultured cells, with the cut apparently occurring somewhere near the beginning of the β-amyloid segment.

A discovery made at the end of 1987 of a link between protease inhibitors and β-amyloid is particularly intriguing in view of the probable participation of proteases in deposition of the protein. Carmela Abraham and Huntington Potter of Harvard Medical School have found that the protease inhibitor α_1-antichymotrypsin is consistently present in β-amyloid–containing plaques.

They have identified it in the senile plaques of Alzheimer's disease and Down's syndrome and also in the vascular β-amyloid deposits that occur in a rare genetic disorder, known as "hereditary cerebral hemorrhage with amyloidosis—Dutch type." The α_1-antichymotrypsin may contribute to plaque formation in Alzheimer's disease by inhibiting the β-amyloid–degrading proteases. Synthesis of the inhibitor is increased in Alzheimer's brains, Potter notes.

In addition, the precursor protein itself can be made either with or without an insert encoding another kind of protease inhibitor, known as the Kunitz type. Researchers have been trying to find out if the presence of the inhibitor sequence fosters plaque formation or prevents it. The answer could go either way—and at this early stage there is evidence in support of both positions.

The inhibitor sequence could foster plaque formation by inhibiting the proteases

that would otherwise prevent β-amyloid from accumulating in the brain. In agreement with this possibility, Rachel Neve and her colleagues have found a relative shift in favor of the synthesis of the precursor protein with the inhibitor sequence in some affected areas of Alzheimer's brains.

In contrast, Steven Younkin of Case Western Reserve University School of Medicine and his colleagues have found the opposite, an apparent shift in favor of the synthesis of the precursor without the inhibitor sequence in Alzheimer's brains. This finding implies that the presence of the inhibitor sequence might help to prevent β-amyloid deposition by retarding the action of the proteases that release the peptide from the precursor protein.

Another unanswered question concerns the source of the β-amyloid of Alzheimer's plaques. Although most researchers think that it is a product of brain neurons, some suggest that it might be either transported into the brain in the blood or made in the linings of the blood vessels. They note that in other diseases characterized by abnormal protein deposits, the proteins come from the blood. Moreover, β-amyloid deposits occur in the blood vessels in Alzheimer's brains as well as in the brains of individuals with the Dutch cerebral hemorrhage disease.

Investigators are also looking at factors that control the expression of the gene encoding the β-amyloid precursor protein in their efforts to pin down the defect causing plaque formation in Alzheimer's brains. Some evidence suggests that the activity of the gene is higher than normal in the brain areas that degenerate, although there is not a perfect correlation between the areas of high activity and the areas of damage.

In any event, because no defects have been found in the gene for the β-amyloid precursor protein that might account for its increased expression in Alzheimer's disease, researchers have had to look for other factors that might influence expression of the gene. Two of the leading candidates are interleukin-1 and nerve growth factor.

Interleukin-1 is a protein with a wide range of activities inside and outside the immune system. It plays a key role, for example, in the induction of inflammatory responses. Dmitry Goldgaber's group at the State University of New York in Stony Brook has recently shown that interleukin-1 stimulates expression of the β-amyloid gene.

Moreover, according to Sue Griffin of the University of Arkansas School of Medicine in Little Rock, production of interleukin-1 is elevated in the brains of Alzheimer's and Down syndrome patients. "What she found was really amazing," Goldgaber says. "The number of interleukin-1–positive cells was dramatically increased in the Alzheimer's disease and Down syndrome patients."

The interleukin-1 is produced, Griffin says, by the nonneuronal glial cells of the brain, primarily by the cells of the microglia type. Indications are that the glial cells become active and begin producing interleukin-1 before the plaques and other pathological changes occur in the brains of the Alzheimer's and Down's patients. This might then be an early event in the genesis of β-amyloid deposits and plaques.

Nerve growth factor is another agent that increases expression of the β-amyloid precursor gene, according to Neve and William Mobley of the University of California, San Francisco. "It may well be that this perfectly normal gene, whose expression might be needed for neurons to grow, might be regulated by nerve growth factor," Mobley says. Researchers showed a few years ago that the growth factor is necessary for the development and survival of brain neurons, including one of the main types that degenerate in Alzheimer's disease.

The possibility that nerve growth factor stimulates synthesis of the β-amyloid precursor protein is particularly interesting in view of Cotman's suggestion that brain neurons might be attempting to grow as a way of compensating for the degeneration that occurs in Alzheimer's disease. The ironic aspect of such a situation is that it might ultimately make matters worse by leading to plaque formation.

Additional factors may also help to regulate the expression of the β-amyloid precursor gene. Beyreuther and Masters have dissected the regulatory region of the gene and found that it is complex, with the potential to respond to several different control factors. The regulatory region includes, for example, a "heat shock promoter," which would allow it to respond to increased temperature and other stresses.

If the explosion of research on β-amyloid during the past year has not solved the mystery of Alzheimer's disease, it has at least given researchers a wealth of leads to follow, almost an embarrassment of riches, Selkoe says. By defining the molecular events that lead to β-amyloid deposition in plaques, researchers may ultimately be able to work backwards and identify the primary Alzheimer's defect. ■ JEAN L. MARX

Species Questions in Modern Human Origins

The extraordinary difficulty of identifying species from fossils exacerbates the challenge of understanding human origins

A YEAR AGO *Newsweek* did a cover story on the origin of modern humans—the best selling issue of the year—which identified Africa as the Garden of Eden, 200,000 years ago. Pictured on the cover was a very modern-looking couple, black, with apple and serpent appropriately placed. "This tells you something about the recently acquired appeal of the subject," observed Christopher Stringer, of the British Museum (Natural History), London. Speaking last week at a workshop at New York University, Stringer went on to say: "But you have to remember that, black though Adam and Eve probably were, they were not *modern* Africans, as portrayed by *Newsweek*; they were the ancestors of all of us and therefore would have looked different."

That the news magazine might have been ensnared by this paleoanthropological nuance should not be surprising, given the rampant confusion among the professionals over this very same issue. "Many anthropologists simply fail to come to grips with the biological realities surrounding the origin of modern humans," says Ian Tattersall, of the American Museum of Natural History, and a workshop participant. "There is an endemic problem of how we recognize species in the fossil record, particularly the human fossil record," he told *Science*.

As Stringer and Peter Andrews, also of the BM(NH), outlined in *Science* last March (11 March, p. 1263), there are two models for modern human origins, which represent extremes on a continuum of possibilities. One, the regional continuity model, argues that modern human geographical groups (races) are the product of local evolution over a very long period of time in all parts of the Old World, essentially going back a million years when human ancestors first left Africa. The second