it can give the new universe a kind of jump start. Furthermore, since Einstein's equations seem to rule out any attempt to make a white hole by compressing ordinary matter—it would just form a black hole—the enterprise seems stymied.

However, says Guth, there may be a way out. Consider the vacuum: ordinary, empty space. According to quantum field theory it is not really empty. On a submicroscopic scale it is constantly undergoing quantum fluctuations in energy and density, rather like a boiling cauldron. Indeed, he says, these oscillations are so violent and so rapid that the vacuum might very easily be creating tiny inflationary regions all the time, even without a white hole. None of these regions would last for more than an instant. And yet, even that instant might be sufficient for the inflation/pinch-off mechanism to come into play. In other words, says Guth, new universes may be constantly coming into existence all around us, spontaneously and invisibly. And conversely, since quantum fluctuations are not restricted by Einstein's equations in the same way black holes are, it is entirely possible that our own universe came into existence this way.

"Now we have the mathematical tools that allow us to seriously discuss the prospects of creating a universe in your basement."

Of course, says Guth, one has to take these speculations with a liberal grain of salt. For example, the calculations that led to the aneurysm solution and the necessity of a white hole assume that our own space-time is perfectly flat, and that the high-density region is spherically symmetric. The assumptions are necessary to make the equations tractable, but they are oversimplified, to say the least. Nonetheless, Guth believes that these idealized solutions do reveal the essence of what would happen in more realistic situations. He and his colleagues are currently trying to formulate a more quantitative calculation of universe formation in the quantum vacuum, to see if the qualitative arguments really hold up. ■

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Defect in Alzheimer's Is on Chromosome 21

The genetic defect in Alzheimer's disease is located on the same region of chromosome 21 that contains the gene for brain amyloid, a protein that accumulates abnormally in the brains of both Alzheimer's and Down's patients

SOMETIMES in scientific research, concepts and technologies mature in parallel to produce a major advance. This has just occurred in Alzheimer's research. New data from one group of investigators show that the genetic defect in familial Alzheimer's disease patients is located on chromosome 21—the same chromosome of which there is an extra copy in Down syndrome. Meanwhile, results from two other groups indicate that the gene coding for β amyloid protein, which accumulates in the walls of blood vessels and in the neuronal tissue of both Alzheimer's and aged Down's brains, also maps to chromosome 21. (See pp. 877, 880, and 885 of this issue.)

The new results directly support the notion that at least one form of Alzheimer's is inherited and that a similar genetic defect may occur in both familial Alzheimer's and Down syndrome. Results from a fourth research team show that abnormal amyloid plaques appear in the brains of a wide range of aged mammals as well as humans and suggest that aged nonhuman primates can serve as animal models for certain aspects of Alzheimer's disease. (See p. 873 of this issue.)

Patients with Alzheimer's disease progressively lose their ability to remember and reason. In later stages of the illness they become completely helpless and ultimately die. Physicians describe two forms of the disease—one that occurs fairly early in life at about the age of 50 and another that occurs much later. The strongest evidence that at least one form of Alzheimer's is inherited comes from studies of families in which the disease occurs early, although not all early onset Alzheimer's is clearly inherited and the so-called sporadic or later form may also turn out to have a genetic cause.

"We now have the first clear-cut indication that those families with an inherited form of Alzheimer's disease share an abnormal gene that is located on chromosome 21," says James Gusella of Massachusetts General Hospital (MGH) and Harvard Medical School. He and Peter St George-Hyslop, also of MGH and Harvard, head a large international group of scientists who traced Alzheimer's through several generations of four families in which an autosomal dominant gene causes the disease. They discovered two genetic markers that identify the region of chromosome 21 containing the defect, but Gusella says that it is not yet appropriate to use the markers to predict who might develop Alzheimer's because more than one gene locus may be involved.

The second team of investigators led by Rachel Neve and Rudolph Tanzi, of Harvard Medical School, cloned a complementary DNA (cDNA) probe for β amyloid protein and localized the gene to chromosome 21. "The fact that the gene for β protein is on human chromosome 21 may be a coincidence," says Neve. "The β protein gene may not cause Alzheimer's disease, but it's in the same region of chromosome 21 as the gene described by the Gusella group."

Tanzi and Neve also show that production of messenger RNA (mRNA) for β protein is increased in fetal Down's brain, which suggests that the extra dosage of chromosome 21 and the gene for β protein may lead to the abnormal deposition of amyloid protein in the brains of these individuals. They also find that the mRNA for amyloid exists in many human tissues in addition to brain.

A third research group has also cloned a cDNA for the brain amyloid protein gene and similarly finds it on chromosome 21. "The amyloid polypeptide that is found in plaques is a very short protein, about 42 amino acids long," says Dmitry Goldgaber of the National Institute of Neurological and Communicative Disorders and Stroke. "But the native protein is many times larger than the final protein." Goldgaber and Carlton Gajdusek, also of NINCDS, and their colleagues postulate in their paper that extracellular deposits of "amyloid in Alzheimer's disease and Down syndrome may well be formed from a precursor synthesized in neurons as well as in other cells, such as microglia and brain macrophages."

The fourth group of investigators, Dennis Selkoe of Harvard Medical School, Linda Cork and Donald Price of Johns Hopkins University School of Medicine, and their

colleagues, find an abnormal accumulation of amyloid protein filaments in the brains of several species of aged mammals in addition to humans. They conclude that the protein is highly conserved in evolution and suggest that aged nonhuman primates may serve as animal models in which to study certain aspects of Alzheimer's disease. "I don't want to push the idea that aged mammals have Alzheimer's dementia," says Cork. "But they do have behavioral deficits that correlate with age and they share some morphological features associated with human Alzheimer's, so in that sense they are good models."

The experimental approaches used by all four groups of researchers depend on recently developed techniques. For instance, Gusella and his colleagues used genetic linkage analysis to determine that the long arm of chromosome 21 fairly close to the centromere contains the gene or genes for familial Alzheimer's dementia. The researchers characterized anonymous DNA markers, loci on chromosomes that are identified with cloned pieces of DNA of unknown function. These can be used to detect variations in the nucleotide sequences of DNA from individuals with Alzheimer's and their relatives. The DNA variations, known as restriction fragment length polymorphisms, vary widely among individuals, and the crucial test is to see if there is a correlation in the inheritance of the disease and a particular pattern of the markers, Gusella says.

Both the Neve and Tanzi team and the Gajdusek and Goldgaber group isolated cDNA clones that encode the amyloid polypeptide, and, in collaboration with Gusella, Neve and Tanzi used polymorphisms and the anonymous DNA markers D21S1/D21S11 to map the β protein gene to chromosome 21. Using different methods, Selkoe and his colleagues developed a panel of antibodies that stain brain amyloid. The antibodies cross-react with plaques from Alzheimer's brains and those from aged monkey, orangutan, polar bear, and dog.

Despite the significant contributions of the new results, however, questions and controversies remain about Alzheimer's disease. For instance, is the gene that causes familial Alzheimer's disease the same as the gene for β amyloid protein? Gusella contends that the genes may not be identical. He points out that the region of chromosome 21 identified by the DNA markers could contain 500 or so different genes. The fact that the gene for β amyloid protein falls within or near this region could be a coincidence, he says.

Tanzi and Selkoe, however, regard β protein abnormalities as an important and early part of the disease process, although neither is yet ready to say that an abnormal gene for β protein causes familial Alzheimer's. "My personal feeling is that all Alzheimer's is familial," says Tanzi. "It may all come down to the same chromosome locus, but I'm not saying that it has to be the β protein gene. The amyloid protein could be precipitated abnormally by different factors in the brain's microenvironment, which varies among individuals. This may help explain why people get Alzheimer's at different ages. Another possibility is that the actual defect may be an abnormal promoter of the β protein gene." Selkoe emphasizes that if the gene for β protein is not the same as the gene for familial Alzheimer's, the two genes would have to be very close together.

"We now have the first clear-cut indication that those families with an inherited form of Alzheimer's disease share an abnormal gene that is located on chromosome 21."

Other unanswered questions concern the type or types of cells that make abnormal amyloid deposits and the mechanism by which they form. All human tissues examined by Neve and her colleagues have at least some mRNA for β protein, but for an unknown reason abnormal amyloid deposits are unique to brain.

"Amyloid deposition in the brain is clearly a normal aged-linked phenomenon," Selkoe says. "But in Alzheimer's and aged Down's patients there must be some additional mechanism that leads to the greater deposition of β protein." He and Tanzi postulate that the endothelial cells lining blood vessels in and around the brain may mediate the abnormal process by which amyloid filaments accumulate.

Still another key issue has been whether the plaques of amyloid β protein and a different brain abnormality in Alzheimer's, neurofibrillary tangles (NFT), are formed by the same cells and are therefore part of the same degenerative process. Selkoe thinks that the abnormally accelerated deposition of amyloid in Alzheimer's and Down's patients over the age of 35 or 40 may then trigger the less specific formation of NFT. And because neurons that secrete different transmitters contribute to the tangles that often surround plaques, he postulates that amyloid itself may be toxic to neuronal tissue.

But it is still not known how other data about abnormal brain deposits in Alzheimer's fit into the picture. For example, are the abnormal phosphorylation of tau proteins, which are associated with the paired helical filaments of NFT, and the production of an abnormal 68-kilodalton protein found in Alzheimer's and aged Down's brains somehow related to the defect in familial Alzheimer's dementia that is located on chromosome 21?

At this point it is impossible to identify which brain abnormalities in Alzheimer's represent its underlying cause and which are effects of the disease process. Neither amyloid plaques nor neurofibrillary tangles are unique to Alzheimer's disease, although their brain distribution in Alzheimer's—to the hippocampus, amygdala, and cerebral cortex in particular—is somewhat specific. Whether substances, such as nerve growth factor (NGF), that promote the survival of neurons in these brain regions are somehow related to the disease process is also being investigated. Gusella says, however, that the gene for NGF is not on chromosome 21.

Where do the four groups of researchers go from here? Gusella suggests that the next and most important step is "to determine exactly where the defective gene is—by finer marker studies, including the gene for amyloid, and using additional families." Tanzi indicates that his goal is "to find the genetic basis of the defect. Is it gene duplication, gene mutation, or abnormal processing of the β protein?" Neve plans to explore "the normal biological role for the β amyloid protein and its precursor." Goldgaber wants to know "if amyloid is a normal protein that for some reason becomes abnormal in Alzheimer's or if a normally silent β protein gene is induced by the disease." Price advocates using "in situ hybridization with nucleic acid probes to determine exactly which cells make amyloid."

Taken together, the new results show that one or more genes causing familial Alzheimer's dementia are located on the same region of chromosome 21; one of the genes in this region codes for the β amyloid protein that forms the cores of the neuritic plaques in Alzheimer's and aged Down's brains; the mRNA for β protein occurs in many human tissues in addition to brain; and abnormal deposits of amyloid occur in the brains of a variety of aged mammals. None of the evidence conclusively identifies a cause for Alzheimer's disease, although an abnormality in the gene coding for amyloid β protein or in the processing of its precursor protein is a strong candidate. β amyloid protein appears to be highly conserved and probably has some fundamental, but still unknown, role in normal cell function. ■

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