Anatomy of Alzheimer's

Do immune proteins help destroy brain cells?

By KATHY A. FACKELMANN

"You keep the parts of the complement system separated, like the parts of an atomic bomb," says Patrick L. McGeer of the University of British Columbia in Vancouver. "You begin to assemble the complement proteins and you're likely to do a lot of damage."

McGeer is a neuroscientist with a healthy respect for the complement system—a particularly lethal group of about 25 proteins in the immune system that helps destroy disease-causing microorganisms. He and other scientists now suspect the complement system may play a role in Alzheimer's disease.

During the 1980s, McGeer and other researchers gathered evidence suggesting a link between the complement system and Alzheimer's, a cause of dementia in up to 4 million people in the United States. Now, a California team reports that brain cells taken from people with Alzheimer's disease appear to manufacture certain complement proteins.

These findings hint that Alzheimer's disease results when the explosive complement system is unleashed not on a microbe, but against the fragile cells of the brain itself. The theory remains highly speculative, yet an Arizona team has taken the next step: They are testing an Alzheimer's treatment that may prevent the immune system's misguided attack.

The urgent pace at which Alzheimer's research moves forward may be explained by the fact that as yet no cure exists for the disease.

Dementia refers to a group of symptoms, such as forgetfulness and confusion, that are often associated with old age. Yet many researchers believe that the loss of mental agility is not a normal consequence of aging, but rather the result of a disease process such as Alzheimer's, stroke, Huntington's disease, or Parkinson's disease.

Alzheimer's disease first becomes evident in the mundane tasks of everyday life: A middle-aged woman forgets where she left the house keys. In most cases, people attribute such a lapse to a particularly busy day, an emotional upset, or a variety of other distractions. And in most cases, that explanation proves correct.

For the person with Alzheimer's disease, however, such lapses gradually get worse. The afflicted person may need to compile extensive lists simply to get through a routine day. He or she may not remember how to get home from the grocery store or how to write out a check. Family members may notice a change in behavior or personality. For example, people with Alzheimer's disease may suddenly start to act in a belligerent or agitated manner. As the disease progresses, people with Alzheimer's disease may lose control of their bladder, need assistance with grooming, eating, and other daily activities, and eventually lapse into a vegetative state.

Despite the devastation it creates, scientists still know very little about what causes Alzheimer's disease, which was named after the German physician Alois Alzheimer. Since his detailed description of the disorder in 1907, researchers have put forward a wide range of theories to explain its cause. Some scientists believe a slow virus or environmental poison may initiate the disease. Others have noted that Alzheimer's disease runs in families and believe that some people inherit a predisposition to the illness.

Under magnification, brain tissue taken during autopsy from a victim of Alzheimer's disease shows abnormal yarn-like deposits, called neurofibrillary tangles. In addition, the gray matter of the brain will appear pocked with "plaques." These plaques are made up of dying nerve cell components surrounding a core of beta amyloid protein, a fibrous material that is the subject of an intense, ongoing research effort (SN: 3/7/92, p.152). Both the plaques and the tangles occur in areas of the brain known to be involved in memory and intellectual functioning.

Interest in the complement system was piqued among Alzheimer's investigators during the late 1980s, when Canadian researchers led by McGeer and European teams began to study brain tissue taken during autopsy from people with the disease. The researchers discovered complement proteins buried within the telltale plaque and neurofibrillary tangles. This finding galvanized a team in Los Angeles.

"That evidence led us to wonder if the complement system, which is such a destructive system, could potentially be involved in the neurodegenerative events in the Alzheimer brain," says Steven A. Johnson, a neuroscientist at the Univer-

Steven A. Johnson

This picture shows messenger RNA for a complement protein found in brain tissue taken from a patient with Alzheimer's disease. The neurons containing this messenger RNA glow brightly in this image of the hippocampus, a brain region involved in learning and memory.

sity of Southern California (USC) in Los Angeles.

This line of reasoning by Johnson, McGeer, and others runs counter to traditional thinking about the immune system and the brain. "There's been a sort of dogmatic view that the brain is an immunologically privileged site," Johnson says, noting that most scientists believe that the so-called blood-brain barrier keeps most components of the immune system out of the brain, where an immune response could cause serious damage.

Indeed, many scientists offer a far less interesting explanation for the presence of complement proteins in the brains of Alzheimer's patients. They believe that when these patients died, complement proteins floating in the bloodstream managed to slip past a damaged or leaky blood-brain barrier. If correct, the finding of complement proteins would represent merely an artifact and would provide scientists with no new information about Alzheimer's disease, notes Caleb E. Finch, director of the neurogerontology program at USC.

Such views deterred many scientists from exploring the immune system-Alzheimer's link any further. However, the Los Angeles team had completed other research suggesting that brain cells actually manufacture a substance that inhibits or slows the complement system. That finding hinted that the brain did indeed have complement activity going on, and the team began to wonder if brain cells were actually churning out deadly complement proteins. Johnson and Finch began to work on experiments designed to find out more about complement proteins.

In the first study, Finch, Johnson, Giulio M. Pasinetti, and their colleagues created an animal model for Alzheimer's disease. With toxic chemicals or a tiny knife, they damaged nerve pathways in rats' brains to mimic the nerve cell injury seen in the brains of humans who develop Alzheimer's disease. In response to the injury, the rats' brain cells stepped up their production of two types of messenger RNA, molecules that carry the genetic blueprint that tells cells to synthesize specific proteins. In this case, brain cells called microglia cranked out messenger RNA coding for two types of complement proteins.

The rat experiment, reported in the November EXPERIMENTAL NEUROLOGY, suggested that rather than leaking past the blood-brain barrier, complement proteins found in the brain were produced locally by microglial cells. But would the same thing hold true for humans?

To find out, the Los Angeles team obtained brain tissue from seven men and women with Alzheimer's disease who had undergone an autopsy after their death. The group also obtained brain tissue at autopsy from six men and women who were about the same age as the Alzheimer's patients but who did not suffer from dementia.

The researchers discovered that neurons, as well as microglial cells, produced messenger RNA for the two types of complement proteins. The fact that microglia may produce an immune protein didn't come as much of a surprise. These cells are similar to macrophages, immune cells found in the bloodstream, Johnson notes; however, microglia are not considered part of the immune system. Many scientists believe that microglial cells may cruise into the brain during fetal development and do some of the immune system's work once they get there.

However, the scientists did not expect neurons, the information-storing cells of the brain, to produce the messenger RNA for complement proteins. "That's a pretty unexpected finding," Johnson says, noting that this is the first report suggesting that neurons manufacture the immune proteins. Indeed, other scientists express surprise at this result. "I think that finding needs to be confirmed," McGeer says.

The USC team also discovered that brain tissue from the subjects with Alzheimer's disease showed a two- to threefold increase in messenger RNA coding for the two complement proteins. Their results will appear in the November/December NEUROBIOLOGY OF AGING.

If brain cells do manufacture complement proteins, something in the brain may increase the activity, or "turn up the volume," of this system, Finch says. The complement system may act in a constructive fashion in the normal brain, perhaps mopping up the debris left when neurons die of old age, he speculates. But that routine process may go awry in the brain of the Alzheimer's patient, leading to the revved-up and very dangerous complement attack.

The Los Angeles scientists emphasize that the complement system may play only a supporting role in the drama of Alzheimer's disease. Some other factor, perhaps a bad gene, a virus, or an environmental toxin initiates the disease process; complement merely makes the problem worse, Finch suggests. But what gets complement so riled up in the first place?

"That really has been the crux of the matter," says neuroscientist Joseph Rogers at the Institute for Biogerontology Research in Sun City, Arizona. Rogers' team has been studying how and why this system gears up to do its job.

In the rest of the body, the complement system gets involved in the fight against disease in the following way: After a microbe enters the bloodstream, white cells secrete antibodies that attach themselves to the surface of the invader. The first complement molecule, which is called C1Q, recognizes the attached antibody and activates the next complement protein – and so on down the line. The end result is a doughnut-shaped complex that kills the invader. A side effect of this cascade of proteins is the characteristic redness, swelling, and warmth associated with an inflammation.

That classical notion of complement activation runs into trouble when it comes to the brain, where immune components are generally excluded by the blood-brain barrier. However, Rogers' group knew that a few rare substances will trigger the complement system directly, without the help of an antibody.

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New research by Rogers' team suggests that the beta amyloid protein itself – the fibrous stuff that forms the core of plaques – can bind with C1Q and set off complement's toxic cascade. They detail their results in the Nov. 1 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Once activated, the complement system might set up a vicious cycle in which the inflammation produced in the brain tissue leads to more plaque production and cell death, Johnson says. The whole process may get started many years before the afflicted person notices any symptoms, he adds.

"It could be a very subtle and slow, but continuously destructive mechanism that will be very difficult to track down," Johnson says. "We're not going to say that the complement system has a role yet. But it has the potential."

The USC researchers have yet to prove that human brain cells actually manufacture complement proteins, Johnson cautions. The messenger RNA indicates that the cell has the capacity to make the

protein, but it does not show that the cell's protein-making machinery actually spits out these toxic molecules, Finch adds.

"Our work suggests that there is a potential for a destructive mechanism in the brain that is related to this complement system," Johnson says. "That's probably as far as it can be taken [for now]."

If future research does confirm the link between the complement and Alzheimer's disease, it may suggest a change in treatment for the disorder. To date, researchers have not found anything that decisively halts or reverses the symptoms of dementia (see sidebar).

"I'd hate to speculate a lot," Johnson says. "But if you can track down a problem like this, then I think you're much closer to being able to design a treatment."

Other scientists are already pursuing the treatment angle. Rogers and McGeer believe that therapy with drugs that dampen the inflammatory response might slow the pace of Alzheimer's disease. Their hope is that such medications could prevent the debilitating symptoms altogether if given early in the disease process.

In a letter published in the April 1990 LANCET, McGeer and Rogers put forward the controversial hypothesis that people with rheumatoid arthritis appear to be protected from Alzheimer's disease, perhaps because the anti-inflammatory drugs they take inhibit the complement system.

The investigators looked at several different kinds of prevalence data and found an unexpectedly low prevalence of Alzheimer's disease among people with rheumatoid arthritis, which occurs when the immune system begins a misguided attack on the joints, Rogers notes.

"If complement-mediated attack is one of the mechanisms that would cause damage to the Alzheimer's brain, then you might have some possibility of controlling that by using anti-inflammatory drugs," he adds.

The researchers don't have proof that such a tactic will protect people from the ravages of Alzheimer's disease. The only way to test such a theory is to give anti-inflammatory drugs to people with the disease.

"We have done that," Rogers says, noting that his team has submitted a paper to a journal for publication. "I cannot comment beyond that, except to say that the results appear to be encouraging," he says.

In the end, the hypothesis that the immune system plays a role in the development of Alzheimer's disease remains just that: a hypothesis. And there are other, equally compelling theories that aim to explain this disease.

Johnson and the others know that. Yet they still believe the complement system somehow leads to brain cell death and dementia. They also know that the field remains littered with good ideas that didn't pan out.

"It could turn out to be a big bust in the next several years," Johnson admits. "But I think it's a good lead." □

Tacrine: Reversal of fortune?

In November 1986, California psychiatrist William K. Summers reported that 12 people with Alzheimer's disease had improved dramatically after taking an experimental drug now known as tacrine (SN: 11/15/86, p.308). These results, including the report that one Alzheimer's patient had resumed playing golf and another had gone back to work, spurred a number of clinical trials designed to test the drug's efficacy.

Since that time, researchers have reported mixed results on tacrine's efficacy and raised concern about liver damage (SN: 3/23/91, p.180).

Now, two new studies add to the growing file on tacrine. They both indicate that this experimental drug does provide benefits to some people with Alzheimer's disease, but the improvements appear modest.

A study in the Nov. 11 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA) suggests that some people with Alzheimer's disease who took tacrine showed significant improvements on tests of memory and intellectual ability. Although there were no dramatic turnarounds, some study participants were able to recognize family members after taking the drug, notes lead researcher Martin Farlow at the Indiana University Medical Center in Indianapolis.

Farlow and his colleagues at 21 U.S. and two Canadian medical centers began their study by recruiting 468 people with mild to moderate Alzheimer's symptoms. The researchers gave patients one of several different doses of tacrine capsules or a placebo. Neither the investigators nor the patients knew which patients received the drug and which got the inactive pills.

After 12 weeks of treatment, the people receiving tacrine showed a statistically significant improvement in the Alzheimer's Disease Assessment Scale, a test designed to measure memory and cognitive abilities. People who received the highest dose of tacrine (80 milligrams per day) showed the greatest improvement on this test, a finding which indicates that response to treatment increases with higher doses, Farlow says.

In addition, tacrine-treated patients exhibited improvement in the Clinical Global Impression of Change, a subjective scale completed by both doctors and family members. This scale helps the researchers gauge any overall change in a patient's ability to function, Farlow says.

About 25 percent of patients taking tacrine developed asymptomatic elevations in liver enzymes circulating in the bloodstream. These enzymes can be an early warning of liver damage, but the problem disappeared when patients stopped taking tacrine, Farlow says. Side effects associated with the drug included nausea, vomiting, diarrhea, and rash.

The second study – presented in part at a U.S. Food and Drug Administration advisory panel meeting last year (SN: 3/23/91, p.180) – shows marginal improvements as a result of tacrine treatment. Kenneth L. Davis of the Mount Sinai Medical Center in New York City and his colleagues studied 215 people with probable Alzheimer's disease who had mild to moderate impairments in memory and cognitive abilities. About half the group received varying doses of tacrine, while the remainder got a placebo. After six weeks, the team discovered that patients getting a tacrine treatment held their own in tests of cognitive ability, while those on placebo got progressively worse. Yet the investigators could detect no across-the-board improvement in people receiving tacrine, says researcher Lon S. Schneider of the University of Southern California in Los Angeles.

Taken together, the two studies add evidence to the belief that tacrine does provide relief, albeit modest, to victims of Alzheimer's disease, comments Gary W. Small at the University of California, Los Angeles. Small believes that Alzheimer's disease has more than one cause. Therefore, tacrine may benefit just a subset of patients, he says in an editorial that appears in the Nov. 11 JAMA.

Alzheimer's disease results in the death of brain cells known to make acetylcholine, a crucial neurotransmitter. Tacrine works by inhibiting an enzyme that breaks down acetylcholine, thus increasing the amount of this neurotransmitter that lingers in brain tissue, Small says.

Officials at the Warner-Lambert Co., which manufactures tacrine, remain confident of the drug's ability to clear the remaining regulatory hurdles at the FDA. The agency has yet to approve tacrine, but it has allowed people with Alzheimer's disease to obtain the drug through a limited program, Small says.

– K.A. Fackelmann