New Alzheimer's Therapy Suggested

A small trial hints that an anti-inflammatory drug slows Alzheimer's disease, thereby supporting the idea that inflammation contributes to the pathology

One of the most hotly debated issues in neurobiology these days concerns the cause of the brain degeneration found in Alzheimer's disease. Many researchers think that the abnormal deposition in the brain of a small protein called β-amyloid leads to the damage. But this idea is by no means universally accepted and other possibilities are also under investigation. One of the more radical of these—that Alzheimer's is a chronic inflammatory disorder similar to arthritis—now seems to have gained some clinical support. At a meeting sponsored by the pharmaceutical industry and held in Philadelphia in early April, neurologist Joe Rogers of the Sun Health Research Center in Sun City, Arizona, presented the results of a small pilot study in which the nonsteroidal anti-inflammatory drug indomethacin, commonly prescribed for arthritis, appeared to slow the advance of Alzheimer's dementia in a group of 14 patients over a 6-month period.

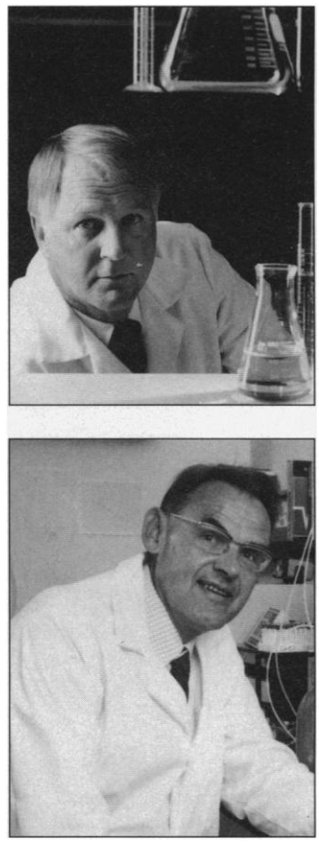
There are currently no good drugs for treating Alzheimer's, and it would be good news indeed if anti-inflammatory drugs could slow, or perhaps halt, the progression of the disease. "Imagine having only to take aspirin or aspirin-like compounds [for Alzheimer's]. That would be terrific," says Zaven Khachaturian, who oversees Alzheimer's research at the National Institute on Aging. Nevertheless, Khachaturian cautions that these new results are far from proof that nonsteroidal anti-inflammatory drugs (NSAIDs) like indomethacin are even moderately effective. Rogers agrees. He notes that NSAIDs can have serious side effects, which include ulcers and other severe gastrointestinal problems, and that their use would not be justified without much more definitive proof of therapeutic benefit. And Patrick McGeer, a University of British Columbia neuroscientist who is a longtime collaborator of Rogers, warns that another kind of anti-inflammatory drug, the steroids, may actually be dangerous since animal studies have shown they can be toxic to neurons.

The indomethacin trial included 44 patients from Sun City, half of whom received indomethacin and half placebo. The study was "double-blinded," meaning that neither the patients nor the people monitoring their condition were told who was getting the drug. Using four standard cognitive skills tests, Rogers' group measured the severity of the patients' dementias at the start of the trial and after treatment ended 6 months later. Indomethacin's gastrointestinal side effects reduced the total number of patients in the treatment group to 14 by the end of the trial. But the placebo group suffered dropouts, too, although for a different reason. "We lost about 20% of our placebo patients because they went down hill behaviorally, so much that they wouldn't take medicine or sit for the test anymore," says Rogers. "That didn't happen with the indomethacin patients." Overall, two of the four cognitive tests indicated a significant slowing in the deterioration of the treatment group. In particular, the mini-mental status exam, widely recognized as a fairly accurate measure of Alzheimer's dementia, indicate that the cognitive abilities of the patients on indomethacin remained stable over the 6 months' course of therapy.

Rogers and McGeer emphasize that the trial was too small and too short to draw conclusions about indomethacin's efficacy, and the drug's distinctive side effects may have "unblinded" some patients, thus allowing at least minor, unconscious biases to creep into the results. But those results are sufficiently encouraging that Rogers has set up a larger indomethacin trial, funded by the Sun Health Research Institute and including about 120 patients. The results should be available next spring.

While there is still ample reason for caution, the Sun City indomethacin trial comes at a time when there appears to be growing acceptance of the idea that inflammatory responses may contribute to Alzheimer's, and that NSAIDs may have some efficacy. "I think that has to be considered as a possibility," says Bruce Yankner of Harvard Medical School, one of the best known proponents of the β-amyloid theory.

Another indication of the growing interest in the inflammatory hypothesis comes from the pharmaceutical industry. The Eli Lilly-backed biotech firm Athena Neurosciences in South San Francisco runs one of the world's largest Alzheimer's research programs. While the company has long advertised its massive effort to find inhibitors of β-amyloid production, it has also been quietly trying to develop NSAIDs for Alzheimer's for the past 4 years. "There is very good reason to suspect that inflammation is part and parcel of Alzheimer's disease and contributes to the ongoing dementia that the patient experiences," says Ivan Lieberburg, who runs Athena's Alzheimer's program.



Inflammation theorists. Patrick McGeer *(top)* and Joe Rogers argue that inflammatory processes may be part of a vicious cycle in Alzheimer's disease.

Some of that "good reason" comes from investigations by Rogers and McGeer over the past several years. One of the characteristic pathologic features of Alzheimer's brains, for example, are the "senile plaques," areas of degenerating nerve terminals surrounding cores of aggregated and insoluble fibrils of β-amyloid. In 1987, McGeer and his British Columbia colleagues found that plaques in brains obtained at autopsy from Alzheimer's patients are also filled with reactive microglial cells, cerebral representatives of the immune system's monocytes and macrophages, which contribute to inflammatory responses.

Microglial cells often perform a housekeeping role, devouring neurons that have been killed or wounded for whatever reason. But McGeer's studies suggested that the microglial cells in the Alzheimer's plaques were doing more than scavenging dead neurons. They indicated that the cells secrete the so-called complement proteins, which can kill cells when the proteins are appropriately activated, as they appeared to be in the lesions. This result, among others, made McGeer wonder whether the microglial cells and their associated biochemical weapons were destroying healthy bystander neu-

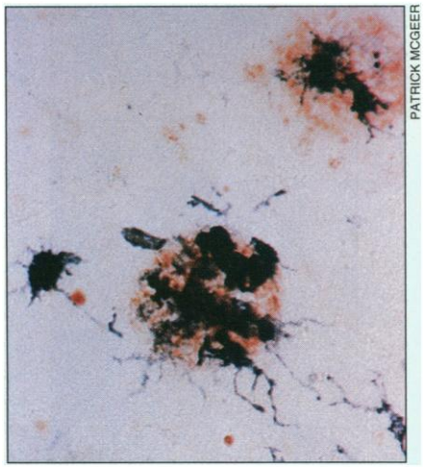
rons as well. If so, this inflammatory activity, which could be triggered by any number of factors, could create a vicious spiral of nerve cell death until dementia ultimately set in.

McGeer reasoned that if he was right, individuals with autoimmune diseases such as rheumatoid arthritis, who take anti-inflammatory drugs over long periods of time, should have a reduced incidence of Alzheimer's disease. So with Rogers, whom he had met at a conference at Cold Spring Harbor in 1988, and who had independently been investigating immunological mechanisms in Alzheimer's disease, McGeer conducted a retrospective study of Alzheimer's incidence in rheumatoid arthritis patients and of rheumatoid arthritis incidence in Alzheimer's patients. Using Canadian and American hospital data covering more than 12,000 patients older than age 64, McGeer and Rogers found what appeared to be an abnormally low number of patients who had been diagnosed with both diseases. For example, only 0.39% of those diagnosed with rheumatoid arthritis had also been diagnosed with Alzheimer's, whereas in the general population, the same age group had an Alzheimer's prevalence of 2.7%. Not long afterward, the two researchers found their hypothesis bolstered by a similar study, reported in the British *Journal of Rheumatology* in 1989 by a group of physicians in London.

But there is at least one contradictory study. In 1991, researchers at the Mayo Clinic in Rochester, Minnesota, led by epidemiologist Mary Beard, found an apparently normal incidence of Alzheimer's in patients treated at the Mayo Clinic who had been diagnosed as having rheumatoid arthritis. The reason for the discrepancy is unclear.

In any case, 1991 brought additional evidence in favor of the inflammatory hypothesis from an unexpected source. Nobuo Harada, a local government health official, noted what appeared to be an extremely low incidence of dementia in a leper colony on the island of Nagashima. Following up on that observation, McGeer, Harada, and several Japanese colleagues performed a study in about 4000 aged Japanese leprosy patients. The result: The incidence of dementia was only 2.9% in those taking the leprosy drug dapsone, which also has anti-inflammatory effects, but 6.25% among those who had not taken the drug for 5 years. Another group of Japanese researchers, led by Yoshio Namba at the Tokyo Institute of Psychiatry, analyzed the autopsied brains of 16 leprosy patients, all of whom had probably been treated with dapsone. They found an unusual absence of senile plaques in the leprosy patients' brains compared to those of age-matched controls.

Even if Rogers and McGeer's supposition that inflammation in the brain contributes to Alzheimer's development is correct, it would not rule out a role for β-amyloid. Aggregated β-amyloid may kill nerve cells directly as many researchers now think. But in addition, McGeer and Rogers suggest, the protein may also play an integral part in the inflammatory response in the brain. Last year, cooperating with Neil Cooper's group at the Scripps Clinic and Lieberburg's at Athena, they showed that aggregated β-amyloid activates the cell-killing complement proteins. "I would say β-amyloid is probably modestly toxic by itself in a compacted form, and probably very toxic when it has attracted the immune system," Rogers concludes.



PATRICK MCGEER

Double whammy? Senile plaques show β-amyloid *(brown color)* and agglomerations of reactive microglia *(purple)*, which contribute to inflammatory responses.

Moreover, although most researchers think that nerve cells are the major source of the brain's β-amyloid deposits, Henry Wisniewski, who runs a large Alzheimer's research laboratory at the New York State Institute for Basic Research in Developmental Disabilities on Staten Island, has come up with results suggesting that microglial cells produce it. "It looks like the microglial cells play a key role [in the formation of amyloid deposits]," Wisniewski says. If he's right, the net result could indeed be a vicious spiral of nerve cell destruction as microglial cells move in to clear out dying neurons and unleash still more damaging weapons, including the complement proteins and more β-amyloid.

The publication of the results of the indomethacin pilot study later this summer will attract attention to the role of inflammation in Alzheimer's. But Rogers already has at least one tangible indicator of the increasing seriousness with which his and McGeer's hypothesis is being taken. "My calendar this spring has been filled," he says, "with visits to drug companies."

–Jim Schnabel

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ASTRONOMY

A New Way To Rev Up a Fast Pulsar

It's not easy to make a millisecond pulsar. First, you have to crush a star into a ball of neutrons just a few kilometers across and set this neutron star spinning rapidly, sending out lighthouse beams of radio waves that sweep across the sky with each revolution. And that's just for starters. Ordinary pulsars spin several times a second; to qualify as a millisecond pulsar, these unlikely objects have to spin hundreds of times faster. Now astronomers are finding to their surprise that, hard as the task is, there may be more than one way to do it.

Since the first millisecond pulsar was discovered 10 years ago, most astronomers have assumed that these objects start out as ordinary pulsars, which are thought to be the cinders left over from the stellar explosions known as supernovas. The theory holds that late in the life of a pulsar, when it is slowing down and its signal is weakening, it can be reborn as a millisecond pulsar when it gains mass and spin from a nearby star. But x-ray and radio observations are now hinting that many of the galaxy's millisecond pulsars may have skipped that earlier life. The recent results support a competing idea, that some millisecond pulsars are born when an ancient, compact star known as a white dwarf steals enough material from another star to collapse under its own weight into a fast-spinning neutron star. Says Yale University astrophysicist Charles Bailyn, an advocate of the white dwarf scenario, "This is the first qualitative advance in understanding the origin of millisecond pulsars over the last 5 years or so."

The idea that millisecond pulsars are resurrected ancient pulsars originated soon after the first one was discovered in 1982 by Donald Backer of the University of California, Berkeley, and his colleagues. Ordinary pulsars are born with powerful magnetic fields, which create a kind of friction that rapidly slows their rotation, but Backer's millisecond pulsar and others discovered soon afterward were losing speed quite slowly. That meant their magnetic fields had to be weak, which theorists took as a sign of extreme age—a few billion years or so. A neutron star that old, though, should be spinning much slower than run-of-the-mill pulsars, not hundreds of times faster.

The leading explanation for the paradox is that these pulsars were "recycled" when they drew in material from a close