Alzheimer's disease (see following story).

In addition, several long-term observational studies, including some presented at the meeting, suggest that people who get a lot of antioxidants, such as vitamin C or E, in their diet or as supplements are less likely to develop Alzheimer's disease. And some evidence suggests that Alzheimer's disease patients decline more slowly if given vitamin E. DeKosky and colleagues have completed recruitment of a prevention trial to test whether another antioxidant, called ginkgo biloba, can slow Alzheimer's disease. They expect early results in a year and a half.

Other evidence points to the possibility of using the hormone estrogen to stave off Alzheimer's disease. But that approach became more problematic this summer when leaders of the Women's Health Initiative announced that they were suspending a long-term, placebo-controlled trial of hormone replacement therapy (HRT) due to an unacceptable risk for breast cancer, heart attack, and stroke (*Science*, 19 July, p. 325). Even so, the National Institutes of Health (NIH) in Bethesda, Maryland, is sponsoring an Alzheimer's disease prevention trial using HRT, and Marcelle Morrison-Bogorad of the National Institute on Aging says there are no plans to suspend recruitment. She points out that animal and cell studies suggest that estrogen helps neurons make connections and interferes with the production of β amyloid.

The NIH study should reveal whether HRT holds off Alzheimer's disease. But at the meeting, Norman Relkin of Weill Medical College of Cornell University in New York City reported that estrogen supplements given to women who already have Alzheimer's disease didn't help their symptoms and caused an unacceptable number of side effects.

Several researchers at the meeting remarked on the change in atmosphere since the conference first convened in Las Vegas in 1988. "Fourteen years ago, we couldn't talk about drugs," says Agneta Nordberg of the Karolinska Institute. Prevention and treatment trials will take years to give clear results, but Melbourne's Masters points out that the field is keeping "a lot of irons in the fire." Perhaps in another 14 years, Alzheimer's disease patients will raise a toast to researchers with a cocktail of drugs that slows down or stops the disease in its tracks. **–LAURA HELMUTH**

ALZHEIMER'S DISEASE

▶NSAIDS FOR PREVENTION?

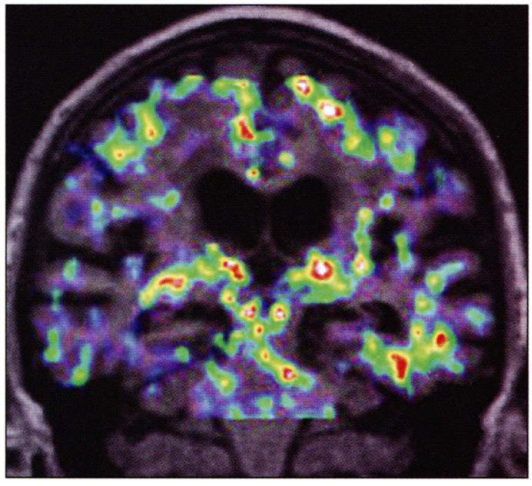
Protecting the Brain While Killing Pain?

Epidemiological studies link use of certain analgesics to a decreased risk of Alzheimer's disease. But the link has yet to be tested experimentally, and researchers are fiercely debating just which drugs to test

STOCKHOLM—Even to skeptics of epidemiological studies, the data look pretty impressive. More than 20 reports over the past decade have indicated that taking certain painkillers for many years reduces the risk of developing Alzheimer's disease, the dreaded brain disease that robs people of the ability to think. "The observational data are remarkably consistent," says John Breitner of the University of Washington, Seattle.

Still, most Alzheimer's disease researchers are reluctant to recommend popping the painkillers, known as NSAIDs (for nonsteroidal anti-inflammatory drugs), routinely, the way some people take calcium supplements to ward off osteoporosis. Because NSAIDs can have serious side effects, such as potentially fatal gastrointestinal bleeding, these researchers are waiting for controlled clinical trials to show that the protective effect is real, robust, and worth the risk. One large-scale clinical prevention trial designed to answer just that question is now getting under way. But at the International Conference on Alzheimer's Disease and Related Disorders held here last month, many participants expressed concern that the trial is testing the wrong drugs.

The debate arises in part from disagreements over how NSAIDs might protect against Alzheimer's disease. An early and reasonable hypothesis was that NSAIDs soothe what Patrick McGeer of the University of British Columbia in Vancouver calls the "raging inflammation" seen in the brains of people with Alzheimer's disease. Immune cells encircle the abnormal plaques that are one of the defining pathological features of the disease. Subduing this response, the theory goes, prevents hyperactive immune cells from targeting nearby neurons and destroying them.



Raging inflammation. A marker for immune cells called microglia shows extensive inflammation in the brain of an Alzheimer's disease patient.

CREDIT: CAGNIN *ET AL.*, *THE LANCET* 358, 461 (2001)

Recently, others have begun to question this model, pointing out that NSAIDs have several additional powers that might instead underlie their ability to fight Alzheimer's disease. For example, they can protect against the oxygen radicals also thought to contribute to the brain damage. And since late last year researchers have been buzzing about another new NSAID trick, discovered in cultured cells: Some of the drugs dampen production of the most toxic form of a peptide called β amyloid whose deposition in the brain is thought to seed plaque formation. Chillingly, though, other NSAIDs—including two now being tested for possible protection against Alzheimer's disease—encourage production of this particularly toxic type of β amyloid.

The finding sent epidemiologists scrambling to reanalyze their data for any differences in the effects of various NSAIDs. Conference reports from two massive population studies gave conflicting results: One suggested that any NSAID can protect against Alzheimer's disease; the other suggested that only those NSAIDs that inhibit the more virulent β amyloid are protective. But animal studies reported here confirmed that NSAIDs have the same influences on β amyloid in vivo as they do in vitro, further raising the possibility that some NSAIDs might conceivably exacerbate Alzheimer's disease.

Aches and gains

Interest in using NSAIDs to prevent Alzheimer's disease dates to 1990, when physician and neuroscientist McGeer reported a curious coincidence. His team discovered that arthritis patients, who take regular doses of NSAIDs to control their pain, have an unusually low risk of Alzheimer's disease. Since then, this apparent benefit of NSAIDs has shown up in several other epidemiological studies, including some on twins.

But such epidemiological studies have

some inherent problems that leave room for uncertainty about their results. For instance, getting solid information on drug use is tricky, particularly in retrospective surveys in which people have to remember what drugs they once took and in what doses. People with Alzheimer's disease by definition have poor memories, and their relatives might not have kept close track of such things. One large study avoided such problems by gathering the participants' pharmaceutical records for 8 years from a citywide computer system in Rotterdam, the Netherlands. It came to the same conclusion as McGeer.

Starting in 1990, Bruno Stricker of Erasmus Medical Center in Rotterdam and colleagues followed more than 7000 people over age 55 who did not show signs of dementia at the time the study began. The pharmacy records told them which types of NSAIDs and other drugs people picked up and how often they went back for refills, and the researchers tested the participants for various types of dementia several times during the 1990s. Compared to people who didn't take NSAIDs, the team reported last year in *The New England Journal of Medicine*, those who took the drugs for at least 2 years had an 80% reduction in their risk of developing Alzheimer's disease.

Dramatic though such findings might be, Stricker points out, "observational data are never the final proof." Alzheimer's disease develops slowly, and perhaps, Stricker suggests, people with incipient Alzheimer's disease don't experience pain in the same way as those without the brain degeneration, or they might be unable to express their discomfort and seek help. If so, they might have taken fewer NSAIDs than their healthy peers, but the NSAIDs themselves wouldn't have had any influence over who came down with the disease.

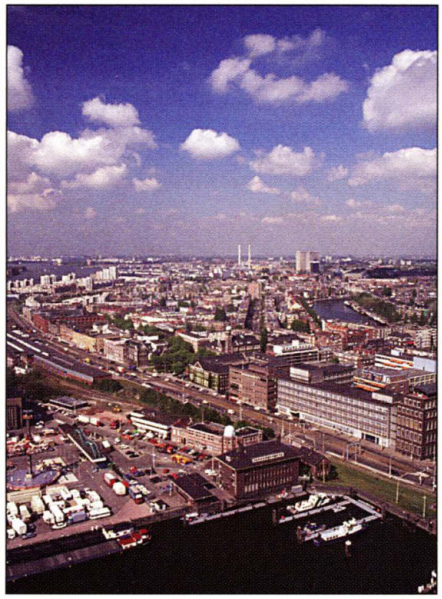
To get a better fix on NSAIDs' presumed protective effects, both the drug companies and the National Institute on Aging (NIA) in Bethesda, Maryland, have conducted placebo-controlled, blind studies of people already diagnosed with early-stage Alzheimer's disease. They all failed to show a benefit, says Steven Ferris of the Silberstein Aging and Dementia Research Center at New York University. Paul Aisen of Georgetown University in Washington, D.C., described the results of the largest such study, including 351 patients with mild Alzheimer's disease. In one year, he reported, patients taking either the NSAID rofecoxib (sold as Vioxx) or naproxen sodium (sold as Aleve) declined just as rapidly as those on placebo.

Breitner, for one, wasn't surprised. The epidemiological data show "little benefit [of NSAIDs] once you have dementia," he says. "Primary protection trials are the only ones with a chance of benefit."

Breitner is now leading an NIA-funded prevention trial that aims to determine whether NSAIDs do indeed protect against Alzheimer's disease. His team has recruited about 1000 of the planned 2625 participants at sites throughout the country. Volunteers commit to taking a mystery pill—either placebo, naproxen, or celecoxib (sold as Celebrex)—twice a day for 5 to 7 years.

Drug choice questioned

Naproxen was chosen for the prevention trial partly for convenience. The drug company that makes it was already providing unmarked pills for the earlier NIA treatment trial and offered to continue the service. As Marcelle Morrison-Bogorad of NIA says, "the National Institutes of Health is impartial [about which drugs to test], but we try to save money."



Data trove. Pharmaceutical records from the Dutch city of Rotterdam suggest that long-term NSAID use inhibits Alzheimer's disease.

CREDIT: DAVID CUMMING/EYE UBIQUITOUS/CORBIS

Some people have been second-guessing this choice, however. Last year, Edward Koo of the University of California, San Diego, and colleagues reported that naproxen, rofecoxib, and celecoxib are among the NSAIDs that spur neurons in lab cultures to produce the more dangerous version of β amyloid, which contains 42 amino acids rather than the standard 40. Other NSAIDs, Koo's team found, reduce β amyloid 42 (Aβ42) production in favor of a relatively harmless form, Aβ38. These include ibuprofen (sold as Advil or Motrin), sulindac, and indomethacin.

In research presented at the meeting, Koo, Todd Golde of the Mayo Clinic in Jacksonville, Florida, and colleagues provided evidence for a possible mechanism by which NSAIDs might influence which β-amyloid molecule is produced. The peptide is clipped from a larger protein by a poorly understood enzyme called γ-secretase, and the researchers found hints that NSAIDs might alter how that enzyme functions by interacting with one of its components.

Koo admits that the experiments indicating that NSAIDs influence β-amyloid production have used enormous doses of the drugs, and he says it's too soon to tell whether this mechanism might underlie a protective effect of some NSAIDs: "We're only looking at an Aβ42 effect. Whether that explains all the epidemiology, we don't know."

The epidemiology itself provides conflicting evidence about whether reduction of Aβ42 is key to the NSAIDs' protective effects. After hearing about Koo and colleagues' work, Stricker reexamined the data from the Rotterdam study. Although the effect wasn't significant, he says that the protective effect of NSAIDs was apparent only for the drugs shown to lower Aβ42. Breitner, however, came to a different conclusion. In addition to coordinating the prospective trial, he helps run a longitudinal study of people in Cache County, Utah—the longest lived in the United States. His reanalysis suggests that both naproxen and aspirin, neither of which reduces Aβ42, do protect against Alzheimer's.

Given the current uncertainties about the effects of naproxen and celecoxib, some argue that it's not worth the risk to use them in an expensive prevention trial, particularly if other drugs stand a better chance of protecting volunteers. If some drugs are known to decrease Aβ42, "shouldn't those be the ones [to test]?" asks David Morgan of the University of South Florida, Tampa. "Is it justifiable to continue if you're not sure you have the best one?"

The problem might be especially acute for naproxen, one of the older NSAIDs that eases pain by blocking two related enzymes, Cox-1 and Cox-2. As a result, it runs a high risk of causing gastrointestinal (GI) bleeding and perforated ulcers. In contrast, celecoxib, a specific Cox-2 inhibitor, is easier on the GI tract. Breitner also points out that there's another reason for testing celecoxib, even though it doesn't have as long a protective history as the older drugs. Cox-2 is overactive in the brains of people with Alzheimer's disease, and he says it's worth seeing whether the relatively safe selective Cox-2 inhibitor will stall the disease as well as the older, nonselective NSAIDs.

In any event, NIA has no plans to change the study, Morrison-Bogorad says: "There's lots of talk that these might not be the right drugs, but some believe it's as good a combination as any." Recruitment has been slower than anticipated, but barring unacceptable side effects or other circumstances that would shut down the trial, Breitner expects results by 2009.

–LAURA HELMUTH