As researchers come to better understand their foe, they're devising more means of attacking it. The 4000 attendees at last month's Alzheimer's disease conference heard about progress on several fronts

New Alzheimer's Treatments That May Ease the Mind

ALZHEIMER'S DISEASE

At a meeting in Stockholm, researchers discussed an array of new ideas for treating and preventing Alzheimer's disease. This special focus provides an update and explores a debate over which drugs to test in a prevention trial.

▶**NEW THERAPIES**

NSAIDS FOR PREVENTION?

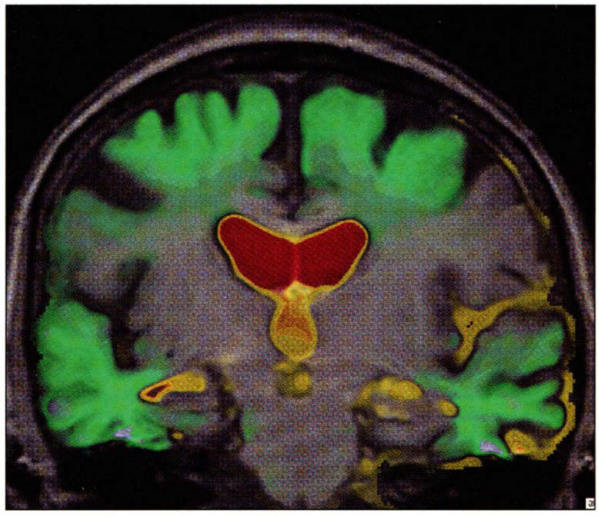
STOCKHOLM—Children argue about what's scarier: ghosts or monsters? Fire or sharks? Adults aren't above idly comparing their own fears. Which would be worse: cancer or heart disease? A car crash or AIDS? But a strong case can be made that the scariest thing about growing old is the risk of mind-robbing Alzheimer's disease. Its prevalence increases each decade until, by some estimates, people in their 90s stand a 50–50 chance of having developed the disease. As the average life-span increases in most parts of the world, "the more important treatment of this disease becomes," says Jan Carlstedt-Duke of the Karolinska Institute in Huddinge, Sweden.

Alzheimer's researchers gathered here* last month with a sense of urgency and optimism about possible treatments—and perhaps preventions—for the disease. Alzheimer's is a wily adversary. Its end product—the widespread death of brain neurons—has been linked to several different insults, including inflammation, oxidative injury, and the deposition of abnormal clumps of a small protein called β amyloid. This complexity makes the disease a challenge to investigate, says Lennart Mucke of the Gladstone Institute of Neurological Disease in San Francisco, "but it implies a diversity of therapeutic opportunities."

Researchers have responded to this diversity, and at the meeting they reported on progress or failures with several different approaches. Some strategies are aimed at β amyloid, seeking either to block its production or to clear the abnormal buildup of the peptide from the brain. Others soothe inflammation, absorb oxidative damage, or try to bolster the function of flagging neurons. Although a few of these therapies are already in use or in clinical trials, even more are at a "proof of concept" stage. "What we're seeing now is lots of first steps," says Colin Masters of the University of Melbourne in Australia.

Secretase inhibitors

One of the defining features of Alzheimer's disease is the accumulation of so-called senile plaques at the ends of degenerating brain neurons. The active ingredient in these plaques, and the main player in Alzheimer's damage, is thought to be β amyloid, making it a favorite target for new therapies (*Science*, 19 July, p. 353).



Time lapse. Treatments aim to arrest the shrinking in brains with Alzheimer's disease. Areas smaller after 2 years with the disease are green; red fluid-filled ventricles have expanded.

β amyloid is produced by two enzymes that clip it from a longer protein called, straightforwardly enough, β-amyloid precursor protein (APP), the function of which is currently unknown. Researchers believe that blocking one or both of these enzymes, dubbed β- and γ-secretase, will decrease the amount of β amyloid in the brain and thus either prevent Alzheimer's disease or slow its progression.

The race to find inhibitors of the two secretases has been intense. William Thies of the Alzheimer's Association in Chicago estimates that about 100 such compounds have tested positive in mice engineered to develop Alzheimer-like β-amyloid deposits. Results are often hard to come by, however, because much of the work is proprietary and unpublished. But word has it that, for still unknown reasons, most of the effective compounds work on γ-secretase.

At the meeting, Patrick May of Eli Lilly and Co. presented data on a γ-secretase inhibitor that, at low doses, dramatically reduces the amount of β amyloid in mice without inducing common side effects, such as interfering with an important cell signaling pathway called Notch. The company won't confirm rumors that the compound is in clinical trials. Stephen Freedman of Elan Pharmaceuticals in South San Francisco presented similar data for another γ-secretase inhibitor.

In addition, a few teams are reporting some success with β-secretase inhibitors. For instance, Wan-Pin Chang of the Oklahoma Medical Research Foundation in Oklahoma City described several that abolish the production of β amyloid in engineered mice.

Metal chelation

Although β amyloid might be a prime instigator of Alzheimer's plaque formation, it doesn't work alone. Its partners in crime include metal ions such as zinc and copper, both of which become more concentrated in the brain with advanced age. In the early 1990s, Ashley Bush of Harvard University discovered that these metals induce β-amyloid aggregation; without them, senile plaques in brain tissue samples dissolve. What's more, the combination of β amyloid with metal ions produces huge amounts of hydrogen peroxide in the brain, causing oxidative damage.

Masters and Bush have a strategy for removing metal ions from brains of patients with Alzheimer's disease (*Science*, 17 November 2000, p. 1273). At the meeting, Masters reported the results of a small phase II clinical trial suggesting that their approach might slow progression of the disease. The researchers exploit an antibiotic called clio-

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* The 8th International Conference on Alzheimer's Disease and Related Disorders, Stockholm, 20–25 July.

quinol that chelates (chemically binds) metal ions. Clioquinol was withdrawn in 1970 after it was linked to a deadly vitamin B-12 deficiency in patients in Japan, but the drug never lost its approval from the U.S. Food and Drug Administration. For their trial in Alzheimer's patients, Bush says, the researchers gave participants vitamin B-12 supplements to avoid the potential side effect.

The trial enrolled 36 patients with moderate Alzheimer's disease; half took clioquinol and half, a placebo. The researchers assessed the patients' mental abilities at the beginning and end of the 9-month trial. Those on placebo seemed to degenerate more rapidly than those taking the drug. Although the difference only approached statistical significance, the results were sufficiently encouraging that the team is now designing a larger treatment trial that will enroll a few hundred patients, says Robert Cherny of the University of Melbourne.

Vaccines

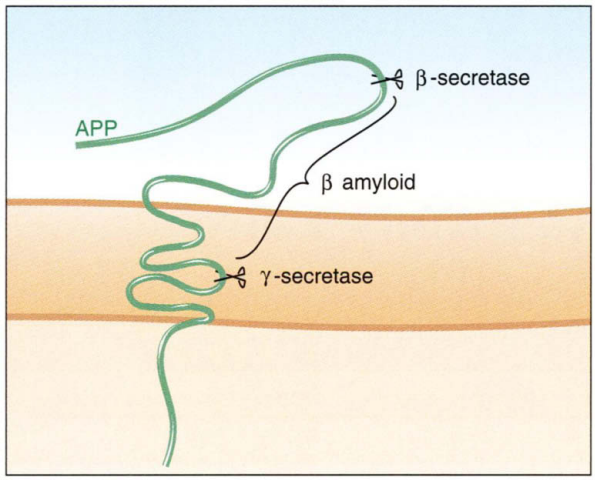
Other researchers have enlisted the immune system to help clear β amyloid from the brain, although few potential treatments have aroused as much hope and dismay as this one. Pioneered by Dale Schenk of Elan, the idea was to use β amyloid itself to train the immune system to seek out and destroy β-amyloid deposits. Early animal studies showed that vaccination with the peptide prevented buildup of β amyloid in young mice genetically engineered to make plaques and allowed older mice to rid themselves of most of their plaques. Phase I clinical trials in the United States and the United Kingdom suggested that the vaccine was safe (*Science*, 21 July 2000, p. 375), and a phase II trial was begun with 375 patients in the United States and Europe.

Christoph Hock of the University of Zürich, Switzerland, reported at the meeting that patients vaccinated with β amyloid produced antibodies that bound to plaques and other forms of β amyloid in tissue taken from other Alzheimer's patients at autopsy. However, the trial had to be halted last year after about 5% of the patients came down with meningoencephalitis, a potentially deadly inflammation of the brain and surrounding membrane. The news was "quite disappointing" and came as a "huge surprise," said Sangram Sisodia of the University of Chicago at the time.

Still, many researchers aren't ready to write off the approach. The original vaccine primed the immune system to fight the full β-amyloid peptide, but Elan's Peter Seubert reported that it might be possible to design a safer vaccine using a snippet of the peptide. Mouse studies have shown, he says, that the fragment of β amyloid that induces the immune system to clear out the peptide is different from the fragment that provokes the more dangerous T cell immune response that probably underlies the patients' brain inflammation. It should be possible to design a vaccine that stimulates the beneficial immune response but not the other type, he predicts. Seubert says Elan is also experimenting with mass-produced antibodies that can be injected directly into the body, avoiding the need to stimulate the patient's immune system.

Statins

Cholesterol is another major player in Alzheimer's disease pathology, researchers have come to realize in the last few years (*Science*, 19 October 2001, p. 508). People with high cholesterol levels are more likely to develop the disease, and epidemiological studies suggest that lowering cholesterol levels, particularly by taking drugs from the statin family, reduces one's risk.



Source of trouble. Two secretase enzymes cut β amyloid free from the longer protein APP, which is located in the cell membrane.

Cholesterol apparently contributes to Alzheimer's development by fostering β-amyloid production. Indeed, an autopsy study presented here by Miguel Pappolla of the University of South Alabama in Mobile indicated that every 10% increase in blood cholesterol levels doubles the risk of having β-amyloid deposits in the brain.

At the meeting, Konrad Beyreuther of Heidelberg University in Germany presented results from the first clinical trial of statins in people with mild Alzheimer's disease. In a double-blind 26-week study, 17 patients received a placebo and 20 took the highest allowed dose of the drug. Researchers monitored patients' scores on a standard cognitive test and found some evidence that the statin had helped. Although the difference wasn't significant, those taking placebos had a bigger drop in their standardized test score than those on the statin.

Bolstered by epidemiological research and this preliminary study, Leon Thal of the University of California, San Diego, and colleagues are launching a larger clinical trial. It will enroll 400 Alzheimer's disease patients starting in September and compare the progress of the disease in those taking statins versus those taking placebos.

Neurotransmitter targets

The only drugs currently approved in the United States for treating Alzheimer's disease are cholinesterase inhibitors. They don't attack the disease but help the brain compensate for the loss of neurons that communicate via the neurotransmitter acetylcholine. The treatment, which prevents an enzyme from breaking down acetylcholine, appears to slow progression of the disease, although the improvement isn't dramatic.

In Germany, however, the standard prescription for Alzheimer's disease is a drug called memantine that works on a different neurotransmitter system. It blocks the action of the neurotransmitter glutamate, which is overproduced in the brains of people with Alzheimer's and other diseases and can overexcite neurons to death.

Memantine is now in phase III clinical trials in the United States. At the conference, Barry Reisberg of New York University Medical Center reported the results of one trial, which included 252 people with advanced Alzheimer's disease and lasted 52 weeks. It showed that patients who received memantine maintained more mental abilities and were less impaired on a survey of "activities of daily living" than patients who took placebos. The benefits, like those with the cholinesterase inhibitors, were modest. But as Ezio Giacobini of the University of Geneva in Switzerland pointed out, there's no reason the two types of drugs can't be given together or in combination with other treatments yet under development.

An ounce of prevention ...

Alzheimer's disease usually develops slowly, taking many years to get to the point where symptoms become noticeable. Therefore, many experts think that it might be more promising to try to prevent the disease. Because most cases occur in the elderly, delaying the average onset time of Alzheimer's disease by as little as 5 years would halve the disease's prevalence, says Steven DeKosky of the University of Pittsburgh.

Researchers are now testing a variety of interventions that have turned up in epidemiological studies as preventing or slowing the onset of Alzheimer's disease. One such idea is to give anti-inflammatory drugs called NSAIDs to people with a family history of

ILLUSTRATION: C. SLAYDEN

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?

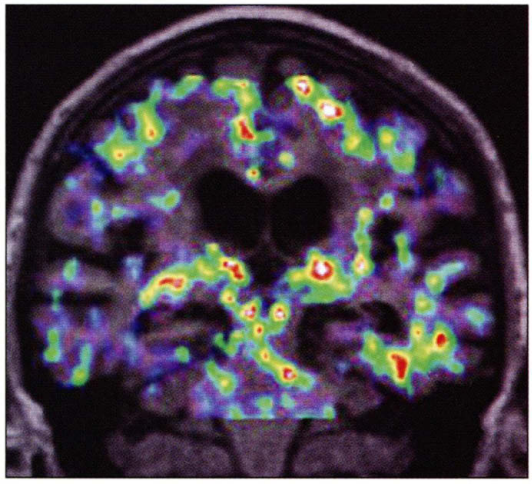
Protecting the Brain While Killing Pain?

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