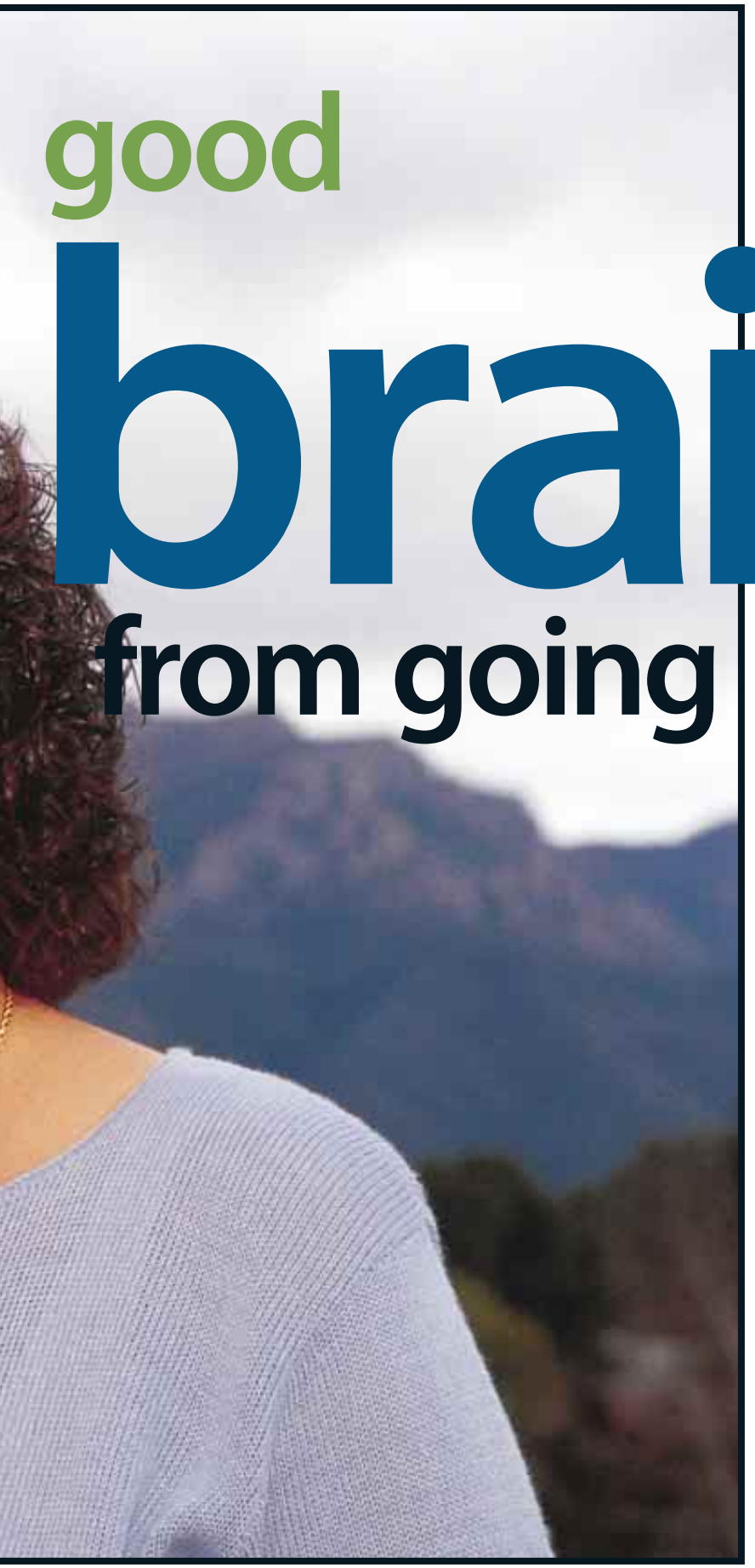
thwarting

major killers

preventing

TWO CLUES: Studies of identical twins—including Sonja Buth and Wilma Bruno (*right*)—in which only one sibling (Buth) has Alzheimer's may determine to what extent genes and the environment contribute to the disease.

JAMES ARONOVSKY *Zuma Press*



good brains from going bad

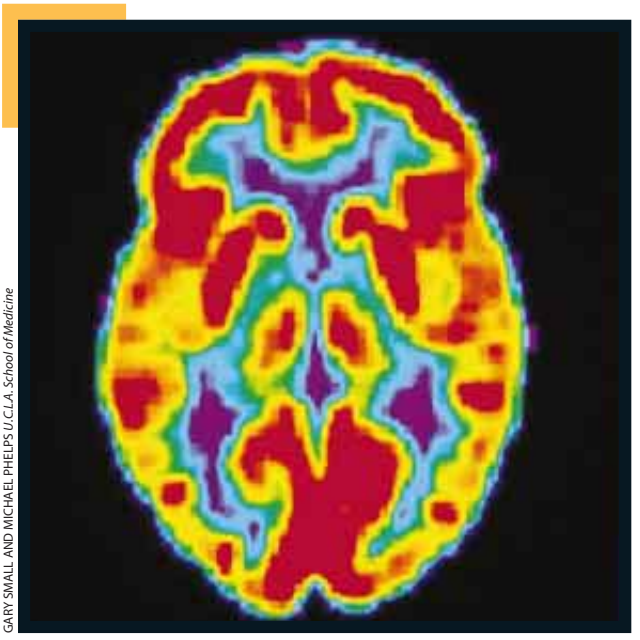
THE FIGHT AGAINST TWO LIFE-ROBBING DISEASES, ALZHEIMER'S AND PARKINSON'S, HAS JUST BEGUN

BY MIA SCHMIEDESKAMP

It's hard to believe now, but 30 years ago the average layman *and* the average doctor thought that "senility" was the result of either normal aging or hardening of the arteries. "What do you expect from an old person?" people would say. Mercifully, science has enlightened this rather Dickensian view. Today we may be close to understanding what causes the major neurological diseases of old age, which ravage mental and physical function—the very stuff of life—and in their extreme form can kill.

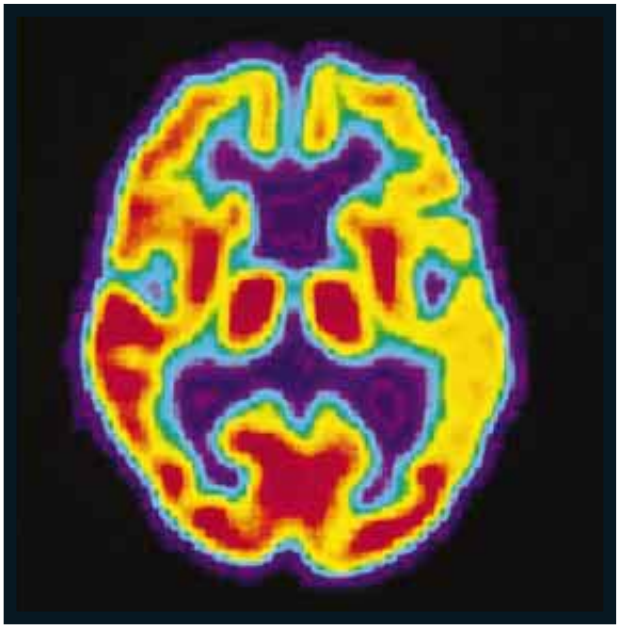
But that does not mean we've found cures for the four million Americans suffering from Alzheimer's disease and the one million with Parkinson's. The numbers could swell fourfold by 2040 as baby boomers reach old age. Legions of us worship at the temples of Physical Fitness and Cooking Light, in an attempt to ensure strong bodies at retirement. But what can we do when it's our brains that betray us?

The silent siege of Alzheimer's causes a relentless deterioration of memory and bodily control. The disease is a formidable foe. Most Alzheimer's patients are in their 70s and beyond, and those who survive into its final stages lose the ability to speak, walk, even lift their head as their brain slowly shuts



GARY SMALL AND MICHAEL PHELPS U.C.L.A. School of Medicine

BRAIN SCAN: Reds and yellows indicate a brain's glucose metabolism. There is a progressive decrease from a normal older person (*left*) to mild Alzheimer's (*below*) to advanced disease (*right*), which resembles activity in an infant's brain (*far right*).



down. Given how debilitating the physical throes are, it is confounding that the disease first appears years earlier as mental troubles such as chronic forgetfulness and difficulty handling routine chores. Indeed, the onset is so elusive that doctors are only now determining where normal aging of the brain stops and Alzheimer's begins.

The borderland is a state called mild cognitive impairment (MCI). Individuals with MCI aren't demented, but they do perform worse than their peers on memory tests. They sense they are forgetful, and somebody close to them has probably noticed it, too. Otherwise, they do quite well, although demanding tasks such as mastering new technology may prove challenging.

People who meet the criteria for MCI will evolve to clinical Alzheimer's disease at a rate of 10 to 15 percent a year, according to Ronald Petersen, director of the Mayo Alzheimer's Disease Center. "That's in contrast to normal elderly people,"—without MCI—"who do so at a rate of 1 to 2 percent a year," he says. Barry Reisberg, clinical director of the Silverstein Aging and Dementia Research Center at New York University, finds similar trends. When he tracked people with MCI in their early 70s, about two thirds progressed to Alzheimer's within four years.

Images of the brain can help pinpoint those most at risk. The hippocampus—a structure closely tied to memory—atrophies and shrinks in Alzheimer's patients. The decline is evident even during MCI. Someday a combination of memory tests and magnetic resonance imaging may offer early warnings to those destined for Alzheimer's—valuable information if drugs are developed that can prevent the disease or stop its progression.

Elderly people who feel forgetful but perform well in cognitive tests—Petersen refers to them affectionately as "the worried well"—develop Alzheimer's at much lower rates, about 12 percent over four years in Reisberg's study. All that's necessary, Reisberg says, is "to reassure them."

Older people these days do seem quick to diagnose themselves or loved ones as having Alzheimer's when they are just experiencing simple forgetfulness. The knee-jerk response is in part the result of stepped-up media coverage.

So what *should* set off alarms? Failure to remember important items with increasing frequency, Petersen says—"things that you would have remembered without question six months ago"—especially if other people also say they see a change in you. "It's not that you misplaced your keys," adds Richard Mohs of the Mount Sinai School of Medicine. "It's that you can't figure out what you would do to get them back."

Mohs points out that everybody gets more forgetful with age. "The rate at which people can put new information into memory does slow down. When they say, 'I forget more,' it's usually that they just didn't learn it quite as well." Elderly people can boost memory by taking extra time and care to learn new information.

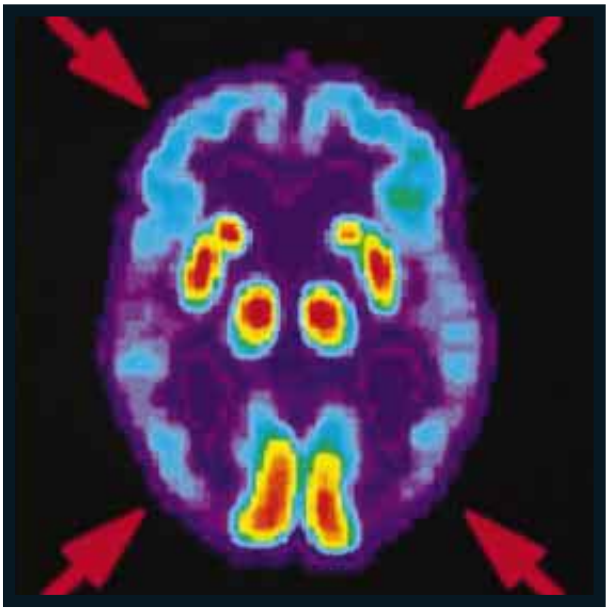
Rays of Hope

Once Alzheimer's is diagnosed, families can brace for the future, but the medical profession finds itself at something of a loss. Neurotransmitter-boosting drugs such as Aricept help about 50 to 70 percent of patients, according to Peter Rabins of the Johns Hopkins School of Medicine, but their efforts are modest. Rabins says, "I ask families to think back to what the person was able to do seven or eight months ago; that's an average improvement." Although this reprieve is precious, it's unclear if any improvement can last longer than a few months. For now, managing Alzheimer's consists mainly of

emotional and practical support, plus strategies to help patients retain skills and live a full life [*see box on next page*].

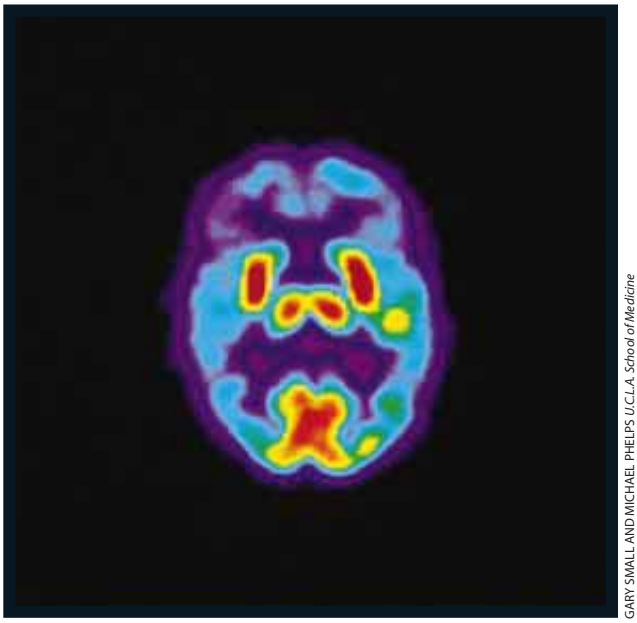
An ounce of prevention may be worth a pound of cure. Various studies, including a landmark University of Kentucky study of elderly nuns belonging to the order of the School Sisters of Notre Dame, suggest that the brain's ability to resist dementia is greater if it has been mentally stimulated throughout life. "If you don't use it, you lose it," exhorts the University of Kentucky's William Markesbery, part neuropathologist, part personal trainer.

Richard Mayeux, director of the Taub Institute on Alzheimer's Disease and the Aging Brain at Columbia University, also finds that people with complex jobs have reduced risk of Alzheimer's no matter their education—suggesting again that intellectual challenge throughout life is important. Mohs of Mount Sinai suggests exercising the brain by reading, taking classes and joining intellectually engaging clubs.



Caring for the body is a good idea, too. People who are aerobically fit tend to suffer less cognitive decline with normal aging. Intriguingly, when Fred H. Gage of the Salk Institute for Biological Studies in La Jolla, Calif., allowed mice to run at will—about five kilometers a day on average—they generated many more new neurons in their hippocampi compared with their cage-potato counterparts. Others have found that prolonged stress actually leads to hippocampal atrophy.

The search for ways to slow or prevent Alzheimer's is widening. The nuns, as well as identical twins and a group of women in upper Manhattan, are the primary test subjects. Many of the School Sisters nuns donate their brains to the University of Kentucky's Sanders-Brown Center on Aging; Markesbery, the center's director, has examined them and others. One remarkable thing he sees are organs rife with the lesions characteristic of Alzheimer's—from individuals who were not demented.



GARY SMALL AND MICHAEL PHELPS *U.C.L.A. School of Medicine*

Perhaps these brains had something extra in reserve, or maybe they avoided stroke. Dementia from vascular disease alone is fairly uncommon in the U.S. But among nuns with the brain lesions of Alzheimer's, those who also had tiny strokes were more likely to be demented. To lessen the risk of stroke, Markesbery advises people to eat right, exercise, not smoke, and keep blood pressure and diabetes under control—good advice in any case.

Aging women in upper Manhattan point the way to another possible protection: estrogen. "For women who took estrogen in the postmenopausal period, the risk of developing Alzheimer's disease subsequently was reduced by half," explains Mayeux, who monitored about 1,100 New York City women for up to five years for the appearance of Alzheimer's. The women who had taken estrogen for longer than a year showed the greatest benefit.

Studies in Minnesota, Baltimore and Italy have yielded similar results, and researchers hope that estrogen can also help prevent dementia in those with Parkinson's disease. But estrogen is a powerful hormone; although many women take it to mitigate the effects of menopause, it is implicated in promoting certain cancers of the reproductive system. Until clinical trials better establish the ratio of risk to reward, Mayeux doesn't recommend taking estrogen solely to protect against Alzheimer's.

Scientists are eager to devise drugs that imitate estrogen's positive role in cognition without subjecting women to an increased risk of cancer. Estrogen may stave off Alzheimer's disease by directly influencing nerve cells in the brain. Researchers hope to find chemical substitutes that affect only these cells. Such drugs might benefit men, too: males produce estrogen from testosterone, and testosterone levels wane with age. The right estrogen might delay Alzheimer's in men without subjecting them to the feminizing effects of traditional hormone therapy.

Other promising leads come from studies of identical twins. In the early

coping with alzheimer's

Talk of an eventual cure for Alzheimer's generates a lot of excitement, but millions of people must deal with the devastation of the disease right now. Much depends on creative coping.

Barry Reisberg of New York University has studied the course of Alzheimer's for more than two decades. He argues that the characteristic decline can be understood best as a reversal of childhood development. The sufferer incrementally loses the ability to handle finances, then to dress, then to be continent, speak, walk and sit up.

This view must be handled with caution, so that the adults are not infantilized. But it may be useful in guiding caregivers. "A [late-stage] Alzheimer's patient requires the same amount of care as an infant," Reisberg says, and he doesn't mean just feeding and bathing. "You would read to an infant; you should be reading to the [late-stage] Alzheimer's patient, too." What the Alzheimer's sufferer needs most is attention and activity. Simple exercise reduces agitation. Visiting them when they get restless at night calms them.

About two thirds of Alzheimer's patients are cared for at home by family, according to Peter Rabins of the Johns Hopkins University School of Medicine. This can be tough. The founding of the Alzheimer's Association in 1979 focused resources to help those family members, he says. What the families need is practical assistance: an aide to help with bathing, day care so the breadwinner can work, and emotional support.

Teaching families specific coping strategies can alleviate depression—among patients and caregivers alike. "Oftentimes it's just become this stressful, difficult situation," says Linda Teri of the University of Washington. "The patients can't do things they used to enjoy, they get frustrated, and the caregivers may not understand what they still like to do."

One important focus is identifying appropriate pastimes. The family members of one former professor with Alzheimer's discovered a pleasant, stimulating activity after recalling how he loved doing the *New York Times* crossword puzzle. They found a variety of children's word puzzles he could still handle. "You give caregivers strategies, ideas," Teri says, "and they come back and say, 'We had a nice day yesterday. We haven't had that in a long time.'" —*M.S.*

NEW DAY: Patients with advanced disease relearn basic skills at the Maria Wolff Alzheimer's center in Madrid.

MARIA WOLFF ALZHEIMER'S CENTER

1980s John Breitner, now at the Johns Hopkins School of Public Health, helped to show that Alzheimer's disease aggregates in families: "If you could follow hypothetical relatives of somebody with the disease, let's say siblings, out to age 90 or 95, then almost half those siblings would themselves get the disease—a much higher rate than in the general population." To tease out how much of this aggregation is a result of genetic inheritance, rather than shared family environment, several groups studied the occurrence of Alzheimer's in identical and fraternal twins. The studies suggest that one half to three fourths of a person's disposition to Alzheimer's is inherited. But that leaves plenty of room for outside influences.

At Duke University, Breitner and his colleague Brenda Plassman focused on twin pairs in which only one twin had Alzheimer's. The disease often develops in the initially unaffected twin after a lag, but in some identical pairs the second twin remains free of disease for 20 years after it appears in the first, in one case almost two decades. The researchers studied the histories, lifestyles, infirmities and medications of many pairs. "What surprised us," Breitner says, "was an unexpected association between use of anti-inflammatory drugs and the absence of disease in the unaffected twin."

Many studies have since suggested that nonsteroidal anti-inflammatory drugs, such as ibuprofen, are associated with a reduced risk of Alzheimer's, but other results have been contradictory. The jury is also out on other substances proposed as neuroprotective, including very high doses of vitamin E, until more studies are completed. The wait for definitive answers shouldn't be long. Several trials sponsored by the National Institutes of Health or pharmaceutical companies are already under way, testing anti-inflammatories and vitamin E in hundreds of subjects with mild cognitive impairment. A group led by Breitner at Johns Hopkins is seeking over 2,600 older persons with a family history of Alzheimer's-like dementia for a randomized prevention trial that could nail down the role of anti-inflammatories.

Markesbery advocates a regimen including high doses of vitamin E, C and folic acid, plus nonsteroidal anti-inflammatories for those at highest risk of Alzheimer's—people whose close relatives have the disease, for example. But physician supervision is required; some of these compounds thin the blood and can cause gastrointestinal bleeding. "Right now we're not recommending it for those who don't have the risk factors," Markesbery notes. Eric B. Larson, a longtime Alzheimer's researcher at the University of Washington Medical Center, says, "In my own practice, I don't recommend taking any drug for the principal purpose of preventing cognitive decline. There's nothing out there that's convincing enough."

Greater insight may come from understanding the mechanisms underlying Alzheimer's disease. There are many competing theories. One of the strongest—and the one most drug companies are pursuing—is that the primary villain is a protein fragment called Aß (A-beta) that clumps into plaques in Alzheimer's-affected brains. Aß results when a ubiquitous protein called amyloid is snipped to pieces by two enzymes called proteases. Aß is present in everyone, although no one is sure what it does. But when disposal of Aß can't keep up with its production, trouble may loom. Various genetic mutations that cause rare early-onset Alzheimer's increase the production of Aß, whereas two other genes altered in late-onset disease may be important for clearing Aß.

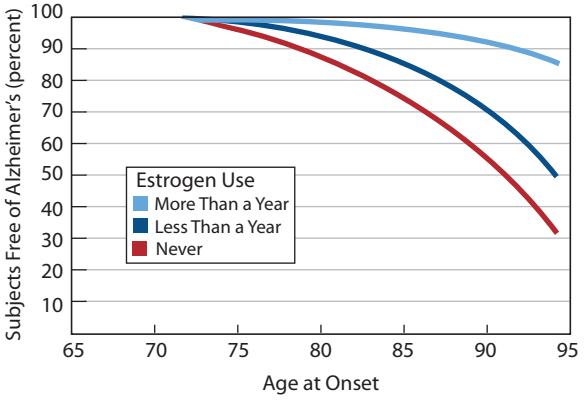
Anti-inflammatory drugs may reduce risk of the disease.

Protease-inhibiting drugs are in the works at several pharmaceutical companies, in hopes that simply cutting back Aß production will prevent Alzheimer's. "Drugs are about to enter clinical trials. They really exist, and they reverse plaque lesions in mice," reports Dennis Selkoe of Harvard Medical School, who has been hunting down Aß for years. Similar medicines have met with great success in the past, including the protease inhibitors that have recently revolutionized HIV treatment. But even if the new drugs block Aß overload and plaque formation, it remains to be proved whether that's enough to beat Alzheimer's. And there are always worries about side effects.

Another promising approach is vaccination to spur the body's own immune system to clear Aß. Mice that overproduce Aß develop Alzheimer's-like plaques as they age; immunization with Aß not only prevents the appearance of such plaques in young mice but reduces the extent of existing plaques in older ani-

delaying alzheimer's

with estrogen



AFTEREFFECT: In a Columbia University study, women who had taken estrogen for postmenopausal treatment also postponed the onset of Alzheimer's.

LAURIE GRACE

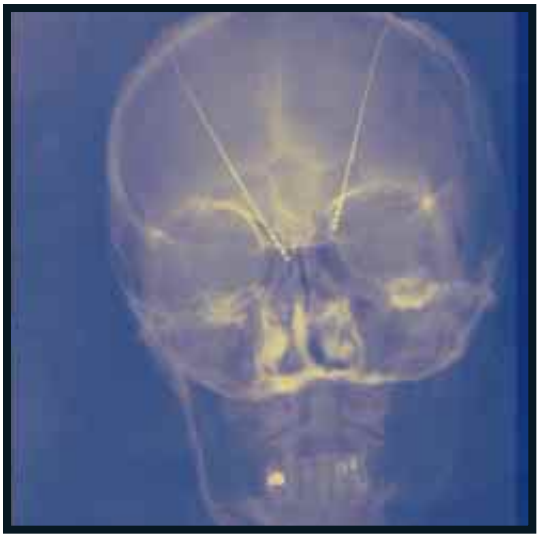
mals. Human clinical trials are now under way at Elan Pharmaceuticals, a firm in South San Francisco that Selkoe helped to start in the 1980s. "Drug companies are working 24 hours a day, and so am I," he explains. "My wife says, 'Why don't you get going—you're going to get the disease before you cure it.' I don't want that to happen."

Calming the Parkinson's Storm

Stronger signs of hope for fighting neurodegenerative disorders may be found in the history of treatment for Parkinson's disease, which strikes at age 60 on average. With no reliable treatment decades ago, its onset often meant a quick decline to years of crippling tremors and rigidity. There has since been some success with a drug called levodopa. The first whisper of tremor or a slightly odd gait means that a Parkinson's sufferer has already lost 70 or 80 percent of a tiny segment of the brain that churns out the signaling chemical dopamine. Without dopamine, neurons that control motor activities go haywire, leading to shaking, slowness and rigidity. As more and more dopamine-producing neurons die, sufferers can develop balance problems, crippling distortions of the hands and feet, and episodes of freezing in midstep. Late-stage Parkinson's often means confinement to bed and wheelchair.

Levodopa can't halt the progress of the disease, but it can replace missing dopamine, with miraculous effect. Many of those afflicted with Parkinson's are symptom-free after their first dose. Doctors started relying on the drug in the late 1960s, and today it is almost universally prescribed. "Levodopa was really one of the great biological successes of the century," says C. Warren Olanow of Mount Sinai.

SILENT SHOCK: Electrodes inserted deep into the brain deliver current from a battery implanted near the collarbone to quiet misfiring neurons that cause severe Parkinson's disease.



MICHEL F. LÉVESQUE *Cedars-Sinai Medical Center*

Like most classic heroes, though, levodopa has a dark side. At first, its benefits last hours on end, but after five or 10 years many patients take levodopa much more frequently and still can't get a consistent effect. "You could be in a grocery store, reaching into your purse to pay, and all of a sudden you go 'off'—you can't move, and you don't know when you're going to come 'on' again," says neurologist Jerrold Vitek of Emory University. "One patient told me about being bent over his couch to pick something up, and he froze like that for two hours." Many people also develop involuntary motions in response to the drug.

The new challenge of Parkinson's treatment is to smooth out levodopa's effect or retire the chemical altogether. One long-standing strategy is pairing levodopa with other drugs. Some compounds ensure a richer stream of levodopa to the brain. Others act to delay temporarily the onset of levodopa therapy as long as possible. Then there is brain surgery. It turns out that certain neurons that go awry in Parkinson's are actually hyperactive; by burning a tiny hole in specific brain regions, surgeons can quell tremor and alleviate rigidity to various degrees.

But the burning may not solve all problems, and it destroys brain cells, perhaps healthy ones needed for other functions. More and more, surgeons are switching to deep brain stimulation (DBS). In this technique, an electrode inserted deep into the brain and powered by a battery implanted near the collarbone silences neurons that would otherwise misfire.

DBS can turn some patients' lives around. Before the new surgery in 1998, Vern Setterholm's Parkinson's disease had advanced to such a degree that he had trouble handling silverware, dressing himself, even shaping his face into a smile. Now the tremor in the 81-year-old retired executive's right hand is gone, he can grin, and he enjoys exercise class a few times a week. Asked whether he'd have this new kind of brain surgery again, Setterholm shoots back, "If they wanted me tomorrow, I'd be there."

Olanow says he has patients who are "totally unable to be controlled with medicine. They are frozen, cannot move. We turn on the stimulator, and they get up and start walking. It's absolutely amazing."

The use of DBS to control Parkinson's symptoms was pioneered in France. Although still experimental, using DBS in the thalamus and other brain structures to ameliorate crippling rigidity is becoming more popular. One great payoff: DBS often reduces the side effects of levodopa, which can then continue

to be used to manage the disease. Steven Gaede of St. John Medical Center in Tulsa, one of the first Americans to perform the procedure, figures that about 1,000 DBS operations were done in the U.S. last year.

Currently DBS is used for advanced Parkinson's patients, those "at the end of the rope," Vitek says. There's talk of starting much earlier, to slow Parkinson's before its effects become extreme. Ethical questions abound, though; the risk of major complications is 3 to 5 percent, and the benefits of early use are still highly speculative.

The next dream is replacing the dopamine-producing neurons that die in Parkinson's. In one experimental approach tried at several research centers, surgeons transplanted human fetal neurons that produce dopamine into the brains of Parkinson's patients, hoping to restore some normal dopamine manufacture. They've achieved modest success so far. Ideally, the transplanted cells would come from the patients themselves. This notion was outlandish just a few years ago, before scientists proved that even adult human brains generate new neurons from precursors known as stem cells. Gage of the Salk Institute says of his experimental work with animals, "We and others have shown that if you take primitive cells from a lab culture, you can actually put them into parts of the brain that are damaged, and they can turn into cells that are appropriate for whatever is happening in that part of the brain."

Physicians are eager to harness this astonishing potential. Already neurosurgeon Michel F. Lévesque of the Cedars-Sinai Medical Center in Los Angeles has launched the first clinical trial using patients' own cells for transplant. From a snippet of brain taken during surgery, he says, "we are able to identify about 10 to 15 neural stem cells on average." Properly fed, these cells multiply into the millions over four to six months and are coaxed into becoming dopamine-producing neurons that can be placed back in the patient's own brain. Levesque has performed one such transplant so far and expects to do 12 more, but it's far too early to judge the results.

Perhaps the only breakthrough more exciting than giving people a shiny new set of dopamine-producing neurons would be helping them keep the originals. But no one knows what causes Parkinson's disease. The idea of a toxin is intriguing. In the 1980s drug addicts who shot up with a relative of morphine resembling a pesticide came down with the classic symptoms of Parkinson's. Vitek says that although some patients seem to be genetically predisposed to acquire the disease, it's also possible that "exposure to an environmental insult gets the ball rolling." The details remain a mystery.

Researchers are busy testing hundreds of drugs, hoping to toss a molecular monkey wrench into whatever process kills the neurons. The most promising clinical trial began in the late 1980s and involved 800 early-stage Parkinson's patients at 28 research centers. The patients given a drug called selegiline delayed levodopa therapy about nine months longer than those on a placebo. It's not clear how much of the effect was a result of preventing the disease's spread, rather than relieving its symptoms. (The brains weren't dissected because the patients still needed them.) "But there is no question that selegiline slowed the appearance of disability in Parkinson's patients," says Olanow, who sat on the study's steering committee. Whether for treatment or prevention, that's good news.

KAMENKO PAJIC *AP Photo*

VISIBILITY: Awareness of Parkinson's has been raised by public figures, such as U.S. Attorney General Janet Reno, who have disclosed they are battling the disease.

Mia Schmiedeskamp *holds a Ph.D. in biochemistry and contributes regularly to* Scientific American Presents.

Further Information

Alzheimer's Disease: A Guide for Families. Lenore S. Powell and Katie Courtice. Perseus Press, 1993.

The Alzheimer's Association outlines strategies for coping and has details of treatment at www.alz.org on the World Wide Web. By telephone, call 800-272-3900.

The American Parkinson's Disease Association offers information on treatment and helping patients at www.apdaparkinson.com on the World Wide Web. By telephone, call 800-223-2732.