PTEN mutations often arise in large, late-stage tumors, when cells may be competing to survive in a nutritionally deprived environment. The change would then help them continue to grow anyway.

Although PTEN's link to PKB signaling could explain a lot about its biological behavior, it's obvious that plenty of questions remain. One major issue concerns whether PTEN's effects are entirely due to its lipid phosphatase activity. Researchers so far haven't had much luck in finding protein targets, but they haven't eliminated the possibility that such proteins might be lurking somewhere in the cell.

"We haven't reached the end of the story," predicts Pandolfi, who says he has received dozens of requests for his knockout mice from researchers who want to determine whether their "beloved kinases" are PTEN targets. And that's just fine with Cavenee. "I think we'll see lots of disparate results before we understand what's going on," he says. "To me that makes studying PTEN really interesting." **–KAREN HOPKIN**

Karen Hopkin is a free-lance writer in Bethesda, Maryland.

NEURODEGENERATIVE DISEASES

Alzheimer's Treatments That Work Now

Behavioral interventions developed by social scientists can ease the pain of Alzheimer's disease for both patients and caregivers

Alzheimer's disease is a ruthless decaying of the mind, devastating to those afflicted and to family members who witness their decline. Within the past few years, researchers have made some progress on treatments that might delay the relentless neurodegeneration, but prevention or cure is still out of reach. Millions of people suffer from the disease, and half a million of those in the final stages languish in U.S. nursing homes, incontinent, their bodies frozen by a severe stiffening called contractures, unable to speak or even recognize family members.

While neuroscientists and geneticists search for a way to turn back the clock on the ravages of Alzheimer's, another avenue of research—behavioral research conducted by psychologists, social workers, and nurses—is already providing therapies to relieve some of the suffering of the patients and their caregivers. Such behavioral therapies are far from a cure, and they may not even arrest the underlying disease process. Nevertheless, they represent "an area that cannot be ignored, because we can have such a quick, practical impact on so many people," says Zaven Khachaturian, a former associate director of the Neuroscience and Neuropsychology of Aging Program at the National Institute on Aging who is currently with Khachaturian, Radebaugh, and Associates, an international consulting group on Alzheimer's disease in Potomac, Maryland. Caregivers as well as patients stand to benefit, he notes (see sidebar).

Over the years, Alzheimer's experts have learned that every patient goes through a predictable decline, from forgetfulness at the early stages to an inability to speak and walk as the disease runs its course. Research suggests that patients may lose some abilities faster than necessary because their caregivers underestimate what they can still do for themselves. This is leading to a "use it or lose it" approach to Alzheimer's, in which researchers gauge what patients can still be expected to do and then help them retain those skills. Studies have shown, for example, that behavioral therapy can slow or temporarily halt patients' loss of urinary continence and of their abilities to dress themselves and communicate their needs.

Research done in the past decade also shows that behavioral strategies can reduce many disruptive behaviors common in Alzheimer's patients, such as screaming, wandering, or hitting. In the past, institutions have tried to control such problems by giving the patients antipsychotic drugs or physically restraining them—measures that can cloud the patients' minds even further or increase their agitation. The behavioral approaches instead seek to find the causes of the troubling behaviors and avoid triggering them. "What all this comes to is a new science of Alzheimer's management," says one of the pioneers of the research, New York University (NYU) psychiatrist Barry Reisberg. The next major challenge is to disseminate what researchers are learning to families and community nursing homes outside the orbit of major research centers.

School time. Alzheimer's patients with developmental ages of 2 to 5 learn to brush their teeth at this Madrid day care center.

CREDIT: THE MARIA WOLFF ALZHEIMER CENTER, MADRID

Return to childhood

Many of the recent advances in behavioral therapy arise from viewing Alzheimer's disease as a regression toward infancy. That idea is not new: Aristophanes and Shakespeare both compared old age to a second childhood. But Reisberg and his colleagues recently have established that the stages of Alzheimer's disease accurately mimic such a regression: Patients lose the ability to hold a job, handle finances, pick out clothes, dress and bathe, control their bladder and bowels, and speak, all in faithful reversal of the order those skills were acquired as a child.

As they make this backward march through development, Alzheimer's patients can be assigned "developmental ages." Researchers have found that by providing training appropriate to those ages, they can help the patients retain longer some of the skills they would otherwise lose.

For example, a simple method originally developed to toilet-train retarded children helps Alzheimer's patients maintain continence longer. In the late 1980s, Jack Schnelle of the University of California, Los Angeles, showed that the method called "prompted voiding," in which aides visit patients every 2 to 3 hours to offer to take them to the restroom, helped some incontinent patients retain bladder control. The technique is different from merely taking the patient to the restroom on a schedule, says psychologist Louis Burgio of the University of Alabama, Tuscaloosa, who has studied prompted voiding. By asking whether the patient needs to go, he explains, "it tries to use what is left of the patient's self-knowledge, so you don't make them overly dependent on staff."

Cornelia Beck, a nursing researcher at the University of Arkansas for Medical Sciences in Little Rock, has shown that a similar approach works for another basic activity—dressing. She suspected that patients were losing skills such as dressing and feeding

themselves because they were not encouraged to use them. So she set out to see if they could be retrained. Rather than dressing the patients, aides in her study would suggest that an arm goes into a sleeve, or touch the patient's arm or mimic putting their own arm into the sleeve, to encourage the patients to do it on their own.

After 6 weeks, 50% of the patients improved their ability to dress themselves by 1 to 3 points on an 8-point scale ranging from helplessness to independence; 25% improved by 4 to 6 levels. Patients who had been dependent on aides to dress them could now dress themselves, with guidance.

Even communication can be improved with behavioral strategies. For example, some typical behaviors of Alzheimer's patients, such as repeated questions or nonsensical speech, appear to be failed efforts to communicate. Michelle Bourgeois, a speech pathologist at Florida State University in Tallahassee, developed a strategy to improve communication with Alzheimer's patients, using a "memory book." This contained pictures of family members and nursing home aides and a schedule of daily activities, illustrated with a clock face showing the time and pictures of the activities.

The aides spent time with the patients looking at the book and, when the patients asked repeated questions, gently referred them to the right page of the book for the answers. Use of the memory aid "results in less nonsensical vocalization and more appropriate types of conversations" between patients and nursing home staff, says Burgio, who collaborates with Bourgeois.

An understanding approach

In addition to looking at how to help patients retain skills, researchers are developing new ways to control problem behaviors. For example, NYU neurologist Emile Franssen and his wife and co-worker, nursing researcher Liduïn Souren, have found that some problem behaviors are the physical consequences of the disease itself.

By studying 2400 Alzheimer's patients at various stages of the disease, Franssen identified infantile reflexes that appear in Alzheimer's patients as they decline and a muscle stiffness that he calls paratonia, which can eventually develop into crippling contractures. Both changes can cause problem behaviors. "If you move the limbs of a patient [briskly], paratonia increases," says Franssen. "The caregiver may interpret that reaction as a willful resistance."

Still smiling. Social support has kept this woman with late-stage Alzheimer's (center) from the bed-bound withdrawal most of her counterparts suffer.

CREDIT: LIDUÏN SOUREN/NEW YORK UNIVERSITY

At least one of the reflexes—a strong grasping reflex—can also cause problems, for example when a caregiver tries to guide a patient out of a chair by the elbow and finds that the patient grabs the arms of the chair in an apparent refusal to get up. Patients may also reflexively grab a caregiver's hair or clothing. Franssen says that caregivers at nursing homes "often misinterpret [this behavior] as aggressive." But it's not. "It is an inability to cooperate rather than an unwillingness," says Franssen. Rather than struggling and upsetting the patient, the caregiver can release the grip by merely stroking the back of the patient's hand.

Other troubling behaviors arise because Alzheimer's patients are agitated. They may scream, plead, pace, disrobe, rummage through people's possessions, hit, kick, or bite. "When I started [14 years ago], people treated agitation as either a psychotic sort of behavior or a nuisance that comes with dementia," says psychologist Jiska Cohen-Mansfield of the Research Institute of the Hebrew Home of Greater Washington in Rockville, Maryland. "Their response was either psychotropic drugs, restraining, or ignoring. It made life pretty miserable for everybody."

Cohen-Mansfield suspected that the behaviors were driven by unmet needs. She had assistants watch patients around the clock, noting what triggered the behaviors. Patients tended to scream or moan, for example, when it was dark and they were alone. Thinking that this might reflect fear or loneliness, Cohen-Mansfield tried three interventions: Assistants would either stop by and visit with the patients at the problem time, play the patient a videotape of a family member talking to them, or play music they had once enjoyed.

Caregivers Need Healing, Too

Many family members of Alzheimer's patients want to keep their loved ones out of nursing homes. But the burden on these caretakers is overwhelming: They have a higher than average risk of serious illness, and psychologist Linda Teri of the University of Washington, Seattle, found that 75% of family caregivers show signs of major depression. So some researchers are looking for ways to relieve the caregivers' burden.

One easy way for family caregivers to get relief is to take the patient to a day care center a few times a week, says psychologist Steven Zarit of Pennsylvania State University in University Park. He and his colleagues reported in the September *Journal of Gerontology and Social Sciences* that caregivers who did so showed significantly less stress, anger, and depression than a control group. But, says Zarit, "studies of how many [family caregivers] use formal services of any kind show that the numbers are very low." Social worker Lisa Gwyther of Duke University explains that Alzheimer's caregivers often put off using services even when they know about them. "They delay use longer, far beyond what a professional would recommend."

But when families are strongly encouraged to use services, the results can be dramatic. New York University epidemiologist Mary Mittelman enrolled 206 spouses who were caregivers for Alzheimer's patients into a study and gave half of them a package of support services, including training to manage behavioral problems, support groups, and counseling for the entire family. Those in the control group got help when they asked for it but were not in a structured program. Mittleman's results, published in *The Journal of the American Medical Association* in December of 1996, showed that caregivers receiving the support package delayed placing their spouses in nursing homes by an average of a year, compared to the control group.

Just learning to manage the patient's problem symptoms can give caregivers a big boost. That's where the behavioral strategies psychologists are now developing (see main text) can come in. Teri, for example, had caregivers recall activities that the patient used to enjoy and then adapt a few of them to the patient's present cognitive level. For example, a crossword puzzle lover may still be able to do children's crosswords. After 9 weeks of the program, the patients and caregivers both scored significantly better on depression scales. "Not only did the patients get better," notes Teri, "but the caregivers got better too." **–M.B.**

"It really made a difference," she says. The patients responded to all three approaches; as a group, their screaming or moaning dropped by roughly half in response to one-on-one interactions or the videotape, and by one-third in response to music.

In Cohen-Mansfield's study, the one-on-one interaction produced the biggest results, and in general researchers are finding that social interaction helps slow behavioral decline. Reisberg cites two striking cases: women with late-stage disease whose wealthy husbands have lavished professional attention and care on them. Normally people at their stage are bed-bound and withdrawn, but these women attend social events and appear to enjoy life. "They are doubly incontinent and say not a word, but they are happy," he says.

Back to school

For families who can't afford costly private care, many parts of the country have day care centers for Alzheimer's patients, where they engage in developmental-age–appropriate activities, such as games or relearning daily living skills such as brushing their teeth. "The patients respond to the activities and the socialization," says Reisberg. Medication can be lowered, the patients become less agitated, "and when they come back at the end of the day, they have a lot to say to their family. It's a lot like school."

With all the new behavioral interventions, there is one caveat researchers have learned: The success of a program depends absolutely on caregivers' diligence in carrying it out. Studies by Alabama's Burgio and UCLA's Schnelle have shown that nursing home staff members tend to drop new techniques unless they are continually urged to use them. For example, a follow-up of Bourgeois's memory book study found that once the researchers left, says Burgio, "the memory book use went down."

Burgio developed a program to combat this problem, adapted from motivational programs used in industry, which combines monitoring of the nursing home staff with incentives for good performance. In a carefully controlled trial, staff members who received his program consistently used the interventions they had learned for months, while those not in the program tended to drop the interventions when the training period ended. Burgio says he tells nursing homes that are interested in behavioral therapies, "if you aren't going to use a staff motivational program, don't even bother with the behavioral intervention, [because] it won't be used."

Indeed, the new behavioral methods face many hurdles. "It is a really long road," says Teresa Radebaugh of Khachaturian, Radebaugh, and Associates, "to take something that is well tested, well described, carefully peer reviewed, and published, but done in a sophisticated setting ... and get it out to a nursing home in a small town." Burgio agrees: "A lot of people still believe [nursing homes] should be following a custodial model, not a treatment model. It will take another 10 years before people are really accepting of the treatment model." But these researchers are committed to spreading their word and making life a bit easier for Alzheimer's sufferers and their caregivers. —MARCIA BARINAGA

ASTRONOMY

Meteor Shower Sets Off Scientific Storm

The return of comet Tempel-Tuttle has triggered a debate over whether its debris poses a threat to the world's satellites

BOSTON—During a cold and clear night in 1833, hundreds of people here rushed outdoors to watch falling stars so thick they looked like a light snowfall. This past February the comet responsible for that spectacular meteor storm—comet 55P/Tempel-Tuttle—swung around the sun after a 33-year absence from the solar system. And on 14 November, Earth will start plowing through a fresh stream of particles that boiled off its surface and were left behind. But this time the show is of interest to more than just idle skywatchers: Its intensity is a matter of some debate among scientists and great concern to those who operate satellites that may encounter the comet's trail.

The annual displays, called the Leonid meteor showers, were recorded over 1000 years ago by Chinese astronomers and are often most dazzling just after the return of Tempel-Tuttle. But unlike 33 years ago, today the space above the protective atmosphere is filled with satellites full of sensitive electronics that provide global communications, warn of missile launches, and gather research data.

Just how seriously to take the danger from Tempel-Tuttle's dust is a matter of dispute between NASA, on the one hand, and the U.S. Air Force and Canadian astronomers on the other. "Could everyone lose their pagers and their television connections? All that is possible," says Lt. Col. Don Jewel, deputy chief scientist for the U.S. Air Force Space Command. But some NASA researchers say the concerns are overblown. "People hear a storm is coming and there is all this excitement—far more than the threat deserves," says Donald Yeomans, an astronomer at NASA's Jet Propulsion Laboratory in Pasadena, California.

Spectacular shower. This woodcut depicts the 1833 Leonid shower over Niagara Falls.

SOURCE: 1998 SKY AND TELESCOPE

Part of the disagreement about risk reflects different interests. Whereas NASA researchers are eager to study the little-known composition of the comet, Air Force and Canadian officials are more concerned about its effect on the global satellite network. So each group is going its separate way in monitoring the 1998 Leonids.

The comet has a path roughly intersecting Earth's orbit (see drawing). Based on that trajectory, the best viewing site for the peak night of showers on 17 November will be in Asia. Teams of Air Force and Canadian astronomers will set up camp in the Gobi desert of Mongolia and the Australian outback to gather real-time data and alert satellite operators if the shower turns into a storm. Meanwhile, NASA will fly airborne observatories to observe the sun's glow off meteoroids, the persistent meteor trains, and the neutral atom and particle debris.

Most satellite owners, including NASA, aren't taking any chances, recalling the stray meteoroid that is believed to have knocked out the European Space Agency's (ESA's) research satellite Olympus in 1993. NASA will turn the Hubble Space Telescope's optics away from the stream of particles and ground its shuttle, while Mir cosmonauts likely will retreat to their escape capsule as