Considering the toll Alzheimer's and Parkinson's takes on our communities, we prodded Pitt's neuro-gurus with questions: Who is the most vulnerable? What causes these diseases? What's the next best hope?

ALZHEIMER'S AND PARKINSON'S: 5.5 MILLION AMERICANS AFFLICTED AND STILL COUNTING. IS THERE NO STOPPING THESE DISEASES?

BY DOTTIE HORN AND LEAH KAUFFMAN

STOLEN LIVES

Losing the ability to move or think or remember. Being caught in the grip of an inevitable, progressive decline. Not knowing which symptoms you'll develop or when. Neurodegenerative diseases are among the most-feared illnesses.

Four-and-a-half million Americans have Alzheimer's disease and another 1 million have Parkinson's, the two most common neurodegenerative diseases. Because of the aging population, as many as 14 million Americans could have Alzheimer's by 2050.

Alzheimer's causes memory loss and dementia by disrupting the physiology of the brain and altering neurotransmitter levels. In Parkinson's, the dopamine neurons die, resulting in movement problems, such as telltale tremors, stiffness, walking difficulties, and other symptoms. Both the suffering these diseases bring and the societal cost of caring for those affected are staggering.

ILLUSTRATIONS | MICHAEL LOTENERO

In 1999, the School of Medicine created the Pittsburgh Institute for Neurodegenerative Diseases (PIND) to foster a community of scientists focused on these two enormous disease burdens as well as Huntington's, ALS (amyotrophic lateral sclerosis), and other conditions. In 2000, PIND received a $10.8 million gift from the Scaife Family Foundation and the Scaife Charitable Foundation, one of the largest gifts the University has ever received. Ten million of the gift (matched by $10 million from UPMC) is being used to construct a PIND floor in the new Biomedical Science Tower 3. (The Scaife money also funds a seed grant program, supporting new neurodegeneration researchers.) PIND moves into its new home later this year. The institute's "open lab" layout, where one scientist's space is contiguous with another's, is designed to spark freer exchange of ideas among investigators of different backgrounds. Add Pitt's all-star faculty lineup to that equation, and the prospects for the school to make even more substantial contributions to efforts to understand and treat these debilitating diseases start to look very good indeed.

In November, Timothy Greenamyre, professor of neurology, took over the leadership of PIND, following in the footsteps of Steven DeKosky, chair of neurology. DeKosky, an MD, heads Pitt's Alzheimer's Disease Research Center and just won the Ronald and Nancy Reagan Research Institute Award. Greenamyre, an MD/PhD known for his work on pesticides and other causes of Parkinson's, came to Pitt from Emory University. He has served on numerous National Institutes of Health committees and on the scientific advisory boards of the Michael J. Fox Foundation for Parkinson's Research and the Parkinson's Study Group. Other Pitt neurology professors instrumental in the development of PIND include Michael Zigmond and Robert Moore. Zigmond, a PhD, is an expert on why cells die in Parkinson's and how they might be protected. Moore, an MD/PhD, is interested in biomarkers for Parkinson's.

Considering the toll Alzheimer's and Parkinson's take on our communities, we prodded these neurogurus with questions: What sets off these diseases? Is there a way to avoid them by how we live our lives? Who is most vulnerable? What's our next best hope? What we learned, you'll find on these pages. However, the most difficult questions—like how to tell Dad that he needs to hand over his car keys for good—we may have to answer ourselves.

CULPRITS

WHY DO PEOPLE GET ALZHEIMER'S AND PARKINSON'S?

ROGUE PROTEINS

In Alzheimer's, "We know that two different kinds of proteins in the brain are processed in a way that they aren't supposed to be," says DeKosky. A protein called tau forms tangles within neurons; and at some point, a protein known as amyloid-ß amasses into plaques between neurons. It's thought that the plaques probably contribute to the formation of tangles. Indeed, recent research shows that when plaques are cleared from mouse brains, so are very early tangles.

BANDING TOGETHER FOR NO GOOD

Proteins get together in suspect ways in Parkinson's, as well. In people with this disease, the protein alpha-synuclein forms abnormal clumps within the brain's dopamine cells. This brings up a chicken-or-the-egg question: Do the clumps themselves cause trouble, or is the disease caused because the protein—which is taken out of action once it bands into the clump—no longer does its usual job? No one knows.

DOES IT RUN IN THE FAMILY?

In 5 to 10 percent of Parkinson's patients, the disease is inherited—what's known as familial Parkinson's. In these cases, the disease is caused by a single genetic mutation. So far, researchers have identified five genes that, when mutated, cause the disease. Scientists have also identified "susceptibility genes." These genes don't cause Parkinson's but, when mutated, increase a person's risk of developing the disease.

A rare and particularly devastating form of Alzheimer's, which strikes decades earlier than most cases, is caused by inherited gene mutations. The more typical late-onset Alzheimer's is often associated with a gene called APOE4, but not everyone with it gets the disease. Most cases are not attributable to heredity—yet. DeKosky says it's unlikely that a gene as powerful as APOE4 remains undiscovered, but that "there probably are other genes out there that have effects." To accelerate this research, the National Institute on Aging sponsors a bank of genetic material from families with two or more cases of late-onset Alzheimer's.

PESTICIDES

People who are exposed to pesticides at work as well as those who live in a farming area and drink well water are three to seven times more likely to get Parkinson's than the population at large. Pitt's Greenamyre has shown that chronic, low-dose exposure to the pesticide rotenone causes Parkinson's disease in rats and monkeys.

FREE RADICALS

Oxidative stress—the damage caused by free radicals—is probably part of the process that causes protein clumping seen in Parkinson's patients. Free radicals can make proteins bind together and can also throw a wrench into the garbage-removal system that would normally rid the cell of aggregating protein.

Unusual oxidative stress is apparent in Alzheimer's, too, but it isn't clear if that's a cause or a symptom.

DYSFUNCTION WITHIN CELLS

Mitochondria are the major source of the free radicals that are generated within a cell. When mitochondria aren't working properly, they produce many more free radicals than when they're functioning normally. Accumulating evidence suggests that dysfunctional mitochondria are linked to the oxidative stress associated with Parkinson's. But there's a mystery involving the mitochondria. Parkinson's patients have a defect in a certain mitochondrial enzyme (called complex 1) throughout their bodies—yet, apparently, only the dopamine cells in the brain malfunction. No one knows how a systemic defect can have such a selective effect.

HEAD TRAUMA

Several teams, including DeKosky's, have described Alzheimer's-like plaques in patients with traumatic brain injury, even as soon as two hours after an injury. What's the connection? DeKosky and colleagues have shown that plaque-forming proteins increase after injury; they may leak from traumatized neurons. ■

WHAT HELPS? WHAT HURTS?

ARE THERE RISK FACTORS INHERENT IN WHO WE ARE AND HOW WE GO ABOUT OUR LIVES?

AGING

The biggest risk factor for typical late-onset Alzheimer's disease is advanced age. Just about 3 percent of Americans ages 65 to 74 suffer from Alzheimer's, but up to half of those who are 85 or older may have it.

Parkinson's strikes at an average age of 60 and is most common in those in their 70s and 80s.

SMOKING

Repeatedly, studies have found that smokers have a decreased risk of developing Parkinson's. No one knows why. "Obviously we don't want to recommend to people that they smoke, but if we could find out what it is about smoking that decreases risk, that would be important," says Greenamyre.

And nicotine, curiously, reduces the plaques found in Alzheimer's; however, in a mouse model it promotes the formation of tangles.

EXERCISE

Lace up those tennies. Exercise stimulates the growth of new neurons and increases the number of synapses and capillaries in the brain. (More capillaries mean better distribution of nutrients.) Exercise also increases the concentration of naturally occurring protective agents in the brain. In a 2001 paper published in the *Journal of Neuroscience*, Zigmond and his collaborators were the first to show that, in a rat model, exercise helps protect the brain against Parkinson's. In his current studies with rats, Zigmond is examining how exercise protects the brain and what sort of exercise regimen is best. (Rodent pilates?) He's also part of a small pilot study examining the impact of exercise on Parkinson's patients.

CAFFEINE

Consuming caffeine decreases your risk of developing Parkinson's. The more caffeine ingested, the less your risk. But before you make another pot of java, keep in mind that there are good reasons to kick the caffeine habit. For example, those with coronary artery disease or chronic renal disease should stay away from the brown stuff. There's also data showing adverse effects of caffeine use during pregnancy and with other conditions.

GENDER AND HORMONES

Men develop Parkinson's up to twice as often as women. Why? We don't know. Some researchers are exploring whether estrogen helps protect against Parkinson's.

There is no definitive evidence of a higher incidence of Alzheimer's in either men or women. Although studies have shown less cognitive impairment in women who used hormone replacement therapy after menopause, estrogen treatment did not slow the course of Alzheimer's when given early on and actually slightly increased the risk of dementia when studied as a preventative.

BAD BLOOD

One Pitt study found that cardiovascular disease results in a 30 percent increase in Alzheimer's; another study found a 39 percent increased risk of Alzheimer's in people with diabetes and elevated insulin. Accordingly, the Alzheimer's Association asks you to "Maintain Your Brain," that is, adopt healthy habits as a means of postponing Alzheimer's.

"For all we talk about prevention, what we're really talking about is delaying the manifestations of the disorder," says DeKosky. "Could we push it back five years? That would halve the number of cases in this country. That's our strategy until we have a very specific way to stop it from occurring." ■

STOLEN

CURRENT TREATMENTS

WHAT'S THE STANDARD OF CARE?

PARKINSON'S

In 1961, Oleh Hornykiewcz, a Viennese pharmacologist, discovered that dopamine neurons died in the brains of people with Parkinson's. In 1967, levodopa, a naturally occurring enzyme, was first used as a Parkinson's treatment. Ingested orally, levodopa is transported to the brain, where it is converted to dopamine. It replaces the dopamine no longer produced by the damaged neurons and reduces Parkinson's motor symptoms, including slow movement, stiffness, and tremors. More recently, drugs that mimic dopamine's molecular role have been used to treat the disease, often in conjunction with levodopa. These "dopamine agonists" generally improve motor symptoms. Levodopa and dopamine agonists are the most commonly prescribed treatments for Parkinson's.

ALZHEIMER'S

Among other treacheries, Alzheimer's disrupts a network of cells that use the neurotransmitter acetylcholine. Although acetylcholine can't be given medicinally, levels of it are increased by drugs that interrupt its normal breakdown, resulting in improvement or temporary stabilization for patients.

A newer drug holds promise, as well. Cells responsible for memory storage and learning rev into high, sustained activity when powered by the neurotransmitter glutamate. But too much glutamate floods Alzheimer-afflicted brains, overstimulating receptors and killing cells—imagine how a moped souped up for jet propulsion would rip itself apart. The newest drug approved for the treatment of Alzheimer's, memantine, blocks one kind of glutamate receptor, permitting enough activity for cognition while protecting neurons from overstimulation. ■

RARE TREASURE

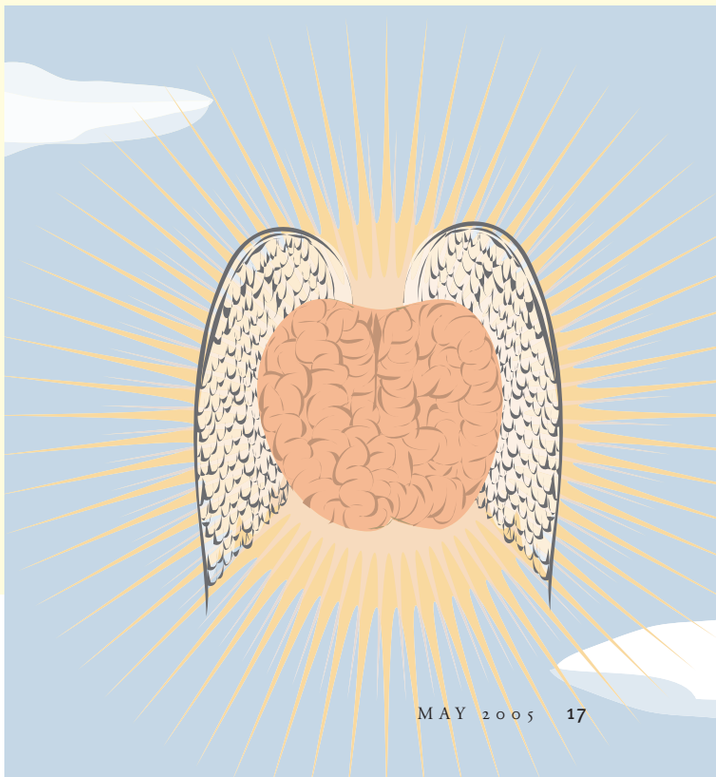
Nuns and priests from more than a dozen Catholic orders are volunteers in two long-term studies of aging and Alzheimer's, one run by the University of Kentucky in Lexington, the other by Rush University Medical Center in Chicago. Participants not only undergo yearly cognitive and physiological testing, but also donate their brains at death whether or not they have Alzheimer's—meaning scientists now have a stable supply of diseased and healthy brains to study—a rare treasure.

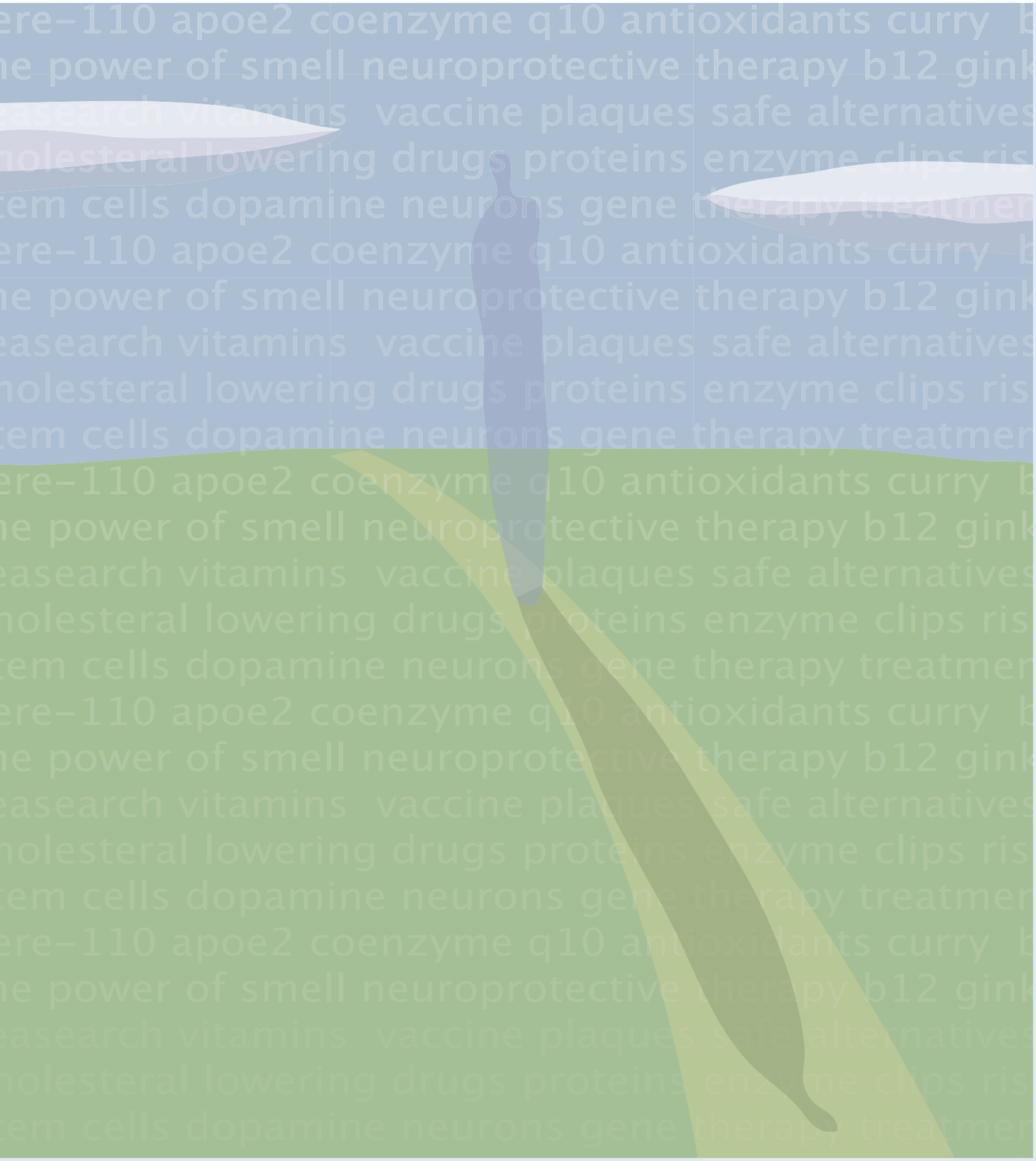
Nearly 700 Roman Catholic School Sisters of Notre Dame from chapters all over the country volunteer in Kentucky's so-called Nun Study. You may recall one of their most surprising—and widely reported–findings: In the '80s it was reported that women in their 20s with the least facility with written language, as demonstrated in archived autobiographical essays, had more cognitive impairment in old age and more culprit tangles among neurons in their brains at autopsy than their eloquent contemporaries. But what does this really tell us? Does exercising your brain when young protect against Alzheimer's? Or does Alzheimer's cause subtle cognitive deficits as early as one's 20s? We can't answer that yet, says Pitt's Steven DeKosky.

But then there were other findings that appeared to link learnedness and late-life lucidity. The Religious Orders Study at Rush found that the more years of formal education participants had, the higher the level of cognitive function they were able to maintain, even when their brains were riddled with plaques associated with Alzheimer's. DeKosky, who collaborates with the Rush team, reminds us again that correlation is not causation: Formal education may train people's brains to solve problems like the ones in neuropsychological tests in novel ways, ways that work around damaged neurons. And animal studies have shown that mental stimulation builds thicker brains with more synaptic contacts; perhaps people with similarly bulked-up brains maintain cognitive function even as they lose tissue to disease.

"When we look at... a population and come up with a finding that says, 'Yes, [education] is protective,' the explanation is in fact that which made us hypothesize that we might see this in the first place," says DeKosky. "But we certainly can say, 'Look, this will not hurt you.'"

One of DeKosky's roles in the Religious Orders Study is to characterize the brain pathology of mild cognitive impairment, which is often a precursor to Alzheimer's. To his surprise, a brain enzyme that was thought to be deficient in mild cognitive impairment is actually overabundant, probably produced at higher levels to compensate for dying neurons. Another finding is that a type of neuron thought to be completely devastated by Alzheimer's actually dies off in a certain pattern; some of those neurons even persist through the worst of the disease. In a disease with such a long course, these findings will help doctors know what to treat and when. "It's helping us to map out the most vulnerable areas," says DeKosky, "[to understand] at any specific level of severity of the disease, what is the underlying structure of what's left? What's dead, what's hurt, and what needs to be saved?" *—LK*




ere-110 apoe2 coenzyme q10 antioxidants curry
ne power of smell neuroprotective therapy b12 gink
easearch vitamins vaccine plaques safe alternatives
holesteral lowering drugs proteins enzyme clips ris
tem cells dopamine neurons gene therapy treatmen

WHAT'S AROUND THE BEND?

WILL COMPOUNDS OUR OWN BODIES PRODUCE PROTECT US FROM THESE DEGENERATIVE DISEASES? DO ANSWERS LIE IN VITAMINS? IN MORE OUTINGS TO INDIAN RESTAURANTS?

SHOOT TO CURE

Alzheimer's has no cure and few palliative treatments. So when Elan Pharmaceuticals announced in 1999 that its vaccine cleared Alzheimer's plaques from mice, it seemed that there would finally be a new, robust therapy for the disease. A limited trial of the vaccine began in 2001—the company suspended it a year later when four of the 97 participants showed signs of encephalitis. The good news? In the two years after they were immunized, the patients who mustered the highest antibody response had less cognitive decline than controls, and autopsies of participants who have died since treatment confirm clearance of plaque from the brain.

Seeking a safer alternative than stimulating the patient's own immune system, Elan developed a treatment of lab-made antibodies to thwart plaque. Pitt's Alzheimer's Disease Research Center was one of just four centers participating in safety trials last year and will now participate in Phase II trials to judge the antibodies' effectiveness.

PARALLEL PLAQUES

People who use cholesterol-lowering drugs have a reduced risk of developing Alzheimer's—perhaps by a whopping 70 percent. DeKosky's team is participating in a National Institute on Aging–funded multicenter trial of Zocor to study how it influences cholesterol and Alzheimer's risk; similar trials are under way on other statins. It appears that statins promote the normal breakdown of the protein that is mismetabolized into plaques.

CUT AND PASTE

Alzheimer's plaques result when the wrong enzyme clips a protein in the wrong place. Eli Lilly has successfully completed a safety trial of a drug that shuts off that errant enzyme. Therapies aimed at other enzymes are in earlier stages of development.

Alzhemed, a new drug developed by the Canadian firm Neurochem, inhibits the action of a sticky carbohydrate molecule that helps protein bind into plaques. Pitt's Alzheimer's Disease Research Center will participate in efficacy trials of the therapy.

PRO ANTI-INFLAMMATORY

Large-scale studies of other diseases show that people who took nonsteroidal anti-inflammatory drugs for several years had a reduced risk of Alzheimer's. In 2001, the National Institute on Aging embarked on a prevention study involving up to three years of treatment with the anti-inflammatories celecoxib and naproxen but halted it in December 2004 when an unrelated cancer trial linked celecoxib to increased risk of heart attack and stroke. The search for anti-inflammatories from other drug classes continues.

THOSE MUCH-TALKED-ABOUT STEM CELLS

Replacing the cells that die in Parkinson's with new dopamine neurons derived from stem cells may one day cure the disease—but this avenue of research is probably the furthest from realization. Why? For one, getting stem cells to turn into dopamine neurons is tricky. "Right now, we have very little control over how stem cells differentiate," says Greenamyre.

SPECIAL DELIVERY

Delivering genes into Parkinson's-afflicted cells could stimulate the cells to produce more naturally occurring protective agents, which might revive dying neurons. But there's at least one problem with this approach. Once a gene therapy treatment is delivered, it can't be reversed. What if the cell starts pumping out so much of the protective agent that the patient has unexpected side effects? Researchers are now trying to develop reliable methods to turn the gene on and off once it has been delivered into the cell.

Similar strategies are being applied to Alzheimer's: A small safety and tolerability study of a compound called CERE-110 is happening now. In the study, patients receive a shot of the compound. The needle is placed in the basal forebrain (the site most often affected by Alzheimer's), where the compound ushers into cells a gene for nerve growth factor. Another gene, APOE2, confers protection from Alzheimer's. Lilly Research Laboratories recently reported that when mice with Alzheimer's-like plaques had the gene injected into their brains, 30 to 50 percent of the plaques were cleared from the brain's memory center.

LOOK WITHIN

Our bodies may already manufacture solutions for staving off neurodegeneration. The brain produces compounds that promote cell survival; they're called trophic factors. Studies suggest that boosting the levels of trophic factors within neurons might help shield them from Parkinson's. One trophic factor in particular—GDNF—has been the focus of much Parkinson's research. Pitt's Michael Zigmond studies how GDNF protects neurons. Other researchers are trying to find ways to effectively deliver GDNF, which doesn't cross the blood-brain barrier, to patients. So far, clinical studies have shown mixed results.

Along the same lines, researchers may already have their hands on the first neuroprotective drug for Parkinson's. Patients treated with coenzyme Q10, an antioxidant produced normally by the body, showed improvement. When patients took the enzyme orally in high doses, they had fewer disabling symptoms—the higher the dose administered, the more the patient benefited. The enzyme appeared not only to relieve symptoms but to actually slow the progression of the disease. Yet the study of 80 patients was too small to be conclusive.

"The treatments that we have right now for Parkinson's, as far as we know, just treat the symptoms," says Greenamyre. "They don't keep the disease from getting any worse. So the Holy Grail right now is neuroprotective therapy, treatments that are either going to slow or prevent the progression of the disease."

VITAMIN ENRICHED

In 1998, after a large clinical trial, researchers reported that high doses of vitamin E, an antioxidant, showed no benefit in slowing the progression of Parkinson's. Afterward, the idea of treating Parkinson's patients with

antioxidants fell out of favor, says Greenamyre: "People assumed that because vitamin E didn't work, that no antioxidant would work. But it turns out that vitamin E doesn't get into the brain very well, and the researchers might not have used high enough doses." If there were a way to deliver more vitamin E into the brain—through higher doses or by modifying the molecule so that it crosses the blood-brain barrier more easily—E might be just the thing.

Vitamin E may do double brain duty. When taken with vitamin C, at levels a bit higher than the U.S. recommended daily allowance, it reduces the risk of sporadic Alzheimer's.

And as it turns out, vitamins that keep our cardiovascular system in balance may keep us sharp as well. An amino acid called homocysteine is metabolized with help from folate and vitamins B_6 and B_{12}. When these vitamins are deficient, too much homocysteine circulates as the brute in a broad swath of cardiovascular destruction. In one study, people with the highest levels of this amino acid had nearly twice the risk of developing Alzheimer's within a decade or so. Pitt is participating in a study of folate, B_6, and B_{12} to see whether these vitamins reduce cognitive decline in early Alzheimer's.

GO HERBAL?

While ginkgo biloba is hawked as a memory enhancer, Alzheimer's researchers are interested in it as a powerful antioxidant and therefore, a potential preventative. To determine whether daily ginkgo intake maintains cognitive function, DeKosky is heading a five-year, multicenter study of 3,000 elderly people without dementia.

CURRY CURIOUS

Mary Ganguli, a Pitt professor of psychiatry and epidemiology, was the first to report on the low incidence of Alzheimer's in the Indian subcontinent. She compared populations in Ballabgarh, India, and the Monongahela Valley, where the rate of Alzheimer's is nearly four times higher. A new study shows that the Indian diet may contribute to this difference. Curcumin, the tasty stuff that gives curry its amber glow, prevents plaque buildup in rodents. When injected into the veins of mice with Alzheimer's-like plaques, curcumin was able to cross the blood-brain barrier. (Bridging this divide has been a big challenge to the development of new therapies.) ■

IF WE CAUGHT IT SOONER

COULD WE STOP NEURODEGENERATION IN ITS TRACKS?

By the time people develop symptoms of Parkinson's, 80 percent of their dopamine neurons have already been damaged. If researchers can develop therapies that prevent or slow degeneration related to Parkinson's, doctors will want to administer them early—before symptoms develop. But how can anyone diagnose Parkinson's before a patient has symptoms? The clues may be just a sniff or tap away (see "Do You Smell That?").

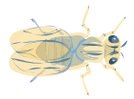
Likewise, as research reveals aspects of the Alzheimer's disease process that begin long before cognitive decline is obvious, the window for intervention widens. But, here again, it isn't always clear who needs treatment, though Pitt researchers are making great strides in this area. Last year, with collaborators in Sweden, William Klunk and Chester Mathis, of the departments of psychiatry and radiology respectively, were the first to view plaques in living patients. They just received the prestigious MetLife Foundation award for that work.

And there are other clues to the presence of the disease. Alzheimer's patients often first experience mild cognitive impairment, which includes subtle deficits that don't interfere with everyday living—like more memory loss than is typical for one's age. DeKosky's autopsy studies of people with mild cognitive impairment (who succumbed to other illnesses) show that about 60 percent had Alzheimer's pathology in their brain tissue, so there are compelling reasons to begin neuron-preserving therapies early. Unfortunately, a PIND study shows that mild cognitive impairment is recognized by primary care physicians just 23 percent of the time. Now researchers are looking into what variants of the condition are likely to progress to Alzheimer's. They're hoping to find biomarker and imaging tests that are sensitive and cost-effective enough for mainstream clinical use. And they're assessing neuropsychological tests for detecting mild cognitive impairment. For example, Judith Saxton, a PhD associate professor of neurology and psychiatry, is developing a test that runs on a tablet PC; patients can take it while they wait to see a doctor.

"I think it's extremely important to diagnose [these diseases] early," says Greenamyre, "particularly if we are on the track of neuroprotective therapies. The earlier you begin it, the better." ■

DO YOU SMELL THAT?

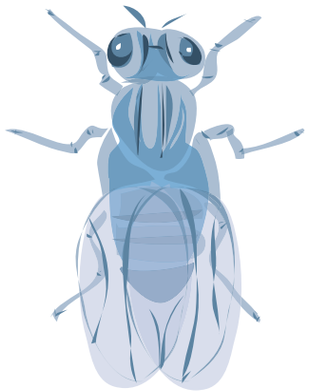
Early detection may come down to a puzzle of the proboscis. Your ability to detect certain odors may help your doctor determine whether you have Parkinson's disease—before you ever develop symptoms. Another clue may be how fast you can tap your foot. Pitt neurologists discovered that these two markers correlate well with impairment of dopamine pathways in the brain. Robert Moore and Nicholas Bohnen, assistant professor of neurology and radiology, figured this out by studying people who had an inherited form of Parkinson's but hadn't reported any symptoms.



MUTANT FLIES!

THESE BUGS MAY SAVE OUR BRAINS

BY DOTTIE HORN



In a glass vial, fruit flies climb the walls. They're gnat-like specks, the same flies likely to gather around ripening fruit left on a kitchen counter. Today, Michael Palladino's lab is nearly filled to capacity—up to 200 flies per vial, 60 vials per metal rack, dozens of racks arranged on shelves that line the walls. All total, he's looking after about a million flies. There are a few normal flies, and 500 different types of mutants, mutants galore. This PhD assistant professor of pharmacology wants to help find new drugs to treat neurodegenerative diseases. To help him in this endeavor, he has enlisted this made-to-order army of *Drosophila*.

Palladino's fly-brain story starts back in 2000. That's when he treated some flies with a chemical to "mutagenize" them. Mutagenizing a fly means you introduce a random mutation into one of its genes. Palladino's lab came up with and examined about 600,000 flies, each with a different single random mutation. He'd produced flies that had a strange eye color or were missing a bristle—those didn't interest him. Palladino was looking for flies that behaved abnormally.

He picked out the flies that were acting oddly. Some didn't walk well, had problems flying, or couldn't mate normally. Others appeared fine at first but became paralyzed if you raised the room temperature to 98 degrees Fahrenheit. Some didn't respond well to being "vortexed." Vortexing flies means taking the little vial they're in and shaking it. A normal fly is unfazed, but Palladino found that some mutants were temporarily paralyzed by the shake-up. Altogether, out of 600,000 flies, he found 200 that had some kind of behavioral problem.

One by one, Palladino started looking at the brains of those 200 flies. The aberrant behaviors were really just a screening device. (He kept in mind the behavior might have been caused by brain damage.) His underlying goal was to find mutants with neurodegeneration. Of the 200, he found 15.

A fly neophyte visiting his office looks at the numbers—600,000 to 15—and makes the mistake of saying, "Only 15?"

"You say 'only,' but that's great," the young scientist replies with a laugh. Finding those 15 mutants monopolized a year and a half of his scientific life.

But finding the mutant flies was just the first step. His next challenge was to use them to investigate what might protect the brain.

For one study, he picked out a strain whose mutation resulted in neurodegeneration. These flies were paralyzed by heat. Two generations and mutations later, he'd created a brood of flies—about 100,000—with the initial neurodegenerative mutation and a second random mutation. Palladino was hoping to find flies among this generation whose second mutation somehow compensated for the first. He wanted flies that had inherited the mutated neurodegeneration gene but didn't exhibit neurodegeneration. Examining all 100,000 brains would have taken ages, so he looked for flies that no longer became paralyzed when he raised the temperature. Of the 100,000, he found 30 that could continue moving in a heated vial.

Now he's in the process of inspecting the brains of those 30. If he finds one with a normal brain or with minimal damage, he will look for the gene that conferred the protective effect. His hope is to find proteins, and perhaps a whole pathway of biochemical events in the brain, that can offer protection—even in the face of adverse events like a mutation that might contribute to a disease like ALS.

He and others could then look for chemical compounds that would make this protective pathway more active.

"Using that approach for studying neurodegeneration is a great idea," says David Featherstone, assistant professor of biological sciences at the University of Illinois at Chicago.

"It does two things—it identifies potential drug targets, but it also sheds light on the process [of neurodegeneration] itself. So, in a way, it kills two birds with one stone."

"If there's a pathway that you can modulate that acts as a general neuroprotectant, then it wouldn't matter whether we're talking about Alzheimer's, ALS, Huntington's—it's all the same; neurons are dying," says Palladino. "If we can find a way to slow or stop that process, that's exactly what we need." ■

HOW TO MAKE COFFEE

THE WORLD CHANGED WHEN MY DAD FORGOT | BY CINDY GILL

One Saturday when I was 8, my Dad began loading his saltwater fishing gear into the trunk of our family's Ford Fairlane. I must have been watching him pack with pleading eyes. I loved riding in the car with him, whether it was short drives to the grocery store or longer trips to visit my grandparents in New Jersey. There was something about his confidence in the driver's seat that made me feel safe and happy.

Whatever the reason, I was thrilled that day when he asked me to tag along—just me, not my pregnant Mom, not my little brother. After lunch, we left our suburban ranch house on the outskirts of Richmond, Va., and headed for the salt air of Virginia Beach.

When the weather was good, he liked to drive with the window down and the breeze gushing in. He would gently guide the steering wheel as if he were a wizened captain at the helm of a boat he had piloted for years. I can still see him behind the wheel, a handsome 34-year-old, with blonde short-cropped hair, in a white cotton crew shirt and khaki pants.

When he drove, he was relaxed, even joyful. I think driving pushed his worries aside. It pulled him out of his life as a struggling industrial salesman and father with too many bills, two children, and a baby on the way.

On the road, he was free. To be allowed into that world was special, and I knew it, even then.

I don't remember a lot of specifics from that all-night fishing trip. Just a long, long pier, a sense of dark humps of water moving, and the whooshing beat of the ocean against the shore. I don't even remember how many fish Dad caught, or if he caught any—that wasn't the point, really. It was just to be out there, together, under a canopy of stars.

Through the night, he drank black coffee from white Styrofoam cups. He started drinking coffee as a teenager in the navy, standing watch on the deck of a destroyer escort in the North Atlantic. At home, I rarely saw him without a cup nearby—and that never changed in all the years I knew him, until one day toward the end of his life.

It was midweek and, after work, I drove the 10 miles to the small apartment set on a hilltop, where he lived alone. I knew the routine well. From the parking lot, I walked to the complex's main door and used the security code to enter. The door opened onto a portico, where a broad sidewalk stretched the length of a city block and circled around a grassy commons.

As I walked from the main entrance, I looked toward Dad's place. I liked to see his apartment lights glowing in the darkness. I expected to see him where he always sat—at his small, round kitchen table, drinking coffee and smoking Kent 100's. He'd probably need a shave, and he might still be wearing pajamas. But he was 73 years old, and I figured he deserved some slack.

His apartment was the last one on the right side. Number 7. It had a tiny covered front patio, with just enough space for two lawn chairs. From here, Dad had a perfect view of fields and woodlands, which reminded him of his days as an outdoorsman. After my visits, he would often stand on the patio and watch me leave, waiting until I reached the main door before waving his last goodbye.

As I approached his place, it was mostly dark. The porch light was off, even though I had called him during the workday to say I would visit. I knocked on his door. It took several knocks for him to answer. "Oh!" he said, as he opened the door. "This is a nice surprise. I didn't know you were coming."

The dining room and kitchen lights were off. He had been in the living room watching TV. More than a year ago, I'd taped the remote control so that only the power button and the up-down buttons for volume and channel selection were usable. It had become clear that Dad couldn't handle anything more complicated. He'd already stopped collecting and listening to music and comic recordings. (When I was a kid, the voices of Andy Williams, Julie London, Bill Cosby, and Ray Stevens kept us company.) Now, even a manual radio tuner befuddled him.

I flipped on the kitchen light. The sink was nearly empty. No pans. No glasses. No coffee cups. It had been two days since my last visit, and usually the sink held a pile of unwashed dishes.

"Dad, have you been eating?" I asked.

"I think so," he said, then chuckled. But it was clear he was uncertain.

"What did you have for supper?"

He hesitated, looking at me blankly, then said, "I'm really not sure."

Then I noticed his Mr. Coffee brewer, with its patina of stains from constant use. The machine wasn't in its usual place on the counter. A few clean coffee filters were strewn nearby. A red Folgers can sat on the Formica, unopened. *No coffee cups*. My father had forgotten how to make coffee.

In this small moment, I understood the ferocity of Alzheimer's. The disease had been whittling away at him, and the whittling had deceived me. It had started simply enough. Repeating comments made only minutes earlier. Forgetting to pay bills. Leaving milk and meat in the refrigerator too long. At one point, he began telling my brother, my sister, and me that he felt like "a short boy in tall grass." He'd laugh about it, but I could tell it scared him. He was getting lost.

Then he began really getting lost on drives to familiar places. Eventually his doctor insisted that he give up his car. On the spot, Dad gave me the keys to his decade-old Pontiac Grand Prix, which still amazes me. Driving was his last great love, his final shred of independence.

He slipped further and further into some fog, where time had stopped. He couldn't tell you the day, or the year, or much else. He was reduced to a craggy, silver-haired man sitting at a small kitchen table, drinking coffee and smoking cigarettes.

But then his disease took even that away from him. Not long after he forgot how to make coffee, we moved my father to an assisted-living setting that specialized in Alzheimer's disease. Less than a year later, he was dead.

On the day he died, I was driving his battered Grand Prix. When I left his bedside and returned to the parking lot, the afternoon sun lingered in a sea of white clouds. It was a Saturday much like the one we'd shared at Virginia Beach. I walked over to the Pontiac, but the driver-side door wouldn't open. The lock had inexplicably jammed. Nothing I tried would open it. Despite many attempts over several weeks, that door never opened again. I like to think it's because my Dad has reclaimed what was his. He is driving his very own car on a scenic road, past fields and woodlands, toward salt air. He has the window down, the radio on, and he remembers everything. ■

Cindy Gill is editor in chief of Pitt Magazine.

If you have a story to share about how neurodegeneration has changed your life, we encourage you to send us a letter about it (medmag@pitt.edu).