UNTANGLING

MY mother's dementia was inexorable and unyielding, my friend wrote. *Her short-term memory went first while she retained her long-term memories. Then these, too, began to slip. She frequently talked about being with her mother, and I believe that she still had enough comprehension that she was looking for the comforting embrace of her mother to help her through her troubles. She came across as a scared little girl, and I couldn't figure out how to provide that comfort for her.*

As time went on, I would go to see her, and there would be no recognition of me on her part. She developed a 1,000-yard stare, focusing not on me but on some focal point far beyond me. Frequently during these stares, her eyes would come into focus on my features, and she would break down crying and give me a hug. It was as if she knew I was someone special to her, but she couldn't define the relationship. Soon she would drift back into her own world, and eventually, she stopped recognizing me in any evident fashion. I came to expect that, although I held out hope that some day we could connect as mother and son and have one last meaningful conversation so that I could tell her I loved her, and to thank her for everything she did for me. That moment never came.

When the facility determined that she had reached a point where she had to move into the 24-hour-care wing, I consoled myself with the thought that she would not realize what was going on, and the transition would be relatively seamless. I was wrong, grossly and heartbreakingly wrong. As soon as I walked her over into the health-care wing, she immediately broke down crying and said, "I never thought it would come to this."

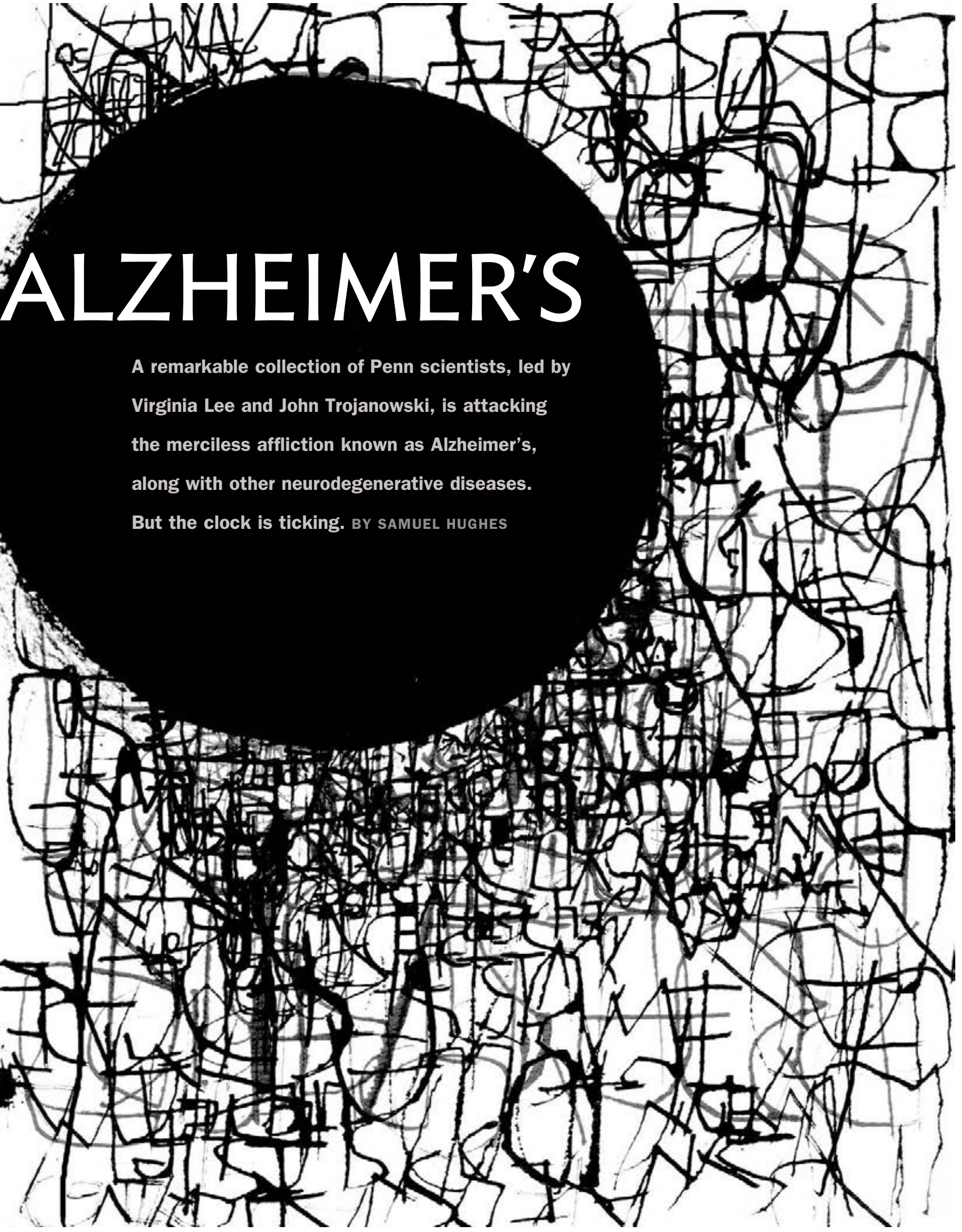
"Of all the things that can go wrong in aging, the loss of the mind is far and away the worst and most feared. And here, I believe, is the greatest of all opportunities for medical science in the improvement of the human condition."

—LEWIS THOMAS, *The Fragile Species.*

Perhaps you know someone: a mother, a grandfather, a college friend, a spouse. If not, you will. Right now more than 5 million Americans have some level of Alzheimer's disease, and the numbers are only going to get worse. On January 1 the first wave of baby boomers began hitting the beaches of old age. Behind them, the twilight flotillas stretch all the way to the horizon, waiting to discharge the next wave into the withering fire of dementia.

"We are beginning to enter a time where there's going to be a huge escalation of Alzheimer's patients," John Trojanowski Res'80 is saying. "The baby boomers are entering the lifespan where every five years the incidence of Alzheimer's will double." There are 70 million baby boomers in the United States, he adds. Without a cure, "35 million will have Alzheimer's by the time they reach 85."

 ILLUSTRATION BY ANASTASIA VASILAKIS



ALZHEIMER'S

A remarkable collection of Penn scientists, led by Virginia Lee and John Trojanowski, is attacking the merciless affliction known as Alzheimer's, along with other neurodegenerative diseases. But the clock is ticking. BY SAMUEL HUGHES

He pauses for a moment to let that sink in.

"We have the people," he adds. "We have knowledgeable scientists. We have ideas. We have technologies. We have model systems. We have all the apparatus in place. We just need the resources to ramp up our efforts for drug discovery."

Trojanowski (the William Paul Measey-Truman G. Schnabel Jr. Professor of Geriatric Medicine and Gerontology, and professor of pathology and laboratory medicine) is good at this big-picture stuff. He's no slouch at the small-picture stuff, either, which goes down to the cellular level and beyond, to the very proteins and peptides of dementia. But when he plunks his lanky self into a chair in his modest office in the Maloney Building at HUP, affixes his large, deep-set eyes on his interlocutor, and starts talking, he's a compelling speaker, segueing effortlessly and eloquently from one talking point to the next, answering questions before they're even asked. Which is a good thing, since he's become something of a spokesman on Alzheimer's and other neurodegenerative diseases, and there's a lot at stake.

Every now and then he tosses out a grandiose-sounding phrase like "a world without Alzheimer's," but he quickly brings himself back to reality—pointing out that *cure*, for example, is a relative term.

"A home run in my mind for an Alzheimer's drug would be something that delays the onset of progression by as little as five years," he says. "The economic modeling tells us that if we had a therapy that would slow progression by five years, within the next 40 or 50 years we would reduce the incidence of Alzheimer's disease by 50 percent. So 50 percent fewer people get the disease because they die from something else.

"The average age of onset of Alzheimer's is 73, 74 years old," he adds. "So if you give people a pass on Alzheimer's for another five years, then many will die of something else—a heart attack or what have you—but they won't incur all the costs."

We're talking real money here, by the way. The Alzheimer's Association estimates the annual cost of Alzheimer's care in the US now at about $172 billion. Globally, the cost is about $604 billion, and by 2050, that number could rise as high as $3 trillion, Trojanowski says. A five-year delay could cut that number to around $1.5 trillion. "Half of $3 trillion is certainly a lot of money," he adds. "But it's far less than $3 trillion."

Trojanowski is just one half of the remarkable husband-and-wife scientific team whose better if less grandiloquent half is Virginia M.-Y. Lee WG'84, director of the Center for Neurodegenerative Disease Research (CNDR), the John Ware 3rd Professor in Alzheimer's Research, and professor of pathology and laboratory medicine. Having just finished an 80-minute interview with Lee, whose office is next door to Trojanowski's in the Maloney Building, I'm frankly exhausted, though not unpleasantly so. Lean, petite, and practically crackling with energy, she has just brought me up to speed very fast and in minute detail on the small-picture side of their work—the intricate workings of the brain and its cells, the genetic mutations and misfolded proteins and destabilized microtubules, the efforts to find molecules that can cross the blood-brain barrier—as well as the deeply entwined fibrils of Penn's neurodegenerative disease centers and programs.

Explaining that last part is no easy task. In addition to directing the very complex CNDR, Lee co-directs the Marian S. Ware Center for Alzheimer's Drug Discovery Program, and has a firm hand in many other related ventures. Like Trojanowski, she is a highly productive and prolific researcher who, along with her colleagues, churns out dozens of influential papers each year. Two years ago she received the Alzheimer's Association's Khalid Iqbal Lifetime Achievement Award, and that's only the most recent honor. For those who like metrics, Thomson Reuters Essential Science Indicators ranks her No. 6 in the world in the neuroscience and behavior category. Fourth on that list is Trojanowki, who is also co-director of the CNDR and of the Ware Program, and director of Penn's Institute on Aging (IOA), its Alzheimer's Disease Center, and its Udall Center for Parkinson's Research.

The two are "at the forefront of the field of aging and dementia with their work on biomarkers and the role of tau [proteins] in neurodegenerative diseases," says Ronald Petersen, director of the Mayo Clinic's Alzheimer's Disease Research Center and the man who treated former President Ronald Reagan. "They are not reluctant to pose bold and creative hypotheses that are intended to refocus our thinking on the underlying processes."

Given the collaborative nature of their work, teasing out the threads of their individual efforts can be a challenge. Which doesn't seem to bother either of them.

"John and I really work together in most things we do," says Lee. "Our skill sets complement each other." Or, as she put it in a recent video for *Alzheimer's Weekly*: "In 1985, we decided to do a little experiment to see if we could collaborate and not kill each other."

When Alois Alzheimer examined the brain of a patient known as Auguste D. in 1906, he found that brain cells had died "on an immense scale," as Ralf Dahm, author of *Alzheimer: 100 Years and Beyond*, put it. "In the neurons that remained Alzheimer noticed thick, strongly staining fibrils. Moreover, the cortex was full of plaques of unknown composition."

Those plaques and tangles are still the dominant feature of the disease that bears Alzheimer's name. But after his seminal discoveries, not much happened on the Alzheimer's front. The disease was first mentioned in *The New York Times* in the 1930s, Trojanowski notes; the second time wasn't until the '50s.

"For many years Alzheimer's disease really was not on anyone's radar screen," says Lee. "Fifty years ago people don't even think it's a disease. They just think that Grandma is getting old and a little bit forgetful."

It wasn't until 1976, when Robert Katzman—an Alzheimer's activist and neurologist at UC-San Diego who founded the Alzheimer's Association and the Alzheimer's Disease Research Center—wrote an editorial titled "The Prevalence and Malignancy of Alzheimer's Disease" in *Archives of Neurology* that the medical community really woke up to the seriousness of the situation.

For Trojanowski, the "modern molecular era of Alzheimer's disease research" began in 1984 when George Glenner and Cai'ne Wong isolated the beta-amyloid peptide from the amyloid deposits in the brains of Alzheimer patients. "It wasn't genetics," he says. "It wasn't fancy-schmancy GWAS

CANDACE DICARLO

[genome-wide association study]. It wasn't proteomics. It was old-fashioned biochemistry and neuropathology." From that discovery, he adds, "we went to identifying the mutations in the gene that caused Alzheimer's disease. And from there we went to animal models and on to drug discovery."

Thirty years ago the late, great medical essayist Lewis Thomas called Alzheimer's "the disease of the century." While AIDS may have justifiably stolen the spotlight in the 20th century, the demographics and staggering costs associated with Alzheimer's make it well-positioned to reclaim the title in the 21st.

"When Alzheimer described Alzheimer's disease in 1906, life expectancy was 48, and the top 10 or 20 causes of death were infectious diseases," points out Trojanowski. "A hundred years later, people are living to an average age of 78 in developed countries. And now Alzheimer's, which was ignored, has become an epidemic. Alzheimer's has replaced diabetes as the sixth leading cause of death in developed countries.

"The current [global] cost of Alzheimer's disease is $604 billion," he adds. "If those costs were the economic output of a country, then the cost of Alzheimer's care would mean that Alzheimer's is between Turkey and Indonesia as the 17th-largest economy in the world. If it were a company, it would be the largest company in the world, larger than Walmart and Exxon Mobil. It's affecting China, Southeast Asia, Australia, Indonesia. So it is a global problem. A global epidemic—with horrendous costs.

"We really owe it to ourselves and future generations to create a world without Alzheimer's disease," he adds. "And I think we can. Twenty years ago I wouldn't have said that. We didn't know enough. When asked at support groups by families that had an Alzheimer's patient, I would almost tearfully have to say, 'I have no idea.' As a physician, to admit that there was nothing that you could do—and that you had no idea when something could be done—was emotionally difficult. And now it's changed so dramatically that I say the cure will come as quickly as the American people want it to come."

IN 1991, the same year they found conclusive proof that the tangles in Alzheimer's were formed from tau proteins, Lee and Trojanowski founded the CNDR (www.med.upenn.edu/cndr), which has become the main nerve center of their work. It's one of those "centers without walls," and its 55 researchers and support staff collaborate with another 40 faculty members around the School of Medicine and across the University. (It should be noted that the School of Nursing does important work related to Alzheimer's and other neurological diseases that doesn't fit into the scope of this article.) They conduct clinical and basic research across a swath of disciplines, probing the causes and mechanisms of brain dysfunction and degeneration in Alzheimer's, Parkinson's, frontotemporal disease (FTD), amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), and other neurodegenerative disorders.

This is not just a dumping ground for research projects that can't find a home anywhere else, by the way. There are key pathological connections between those disorders, whose common thread is the "fatal attraction" of certain brain proteins. Five years ago, for example, Lee led an international team that identified a misfolded protein, TDP-43, that causes both ALS and FTD.

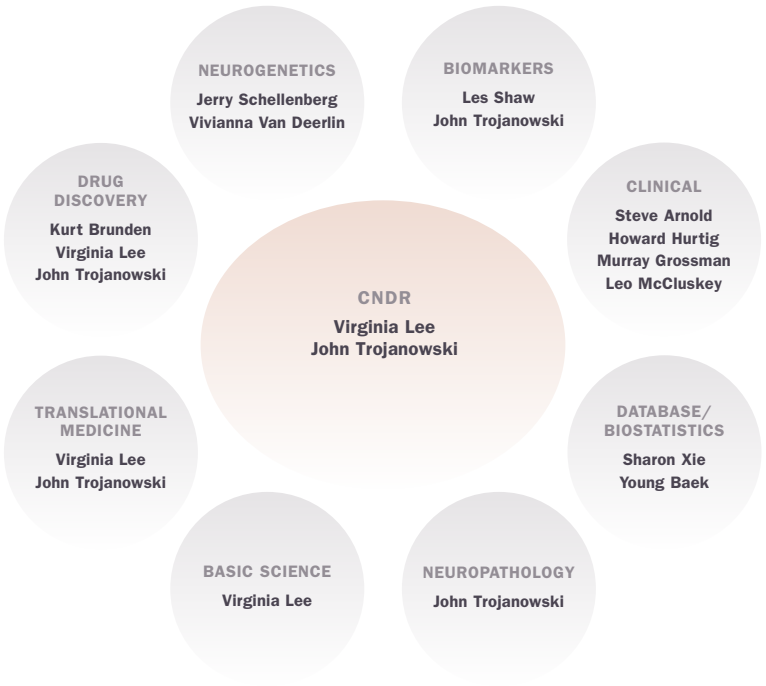
In creating the CNDR, Lee drew on organizational skills learned while earning her MBA from Wharton in her spare time. That was in the early '80s, when she was concerned about the Reagan administration's plans to privatize the NIH and thought she might need to hone her executive skills.

"At a subconscious level it probably helped me tremendously in terms of organizing the center," she says. "At that time we have small labs, and John has maybe three or four people; I have maybe the same number of people working for us. Since the late '80s he and I really put our heads together and said, 'How can we organize an infrastructure so that we can really, truly study Alzheimer's disease and other neurodegenerative diseases?'"

That infrastructure, she adds, "turned out to be extremely valuable."

"I can't really think of another university in the United States—or anywhere in the world, really—where there are centers of excellence in Alzheimer's, Parkinson's, frontotemporal disease, and ALS," says Trojanowski. "And where one or two exist, they often don't interact as seamlessly as we do. I don't know if you want to attribute to this Benjamin Franklin, but there is a culture of collaboration at Penn, of collegiality, that makes it possible to reach across departments, disciplines, schools."

He points to the new integrated neurodegenerative disease database (INDD) that incorporates massive amounts of information from living patients and provides a "valuable tool for generating data sets in comparative studies on several neurodegenerative diseases," in the words of an abstract for the Alzheimer's Association's newsletter. This is the kind of achievement that might not make for front-page headlines, but it makes scientists very happy—and helps them be productive.



VIRGINIA LEE

When those patients die, "we then have autopsy information on them, we have genetics," Trojanowski explains. "And this is for each of the four disease categories. I know of no common database like this in the country where people have said, 'We'll all put our data into the same database archives; we'll all have

THE ETHICS OF ALZHEIMER'S

Jason Karlawish, associate director of the Penn Memory Center and associate professor of medical ethics and medicine, investigates bioethical issues that center around one powerful question: "How do you respect the humanity and dignity of people whose brains are failing, in a world where what our brain does very much defines who we are and the nature of our selves?"

Karlawish, who's also a senior fellow at the Center for Bioethics, has been probing these issues since he began studying the ethics of informed consent as a geriatric-medicine fellow at the University of Chicago 14 years ago. One of the questions that sparked his interest then was, *How do we enroll people with Alzheimer's disease in research if one of the very symptoms of the disease is trouble making decisions?* Related to that was, *Since Alzheimer's patients typically lack awareness of the nature and severity of their cognitive and functional problems, how do we know that a patient is better because of a drug?*

Though the issues are still as challenging now as they were then, the work that he and others in the field have done have provided some important guidance.

"We have shown that it's possible to measure someone's ability to make a decision, and we've developed methods that show that people can still retain the ability to appoint a trusted proxy, even if they can't make the decision to be in research themselves," says Karlawish, who directs the education, recruitment, and retention core within Penn's Alzheimer's Disease Center. "Most older adults support even risky research" to advance the progress in treating Alzheimer's, "and the key driver to that support is an overall trust and belief in research."

Given that Alzheimer's now appears to start long before the symptoms occur, Karlawish believes the United States needs to "get serious about funding research that recognizes" that fact and "allows us to identify the people who are most in need of intervention"—so those interventions can be timed "in a way that not only reduces disability in the population but reduces the cost of the disease and the cost of the treatment."

As we start to identify those at risk, "we have to think about the kind of culture of monitoring that we're going to create around them," he says. "We don't want to get into a culture where the endless monitoring starts to rob people of their sense of independence, freedom, and dignity."

Some of the hardest decisions for family members and other caregivers concern patients in that grim area between mild cognitive impairment and severe impairment—especially when finances are involved, since the ability to handle money is often one of the first things to go. "I spend a

access to it; we'll be able to work with it and publish with it and use it to do collaborative studies as well as individual studies."

"We wanted to develop the infrastructure [of the CNDR] because we want to study the brains of patients with the disease," says Lee. "So how do you get the brains? John is a doctor, but he's a neuropathologist. He doesn't see patients. So we said, 'OK, we've got to collaborate with a neurologist and also other individuals like psychiatrists that see these patients.'"

Not that those colleagues are complaining. Steve Arnold, a professor of psychiatry and neurology and director of the Penn Memory Center, cites the combination of "extraordinary talent," the "vibrant, open-source atmosphere," and individual collegiality as a key reason behind the success of the Alzheimer's and other neurodegenerative-disease programs at Penn.

"It's very easy to find people who are interested in the same types of things that you're interested in, and who are happy or eager to collaborate and work with you," says Arnold. "The collaborative atmosphere is really great—unlike some other institutions, where people are so balkanized."

"We've got a great group here that represents a lot of the areas—from genetics to drug discovery to model organisms to everything in between," adds Gerard Schellenberg, professor of pathology and laboratory medicine (see sidebar on p. 40). "It makes for a really great critical mass."

All told, there is enough concentrated scientific and organizational brainpower here to blow the plaques and tangles of Alzheimer's and its neurodegenerative relatives out of the water. Just when that will happen, of course, remains to be seen.

"Sometimes in any given year progress seems incremental," says Schellenberg. "I mean, we haven't cured the disease. We don't have a drug treatment yet. But we know so much more. When I started 30 years ago there were no drugs being tried. And then we had one drug approved. And now there are large numbers of drugs in trial, based on the knowledge that was generated by academic groups. So there's been a payoff in knowledge in terms of getting stuff into clinical trials."

Recently Trojanowski, Lee, and a number of their Penn colleagues put together a proposal for a series of Comprehensive Alzheimer's Disease Centers around the country that would serve as kind of ramped-up CNDRs. Trojanowski envisions four or five of them (including one at Penn), each conducting "multidisciplinary patient-oriented clinical and basic science research" to improve understanding of and treatments for Alzheimer's, Parkinson's, FTLD, ALS, and vascular dementia "in the most cost-effective and efficient manner possible." While each center would cost an estimated $20 million a year, Trojanowski and his colleagues argue forcefully that the results would lead to very significant savings in the cost of national healthcare.

"I've circulated that proposal to a number of donors and elected officials," says Trojanowski. "I've met with [US Senator] Bob Casey and shared it with him. It's something I'm willing to talk to anyone about and to push forward, but it's so far unfunded."

THE value of having Lee and Trojanowski under one roof—the Maloney Building by day, at home in Center City Philadelphia—may be impossible to gauge by any known metric. But the synergy is undeniable.

"We talk science all the time," says Lee. "I mean, it's a lifestyle. It's what we do and part of our life. Even in a restaurant or on a plane or whatever, if I have an idea, I say, 'What do you think about this?'"

They met in a Boston bar in 1976, when she was a postdoctoral fellow at Children's Hospital Boston and he was about to begin his first residency at Harvard.

lot of time trying to help family members work through the issue of *What choices do I give my relative?* versus *What choices do I take away?*" Karlawish says. "The financial-services industry has woken up to the fact that they're on the front line of screening for Alzheimer's disease, and they're beginning to fumble around with how to restructure the way they deliver services and work with elderly clients—so that they're allowed to have the independence to manage their money, but that we minimize the hazards that can occur when people begin to lose those abilities."

Another knotty issue is voting, and Karlawish has led several studies into the ethics and practical concerns surrounding it. While no one wants to see someone in the far-gone stages of Alzheimer's pushed into a voting booth by an unscrupulous ward leader, tests have been developed that can gauge a person's competence, and denying someone with a mild form of Alzheimer's the right to vote is equally troubling.

"We want people who want to vote to be able to vote in a way that is fair and free and un-coerced," says Karlawish. "We have now three studies that show that the majority of long-term-care residents need assistance. So the issue is how to properly assist them. That's the approach taken in Canada."

He argues forcefully that the US needs to develop a "robust national system of mobile polling," one that is sensitive to local needs and laws, and adds: "We need to start to have long-term-care leaders and facilities partner with elections officials to develop mobile polling, to get elections officials into the long-term-care facilities to conduct the balloting, and take it out of the hands of well-meaning but frankly overworked and undertrained long-term-care staff."

One study in Vermont nursing homes showed that mobile polling "reduces an enormous amount of staff worry and concerns," says Karlawish. The practice "minimizes disenfranchising people on the basis of deciding that they can't vote," and also "minimizes fraud. And most pointedly, the nursing-home staff and the elections officials both agreed that it really maximized the dignity and quality of life of the residents. These elderly residents sort of felt like they were back and part of the world again, voting like everyone else does."

Having spent 10 years on this issue, starting in the wake of the 2000 presidential election in Florida, Karlawish says he's come to believe that it's not only about voting "but about a deeper, larger issue, which is, what do we mean when we say 'We the people' in the United States? I like to think that persons with dementia are still part of 'We the people.'"

With its strengths in Alzheimer's research and in bioethics, Penn is the ideal place to examine these issues, he adds. "It's a perfect blending of mentors, resources, and a university environment that was welcoming—saying that we can ask questions of bioethics about the science of Alzheimer's disease."*–S.H.*

"John walked by and I opened my mouth and said, 'Haven't I met you someplace before?' not knowing that it is a classical pickup line," she told *Nature Medicine.* It turned out that they had indeed been in the same seminar a couple of years before.

Her voice still carries a trace of an accent from her native China (she was born in the southwestern city of Chongqing), though she has moved around so much that the phonology of her English would probably stump most experts. She studied at the Royal Academy of Music in London, earned her master's in biochemistry from the University of London and her PhD in biochemistry from UC-San Francisco, and spent a post-doc year at the University of Utrecht and five years in experimental pathology at Harvard Medical School. Then came a restless year at Smith Kline & French (now GlaxoSmithKline), from which she came to Penn's School of Medicine in 1981. By then Trojanowski had given up a promising post at Massachusetts General Hospital to follow her to Philadelphia.

Both Lee and Trojanowski have reputations for being outspoken, even blunt, as well as for having very high standards. "Their scientific fights are legendary and public, but productive," *Nature Medicine* noted.

When I mention that assessment to Lee, she doesn't bat an eye.

"The thing is that, if you're married, and if you cannot treat each other as colleagues when you actually work professionally, then it just won't work," she says. "If I don't agree with him, I have to say so. And if he doesn't agree with me, he has to say so, too. But because we are married, I can be even more honest with him with my opinion. Whereas if I don't want to offend a colleague, then I might not be so upfront, so blunt and honest about everything."

As she talks about the personal side of their relationship, I notice, even her body language softens.

"We actually have a great time working together," she adds. "We really have a very special relationship where we do enjoy each other's company, as well as from the work point of view and also from just being married and living together. I mean, I don't know how we did it. But I think it's amazing. People are even more amazed because we share the same office at home. Even though we're together 24/7, I want to be with him all the time."

A few minutes later, Trojanowski knocks on the door and enters, all six-foot-three of him. After Lee fills him in on the ground we've covered, he suddenly emits a high-kilowatt scowl: Apparently she hadn't sent him some information he needed before an important meeting.

"You were supposed to send me that email!" he says, glaring with those cavernous eyes in a terribly accusing way. Then he fires a really robust barnyard epithet at her. This is great theater—*Mom and Dad are fighting! In front of company!*—and I sneak a peek to see how Lee is responding.

Turns out this brilliant, high-powered, no-nonsense scientist is giggling like a high-school senior who just got her boyfriend in trouble by sending him an inappropriate text message in class. Thirty seconds later, as best as I can tell, both of them have completely forgotten about it. If they ever bag science, they could go into business as extreme marriage counselors.

"They clearly have between them a very unique marriage and relationship," says Kurt Brunden, scientific director of the Ware Alzheimer's and Benaroya Parkinson's Disease Drug Discovery programs, with a laugh. "It's one that wouldn't work for everyone, but it seems to suit them just fine. They're pretty much 24/7 when it comes to science. They're not shy about disagreeing with each other in public, but they never seem to hold a grudge. They'll have at it, and the next day it's another day.

"I think in general it takes a certain type of person to work under them here at the center, because you have to have a little bit of a thick skin," Brunden adds. "Just as they talk to each other, they'll often talk to others with that same kind of general directness. But they've been great to me."

The very talented people they've assembled clearly like working for and with them.

"They have high standards, but they're also extremely caring and supportive," says Vivianna Van Deerlin, associate professor of pathology and laboratory medicine and director of the molecular pathology lab at HUP. "So if you demonstrate to them that you're motivated, you're hard-working, and you're contributing, they will support you." That support might take the form of referring a junior colleague to speak or present at meetings, or designating them as senior author on a journal article. Those trainees who can "maintain a high level of effort and dedication," she adds, "will be rewarded with a strong foundation in analytical thinking and research skills."

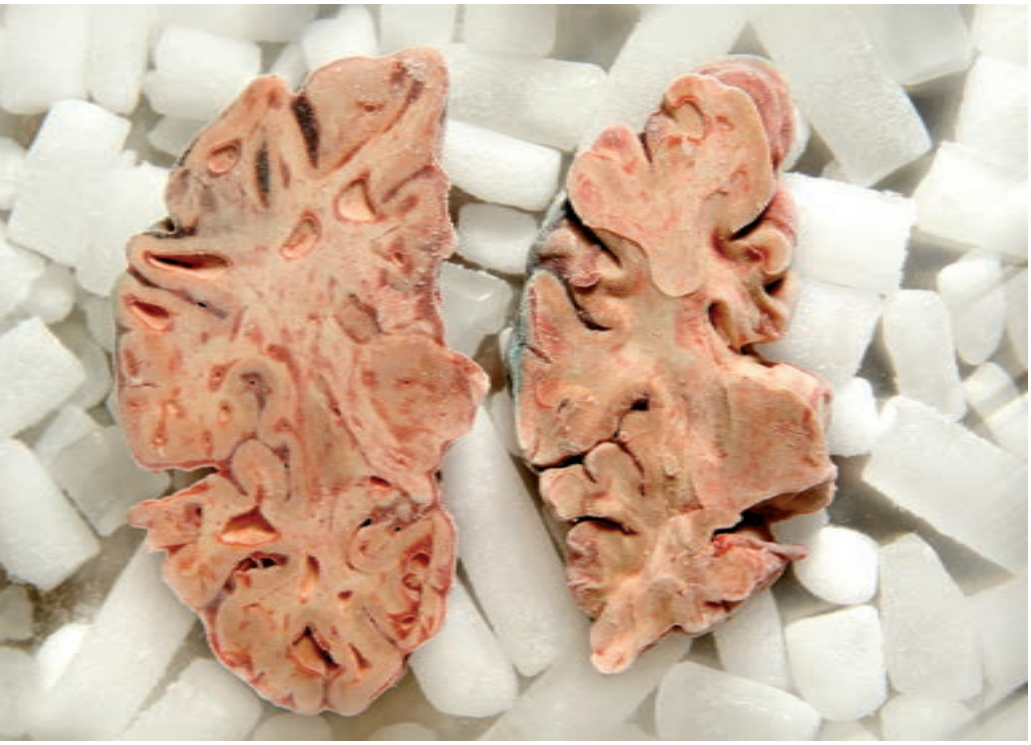
Like others, Van Deerlin cites a certain professional generosity about Lee and Trojanowski. "They don't hog things. I mean, they're careful, fiscally as well as with samples. But they're very, very collaborative, not only with our own program but also nationally and internationally."

Beth McCarty Wood, a genetics counselor in the CNDR, cites another kind of support, one that concerns patients and their families.

"Occasionally I'll get a phone call out of the blue, and it'll be from John, and he'll tell me he just spoke to a family, and that he himself went over their autopsy results and the issue of genetics came up, and he felt it would be very important for them to talk to me," she says. "And he immediately initiated getting me and the family in contact with each other. It wasn't an email; it wasn't a passing note in the hall. It was an immediate phone call to let me know, 'Beth, this is a family that has questions, that needs help. Can you please get in touch with them as quickly as possible?'"

TAU tangles or amyloid plaques. Pick your poison. Of the many advances in Alzheimer's research to which Penn scientists have contributed over the last 20 years, none, arguably, has been as significant—or involved as much perseverance—as the efforts by Lee and Trojanowski to move the focus of research back in the direction of tau. They were the first to discover, back in 1991, that the tangles in Alzheimer's were formed of tau proteins, and they have continued to make important discoveries in that area despite a movement toward research involving beta-amyloid plaques.

"There used to be a joke back in the '90s that it was a religious debate," Kurt Brunden is saying. "You had the Baptists—the beta-amyloid peptides—versus the tauists, right? John and Virginia have always clearly been in the tauist camp. John I would say is a pure tauist. Virginia is a tauist with an acceptance of the Baptist religion. She recognizes that the amyloid beta does play a role—and John grudgingly so, probably. But they were clearly at the forefront of the tau ideas.



What's Lost: a healthy brain slice (left) and one with Alzheimer's.

"Back in the '90s, or even the late '80s, they were fighting an uphill battle, because everyone at the time was focusing on a-beta peptide," he adds. "And in the scientific community, to persevere, sometimes you have to have some thick skin to keep selling your point when the others are naysayers."

Tau's main function in the nerve cell is to assemble and stabilize microtubules, which can be likened to train tracks or interstate highways in the way they allow proteins to be transported within the cell. Each neuron has an axon, a long fiber that conducts electrical impulses that act as messages, sort of like a fiber-optic cable.

Back in 1994, "John and I hypothesized that because tangles form in nerve cells, perhaps that kicks tau away from its normal function, which is to stabilize the microtubules," says Lee. "If the microtubules—that interstate highway—collapse, then soon no transport occurs. And then people in the small town will starve to death, right? So if the microtubules stop working, eventually the axon will collapse, and then the neuron will die. So we thought, 'OK, if you can stabilize this microtubule, maybe you can retard the degeneration of the nerve cells.'"

But tau and its tangles got short shrift for a couple of reasons. For one thing, the gene that produces beta amyloid—the APP, or amyloid precursor protein—had already been discovered in 1984, giving researchers something very tangible to work with.

"Families have mutations on the APP gene that are inherited," Lee explains. "You have two copies of your gene; you get one bad copy from either of your parents, and you will get the disease. So that's huge in terms of implicating that pathway, or that protein, in a disease."

Furthermore, while nobody was denying that tau was the stuff of tangles, tau aggregates were found in the brains of patients with other, non-Alzheimer's neurodegenerative diseases as well. That led some to argue that the tau tangles were a reaction to beta amyloid, not a primary cause of Alzheimer's. Even when tau mutations were identified in patients with frontotemporal lobar degeneration (FTLD), proving that tau tangles alone can cause a neurodegenerative disease, notes Lee, "people say, 'Fine. But that's a different disease.'"

As a result, researchers in the academic community and in the pharmaceutical industry "would rather focus on beta amyloid," says Lee. "Because so many people are working on the biology of APP and also the production of beta amyloid, we know a lot about the process of amyloid production. We know the identity of the enzymes. And when you have enzymes, pharmaceutical companies are very, very happy. They can inhibit these enzymes and see whether they can reduce production of beta amyloid."

But, she adds, "they're having a lot of problems with that approach." In one clinical trial that began in 2000, patients developed complications; some died of Alzheimer's. And yet when pathologists examined their brains, "the amyloid, by and large, in specific areas, are cleared." In other words, they succeeded in getting rid of the amyloid plaques—but it hadn't done any good.

"We now realize that Alzheimer's disease actually starts very much earlier than the symptoms appear," she says. "So you can get rid of plaques. But the reason the patients are not improving could well be because the [tau] tangles are already there, and they're not going away. They're really targeting the neurons to die."

One result of that "Baptist" dominance was that whenever an Alzheimer's conference was held, nearly all of the sessions were "filled with people studying beta amyloid or APP processing and so on," says Lee. "So the amount of funding, the number of scientists that work on beta amyloid versus tau, is like 10 to one.

"Science is like anything: there's fashion," she adds. "People have the mass mentality."

"There's over a billion dollars that pharma is spending on clinical trials," says Trojanowski. "But almost all of them—hundreds of them—are focused on a-beta. I think three or four are focusing on tau. A-beta was a good bet, a very popular target, beginning 10 years or so ago. But there's been some dramatic failures of clinical trials that put into question the a-beta cascade hypothesis, which explains all Alzheimer's disease by virtue of the accumulation of a-beta. And while we acknowledge the importance of that hypothesis and the benefits that may accrue from shutting down a-beta," those benefits have not yet occurred.

"We have made the case for years that there should be an equal investment in tangles as targets for fundamental research, but also for drug discovery," he adds. "Companies are beginning to see the wisdom of going after tau pathology with drugs."

CANDACE DICARLO

CROSSING THE **VALLEY OF DEATH** WITH BIG PHARMA

Last March, an agreement designed to generate new drug candidates for Alzheimer's disease was announced. One of the partners was AstraZeneca, the global pharmaceutical firm. The other was Penn, specifically the Center for Neurodegenerative Disease Research (CNDR). A press release from Penn Medicine noted that the CNDR "will provide rapid access to unique state-of-the-art drug compound screening assays and knowledge of the biology of tau," while AstraZeneca's scientists will supply "basic research with access to the technologies and skills required to discover and develop new drug molecules."

Each party has a lot to offer the other in the way of skills and resources. If successful drugs emerge and become financially successful, both parties will benefit in terms of royalties and milestone payments. More important, patients will benefit.

"I really think this is one of the models for the future," says Virginia Lee, "particularly in view of the reduced funding from the government and for academic research."

Which isn't to say there won't be any raised eyebrows at the notion of a prestigious private university partnering with Big Pharma.

"If I had the cure for Alzheimer's in my pocket right now, it would go nowhere," John Trojanowski responds. "I don't have the resources to take that forward and carry it through all the steps required for FDA approval, so it can be a drug made available to clinicians. We have to form partnerships to succeed in the mission of finding cures. That can be done in an ethically correct way, with integrity, and to the benefit of the public."

The agreement with AstraZeneca was one of the things envisioned back in 2004 when the Marian S. Ware Alzheimer Program was launched at Penn Medicine, sparked by a $6 million gift from Marian S. Ware, a longtime supporter of the University and advocate for medical research and Alzheimer's treatment. The three-pronged program, which also involved the School of Nursing, focused on drug discovery, clinical research, and care management for Alzheimer's patients.

In the past, the model worked like this: a university would do the basic research, which mostly involved identifying specific molecules to be targeted, explains Lee. "And very quickly academia would hand that over to a biotech company, generally funded by venture capital. They would then develop an assay. They do drug discovery [and] drug development.

"Often, once the biotech reaches a certain size, and if they have some really good product, they would be bought by a pharmaceutical company," or the two would form a partnership, she adds. "They would then complete the later-stage clinical trial, and then lead to FDA approval."

But in the last 10 years or so, for a variety of reasons, the number of biotech companies has shrunk, and the pipeline for developing drugs has dried up alarmingly. The result was what researchers call the Valley of Death for drug development. And lo, into that valley comes the research university.

"We've expanded to fill this void and do all the drug discovery, and also to do the preclinical studies," says Lee. "And I think it's fair to say that we can actually extend all the way and interact with pharmas as well."

Kurt Brunden, the scientific director of the Ware Alzheimer's and Benaroya Parkinson's Disease Drug Discovery programs at Penn, began his career at the University of Mississippi Medical Center, then moved to Gliatech, a startup biotech company (whose board of advisors included Virginia Lee), becoming vice president of research. From there he went to Athersys, a clinical-stage biopharmaceutical company.

But by 2007, "pharmaceutical output and productivity were very low," he says, partly because of a more cautious approach to drug approval by the FDA, and also because of various "productivity issues within the companies." Waves of mergers and reorganizations didn't help; neither did the financial crisis. The bottom line is that US-based pharmaceutical companies have laid off more than 100,000 people in the last few years.

When he heard about the Ware program, Brunden found himself "quite intrigued by this concept of, in essence, starting what could be thought of as an academic biotech company here at Penn"—even though, historically, drug discovery "is not what academics have done," mainly because of the multiple disciplines involved and the need for a large "critical mass" of scientists and financial resources. As a result, "it's only the more prestigious centers that have the kind of infrastructure and the ability to draw these types of funds that are going to succeed.

"But I do think that there is a place for academic drug discovery, particularly given the current trends in the industry," he adds. "The idea is not to compete with Big Pharma, because that would be suicide for a group our size. It's to complement Big Pharma's efforts, and hopefully facilitate some of the things they're trying to do."

"Ware enabled us to get our drug-discovery program launched," says Lee. "Without that we would never be able to be where we are right now."

Having developed molecular targets and developed assays, she adds, "we want to move some of the preclinical studies further along so we can partner with a pharmaceutical company, which will have much larger resources, to get this into clinical trial."

Over the past 20 years, the CNDR has developed "a vertical integration for drug discovery," she says, which includes "all the models and assays we have developed—mouse models, cell-based models." The drug-discovery program can draw on all that to "identify small molecules that may be the first generation of therapeutics for the treatment of Alzheimer's disease.

"Drug development is really very, very expensive," Lee adds. "And what we have that is unique is the collective knowledge and resources—in terms of human brain samples and all the knowledge we gain from genomics and from biomarkers, from pathology, from patient information—as well as all the things that we do in the laboratory. They are all interconnected. And all of this information is fed into our drug-discovery program"—at a fraction of the cost that would be incurred by a pharmaceutical or biotech company.

The important thing is that "everything has to be done aboveboard," she adds. "All of the deals, like the AstraZeneca deal, go through the Center for Technology Transfer, and then the money is handled by the University.

"So these are important experiments that we are doing now," she adds. "We're really pioneers in developing this type of structure, in collaboration and partnership with pharmaceutical companies. And I think that it's absolutely essential to do that if we want to treat diseases."–*S.H.*

THE FIRST DRUG that Trojanowski and Lee proposed to replace the lost tau was Taxol, a cancer drug that binds microtubules and thus blocks mitosis (cell division).

"We actually had a patent issued in 1996 for Taxol, and we showed Taxol did work in a mouse model," says Trojanowski. "But we couldn't improve its pharmacology so that enough got into the brain to be a usable drug."

So, with the help of Amos Smith, the Rhodes-Thompson Professor of Chemistry, they tried something else: another family of microtubule-stabilizing drugs called epothilones. One in particular, epothilone D, has worked in mouse models, and can cross the blood-brain barrier. The only catch is, somebody else has the patent on them.

"Unfortunately for us, there's a small company, Kosan, that owned the intellectual property for epothilone D," says Lee. "It was bought by Bristol-Myers Squibb two years ago. And they are quite aware of our work."

As a result, "we at the University may not make a gazillion of dollars," she adds. "But it's OK, if we're going to help people. So we are actually working with Bristol-Myers Squibb to try to help them with the clinical trial. They're very happy with our results."

"We now realize that Alzheimer's disease actually starts much earlier than the symptoms appear," says Virginia Lee. "So you can get rid of plaques. But the reason the patients are not improving could well be because the tau tangles are already there, and they're not going away. They're targeting the neurons to die."

"We're pleased and proud that what we had conceptualized and proposed as a therapy is going forward," says Trojanowski. "The experiments with epo D in mice were our experiments. We did them. Bristol-Myers Squibb has done them as well." It's always possible that epo D "could crash, like other therapies, but at least it will get its day in court, if you will, in a clinical trial," he adds. "So that is very, very exciting. If it's successful, it will hopefully bring more stakeholders—pharmaceutical companies, biotechs—into the game."

OF course, there is always the possibility that researchers at Penn or elsewhere will discover a new dimension to the problem. Steve Arnold, for one, wonders whether both amyloid and tau are "secondary to something else" in the more common, late-onset forms of Alzheimer's.

"That worries me, that there's some kind of change in the way older cells handle misfolded proteins," he says. "I think that proteins misfold all the time, and we have a whole waste-clearance system for getting rid of them. And that changes with time. And I wonder whether the common forms of Alzheimer's disease are essentially a waste-management problem, that the cell can't clear the misfolded proteins, and it starts to choke on itself."

Some epidemiologic studies show that "about 10 percent of people have a head full of plaques and tangles, severe pathology in the brain, and yet they're not demented," Arnold points out. "And on the other hand, you have maybe 10 percent or 12 percent of people whose brains are clean of pathology, and yet they're very demented. So there are other biological factors going on that seem to determine this."

One possibility is that some people are simply "more resistant to the toxic effects of plaques and tangles," he adds. But there could be other explanations. One, believe it or not, involves insulin.

"It looks as though there are major abnormalities in insulin-signaling in brain cells," says Arnold. "One hypothesis that we're following up is that amyloid-beta oligomers [two or more conjoined molecules] actually damage the ability of insulin to signal. Some people have referred to Alzheimer's disease as Type III diabetes. We have to flesh this out, but given how much we know about diabetes—and much of the knowledge coming from the diabetes and metabolism people here at Penn—it opens up new therapeutic avenues to think about. In Alzheimer's we're talking about insulin resistance in the brain. Can we use some of the same medicines that are being developed to sensitize insulin receptors to perhaps prevent or slow down Alzheimer's disease?"

In the meantime, assuming that tau and beta amyloid are still among the usual suspects, the key is to discover their presence in the brain as early as possible. Hence the importance of biomarkers.

This past October, the NIH announced it was expanding the Alzheimer's Disease Neuroimaging Initiative (ADNI), a public-private partnership, to find biomarkers for Alzheimer's. This phase of the study will involve 550 volunteers "in the earliest stages of cognitive impairment," said National Institute on Aging Director Richard Hodes, and "should give us new insights into the onset and progression of Alzheimer's disease."

"If you're trying to come up with a molecule or drug that diminishes the formation of senile plaques, ideally you want to get into the patients a decade before they show dementia, because that's when senile plaques are formed," says Kurt Brunden. "One of the clear potential advantages of tau-based therapy is that it appears that the tau tangles form later in the disease, more in concert with the onset of dementia. Unlike the plaque-based therapies, you can probably treat with a tau-based agent at an early stage of the disease—but one that at least is diagnosable at this point—and still have an impact. That's our hope."

ODDLY ENOUGH, tau was the first component of Alzheimer's that could be identified as a potential biomarker, says Lee. That was back in 1995.

"We and others have shown that you can look at the level of tau in the spinal fluid and be able to distinguish between patients that have Alzheimer's disease and the control group," she says. "Then, later on, in the late '90s, it was shown that the beta amyloid, too, could be a biomarker for Alzheimer's disease." But it wasn't until two years ago—thanks to a great deal of work by Les Shaw, professor of pathology and laboratory medicine and co-director of the Penn ADNI Biomarker Core—that an effective, accurate test measuring tau and beta amyloid in cerebrospinal fluid was standardized and validated, and the results published in *Annals of Neurology*. The test proved to be 87 percent accurate overall, and 96.4 percent accurate among those with autopsy-confirmed Alzheimer's.

"You have to have the right samples, with very careful longitudinal follow-up, to be able to compare the tau and a-beta in the spinal-fluid at baseline—when you actually complain of a

GENETIC DRAGNET

Early last month the International Genomics of Alzheimer's Project (IGAP) was launched, with the goal of discovering and mapping genes that contribute to the disease. Four groups from Europe and the United States are participating; one is the Alzheimer's Disease Genetics Consortium (ADGC), led by Penn's Gerard Schellenberg, professor of pathology and laboratory medicine.

Identifying those genes "will help lead us to the cause of the disease, identify proteins and other new targets for drug development, and provide genetic methods for determining which people are at greatest risk for Alzheimer's disease when preventative measures become available," says Schellenberg, who two years ago received an $18.3 million grant from the National Institute on Aging (NIA) to lead the ADGC's study to identify what he calls "susceptibility genes."

Back in 1995, when Schellenberg was at the University of Washington, he discovered a "very virulent" genetic mutation in a group of people known as the Volga Germans, whose ancestors had migrated from Germany to the Volga River region of Russia. The presenilin-2 gene wasn't just a risk but a direct cause of early-onset Alzheimer's, he explains. Knowing that his own family were Germans whose ancestors had moved to Russia, he "immediately went home and checked"—and found to his relief that they had migrated to the Black Sea, not the Volga.

His current research involves genes that may contribute to Alzheimer's risk, which he hopes will not only help identify people who are at risk of getting the disease, but also contribute to a cure.

"Genetics starts you down the pathway of generating knowledge," which then can be used to explore whether a gene is a good drug target, says Schellenberg. "And it does so in a way that's not dependent on previous pathways. Some of the drug discovery right now is the path that started with the neurophysiology of Alzheimer's disease," namely beta-amyloid plaques and tau tangles.

But finding the genetic mutations that lead to the disease requires casting a wider net than just the tau and beta-amyloid pathways. In recent years that net has been greatly expanded by technological advances such as a genotyping-array chip that allows researchers to "sample all that genetic variability in the human population," in Schellenberg's words.

"There are 30,000 genes, and I'm going to let genetics and nature tell me which ones are important for risk," he says. "I'm trying to generate new bases of knowledge, because so far we don't have a therapy based on tau, and we don't have a therapy based on a-beta. So if those don't work or don't give us the complete answer, we need new leads."

Finding a susceptibility gene "tells you that gene and that protein is important for the disease, but it doesn't tell you how," he adds. "So the next phase is to actually pursue the function of the risk genes we're coming up with."

The fact that 29 Alzheimer's centers across the country contributed to his most recent genetic study, which has 140 co-authors, makes him "incredibly happy with the way people are working together." Those findings show that "the more samples you have, the more genes you can identify," he adds. "And with this international collaboration, we should have over 20,000 cases put together."

Another example of collaboration was sparked by the NIA directing the centers to use standard measures to evaluate patients and put that information into a central data repository. "My role is to say, 'Hey, let's do genetics," Schellenberg says. "Let's get the DNA samples for all these people. The data's already centralized, and we'll get genetic data and mix it all together.'"

Vivianna Van Deerlin, who directs the molecular pathology lab at HUP, is in charge of some of the genetic testing performed at Penn. She points out that not all of those genes identified as risk factors or disease genes are available for testing in her clinical lab. Some genes are patented, which can limit her clinical lab from using "a particular gene for clinical testing, like presinilin-1 for Alzheimer's disease." (The controversial issue of private companies "owning" genes is a subject for another time.)

"We currently have clinical testing for tau and progranulin mutations available," which are used to confirm research testing results "or for families with a history of frontotemporal lobar degeneration who would like to have a clinical test performed to try to find an answer to their family's disease," says Van Deerlin. "For my research lab, which is separate from the clinical lab, our efforts are aimed at collecting a large bank of DNA samples, testing them for known gene mutations, and using the DNA samples for gene discovery."

memory impairment—to a year later, and determine the changes in your spinal fluid," explains Lee. All that standardization led to a test that can, by "looking at changes in the spinal fluid tau and a-beta level, predict whether or not you have converted, or you will convert, to Alzheimer's disease."

On January 20, the FDA conditionally approved a new PET-scan technique for detecting amyloid plaques in the brain. (Final approval is conditioned on the development of an effective training program for reading the scans.) The scan uses Amyvid (florbetapir), a radioactive tracer that was developed and patented by Penn and licensed by Avid Radiopharmaceuticals, a small biotech company based in the University City Science Center.

Avid, which was purchased this past December for $800 million by Eli Lilly, was founded six years ago by Dan Skovronsky Gr'00 M'01, and its chief scientific advisor is Hank Kung, a former Penn professor of radiology and pharmacology.

"Dan Skovronsky's original experiments were done in our laboratory, on this floor, and discussed in our conference room back in '98, '99," says Trojanowski. "Dan was a graduate student of Virginia's when he was doing this work. Then, while training with me in neuropathology, he went on to start Avid, which raised $70 million, which enabled him to hire 60 people over on Market Street. So when people in Congress discuss budgets, they should be mindful that some of the things we do not only have an impact on health and lowering the cost of healthcare, but also generating new industries such as Avid Radiopharmaceuticals, which has been a blockbuster success.

"In other words," he adds pointedly, "creating jobs."

After someone with a "strong family history sees one of our collaborating neurologists," she explains, "we usually first screen for mutations in known genes associated with the disease. We can then make correlations with the clinical data, the biomarker data, the neuropathology data. Together, that information provides a complete picture of the disease, which can be used to improve diagnosis and prognosis, and eventually therapy."

In order to integrate all that genetic, clinical, biomarker, and neuropathology data, "it was necessary to design a novel integrated database," Van Deerlin notes. "We hope that this database, which continues to develop and grow, will some day be directly linked to the patient's medical records to maximize its utility as a research tool." Even now, their "bank of really well-annotated samples" of DNA, RNA, plasma, and CSF" (cerebrospinal fluid) is linked to extensive clinical and family-history information.

Finally, "while it's not pleasant to talk about people dying, we have autopsy confirmation for a large number of those who do die of the disease, as well as autopsies of normal controls," she adds. "Controls are one of the hardest things to get, but also one of the most important—many of our discoveries are enabled by normal individuals dying and contributing their brain."

According to Beth McCarty Wood, a genetics counselor with the CNDR, Alzheimer's patients and their families "have become much more interested in genetics" since she began working there seven years ago. "People are really interested in any kind of testing that can better explain why they or their loved one got the condition, as well as determining the risk for other family members to have Alzheimer's disease or FTD.

"We're very fortunate that our patients have been highly motivated to help the research center," she adds. "Genetics can sometimes seem sort of scary. If people don't understand exactly how the research is being done, it might not be something that they think of getting involved in."

The knowledge gained from genetics now goes beyond just getting or not getting the disease. Last year, David Wolk, assistant professor of neurology, led a study that broke down the ways that the APOE-e4 gene, a known risk factor for Alzheimer's, affects patients with even mild forms of the disease. Those who had that form of the gene performed worse on memory tests and had more prominent abnormalities in brain regions critical for memory than those who didn't. But those with mild Alzheimer's who *didn't* have that variant performed worse on tests of attention, language, and executive function, a result borne out by more prominent abnormalities in the brain regions critical for those abilities.

Once preventative options are available, "the whole field of genetics and neurodegenerative conditions will be greatly impacted," says Wood. "Right now, if someone knows they're at risk for a gene mutation that causes the disease, the only reason to get tested is for [their] own personal reasons, whether it's making decisions about children or about retiring. But once there's a medical option we can give them, to delay progression of the disease or to prevent the disease entirely, we're going to see many more people wanting to have genetic testing to determine their risk."*–S.H.*

TWO months ago, President Obama signed the National Alzheimer's Project Act (NAPA) into law. It creates, in the words of a statement by the Alzheimer's Association, a "coordinated national strategy to confront one of America's most feared and costly diseases," one that "will only plague more baby boomers as they age."

Using the recommendations of the Alzheimer's Study Group—an independent, bipartisan panel that will evaluate the government's current efforts to combat the disease—NAPA will produce a national strategic plan to confront the epidemic and establish an inter-agency council to work with the Department of Health and Human Services to give a full assessment of what needs to be done to cope with the disease on multiple fronts, including care, research, and support.

"I think it's good news, in terms of expecting or hoping that there may be an increase in funding," says Lee. "But at the same time, our economy is not good, and it's unclear whether there would be an appropriation of funds for this effort. So it's all very well that Obama signs this bill. But without funds or ways in which we can implement what is in the bill, it's really purely symbolic."

"You could be cynical, or maybe realistic, and say it's not going to have much of an impact, but I think it's a big step forward," says Trojanowski. "It's symbolic right now, but I'm hoping that someone who occupies the office of the Alzheimer's czar would know a lot about Alzheimer's, wouldn't just be a political hack and keep the seat warm, and would be an eloquent bully, a fear monger, seductive, cajoling, to do what I think this country absolutely has to do to see Alzheimer's disease for the epidemic that it is, to save our country from financial disaster."◆