

anniversary

By Thomas W. Durso

It is the most common type of dementia, affecting 4.5 million Americans.

It is a truly devastating disease, one that mercilessly robs its victims of their memories and cognitive capacity while forcing their loved ones to watch helplessly as they gradually lose the ability to function on a daily basis.

It costs the county more than \$100 billion per year. If current models hold, the number of sufferers and the cost to treat them could quadruple in the next 40 to 50 years.

Yet when the world's foremost Alzheimer's disease researchers and leaders in the field met in Tübingen, Germany, in November to commemorate the centennial of the disease's discovery, the prevailing mood was one of optimism. That was the view of John Q. Trojanowski, M.D., Ph.D., G.M.E. '80, director of Penn's Institute on Aging and of the Alzheimer's Disease Center.

"We have now been at work for 100 years trying to solve Alzheimer's disease," says Trojanowski, the William Maul Measey-Truman G. Schnabel Jr., M.D., Professor of Geriatric Medicine and Gerontology, who was an invited participant at the gathering. "You could write off the first 50 or 70 years of that as having been modestly effective in advancing understanding. The last 20 years have been a phenomenal success. . . . There really has been a revolution."

In 1906, Alois Alzheimer, a German psychiatrist, presented his findings on a patient, Auguste D., whom he described as having suffered from an unusual brain disorder of the elderly. The woman had

died earlier that year in her mid-50s, and what Alzheimer discovered when he examined her brain were the plaques and tangles emblematic of the disease that now bears his name.

"Alzheimer: 100 Years and Beyond" celebrated the achievements of the last century and featured presentations on the latest developments in virtually every aspect of the disease. Among the scientists who presented were Trojanowski and Virginia M.-Y. Lee, Ph.D., M.B.A. '84, professor of pathology and laboratory medicine, the John H. Ware 3rd Professor in Alzheimer's Research, and director of Penn's Center for Neurodegenerative Disease Research. Trojanowski and Lee, who are married, together have written numerous well-regarded papers on neurodegenerative diseases.

From Alzheimer's discovery in 1906 until the early 1980s, "things were being done, . . . but not very much," says Trojanowski. "The beginning of the molecular era was probably 1984, with the Glenner and Wong discovery of the amyloid beta peptide that forms the plaques in Alzheimer's disease. That put a molecular face on a pathology. It was like finding the virus that causes AIDS or the prions that cause mad cow disease."

Beginning with that discovery, researchers have spent the last couple of decades honing findings on Alzheimer's to the extent that what has been learned through basic science is now being translated to drug discovery.

"In 1984, when this discovery was made, there were no disease-modification

therapies," Trojanowski notes. "Now there are 60 clinical trials of drugs that are directed at various targets in the disease pathways. Maybe it'll be our bad luck that none of them will work, but I can't believe that will be the case."

Trojanowski was by no means the only scientist at the centenary conference to exude such optimism.

"All of us went there mindful of the

TAKING THE INITIATIVE AGAIN

Established in 2004 through a gift of \$6 million from Marian S. Ware, a longtime supporter of the University, the Marian S. Ware Alzheimer Program is a set of collaborative initiatives between PENN Medicine and the School of Nursing to advance drug discovery, clinical research, and patient care related to Alzheimer's disease. The drug discovery initiative seeks to identify novel compounds that may prevent or ameliorate the onset or progression of Alzheimer's disease.

Heading drug discovery for the program are John Q. Trojanowski, M.D., Ph.D., G.M.E. '80, and Virginia M.-Y. Lee, Ph.D., M.B.A. '84, both of whom were invited guests at November's centennial observance of the discovery of Alzheimer's disease in Germany. According to Trojanowski, "Many of us feel there's enough information now, which is very different from 20 years ago, to be very deliberate in pushing drug discovery." At this point, he



At the conference commemorating the centennial of the discovery of Alzheimer's disease, one Penn representative finds that optimism prevails.

Last fall, Virginia Lee and John Trojanowski visited the home of Alois Alzheimer as part of the centennial celebration. A plaque honoring Alzheimer is visible behind them.

opportunities and of the progress that has created these opportunities," he says. "We were full of enthusiasm that in our lifetime serious drugs with the possibility of modifying the disease's onset and progression will emerge. For scientists that is exhilarating." He concedes that treatment for Alzheimer's disease has not reached the stage of AIDS treatment yet, "but I remember the AIDS epidemic at the very

beginning, and the sense of pessimism that it would be a long time before therapies were developed. Now people are living longer and longer" with the virus.

Actually, people are living longer and longer, period, which helps to explain why treating Alzheimer's disease is so important. In the century since the disease was discovered, life expectancy has risen from about 50 to the mid-to-late 70s. Alzheimer's once was a rare occurrence simply because people did not live long enough to develop it. No more.

As Trojanowski observes, "This is what has gotten many people's attention – not just the scientists in the room, but also politicians, demographers, sociologists, and so forth. If you think about 20 million people who for 10 or 20 years will need caretakers to take care of them, that will be an enormous cost."

And so, according to Trojanowski, therapies that delayed onset of Alzheimer's by as little as half a decade could have enormous benefits, in terms of both "the human price" and the enormous costs of treating those with the disease. "There are models that show you would reduce incidence and prevalence by 50 percent."

The key to delaying the onset of Alzheimer's, Trojanowski notes, is to determine the likelihood that it would develop in a person as early as possible. Once the disease takes hold, it is irreversible.

"We need to identify people before the nerve cells are gone. What was clearly something we all agreed at this meeting was important to do was to look for pre-antecedent markers of the disease so we

can identify someone age 40 or age 50 and say, 'You've got a 90-percent risk of Alzheimer's, and do this and this and this and take this drug.' There's a lot of interest in that."

While those who attended the conference spent a good deal of time looking forward, there was also considerable retrospection regarding Alzheimer himself.

"This guy was just a regular doctor," says Trojanowski, marveling. "He had the insight and the good fortune to be in the right place at the right time to make this discovery that was obviously of seminal importance. Maybe five years later someone else would have made the observation, but you have to give credit where credit was due."

Alzheimer "could have been off playing golf all the time," but instead chose to conduct research, using his wife's fortune to fund it. Those who study Alzheimer's today continue that legacy with "this sense of mission that this is such an important disease to do something about that we have devoted our lives to it."

"What I hope is that 100 years from now, we're celebrating the fact that hardly anybody remembers Alzheimer's disease," he says. As Trojanowski imagines it, this scenario could indeed happen if society decides to apply "all available resources" to curing the disease.

"There is reason for optimism, but we have to get our act together. We have to wake up and do something now, because the natural disaster that Alzheimer's disease will bring to our nation far exceeds Katrina or any other natural disaster you and I know." ■

FAST ALZHEIMER'S DISEASE

continues, "while basic science still should be supported to advance understanding, we all feel there should be a road map, increased efforts to try to translate insights into Alzheimer's disease into therapies. That will happen at pharmaceutical companies, but now universities are much more engaged in drug discovery."

In the Ware program, "We're trying to come up with targets that are 'druggable' and then trying to identify drugs that will hit those targets."

One promising approach makes use of a robotic system to screen tens of thousands of compounds for their ability to inhibit the formation of Tau fibrils, which Lee and Trojanowski believe play a crucial role in the development of Alzheimer's disease. The high-capacity screen produces many "hits," which are being evaluated and then chemically modified to produce potential candidates for clinical testing.