Are we close to conquering one of the most puzzling diseases of our time?

BY LINDA MARSA

More than a hundred years ago, German physician Alois Alzheimer did a grim postmortem analysis of the dementia-ravaged brain of one of his patients. He hoped to unmask the biological roots of her severe and rapid mental deterioration and bizarre mood swings.

Her name was Auguste Deter, and she was admitted to the Hospital for the Mentally Ill and Epileptics in Frankfurt in 1901. When Alzheimer first interviewed the 51-year-old woman, she was enveloped in a fog of confusion, and she exhibited delusional behavior: She was intensely jealous of her husband; she sometimes would start screaming, thinking people wanted to kill her; and she became wild and uncontrollable. She died five years later.

When Alzheimer examined thin slices of her brain under a microscope, he noticed that nestled right next to the labyrinth circuitry of healthy nerve cells were small clumps of hard, barnacle-like
The accumulation of spaghetti-like strands that choke the neurons. This disrupts the flow of electrical signals that travel through the nerve cells, ultimately causing them to wither and die. The buildup of twisted tau deposits also destroys surrounding nerve cells and eventually wastes away vast swathes of brain tissue. Other vital structures, the axons and dendrites—known collectively as neurites—that project from the nerve cells and send and receive messages are dependent on this neural transport network. When this network is disrupted by tau tangles, it can trigger a chain reaction of damage in the memory and cognitive circuitry of the brain, accelerating mental deterioration.

Amyloid and tau are both naturally occurring proteins. The body produces amyloid plaques and then eliminates them in a normal biological process of decay and renewal. In some instances, amyloids may even serve a protective function; recent studies indicate they can act as molecular guardians that mute the body’s immune reactions. They also mop up the errant cells involved in inflammation after an injury. But for reasons that are yet unknown, when Alzheimer’s develops, this protein divides improperly and creates a form called beta amyloid, which is toxic to neurons in the brain. When this happens, the brain generates plaques, which accumulate around the neurons and eventually disrupt the signaling system between brain cells.

Tau proteins, for their part, are vital to the structural integrity of neurons, acting like girders that stabilize synapses—the bridges that allow electrical impulses to cross between neurons. But at some point, tau goes astray, too, and the nerves lose their structural support, causing the cells to collapse and die. In fact, tau tangles may be the real culprits behind memory loss, since they’re dependent on this neural transport network.

A DEADLY CASCADE

We now know that plaques are clusters of protein fragments called beta-amyloid peptides. They collect outside the nerve cells in the brain and disrupt the signaling system between neurons, blocking them from relaying messages. This communication breakdown explains why Alzheimer’s patients suffer progressive memory loss, confusion and increasing difficulty doing daily tasks. In contrast, the tau protein wreaks havoc inside nerve cells, causing the accumulation of spaghetti-like strands that choke the neurons. This disrupts the flow of electrical signals that travel through the nerve cells, ultimately causing them to wither and die. The buildup of twisted tau deposits also destroys surrounding nerve cells and eventually wastes away vast swathes of brain tissue. Other vital structures, the axons and dendrites—known collectively as neurites—that project from the nerve cells and send and receive messages are dependent on this neural transport network. When this network is disrupted by tau tangles, it can trigger a chain reaction of damage in the memory and cognitive circuitry of the brain, accelerating mental deterioration.

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“Tangles drive the dementia and drive the nerve degeneration,” says Tanzi, who also is director of the Genetics and Aging Research Unit at Massachusetts General Hospital. “If you don’t get tangles, you don’t get the disease. Once tangles form, they spread like wildfire and keep spreading. It is the biggest gap neuron outward reading is, how does amyloid drive tangle formation?”

Scientists are beginning to find some clues, through genetic fingerprints and with technologies that allow researchers to watch plaques form.
Until recently, the only way to look at human plaques was by analyzing the brains of people who died from the disease—a challenge one scientist compared to looking at a car wreck and trying to puzzle out the accident’s cause. We can’t just simply peel away a living person’s skull to watch what happens in real time. But now, a crucial puzzle piece could lead to the development of therapies that can stop the disease in its tracks. It began in 2008, when Harvard researchers fingered the CD33 gene in a groundbreaking discovery. This microglial cell, which is a powerful marker for amyloids or tau proteins that trigger late-onset Alzheimer’s disease, about 40 percent of those diagnosed have this DNA variant. “Instead of cleaning up when neurons die, the microglia assume they’re under attack when they see too much cell death and kill nerve cells as collateral damage,” says Tanzi, who led the research team. “It is now clear CD33 is the main switch that triggers the microglia to change from a neuroprotective to a neurotoxic function.”

Finding a compound to block this rogue gene and turn it off, he believes, could stem the damage inflicted by the amyloids.

In fall 2013, Tanzi’s group made what has been hailed as a “paradigm-shifting” genetic discovery that helped settle the debate over whether it’s amyloids or tau proteins that trigger late-onset Alzheimer’s. After conducting experiments with an animal model, the team discovered that mice that are good surrogates for Alzheimer’s, they found that a gene called ADAM9 makes an enzyme called alpha secretase, which prevents the formation of beta amyloid. But the mutant form of the ADAM9...
gene did exactly the opposite: It blunted the action of the enzyme, resulting in the production of more of the toxic proteins. “People with this gene mutation usually get Alzheimer’s at around age 70 because of the buildup of amyloidous due to the reduced activity of the protective enzyme,” says Tanzi. Researchers are now testing modulators of these enzymes in the lab to see if they can fix this and prevent plaque production.

But it’s not just the bad actors that are being fingered. Researchers have also uncovered snippets of DNA that seem to halt the development of the brain disease, even in people whose genes put them at higher risk. Icelandic scientists studying the DNA of 1,795 of their citizens unearthed a rare errant gene — only 1 in 10,000 people of European descent carry the mutation — that slows production of plaques in the brain. They found that people who were 85 or older and didn’t have Alzheimer’s— or any decline in mental acuity, for that matter — had the mutant gene four to five times more often than those who had the disease. What the researchers found especially astonishing is that this was true even in octogenarians with two copies of the APOE-4 gene, which is present in about 90 percent of 80-year-olds with Alzheimer’s. About 25 of the people over age 85 had two copies of APOE-4, yet not one of them had the disease.

The next step is to figure out how the protective gene works and then develop a treatment that mimics its action. Accomplishing that feat would represent a giant leap toward a genuine cure. “The gene has been cloned, and we know it interferes with the production of toxic amyloid fragments,” says Ralph Nixon, a professor of psychiatry and cell biology at New York University School of Medicine and a past chair of the Medical and Scientific Advisory Council of the Alzheimer’s Association. “But we don’t know precisely the mechanism by which it is operating — that’s the work that needs to be done.”

HOPE ON THE TREATMENT FRONT

Advances in deciphering the genetics of Alzheimer’s—not only ferret out common DNA variants that more reliably predict risk, they also provide new clues to potential biological targets for drug development. The goal is to somehow prevent, stop or even reverse the disease. Until now, most promising treatments have fallen by the wayside. Drug companies have lost billions in Alzheimer’s therapies that looked good in early research but failed in larger clinical trials, leading one report to characterize the field as “a graveyard of hope.”

But those treatments were tested on people who already had symptoms of the disease. Recent studies in those with an inherited form of early Alzheimer’s detected the presence of rogue amyloid proteins up to two decades before symptoms emerged, suggesting that washing out before symptoms appear those genetically predisposed to develop Alzheimer’s. One study, known as DIAN (Dominantly Inherited Alzheimer’s Network), involves more than 200 people in the U.S., Britain, Germany and Australia. The other, the Alzheimer’s Prevention Initiative, encompasses 300 members of an extended family of about 5,000 who live in Medellin, Colombia, and the surrounding mountain villages. The DIAN study is composed of families with an inherited form of early Alzheimer’s; many relatives have the disease or have died from it. People who harbor the mutant gene sometimes have symptoms in their 30s and 40s, usually around the same age that their parents started to show signs. On average, most develop symptoms before age 45 and are diagnosed with dementia by age 51. No one with this rogue DNA escapes this terrible fate.

DIAN participants were given one of two drugs, called gantenerumab and solanezumab. Both are antibodies that bind to amyloid proteins and help remove the toxic proteins from the brain before they have a chance to turn into plaques. In the study of the Colombian family members who develop early-onset Alzheimer’s, scientists are testing another drug, crenezumab, which acts similarly to the other drugs. If these therapies can somehow halt or slow the development of memory loss or confusion or plaque formation, it might be possible to slow the progress of the disease.

Because the subjects in these closely watched studies are at such a high risk, researchers should know within the next few years if the experimental drugs will halt or delay the onset of the disease. The characterization of these families has been so thorough, based on all their siblings and parents, that we know when any one person will start to develop cognitive deficits,” says Ronald DeMattos, an Alzheimer’s researcher at Indianapolis-based Eli Lilly and Co., which makes solanezumab and is co-sponsoring the DIAN trial. “If they progress more slowly than usual within that time frame, that would suggest these treatments are having their desired effect.”

But what about people who don’t have a strong familial history of the disease? In the past year, two other long-term clinical trials began to test therapies that might either prevent or delay Alzheimer’s in healthy volunteers who are not genetically at risk of developing the early-onset form of Alzheimer’s. One study, called A4 (the anti-amyloid treatment in asymptomatic Alzheimer’s trial), will test solanezumab in 1,000 cognitively normal people age 65 to 85, who have abnormally high levels of amyloid proteins. Participants will be selected based on the results of a PET brain scan to detect the presence of amyloid plaques.

Another study, called the TOMORROW study, will give an FDA-approved diabetes drug, pioglitazone, to healthy volunteers to see if it can delay the symptoms of cognitive impairment. The clinical trial will eventually encompass 5,000 participants who harbor two specific genes linked to Alzheimer’s: APOE and TOMM40. An observational study conducted by German scientists in 2014 suggests that long-term use of this drug may protect against dementia. Using prescribing information from a German database, they looked at 145,000 adults 60 or older who did not have dementia. During follow-up six years later, they found that 10 percent of the cohort — about 14,000 people — developed dementia, but the risk was lower in those who were taking the diabetes medication. “People with diabetes may have an increased risk of Alzheimer’s,” says Keith Fargo, director of scientific programs and outreach at the Alzheimer’s Association. “The drug may reduce these odds by controlling glucose metabolism and because it has an anti-inflammatory effect. Many researchers now believe inflammation plays a big role in Alzheimer’s. And in another advance, a research team led by Tanzi has concocted what they call Alzheimer’s in a dish. The team used human embryonic stem cells — which can transform into any cell of the body — and cultured them in a mixture of chemicals to grow human brain cells. Then they implanted Alzheimer’s genes into the neurons, which obligingly began churning out the telltale clumps and tangles that characterize the disorder.

“Within six weeks, the nerve cells produced amyloids, and within eight weeks, we got tangles,” says Tanzi. “This is a much better model than what we have, and it’s faster and cheaper. We can now screen drugs within two months in a dish.”

This discovery will solve one of the key stumbling blocks in designing therapies, the lack of a human model that can shed light on how the disease progresses. Scientists characterize the advance as a game changer that could dramatically accelerate the testing of new drug candidates.

It’s likely that a combination of strategies will slow the disease’s progression, using a cocktail of medications aimed at shutting off targets in much the same way AIDS and many cancers are now treated.

“We’ve been operating under the assumption that a single drug would do the trick in terms of reversing the deficits,” says Frank LaFerla, director of the Institute for Memory Impairments and Neurological Disorders at the University of California, Irvine. “But it’s like trying to put out a raging fire with a bucket of water. Once a fire reaches that point, you need to bring out the firetrucks and helicopters.”

Linda Marsa is a contributing editor for Discover and author of Fevered: How a Hotter Planet Will Hurt Our Health and How We Can Save Ourselves (Rodale).