In 1906, a German physician by the name of Dr. Alois Alzheimer examined the body of a woman who had died of a mysterious mental illness. He detected a peculiar and unexplained change in her brain tissue: abnormal clumps and tangled bundles of fibers. Often called amyloid plaques, because they are formed due to high levels of amyloid peptides, these clumps are actually harmful deposits of plaque found between neurons. The fibers are called neurofibrillary tangles. And the plaque and fibers are now known to be signs of Alzheimer’s disease, but achieving a diagnosis does not produce a treatment, and that pursuit has become more serious as the population of the United States is aging.

Recently, hope has arisen that an effective treatment for Alzheimer’s disease may become a reality, and the hope quite literally is in the blood. More specifically, in the antibodies found in human immunoglobulin, the essence of intravenous immune globulin (IVIG).

Currently completing a Phase II clinical trial, researchers and scientists at NewYork-Presbyterian Hospital/Weill Cornell Medical Center have discovered that antibodies found in IVIG could protect the brain from Alzheimer’s disease. These antibodies could essentially preserve the brain by reducing the harmful levels of amyloid peptides, thus inhibiting formation of the amyloid plaque.

The research is essentially directed toward patients with mild to moderate cases of Alzheimer’s disease. “Mild is really the earliest categorization that we currently have available. When you first get diagnosed, it’s very slight discreet memory difficulties, and you’ve ruled out everything else,” said Dr. Maria Carrillo, director of medical and scientific relations at the Alzheimer’s Association. “And you have a 90 percent certainty that this is Alzheimer’s disease, we classify those folks as mild.”

Alzheimer’s disease progresses over a period of time, and the rate of progression varies from person to person. For people with moderate Alzheimer’s disease, there are more than just mild, slight memory problems. “They start experiencing confusion, they start to not recognize their family members, they’ll start to have difficulties performing everyday tasks such as dressing themselves,” Dr. Carrillo explained.

What Causes Alzheimer’s Disease?

Although the complete understanding of what causes Alzheimer’s disease is relatively unclear, research has targeted a particular protein called beta amyloid, which naturally
occurs in the human body. “Beta amyloid is a kind of lynchpin in a cascade of events that we think eventually lead to the disease,” said lead researcher Norman Relkin, MD, associate professor of clinical neurology and neuroscience at Weill Cornell and director of the Memory Disorders Program at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. “Amyloid is produced in our body, in particular, in our brain, in a natural form, which is fairly benign and which we live with for a good portion of our lifespan without having any difficulty.

“We recognized that this protein was the center of the plaque that accumulates in an Alzheimer’s disease brain, and in the brains of many elderly people without Alzheimer’s,” Dr. Relkin continued. “In recent years, it’s come to light that, in the process of going from the single molecule of amyloid to the insoluble clumps that accumulate in the brain, there are some intermediates. And these intermediates are soluble aggregates. They’re small clumps of molecules that stay in solution and which are highly toxic to brain cells.”

These aggregates, commonly known as oligomers, “bind to the membranes of brain cells and can actually punch holes in them,” Dr. Relkin explained. “They can bind to the connections between brain cells and block the transmission of impulses between them and thereby interfere with memory and other thinking ability. So, we set out to find a way to get rid of amyloid, but discovered even more in the process.”

The Trials

The first attempt of using anti-amyloid therapy occurred in 1999 when scientists at Elan Pharmaceuticals, using animal models, developed a vaccine targeting the single molecules. “The vaccine causes the body to produce antibodies against amyloid, which in animal models cleared the plaques out of the brain—quite a remarkable result,” Dr. Relkin said.

However, in 2002, when the vaccine method was used on humans, there were some severe side effects including “brain inflammation in about 6 percent of people who were vaccinated, and two out of the 300 people who got the initial treatment died as a result,” Dr. Relkin explained.

Because of these adverse reactions, the trials for this vaccine method were stopped. “It was really in that context that we turned to IVIG, because now we have some evidence that antibodies could exert some therapeutic benefit, but we were concerned, of course, about safety,” Dr. Relkin said. “Here’s where IVIG offered some very clear advantages because there was a 25-year record of use and an established record. We knew what we had to watch out for.

“In 2004, we started a small trial. And the basic reason for that trial—it was only eight patients—it was to examine whether, if we gave IVIG to Alzheimer patients, it would be tolerated and it would raise levels of antibodies against amyloid and, as a consequence, change the levels of amyloid in the blood and the spinal fluid. The study was a success in terms of showing all of those things.”

With the success of the 2004 trial, Dr. Relkin and his team began to further research the advantages of IVIG therapy for the treatment of Alzheimer’s disease. “In 2006, we started a Phase II trial. Now we were much more interested in seeing what the clinical effects were,” Dr. Relkin explained. “We did a full placebo-controlled double-blind study with biological markers and brain imaging. And we’re still in the process of completing that study, but we did the preliminary interim analysis from six months of double-blind placebo-controlled work, and they were positive again. So, we replicated our results from the first study.”

Dr. Relkin’s work did not go unnoticed. “In 2007, the National Institutes of Health awarded us a grant close to $8 million for initiation of a Phase III study,” he said. “This past summer, Baxter committed additional funds to permit us to do a much bigger and better Phase III study that is now getting under way in 2008.”

Supply: A Delicate Balance

With this exciting new discovery comes the topic of IVIG supply. Will there be enough IVIG to meet the demand when, and if, it is approved for the treatment of Alzheimer’s disease? This is a topic familiar to Dr. Relkin, one that he and his team have considered.

“Alzheimer’s disease represents a very new direction for intravenous immune globulin therapy and one which kind of has an inherent problem,” Dr. Relkin explained. “There is a relative shortage of IVIG for its approved indications. There’s a lot of off-label use, and there have been shortages where people who have diseases for which IVIG is clearly life-preserving had their supply threatened.


2 Phase II interim results will be presented for the first time at the American Academy of Neurology meeting in Chicago, April 17, 2008.
“One of the things that we’re very aware of … is that there’s some anxiety on the part of IVIG users with other diseases about this particular indication,” Dr. Relkin said. “If this is approved as a treatment for Alzheimer’s, the concern is that it would basically bankrupt the supply of IVIG and potentially deprive other people of that supply.”

Although the issue of supply is a factor that troubles many, Dr. Relkin is optimistic and believes it is not going to become an “either-or proposition—that people either get it for Alzheimer’s or get it for these other indications. He elaborated. “We’re working both on understanding how IVIG works on Alzheimer’s disease and taking from that ways of either increasing supply or coming up with alternatives based upon the mechanism.

“We’re not doing this blind to the other side of the coin, which is that IVIG is an effective treatment for many other diseases, and we have no intention of bankrupting the supply.” Dr. Relkin suggested there would likely be a gradual transition to IVIG, if approved, and the supply would be “controlled and the supplies will be increased and there will be other steps taken to prevent it from toppling the balance of distribution of IVIG.”

New Findings

In their research, Dr. Relkin and his team have found some new and unexpectedly positive results regarding the effects of IVIG in Alzheimer’s disease patients. “We’ve discovered that the antibodies that we originally measured in IVIG could not account for the effects that we were seeing. There were too few to cause such large changes in the amyloid levels and the spinal fluid,” Dr. Relkin explained. “We went back, and we and another group have found new antibodies that were not previously known to exist present in much higher quantities.

“And what’s extremely interesting about these antibodies in IVIG, and in our blood, is that they bind not to the single molecules of amyloid but the clumps. So, they don’t recognize the chemical structure of amyloid; instead they recognize the folded shape and aggregated form that the amyloid assumes when it becomes toxic. And this has led us to question whether this, in fact, might be part of a natural body defense against diseases like Alzheimer’s.”

This surprising discovery has enabled the researchers to reduce the doses of IVIG and could, Dr. Relkin said, potentially lead to the development of a synthetic antibody, which would provide the same treatment and relieve the dependency on IVIG. “We’re now using one-tenth the amount of IVIG that we initially started studying, because we recognized that we had more antibodies present than we initially appreciated,” Dr. Relkin explained. “It’s intriguing that we have antibodies at all against a protein that we produce from birth because most of the time the body does not do that, it’s tolerant of its own proteins. But it appears that the body differentiates between amyloid in its native form and amyloid in its toxic, age-related form. And these antibodies are produced and bind to the amyloid protein, and we’re showing now it reduces its toxicity and fosters its clearance from the body.”

Moving Forward

Dr. Relkin expects the Phase III trial to be completed in 2010 or 2011. “It’s a pivotal trial, so the intention is to submit it to the FDA for potential regulatory approval of an indication.”

With their long-term trials showing sustained benefits, Dr. Relkin and his team will continue to treat their Phase II patients out to two years and beyond. “So far, it has been an extremely enlightening experience,” Dr. Relkin said. “And happily, it’s also led to some patients getting better, which is something that we ultimately, of course, want to see happen. We have patients from our regional study who are now in their third to fourth year of treatment and have enjoyed sustained benefits. We are really, really happy about that.”

Although these new developments are extremely promising, Dr. Relkin is cautious. “I certainly would not refer to this [IVIG] as a cure. I think that this is an important step forward in treating a disease … which is reaching epidemic proportions and increasing very rapidly. And I think it’s a window into how we’re going to treat Alzheimer’s disease in the future. But it’s not the final answer to the problem.”

Dr. Relkin said that Alzheimer’s is the result of increased human longevity. “And, because of that, we are now facing a situation where it really is desperate, almost, that we find a way of at least halting the progression of the disease. If we can do that, if we can delay the start of the illness, people will die of better causes and of old age before they develop dementia from Alzheimer’s.”

And there are millions of families around the globe who share Dr. Relkin’s vision.