

IN SESSION with Norman R. Relkin, MD, PhD

Alzheimer's Disease: Potential Therapies, Vaccines, and New Discoveries on the Horizon



Dr. Relkin is associate professor of Clinical Neurology and Neuroscience at Weill Cornell Medical College, attending neurologist at New York Presbyterian–Weill Cornell Hospital, and founding director of the Weill Cornell Memory Disorders Program. His research has led to improvements in the diagnosis, treatment, and prevention of Alzheimer's disease and other forms of dementia. His work on genetics, biomarkers, and brain imaging has improved prediction and differential diagnosis of dementia.

If people had lived to be on average 90–100 years of age a thousand years ago, would we see the same incidence of Alzheimer's disease?

In some respects, Alzheimer's disease is a product of the 20th century because it was not until the advances in medicine, nutrition, and sanitation—the general longevity-promoting advances of the 20th century—took place, that we started to see significant amounts of Alzheimer's disease in the general population. Several factors have been implicated in the development of Alzheimer's disease. Age is certainly the most robust risk factor. Family history and genetics also play a role. While disease-causing genes for Alzheimer's disease are relatively rare, there are genetic susceptibility factors that are more prevalent. The strongest of these is apolipoprotein E4 (APOE-ε4), since as many as 50% to 60% of Alzheimer's disease patients carry that allele.

From the standpoint of environmental risks, there are no specific toxins or viruses that have been conclusively linked to Alzheimer's disease, but there is some evidence for environmental precipitants. If I were going to try to encapsulate this into an overarching theory, it is that Alzheimer's is a complex genetic disorder. This means that everyone has a certain risk of developing the disease, but if a person has unfavorable genetic makeup

and/or life exposures, he or she is more likely to develop the disease at a younger age. Likewise, if a person has a favorable genetic makeup and/or life exposures, it may prevent the development of the disease until a very advanced age.

Are people now being tested more frequently for APOE-ε4?

This area is controversial. A recent development is the commercialization of genetic testing by companies such as 23andMe, that provide direct-to-consumer genetic tests that include susceptibility factors for Alzheimer's disease.

I took part in an Ethical, Legal and Social Implications-funded National Institutes of Health study called the REVEAL Project, in which we provided Alzheimer's risk assessments based upon family history and genetic tests. Certainly among the family members of Alzheimer's patients and people who have cared for individuals with Alzheimer's disease, there is often a fairly strong desire to know this information.

What is interesting is that when information is imparted, even finding out that the individual possesses the APOE-ε4 allele and is at increased risk is sometimes a relief. That sounds paradoxical, but I think many people who have Alzheimer's disease in their

This interview took place on December 7, 2009, and was conducted by Norman Sussman, MD.

Disclosure: Dr. Relkin is a consultant to CSL Bering and Eisai Research; has received support for research on IVIG in Alzheimers from the National Institute of Aging and Baxter Inc.; has received additional grants for research from Citigroup, the Leon Levy Foundation, Pfizer, and the Woodbourne Foundation; and has received honoraria for speaking from Eisai and Pfizer;

family live with a kind of sword of Damocles over their head, and knowing where they stand on a more rigorous scientific basis actually lowers their anxiety. In some cases, the risk ends up being a lower number than they themselves estimated for without the benefit of genetic testing.

Is there any benefit to starting on an anti-Alzheimer's drug when you know you are at risk? What do these drugs do and would their mechanism preclude early disease progression?

The medications that are currently available do not have proven benefits for disease prevention. There has been a great deal of therapeutic nihilism about Alzheimer's disease, as well as diagnostic nihilism. This is the point of view that if the disease cannot be stopped or prevented, there is not much point to predicting or diagnosing it.

This is compounded by some outdated teachings that Alzheimer's disease cannot be diagnosed during life. In fact, it can be diagnosed in a living individual with certainty that approaches that of autopsy, using modern diagnostic tests and following the diagnostic guidelines that changed in the late 1990s and early 2000s. These days, physicians do not use the diagnosis of exclusion method anymore, where everything else is ruled out leaving the remaining diagnosis to be Alzheimer's disease. Instead, there are methods of direct diagnosis, and in the near future there will be some really, really exciting new technologies, including amyloid imaging to visualize plaques in the brain as well as other biomarker-based evaluations that can add to the diagnostic certainty in really quite remarkable ways.

Because the pathology of Alzheimer's disease begins many, many years before the onset of symptoms, it is imminently predictable. With that comes the question: what is the point of diagnosing the disease if there is nothing one can do to stop it? From the vantage point of a translational clinical scientist with one foot in the clinic and the other in the laboratory, I believe that there are some treatments on the horizon that will be a considerable advance over what we have available today. These therapies will go beyond what is now called symptomatic relief that sets the disease symptoms back a few months and may slow the rate of progression marginally. In the next few years we are going to see the emergence of a new generation of disease-modifying therapies. Will those therapies be applicable to the prevention of the disease? While that remains to be determined, I am very optimistic. In fact, I think that some of the therapies currently under development will actually be more effective as preventions than they will be as treatment once the disease is manifest.

The problem is that right now, owing to the way that regulatory bodies approve treatments for Alzheimer's disease, most of the drug development is being conducted with patients who are already in a fairly advanced stage of the disease. The models and motivation for conducting prevention studies are still fairly limited. That will change, though. We are just seeing the emergence

of new prevention paradigms, and both government and industry sponsorship of those approaches are coming to clinical trials right now. I think there has been a recognition on an international as well as national level that Alzheimer's represents a public health priority. The numbers are quite startling; within the United States alone more than 5.5 million Americans are affected. The estimates are that there will be up to 14–16 million patients in the US alone by 2050 unless some intervention is found.

I frequently point out that if we find a treatment that actually arrests the disorder, and we administer it exclusively to individuals who already have the disease, the prevalence of Alzheimer's disease will actually go up. The reason for that is fairly easy to understand: Alzheimer's disease is a fatal disorder, and frequently individuals who develop it have a shortened life expectancy. If a treatment arrests the disease after the onset of dementia, the patient will live out his or her normal life expectancy. Thus, ultimately, there will be more people walking around with the disease. In a way, this is really what happened in the 20th century, because we focused on keeping people alive rather than quality of life. People survive to very advanced ages, and we are seeing more age-related disorders as a consequence. The way out of the conundrum is to prevent the disease, that is, to administer a disease-arresting treatment before the symptoms of dementia begin.

What is the amyloid hypothesis of Alzheimer's disease?

The amyloid hypothesis has been the prevailing theory of Alzheimer's disease causation for ~20 years. It replaced the cholinergic hypothesis, which was the idea that deficiencies in cholinergic neurotransmission were the basis for the disease.

The original amyloid hypothesis is showing its age. Most of us in the field no longer ascribe to the original hypothesis, which was that the deposition of amyloid in the form of plaques set in motion a cascade of events which ultimately led to the death of brain cells and the development of dementia. There are newer versions of the amyloid hypothesis. One which I am relatively fond of is called the amyloid oligomer hypothesis. This hypothesis implicates small soluble aggregates of the beta amyloid peptide as the culprit in disease causation rather than the large insoluble amyloid deposits that make up the brain plaques of Alzheimer's disease. The basic idea is that these small soluble aggregates can account for a lot of what we see in terms of the phenomenology and pathology of Alzheimer's disease. They are extremely potent inducers of amnesia. In fact, one study that compared amyloid oligomers to scopolamine, a drug that is commonly used in anesthesia to induce amnesia, found that oligomers of amyloid were ~10,000 times more potent in inducing memory loss than scopolamine.¹ These may be the most potent amnesia-inducing agents known to man. As a consequence, it is not a surprise that the key feature of Alzheimer's disease is memory loss.

Again, I think there are many lines of evidence pointing in this direction, but the basic answer to your question is there is still a lot of enthusiasm about targeting amyloid, and we still believe that the abnormalities of amyloid processing are a very early and fundamental element of the pathologic cascade that leads to Alzheimer's disease.

However, the exact form of amyloid that we need to target, and what we need to do to prevent the disease, is still a matter of debate.

What is the rationale for using intravenous globulin?

Until the late 1990s, the concept of the immune system playing any role in Alzheimer's disease was rarely discussed. In 1999, Dale Schenk, PhD, and colleagues,² published a landmark study in which they showed in animal models of Alzheimer's disease that if one vaccinated with the amyloid protein, antibodies against amyloid were generated. They showed two remarkable effects. One is that if administered to young animals, the vaccine would prevent the development of plaques. An even more remarkable aspect of that study was when they gave the vaccine to animals that were older and already had plaques in the brain, the plaques disappeared. For those of us in the field, this was a truly unexpected and extremely remarkable result. It had taken scientists using the strongest acids and most caustic solvents until the early 1980s to be able to dissolve amyloid aggregates in a test tube. It was really thought that once these sand-like concretions in the brain were formed, there would be no way to get rid of them. So, the finding that antibodies could rid the brain of amyloid plaques really set in motion a paradigm shift in the Alzheimer's field.

Upon reading about that study, my colleagues and I asked an obvious question, which is, if a vaccine generating anti-amyloid antibodies could have such potent effects on the underlying pathology of Alzheimer's in an animal model, were there people in the general population who had these antibodies as a kind of natural defense? The following year, we started looking for these antibodies in the blood of normal volunteers and patients with Alzheimer's disease, and we found that, indeed, most of us have in our blood antibodies against amyloid. The levels of these antibodies vary from individual to individual, but on average they are lower in patients who have Alzheimer's disease than in age-matched normal individuals. That was the germ of the idea that led us to test a commercially available immunoglobulin preparation called intravenous immunoglobulin (IVIG) as a potential treatment for Alzheimer's disease. IVIG has been around for almost 30 years as an approved treatment for various immune deficiency disorders, some forms of cancer, and autoimmune diseases. It is prepared from the blood of several thousand healthy plasma donors, and it contains within it most of the IgG antibodies that all of our bodies produce. It is a kind of "kitchen sink" approach immunotherapy in that the clinician throws all the antibodies in the human repertoire at the patient, hoping that those which target the amyloid pathology and those which exert an immunomodulatory effect will be of benefit.

Do you find some people develop rheumatoid or immune-based diseases because they have antibodies to other parts of their physiology?

That is a really interesting thing about IVIG. In fact, the body is normally in a state of balance as far as these naturally

occurring endogenous antibodies are concerned. While there are a small percentage of people in the donor pool who may have those autoimmune disorders, there is a much larger percentage of people who have antibodies that block those kinds of diseases. In net, administering a mixture of antibodies like this to people has a therapeutic effect. That is why IVIG is so widely used as a first-line treatment in many autoimmune conditions, as well as immune deficiency disorders.

Are donors screened for antinuclear antibodies, rheumatoid factor, or the like?

They are screened for human blood-borne transmissible disorders. In the early years of IVIG production, there were some cases of transmission of hepatitis, for example. Now the screening and manufacturing processes are so scrupulous that there have not been any cases of human transmissible diseases for many years. Do people have paradoxical reactions or negative reactions to IVIG? Yes, they do sometimes, but they are usually in the form of allergic reactions, or in some cases cytokine-induced responses, like fever and chills or rash, rather than induction of autoimmune disorders.

Were there some bad reactions when researchers first conducted these studies with vaccines?

Let me distinguish between vaccines and passive immunization. The outgrowth of the study by Schenk and colleagues² was a human vaccine called AN1792, that was fast-tracked into human trials. It went through a single-dose Phase I study without incident, and then to an international Phase II study. Approximately 300 patients were vaccinated. The study was stopped suddenly when 6% of the vaccinated individuals developed meningo-encephalitis, a swelling of the brain. In some cases the swelling was quite severe. There are some reports that the vaccine, as it was eventually formulated, was mixed with an adjuvant that sometimes provokes and may have generated the wrong type of immune response, leading to intolerable side effects.

It was in that context that many individuals, myself included, turned to an alternative way that has been used successfully for over a century of conveying immunity, called passive immunization. That involves taking antibodies from another source, in this case human donors, to give to patients. More commonly among trials being conducted by industry, humanized mouse monoclonal antibodies are employed. The concept is different from vaccines. Rather than relying on the individuals to generate an immune response, passive immunization takes a therapeutic antibody or antibodies and delivers them in a known dose through, typically, an intravenous infusion at a fairly frequent interval. The downside of it is that you need to keep giving the antibodies in order to maintain the immune response, whereas the vaccination tends to be very long-lasting in its effect. However, by the same token, if there is a side effect, the effects of the passive immunotherapy wear off fairly quickly. I

think it is a much better way to develop a treatment for Alzheimer's disease than a vaccine because individuals who volunteer to test passive immunotherapy are not doomed to suffer the effects of any adverse reaction that may occur for the rest of their lives.

Would a very wealthy individual be able to line up a physician and just keep getting IVIG?

That is a sensitive topic, and I say that for a couple of reasons. IVIG is very expensive. I think implicit in your question is the recognition that at the current market prices, the amount of IVIG that we administer in our Alzheimer's disease studies would cost an average of \$50,000–\$70,000/year per individual if people purchased it themselves. Thus, this would truly only be something that rather wealthy individuals could do until IVIG treatment for Alzheimer's disease is approved. IVIG treatment for Alzheimer's disease is not reimbursed by any third party payer and certainly not by Medicare or Medicaid for this indication.

I would like to emphasize a couple of very important points here relative to the inadvisability of off-label use of IVIG for this purpose. The first is the slippery slope idea, which is that just because something is in clinical trials does not mean that it should be used as a therapeutic entity. There is also the very serious concern—since there are so many individuals with Alzheimer's disease and IVIG is in limited supply—that if lots of people did in fact buy IVIG for this purpose it would bankrupt the supplies that are being used to treat the disorders for which IVIG is approved. I refer to disorders for which IVIG is a life-or-death intervention. A child, for example, with congenital immune deficiency will quickly succumb to infection if they are not treated continuously with IVIG. Thus, off-label use is not something that should just be done casually.

Having said that, I am aware that there are people who are doing exactly what you described. The numbers I think right now are fairly limited, but it is something which, in general, I think is inadvisable for most people at this time.

Are you working on any alternatives in clinical trials to IVIG that would be both affordable and mass produced?

Yes, but let me broaden the question to say what is going on within the field. Worldwide, there are close to 100 therapeutic interventions that are being studied. I am aware of 15–20 potential immunotherapy products which are now under development as potential Alzheimer treatments. Most of those are monoclonal antibodies. IVIG is relatively unique in being a human antibody mixture.

Although many of them are targeting amyloid, the concept that we have enough knowledge to specifically target an antibody is questionable. That is why my efforts have focused on a top-down approach—to take all the antibodies that the human body produces and begin to hone down on the specific ones that

are contributing to what we are seeing in our clinical trials as therapeutic responses.

Over the past 3 years in particular, we have been isolating antibodies from IVIG that we feel are candidates for contributing to its therapeutic effects in Alzheimer's disease. We have found numerous new antibodies, some of which are quite remarkable in their properties and potentially have applicability not only to Alzheimer's disease but other neurodegenerative disorders as well.

However, the process of taking newly discovered antibodies into the clinic is a very long one. While IVIG is here and now, new antibody therapies, based upon what we find in IVIG, are likely to take up to a decade to develop.

Is it true that mice do not get Alzheimer's disease?

It is true under normal circumstances, and even when we modify them transgenically. Alzheimer's disease in an absolute sense is a truly human disease. I think that is an interesting and as yet not fully explained phenomenon. Though we do see diseases that resemble Alzheimer's disease in aged monkeys, aged dogs, and a few other species, the full-blown pathology of Alzheimer's disease with plaques and tangles and all the other elements that we associate with the disease seem to be unique to the human species.

Is there anything important that you want to add in terms of what we can expect or where you think the next breakthrough will come?

There are two other areas that we should briefly touch on. One is a time frame for immunotherapy, and the other is what else is on the horizon in terms of Alzheimer's therapy. There are at least three Phase III studies, the IVIG study I am leading among them, that are anticipated to be completed by 2012. There are other approaches to anti-amyloid therapy that do not involve immune therapy. One is a γ -secretase inhibitor that affects one of the enzymes that is involved in the production of β -amyloid. This has advanced into Phase III trials as well.

The year 2012 is not that far off, but even before that there is at least one other major pharmaceutical that is likely to complete its Phase III trial. Dimebon hydrochloride was originally an anti-histamine used in Russia which was retested more recently as a potential treatment for a number of disorders and showed what seemed to be particular promise for Alzheimer's disease. That will probably be the next drug to release results from a pivotal trial, and the US Food and Drug Administration has actually allowed the Russian Phase II trial to count as one of the two pivotal trials that it normally requires for approval of a new agent. If the Phase III trial of dimebon hydrochloride is successful, it would stand to be the next approved therapy for Alzheimer's disease.

The mechanism of action of dimebon hydrochloride is somewhat controversial. It was originally thought to have some of

the same properties as existing approved therapies, but it has since proven to be a very poor cholinesterase inhibitor and a poor *N*-methyl-D-aspartate receptor antagonist. More recently, the companies that have been involved in its development have found some evidence for effect on mitochondria, which would represent an entirely new mechanism and new therapeutic target for Alzheimer's disease therapy. We will have to wait for the results of the US and international Phase III trial to know if it works. Again, in terms of things that are coming up next, that is probably the biggest blip on the radar screen.

Some psychiatric medications cause cognitive side effects such as profound memory problems. Are you aware of anybody trying to reverse-engineer why this occurs?

Some psychiatric drugs have known cholinergic side effects which, given the involvement of the cholinergic system in memory, is a well-known phenomenon. For topiramate in particular, I do not think the explicit mechanisms of its cognitive side effects are known. I will say that there is some recent evidence that has emerged from one of the technologies that is now being used more routinely to evaluate the effects of drugs on the brain—volumetric magnetic resonance imaging—that have shown some negative effects of commonly used drugs on the rate of atrophy of the brain. I am alluding to some evidence that has emerged for accelerated brain shrinkage in individuals who are given these agents.

There may be some as yet undiscovered mechanisms of neuronal toxicity that these agents are exerting. There is also the remote possibility that there is some effect on brain water or other artifactual ways in which the agents are appearing to cause accelerated brain shrinkage. However, the data that I have seen

so far does give me some cause for concern about using these agents chronically.

There is a great need right now for new agents to treat behavioral disturbances associated with dementia in the elderly, especially given the black box warnings and fairly dire consequences of using both classical and novel neuroleptics in that population. I think we are facing a potential disaster in that area because many physicians are becoming reticent to use these agents, and yet the behavioral disturbances themselves can cause equal or greater risk than the side effects of the neuroleptics themselves. We are in a kind of quandary as far as that is concerned, and there definitely is a need for more drug development and testing in that domain.

Do you have any last words?

There are many very promising and unprecedented therapies that are showing very substantial promise. Some of those include drugs which are in our current pharmacopoeia.

What I think is very exciting is we now have the technologies to test whether drugs have these neuroprotective and neuro-restorative effects. I think that we are going to start seeing, particularly in the next decade, an entirely new way of approaching both neurologic and psychiatric diseases as a consequence. *PP*

REFERENCES

1. Cleary JP, Walsh DM, Hofmeister JJ, et al. Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. *Nat Neurosci*. 2005;8(1):79-84.
2. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature*. 1999;400(6740):173-177.