Bob's Last Marathon
Living the Alzheimer's Journey

TRANSCRIPT

Beyond Plaques and Tangles—Understanding Alzheimer's Disease

Dr. Arnold: Before we dig into specifics about the treatment landscape in Alzheimer's disease, I'd like to just refresh people on some of the terms and concepts we use in the field. So for all of us, memory and thinking slow down as we get older. We have more senior moments, it's harder to multitask, and it takes longer to get things done. But while it takes more effort, we still manage our lives independently.

Dementia is the term we use when we have more than mild cognitive difficulties where it affects our day-to-day independent functioning and we require assistance. And this will affect a third to a half of us as we commonly live into our 80s or 90s or even beyond now. Dementia is not normal aging. It indicates that there's a disease affecting the brain. Alzheimer's disease is by far the most common disease causing dementia, but other diseases like vascular dementia from strokes and mini-strokes, Parkinson's disease–related problems, different frontal lobe dementias, and a long list of other rarer diseases can cause dementia.

If you examine brain tissue under the microscope after someone dies, each of these diseases has its own signature lesions in the brain that you can see. For Alzheimer's disease, the signature lesions are the so-called senile plaques made out of amyloid protein and the neurofibrillary tangles that are made out of tau protein. In vascular dementia, it's atherosclerosis in the large blood vessels feeding the brain or narrowing of the small vessels deep inside the brain. For Parkinson's-related diseases, it's the Lewy bodies made out of a protein called alpha-synuclein. And other diseases have their own pathological lesions that define them.

But these lesions that we see in the microscope aren't the whole story. They may be just tips of the icebergs. We know that there are many complicated cellular abnormalities going on that we can't really see under the microscope, problems in cell metabolism, abnormal functioning of genes, inflammation, oxidative stress and more. And to varying degrees, all of these exist in vicious cycles with the amyloid, tau, and synuclein or other protein abnormalities that define the different types of dementia.

In Alzheimer's disease and all of these diseases, the final common pathway from all these different factors to memory loss is malfunction and degeneration of synapses. Synapses are the connections between brain cells. Vast networks of brain cells need to fire in concert for us to think, to learn and remember. If the connections between brain cells aren't working or are lost, brain cells won't activate together and cognitive activity fails, and Dr. Strittmatter will be telling us more on this.

In trying to discover and develop new treatments to prevent, to slow down or cure Alzheimer's disease, most of the attention over the last 20 years has focused on the amyloid plaques that define the disorder. Some of the approaches try to prevent the production of amyloid protein itself in the brain, others have tried to prevent amyloid from misfolding or clumping up in the brain, and of greatest interest in the news recently have been the immunotherapies. With these immunotherapies, you administer monoclonal antibodies by vein once a month or so, and these antibodies are designed to attack bad amyloid in the brain and clear it out.

One leading immunotherapy, aducanumab or Aduhelm by Biogen, recently received accelerated approval from the FDA. Other major drug companies are right behind. And these immunotherapies do effectively clear the brain of its amyloid and we can see this with a PET scan. But aducanumab's approval has been very controversial. Two large Phase III clinical trials showed that it can successfully clear amyloid in the brain even back to normal, but people's dementia, their clinical symptoms of memory loss and their problems with daily functioning, still got worse. And it's still not clear from the data whether the rate at which their symptoms

worsened slowed down at all. But overall, people still got worse despite removing the amyloid. So what does this mean? To me, it says that in people who already have cognitive impairment due to Alzheimer's disease, removing amyloid alone is not enough to stop the disease. Maybe it's necessary to do that, but it's not sufficient. And more likely, we'll need to get rid of amyloid in combination with therapies for the other factors contributing to progressive decline. We're still learning about this.

Now, tau tangles are the other signature lesions of Alzheimer's disease. And the amounts of tau tangles in the brain actually correlate a lot better with the severity of dementia than amyloid does. So perhaps if we can reduce tau tangles in the brain, that will stop the dementia from getting worse. Tau has been a harder target to develop drugs against than amyloid. It's a more complicated protein in a lot of ways. But there are now tau trials that are in clinical development. We're still waiting for the results to come in. It's still too early to tell how well they'll work.

But whether we are targeting amyloid, tau, inflammation or anything else, our ultimate goal is to save our synapses. If we can protect or even regrow the connections between brain cells, we can preserve our cognitive functioning and stop dementia. There's really no one better to help us understand this than Dr. Strittmatter, who has done such seminal work in both the laboratory and clinic on the growth and maintenance and regeneration of synapses.

Dr. Strittmatter: Thanks very much, Dr Arnold. Billions of neurons in the human brain create a complex electrical network that underlies cognition. In a sense, you could say a biological supercomputer, but even more than that. The electrical impulses in one neuron are transmitted over long distances via nerve fibers called axons. However, when the signal gets to the end of one cell, it can't get into the second cell. The cells are insulated from one another, and it's these synapses which are the specialized contacts between neurons that allow an electrical impulse in the first cell to be converted to a chemical signal which diffuses to the second cell and then triggers an electrical impulse in that cell, all of this through neuronal biochemistry. And we call that chemical that goes from one cell to the other a neurotransmitter.

What's important in Alzheimer's is that these synapses are highly vulnerable to the neurodegenerative process. And as Dr. Arnold mentioned, if you lose synapses, you no longer have a neural network and then you have cognitive symptoms. So this is really at the crux of Alzheimer's disease. Importantly, synapses are not damaged by one thing in Alzheimer's. They're really damaged by a collection of factors: of course, aggregated beta amyloid, but also aggregated tau, inflammation, in particular in the microglial cells of the brain, and metabolic changes, the poor use of glucose, the accumulation of reactive oxygen species. And it's really all these factors together which synergistically damage the synapse. And once we don't have synapses in the brain, then we don't have cognitive function and we have mild cognitive impairment and the progression of dementia.

Here, timing is critical. Amyloid builds up very early. It's actually one of the first things we can detect clinically in the entire Alzheimer's process. But synapses and cognition may actually be okay for 5, 10 or even more years while this amyloid builds up. Eventually though, there's inflammation, tau starts to accumulate, and it's in this phase that synapses are lost because of the coalescence of these multiple factors, and people develop mild cognitive impairment we see the first time they come to the clinic with complaints. We know a lot about this from new brain imaging studies and the pathology of individuals who come to autopsy very early in the disease.

Later in the disease, in the moderate and severe phases of Alzheimer's when even basic functions are lost, there's actually a death of the neurons themselves. So it starts with accumulation of proteins, inflammation, loss of synapses, and then eventually the neurons start dying and there's widespread

shrinking or atrophy of the brain. So all of this points to synapse loss really being at the crux of the initial symptoms of cognitive dysfunction. And not only is it the thing that causes neural network failure, it's the location where these multiple factors—amyloid, tau, inflammation, metabolism—come together, and in a synergistic way, produce the symptoms. That's what, in part, makes Alzheimer's a complex disease, a hard target to solve completely with any one approach.

What can we do with this knowledge about synapses? Can we leverage this, discover new therapies? I would say the answer is yes. Laboratory experiments can delve into the idea that synapses are lost and try to understand, at a molecular level, why these synapses are lost in response to these multiple factors. Once we can nail down the mechanisms, then we can try to intervene. If we can intervene to preserve synapses in the brain, even if there's still amyloid and tau and inflammation, we'll have synapses, we'll have a neural network and cognitive performance will be adequate.

As an example, in my own lab here at Yale, we've studied how amyloid, misfolded amyloid beta, triggers synaptic damage, and we've uncovered a pathway that involves a protein called metabotropic glutamate receptor 5 or mGluR5. But the point is that that target is required for synapse loss and memory deficits in laboratory models of Alzheimer's, animal models. And armed with that knowledge, we've developed some compounds that can restore synapses and recover memory function, again in laboratory models, and there's a startup company that's now advancing one of those into early clinical trials.

One way to use knowledge about synapses is to develop new approaches to therapy for Alzheimer's. But equally important, I think, is that this gets us biomarkers for the disease. *Biomarkers* means many different things. Of course, we've probably heard about amyloid beta and tau as biomarkers. They can be measured by PET scans, by CSF, that is cerebrospinal fluid or plasma measures. And these are diagnostic markers in the sense that when they're detected, one can be certain to some degree that Alzheimer's is present as opposed to the other causes of dementia. But biomarkers can also reflect the disease itself and be therapeutic biomarkers.

What about for synapses? I just told you they're tightly correlated with memory and cognition. Can we actually measure synaptic density in the clinic as the disease progresses? There's one method that's been around for quite a while that's based on the brain's utilization of glucose. The brain uses a lot of energy. The brain uses a lot of glucose to drive synapses and cognition. And so by labeling glucose, injecting it and then scanning the brain, one can tell whether different regions of the brain are using glucose at the rate that they should. And in Alzheimer's disease, certain regions of the brain stop using glucose as effectively and that can be detected on a PET scan and it's tightly correlated with the progression of mild cognitive impairment and mild Alzheimer's disease, a so-called surrogate endpoint.

The advantage of this is that that measurement is actually detecting synapses as opposed to measuring memory and cognition. These are highly variable day-to-day. Memory performance can change a lot, but if we want to actually track synapses, we can do it indirectly with this well-known PET measure. However, there's actually been a further development. Recently, another group at Yale developed a way to use the derivative of an anti-epileptic drug to directly measure the synapse structures in the brain. So this is based on a drug called levetiracetam. When it's been labeled and injected, it will bind to the synapses in the brain, and the signal in the brain is a direct measure of how many synapses are present.

This has been used already in Alzheimer's studies and there's a tight correlation with the progression of the downhill course in mild and early Alzheimer's disease. So this allows one to really have a way to track this synapse loss. No matter what drug one may want to develop to make a difference in the progression of Alzheimer's disease, by having these tools, we have a

much better way to accelerate the drug development process.

So overall, I'm going to say there is recognition that we've gone beyond amyloid and tau. We recognize the role of inflammation, metabolic changes, and the fact that synapse loss is at the nexus of all these factors really takes us much farther in understanding Alzheimer's, and I think it gives us a lot of optimism and hope that rather than testing amyloid lowering over and over again, there are many more shots on goals that we can take that we can test in the clinic and get meaningful answers and really get to something which, either alone or with combination therapy, makes a difference in Alzheimer's disease.

Steven E. Arnold, MD

Professor of Neurology
Harvard Medical School
Managing Director
Interdisciplinary Brain Center, Massachusetts General Hospital

www.actru.org

Stephen M. Strittmatter, MD, PhD

Vincent Coates Professor of Neurology
Professor of Neuroscience
Director of Cellular Neuroscience, Neurodegeneration and Repair Program
Yale School of Medicine

https://medicine.yale.edu/cnnr/