

A conversation with Dr. David Holtzman, May 1, 2015

Participants

- David Holtzman, M.D. – Andrew B. and Gretchen P. Jones Professor and Chairman of Neurology; Professor of Developmental Biology; and Associate Director of the Alzheimer's Disease Research Center, Washington University in St. Louis School of Medicine
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Note: These notes were compiled by the Open Philanthropy Project and give an overview of the major points made by Dr. David Holtzman.

Summary

The Open Philanthropy Project spoke with Dr. Holtzman of Washington University as part of its investigation into Alzheimer's disease. Conversation topics included how to conduct more effective clinical trials, promising areas of research, and the need for additional funding and research.

Conducting more effective clinical trials

Dr. Holtzman believes that previous human trials on Alzheimer's drugs were unsuccessful because researchers designed them before the field had figured out a number of important variables. Early trials used ineffective dosages of the therapeutics, were conducted too late after the onset of the disease, targeted the wrong population, and/or focused on treatment rather than prevention.

Symptoms lag onset of pathological changes in the brain

The two proteins most closely associated with Alzheimer's disease (AD) are Amyloid beta or A β , which forms amyloid plaques in the brains of AD patients and tau, which forms abnormal aggregates called neurofibrillary tangles inside neurons of patients. A β starts to build up ~15 years before a patient begins to show symptoms of patients with AD. The aggregation of A β appears to be permissive: it facilitates the formation of neurofibrillary tangles and allows the development of other pathological processes in the brain. Tau begins to accumulate in the medial temporal lobe of the brain approximately five years before cognitive impairment occurs. Tau related changes are correlated with clinical impairments seen in AD.

Preventing versus removing amyloid deposition

In animal models of AD, the most effective therapy is prevention. If researchers treat mice with anti-A β antibodies as soon as amyloid plaques start to develop, they can prevent further amyloid accumulation. Most of these therapies do not work well to remove amyloid once it is already present in a mouse's brain. In contrast, human trials have focused on removing amyloid plaques. In Dr. Holtzman's view, if researchers could begin administering a therapeutic to individuals at high risk of

developing AD 10-15 years before the development of clinical symptoms, they may be able to block amyloid deposition in the brain as well as the resulting pathologic changes. For some patients, this would mean starting treatment as early as age 50, but Dr. Holtzman believes that this approach may be required to prevent AD.

Trials focused on early-onset AD

The inclusion of patients with late-onset Alzheimer's (AD occurring after the age of 65) in earlier clinical trials made identifying effective treatments more difficult. Between 70 and 75 percent of dementia patients over the age of 70 suffer from multiple types of dementia, and approximately 25 percent of the participants in some previous trials did not have AD at all. It can be difficult to differentiate pure AD from other dementias. This is particularly true for dementias associated with accumulation of the protein synuclein, for which there is currently no clinical method of detection. Since these early trials only targeted the AD component of dementia in patients who often had multiple types of dementia, it is not surprising that the treatments did not have a large effect.

Younger Alzheimer's patients are more likely to have pure AD (i.e. without other types of dementia) and, according to Dr. Holtzman, should be the focus of initial clinical trials targeting A β or tau. These patients are sometimes individuals with familial mutations strongly associated with development of Alzheimer's before age 65. Individuals who have two copies of the *APOE4* allele, a strong genetic risk factor for late-onset AD, comprise another patient population that has a higher likelihood of developing pure AD and therefore may lead to productive clinical trials.

Of note, researchers' ability to better identify individuals who have AD through the use of biological markers and imaging as well as clinical symptoms makes results from recent trials more useful.

Food and Drug Administration approval

Historically, drugs have been tested and approved for patients with symptoms from a disease. For example, cholesterol-lowering drugs (a class of drugs called statins) were initially approved for patients with high cholesterol as well as a history of a cardiovascular event such as heart attack or stroke. After statins were shown to be successful in preventing subsequent cardiovascular events, they were approved for use in people with only high cholesterol to prevent an initial cardiovascular event.

Dr. Holtzman believes that in order for the Food and Drug Administration (FDA) to approve trials for testing preventative therapeutics for AD, it is likely that researchers must first show that the therapies are effective in individuals with symptomatic AD.

The future of AD research and treatment

Promising therapies

Many researchers are now studying connections between the immune system and Alzheimer's disease. Some of the genetic risk factors recently discovered are genes expressed in microglial cells, which are the primary immune cells in the central nervous system.

A promising line of research is immunotherapy, in which antibodies target A β and tau to decrease their levels in the brain. Another area of interest for pharmaceutical companies investing in clinical trials is inhibition of β -secretase (BACE), which stops the formation of A β . Depending on trial outcomes, researchers may be able to start administering some combination of these treatments in three to six years.

Amyloid deposition screening

In the future, Dr. Holtzman envisions a scenario in which everyone over the age of 50 would be screened every 10 years for markers associated with AD. If tests show signs of AD, the patient would then begin treatment to prevent further pathology well ahead of the development of any symptoms. Screening may be done through imaging of amyloid or tau deposition, biochemical markers of neuron damage or markers of synaptic activity.

The need for additional research and funding

Research on ApoE4

The presence of the *APOE4* allele in a person's genome confers an increased risk of developing AD. *APOE4* is a much better genetic indicator of risk for AD than the gene variants associated with other common health problems such as stroke, heart attack, and diabetes. However, the ApoE protein is incompletely understood for several historical, as well as, structural reasons:

- When researchers discovered the *APOE4* allele, they did not reach a consensus on the best path forward in order to understand the connection between the ApoE4 protein and AD.
- The ApoE4 protein is a lipoprotein, which is a molecule made of both protein and lipids. Working with this type of molecule requires expertise many neuroscientists lack. (This knowledge is more frequently found in the cardiovascular field.) There are even fewer researchers who study lipoprotein metabolism in the brain.
- The ApoE4 field is small. Therefore, when one group publishes their work there may not be another group interested in, or capable of, validating their results.
- The small size of the field also means that it can be insular. ApoE4 research could benefit from fresh thinking of additional groups who have not yet worked in this area, including new collaborations and contributions from scientists in other fields.

Funding levels are low relative to other diseases

Dr. Holtzman believes that researchers are tackling the correct questions in order eventually treat or prevent AD, but that the overall funding level for Alzheimer's research is insufficient. Most of the government support for AD research comes from the National Institutes of Health (NIH). Taking into account the impact of Alzheimer's disease, the NIH underfunds AD relative to other diseases such as cancer and HIV. Although the cost of Alzheimer's disease is similar to that of all cancers combined, the NIH provides roughly 10 times the amount of funding for cancer research as for AD.

The lack of funding affects the ability of researchers to find treatments and discourages talented researchers from joining the field.

The looming Alzheimer's crisis

One reason for the lack of funding may be that the most devastating societal impacts of Alzheimer's disease are likely to be felt in the future. By 2050, researchers estimate that there will be approximately three times as many people suffering from AD as there are currently. The US spends roughly \$200 billion per year in healthcare costs associated with Alzheimer's; by 2050, researchers estimate that amount will expand to \$1 trillion, not adjusted for inflation. This is such a large increase that it is incompatible with most of our current economic models.

Recently, Alzheimer's disease has started to attract more attention and this has had some impact on the field. There has been more funding from foundations, and while the NIH Alzheimer's budget is still small, it is the only area that has received additional funding in recent years.

*All Open Philanthropy Project conversations are available at
<http://www.givewell.org/conversations>*