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Alzheimer Research Forum Report: Tübingen: Researchers Reminisce and Predict at Alzheimer Centennial Conference

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Alzheimer Research Forum

On Saturday, 3 November, 1906, Alois Alzheimer traveled from Munich, where he lived and worked, to Tübingen. That afternoon, he was to address the 37th convention of Southwestern German psychiatrists, who were then called, cruelly, "Irrenaerzte" ("insanity doctors, alienists"). Eighty-eight colleagues filled the auditorium in the Clinic of Psychiatry at the University of Tübingen, including Franz Nissl of tissue stain and Nissl body fame, and the child psychologist C.G. Jung. To them, Alzheimer presented his first, signature case of the disease that his boss Emil Kraepelin would later name in honor of his protégée. Alzheimer recounted in meticulous detail how Auguste D's unusual disease had progressed. He also projected images of the plaques and tangles that he spotted in her brain after she had died in Frankfurt and he'd had her brain shipped in a wooden crate by train to Munich. Alas, his prescient observations met with deafening silence. No one asked a question. The local newspaper, Tübinger Chronik, laconically noted Alzheimer's talk in one sentence: "Private docent Dr. Alzheimer (Munich) reported a curious, severe disease process that caused significant shrinkage of nerve cells within 4.5 years." The newspaper devoted most of its convention coverage to more fashionable issues in psychiatry at the time: hypnotic sleep to cure anxiety, childhood trauma as the cause of adult melancholy, and more generally an impassioned debate about Sigmund Freud and psychoanalysis. As a group, psychiatrists were not ready to contemplate disturbances of the mind as specific organic diseases of the brain.

One hundred years and 20 million patients later, 180 scientists and guests from all over the world met in the same graceful building on a hillside above the medieval town of Tübingen to commemorate Alzheimer's achievement in three days of public and scientific events. Led by Mathias Jucker, at the Hertie Institute in Tübingen, the organizers decided to host the conference in the historic clinic. Because seating there is limited, the organizers were unable to invite as many scientists as they wished. To share the event more widely, they have made an on-demand video stream (www.alz100.de/video_stream.html) of both full days of scientific talks freely available for download. For this reason, this news story will not cover any presentation in detail. Rather, it offers tidbits of the flavor and themes at this unique event.

The first day afforded a luxury in which young investigators can rarely indulge: a look back in time to the early pioneers in AD research, with talks given by Robert Terry himself, looking fit and feisty as ever, along with colleagues who worked with him. The second day featured current concepts and a session that expressly encouraged wild predictions about the future. This session offered hilarity as some speakers hedged for fear of "making an elephant's ass out of themselves," while others proclaimed themselves perfectly happy to do so and prophesied away.

Some talks were emotional as pioneers shared memories of colleagues who have passed away. Some illuminated historical context as speakers quizzed each other on how they interpreted their key findings in the conceptual framework of the time. Be transported back

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to a time when research was conducted – quelle horreure! – without computers, without PubMed, without Western blots or antibodies. You will find animated discussion about what people thought in those early days when the data stared them in the face but the implications had not been worked out yet. For a look back, a look around, and then a look to the future, readers may want to consider running the program in lunch hours and journal clubs and discussing it with their students and postdocs. Importantly, watch the program to remind yourself of the many colleagues who coauthored the milestone discoveries listed in the program, or who were independently working on the very same problem.

Here are some selected historic teasers. Terry recalled Robert Katzman's 1976 editorial in Archives of Neurology that attracted neurologists and biochemists to a small field that had before been the province of neuropathologists including Henry Wisniewski. Katzman spread the idea that early-onset AD and what was called senile dementia are largely one disease. This put AD on the map as a public health issue and set the stage for the founding of the National Institute on Aging and a steep increase in research funding under its AD program director Zaven Khatchaturian, who helped build a national AD research infrastructure. Khalid Iqbal dug up original data on early work to isolate tangles gathered before the advent of now-ubiquitous techniques such as immunoprecipitation. Peter Davies recalled scientists' excitement when they began to understand the cholinergic deficit in AD. The first chance of treatment emerged on the horizon as the scientists hoped to repeat the success of the Viennese physician-researcher Oleh Hornykiewicz, who experimented with clinical use of L-dopa and laid the groundwork for the subsequent introduction in 1967 of oral L-dopa as the first effective drug to treat a neurodegenerative disease. Davies recalled how his collaborators experimented in the clinic, treating AD patients with choline bought from a pharmacy across the street. The subsequent development of today's widely used cholinesterase inhibitors is history, though they help less with AD than L-dopa does with PD.

A special highlight of the conference was the appearance of Cai'ne Wong, who published his seminal work isolating beta amyloid while he was a technician with George Glenner. Wong had left science for a career in writing, and most AD researchers working today have never seen him. In his search for original research records, Wong discovered that many had been inadvertently destroyed a few years after Glenner's lab was disbanded following his early death from a systemic amyloidosis. Glenner was a competitor of Colin Masters, but also a frequent collaborator, as Masters himself noted in Tübingen. Indeed, the two had met to basically divvy up the prize, deciding that Glenner would go after vessel amyloid and Masters after the core plaques.

Wong also said that Glenner was so disenchanted with the journals Nature and Science that he did not even consider submitting his seminal discovery to them, publishing it instead in Biochem & Biophy Research Communications. In absentia, Nature or Science editors took repeated stabs on the familial theme that they sometimes don't know a good thing when they see it. Take heart, researchers everywhere; you are in good company! For example, few American AD researchers know that Jean-Pierre Brion at the Free University of Brussels Medical School published a landmark paper on tau protein in neurofibrillary tangles as early as 1985, three years before Michel Goedert confirmed and extended his findings. Why? Nature had snubbed Brion and he then decided against English altogether, publishing instead in French in Archives de Biologie (Bruxelles). And not all will know that as early as 1987, before proteasomal degradation was understood, Yasuo Ihara already showed that ubiquitin is an integral part of neurofibrillary tangles. (In their defense, this last finding the Science editors were prepared for.)

Also already in the 1980s, imaging hippocampal atrophy for an early diagnosis of AD began to take shape with the pioneering work of Mony de Leon, first with CT but soon after with MRI and PET. Sadly, one of his more important papers appeared in PNAS on September 11, 2001, just as he, a New Yorker, saw the towers fall, de Leon told the audience.

Konrad Beyreuther is credited with breaking, by an inch, the tape across the publication finish line in the fierce 1986 race to clone the APP gene. Other groups who hotly pursued APP include Dmitry Goldgaber and Carlton Gajdusek, Rudi Tanzi and Rachael Neve (both published a day after Beyreuther), Nikolaos Robakis and Henry Wisniewski, Barbara Cordell (who filed a patent), and also Carmela Abraham, Dennis Selkoe, and Huntington Potter, who instead cloned the amyloid plaque component α1-antichymotrypsin. These rivalries were recalled when Beyreuther noted the day and minute when his group first knew they had the right clone (23 October 1986, 11:12 p.m.), and Goldgaber recalled his research leading up to the clone he presented at that year's Society for Neuroscience conference in Washington, D.C. At the time, the field considered APP cleavage mostly abnormal. That began to change in

1992, when Christian Haass and colleagues in Dennis Selkoe's group showed that cells throughout the body normally make and secrete the Abeta peptide. The next big prize many labs are chasing these days is a high-resolution crystal structure of APP, or of presenilin and other γ-secretase complex components.

A theme that reached from the historic session into the future concepts session is the idea of genetic heterogeneity in neurodegenerative disease. Peter St. George-Hyslop started the thought when he chose to speak about it rather than about the finding he is best known for, that is, the discovery of the presenilin 1 gene. His earlier realization, published in 1990, that changes in several different genes can cause Alzheimer disease, broadened the field and has been widely borne out. Other speakers extended the notion to speculate that neurodegeneration will in the future be considered a spectrum disorder. Christine van Broeckhoven suggested that forms of hemorrhagic stroke, Alzheimer disease, and frontotemporal dementias can be reasonably seen as occurring on a continuum, and Monique Breteler noted that overlaps between these different origins of dementia are seen at the level of imaging and human symptoms. Furthermore, Virginia Lee outlined significant overlap at the level of pathology across a range of dementing disorders involving the proteins tau and α-synuclein.

The future session saw talk about prevention. Breteler cautioned that population-based prevention strategies eventually will have to deal with the way dementia occurs most often, that is, mixed up with numerous co-morbidities. She urged that ways be developed to treat dementia in community populations, not just AD in carefully defined and selected groups as is done for clinical trials. Another prediction is that we will be able to deal with AD much like doctors handle atherosclerotic cardiovascular disease these days: use a simple, fluid-based test to screen people for their risk of developing AD and prescribe a preventive medicine, if needed. Nick Fox held out the provocative notion that we will carry data about our brain on memory sticks, that is, that we will obtain high-resolution brain scans periodically in mid-life that will alert us to the first signs of atrophy or metabolic loss and tell us when to intervene therapeutically. Such scans would represent a sort of reverse growth chart of the brain from the ones used in routine pediatric care. No matter which vision the speakers favored, they agreed that the field needs to find designs for smaller, faster, cheaper prevention trials than the ones considered the gold standard today. An urgent priority toward that goal is that a biomarker be validated in the context of a clinical trial. Then it could be accepted as a surrogate outcome first in small, focused intervention trials, and eventually serve to shorten prevention trials. All this will still take at least two decades, Breteler estimated.

The amyloid hypothesis continues to dominate the field, perhaps even more so now that its first fruits are being put to the test in the clinic. Even while this is happening, however, John Hardy called on the field to consider alternative explanations of the available data. He said he is troubled by "too much good news" in that amyloid deposition is all too easy to treat in mice, even as the leap from mice to humans seems as questionable as ever. Efforts to translate mouse treatments to humans have either failed, shown feeble effects, or are still underway. Hardy urged that the field not take clinical success of the amyloid hypothesis for granted and put effort into developing more rigorous alternatives. Two ideas Hardy considered worth exploring are the presenilin inhibition hypothesis advanced by Jie Shen and others, and a little-noticed suggestion that Abeta serves a role in sealing blood vessels, advanced by Craig Atwood and colleagues. A geneticist, Hardy also urged his colleagues not to assume that genetics will be able to explain all risk for neurodegenerative disease, but to take the power of stochastic events into account as well. The conference closed with a plea from Bengt Winblad not to dismiss people with advanced AD as beyond help. Even in a completely mute state, the person remains, and deserves the best care to the end. The conference dinner welcomed conference-goers at the same restaurant that the 37th psychiatry convention had patronized in 1906. And the event closed with Harald Steiner's announcement that the Hans and Ilse Breuer Foundation will award its 2007 Alzheimer research prize to Eva-Maria Mandelkow to advance her research on the role of tau protein.

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