Profile

Bruno Dubois: transforming the diagnosis of Alzheimer's disease

It's not uncommon to find that medicine runs in families, but in the case of Bruno Dubois the association is a little more extreme. From his father all the way back for five generations, the Dubois family has been associated with medicine. Even more incredibly, each generation has cultivated an interest in the relationship between the brain and behaviour. His great-great-great-grandfather kept up a correspondence with one of the fathers of modern neurology, Duchenne de Boulogne, while his grandfather was trained by Joseph Babinski at the Pitié-Salpêtrière Hospital in Paris, France, where Dubois and his father both trained, and where Dubois now leads a team at the Brain and Spine Institute (ICM).

Far from being boastful when it comes to his rich neurological pedigree, Dubois rather shies away from talking about his family. He's far more comfortable, and instantly engaging, when he's talking about the work of his Cognition, Neuroimaging, and Brain Diseases team at the ICM.

The team grew at the interface between the departments of neuropsychology and neurochemistry, which were led by Dubois' two great mentors, François Lhermitte and Yves Agid, respectively, with the aim to further our understanding of the role of the frontal lobes in the organisation of the systems that underpin cognition. And what happens when those systems go wrong? Naturally, neurodegenerative diseases are a major focus of the team's research and of Dubois' clinical work, and eagle-eyed readers of *The Lancet Neurology* will probably already have recognised Dubois as an author of several seminal papers that have changed the way Alzheimer's disease is conceptualised.

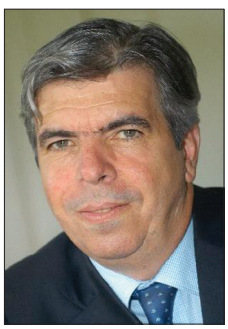
In 2007, Dubois was a leading member of the International Working Group that proposed new diagnostic criteria for Alzheimer's disease in a paper that has had a profound influence on the way Alzheimer's disease is approached. "Before the 2007 paper, I used to say there were three main rules for the diagnosis of Alzheimer's disease", Dubois explains. "First, the definitive diagnosis of Alzheimer's disease can only be made post mortem; second, the clinical diagnosis could only be probable; and third, because it's difficult to diagnose Alzheimer's disease, it can only be done when patients have severe disease, so they are demented", he says, none of which seemed to him to be remotely adequate. "I didn't see why we should rely on a certain threshold of severity before we can diagnose a disease. If I have a little tremor of the right hand you will diagnose Parkinson's disease, you won't wait until I'm bedridden", so his team set about to modernise the way Alzheimer's disease is diagnosed.

"What we said in 2007 is that thanks to biomarkers it is now possible to diagnose Alzheimer's disease clinically with a high specificity, because we have a biological signal of the disease", Dubois explains. Using structural MRI, molecular neuroimaging with PET, and CSF analyses combined with objective evidence of an amnestic syndrome of the hippocampal type, Alzheimer's disease can now be diagnosed with a high degree of accuracy early in the course of disease before dementia onset, a stage the authors termed the prodromal stage of the disease. This radical change from defining Alzheimer's disease as a clinical pathological entity to defining it as a clinical biological entity sparked a huge debate about how best to break down and describe the different stages of Alzheimer's disease, and in 2010 the working group proposed a new lexicon for the disease. "Alzheimer's disease is no longer defined as dementia", says Dubois. "It's a disease which starts with the first clinical symptoms. Within the preclinical state we can identify two different situations: preclinical Alzheimer's disease, where patients are mutation carriers and will definitely develop the disease, and a second group that we call 'asymptomatic at risk', meaning those people who are biomarker-positive for Alzheimer's disease, but cognitively normal, and we don't know whether they will develop the disease".

Now the working group are back with a new paper that looks to further refine the new diagnostic approach they set out 7 years ago. "We decided to be more precise about which biomarkers we should rely on", Dubois explains, "and disentangle which biomarkers have a real value in terms of specificity, and which are less specific and are more useful for prognosis. So this paper is to simplify the diagnosis of Alzheimer's disease".

Being able to diagnose Alzheimer's disease more easily, earlier, and more accurately could have a marked effect on the design of clinical studies, Dubois argues. "Studies of solanezumab for Alzheimer's disease have shown that there is a 36% rate of false diagnosis of Alzheimer's disease in clinical trials that were made in expert centres but based only on clinical criteria. So the use of biomarkers significantly increases diagnostic accuracy, and that's very important, because when you're developing disease-modifying agents that are specifically linked to biological events, you need to be 100% certain that patients do have the disease you are trying to treat". In the shorter term, he's hopeful that an increasing appreciation of the early, prodromal clinical phase of the disease will change the way people think about Alzheimer's disease as entirely synonymous with dementia. "I don't want to say Alzheimer's disease is a benign disease, it's terrible, but over time you can have several years without a significant impact on your daily life", he says, "I hope we can change our view of the disease".

David Holmes



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