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We now have powerful tools to detect pathology early, but pathology does not equal disease, and risk does not equal destiny.

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This conversation with Bruno Dubois offers a clear, experience-driven perspective on how Alzheimerâ??s disease is being redefined, from diagnosis and biomarkers to prevention and early intervention. Drawing on decades at the forefront of neurology, he challenges simplified biological definitions, explains why risk must be stratified with rigour, and outlines a future in which care shifts decisively upstream. The interview brings scientific depth together with clinical responsibility, setting out why precision, ethics, and timing now matter more than ever.

What roles do you currently hold, and how has your career shaped your focus on neurodegenerative diseases?

I am Professor Emeritus of Medicine at Sorbonne UniversitÃ© in Paris and former Head of the Neurology Department at PitiÃ©-SalpÃªtriÃ¨re University Hospital. Over the course of my career, I have directed the Institute of Memory and Alzheimerâ??s Disease, known as IM2A, and led the Inserm U610 research unit on cognition and neuroimaging at the Paris Brain Institute. I currently coordinate the French National Reference Centres for Rare Dementias and for Young-Onset Alzheimerâ??s Disease, as well as the Paris Centre of Excellence in Neurodegeneration. I am also the past President of the French Society of Neurology and a full member of the French National Academy of Medicine.

My work has long centred on neurodegenerative diseases, particularly Alzheimerâ??s disease and Parkinsonâ??s disease dementia. I spent many years working on Parkinsonâ??s disease dementia, including its clinical characterisation and diagnostic criteria, before progressively focusing more closely on Alzheimerâ??s disease. Across both fields, my main interest has been the relationship between clinical symptoms, biomarkers, and disease progression, and how these elements should be integrated into a rigorous and ethically sound diagnostic framework.

How has your work with the International Working Group shaped the definition of Alzheimerâ??s disease, and why do you challenge biomarker-only approaches?

I led and coordinated the International Working Group (IWG) on Alzheimerâ??s disease diagnostic criteria, which produced successive consensus frameworks in 2007, 2014, 2021, and subsequent updates. These criteria were developed to reflect advances in biomarker science while maintaining a clear clinical foundation. Our position is that Alzheimerâ??s disease must be defined as a clinical-biological entity. Diagnosis requires both a well-defined clinical phenotype and biological evidence of the disease. Biomarkers are indispensable, but they cannot stand alone.

This approach contrasts with the research framework proposed by the US Alzheimerâ??s Association, which defines Alzheimerâ??s disease purely on biological markers, even in individuals without symptoms. From our clinical and ethical perspective, this is problematic. Alzheimerâ??s disease is a clinical disease. While pathological changes may precede symptoms by many years, biomarker positivity in cognitively normal persons should indicate risk, not disease, because the majority of them will never develop a clinical disease in their lifetime. Labelling asymptomatic individuals as having Alzheimerâ??s disease creates significant medical, psychological, and ethical risks.

Clinical rigour is particularly important because subjective memory complaints are extremely common after the age of 60. In most cases, these complaints are not linked to true memory impairment, but rather to attention difficulties associated with ageing, sleep disorders, anxiety, or depression. A complaint alone does not constitute an Alzheimerâ??s phenotype. The danger today is that individuals with subjective complaints may undergo biomarker testing and, if positive, be diagnosed with Alzheimerâ??s disease despite normal cognition. Our role, as we see it, is to act as a safeguard, ensuring that biomarkers support careful clinical diagnosis rather than replace it.

What have your research findings revealed about early disease stages, risk stratification, and the limits of current treatments?

Until 2010, Alzheimerâ??s disease was considered only a dementia. This understanding led me to define the concept of prodromal Alzheimerâ??s disease, a symptomatic but pre-dementia stage characterised by a specific clinical phenotype, the amnestic syndrome of the hippocampal type, supported by biomarker evidence. This differs fundamentally from the broader concept of mild cognitive impairment, which encompasses many heterogeneous causes and lacks pathological specificity unless biomarkers are included.

Looking ahead, my conviction is that the real therapeutic opportunity lies even earlier, in cognitively normal individuals who are at very high risk of progression. This distinction has become central with the emergence of anti-amyloid monoclonal antibodies such as lecanemab and donanemab. These therapies are highly effective at clearing amyloid plaques from the brain, often removing a substantial proportion of the amyloid burden after around a year of treatment. However, their clinical

impact on symptoms remains modest. Trials show a slowing of cognitive decline in early stages, but patients continue to deteriorate. This suggests that once symptoms are established, it is already too late to fully stop the disease process.

However, it would be inappropriate to expose low-risk individuals to treatments that carry potential side effects. The INSIGHT-preAD study, launched in 2013 at PitiÃ©-SalpÃªtriÃ¨re Hospital, followed 318 cognitively normal older individuals with subjective memory complaints using amyloid PET and other biomarkers. The results clearly showed that only a small proportion of amyloid-positive participants progressed to clinical Alzheimerâ??s disease over follow-up. This demonstrates that amyloid positivity is necessary, but not sufficient, to predict clinical conversion. Additional factors are required to distinguish those who are truly on a trajectory towards disease.

The future, therefore, lies in prevention and research centres capable of following cohorts longitudinally, integrating biomarkers with genetic, lifestyle, and clinical factors, and developing robust risk algorithms. By stratifying risk accurately, we can target intervention to those who are closest to clinical conversion and aim, not to cure the disease, but to delay its onset in a meaningful way.

How would you characterise Franceâ??s current ecosystem in neurology and Alzheimerâ??s disease, both in terms of national organisation and international collaboration?

Franceâ??s position in neurology is anchored in a long clinical and scientific tradition that can be traced back to Jean-Martin Charcot at La SalpÃªtriÃ¨re, whose work helped shape modern neurology. That legacy still informs the strength of the field today. At a policy level, a decisive moment was the Alzheimer Plan 2008-2012, launched under President Nicolas Sarkozy, which introduced a structured national framework to improve diagnosis, care, research, and patient support. This programme brought coherence to the organisation of dementia care and created stronger links between clinical activity and research.

At the heart of this system is the national network of Centres MÃ©moire de Ressources et de Recherche, known as CMRR. These specialised memory centres, based in university hospitals and numbering around 25 across the country, have a dual mission. They provide expert diagnosis and management of cognitive disorders while coordinating regional memory consultations and supporting clinical research and therapeutic studies. The broader network of memory consultations offers front-line assessment and follow-up, with more complex cases referred to the CMRR for advanced evaluation. Multidisciplinary teams, typically involving neurologists, neuropsychologists, geriatricians, and other professionals, allow care and research to remain closely integrated and facilitate patient access to clinical trials.

This clinical infrastructure is complemented by a strong neuroscience research landscape, including major centres such as the Paris Brain Institute and other university-linked groups in cities such as Bordeaux and Marseille. Internationally, France is fully embedded in global collaboration. We participate in large, multinational clinical trials coordinated by the pharmaceutical industry and are actively involved in European research programmes, with close exchanges with colleagues in countries such as Germany and the United Kingdom. Taken together, this combination of historical depth, structured national organisation, and international integration underpins Franceâ??s standing in the global neurology and Alzheimerâ??s disease field.

What do recent advances in amyloid- and tau-targeting therapies reveal about the current and future treatment landscape in Alzheimerâ??s disease?

Therapeutic progress in Alzheimerâ??s disease has, for the moment, converged around the amyloid cascade, largely because anti-amyloid monoclonal antibodies have delivered consistent and reproducible biological effects. These agents reliably reduce amyloid plaque burden in the brain and, when introduced at early stages of the disease, are associated with a modest but measurable slowing of clinical progression. Although the magnitude of symptomatic benefit remains limited, the fact that an effect on clinical outcomes can now be demonstrated marks a meaningful turning point for the field and provides partial support for the amyloid cascade hypothesis.

At the same time, tau pathology is unquestionably central to the disease process. Tau lesions emerge early in medial temporal regions and, in the presence of amyloid pathology, tend to propagate to wider cortical areas. Alzheimerâ??s disease is therefore best understood as the result of a dynamic interaction between amyloid and tau, with amyloid facilitating the spread of tau-related pathology. Despite this biological relevance, therapeutic strategies directly targeting tau have not yet yielded consistent clinical benefits in trials. By contrast, amyloid-directed therapies have shown robust biomarker effects alongside modest clinical slowing. For now, amyloid therefore remains the most solid therapeutic target available, even as it is clear that addressing amyloid alone will not be sufficient to fully modify the course of the disease.

How close are we to the routine clinical use of biomarkers in Alzheimerâ??s disease, and how should they be integrated responsibly into practice?

We now have three complementary biomarker approaches, and the real question is no longer whether they work, but how they should be used. Amyloid PET has clear diagnostic value, yet in France it has never been a routine tool. Its use remains selective, largely shaped by authorisation and reimbursement constraints, and is typically reserved for specific situations such as atypical or mixed clinical presentations or younger-onset cases, rather than everyday memory-clinic practice.

Cerebrospinal fluid biomarkers obtained through lumbar puncture are, by contrast, well established in specialist memory settings. When performed using standardised procedures, lumbar puncture is generally well tolerated and supported by extensive safety data. In our centre at PitiÃ©-SalpÃªtriÃ¨re, we perform several hundred procedures each year because it remains a practical and reliable way to confirm Alzheimer pathology when the clinical syndrome points clearly in that direction. This reflects a principle that has guided my work throughout: Alzheimerâ??s disease must be approached as a clinical-biological entity. Diagnosis begins with a well-defined clinical phenotype and is then confirmed by biological evidence, closely echoing Alois Alzheimerâ??s original clinico-pathological reasoning. In typical Alzheimerâ??s disease, the clinical presentation is not ambiguous. It is a recognisable amnestic syndrome of the hippocampal type that can be identified early through structured cognitive assessment, but clinical features alone are not sufficient without biomarker confirmation.

The most recent and potentially transformative development is the emergence of blood-based biomarkers, particularly plasma phosphorylated tau, such as p-tau217. These markers correlate strongly with amyloid pathology and represent a major step towards simpler and more accessible biological confirmation. Used appropriately, they could reduce reliance on lumbar puncture and streamline diagnostic pathways. Interpretation, however, is critical. The distinction between normal and pathological values is not absolute, which makes a two-threshold approach essential, allowing confident exclusion at low levels, strong suspicion at high levels, and further confirmation for

intermediate results using cerebrospinal fluid biomarkers or amyloid imaging.

The central risk lies in uncontrolled use. If blood biomarkers are applied indiscriminately, especially in cognitively normal individuals with subjective complaints, there is a real danger of equating biological changes with disease and delivering information that may have significant psychological and social consequences without clear clinical meaning. Biomarkers have fundamentally transformed the field, shifting Alzheimerâ??s disease from a diagnosis of probability to one supported by in vivo biology, something that was not possible before the mid-2000s. At the same time, they impose a new responsibility. We now have powerful tools to detect pathology early, but pathology does not equal disease, and risk does not equal destiny. The challenge is to integrate these tools into clinical practice with rigour, restraint, and ethical clarity, rather than allowing technical progress to outpace clinical judgement.

What are you most looking forward to in the coming years, and how do you see the next phase of Alzheimerâ??s care taking shape?

The most immediate milestone is the realisation of the Centre dâ??Excellence et de Recherche sur la Maladie dâ??Alzheimer et maladies dÃ©gÃ©nÃ©ratives (CERMAD). Conceived as a purpose-built facility within the PitiÃ©-SalpÃªtriÃ¨re hospital campus, CERMAD is designed to bring clinical care and research into closer alignment, with a clear focus on early identification of neurodegenerative disease and intervention at the earliest possible stage. Construction is expected to begin in early 2026, with completion planned for 2027 and an inauguration currently projected for March of that year. The initiative is being made possible through private funding and philanthropy, supported by a dedicated association established to ensure long-term sustainability. CERMAD is intended as a prevention-oriented centre, combining structured risk assessment, biomarker-informed follow-up, and early-phase therapeutic research.

Beyond the building itself, my broader hope is that CERMAD, together with comparable centres in places such as Geneva and Amsterdam, will help drive a shift towards prevention-focused models of care. People would come not because they are already ill, but to understand their individual risk. When that risk is low, the response should focus on modifiable factors such as cognitive stimulation, hearing correction, cardiovascular health, physical activity, and social engagement. When the risk is very high, future strategies may include early pharmacological intervention, potentially using short courses of anti-amyloid monoclonal antibodies, with the aim of delaying the onset of clinical disease rather than treating it once established. Biomarkers would be reassessed over time, allowing decisions to be refined as risk evolves.

This vision remains prospective and will require robust clinical evidence, but it reflects a clear direction for the field. Even a modest delay in the transition from biological risk to clinical disease would represent a major advance. The possibility of moving Alzheimerâ??s care upstream, from late-stage intervention to anticipation and prevention, is what I find most compelling as we look ahead.

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