Alzheimer disease (AD) has until recently been regarded as a dementia syndrome and diagnosis was not made until the patient evidenced sufficient cognitive decline to manifest a dementia syndrome with cognitive and functional decline. Definite diagnosis of AD required a postmortem confirmation. This conceptualization and diagnosis of AD are currently undergoing a major transformation, due to both the introduction of biomarkers into the field and the recognition that the clinical stage of the disease is preceded by a long silent asymptomatic phase and a predementia symptomatic period. The first meaningful step leading to this reconceptualization was taken by an International Working Group (IWG) led by Bruno Dubois in 2007. The IWG criteria offered a redefinition of AD as a dual clinicobiological entity that could be recognized in vivo, before the onset of dementia, on the basis of a specific core clinical phenotype comprised of an amnestic syndrome of the hippocampal type and supportive evidence from biomarkers reflecting the presence of an Alzheimer-type pathologic condition. A direct consequence of the introduction of the IWG criteria has been a redefinition of the disease—considered to be a clinicobiological entity—with a long asymptomatic period, the preclinical or presymptomatic stage, preceding the symptomatic one or clinical stage of the disease.

This shift in the conceptualization and diagnosis of AD opened the door for earlier and more specific, biomarker-supported, diagnosis of the disease. The diagnosis can now be established in the prodromal stage of the disease before the occurrence of dementia. This fact has already generated several consequences: initiation of clinical trials at a predementia stage with disease-modifying drugs and implementation in research and academic centers, earlier disease diagnosis, and investigation of early transitional stages of the disease from normal to mild impairment and from mild impairment to mild dementia. The clinical stage can now be detected in mildly symptomatic patients before dementia appears, offering the subject the possibility of making valuable decisions while still competent. Because there is consensus that the diagnosis should be implemented only in the clinical stage of the disease, the
essence of the new IWG diagnostic criteria relies on the recognition of this dual aspect for the diagnosis of AD: a specific clinical presentation that is related to a well-defined underlying pathologic abnormality detected through biomarkers.

Biomarkers are required for the diagnosis of AD in the IWG approach. Patients must exhibit either pathophysiologic or topographic abnormalities characteristic of AD. Pathophysiologic markers include the molecular signature of AD in the cerebrospinal fluid of low amyloid beta (Aβ) peptide with elevated levels of tau or hyperphosphorylated tau or abnormal amyloid imaging with one of the available ligands specific for fibrillar Aβ. Topographic markers include medial temporal/hippocampal atrophy on magnetic resonance imaging or bilateral parietal hypometabolism on positron emission tomography. The increasing knowledge of biomarkers, their role in diagnosis and in determining disease evolution, and better understanding on the disease continuum, with its initial clinically silent preclinical stage and mildly symptomatic prodromal one, have completely shifted the AD field from the old conceptualization of AD as a dementia—not now recognized as the end-stage disease—into a highly evolving field of knowledge and potential early diagnoses and treatments. This volume presents a comprehensive view of this new understanding of the disease with the attendant possibilities offered by the biomarkers (both those currently in use and those being developed) as well as potential therapeutics.

This milestone volume shares the current, up-to-date knowledge and understanding of the possibilities offered not only by biomarkers but also by this new conceptualization of the disease. Each article, written by world-renowned experts, summarizes an area of knowledge relevant to early diagnosis and offers a window into the future on research and clinical practice. The issue also covers the state of the art on clinical trials for prodromal and very early AD and how the clinical diagnosis may evolve in the near future.

In summary, there is increasing consensus on AD as a clinicobiological entity in which biomarkers, especially pathophysiologic markers revealing the underlying pathologic condition, and clinical assessment reveal the corresponding clinical deficits. This reconceptualization of the disease is for the first time creating the possibility of intervening through clinical trials in the predementia stage of the disease. This issue crystalizes the current understanding and knowledge of AD by offering a thorough overview of the state of the art of this fascinating and evolving field.

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