

Preface

The downside of the current tendency to prolonged life expectancy in developed countries is the increase in diseases associated with advanced age, especially those involving the central nervous system (CNS). Foremost among these is sporadic Alzheimer's disease (AD) which leads to dementia (Brookmeyer et al. 2007; Qiu et al. 2009; Reitz et al. 2011; Mayeux and Stern 2012). Nevertheless, today, despite all efforts on numerous fronts, no causal or disease-modifying therapy is available (Doody et al. 2014; Salloway et al. 2014). AD is a neurological disorder of the human CNS. The pathological lesions associated with the AD process require an unusually long period of time to evolve, but, in the final analysis, they result in clinically recognizable impairment of higher brain functions.

This book is written for a readership that is to some extent familiar with the anatomy of the human nervous system and is interested in the changes it undergoes during the AD process. As in the previously published book on sporadic Parkinson's disease from the same Springer series (Braak and Del Tredici 2009), the present effort approaches and interprets the pathological process in AD chiefly from a neuroanatomical perspective. However, we want to make the text readable for non-experts, *inter alia* by including throughout it both introductory and more detailed explanations pertaining to important anatomical relationships that facilitate understanding the material but that are not available in standard textbooks or only cursorily explained therein, e.g., the anatomy of the entorhinal region.

Clinically, AD only occurs in humans, and the hallmark lesions underlying the disease process predominantly are found in the human CNS. Thus, there are no truly adequate animal models for AD (Rapoport and Nelson 2011), although the implications of this reality are largely overlooked in much current research. For the past 25 years, an amyloidocentric understanding of AD research has largely ignored opposing data and arguments, thereby leaving aside important questions that still require answers (Maarouf et al. 2010). The authors focus on fundamental aspects of the AD process as a whole with the intention of encouraging alternatives to the A β -centered understanding of AD.

As indicated by its title, this book deals mainly with morphologically recognizable deviations from the normal anatomical condition of the human CNS. The

AD-associated pathology is illustrated from its beginnings (sometimes even in childhood) until its final form that is reached late in life. The AD process commences much earlier than the clinically recognizable phase of the disorder and its timeline includes an unusually extended non-symptomatic phase. The further the pendulum swings away from the symptomatic final stages towards the early pathology, the more obvious the lesions become, although from a standpoint of severity they are more unremarkable and, thus, frequently overlooked during routine neuropathological assessment. For this reason, we decided to deal with the hallmark lesions in early phases of the AD process in considerable detail. Clinically manifest cases of AD, on the other hand, display extensive disease-associated lesions that, as a rule, are accompanied by non-AD-related pathologies, including vascular changes and concomitant neurodegenerative disorders.

For a constitutive introduction to the morphology of AD, one of the authors (HB) owes a special debt of gratitude to an American colleague, Thomas L. Kemper, MD (Department of Anatomy and Neurobiology, Boston University School of Medicine), who also conveyed to him the fascination with the idea that AD is a disorder that adheres to the conditions of human neuroanatomy. The authors thank the Goethe University Frankfurt (The Braak Collection). They are also thankful for valuable comments provided by Khalid Iqbal, PhD (New York State Institute for Basic Research in Developmental Disabilities) and Michel Goedert, MD (MRC Laboratory of Molecular Biology, University of Cambridge). They wish to express their appreciation to Horst-Werner Korf, MD (Dr. Senckenbergische Anatomie, Goethe University, Frankfurt) for the invitation to prepare this book, Albert C. Ludolph, MD (Department of Neurology, University of Ulm) for support and helpful discussions, and Ms. Anne Clauss from Springer (Heidelberg) for careful editing of the text. They also are grateful to Jürgen Bohl, MD (formerly Department of Neuropathology, University of Mainz) for ongoing support, Ms. Simone Feldengut (Tables, silver staining, immunocytochemistry), Ms. Siegrid Baumann, Ms. Gabriele Ehmke, Ms. Julia Straub (immunocytochemistry), Mr. Hans-Jürgen Steudt (Olympus Germany, Stuttgart) for technical assistance, and Mr. David Ewert (Department of Neurology, University of Ulm) for the many hours spent preparing and helping to design the illustrations. In view of the breadth of the subject matter, it was necessary to weigh the bibliography in favor of more recent original studies and reviews. In other words, it was not the authors' intention to supply an exhaustive survey of all of the pertinent literature from the AD field.

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