

# Contents

<b>1</b>	<b>Prologue</b> . . . . .	<b>1</b>
<b>2</b>	<b>Introduction</b> . . . . .	<b>3</b>
2.1	Sporadic AD Is a Proteinopathy Linked to the Development of Intraneuronal Inclusions of Abnormal Tau Protein Which, in Later Phases, Are Accompanied by the Formation of Extracellular Plaque-Like Deposits of Amyloid- $\beta$ Protein . . . . .	3
2.2	Some Neuronal Types Exhibit a Particular Inclination to the Pathological Process While Others Show a Considerable Resistance To It . . . . .	6
2.3	Consistent Changes in the Regional Distribution Pattern of Intraneuronal Inclusions Make a Staging Procedure Possible . . . . .	9
<b>3</b>	<b>Basic Organization of Non-thalamic Nuclei with Diffuse Cortical Projections</b> . . . . .	<b>15</b>
<b>4</b>	<b>Microtubules and the Protein Tau</b> . . . . .	<b>21</b>
<b>5</b>	<b>Early Presymptomatic Stages</b> . . . . .	<b>25</b>
5.1	Stage a: The Appearance of Abnormal Tau in Axons of Coeruleus Projection Neurons . . . . .	25
5.2	Stages b and c: Pretangle and Tangle Material Develops in the Somatodendritic Compartments of Coeruleus Neurons and Similar Lesions Appear in Additional Brainstem Nuclei with Diffuse Cortical Projections . . . . .	28
5.3	Survival of Involved Neurons, Loss of Neuronal Function, and Degradation of Remnants After the Death of Involved Neurons . . . . .	33

<b>6</b>	<b>Basic Organization of Territories That Become Sequentially Involved After Initial Involvement of Brainstem Nuclei with Diffuse Projections . . . . .</b>	<b>37</b>
6.1	The Cerebral Cortex . . . . .	37
6.2	The Amygdala . . . . .	39
6.3	The Entorhinal Region and the Presubiculum . . . . .	41
6.4	The Hippocampal Formation . . . . .	44
6.5	Cortical Gradients in Differentiation, Myelination, and Pigmentation . . . . .	50
6.6	Interconnecting Pathways . . . . .	51
<b>7</b>	<b>The Pattern of Cortical Lesions in Preclinical Stages . . . . .</b>	<b>57</b>
7.1	Stages 1a and 1b: Development of Inclusions in Axons and of Pretangle Material in Transentorhinal Pyramidal Cells . . . . .	57
7.2	NFT Stages I and II . . . . .	61
7.3	Prevalence of Stages a–II . . . . .	64
7.4	The Problem of Selective Vulnerability and the Potential Transmission of Pathological Changes from One Neuron to the Next . . . . .	70
7.5	Imaging Techniques and Soluble Tau as Biomarker in the CSF . . . . .	72
<b>8</b>	<b>Alzheimer-Associated Pathology in the Extracellular Space . . . . .</b>	<b>75</b>
8.1	The Amyloid Precursor Protein and the Abnormal Protein A $\beta$ . . . . .	75
8.2	Sources and Secretion of A $\beta$ . . . . .	77
8.3	Transient Extracellular A $\beta$ Deposits . . . . .	85
8.4	Mature Forms of A $\beta$ Deposits and Plaque Degradation . . . . .	86
8.5	Phases in the Development of A $\beta$ Deposits . . . . .	87
8.6	Formation of Neuritic Plaques (NPs) . . . . .	89
8.7	Cerebral Amyloid Angiopathy . . . . .	89
8.8	Soluble A $\beta$ as a Biomarker in the CSF . . . . .	92
<b>9</b>	<b>The Pattern of Lesions During the Transition to the Symptomatic Phase and in Fully Developed Alzheimer's Disease . . . . .</b>	<b>95</b>
9.1	NFT Stage III: Progression into the Basal Temporal Neocortex, Including Portions of the Fusiform and Lingual Gyri, Involvement of Superordinate Olfactory Centers and the Limbic Thalamus . . . . .	95
9.2	Involvement of Neocortical Chandelier Cells . . . . .	99
9.3	Are Stages a–III Part of the AD-Associated Pathological Process? . . . . .	101
9.4	Basic Organization of Insular, Subgenual, and Anterior Cingulate Regions . . . . .	105
9.5	NFT Stage IV: Further Progression of the Lesions into Proneocortical and Neocortical Regions Governing High Order Autonomic Functions . . . . .	106

9.6	Macroscopically Recognizable Characteristics of Advanced AD . . . . .	109
9.7	NFT Stage V: Fan-Like Progression of the Neocortical Pathology into Frontal, Superolateral, and Occipital Directions and its Encroachment on Prefrontal and High Order Sensory Association Areas . . . . .	109
9.8	NFT Stage VI: The Pathological Process Progresses Through Premotor and First Order Sensory Association Areas into the Primary Fields of the Neocortex . . . . .	110
9.9	The Pattern of the Cortical Tau Pathology in AD Mimics the Developmental Sequence of Cortical Lipofuscin Deposits and, in Reverse Order, That of Cortical Myelination . . . . .	111
9.10	The Prevalence of Tau Stages and A $\beta$ Phases in Various Age Categories and Potential Functional Consequences of the Lesions . . . . .	113
<b>10</b>	<b>Final Considerations . . . . .</b>	<b>131</b>
<b>11</b>	<b>Technical Addendum . . . . .</b>	<b>135</b>
11.1	Stock Solution for Physical Developer . . . . .	137
11.2	Campbell-Switzer Technique for Brain-Amyloid Deposits . . . . .	137
11.3	Gallyas Technique for Neurofibrillary Pathology . . . . .	138
	<b>References . . . . .</b>	<b>141</b>