SECTION

IX

ALZHEIMER AND OTHER DEMENTIAS

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As average life expectancies continue to rise dramatically, the aging population is at risk, now more than ever, for Alzheimer disease and other dementias characterized by impaired memory and other cognitive disabilities. In this section, age-associated alterations in cognition, brain structure, and neurochemistry of stroke, Alzheimer disease, and neuropsychiatric manifestations of HIV-1 and AIDS are addressed.

Mohs and Haroutunian summarize the issues involved in early diagnosis of Alzheimer disease. This is an area that has received intense interest, given the hope that future therapies may some day alter the course of the disease. Clearly, in such a circumstance, making a diagnosis at the earliest possible time becomes critical. Ideally, diagnosis in the premorbid state will someday be possible, a possibility further suggested in Chapter 86 by Small, who reviews positron emission tomography techniques that, when combined with the apolipoprotein E status of patients with potential Alzheimer disease, may be a very powerful tool for exceptionally early diagnosis. Yet another aspect of both these chapters, and one that is drawing increasing attention, is the question of the utility of current diagnostic criteria for Alzheimer disease and such potentially related conditions as mild cognitive impairment. Increasingly, these distinctions are becoming blurred.

Parvathy and Buxbaum provide a detailed overview of the molecular and pathologic changes in Alzheimer disease. The work they review increasingly points toward the centrality of amyloid in the pathophysiology of Alzheimer disease and makes the development of transgenic animals that overexpress β-amyloid secondary to the insertion of various human mutations that have been linked to Alzheimer disease in humans so crucial. Chapter 85, by Nixon, is a companion piece to Chapter 83. Whereas Nixon focuses on cellular events, Parvathy and Buxbaum focus on genetic and molecular issues. Of particular interest in Chapter 85 is the discussion of the possible role of lysosomal enzymes in the cellular damage of Alzheimer disease. Chapter 84, by Duff, is a concise summary of developments in transgenics, as well as the challenges the field faces in using these models, particularly from the perspective of relative contributions of tau and amyloid to the pathogenesis of Alzheimer disease. As these models continue to improve and to demonstrate their congruence with the Alzheimer phenotype, they will prove a cornerstone drug discovery in Alzheimer disease. In my chapter, Chapter 87, I try to draw on these advances in cellular and molecular biology to discuss the exciting opportunities for the therapeutics of Alzheimer disease. In addition, I summarize the status of current treatments.

Raskind and Barnes review informative studies of psychopharmacologic management of noncognitive behavioral problems in Alzheimer disease, including depressive signs and symptoms, psychotic symptoms, and disruptive agitated behavior. It is becoming increasingly clear that such behaviors can be even more problematic than the cognitive disturbances. Regrettably, this has been a very difficulty therapeutic area, although one that is now receiving a good deal of attention. The data they review can guide the clinician in making some very difficult choices among a broad spectrum of agents that have been employed to ameliorate the host of behavioral symptoms that patients with Alzheimer disease can display.

Manca, Davies, and Burns discuss the implications of the demographic trend toward an aging population and the economic impact of neuropsychiatric disease. As is appropriate, considerable concern is raised about the magnitude of the economic implications of this disease. Given the need to justify a new therapeutic agent on its cost effectiveness,

this kind of discussion is increasingly becoming a part of drug development.

Since the publication of the *Fourth Generation of Progress,* the recognition of Lewy body dementia has increased substantially. To many clinicians, this is a diagnostic entity that was previously incorrectly diagnosed as either Alzheimer disease with some parkinsonian features or Parkinson disease with dementia. In a wonderfully lucid chapter (Chapter 91), McKeith et al. distinguish dementia with Lewy bodies from Alzheimer disease and provide a detailed account of the clinical features discovered in the 1990s.

An entire new term for a set of diseases, tauopathies, was coined in the last few years, and the group that is largely responsible for characterizing the molecular and cellular pathology of these conditions has contributed a key chapter to this section. In Chapter 94, Higuchi, Trojanowski, and Lee address tau-positive filamentous lesions in neurodegenerative disease.

One of the most active areas of central nervous system therapeutics has been in developing drugs to decrease the cellular disease that follows stroke. Many drugs have shown promise in what seem valid animal models, but, as the chapter by Small, Morley, and Buchan points out, have not been efficacious in the clinic. Nevertheless, as this chapter details, this is a particularly rich area of experimental therapeutics and one of the best examples of the ways in which fundamental advances in neuroscience can drive rational drug development. This theme is made all the more apparent when Chapter 92, by Graham and Hickey, is read alongside Chapter 93, because the former so elegantly summarizes the mechanisms that exacerbate neuronal death resulting from hypoxia and hypoglycemia.

Highly active antiretroviral therapy (HAART) has revolutionized the treatment of AIDS and has had a major impact on the neuropsychiatric manifestations of HIV infection. Evans and Mason address both the neurocognitive functioning and the psychiatric manifestations of HIV-1 infection, as well as its treatment in the HAART era.

Taken together, the chapters in this section are an impressive compendium of advances in understanding and treating some of the worst diseases faced by humans. That so much has been learned in so short a time is truly remarkable, but even more remarkable is the advances that will undoubtedly occur in the future, advances whose foundations are eloquently elaborated in the following pages.

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