NEUROPATHOLOGY OF DEMENTING DISORDERS.
By William R. Markesbery.

Recent years have witnessed a flourishing in the publication of neuropathology textbooks. Not only general volumes covering neuropathology as a whole, but also books on single subjects have appeared in the specialized bookshops. That there are several books on brain tumours is hardly surprising, but the publication of a second textbook on the neuropathology of dementias within one year must reflect increased interest in a previously rather neglected field. Dementia has become a focus of interest, both scientifically and socially; it has an immense impact on health care and health policy. With an increasing ageing population, the incidence of dementia has dramatically increased to reach epidemic proportions. Approximately 15% of those aged 65 have dementia of varying severity and currently there are 20 million sufferers of dementia in the world, indicating the magnitude of the problem. Scientific developments ranging from the bedside to the laboratory bench have also increased our interest in dementias. The sophistication of clinical investigative techniques, the more precise definition of nosological entities, the improvement of neuropathological investigations and the discoveries in both molecular biology and genetics have made research on dementias one of the most exciting and challenging areas of biomedical research. For these reasons it is not surprising that this increased interest is reflected by new publications. This recent monograph has been edited by William Markesbery and his team covers the field remarkably well.

The majority of the authors, about two-thirds of the 33, are from the United States, but the United Kingdom, France, Canada and Sweden are also represented. There are 18 chapters covering various aspects of dementia, of which the first three are introductory. In the first chapter Markesbery overviews dementing disorders, while in the second, Jagust gives a comprehensive background to the neuroimaging of dementing disorders. Dickson describes ageing changes in the central nervous system, the knowledge of these abnormalities is particularly important in the differential diagnosis with Alzheimer’s disease. Three chapters are devoted to Alzheimer’s disease: one each to clinical features, diagnosis and epidemiology (Schofield and Mayeux); to genetics (St George-Hyslop) and to neuropathology including animal models (Donald Price with a large team). These three chapters comprehensively cover what is clearly the single most important dementing condition. The clinical definition of Alzheimer’s disease has perhaps not been as difficult as that of neuropathological diagnostic criteria, but the chapter on clinical symptomatology reflects the heterogeneity of the disease. St George-Hyslop is in an excellent position to review the genetics of Alzheimer’s disease, since he has played such a salient role in this field. The juxtaposition of the neuropathology of human disease with animal models is illuminating and clearly illustrates that the existing models, although improving, do not reflect the complex neuropathology of the human disorder.

Pick’s disease has been, until recently, somewhat neglected in the shadow of Alzheimer’s disease and Markesbery has succeeded in not only reviewing the disease, but also providing a concise differential diagnosis of frontotemporal dementias. It can be argued that for the practising neuropathologist the differential diagnosis of frontotemporal dementias poses one of the most difficult problems. Pick’s disease, corticobasal degeneration, motor neuron disease-associated dementia, the so-called frontal lobe dementia of non-Alzheimer-type and progressive sub-cortical glosis form a true minefield for the unaware or even for those who have considerable experience in the diagnosis of neurodegenerative diseases. Two of these conditions, frontal lobe degeneration of non-Alzheimer-type and dementia in motor neuron disease, have been reviewed by Brun and Gustafson. The diagnosis of dementia in motor neuron disease, even in cases without the typical clinical symptomatology, can be made by the use of ubiquitin immunostaining; this shows positive inclusions both in the granular neurons of the dentate fascia of the hippocampus and in the superficial neurons of the cortex accompanied by abnormal neurites. However, these features are absent in frontal lobe degeneration of the non-Alzheimer-type, leaving this somewhat disputed entity without any reliable diagnostic hallmark lesion. Chromosome 17-linked dementias, now referred to as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) have been defined recently by a Consensus Conference as a clinicopathological disorder and three independent groups have reported mutation in the tau gene. Naturally, Wilhelmsen and Clark could not describe these most recent developments in a fast moving field, but give a good account of the heterogeneous pathology. Dementia with Lewy bodies is the second commonest parenchymatous dementia, although there are considerable geographical variations. Lennox and Lowe have succinctly covered the clinicopathological features, reflecting recent important developments. The clinical and pathological definition of the disease by the Newcastle group has provided useful guidelines. Ubiquitin immunostaining is a reliable diagnostic marker for the demonstration of Lewy...
bodies, but the recent discovery of a mutation in the α-synuclein gene by Polymeropoulos and his colleagues and the introduction of antibodies to α-synuclein have revolutionized research and diagnostic work. α-Synuclein has now become the hallmark of Lewy body pathology whether in idiopathic Parkinson’s disease or in dementia with Lewy bodies. It has also revealed more extensive cellular changes than any of the antibody or staining techniques used previously. Unlike ubiquitin immunostaining, which is positive in a wide range of neurodegenerative diseases, α-synuclein immunostaining is found consistently and extensively in Lewy body diseases and in multiple system atrophy, although there are initial reports of some staining in motor neuron disease and of abnormal neurites in Alzheimer’s disease.

The importance of tau pathology in two neurodegenerative diseases, progressive supranuclear palsy and corticobasal degeneration, can be compared to that of α-synuclein in Lewy body disorders. We have gained considerable insight into the molecular mechanisms of these two disorders by the use of tau antibodies which revealed not only extensive cytoskeletal pathology in neurons, but also in glial cells. Hauw and his team review progressive supranuclear palsy; they have also drawn attention earlier to the extensive cytoskeletal pathology in cortical neurons, thus highlighting an important problem: there is substantial cortical pathology in a disorder which previously has been considered to affect mainly subcortical structures. Tau immunostaining demonstrates extensive glial pathology, particularly involvement of astrocytes; there are astrocytic tangles and thorny or tuft-shaped astrocytes. Corticobasal degeneration, reviewed in an excellent chapter by Revesz and Daniel, has equally benefited from tau immunostaining: tau-positive inclusions are found in the small neurons of the superficial layers of the cortex, in abnormal neurites and in astrocytes. The astrocytic tau pathology is striking: there are astrocytic plaques formed by abnormal astrocytic processes in the grey matter. In both progressive supranuclear palsy and corticobasal degeneration there is also oligodendrogial involvement in the form of coiled bodies, which are not to be confused with glial cytoplasmic inclusions found in oligodendrocytes in multiple system atrophy.

In recent years the interest in Huntington’s disease somewhat shifted from the basal ganglia to the cerebral cortex in which, as realized by ubiquitin immunohistochemistry, there are striking alterations. The authors of this chapter (Kowall and Ferrante) give a balanced account of changes, both in the cortex and in the subcortical white matter. Their review of the neurochemical pathology of the disease guides the reader through a complex field. The chapter on amyotrophic lateral sclerosis–parkinsonism–dementia complex of Guam (Perl) is comprehensive and illuminating. Vascular dementia (Markesbery) has been the Cinderella of dementing disorders and this chapter goes some way to redress the balance. The review of virus-mediated dementias (Achim and Wiley) is exhaustive and gives an excellent account of HIV-encephalitis, in addition to the more traditional viral infections. It is still disputed whether the neuropsychological symptoms of HIV-infections, the AIDS–dementia complex, represent true cortical dementia. The cellular mechanism is also controversial; although generally accepted that there is a high viral burden in HIV-encephalitis, the infection of neuroepithelial cells, neurons and glial cells, remains controversial. On prion diseases, the authors (DeArmond and Prusiner) repeat their fine performance by giving a comprehensive account of the cellular and molecular biology of prion diseases in man and animals. The somewhat neglected field of nutritional and metabolic disorders causing dementias is described in the last chapter (Schochet) to cover vitamin deficiencies, systemic metabolic disorders, neuronal storage diseases and leucodystrophies.

The book is attractively produced in the ‘corporate’ style of the publishing house, Arnold. The layout is clear and attractive and the book is printed on paper of acceptable quality. The standard of the illustrations is generally high; obviously there are some pictures which could be improved, but this is only a minor criticism in a textbook containing so many illustrations. Although it is invidious to single out a particular chapter and reviewers do this at their peril, but the prize for best illustrations, hors concours, should go to the chapter on corticobasal degeneration. Most chapters are well referenced with many recent publications. Again it would be churlish to complain that some of the recent publications are not listed; this cannot be avoided in a book of this type. Each chapter ends with a conclusion, a feature which I find somewhat unnecessary in a book of this standard. The editor and his team of authors should be congratulated for having produced an attractive, informative and up-to-date book.

It is of some interest to compare the two recently published neuropathology textbooks on dementias. The book edited by Margaret Esiri and James Morris and published in 1997 has a wider range of cover: there are individual chapters on familial cerebral amyloid angiopathies, alcoholism, hydrocephalus, head injury and schizophrenia associated with dementia. Moreover, three introductory chapters deal with the definition, clinical features and neuropathological basis of dementia; a brief neuroanatomical description of structures important in dementia and with useful guidelines to practical approaches to pathological diagnosis. This book also features three appendices on morphometric methods, addresses of dementia brain banks and safety precautions to be taken in laboratories involved in the diagnosis and research of dementias. In contrast, the book edited by Markesbery devotes separate chapters to frontal lobe degeneration of the non-Alzheimer-type and dementia associated in motor neuron disease, progressive supranuclear palsy and corticobasal degeneration. It has also the advantage of being published a year later and therefore there is a chapter on chromosome 17-linked dementias. Moreover, this book has many more colour illustrations than that of Esiri and Morris. However, the latter is of a somewhat larger format and contains 440 pages as opposed to the 404 pages of the Markesbery book. The prices are £75 and £125 respectively. The choice is
a difficult one and may depend on personal preferences. Departments and individual neuroscientists with a strong interest in dementias and with a flexible budget may wish to buy both.

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