Developments in Neuropathology in the Past Decade

Neuropathology is a discipline that has broad applications across clinical and research fields involving the central and peripheral nervous systems and skeletal muscle. As a clinical service, neuropathology defines diseases of the nervous system by their structural features through the macroscopic, microscopic and, occasionally, ultrastructural examination of biopsy and autopsy material. Much of the research in neuropathology is centred on the study of human disease and observations that generate hypotheses to be tested by experiments in animal models or in tissue culture. Conversely, results from experimental studies aid the interpretation of pathological features of human disease.

Scientific and clinical advances in the last ten years affecting Neuropathology have been driven by the introduction of new techniques and concepts and by the need to communicate more effectively with those involved in the direct clinical care of patients and with patients and relatives themselves. A spirit of communication and collaboration has strengthened over the last decade through regular Multidisciplinary Team Meetings and collaborative research projects.

Many developments have occurred in the last ten years across the whole spectrum of adult, paediatric and forensic neuropathology. However, in this article, we focus upon some of the changes that have evolved in tumour pathology, an area of primary responsibility for most practicing neuropathologists, and in muscle pathology. We go on to describe progress in the post-mortem diagnosis and in the understanding of neurodegenerative diseases.

Advances in tumour pathology
Neuropathology is often at the centre of the clinical decision making process. The pathological diagnosis of tumours in patients is crucial for their management and treatment. Major changes in clinical practice in relation to tumours of the nervous system have come with the introduction of molecular diagnostics. Molecular evaluation of tumours is now routine (Table 1), but diagnosis remains dependent primarily on the microscopic appearances of a tumour in routine sections stained with haematoxylin and eosin.

Scientific discoveries that hold most promise for a change in clinical practice in relation to tumours of the nervous system have been due to the application of array-based and deep sequencing technologies and by the use of mouse models as a foundation for in vivo therapeutic testing. During the last decade, application of immunocytochemistry

Table 1: Some of the more commonly investigated molecular characteristics of primary CNS tumours. Citation of all of this work is not possible, for a review see reference 1.

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Test</th>
<th>Implication</th>
</tr>
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<tbody>
<tr>
<td>Glioblastoma</td>
<td>EGFR amplification</td>
<td>Distinguish from anaplastic astrocytoma</td>
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<tr>
<td></td>
<td>p53 mutations</td>
<td></td>
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<tr>
<td>Oligodendroglioma</td>
<td>1p/19q Loss (qPCR or FISH)</td>
<td>Deletion on both loci associated with superior survival and treatment response. Linked to histopathological features</td>
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<tr>
<td>Medulloblastoma</td>
<td>NMYC / CMYC PCR</td>
<td>Gains associated with poor prognosis</td>
</tr>
<tr>
<td></td>
<td>Wnt pathway mutations</td>
<td>Associated with improved prognosis</td>
</tr>
<tr>
<td>Atypical Teratoid</td>
<td>INI-1 or BAF47 immunohistochemistry</td>
<td>Mutation in this gene is linked closely with development of such tumours sporadically or genetically</td>
</tr>
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Advances in muscle pathology

The characterisation of new forms of inherited muscle disease has grown exponentially over the last ten years. New proteins whose mutations cause certain phenotypes are described several times a year. Basic histological and histochemical analysis of biopsies, including genetic testing, is often carried out at NCG (National Commissioning Group) centres. This illustrates one way in which specialists high-cost services and professional working practices can be developed and flourish. Data on muscle pathology and genetics are produced at such a rapid rate that published papers and books have difficulty in keeping pace; so many websites (e.g. www.neuromuscular.wustl.edu/) are now the main sources of up-to-date information.

Post-mortem diagnosis and understanding neurodegenerative diseases

Developments in neuropathology in the last decade have played a significant role in the continuing search for the effective diagnosis and treatment of neurodegenerative diseases. An appreciation of neuropathological changes and mechanisms of disease are essential for the interpretation of neuroimaging and of biomarkers in the blood and CSF used in the diagnosis of patients with dementia. Relating the changes in the human brain to those in transgenic mouse models has allowed significant progress in our understanding of disease processes during the last 10 years.

Recognition of genetic abnormalities in familial diseases has had a profound effect on neuropathology and vice-versa. For example, the known genetic causes of Parkinson’s disease include mutations in the α-synuclein gene, reported in the late 1990s. The presence of this synapsen-related protein, as insoluble accumulations in Lewy bodies and in neurites (Figure 2) in sporadic Parkinson’s disease, has stimulated physiological experiments to determine the effects of excessive synuclein on synaptic function. Using transgenic mice that overexpress α-synuclein, whole cell patch clamp recordings have shown that high levels of expression of α-synuclein alter synaptic function and suggest that synaptic dysfunction may occur early in Parkinson’s.

Technological advances have also increased our understanding of CNS disease. Confocal microscopy, together with continuing advances in immunocytochemistry have allowed proteins, tracers and ligands to be co-localised with a degree of accuracy that was previously unknown (Figure 3). This has greatly enhanced our capacity to investigate the functional aspects of tissues and cells in the normal and diseased nervous system.

Alzheimer’s disease

Alzheimer’s disease remains the most common form of dementia world-wide. With an ageing population, it is estimated that there are 700,000 people with dementia in the UK, most of whom will suffer from Alzheimer’s disease. Extracellular plaques of insoluble amyloidβ (Aβ) and intracellular, intraneuronal, neurofibrillary tangles...
REFERENCES