Neuropathology in Context

Introduction

Neuropathology is the naked eye (macroscopic) and microscopic study of the nervous system and its diseases. Its main purpose is to determine the causes and effects of disease in the nervous system; in this way neuropathology plays a major role in the multidisciplinary team of clinicians caring for and investigating patients with neurological disease.

But how did it all start? In this article, I trace the origins of neuropathology, its development through the centuries and its evolution into the 21st Century.

Neuroscience in ancient times

Records of interest in the nervous system date back to Ancient Greece but it was probably Herophilus of Chalcedon (335-280 BC) who first proposed that the brain is the centre of intelligence rather than just a cooling system to chill the ardours of the heart, as taught by Aristotle. Subsequently, Galen, in the second century AD, expanded the then popular pneumatic theory of the brain. This theory proposed that the vital spirit entered through the eyes and was purified in the ventricular system of the brain to form the animal spirit which in turn was distributed around the body by the arteries and nerves. Waste products from this refining process were dispersed into the nose or the sinuses. According to the pneumatic theory, the major functions of imagination, cogitation (thinking) and memory resided in the different parts of the cerebral ventricular system.

These views were still prevalent in the 16th Century in Europe at the dawn of Modern Neuroscience when Vesalius published detailed anatomical drawings of the brain (Figure 1) in his book De humani corporis fabrica in 1543. Vesalius also described neuropathological conditions such as hydrocephalus in children with enlargement of the head and attenuation of the cerebral brain tissue around expanded ventricles that contained excessive amounts of fluid quantified in "Augsburg wine measures".

Early development of neuropathology

With the increasing availability of microscopes during the 19th century, peripheral nerves were the first parts of the nervous system to be studied in detail. Robert Remak described non-myelinated nerve fibres and ganglion cells in 1838.[1] He recounted how he prayed for sunshine in the Berlin winter as microscopes relied upon natural light, so on cloudy days he saw nothing. Remak's contemporary in Berlin, Theodore Schwann, is credited with the description of Schwann cells in 1839, although he described them as a syncytium rather than separate cells surrounding a continuous axon. Augustus Waller, in London, followed with his description of axonal (Wallerian) degeneration in 1850. Detailed descriptions of the anatomy and pathology of separated "teased" nerve fires were published in 1878 by Ranvier in Paris. One of his suggestions for the function of étranglements annulaires (nodes of Ranvier) was that they prevented the semi-liquid myelin from flowing down the nerve while standing. Many neurological syndromes were described in France in the last decades of the 19th century, perhaps most famously by Charcot who also described the pathology of sclérose en plaque (multiple sclerosis).

Development of histological techniques to separate the closely interwoven elements of the nervous system began in earnest in the 1880s with stains to define astrocytes and other cells and with the tinctorial stain for neurons devised by Franz Nissl (1892) while still a medical student (Figure 2). With the introduction of techniques using salts of silver to stain neurons and axons and other cells, Golgi in Italy,

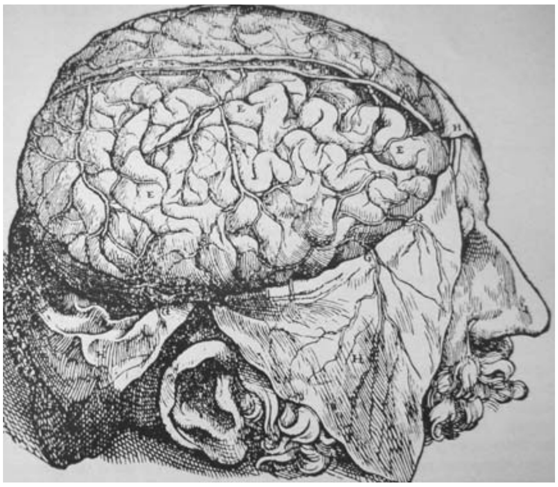

Figure 1: A drawing of the external aspect of the brain by Vesalius in De Humani Corporis Fabrica published in 1543.

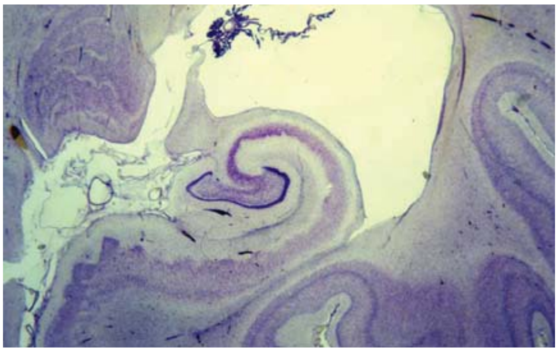

Figure 2: A Nissl stain demonstrating layers of neurons in the hippocampus (centre), cerebral cortex (bottom right) and lateral geniculate body (top left).

Cajal in Spain and Bielschowski in Germany led the way to defining individual neurons, their dendrites and axons and their connections in the nervous system. This allowed close correlation with neurophysiological observations that defined neuronal function. As a direct result of silver staining techniques, Alzheimer (1907) described the histological picture of plaques and neurofibrillary tangles that still form the basis for the pathological diagnosis of Alzheimer's disease 100 years later.

Following the first operation for a brain tumour in the 1890s in London, neurosurgery developed rapidly and so did a closer interest in the classification and diagnosis of brain tumours. This is exemplified by the histological descriptions by Bailey and Cushing in 1926. They based their classification on resemblance of the cytological and histological patterns in tumours to various cell types in the mature and immature nervous system. However, the number of different names for brain tumours expanded so much that in 1949 Kernohan simplified the classification by introducing a Grading System for brain tumours based on their predicted behaviour with Grade 1 at the benign end of the spectrum and Grade 4 at the more malignant end.[2] A similar but modified Grading System has been used in all the World Health Organisation Classifications of Tumours of the Nervous system published between 1973 and 2007.[3]

Descriptive neuropathology flourished during the first half of the 20th century in Europe and the USA and resulted in the first major English language text book of neuropathology, published by Greenfield and colleagues in London in 1958. At that time many diseases carried long

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3. Louis DN, Ohgaki H, Wiestler OD, et al. *WHO Classification of Tumours of the Central Nervous System.* 4th ed. Lyon: International Agency for Research on Cancer. ; 2007.

eponymous titles that are gradually disappearing as the causes or genetic backgrounds of neurological diseases have been defined.

Neuropathology in the second half of the 20th century

This era witnessed an explosion of new technology for investigation and research into nervous system pathology. Electron microscopy was introduced in the 1950s and immunocytochemistry in the 1970s; these two techniques have probably had the greatest direct impact on neuropathology. Electron microscopy revealed the fine detail of brain cytology, showed the arrangement of neuronal and glial structures in the previously featureless neuropil and defined the tight junctions between endothelial cells associated with the blood-brain barrier (Figures 3 & 4). Scanning electron microscopy visualized the three dimensional relationships of many structures in the nervous system and the associated meninges (Figure 5). The introduction of immunocytochemistry allowed the chemical definition of many of the structures discovered by electron microscopy and the more reliable identification of the different types of cell in the normal and diseased nervous system (Figures 6 &7).

With the introduction of computerised tomography (CT) and magnetic resonance imaging (MRI) neuropathology became visible in the living patient. The pathological identities of the lesions seen in CT and MRI scans were determined by correlating the appearances in scans with the histological analysis of biopsies and post-mortem brains. Many thought that the need for neuropathology as a clinical diagnostic service would decline and perhaps disappear altogether and be supplanted by CT and MRI. This did not happen as the gold standard for diagnosis still largely rests upon histological diagnosis, especially for tumours.

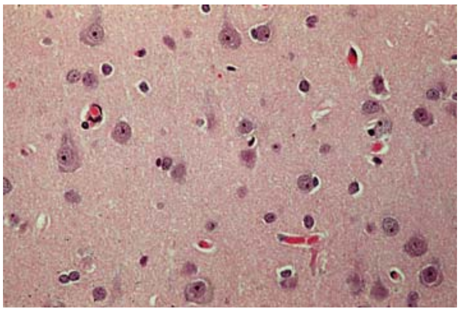

Figure 3: A Haematoxylin and Eosin stained section of cerebral cortex. Neuronal and glial cell bodies are embedded in a featureless pink neuropil.

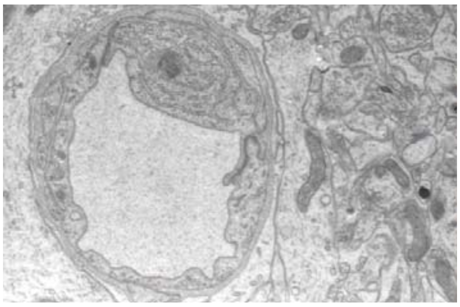

Figure 4: An electron micrograph showing closely packed neuronal and glial processes in the neuropil (right) and a capillary with darkly stained tight junctions between the endothelial cells.

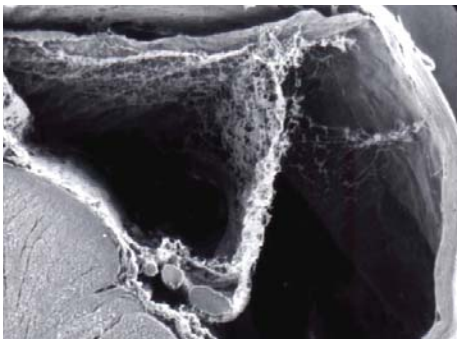

Figure 5: A scanning electron micrograph showing a three dimensional image of a highly perforated, lace-like dorsolateral ligament of arachnoid cells extending from the spinal cord (bottom left) to the parietal arachnoid (top right).

Neuropathology in the 21st Century

The 21st century has seen an increasing role for neuropathology in a wide range of disciplines within neuroscience, ranging from the diagnosis of lesions in individual patients and monitoring the effects of therapy to research into the causes and mechanisms of disease.

Why does it take more than five years or more of postgraduate study to train a consultant neuropathologist? The main reason is the complexity of the nervous system and the wide spectrum of its pathology, ranging from focal disease in the brain and spinal cord (e.g. tumours, infarcts, abscesses and multiple sclerosis plaques) to the more diffuse diseases of the brain such as the many different types of dementia, movement disorders and hereditary diseases. Interpretation of neuropathological specimens requires an in-depth knowledge of the structure and function of the nervous system and a very good working knowledge of clinical diagnostic neurology, neurosurgery and psychiatry.

Much of the work load of a consultant neuropathologist in one of the Regional Neurological and Neurosurgical Centres in Britain is the diagnosis of lesions in the brain, spinal cord, muscle or peripheral nerve in biopsy specimens removed at surgery. Intra-operative diagnosis of tumours, by the use of smear preparations and cryostat sections, is often required. This is followed by a final diagnosis based on paraffin sections stained by histological and immunohistochemical techniques and the correlation of histological findings with the clinical and radiological data.[2] The neuropathological diagnosis usually forms the basis for discussion at the Multidisciplinary Team (MDT) Meetings involving a wide variety of clinicians and scientists (Figure 8). Communication, audit, education and quality control at MDT meetings form a basis for Clinical Governance and the maintenance of high quality care for patients.

The neuropathology of neurological, psychiatric and forensic disorders is usually investigated in post-mortem brains with close correlation between pathology and clinical findings. This process is particularly important for the investigation of dementias, movement disorders and infections. Working with coroners and the police on the examination of medico-legal cases may entail appearances in court, often to argue a case in the face of differing opinions.

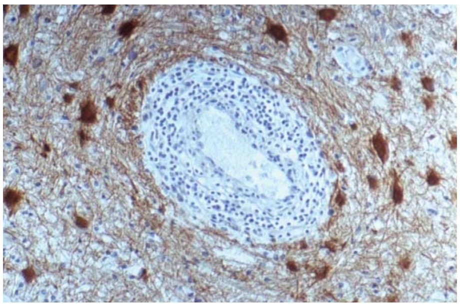

Figure 6: Reactive astrocytes and their processes stained brown by immunocytochemistry for glial fibrillary acidic protein (GFAP). From a case of multiple sclerosis.

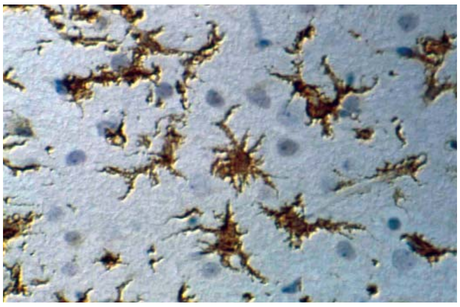

Figure 7: Activated microglia in rat cerebral cortex stained by immunocytochemistry for MHC class II.

Neuropathology in the future

What does the future offer? As long as there are unresolved problems in the causes, diagnosis and treatment of neurological disease, there will be a need for information on the structural aspects and cell pathology of the nervous system. Neuropathology will remain a very important lynch-pin in clinical management and in research. Knowledge of the pathology of the human nervous system will always be required to guide research efforts in experimental neuroscience to the most relevant areas of investigation.

Borders between disciplines in medicine are often blurred and this applies to neuropathology and closely related disciplines in clinical and basic neuroscience. Many neuropathology laboratories combine structural, molecular biological and genetic analyses of tissue samples to gain a complete picture of the disease process affecting the patient. This trend is likely to grow and produce an increasingly integrated approach based on the cell biology of diseases of the nervous system.

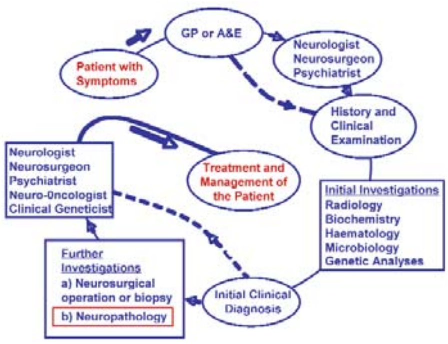

Figure 8: Neuropathology in context with other members of the Multidisciplinary Team involved in the diagnosis, treatment and management of patients with neurological disease.