16 The Changing Face of Neuropathology

Ingrid V. Allen

ORIGINS

1906 was an auspicious year to have been alive: it saw the birth of The Pathological Society of Great Britain and Ireland with obstetrician James Lorrain Smith and attendant midwife William Osler (Cushing, 1924). In that same year the Nobel prize for Physiology or Medicine was awarded jointly to Santiago Ramón y Cajal and Camillo Golgi for their separate studies on the nervous system, using similar techniques, but reaching very different conclusions. These two events, the one of national importance, the other of great international significance, are reflective of the genesis and nature of neuropathology as a subject, rooted in general pathology, but having seminal links with basic and clinical neuroscience. Given its complex origin, neuropathology has developed in a different way from other branches of pathology, and this is reflected in the practice of the subject throughout the 20th century and at the present time. If one takes Rudolf Virchow as an example of the influence of pathology on neuropathology, then we are indebted not only for the broad principles of cellular pathology, but also for specific concepts for which his terms, e.g. 'myelin' and 'neuroglia', have become part of the standard neuropathological vocabulary (Virchow, 1860).

However, it is to Cajal, often described as the father of neuroscience, that we owe the concept of the neuron as the basic unit of the nervous system (Cajal, 1906) and to Cajal and his disputatious but correct younger colleague, Pio del Rio-Hortega, that we now understand the nature and origin of the cells that make up the neuroglia (Cajal, 1909, 1911; Rio-Hortega, 1919). The great contribution of Rio-Hortega to our understanding of neuroglia must be recognised, but the incomplete descriptions of W.H. Robertson are worthy of note (Robertson, 1900; Penfield, 1932).

Anatomists and physiologists before the 20th century had established the phenomenon of cerebrospinal fluid secretion and circulation. It only remained for Paul Ehrlich, a nobel laureate two years after Cajal and Golgi, to establish the concept of the blood–brain barrier (Ehrlich, 1902), and the cardinal discoveries underpinning neuropathology were in place. How then did neuropathology emerge as a distinct discipline? The answer is: very differently in different parts of the world. For example, in Spain and Italy its origins lie in the neurohistological schools of Cajal and Golgi. In France, neuropathology was initially practiced by neurologists under the influence of Jean-Martin Charcot, Professor of Neurology at the Salpêtrière in Paris, who himself made many contributions to neuropathology, and with his friend and fellow neurologist Alfred Vulpian, established a systematic museum of anatomical pathology (Corvisier-Visy and Poirier, 1996). In Germany the main influence came from the German Research Institute for Psychiatry in Munich where Alois Alzheimer, Korbinian Brodmann, Bernhard von Gudden, Emil Kraepelin, Franz Nissl and Walther Spielmeyer, all psychiatrists as well as neuropathologists, made lasting contributions. Similarly in the rest of mainland Europe the links to neuroanatomy and histology were strong, but the practitioners were frequently neuropsychiatrists, of which Sigmund Freud is an example, a knowledgeable neurohistologist and Professor of Neuropathology in Vienna until he left for England in 1938.

ANGLOPHONE CONNECTIONS

In the English-speaking world neuropathology developed rather differently. Here the influence of neurology and neurosurgery is important; for example, in England, Hughlings Jackson, William Gowers, Victor Horsley and R.H. Clarke combined neurophysiological and pathological techniques to elucidate the functions and to understand diseases of the nervous system. The influence of neurosurgery was even stronger in the USA where Harvey Cushing, working with Percival Bailey, established the field of neuro-oncology, while again neurologists were the key influence in the Boston school (Richardson *et al*., 1994). In Canada the influence of neurosurgery is also apparent, where neurosurgeon Wilder Penfield in 1934 realised his vision of a multidisciplinary institute for the study of neurology with the opening of the Montreal Neurological Institute. Throughout the English-speaking world the links of neuropathology with the parent subject of pathology have always been strong. The Institutes of Neurology and Psychiatry in London from the early days had departments of neuropathology, in many cases staffed by those trained in mainstream pathology. British academic departments of pathology, often because of clinical service commitments, usually had at least one member of staff who was an expert on the nervous system.

To summarise, neuropathology is fortunate in having a diverse background, with roots in pathology, anatomy, neurology, neurosurgery and psychiatry. One might facetiously represent the different origins by the use of the paraffin section (pathology!) versus the use of the celloidin section (neuroanatomy!).

The turbulence in Europe in the first half of the 20th century had at least one good effect in that it brought the different practices of neuropathology together. Neuropathologists trained in different ways and from different backgrounds, some of whom were forced to leave mainland Europe and move to Britain or America, began to work together, thus establishing the multidisciplinary framework that is so necessary at the present time. An early example of this blending of disciplines and of collaboration between workers trained in Germany and in Britain is seen in the work of Alfred Meyer and Elizabeth Beck. Both were refugees from Germany: Alfred Meyer trained in psychiatry and neuropathology, and Elizabeth Beck in neuroanatomical techniques. They worked together and with Turner McLardy made the definitive study of the anatomical effects of prefrontal leucotomy (Cavanagh, 2004). Alfred Meyer, while in Germany, had been influenced by the work of his friend Walther Spielmeyer, who among others in the German school of neuropathology considered that definite evidence of ischaemic cell change in the human brain was only apparent some 7 days after the hypoxic event. This view from the Munich school, propagated by Alfred Meyer at the Maudsley Hospital in London, awakened in the young James Brierley a lifelong devotion to the study of cerebral hypoxia. His innovative human and experimental studies, carried out with the cooperation of Alwyn Brown and Brian Meldrum, led to a complete revision of views as to the timescale of cellular changes in brain hypoxia, a conclusion that has profound implications for clinical practice (Graham *et al*., 2005).

KEY FIGURES: GREENFIELD AND RUSSELL

Two figures stand out in the emergence of specialist neuropathology in 20th century Britain. Both remained part of the general family of pathology and contributed to The Pathological Society and to the Association of Clinical Pathologists, but both realised that the complexity of the nervous system, with the requirement for special techniques, necessitated specialisation. Godwin Greenfield (1884–1958) (Fig. 16.1) was for many years pathologist to the National Hospital, Queen Square, London. Described by William McMenemey in his admirable and full obituary (McMenemey and Walshe, 1959) as the architect of British neuropathology, he was very much the clinician's pathologist, remembering above all else that he gave a clinical service. His publications therefore

J.G. Greenfield, MD, FRCP, LLD
(1884–1958)

Figure 16.1 Godwin Greenfield.

are not in the field of experimental neuropathology, but include classical pathological descriptions that still stand, e.g. on measles encephalomyelitis (Greenfield, 1929), on late infantile metachromatic leucodystrophy (Brain and Greenfield, 1950) and on the spino-cerebellar degenerations (Greenfield, 1954).

The year 1950 has great significance for British neuropathology; it was in that year that Greenfield established, with 28 founder members, the Neuropathological club, later to be known from the same year in which the College of Pathologists was founded, i.e. 1962, as the British Neuropathological Society. By the year 2000 when the Society celebrated its 50th Anniversary there were more than 200 active members (Geddes, personal communication). Greenfield could not have foreseen how the formation of the club in 1950 would influence the yet to be formed College of Pathologists. By 1962 British neuropathologists were well organised and through the efforts of the honorary secretary of the Neuropathological Society, Marion Smith, and others, the College from the beginning recognised neuropathology as a sub-specialty with its own slanted examination, for which the present author had the honour to be the first candidate.

Dorothy Russell (1895–1983) (Fig. 16.2), Professor of Morbid Anatomy at the London Hospital Medical College from 1946 until 1960, like Greenfield did much to establish neuropathology as a specialty. Her training was in general histopathology, but the formation of a neurosurgical unit at the London Hospital, led by Hugh Cairns, encouraged Russell to take up neuropathology (Geddes, 1998). She worked with Frank Mallory, Wilder Penfield and Pio del Rio-Hortega and pioneered the use of tissue culture in the study of brain tumours. Her MRC monograph 'Observations on the Pathology of Hydrocephalus' is a classic that remains a key text for the condition. She is, however, remembered most for her contributions with Lucien Rubinstein to neuro-oncology. These included the identification of the so-called 'pinealoma' as a teratomatous lesion, and of 'microgliomas' as distinct from gliomas, now generally accepted as lymphomas.

She was the first woman to become head of a department of pathology in Britain, and her achievements contributed greatly to the advancement of women in British medicine (Rubinstein,

Figure 16.2 Dorothy Russell and Pio del Rio-Hortega, Oxford.

1984). The rarity of women in high academic positions at that time is perhaps typified by her soubriquet – she was always known as 'The Lady'. She was privately warm and caring, but publicly, possibly because of the vigour of her intellect, often described as intimidating (Geddes, 1998). She would probably be surprised today to see the predominance of women in British medical schools and their equal influence with their male colleagues in neuropathology. She received many honours in her lifetime and is remembered eponymously by a biannual lecture, sponsored by the journal *Neuropathology and Applied Neurobiology* and by the British Neuropathological Society.

The different development of pathology in Scotland, Wales, Ireland and the English provinces as compared with London, where historically pathology was not regarded as a separate subject (Foster, 1981), has in many ways been an advantage to British neuropathology. The first chair of pathology was established in Edinburgh in 1831, followed 50 years later by the second at Aberdeen. By the beginning of the 20th century, most medical schools outside London had chairs in pathology, thus providing job opportunities from which all branches of pathology benefited. With the advent of the National Health Service in 1948 and the establishment of regional centres for neurology, neurosurgery, neuroimaging and neuropathology, there were already well-trained neuropathologists to fill the new posts. These regional centres have provided a framework not only for the clinical service, but for teaching, training and research. Research contributions, experimental and clinical, from British neuropathology are therefore wide ranging in subject and from diverse geographical centres. In assessing British neuropathological research output, the value of the National Health Service in ensuring that cases are easily collected and are available for research must be acknowledged. It is invidious to be selective about achievements: sufficient to say that British researchers have contributed to all fields in neuropathology and the strength of

Figure 16.3 John Cavanagh and Harold Millar, Belfast, 1981.

the contributions is reflected in the ensuing publications. Until 1958 the only British textbook of neuropathology was that of Biggart (1936). This small book, described as 'a student's introduction', is elegantly written and displays clarity of thought. For many years it was used widely by pathologists and neurologists in training and ran into three editions. By 1958, however, knowledge had advanced to such a degree that a more detailed textbook was needed; this was provided by Greenfield and is now in its seventh edition (Graham and Lantos, 2002). The 1958 edition of Greenfield's 'Neuropathology' was complemented the following year by Russell and Rubinstein's 'Pathology of Tumours of the Nervous System', which was intended to be an accompanying volume and is now in its sixth edition (Bigner et al, 1998). Of even greater importance for the publication of research findings was the establishment of the journal *Neuropathology and Applied Neurobiology* in 1974, sponsored by the British Neuropathological Society. This initiative was the brainchild of John Cavanagh (Fig. 16.3), Director of the Medical Research Council Group in Applied Neurobiology at the Institute of Neurology in London. Cavanagh became the journal's first editor and it was he who set the high standards that have achieved the international reputation that the journal enjoys today.

CURRENT CHALLENGES

Given the excellence of the tradition of neuropathology in Britain, one must consider what endangers the specialty at the present time. Recruitment to the specialty has long been a problem. Undergraduates get little exposure to neuropathology in their formative years and the training is prolonged with increasing necessity of knowledge of cognate subjects such as neuroanatomy and neuroimaging. The rapid developments in the clinical neurosciences in the last few years, with input from genetics, molecular biology, neuroimaging and neuropharmacology, highlight the centrality of neuropathology in this spectrum of disciplines. Interpretation of results, whether in basic or applied neuroscience, requires precise phenotyping at the level of the whole person, the tissue and the cell. One can only hope that the intellectual excitement that comes from such an approach will continue to attract the very best graduates to neuropathology, be their training medical or scientific.

A further challenge is the wide range of pathological conditions in which neuropathologists providing a clinical service, often few in number in each centre, have to be proficient. Regional

centres were initially established to support the broad spectrum of neurology and neurosurgery. Thus, most neuropathological laboratories process tissue from brain, spinal cord, peripheral nerve, striated muscle, the autonomic nervous system and pituitary. Some laboratories are also responsible for ophthalmic pathology and for cerebrospinal fluid cytology. The range of tissues is great, but the spectrum of diseases is even greater. Thus the practising neuropathologist must be conversant with infections, vascular disorders, inborn errors of metabolism, metabolic and toxic diseases, trauma, epilepsy, neurodegenerative diseases, demyelinating diseases, movement disorders, psychiatric disorders, peripheral nerve and muscle diseases and tumours affecting organs as different as the pituitary and the brain. Not only is the disease range wide, but the clinical age span extends from the perinatal period to old age. With the growth of sophisticated molecular techniques it is doubtful if all regional centres in Britain can retain total proficiency across the broad historical spectrum. Some networking of centres is desirable, and this may follow similar trends in neurology and neurosurgery. Opportunities from increased automation in histopathology generally have focused attention on the requirements for the specialist neuropathology service. Certainly nervous tissue requires special processing and staining, but the next few years will almost certainly see greater automation in histopathology, which should allow neuropathology staff to concentrate on specialist techniques, both classical and innovative. Furthermore, the use of telemedicine, with dynamic-imaging systems, will allow the acquisition of biopsies at one site but their reporting elsewhere at a centre of excellence (Walter *et al*., 2000).

An even greater difficulty is the question of clinical research (Allen, 1996), yet the need has never been greater. For example, the application of the importance of accurate pathological description in the interpretation of gene and protein arrays is acknowledged. These techniques as applied to the nervous system are, at the present time, largely experimental but may soon be important in patient management. It is vital therefore that regional centres of neuropathology have sufficient staff to allow high-quality translational and clinical research to continue.

What then of the distant horizons? Most of the big questions in neuropathology have been posed many years ago but imperfectly answered, largely because of lack of suitable techniques. For example Virchow, writing in 1893, rather than posing a question, made the following statement that is still the subject of intense experimentation:

> ‘every case of descent, in the sense in which Darwin uses the term, that is to say, every deviation from the type of the parent animal, must have its foundation on a pathological accident.’

Considering the tools available to Virchow in terms of microscopy and tissue stains, it is incredible how accurate have been the observations that he and others have made. There have been dramatic technical advances over the 100 years of neuropathology: the initial phase with beautiful and accurate drawings, but bound by the limitations of the light microscope and the available stains; the succeeding era of electron microscopy and enzyme histochemistry; the development of immunocytochemistry with specific antibodies; and *in situ* hybridisation with mRNA probes for cellular and pathogen gene expression. But how exciting the present era with laser capture of single cells, fluorescent *in situ* hybridisation, tissue, gene and protein arrays, and the developments in confocal microscopy and computational science that make these techniques at least semi-quantitative. The opportunities have never been greater.

Cajal in his *Advice for a Young Investigator* (1999) wrote:

> ‘If we knew the entire chemical composition of living cells, results due to the application of a particular staining reagent could be deduced simply from biochemical principles. However, because we are so far from this position, those aspiring to discover new biological methods are forced to submit live tissues to the same blind tests resorted to by chemists for centuries in the hope of now and then finding some unforeseen combination of reactions or mixtures of elements.’

Neuropathologists today can test the veracity of Virchow's statement, using techniques and reagents that Cajal craved!

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