EDITORIAL

Once things had moved on from the assertion of Dr Franz Gall (1758–1828) that the cerebellum is the centre for ‘amativeness’, and with the further conclusion of Sir Victor Horsley (1857–1916) ‘that the cerebellar cortex is the chief first station of representation of the afferent basis of movements of all the skeletal muscles’ (see Brain 2009; 132: 2901–2 and 2011; 124: 2791–4), Gordon Holmes (1876–1965) was able to conclude his studies reported in Brain between 1906 and 1938 with the position that ‘the cerebellum reinforces or tunes up the cerebral motor apparatus, including subcortical structures with motor functions, so that they can respond promptly to volitional stimuli and the impulses from them which excite muscular contractions are properly graded’ (see Brain 2007; 130: 288–98). The proximate cause of cerebellar disease was all too obvious to Holmes working in France during the Great War. The Brodie helmet worn by British troops ‘reduced casualties but was criticized by General Herbert Plumer (1857–1932) on the grounds that it was too shallow, too reflective, its rim too sharp, and its lining too slippery’; it also failed to protect the occipital bone and the brain structures contained therein. But the cause of cerebellar disease seen in civilian practice was less apparent. JG (Godwin) Greenfield (1884–1958) published, at the suggestion of Dr Charles Aring (1904–98), a review of the systemic spino-cerebellar degenerations, and his outstanding monograph (The spino-cerebellar degenerations. Blackwell Scientific Publications) appeared in August 1954. Concerned mainly with hereditary forms of cerebellar disease, Greenfield classifies these disorders as ‘predominantly spinal’, ‘spino-cerebellar’ or ‘predominantly cerebellar’. One of two subtypes of spino-cerebellar disease is ‘subacute spinocerebellar degeneration (carcinogenic and sporadic)’; and one of the four types of predominantly cerebellar degeneration is ‘diffuse atrophy of Purkinje [Jan Evangelista Purkinje (1787–1869)] cells (toxic and carcinogenic)’. In tracing the history of this putative link between cancer and spino-cerebellar degeneration, Greenfield cites Professor (Klaus-Joachim) Zülch (1910–88) whose own classification included 27 patients in two of five subtypes in which cerebellar cortical atrophy is associated with non-malignant systemic disease (Group 3), or ‘comes on later in life in patients suffering from malignant disease’. The course is often cut short by death from cancerous cachexia (Group 2: Deutsche Zeitschrift für Nervenheilkunde 1948; 159: 501–13). Since ‘interest has recently been focused on Zülch’s Group 2 in which subacute cerebellar disease is associated with cancer’, Greenfield covers this topic in particular detail. The case first described by (Bernard) Brouwer (1881–1949) was associated with pelvic sarcoma, and others, reported up to 1951, often implicated ovarian carcinoma with less frequent examples of cancer of the uterus, breast or bronchus. The course is rapid starting with unsteadiness of gait leading to subsequent incoordination of the hands, slurred speech and symptomatic nystagmus, sometimes with dementia, the patient soon becoming bedridden and usually dying within 1 year from onset. The cerebrospinal fluid—on which Greenfield had already written another monograph (The Cerebro-Spinal Fluid in Clinical Diagnosis, 1925)—shows increased lymphocytes and raised concentration of protein with a paretic Lange curve, usually suggesting the diagnosis of disseminated sclerosis. Histologically, there is conspicuous loss of Purkinje cells throughout the cerebellum, but rarely extending to other parts of the central nervous system, and with evidence for perivascular and meningeal inflammation. Beyond these descriptions, the mechanisms involved in cancer-associated cerebellar degeneration were unknown to Dr Greenfield.

But, by 1965, matters had moved on. ‘The idea of a conference on the neurological aspects of the remote effects of cancer arose from correspondence [between Lord Brain (1895–1966) and Forbes Norris (1928–93)]…The specific syndromes described (being) largely new to the medical literature in that they have been widely recognized for only a few years, and some are even detailed for the first time in this volume [The remote effects of cancer on the nervous system. Contemporary neurology symposia: Volume 1, 1965]. In view also of recent endocrinologic, metabolic, and immunologic findings in cancer patients, the time seemed ripe….’. In his introduction, Brain noted that it is neurologists who have drawn attention to these complications of cancer, and he castigates oncologists for having seen but not recognized such common disorders. ‘The failure to notice them hitherto has been a remarkable scotoma in medicine and surgery’. The organizers anticipated that their conference would confirm ideas on disease mechanisms involving secretion of metabolic and endocrine substances, and immunological reactions to the tumours. Moreover, given the recent description of progressive multifocal leukoencephalopathy associated with malignancy (Brain 1958; 81: 93–111; New England Journal of Medicine 1961; 265: 815–23; and see Brain 2004; 127: 1914), they anticipate that general mechanisms of demyelination will also be illuminated. As one contributor, EP (Edward Peirson) Richardson Jr (1918–98), writes: ‘some years ago in the course of the regular post-mortem examination of the brains of patients coming to autopsy at the Massachusetts General Hospital, we encountered cases of a remarkable disorder of the cerebral white matter that was unlike anything we had seen before’. Two of the three patients...
had chronic lymphatic leukaemia and the other Hodgkin’s disease. Taken together, and noting that the various cancer-associated neurological syndromes may also occur as sporadic or familial conditions, Lord Brain speculates that ‘the pathogenesis of all these disorders must surely meet in the territory of the metabolism of nerve cell-bodies, white matter and muscle’. The most obvious clinical syndromes previously recognized are progressive multifocal leucoencephalopathy, subacute cerebellar degeneration in association with carcinoma, carcinomatous amyotrophic lateral sclerosis, carcinomatous neuromyopathy, myasthenia (and thymoma), and the myasthenic state (with lung cancer).

Several putative disease mechanisms are proposed. Whereas ‘there is no basis for assuming a [nutritional] pathogenesis or aetiology [for] the carcinomatous CNS syndromes’…” neoplasms may elaborate structurally altered, hormonally active material which has a different spectrum of biological activities and leads to metabolic changes unexpected from the natural hormones”; and opportunistic viral infection may result from ‘lack of antigenicity of the virus or depressed allergic reactivity of the host’. In a prescient but brief contribution on immunity, Richmond Prehn writes: ‘the profusion or depressed allergic reactivity of the host’. In an epilogue by Brain and Raymond Adams (1911–2008): the disorders should now be classified as encephalopathic, myelopathic, neuropathic and muscular; and the mechanisms are opportunistic viral infection, and altered immune, metabolic, nutritional and endocrine states. Type 2a of the encephalopathy group is a diffuse polioencephalopathy presenting with a range of psychiatric disorders leading to admission of the patient to a mental hospital sometimes with dementia but more often with anxiety, agitation and psychosis and much less prominent disorders of cognition.

On page 1622, Christian Bien and colleagues from Bielefeld, Bonn, Erlangen, Munich and Heidelberg (Germany), Oxford (UK), Sydney (Australia), Barcelona (Spain) and Vienna (Austria) explore specific immune mechanisms in tissue from patients with paraneoplastic or non-paraneoplastic encephalitis in association with antibodies against voltage gated potassium channel complexes, N-methyl-D-aspartate receptors and glutamic acid decarboxylase. They predict, and show, that most cases with antibodies directed at intracellular antigens are specifically associated with CD8 and granzyme-B+ anti-neuronal cytotoxic T cells, compared with those where the immune response targets voltage gated potassium channels in which the immunopathology is characterized by deposition of complement membrane attack complexes; paradoxically, cases with antibodies against N-methyl-D-aspartate receptors show features neither of T cell nor complement-associated immunity. Lenka Mikasova and colleagues from Bordeaux, Lyon and Bron (France) study patients with antibodies targeting extracellular antigen in the context of autoimmune synaptic encephalitis and demonstrate that anti-N-methyl-D-aspartate receptor antibodies alter the expression and synaptic trafficking of GluN2A-N-methyl-D-aspartate receptor; these antibodies block synaptic plasticity—effects that are prevented by activation of ephrin-B2 receptors—indicating that the neurological and psychiatric syndromes result from dynamic displacement of N-methyl-D-aspartate receptor out of the synapse (page 1606).

Four papers deal with deep brain stimulation in the context of Parkinson’s disease, of which two address non-motor features. On page 1463, Eugénie Lhomme and colleagues from Grenoble and Lyon (France) and Genève (Switzerland) assess behavioural complications of dopamine therapy in situations where, with improved postoperative motor scores in the OFF treatment period, medication can be reduced (by ~73%). This is associated with invariable recovery of impulse control disorders, punding and dopamine dysregulation syndrome; and improvements in euphoria, apathy and appetite behaviour. Whether these effects are due directly to subthalamic stimulation or simply the reduced requirement for medication, the management of non-motor fluctuations may nevertheless be a further indication for deep brain stimulation. Eiji Arai and colleagues from Chiba (Japan) study autonomic function following deep brain stimulation for Parkinson’s disease (page 1478); using the 13C-acetate breath test to assess carbon dioxide excretion, they show that gastric emptying is impaired and resistant to therapy with DOPA-derivatives but improves with subthalamic deep brain stimulation perhaps by altering the neural systems that control gastrointestinal function rather than through effects of gut hormones (such as ghrelin).

The papers on speech include two new descriptions. Keith Josephs and colleagues in Rochester (Minnesota, USA) study 37 subjects presenting prospectively over 12 months to define a disorder of primary progressive apraxia for speech, without aphasia but having a spectrum of occasional additional neurological symptoms and signs; the condition is characterized by altered structure and function of the superior lateral premotor cortex and supplementary motor area but without evidence for increased amyloid deposition (page 1522). Marcel Mesulam and investigators from Illinois (USA) report on patients seen early in the course with subtle disturbances of language, subsequently considered to have primary progressive aphasia but not yet meeting agreed diagnostic criteria (page 1537). Combining clinical details, speech and language assessments and brain imaging features, and incorporating some clinical wisdom, they are able reliably to distinguish the existing agrammatic, logopenic and semantic variants of primary progressive aphasia long before the diagnosis could otherwise be made, and they add a fourth variant of mixed primary progressive aphasia characterized by impaired grammatical sentence production and word comprehension. The authors conclude that the requirement for a 2-year delay from onset of difficulty with language before diagnosing primary progressive aphasia is unnecessarily restrictive, and not in the interests of early intervention when this and other forms of neurodegenerative disease are eventually treatable.

In an occasional paper, Els Vanhoutte and investigators from Maastricht, Rotterdam, Helmond, Utrecht, Hoofddorp and Amsterdam (The Netherlands), Baltimore and Boston (USA), Milan (Italy) and Leeds (UK) audit and evaluate the ability of physicians to agree scores on the time-honoured Medical Research Council scale of motor weakness in the context of various polyneuropathies and muscular dystrophies (page 1639); performance is disappointing and the finger pointed at the scale not
the examiners with a recommendation that the six categories are collapsed into four using interval scores to resolve issues relating to local dependence and item (individual muscle) biases. Amongst six papers on genetic and developmental disorders of the nervous system, Marjan Steenweg and investigators from Amsterdam (The Netherlands), Milan and Rome (Italy), Neuherberg, Munich and Hamburg (Germany), Coimbra (Portugal), Florianópolis (Brazil) and Cardiff (UK) use exome-sequencing to identify mutations of EARS2, encoding mitochondrial glutamyl-tRNA synthetase, in a case of infantile-onset mitochondrial encephalopathy (page 1387); they then use the phenotype in that child to confirm that each of 11 similar but previously uncharacterized cases have the same genetic defect. The description of early onset leukoencephalopathy with thalamus and brainstem involvement and high lactate with ‘mild’ and ‘severe’ phenotypes adds to the list of disorders resulting from defective mitochondrial translation.

Returning to the cerebellum, Maria García-Murias and a team from Santiago de Compostela, Coruña and Barcelona (Spain) and Porto (Portugal) describe the phenotype of spinocerebellar ataxia 36 in which substantial expansion of GGCCCTG hexanucleotide repeats at NOP56 is confirmed and cases of this, the most common dominant spinocerebellar ataxia in Galicia (Spain), traced to a founder mutation occurring ~1275 years ago (page 1423); the phenotype is a late-onset progressive cerebellar disorder with abnormal eye movements and deafness, tongue denervation and mild pyramidal tract involvement associated with imaging features that mimic those of olivo-ponto-cerebellar atrophy. In ‘Paraneoplastic syndromes: from remote to clear and present knowledge,’ Josep Dalmau and Francesc Graus review Paraneoplastic syndromes by Robert Darnell and Jerome Posner (Oxford University Press, 2011). Drs Dalmau and Graus explain how, working in the 1950s and 1960s, ‘a superb group of British neurologists and neuropathologists’ that included amongst others Brain, Ronald Henson (1915–94), Henry Urich and Greenfield, pioneered the study of paraneoplastic neurological syndromes—the list of disorders being refined with additions and deletions over time as knowledge advanced (page 1650). Richmond Prehn’s predictions on the immunological basis of these disorders were born out by the demonstration, soon after the 1965 conference, of antibody associated with carcinomatous neuropathies. Josep Dalmau and Francesc Graus chart the slow progress up to publication of Henson and Urich’s monograph on Cancer and the Nervous System: the Neurological Manifestations of Systemic Malignancy (1982) and the era, starting in 1984 around the group of Jerome Posner at Memorial Sloan–Kettering Cancer Centre, where ‘enthusiasm, excitement, hard work and proximity to patients accelerated these studies…any hour of day or night, one could walk in the laboratory and find someone in the middle of an experiment, working in silence during the day and to the rhythm of blues, hard rock or country music at night’. They point out that ‘with clarification of the hazy early clinico-pathological classification of paraneoplastic syndromes, a new foginess…emerged from the expanding number of antibodies…over-simplification of their clinical significance… and devaluation of the neurological examination’. They applaud the clarity that pervades Paraneoplastic syndromes and its rigorous emphasis on neurological examination, and the authors’ ability to sort order from chaos in the far realms of the new empire of immunological neurology. In charting the 40-year history of paraneoplastic syndromes, three periods of activity are acknowledged: clinical and pathological awareness of the various syndromes, the discovery of their immunological mechanisms, and the recognition of disorders associated with antibodies directed against synaptic proteins. Josep Dalmau is associate professor of neurology, Division of Neuro-oncology, Mahoney Institute of Neurological Sciences, University of Pennsylvania, having previously trained as an undergraduate and graduate student in medicine in Barcelona (Spain: where he also retains an appointment), the Sloan Kettering Institute and Cornell University (New York, USA). He has written extensively on paraneoplasia and the nervous system with many original discoveries relating to limbic encephalitis in association with potassium channel autoantibodies and the autoimmune synaptic encephalitides. After medical training in Barcelona, where he is now head of neurology at the University Hospital Clinic, Francesc Graus studied neuro-oncology at Memorial Sloan-Kettering Cancer Centre; he characterized the anti-Hu antibody in 1985 and remains active in the field of paraneoplastic neurological disorders working on the correlation of clinical syndromes and their immunological profiles. Our reviewers conclude that, due largely to the work of Jerry Posner and his many associates, clarity of vision has now filled in the scotoma described by Brain and Norris in 1965 that began half a century earlier with the description of obscure cases of cerebellar degeneration. In From the Archives we review ‘Parenchymatous cortical cerebellar atrophy (chronic atrophy of Purkinje’s cells)’ by Harry Parker and James Kernohan (Brain 1933; 56: 191–212) and ‘Subacute spino-cerebellar degeneration occurring in elderly patients’ by JG Greenfield (Brain 1934; 57: 161–176).

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