EDITORIAL

It took us a mere 50 pages and 13 lines first to print the word ‘headache’ when Brain appeared in April 1878 (Gowers WR. On some symptoms of organic brain disease. Brain 1878; 1: 48–59); and headache has since featured in the main text of a further 1681 articles. Five years earlier, Edward Liveing (1832–1919) had published his monograph On Megrim, Sick-headache and some Allied Disorders (1873); identified by (Fielding) Garrison (1870–1936) and Leslie Morton (1907–2004) in A medical bibliography (1943) as the first important book on headache (item 2408 in the section on ‘Allergy and anaphylaxis’; and also item 3925 in ‘Diseases of the nervous system’), and still listed as such by Jeremy Norman in ‘Garrison and Morton’ (Morton’s medical bibliography, fifth edition 1991; items 2587 and 4549). Dr Liveing places six quotes on the verso of the half-title of his monograph. One, in Latin, is taken from Thomas Willis [(1721–75): Pathologiae cerebri 1667; page 4 in the original, although Liveing cites the 1670 Elzevier (Amsterdam) edition]. In a footnote at page 336, Liveing likens the immediate antecedent of the attack (of megrim) to gradually accumulating tension in the nervous system and the episode itself to a ‘storm’ by which the condition is dispersed, again offering as justification for this metaphor the authority of Thomas Willis: in translation, ‘If anyone shall be displeased at the word Explosion, not yet used in Philosophy or Medicine, so that this Spasmodick Pathologiae, standing on this basis, may seem only ignoti per ignotius explicatio, an explanation of unknown things by more unknown things; it will be easy to shew the effect of this kind of notion, and very many examples and Instances both concerning natural and artificial things, from the analogie of whole motions, in an animated body, both regularly and irregularly performed, most apt reasons are to be taken’ (Dr Willis’s Practice of Physick, 1684).

In the original checklist of texts illustrating the history of medicine (Bulletin of the Institute of the History of Medicine 1933; 1: 333–434), Garrison cites ‘Of the headach’ by Thomas Willis as an earlier definitive account of this common complaint; but Garrison slips up in identifying pages 97–125 of Dr Willis’s Practice of Physick (1684) as the appropriate citation for what are in fact two chapters (‘Of the headach’, pages 105–13; and ‘The prognostick and cure of the headach’, pp 113–25). Morton perpetuates this bibliographic error. Evidently neither looked at a copy of the book since the sheet that should be signed ‘O’ (pages 97–104) was never published, if ever printed; and the pagination of all copies moves from 96 to 105–25 with appropriate continuity and catch-words, an error that Jeremy Norman almost corrects by quoting the first part of the original text in Latin (De anima brutorum: Pars secunda; Cap. I. ‘De cephalgia’, pp 259–78) but omitting the second (Cap II. ‘Cephalgiae prognosis & curatio’, pp 279–306). The English translation of Willis’s two chapters appears first in The Soul of Brutes (1683, pp 105–25). Although separately published in the previous year, the original sheets are also always rebound into the second and third issues of Dr Willis’s Practice of Physic (1684).

Dr Liveing first wrote on headache in his ‘Thesis for the degree of Doctor in Medicine in the Public Schools at Cambridge on April 7th 1870’; and some of that text appears in his monograph. He also reproduces material from his Thruston Address delivered to the members of Caius College, Cambridge in the May term of 1871. On megrim, sick-headache and some allied disorders is dedicated to HH (Henry) Bond (1801–83) and GE (Sir George) Paget (1809–92), each sometime Regius Professor of Physic in the University of Cambridge ‘with the highest sentiments of respect and personal regard by their friend and former pupil, the author’. Peter Latham (1832–1923: Downing Professor of Materia Medica and Therapeutics, 1874–94) published two lectures On Nervous or Sick Headache (1873) delivered at Addenbrooke’s Hospital in Cambridge in March 1872 and February 1873. Never short of a waspish aside, Latham acknowledges the views of ‘my friend Dr Edward Liveing’ which ‘will soon be published in extenso, and will merit and command that attention which is always accorded to the writings of an accurate and observer and an accomplished pathologist—and possibly lead to some discussion’.

Although a medical qualification was first awarded in 1363, and despite the establishment of a Regius Professorship of Physic in 1540 and the tradition of College-based teaching, very few medical students matriculated in Cambridge before the mid-19th century. Those who did always completed their medical education elsewhere; and not until 1975 did the University have a School of Clinical Medicine qualifying doctors based entirely on undergraduate and clinical education in Cambridge. John Caius (1510–73) introduced the study of anatomy into England and dissected two criminals annually at Gonville Hall (Gonville and Caius College from 1557). Later, dissections were performed at the Round House. Prior to the Anatomy Act (1832), the corpses were mostly executed criminals but some also reached Cambridge from body-snatchers; and one, delivered in 1768, turned out to be Laurence Sterne (1713–68), author and former student of Jesus College (from 1733). The nervous system received little attention over this period. Within the University, Francis Glisson [(1597–1672): Regius Professor of Physic, 1636–77] wrote on early concepts of reflex function (Tractatus de natura substantiae energeticae, 1672; and Tractatus de ventriculo et
in intestinis, 1677). In the Colleges, David Hartley [(1705–57): Fellow of Jesus College, from 1727] summarized views on neurology, moral psychology and spirituality explaining consciousness and sensation through his concept of ‘vibratiuncles’ and locating mind in brain (Observations on Man, his Frame, his Duty, and his expectations, 1749; see Brain 2005; 128: 443–6)—ideas that much influenced Samuel Coleridge Taylor [(1772–1834), also a student at Jesus College from 1791–94]. John Haviland [(1785–1851): Regius Professor of Physic, 1817–51] first took seriously the teaching of anatomy and instituted the MB examination in English. Regulations, amended serially after 1829 and aimed at improving the standard of medical education in Cambridge, considered to be at a low ebb, required candidates to attend lectures for two terms each year, not to practice any trade whilst in statu pupillari, to have at least 5 years’ hospital experience and to satisfy the examiners in medicine, surgery and midwifery.

Hospitals existed in Cambridge from the 12th century. Addenbrooke’s Hospital was founded in 1766 with 20 beds through a legacy of £4500 from (Dr) John Addenbrooke (1680–1719) to establish a hospital providing free treatment for the poor. It soon became a general hospital run by a corporation made up of representatives from the University, County and Borough, and individual benefactors. A census of patients in 1863 concluded: ‘a great many chronic cases and nervous disorders are admitted; epilepsy is often admitted and kept a long time’. The hospital was rebuilt on Trumpington Street in 1864 with 120 beds, to designs drawn up by (Sir) George Humphry (1820–96) and (Sir) Matthew Digby Wyatt (1820–77). Investigation was provided by the Pathology Laboratory—established in 1884 under the direction of Charles Smart Roy [(1854–97): professor of pathology, 1884–97] and based initially in the Physiological Laboratory but, from 1889, in the Chemical Laboratory where (Sir) Charles Sherrington (1857–1952) worked on cholera before embarking on his illustrious career in neuroscience. Roy died suddenly in epileptic status after returning from holiday, apparently well, earlier the same day.

Clinical lectures started at Addenbrooke’s in the 1840s and the Natural Sciences Tripos, taken by medical students, was introduced in 1848 and examined from 1851. But after grounding in pre-clinical medicine, London remained the proper place for a doctor to be trained. This was very much the opinion of Humphry [Professor of (Human) Anatomy, 1866–83; Professor of Surgery, 1883–96] and, thereafter, of several Regius Professors of Physic, including (Sir) Humphrey Rolleston [(1862–94): 1925–32]; (Sir) Walter Langdon-Brown [(1870–94): 1932–35]; and (Sir) Lionel Whitby [(1895–1956): 1945–56]. But other influential individuals—(Sir) Michael Foster [(1836–1907): Professor of Physiology, 1883–1903] and (Sir) George Paget [(1809–1892): Regius Professor of Physic, 1872–92]—were in favour of creating a complete medical school and the Board of Medical Studies edged towards endorsing a more comprehensive education in Cambridge, ‘as far as the final MB examination’. With the establishment of professorships in human anatomy (1866, in addition to the 1707 professorship of anatomy), physiology (1883), surgery (1883) and pathology (1884), a medical school was deemed to be in place.

This was the environment in which Liveing and Latham worked; and it soon became strong in basic biomedical science. Langdon-Brown identified the development of physiology under Foster as critical to the development of a medical school in Cambridge: ‘its influence stemmed from the importance of original work of which that on the nervous system was the most striking’. Before taking up the professorship of physiology in 1883, Foster had been appointed praelector in physiology at Trinity College (1870) at the suggestion, amongst others, of the author George Eliot (in reality, Marian Evans, 1819–80) and with the endorsement of Thomas Huxley (1825–95). The Physiological Laboratory opened in 1879. Foster encouraged many young investigators to work on the nervous system. Walter Gaskell (1847–1914) described the organization and function of the sympathetic and parasympathetic nerves and their innervations of the heart (The Involuntary Nervous System, 1916). This work led to an understanding of referred pain by (Sir) Henry Head (1861–1940), also a pupil of Foster, and others; to segmentation in the brain and spinal cord; and, more controversially, to concepts on the structure and function of the central nervous system in the evolution of vertebrates—‘the secret of evolutionary success is the development of a superior brain’. John Langley (1852–1925) also studied the involuntary nervous system (The Autonomic System: Part 1, 1921); he was president of the Neurological Society of Great Britain (which adopted Brain as its official journal) in 1893 despite not being medically qualified. Keith Lucas (1879–1916) discussed the ‘all-or-none’ law of nerve firing and muscle contraction (The Conduction of the Nerve Impulse: revised by ED Adrian and published posthumously, 1917).

Throughout this period, Cambridge was considered to have ‘the worst housed medical school in England’. Although the University provided support in order to protect medical education from too much outside interference, no progress was made on the establishment of a complete medical school, applying the usual argument that the opportunity for clinical experience in the City would not be adequate. Dr Latham remained an intermittent and clandestine thorn in the flesh of Foster and Paget in their efforts to develop a complete medical school and integrate this with Addenbrooke’s Hospital, declaring in his disappointment at not being appointed Regius Professor of Physic that the appointee, Allbutt ‘would enter the wards and have beds over (my) dead body’. Appointed to Cambridge from his post as commissioner in lunacy having worked at the West Riding Lunatic Asylum with (Sir) James Crichton-Browne (1840–1938), Allbutt was a neurologist, inspired by Jacob Lockhart Clarke (1817–80) at St George’s Hospital and Guillaume Duchenne de Boulogne (1806–75). He contributed to the first issue of Brain and wrote on the ophthalmoscope, describing the mechanism of papilloedema (‘choked disc’); the neurotoxicity of tetanus toxin; the hazards of ‘brain forcing’ in schools; and, in his Goulstonian Lectures on ‘Neuroses of the viscera’, psychological factors in the pathogenesis of disease decrying ‘the attribution of ailments in women by fashionable gynaecologists to uterine displacements except in the season of grouse shooting or salmon fishing’. Allbutt is the role model for Tertius Lydgate in George Eliot’s Middlemarch (1874) and the central figure in A St Luke of the Nineteenth Century by Mrs Russell Barrington (1922).

All of this is much better told by Mark Weatherall, consultant neurologist in London (UK) with a special interest in headache, in Gentleman, Scientists, and Doctors: Medicine in Cambridge: 'its influence stemmed from the importance of original work of which that on the nervous system was the most striking'.
1800–1940 (Boydell Press, 2000) where he explains the evolution of medical education in Cambridge and the establishment of experimental physiology and pathology that eventually led to formalization of a complete medical education in Cambridge in the 1970s. In an occasional paper on ‘The migraine theories of Liveing and Latham: a reappraisal’, Mark Weatherall draws on this same rich historical seam in analysing the scientific climate in Cambridge from which emerged Edward Liveing’s theory of nerve storms, borrowed from Thomas Willis, and Peter Latham’s rival vasomotor theory, telling how—despite much attention from contemporary neurologists including John Hughlings Jackson (1835–1911)—criticism of each other and views of the authoritative (Sir) William Gowers (1845–1915) eventually led to the theories of these 19th century physicians being discounted, their work falling into obscurity, and each moving his interest onto other topics: ‘Latham should be credited with being one of the first people to attempt to articulate a vascular theory of migraine that explained the phenomena both of aura and of headache... (but) to see Liveing’s theory as in any sense a precursor to modern neural concepts of migraine is simply not tenable—Gowers effectively demolished the theory of nerve storms in its contemporary sense’. Dr Weatherall acknowledges that ‘many recent accounts of the history of migraine accord a prominent place to Liveing, rather less so to Latham... (and) the resurgence of interest in Liveing may be traced to the advocacy of... Oliver Sacks and (John) Pearce’.

John Pearce, former neurologist in Hull (UK), has written extensively on many aspects of the history of neurology, notably Neurological eponyms [with Peter Koehler and George Bryun (2000)]; and Fragments of neurological history (2003), being essays on many topics expanded from pieces published over many years in Journal of Neurology Neurosurgery and Psychiatry. In ‘A headache history’, he reviews Headache through the centuries by Mervyn J. Edie (Oxford: Oxford University; 2012). Writing both from the perspective of distinguished neurologist with a lifetime of clinical experience and accomplished medical historian, Professor Edie ‘analyses contemporary ideas on headache set in the context of their long and complex histories, sitting the reader in the headache clinic of the 21st century and escorting us across an historical landscape where, surveying with knowledge and enthusiasm and returning often to his favourite oases, Edie celebrates contributions of the many luminaries who signposted the road to modernity but also uses his eclectic and encyclopaedic reading to bring several less well-known figures from the ancient, medieval, renaissance and modern worlds to our attention. He combines scholarship with scientific authority in showing how contemporary views on definition, nosology, phenomenology, classification, mechanisms and treatments were eventually carved from the ancient rough-hewn blocks of cephalalgia, cepheala and hemicranias’. For John Pearce, ‘Of many books and essays devoted to the history of migraine, this... yields the best and most assiduous compilation and criticism, quoting many investigators of headache whose work has been unrecognized or neglected. It is a delight to browse and learn from this elegant, well-written text’.

In addition to the paper on migraine by Nasim Maleki and colleagues from Boston (USA) describing sex-specific differences in brain structure in female migraineur(e)s (page 2546; and see commentary page 2311) in the present issue, papers on vascular neurology include work by Pinki Munot and investigators from London, Sheffield and Birmingham (UK), Houston (USA), Utrecht (The Netherlands) and Aarhus (Denmark) describing a novel phenotype associated with mutations of ACTA2. They show that patients with disruption of Arg179 (and perhaps also Arg258) have complex abnormalities of the internal carotid arteries with regional ectasia and stenosis at sites marking the transition from elastic to muscular arterial walls, but not the collaterals seen in moyamoya disease, features that identify the need to screen for life-threatening dissection of large systemic vessels and the associated gastrointestinal and bladder abnormalities (page 2506).

In 1978, Charlotte Dravet described a disorder characterized by severe myoclonic epilepsy in infancy (Les épilepsies graves de l’enfant. La Vie médicale 1978; 8: 543–8). On page 2329—commenting on the paper by Andreas Brunklaus and colleagues from Glasgow (UK) describing the prognostic, clinical and demographic features of cases having mutations of SCN1A (page 2309)—Dr Dravet tells the story of how ‘Dravet syndrome’ came to be understood as a prototypic disorder illuminating the genetic and ion channel basis for many other epilepsies.

Three papers report the results of clinical trials. Lisa Barkas and a team from Southampton and Cardiff (UK) and Albuquerque (USA) study impaired allocentric spatial awareness in mesial temporal lobe epilepsy and the increased rate of forgetting this particular memory with involvement of the non-dominant hippocampus in patients, and an experimental rodent model of status epilepticus; reversal of the neural damage with fluoxetine corrects the learning deficit but not the accelerated forgetting (page 2358). Fluoxetine is also used by Jee Lee and colleagues from Seoul (Korea) to demonstrate nuclear factor kappa-B dependent matrix metalloprotease mediated inhibition of neutrophil and macrophage migration across the blood–spinal cord barrier in the context of experimental spinal cord injury, reducing inflammation and apoptotic neuronal loss with consequent improvement in locomotor function (page 2375). Nikos Gorgoraptis and investigators from London and Norwich (UK) and Lübeck (Germany) hypothesize that dopamine agonists may increase attention in visual neglect following right hemisphere ischaemic injury and show, in a double-blind randomized placebo controlled trial that rotigotine improves performance on tests of visual search due to selective attention but not general measures of attention, working memory or motor control, irrespective of prefrontal involvement (page 2478). Amongst seven papers on aspects of neurogenetics, Tina Noergaard Munch and a team from Copenhagen (Denmark) assess familial aggregation of primary hydrocephalus in all children born in Denmark between 1978 and 2008 and their family members; they show that 1% of Danes are born with hydrocephalus of whom 3.4% have an affected relative, the risk being highest in same-sex monozygotic twins (35%), falling with degrees of relatedness, and showing a strong maternal parent of origin effect (page 2409). Hydrocephalus has featured in 634 articles published in Brain since 1878; and the suggestion of an hereditary component in determining this congenital abnormality is not new. In From the Archives, we review ‘Chronic hydrocephalus’ by Armand Ruffer (Brain; 13: 117–44 and 240–69).

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