Occasional review

Historical aspects of migraine

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“Spleen sighs for ever on her pensive bed, Pain at her side and megrim at her head.”
(Rape of the lock. Alexander Pope, 1688-1744)

The student of medicine first encountering the migraine literature will immediately perceive the extraordinary amount written, and will sense an unspoken frustrated fascination—a sort of blighted curiosity which pervades many accounts and descriptions. Enlightened self interest may explain some of the attention shown by physicians, since the incidence in our profession is as high as 30%. It is almost impossible to do justice to such a vast literature spanning over 2,000 years, much of which is no longer of easy access and is often reproduced by copies of other authors’ quotations. This account is guilty in part of this criticism. In it I select some of the excellent descriptive writing of the early physicians, and by taking samples of their scholar try to outline their thoughts about the nature of the disorder and its symptoms which are in no small measure responsible for our current insecure concepts.

The Shorter Oxford Dictionary (SOED) cites under MEGRIM, late Mediaeval English:

1. b. = vertigo 1595. 2. A whim, fancy, fad 1593. 3. pl. ‘Vapours’; low spirits 1633. 4. pl. The staggers 1639.

“Thee is troubled with a perpetual migrim; at sea thee wishesth to bee on land, and on land at sea 1631”

The first appearance of “hemicrania” (Greek, half-skill) is cited by the SOED as 1597; this refers to English texts. Thus even before The Plague and the Great Fire, it was used to describe a far wider constellation of symptoms than headache alone; the associations with disturbed balance and sea-sickness, the emotional changes and depression implied by “the vapours” and “low spirits” were evidently well understood. Was it a coincidence that the same word Megrim was also applied in 1836 to Arnoglossus laterna, the scald-fish, or was this some oblique reference to burning headache or perhaps to facial flushing later coined under the name “red migraine”?

Hippocrates (c.460–c.370 B.C.)
It is said that the earliest description of migraine as a periodic syndrome appeared 3,000 B.C. in Mesopotamian poems. Hippocrates provided an account of severe pain in one half of the head associated with disturbance of sight.1

“he seemed to see something shining before him like a light, usually in part of the right eye; at the end of a moment, a violent pain supervened in the right temple, then in all the head and neck, . . . vomiting, when it became possible, was able to divert the pain and render it more moderate.” The cardinal features of the visual aura, unilateral and vomiting with relief of pain were clearly understood. Hippocrates was also an early advocate of drug therapy, mentioning the hellobore family of plants which may have had a diuretic action. The medical schools of Cos and Cnidas both believed in the “four humours” or chief fluids of the body advocated by Empedocles (c.490–430 B.C.), but whereas the Cnidiad were empiricists, observers and classifiers, Hippocrates of the Coan school was dedicated to the study of the causes of disease through direct observation and inference.

Celsus (A.D. 30)
It is sometimes said that there was only one great Roman book on Medicine: De Re Medicina. This large scale encyclopaedia or “Medical Home Companion” was written for rich landowners by A. Cornelius Celsus, a friend of the Emperor Tiberius. Celsus was probably not a doctor and like Pliny had a low opinion of physicians. That Celsus recognised migraine2 and its precipitating causes is evident: “A long weakness of the head, but neither severe nor dangerous, through the whole life. Sometimes the pain is more violent, but short, yet not fatal; which is contracted either by drinking wine, or crudity, or cold, or heat of a fire, or the sun. And all these pains are sometimes accompanied with a fever, and sometimes not; sometimes they afflict the whole head, at other times a part of it;”

Aretaeus (A.D. 81–?)
Aretaeus was born in Cappadocia in about A.D. 81.

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First a native of Alexandria he then moved to Rome. His writings refer to cephalgia: headaches lasting a few days, and cephaele: headaches lasting days or weeks without remission. The pain remains in the half of the head. This is called heterocrania, an illness by no means mild, even though it intermits, and although it appears to be slight it sets in acutely, it occasions unseemly and dreadful symptoms: nausea; vomiting of bilious matters, collapse of the patient, but if the affect be protracted, the patient will die; or if more light and not deadly it becomes chronic; there is much torpor, heaviness of the head, anxiety and weakness. For they flee the light; the darkness soothes their disease: nor can they bear readily to look upon or hear anything disagreeable; their sense of smell is vitiated.

Of this passage, Macdonald Critchley in the first Sandoz Foundation Lecture, rightly comments that the reference to death is foreign to contemporary experience, but suggests that Aretaeus might have observed a patient with aneurysmal subarachnoid haemorrhage. Aretaeus used the word "heterocrania" to indicate its location in half of the skull and clearly described headache attacks recognisable as migraine.

Galen (A.D. 131–201)

Galen distinguished the nature of migraine from other common headaches and used the term "hemicrania": a painful disorder affecting approximately one half of the head, either the right or left side, and which extends along the length of the longitudinal suture. It is caused by the ascent of vapours, either excessive in amount or too hot, or too cold. As ever this famous father figure was preoccupied by the four humours: phlegm, blood, bile (choler) and black bile (melancholy). As Critchley observes, this humoral mythopathology was to stultify medical thinking for some 1400 years.

Caelius Aurelianus (A.D. 400–)

In De Capitis Passione, Caelius Aurelianus, born in A.D. 400 in Algeria, described hemicrania and "crotophon". This term meant a pounding or hammering and was accompanied by vertigo with burning of the eyes, nausea or vomiting. He described lachrymation, noises in the ears and deafness.

In the 7th century, a Greek physician Paulus Aeginata of the Alexandrian school of Medicine recounted the factors which provoked migraine: ... Noises, cries, a brilliant light, drinking of wine and strong smelling things which fill the head. Some as if the whole head were struck, and some as if one half, in which case the complaint is called hemicrania.

There was apparently sparse mention of the disorder and little to advance the Galenic stance of humors as the cause until the 17th century, though it was appreciated and described in lengthy tracts by the distinguished Arabic schools in the 11th, 12th and 13th centuries. Surgical techniques applied included trephining, incisions into the scalp, the application of heated irons and of course blood-letting.

Thomas Willis

Perhaps the greatest forerunner of modern neurology, Willis was familiar with the problems of migraine, both diagnostic and therapeutic. He had a large and thriving practice which counted in its number many titled and famous contemporary figures. In a section, "De Cephalalia" in volume 1 of De anima brutorum (Concerning the souls of brutes) 1672, he distinguished different headache types: "within or without the skull", universal or particular, short, continuing, or intermittent, wandering, uncertain, before, behind or the side, and occasional or habitual. The pain of the head he said is wont to be accounted the chiefest of the Diseases of the Head so common that it is become a Proverb as a sign of a more rare and admirable thing That his head did never ake."

Willis considering aetiology mentioned hereditary factors and recorded cases following injury or an emotional upset. It often began in the morning. Causes were "immediate or remote". He also observed that attacks were sometimes induced by hunger and that polyuria might accompany attacks of migraine: "I have observed in many, a watery and very plentiful urine, either to precede or accompany the fits of the disease."

It was realised by Willis that headaches could betoken more ominous disease of the head. His chapter ends with eight histories of patients with headaches of diverse causes, including examples of migraine and of fatal brain tumour. C. P. Symonds recalled Willis's description of a patient with left sided headache in whom at necropsy occlusion of the right carotid artery was found. He attributed the headache to a compensatory dilatation of the left carotid circulation: an instance supporting his notion of the anastomotic function of the circle which now bears his name. In a previous paper I have outlined the history of cluster headache or migrainous neuralgia and cite Raymond Hierons's suggestion in 1955 that Willis's account may have been the first record of this malady. His patient was a lady who began to suffer from headaches "each afternoon at about 4 o'clock"; this continued daily for some five weeks.

Perhaps the most celebrated migraineur of this period was Anne, Countess of Conway, who had the added distinction of being attended by both Thomas Willis and William Harvey. His concern about this lady's headaches tells us of his understanding of headache mechanisms which was far ahead of his times: "The opening of the skull (trephining) cry'd up by
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many, but rarely or never attempted ... This our most ingenious Harvey endeavoured to persuade a Noble Lady, labouring with a most grievous invertebrate headache, promising a cure from thence, but neither she nor any other would admit that administration.

He doubted the existence of a tumour which would have caused "sleepy distemper" or "deadly convulsions". He considered the headache might have been of meningeal origin according to Spillane who quotes: "beset with little wheals, a Schirrous or Callous Tumor", although even then, "I think opening of the skull will profit little or nothing".

Plainly, Willis was right and had anticipated the conservatism of modern-day physicians which can on occasion be so trying to their surgical colleagues, especially so when vindicated by the passage of time.

Willis's description of the migraine of Anne, Countess of Conway is a classic: Some twenty years since, I was sent for to visit a most noble lady, for above 20 years sick with an almost continual headache, at first intermitting: she was of a most beautiful form, and a great wit, so that she was skilled in the liberal arts, and in all forms of literature, beyond the condition of her sex, and as if it were thought too much by nature, for here to enjoy so great endowment without some detriment, she was extremely punished with this disease. Growing well of a feaver before she was 12 years old, she became obnoxious to pains in the head, which were wont to arise, sometimes of their own accord, and more often upon every light occasion. This sickness being limited to no one place of the head, troubled her sometimes on one side, sometimes on the other, and often thorow the whole encompass of the head. During the fit (which rarely ended under a day and a night's space, and often held for two, three or four days) she was impatient of light, speaking, noise, or of any motion, sitting upright in her bed, the chamber made dark, she would talk to no body, nor take any sleep, or sustinance. At length about the declination of the fit, she was wont to lye down with a heavy and disturbed sleep, from which awaking she found herself better, and so by degrees well, and continued indifferently well till the time of the intermission. Formerly, the fits came not but occasionally, and seldom under 20 days of a month, but afterwards they came more often: and lately she was seldom free. Moreover, upon sundry occasions, or evident causes (such as the change of the air, or the year, the great aspects of the sun and moon, violent passions, and errors in diet) she was more cruely tormentd with them. But although this distemper, most grievously afflicting this noble lady, above 20 years (when I saw her) having pitched its tent near the confines of the brain, had so long besieged its regal tower, yet it had not taken it: for the sick lady, being free from a vertigo, swimming in the head, convulsive distempers and any soporiferous symptoms, found the chief faculties of her soul sound enough."

This is the richest account to date of the variegated symptomatology of migraine, and today we can identify many of the characteristics of the natural history of this affection. Willis did not confine his account of migraine to his experience with Lady Conway. Elsewhere he mentioned a case where a "beautiful and young woman, indue with a slender habit of body, and an hot blood, being obnoxious to an hereditary headache, was wont to be afflicted with frequent and wandering fits of it, to wit, some upon every light occasion, and some of their own accord; that is, arising without any evident cause. On the day before the coming of the spontaneous fit of this disease, growing very hungry in the evening, she eat a most plentiful supper, with an hungry, I may say a greedy appetite; presaging by this sign, that the pain of the head would most certainly follow the next morning; and the event never failed this augury. For as soon as she awaked, being afflicted by a most sharp torment, thorow the whole forepart of her head, she was troubled also with vomiting, sometimes of an acid, and as it were a vitriolock, humor, and sometimes of a choleric and highly bitterish: hence according to this sign this headach is thought to arise from the vice of the stomach."

Of the 17th century Critchley records the curious illusions of Blaise Pascal as possible manifestations of migraine. These consisted of the sudden apprehension of a cavity or yawning precipice sited on his left side; he also produced manuscripts with an extraordinary broad right margin, and in places he would insert peculiar zig-zag designs reminiscent of migraineous teichopsiae. These may have been episodes of homonymous hemianopia, not uncommon in migraine, but despite their euphonious attribution by his contemporaries as "l'Abime de Pascal" it is uncertain whether or not they were of migraineous genesis. Similar in certain respects were the strange visual experiences of the Abbess Hildegard of Bingen: "I saw a great star, most splendid and beautiful, and with it an exceeding multitude of falling sparks with which the star followed ... suddenly they were all annihilated, being turned into black coals..."

These images too evoke suspicions of teichopsiae succeeded by a dense scotoma, both migraineous features; but we have a dearth of description of their headaches.

John Fordyce published in 1758 his De Hemicrania, an account of his own, mainly left sided migraine attacks. He was one of the first to observe the polyuria, prodromal depression and the link with menstruation. Decrying section of the temporal artery, he was a powerful advocate of large doses of valerian obtained from Valeriana sylvestris. By this time the syndrome was well known and was described in many texts and monographs. Fothergill drew attention to
“fortification figures” in the aura, and was impressed by dietary factors, and was perhaps the first to incriminate chocolate as a precipitant of attacks. But, full descriptions were few, though many are the anecdotes relating the migraine of distinguished persons of the era.

Tissot
An extensive account is found in volume 13 of the monumental text of Tissot in 1790, which has the rather impressive title: De la migraine, Oeuvres de Monsieur Tissot, nouvelle edition augmentée et imprimée sous ses yeux. Observing that gastric symptoms might precede or initiate attacks, and that vomiting might herald the termination of the headache he commented: “A focus of irritation is formed little by little in the stomach, and that when it has reached a certain point the irritation is sufficient to give rise to acute pains in all the ramifications of the supraorbital nerve…”

Interestingly, these fine scholar-physicians of the 18th century, who included Whytt, Cheyne, Syndenham and Willis, made no distinction between physical and emotional symptoms. They recognised both, but viewed them as essential manifestations of nervous disorders. The 19th century saw the terms “organic” and “functional”; the latter implying literally a disordered function or altered physiological reaction. This attitude was purveyed in the physically orientated descriptions of Abercrombie, Parry, Romberg, Hall, Mollendorff and in the astronomer Airy and his son. Theories of the nature of migraine begin to embrace the rapidly developing knowledge of medicine and physiology in the nineteenth century. Inflammations and a variety of vascular disorders ranging from cerebral congestion to arterial constriction or dilatation were popular notions. Pituitary swelling or menstrual factors were claimed as causes, and masturbation and hereditary taints were culpable.

Hughlings Jackson (1834–1911)
This Yorkshireman escaped to London from his native Green Hammerton via the Medical School of York along with his equally distinguished friend Jonathan Hutchinson. They were both appointed to the London Hospital, and Jackson to the National Hospital. So profound was his idiosyncratic scholarship, and so prophetic his clinically founded dicta concerning the physiology and integration of the brain, that we naturally turn to his writings for clarification. Unfortunately, he had little to say by way of description, but his pithy footnotes point the way to concepts which are only now finding acceptance. “I believe cases of migraine to be epilepsies (sensory epilepsies). Dr Latham thinks the paroxysm in migraine to be owing to arterial contraction in the region of the posterior cerebral artery; Dr Liveing that there is a “nerve storm” traversing the optic thalamus and other centres. I think the sensory symptoms of the paroxysm are owing to a “discharging lesion” of convolutions evolved out of the optic thalamus, i.e. of “sensory middle centres” analogus to the “motor middle centres”. I believe the headache to be post-paroxysmal.” By middle centres he referred to the basal nuclei which were subservient in his concept to the cortex and associational areas which were the higher centres in terms of cerebral organisation. Jackson arbitrarily classified migraine as of three types: 

(1) Typical: one in which there is a “visual projection”, the well-known zigzag or “fortification” outline is most common, with in some cases a hemianopic area; then comes headache, most often frontal and one-sided, and lastly vomiting. (2) There are subtypical cases, visual projections and nothing more, or headache unprecedented by visual projections and nothing more, or headache unprecedented by visual projections, and not followed by vomiting. (3) There are supertypical cases deserving very particular consideration. In these in addition so to say to the other symptoms, numbness of one side of the body, and when the numbness is on the right side there may also be considerable aphasia. To the inexperienced these cases look far more serious than they are; they do not point to any gross local disease. Some of the symptoms of migraine, the headache among others, are, I think, after effects of the discharge producing the paroxysm.”

Here Jackson was making a plea for a particular approach to advance the philosophy of scientific progress. He pleaded for the “arbitrary study of cases by type (ie classification) which does not prevent us from making at other times and for other purposes rational generalisations.” He clearly differentiated migraine from epilepsy, and used the latter term generically to indicate a “discharging lesion” of the cortex; the differences were accounted for by “the different seats of those lesions”. He was familiar with the links between migraine, epilepsy and what he termed epileptiform seizures and “intermediate forms” of a type which Gowers later referred to as “the borderlands of epilepsy.” Jackson was keen to erect hypotheses or suppositions, in the tradition of Newton, and he decried the Baconian method of induction which were limited to observable and already known facts. As in his work and writings on epilepsy, Jackson’s comments on migraine, though brief, heralded an awakening of speculation which proved invaluable. As he remarked “The use of hypotheses is the method of science.”

Edward Liveing
The best text is without doubt that of Liveing (1873) which spanned over 500 pages. Liveing was
Registrar to the Royal College of Physicians and Assistant Physician to King's College Hospital. His book gave detailed case histories of many migraineurs and included those of celebrated doctors' accounts on their own sufferings, those drawn from history as well as his own patients. He provided full descriptions of the aura and its protean expressions and considered the integral links between migraine and epilepsy, vaso-vagal faints, vertigo, paroxysmal diseases and insomnia and other nervous diseases. Liveing considered the extant theories of migraine at length, under the following headings: (1) The Doctrine of Biliousness, (2) Sympathetic and Eccentric Theories, (3) Vascular theories: (a) arterial cerebral hyperaemia (b) passive venous congestion of the brain (c) vaso-motor hypotheses, (4) The Theory of "nerve-storms" (his own belief).

The first two concepts have been sketched at the beginning of this paper in the allusions to the humourists emphasised by Galen and his successors. The discovery of a nerve supply governing the capacity for arteries to dilate or constrict was (and still is) responsible for the vascular hypothesis. P lethora of the face, and pallor in attacks were of course well known and emphasised the idea that similar changes were occurring in the brain.

E. Du Bois Reymond (1818-1896)
This distinguished physician first discovered that the peripheral passage of a nerve impulse was accompanied by an electrical discharge, the action potential. Writing in 1860 he attributed migraine to "a Tetanus takes place in the muscular coats of the vessels of the affected half of the head; in other words a Tetanus of the cervical portion of the sympathetic". His account gives us an excellent picture of the art of descriptive writing at this time: 'every three or four weeks I am liable to an attack. I wake with a general feeling of disorder, and a slight pain in the region of the right temple which, without overstepping the midline, reaches its greatest intensity at midday; towards evening it usually passes off. While at rest the pain is bearable, but it is increased by motion to a high degree of violence... It responds to each beat of the temporal artery. The latter feels on the affected side, like a hard cord, while the left is in normal condition. The countenance is pale and sunken, the right eye small and reddened... There may be left behind a slight gastric disorder; frequently also, the scalp remains tender at one spot the following morning... For a certain period after the attack I can expose myself with impunity to influences which before would infallibly cause an attack.'

Latham initiated the vascular hypothesis and explained it thus: "contraction of the blood vessels of the brain, and so diminished supply of blood, produced by the excited action of the sympathetic; and that the exhaustion of the sympathetic following on this excitement causes the dilatation of the vessels and the headache". This was to set the foundations for the masterly exposition of Harold Wolff, many years later. Liveing accepted that dilatation of the arteries might explain the headache, but rejected the vascular theory as explanation of the varied content of the aura, its bilaterality in certain patients, the vegetative symptoms throughout the body, and the changes in patterns of attacks. Liveing regarded it as "a form of centrencephalic seizure, the activity of which is projected rostrally upon the cerebral hemispheres, and peripherally via the ramifications of the autonomic nervous system..." In explaining his "nerve storm" theory he considers migraine along with other "neuroses" to be: a primary and often hereditary... disposition of the nervous system itself; this consists in a tendency to the irregular accumulation and discharge of the nerve force... a gradually increasing instability to equilibrium in the nervous parts: when this reaches a certain point, the balance of forces is liable to be upset and the train of paroxysmal phenomena determined by causes in themselves totally inadequate to produce such effects—just as a mere scratch will shiver to dust a mass of unannealed glass..."

Gowers
The famous two volume work Diseases of the Nervous System published in 1886 is accessible,12 and the substantial chapter on "Migraine: Paroxysmal Headache" still provides a surprisingly up to date account of the clinical expressions, variants, complications and aetiology. Here, the reader will find descriptions and interpretations of model clarity. In respect of causation Gowers refers to the two main theories: vascular and neural. Like Jackson, he was impressed by the similarities with epilepsy. But, he stressed: "The peculiarity in the disturbance of migraine is its deliberate character and its limitation to sensory structures. The uniformity of these symptoms in the same case is another feature that must be taken account of in any theory as to their origin. To explain them on the vaso-motor hypothesis we must assume, first an initial spasm of the arteries in a small region of the brain; secondly, that the contraction always begins at the same place; and, thirdly, that it can give rise to a definite, uniform and very peculiar disturbance of function. There is no evidence of the truth of any one of these assumptions... the vascular changes are the result of a disturbance in the sensory centre, or are the effect of associated derangement of vaso-motor centres."

Gowers agreed with the general tenets of the Liveing hypothesis of "nerve storms", but favoured the cortex rather than the thalamus as the main site of deranged neural activity. He anticipated more recent ideas13 14 by allowing that "the peculiar disturbance
might spread to cells of lower centres”. This accords with the current notions\textsuperscript{13,14} which implicate the hypothalamus and brain stem. He found “the cause of the headache obscure”, but considered the brain itself, the meninges or a neuralgia referred from the central disturbance to the periphery. He could conceive that the pain might be the result of a vascular condition, as had Du Bois Reymond, but was unhappy with this concept since at that time the occurrence of arterial pain had not been established.

Treatment was of course primitive, and as it is now, based largely on empirical observation. Gowers mixture remained fashionable and enjoyed considerable success for more than half a century, and still appeared in student texts in the 1950s. It consisted of:

- Liq. trinitiri minims 1
- Liq. strychninae minims 3
- Tinct Gelsemii minims 15
- Phenazone grains 5
- Sodium Bromidi grains 5
- Acid hydrobrom dil minims 10. Aqua Chloroform ad ooz 1. t.d.s.

The use of trinitrine perhaps anticipated the current vogue for the calcium channel blockers which are also vasodilators.

The Twentieth Century

When we come to the present century, research and writings have sprouted and grown in parallel. They are summarised in the well known text of Wolff,\textsuperscript{15} Sacks,\textsuperscript{16} Lance\textsuperscript{17} and of the author.\textsuperscript{18,19} In the 1920s allergy was a popular new idea supported by the putative links between migraine and asthma and urticaria. Although Lance showed these to be no more than the coincident coexistence of very common diseases, modern immunologists have attempted to resurrect this theory in the form of dietary allergy, so far with little conviction. Psychosomatic disorders were the fashion of the 1940s and 1950s following the work of Selye on “Stress diseases”. Research has shown abnormalities of serotonin and prostaglandins; currently a defect of endogenous opioids is a popular notion. But it remains extremely difficult to investigate migraine. The fact is that many of the objective abnormalities on measurement are found in only small numbers of patients; and, observations based on “induced attacks” are nearly always triggered by an artefactual stimulus. Likewise, there is no animal model suitable for experiment. Thus no valid or generally applicable “marker” or constant accompaniment of the disorder has been found.

Our current concepts have evolved in Darwinian fashion from physicians of the past. Migraine can be seen as a reaction or biological adaptation determined by (1) a primary disorder of brain threshold, probably familial, possibly operating at the level of the brain-stem or hypothalamus, in combination with (2) a variety of external precipitating factors which individually or collectively lower this threshold to a critical point when an attack will ensue. Thereafter, the “exhausted” nervous system compelled by migrainous symptoms to rest and retreat from the external stresses, recovers and regains its former threshold until the cycle is repeated.

The primary basal setting of the threshold is a biological circadian function subject to the individual’s physiological and emotional resilience. As such, it is prone to fluctuate and to fall, particularly in response to those complex factors, so difficult of definition, which we recognise as physical and mental stress.

“A form of centrencephalic seizure, the activity of which is projected rostrally upon the cerebral hemispheres, and peripherally via the autonomic nervous system.” Thus wrote Edward Liveing in 1873. We are but a little wiser in 1986.

I am indebted to Dr Macdonald Critchley for permission to quote from his Sandoz Memorial Lecture, 1967.\textsuperscript{4}

References

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