

## Epilepsy: no longer *The Sacred Disease*?

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“Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant, in some cases using custom as a test, in others perceiving them from their utility. It is the same thing which makes us mad or delirious, inspires us with dread and fear, whether by night or by day, brings sleeplessness, inopportune mistakes, aimless anxieties, absent-mindedness, and acts that are contrary to habit.”

This, one of the most extraordinary passages in the history of medical literature - one that should be known to every neurologist, neuroscientist, psychiatrist, and student of human nature - comes from a short monograph on epilepsy, entitled *The Sacred Disease*. This essay, perhaps the earliest example of a medical treatise on a single disease, is found in the Hippocratic Corpus, a ragbag - should one say rattle bag? - collection of medical works first assembled in the ancient library at Alexandria and ascribed to the greatest physician of ancient times, Hippocrates of Cos.

There is little doubt that Hippocrates was a real person, a doctor of considerable renown, but there is equally no doubt that he cannot have written all the works ascribed to him. Even the most superficial study of the styles, language, and philosophies contained in the works of the Corpus show that they are the products of different people of different times and different schools of medicine. Yet *The Sacred Disease* is often considered to be one of the ‘genuine’ works of Hippocrates, in part because of its similarities to other works such as *Airs, Waters, Places*, and in part because, as one critic put it over 100 years ago, it is “a masterpiece of scientific sanity; broad in outlook, keen and ironical in argument and humane in spirit”; in other words, everything that one would want and expect from the pen of the ‘father of medicine’.

The purpose of the author of *The Sacred Disease* is simply to show that epilepsy is not “any more divine or more sacred than other diseases, but has a natural cause, and its supposed

divine origin is due to men's inexperience, and to their wonder at its peculiar character". As the historian Vivian Nutton points out in his magisterial history of *Ancient Medicine*, the author does not deny the possibility of divine healing *per se*, but instead directs his attack at the "magicians, purifiers, charlatans and quacks" who "claim great piety and superior knowledge", whilst they sheltered behind superstition "and called this illness sacred, in order that their utter ignorance might not be manifest".

The author of *The Sacred Disease* belongs to a different tradition, in which an attempt to appreciate the beauty and order of the natural world opened up the possibility of rational understanding of disease, and thereby of prognosis and treatment. The author believed that the origin of epilepsy lay in heredity, and that the seat of the disease was the brain, an organ which the author contended (against the prevailing orthodoxy) was the seat of consciousness, a view held by Plato, but rejected by Aristotle, who favoured the heart. The author describes how in the course of an attack, the "patient becomes speechless and chokes; froth flows from the mouth; he gnashes his teeth and twists his hands; the eyes roll and intelligence fails, and in some cases excrement is discharged". He records that those who are "habituated to their disease have a presentiment when an attack is imminent". He describes how such people run home, or away from company, and hide their heads, ascribing this to "shame at their malady, and not, as the many hold, of fear of the divine".

He provides a rational explanation for each of these symptoms, based on the theory that the health of the body arises from a balance of the four humours - blood, phlegm, black bile and yellow bile. He believes that the attack arises when phlegm blocks the flow of air to the brain - "the most powerful organ of the human body" - rendering the patient "speechless and senseless". The author states that such a build-up of phlegm (not to be identified exactly with the respiratory tract secretions that bear that name nowadays) can prove fatal, a point he supports by noting that if one cuts open the heads of goats afflicted by seizures, "you will find the brain moist, very full of dropsy [oedema] and of an evil odour, whereby you learn that it is not a god but the disease which injures the body. So it is also with a man." The author concludes that the disease "comes from the same causes as others, from the things that come to and go from the body, from cold, sun, and from the changing restlessness of the winds". Each of these, he states, "has a nature and power of its own; none is hopeless or incapable of treatment".

Today, of course, we no longer hold the humoral theories that dominated medicine for two millennia to be true, even if they can still be glimpsed in our description of people's personalities as melancholy, sanguine, or bilious. But the approach to epilepsy taken by the author of *The Sacred Disease* - the careful observation of phenomena, and the attempt to explain those phenomena in terms of our ever expanding understanding of the physiology and molecular biology of the human body - is still valid, and has proved enduringly and increasingly powerful. It was the approach of Hughlings Jackson, and of William Gowers, whose lectures on *The Borderland of Epilepsy*, delivered a little over 100 years ago, provide an ongoing text and context for our understanding of the differential diagnosis of epilepsy.

As we have come to understand what functions are served by the different parts of the brain, we find ourselves increasingly able to correlate seizure semiology with focal pathophysiology. The joy of this process - for neotraditionalists like myself - is that it is all in the history, whether delivered by the patient or by an eyewitness to the attack. It is possible to correlate patients' experiences of déjà vu, rising epigastric sensations, abnormal tastes, fear and so on to abnormal expression of the normal functions of the temporal lobes; to be confident in ascribing versive eye and head movements to focal seizures arising from the frontal lobes; to differentiate the elemental visual hallucinations of occipital lobe seizures from the more complex, evolving nature of migrainous visual aura; and to know that, as our present techniques stand, these clinical correlations are more diagnostically sensitive and specific than EEGs, MRIs, or any other investigation generally available.

The flip side of the fact that epilepsy remains primarily a clinical diagnosis, is that it is an easy misdiagnosis to make. Distinguishing seizure from syncope can be near impossible in some cases, and even in simpler situations where the presence of presyncopal symptoms, and of a rapid recovery from unconsciousness make it easier *not* to diagnose epilepsy, it is still possible to be misled by an episode of incontinence, or by inaccurate descriptions by eyewitnesses asked inappropriately leading questions. It is important, therefore, to be open to this possibility, and quick to reappraise patients who do not respond as expected to first-line anticonvulsants. This process should be helped by recent international consensus that patients who fail to become fit-free after trying two anticonvulsants should be labelled as having refractory seizures, and referred to an epilepsy specialist.

Advances in clinical pharmacology and molecular genetics are impacting upon epilepsy management perhaps more than any other field of neurology at present. The molecular and genetic basis of many epilepsy syndromes is beginning to emerge. Epilepsy has in many cases found to be a disorder of ion channels: at least four such mutations have been shown to result in the common juvenile myoclonic epilepsy syndrome (an important clinical diagnosis to make because of its unremitting nature, and response to very specific set of anticonvulsants); mutations in the *SCN1A* gene have been shown to result in the generalised epilepsy with febrile seizures plus syndrome, as well as the vast majority of the severe childhood epileptic encephalopathies. As yet, however, these advances in pathophysiological understanding have yet to translate into better treatment options, despite the spate of new anticonvulsants that have appeared in the last two decades.

The molecular understanding of the underlying causes of epilepsy has in some cases begun to open up other avenues of treatment, however. In tuberous sclerosis, for example, it has been found that mutations in the affected proteins tuberin and hamartin both cause the inhibition of a protein kinase called mTOR, leading to abnormal cell growth and differentiation, and development of the tubers that characterise the disease. Rapamycin, an antifungal agent discovered in the soils of Rapa Nui (Easter Island), blocks mTOR, and may prove to be an effective agent in blocking the development of epilepsy in this relatively common genetic condition. Another, much rarer, example is the recently-characterised DEND syndrome, which causes neonatal diabetes, treatment-resistant epilepsy, and developmental delay. This has been found to be caused by mutations in *KCNJ11* gene which encodes a subunit of an ATP-sensitive potassium channel, causing a deleterious increase in ion flow which can in some cases be reversed by treatment with sulphonylureas, leading to improvements in diabetic control, epilepsy and psychomotor ability.

While Hippocrates would surely have been delighted, and felt vindicated by such discoveries, he would perhaps be dismayed to find that the shame and stigma of epilepsy that he described two and a half thousand years ago, still exists. Increased social awareness must therefore go hand in hand with increased scientific understanding, if we are to carry through the programme initiated by the brilliant, pugnacious, and energetic author of *The Sacred Disease*.