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Review

Hippocrates, Galen, and the patient with epilepsy. Some new perspectives on the old masters

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ABSTRACT

This article reads the old masters with the eyes of a clinical epileptologist. "On the Sacred Disease" is a flaming pamphlet against beliefs in supernatural causes of epilepsy. Hippocrates' statement that it has natural causes like all other diseases builds primarily on heredity and seat in the brain. Heredity is mainly based on predisposition to epilepsy by an inherited constitution. The cerebral origin follows earlier traditions, supported by the observation of acute traumatic seizures. Infantile hemiplegia following seizures may refer to the H.H.E. syndrome. Bilateral and unilateral tonic-clonic seizures, startle seizures and breath-holding spells are described as well as sleep-related paroxysms (night terror, sleep behaviour disorder, frontal lobe seizures and sleep apnea). Patients' reactions to warnings reveal stigma. Seizures are not random events but result from antagonistic influences in body and environment. The physician's task is to understand these and provide the patient with a comprehensive regimen to keep them in balance.

For Galen, epilepsy was not one disease but included multiple conditions. His standard regimen consisted essentially in a highly disciplined lifestyle, with drugs in a merely supportive function. His novel interest in patients' seizure experiences established the term "aura" and the subjective history of epilepsy. The first account of an aura documents its typical indescribability. Hippocrates and Galen are distinguished from the non-scientific approaches of their time first of all ethically, i.e. by their respect for their patients' dignity and autonomy.

1. Introduction

In epileptology we are so privileged that the two most important fathers of medicine, Hippocrates and Galen, have written about epilepsy. To take care of our heritage, we now and then need to revisit it. Temkin's 1933 analysis of epilepsy in Hippocrates [1] became a cornerstone of his great history of epilepsy, "The Falling Sickness" [2]. It still stands as a classical reference, but he had no practical knowledge of epilepsy which made him miss some relevant points. Walshe [3] drew attention to the fragility of the ancient source material and provided updated translations of "On the Sacred Disease" and "Wounds of the Head", reading them as a modern neuroscientist (see Fig. 1).

More recently, Theodore [4] undertook a linguistic study of the Hippocratic writings and concluded that they had "an understanding of the distinction between 'idiopathic' and 'symptomatic' seizure disorders". He also highlighted that "On the Sacred Disease" relates mental disorders and depression to epilepsy and considers them as brain diseases.

In the present paper, we try to read the old masters with a clinician's eyes, discuss how Hippocrates concluded that epilepsy is a disorder of the brain, and follow how Galen digested and developed the Hippocratic approach. We used the English translations by Adams [5], Jones [6] and Walshe [3], occasionally complemented with the German translation by Capelle [7], all eruditely commented. In case of ambiguities, the Greek original [8] was consulted. Quotations in the text are from "On the Sacred Disease" unless otherwise stated (see Fig. 2).

2. Hippocrates: Nosology

Hippocrates was a Greek physician who assumedly lived from ca 460 to ca 370 BCE. He belonged to the Asklepiad family who considered themselves as descendants of the god Asklepios, and became considered the leading figure of the medical school of Kos. This is about all we know of him. There is a collection of about 60 texts known as the *Corpus Hippocraticum* that were ascribed to him but definitely have various authors. Some of them were written after his lifetime. With all these uncertainties, they represent a level of insight that formed the medical thinking for centuries, and are uncontestedly considered the matrix of

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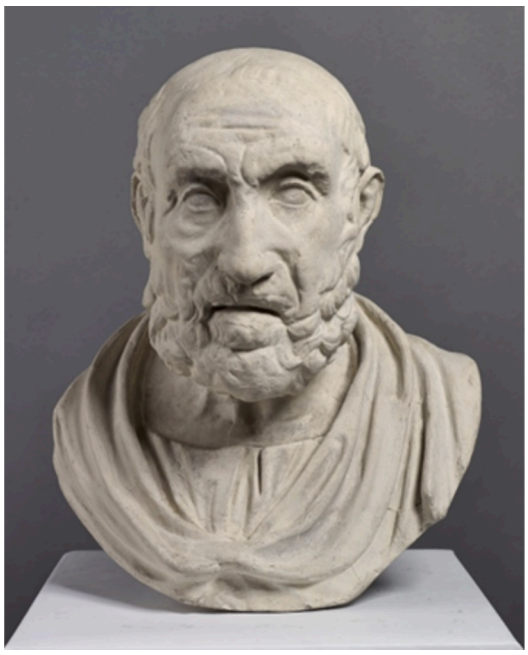

Fig. 1. There are no contemporary portraits of the masters, but artists have later given their idea how they could have looked. This bust representing Hippocrates is by Carlo Albacini (1734–1813) and Filippo Albacini (1777–1858). It shows a thoughtful person full of knowledge, but I see him less authoritative, more like an attentive clinician.

present science-based medicine. As Walshe points out, it is not sure that Hippocrates himself has written any of these texts but, starting with Galen, "commentators have routinely determined that the ones with the best medical work were genuine" [3]. The treatise on epilepsy, called "On the Sacred Disease" is one of them.

Today it is widely known that epilepsy for Hippocrates was a disorder of the brain and had, like all diseases, hereditary causes. "On the Sacred Disease" is first of all a flaming pamphlet against common contemporary beliefs that epilepsy was sent by Gods which he opposes with theological reasons that show him as a genuinely pious person. Like all other diseases, epilepsy has natural causes and is treated with natural methods. Heredity and seat in the brain are the cornerstones of his argumentation, but he treats them quite differently. The assertion of heredity needs reasoning, but it is weak, a mere conclusion by analogy [1]: "If a phlegmatic parent has a phlegmatic child, a bilious parent a bilious child, a consumptive parent a consumptive child, and a splenetic parent a splenetic child, there is nothing to prevent some of the children suffering from this disease when one or the other of the parents suffered from it". It is strengthened, however, by the observation that the (inherited) constitution is decisive: "It occurs in those who are of a phlegmatic constitution, but does not attack the bilious."

In contrast, the doctrine that the brain is the seat of not only epilepsy but also "the other severest diseases" is presented simply as a matter of fact, indicating that it is not a new idea. Indeed, already "in the prehistoric Stone Age, the head was regarded as a vital structure in man's anatomy" [3]. Then, a generation before Hippocrates, Alcmaion of Croton had observed, probably by dissection of animals, the neural connections of eyes, ears and nose to the brain and concluded that the brain was a central organ of perception, understanding and mind [7,9].

There was additional evidence. Acute traumatic seizures are repeatedly mentioned in the Corpus Hippocraticum, e.g. in "Injuries of the Head" where it twice is noted that they start ("the spasm seizes") on the side opposite to the trauma, either early or with some delay if the wound is not successfully treated [10]. Temkin attempts to dismiss this with a curious footnote where he says that "the passages in question all refer to fresh wounds from which the patients usually died within a short time. No connection is ever made between these spasms and epilepsy" [1]. But the negative linguistic reasoning by the absence of something which perhaps did not need to be said is weak, head trauma is and was often survived, and acute traumatic seizures look not different from other tonic-clonic seizures. This cannot have escaped physicians who were attentive enough to note their contralateral onset.

We are inclined to believe that Hippocrates considered epilepsy a disease of the brain on the basis of Alcmaion's conclusions, supported by the observation of traumatic seizures.

Furthermore, epilepsy is not restricted to humans. Of animals, it occurs most frequently in goats, and if you cut open their head you will "find the brain humid, full of sweat, and having a bad smell", proof that "it is not a god that injures the body, but disease." This observation further supports that epilepsy is a cerebral disease.

During intrauterine development, the brain like the entire organism is "purged" to obtain the correct balance of humors. If this fails, disease results as the consequence of excess moisture or phlegm. After a detailed anatomical description of the body's vessels Hippocrates describes how phlegm descends from the brain through the body, producing one seizure symptom after the other, their generation being explained in detail.

Epilepsy is different in different ages. In childhood it is particularly dangerous: most affected infants die "if the fluid production is abundant and the wind is from the south". However, better outcomes are possible: "The children survive, but exhibit notable marks of the disorder; for either the mouth is drawn aside, or an eye, the neck, or a hand. … But for the most it affords relief for a longer interval; for the child is no longer seized with these attacks." Infantile hemiplegia as the result of a seizure event, followed not (or only with delay) by recurrent seizures is suggestive of the H.H.E. (hemiconvulsions-hemiplegia-epilepsy) syndrome, a possible course of prolonged focal status epilepticus in small children [11]. Today we consider it extremely rare [12] but it was more common when no effective treatments of childhood infections and status epilepticus existed.

Older children recover without sequelae but risk that the seizures become habitual if they are not treated effectively. It is rare that people beyond the age of 20 are affected unless the disease started already earlier. When it comes to geriatrics, epilepsy and apoplexy are not clearly separated: "When the disease occurs in very old people, it is fatal or renders them paralytic." The latter happens if the "defluxion of phlegm" is only to one side.

3. Hippocrates: Seizures and ictogenesis

Throughout the text we find observations revealing detailed clinical knowledge. When he gives examples of other diseases that are not by the public considered divine though not being less wonderful than epilepsy, he mentions quotidian, tertian and quartan fevers and madness, but also "persons in sleep groaning and crying out, some in a state of suffocation, some jumping up and fleeing out of doors, and deprived of their reason until they awaken, and afterward becoming well and rational as before, although they be pale and weak; and this will happen not once but frequently". Somewhat surprisingly, we find in a later chapter mostly the same sleep-related events as belonging to epilepsy, one of the indications that the treatise could be compiled of heterogeneous texts. Whatever the reason, it seems that the Hippocratic physicians were undecided where these paroxysms belonged. Traditionally and obviously, they are understood as sleep terror, but they could just as well mean sleep behaviour disorders or frontal lobe seizures. Groaning and crying out fits best with pavor nocturnus, fleeing out of doors with sleep behaviour disorder, recurrence in series with frontal seizures. The "state of suffocation" and subsequent weakness indicate sleep apnea. Easily all four may have been meant, seen as variants of the same thing. Even with our advanced investigations it took us long to sort them out.

The prototypical seizure description is this: "the patient loses his speech, and chokes, and foam issues by the mouth, the teeth are fixed,

the hands are contracted, the eyes distorted, he becomes insensible, and in some cases the bowels are evacuated. And these symptoms occur sometimes on the left side, sometimes on the right, and sometimes in both". It covers the tonic phase of bilateral, unilateral and asymmetric seizures. The clonic phase is mentioned later where he explains the pathophysiology of each seizure symptom.

Warnings are well-known: "But such persons as are habituated to the disease know beforehand when they are about to be seized and flee from men; if their own house be at hand, they run home, but if not, to a deserted place, where as few persons as possible will see them falling, and they immediately cover themselves up. This they do from shame of the affection, and not from fear of the divinity, as many suppose. And little children at first fall down wherever they may happen to be, from inexperience. But when they have been often seized, and feel its approach beforehand, they flee to their mothers, or to any other person they are acquainted with, from terror and dread of the affection, for being still infants they do not know yet what it is to be ashamed."

This is very interesting. Today, we and our patients think most of using warnings for protection and prevention of accidents. In Hippocrates, children are frightened whereas for adults, shame is in the forefront which tells us that epilepsy already in his time was strongly stigmatized. Of all commentators, Theodore [4] was the first to note this.

Beyond his doctrine of natural epileptogenesis (heredity, disturbances of prenatal development and relation to a certain constitution), Hippocrates also has a concept of ictogenesis: when seizures have become habitual they are induced by weather, especially changes of winds where the southern wind appears particularly harmful. Winds act by their ability to render the organism dry or humid, seizures occur when the brain is inundated by phlegm and excess cold phlegm spreads from the brain through the body via the vessels, passes into the warm blood and congeals it.

The dependance of seizures from weather has ever since remained part of lay beliefs about epilepsy but a weak relation has also been proved scientifically [13]. It may be noted that Hippocrates does not relate seizures to the moon phases, another popular attribution. It seems that he did not yet notice the periodicity of seizures in certain patients, and the concept of a person with epilepsy as "moon-sick" (Latin: lunaticus) has other sources.

Hippocrates mentions another possible seizure induction (ἐξ αδήλου φόβου γιγνομένου, ήν δείση μέν ή βοήσαντός τινος) which has given the translators considerable headache. Verbatim it says, "from an unclear fear arising, if one should fear indeed or someone should cry out" (translation by musely.ai). How should this be understood? Traditional readings including Grensemann [14] and Jouanna [15] as "fear of the mysterious" or the like, with a cry floating somewhere or as a separate possibility, are nothing a clinician can recognize. Walshe's conclusion [3] is convincing that it means the patient is startled by an unexpected shout. The reference is to startle seizures, perhaps not the most common seizure type, but not extremely rare either. In 1955, they were among the first types of reflex seizures that were identified [16]. They are particularly common in patients with infantile hemiplegia [17] whom Hippocrates has mentioned above. Like most experienced epileptologists, he will have seen a few cases and been impressed by them.

He talks here about seizure provocation, and another example follows: "while crying, when one cannot quickly recover one's breath, such as often happens to children", an exact perception of breath-holding spells which Hippocrates included in epilepsy.

There are no other unequivocal descriptions of seizure types.

4. Hippocrates: Treatment

From our present perspective, one of the amazing aspects of Hippocrates is that he did not consider epilepsy untreatable. According to him, it is no less curable than other diseases unless when it has prevailed too long. Which remedies did he use? He reports that the magicians, if a patient dies, disclaim responsibility because "they had administered nothing either to eat or drink as medicines, nor had overheated him with baths". This seems indirectly to indicate that medicines and baths were part of Hippocratic treatment. However, instead of details he gives something much more valuable, he explains his therapeutic rationale: "In this disease as in all others it is necessary, not to increase the illness, but to stab it by applying to each what is most hostile to it, not that to which it is conformable". He concluded that "whoever … can render somebody humid and dry, hot and cold by regimen, could also cure this disease".

Here again, Hippocrates follows Alcmaion who was the first ever to define health [7] as consisting in the "equality (ισονομία, isonomia) of contrary powers (wet and dry; cold and hot; bitter and sweet), while diseases were a disruption of this equality that he called 'monarchy'" [9]. This resounds still in the WHO definition "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

The medicines were selected due to their assumed drying or moistening potential, and "diet" (διαίτη) meant not just food and beverage but a comprehensive lifestyle regimen.

Hippocrates' approach is not specific to epilepsy but includes it with the consequence that seizures are not seen as random events but as the result of antagonistic natural influences that it should be possible to modify. Walshe, who with all the condescension of a modern biological scientist presupposes that "the practical value of the Hippocratic work is gone now" misses its essence when he says that the aim was "to wear the malady down, allowing it to be surmounted by nature's healing" [3]. In this view, nature comes in as a numinous *deus ex machina* whereas the patient as a subject disappears. For Hippocratic rationalism, contrariwise, nature follows a set of rules which can be studied, understood and to some extent dealt with. It consists of many antagonistic forces including "things coming and going in the body" and requires constant navigation to be kept in healthy balance because "the changing winds are never calm". In Epidemics Book 1 [18] he defines the art of medicine as consisting "in three elements — the disease, the patient, and the physician. The physician is the servant of the art, and the patient must combat the disease along with the physician." The doctor must strive to understand the various natural forces and develop the regimen which helps the patient combat them.

5. Galen: Nosology

Half a millennium after Hippocrates, times have very much changed. The Roman empire has reached its summit and created a much more heterogeneous society than ancient Greece. Medicine has experienced many developments. A rising new religion, Christianity, takes a strict anti-Hippocratic stance and preaches that epilepsy is not a natural disorder but a possession by demons or evil spirits. At the same time, Galen (129–200 CE) becomes the leading figure of scientific medicine. He stands firmly on the fundament of Hippocratic teaching which he comments and strives to renew.

Galen has written no comment on "On the Sacred Disease" and no treatise on epilepsy but addressed it often as Temkin [2] broadly discusses. Epilepsy is still a cerebral disorder but the cause is not always primarily in the brain. If the seizures start at some point in the body, e.g. in a limb or the epigastrium, the brain is only secondarily involved. The first possibility he calls "idiopathic" (from idios = own and pathos = suffering) or "protopathic" (from protos = primary), the second "sympathetic" (meaning co-affected).

These distinctions over the centuries have undergone many changes, in the modern period into the division idiopathic versus symptomatic, the latter now further subdivided into multiple etiologies. But the concept of idiopathy still stands, even if it is now defined differently, and we owe to Galen the fundamental understanding that epilepsy is not one disease but includes a variety of conditions. Two other aspects are of particular interest.

Fig. 2. Galen, 18th-century engraving by Georg Paul Busch (1682–1759), a convincing image of a physician who had a genuine interest in his patients.

6. Galen and the aura

Hippocrates had wondered about patients' reactions to prodromes and auras and discovered what we now call perceived stigma. Thus, auras were known at least since Hippocrates' time. Galen now took it one step further and became interested in what the subjective seizure experiences were. We know this from a famous anecdote which also established the term "aura", the Greek word for "breeze". Quoting Temkin [2], "when still a young man, Galen, together with other physicians, visited a thirteen-year old boy. The patient told them that the condition originated in the lower leg, and that 'from there it climbed upwards in a straight line through the thigh and further through the flank and side to the neck and as far as the head; but as soon as it had touched the latter he was no longer able to follow.' When the physicians asked him what exactly rose up to the head, he could not tell. But another youth, who was a better observer, 'said that it was like a cold breeze'."

The comment that the other boy was a better observer, however, does not make sense. An aura is a purely subjective phenomenon, there is nothing that can be observed. Perhaps Temkin, who was not a clinician, assumed that all auras were essentially the same or that both boys shared the same experience which, however, is extremely unlikely. The scene is easy to visualize. On a ward round the physicians take the case history and ask the boy to describe his seizures. He succeeds in giving an amazingly meticulous description of the route the symptom takes in the body. In sharp contrast, he is unable to qualify the feeling. He is greatly embarrassed, but his comrade tries to help him out suggesting it could be like a cold breeze. To finish the awkward situation he spontaneously agrees. There was never a feeling of a cold breeze, but the term stuck. The anecdote is fascinating. The first historical account of a seizure experience, it at once documents one of its most characteristic aspects, i.e. its indescribability. Telling the story, Galen and his colleagues not only gave the patient a voice but also initiated the subjective history of epilepsy [19] which later became the domain of writers with epilepsy [20] such as Dostoyevsky [21] or Margiad Evans [22] who transformed the indescribability of their experiences into great literature.

7. Galen: Treatment

The old Greek knew that, if there was no rapid success, epilepsy became uncurable, so their attention was on recent cases. We do the opposite, focusing with good reason on the difficult ones because there we can and must win new ground. Meantime, the new patients are left to the vicissitudes of non-specialist treatment. Most of the recent literature on first seizures is concerned with the simplistic question in which cases drug treatment is already indicated after a first seizure [23]. The much-cited Glasgow first seizure study uses nothing but drugs including the newest [24]. The results are fair, but not spectacular compared with the follow-up of untreated first seizures [25]. Hippocrates and Galen with their comprehensive regimens may have done better.

Whereas Hippocrates only had outlined his therapeutic principles, Galen was quite explicit. Outstanding among his documents is a long letter with recommendations to the father of an epileptic boy [26]. As he had not seen the patient, it probably represents his standard treatment of epilepsy. First of all, it is important to avoid "unexpected daily occurrences" as far as possible. He mentions "frost and violent heat, strong winds and strenuous baths, repulsive food and whirling wheels, lightning and thunder, sleeplessness and indigestion, distress and anger and weariness". At the beginning of spring, the patient ought to be purged. Then he has to adhere to a strict regimen following a detailed daily schedule, rising at daybreak, with a sequence of carefully dosed and designed physical as well as mental exercises and periods of rest, massage of body and head. Certain foods and drinks are prohibited and others recommended. Medicines used are vinegar-honey, juice of squill and wormwood. Drugs, however, are only a means of support, not the treatment itself [26]. Most items on the list are dated and of minor importance. Essentially, Galen says that if you want to control epilepsy you need to adopt a very disciplined lifestyle. Exactly! We concluded the same when we rather successfully applied alternative approaches for twenty-five patients who for some reason had rejected pharmacotherapy [27]. Galen's regimen was probably prototypical. His contemporary Aretaeus of Kappadokia applied a similar scheme which expressly included regular sleep [2].

Medicines were supposed to act by moistening or drying the organism. A review of all the era's materia medica [2] shows that a substantial portion of 45 substances applied in epilepsy do not differ from what was used by quacks. What distinguished the medical men was something else, i.e. their attitude, within the limits of contemporary social discrimination, towards the patients: whereas the incantations of the magicians in Hippocrates' time and the Christian exorcisms of Galen's period treated them as mere passive objects, the physicians accorded them an active role. Hippocrates' principle that the physician is the knowledgeable advisor, but the patient is the one who has to fight the disease is spelt out in the regimens, and Galen added attention to the aura as the patients' authentic experience: respect for their patients' dignity and autonomy, the ethical principles of the Hippocratic Oath applied in practice.

Declaration of competing interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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