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Review

Citing Hippocrates on depression in epilepsy

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ABSTRACT

Objectives: When writing about the bidirectional etiological relationship between depression and epilepsy, neuropsychiatrists often cite Lewis (1934) [Lewis AJ. Melancholia: a historical review. Journal of Mental Science 1934; 80: 1–42] who cited Hippocrates — namely, "melancholics ordinarily become epileptics, and epileptics, melancholics". In this paper, the complicated reference for this citation from Lewis (1934) was critically reappraised.
Methods: The Greek–Latin edition of Hippocratic writings by Ermerins to which Lewis (1934) referred and most volumes of the standard Greek–English edition of the Hippocratic writings in The Loeb Classical Library were freely available as facsimile pdf documents in the Internet Archive (archive.org).
Results: Melancholia (i.e., "the black bile disease") is defined as a persistent mental state of fear and sadness ("Aphorisms", section 6, aphorism 23) which appears more consistent with a dysthymic disorder or depressive personality disorder than an acute (episodic) depressive disorder. Confusingly, the term melancholia also signifies a humoral etiology, namely a surplus of black bile, which causes several distinct diseases including epilepsy (aphorism vi/56). The quote addressing the conversion of melancholia into epilepsy and vice versa was taken from the writing "Epidemics" (book 6, section 8, paragraph 31). The famous treatise on epilepsy, "De Morbo Sacro", does not mention melancholia but instead, attributes epilepsy to two other humors: phlegm and (yellow) bile. This writing proposes an etiological relationship between (inherited) personality and epilepsy, wherein a phlegmatic temperament represents an epilepsy risk while a bilious (choleric) temperament offers protection against epilepsy.
Significance: With only a few clarifications, the neuropsychiatric quotation from Hippocrates and the reference to Lewis (1934) could generally be approved as appropriate. However, the proper framework of the quote seems to be personality and not mood. A more precise reference to a standard edition of "Epidemics" book 6 is also suggested.

1. Introduction

Numerous current publications on depression in epilepsy refer to a comprehensive historical review on melancholia published in the Journal of Mental Science, which was written in 1934 by the first professor of Psychiatry at the Institute of Psychiatry, University of London/UK, Sir Aubrey Julian Lewis (1900–1975). A short biography of this Australian-born pioneer of research in melancholy and depression can be found in the Australian Dictionary of Biography [1], and a more thorough description of his role in the Maudsley Hospital, London was published in 2003 [2]. In his seminal paper, Lewis cited a statement from Hippocrates of Kos (460–370 B.C.; Fig. 1 [3]), which indicates that the ancient physicians were already aware of a bidirectional etiological relationship and shared pathomechanisms of depression and epilepsy [4]. The clinically and etiologically important interaction of these two severe and frequent conditions was only recently discovered (or rediscovered) by epidemiologists [5]. The critical statement from Hippocrates – or more precisely, the group of Alexandrian physicians who supposedly composed the 53 single writings of the "Corpus Hippocraticum" during the Ptolemaic age from the 5th century B.C. to the 1st century A.D. [6] – as quoted by Lewis [4], reads as follows ([4], p. 1):

> "melancholics ordinarily become epileptics, and epileptics, melancholics: of these two states, what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy."

Of note, Lewis places this quotation within a larger conceptual context and a closer examination of the entire first paragraph is revealing (p. 1):

> "The beginning [of the history of melancholia; C.H.] was with Hippocrates (1): 'If fear (phobos) or distress (dysthymia) last for a long time it is melancholia' he wrote, and so fixed the word. He insisted on the special temperament and constitution which tend to melancholia. His notion that black bile and phlegm altered the brain in

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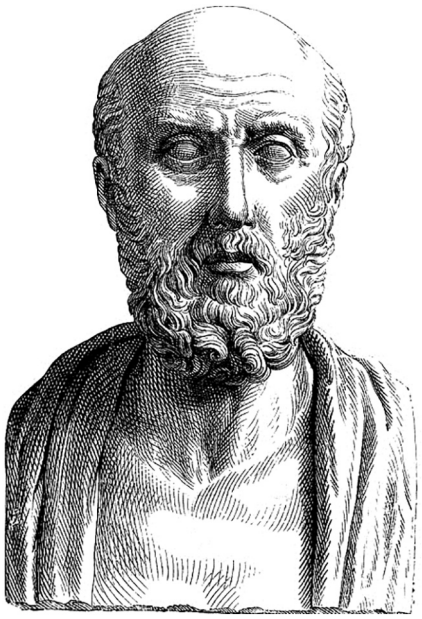

Fig. 1. Hippocrates of Kos (460–370 B.C.) [5].

its hotness and humidity, thus darkening the spirit and making melancholy, was to influence much subsequent speculation, and all classification was reared on his divisions — mania, melancholia, paranoia, phrenitis; but it is evident that for Hippocrates the atrabiliar conditions were numerous, and that the term 'melancholia' covered diverse states, now otherwise regarded. Furthermore, he considered epilepsy and melancholia to be closely related: 'melancholics ordinarily become epileptics, and epileptics, melancholics: of these two states, what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy.' To the seasons he imputes much influence."

Especially important is Lewis' remark that the term "melancholia" is also comprised of diverse states which are now "otherwise regarded", i.e., distinguishable from melancholy (or depression). Thus, in Hippocratic scripts, it remains somewhat unclear if the term "melancholia" indicates a specific mental condition or a humoral etiology of an entire group of different diseases.

Here, the original texts quoted by Lewis [4] are introduced and examined in detail in an attempt to reappraise the frequent citation of Lewis [4] in modern neuropsychiatric texts for both conditions and to more deeply understand the Hippocratic stance on the relationship between melancholy and epilepsy. Of note, a medicohistorical state-of-the-art treatise on the Hippocratic view of neuropsychiatric diseases is out of the scope and intention of the present paper.

2. Detailed work-up of quotations

Lewis [4] provided the following complex reference (1) for the entire paragraph cited above ([4], p. 36):

"(1) Hippocratis et Aliorum Medicorum Veterum Reliquice, edidit Franciscus Zacharias Ermerins. Trajecti ad Rhenum, 1862. Aphor. vi, 23, 56, i, pp. 442, 446; Epidem. Lib. vi, section 8, 31, i, p. 613; Prænotion. 76 et seq., 313, pp. 44, 75. Also Hippocrates, with an English translation by W. H. S. Jones, Loeb Classical Library, ii, pp. 175–6; 'De Morbo Sacro,' xvii, xviii."

Fortunately, the Greek–Latin edition of the "Corpus Hippocraticum" (although from 1859) by the Dutch physician and medical editor Franz Zacharias Ermerins (1808–1871) to which Lewis [4] refers is freely available as a full-text facsimile pdf document in the Internet Archive [7]. As Lewis provided no additional references for the English quotes in the first paragraph of his essay, one might assume that he translated the statements himself. Several other editions, translations, and medicohistorical summaries of Hippocratic writings are also freely available and located in "The Medical Heritage Library" which is part of the Internet Archive [8]. In the following sections, Lewis' reference (1) will be evaluated stepwise according to the sequence provided.

2.1. Aphorisms: Aphor. vi, 23, 56, i, pp. 442, 446

2.1.1. Aphorism 23 from section 6

Aphorism 23 from section 6 ([7], p. 442) in the book "Aphorisms" reads:

"Metus et tristitia si diu perseverent, melancholiae indicium est", which Lewis ([4], p. 1) translated to:

"If fear (phobos) or distress (dysthymia) last for a long time it is melancholia."

The current standard Greek–English edition of the book of Aphorisms in The Loeb Classical Library (volume IV), edited by W. H. S. Jones suggests the following translation ([9], p. 185):

"Fear or depression that is prolonged means melancholia."

According to Lewis [4], this very aphorism kicked-off the century-long development process for defining the concept of melancholia [4]. The term melancholy is defined as a specific and persistent mental condition. In this quote, Lewis cited the terms from the Greek original, φόβος and δυσθυμίη, in parentheses. Persistent states of a negatively altered mood (i.e., dysthymia) still form the core feature of affective disorders. The duration of this state is not further specified. However, as the modern concept of depression is reserved for more acute recurrent courses (ICD-10-CM F33) or single episodes (F32), the Hippocratic concept of melancholia might also be suited to more persistent mood disorders (F34), e.g., dysthymic disorders (F34.1), or alternatively to personality disorders, e.g., other specified personality disorders (F60.89; "depressive personality disorder"). Also, the concept of "chronic depression" fits well here. Interestingly, the frequent comorbidity of anxiety disorder (phobos) and affective disorder (dysthymia) was previously observed by the founding fathers of Western medicine and even defined the condition. Of note, many patients with epilepsy show mild to moderate chronic states of depressed mood [10], and the prevalence of anxiety comorbidity in this population is even higher than for depression (40–50% as compared with 30%) [11]. Thus, the ancient definition of melancholy actually applies to many patients with epilepsy.

2.1.2. Aphorism 56 from section 6

Lewis references aphorism 56 from the same section 6 of "Aphorisms", but it is not cited in the text. In the Latin edition by Ermerins, it reads ([1], p. 446):

"Morbis ab atra bile periculosae confirmationes sunt ad haec mala: ad corporis siderationem, aut convulsionem, aut insanium, aut coecitatem."

In the Greek–English edition by Jones this aphorism translates to ([9], p. 193):

"In melancholic affections the melancholy humour is likely to be determined in the following ways: apoplexy of the whole body, convulsions, madness or blindness."

Thus, the term "melancholic affections" in aphorism 56 from section 6 is not meant to signify melancholia as one specific mental condition (as in aphorism 23 from this section) but instead, refers to the humoral etiology of an entire group of different diseases — all of which are caused

by an imbalance in the atrabiliar or melancholic humoral system (*lat.* atra bilia, *grch.* μέλαινα χολή, *engl.* black bile), usually by an abundance of black bile. Aphorism 56 attributes apoplexy (*lat.,* siderationes), epilepsy (*lat.,* convulsiones), madness (*lat.,* insanias), and blindness (*lat.,* caecitatis) to the melancholic etiology. Lewis denoted this in his short introductory paragraph on Hippocrates and melancholia ("but it is evident that for Hippocrates the atrabiliar conditions were numerous, and that the term 'melancholia' covered diverse states"; [4], p. 1). Of note, melancholy is not listed explicitly as a specific mental disorder. Fig. 2 [12] provides a simplified scheme of the humoralism and the humoral pathology of the Hippocratic school of medicine.

2.1.3. Aphorisms iii/19, 20, and 22

Of note, additional references to melancholia and epilepsy are mentioned in the book of "Aphorisms" but were not quoted by Lewis [1]. In the Jones edition, aphorisms 19, 20, and 22 from section 3 read as follows ([9], pp. 129, 131):

> "(19) All diseases occur at all seasons, but some diseases are more apt to occur and to be aggravated at certain seasons. (20) In spring occur melancholia, madness, epilepsy, bloody flux, angina, colds, sore throats, coughs, skin eruptions and diseases, eruptions turning generally to ulcers, tumours and affections of the joints. … (22) In autumn occur most summer diseases, with quartans, irregular fevers, enlarged spleen, dropsy, consumption, strangury, lientery, dysentery, sciatica, angina, asthma, ileus, epilepsy, madness, melancholia."

In both cases, melancholia is clearly used as the name for a specific condition. In both cases, madness is also listed as a distinct condition (mania?). Common climate effects on the occurrence of both melancholia and epilepsy further corroborate the idea of shared underlying pathomechanisms.

While aphorism 30 from section 3 in the Greek–Latin edition by Ermerins [7] mentions melancholy as a disease which is likely to occur in adulthood (epilepsy is not mentioned here), this entry is omitted from the Jones edition ([9], p. 133).

2.2. Epidemics: Epidem. Lib. vi, section 8, 31, i, p. 613

According to the Greek–English edition of the book "Epidemics" by Smith, "the word 'Epidemics' means 'visits', and may refer to the itinerant physician's visits to the towns in which he practices, or more likely to the visitations of diseases in those communities. (This latter was Galen's interpretation)" ([13], p. 1). The sentences from the Ermerins edition quoted by Lewis read as follows ([4], p. 613):

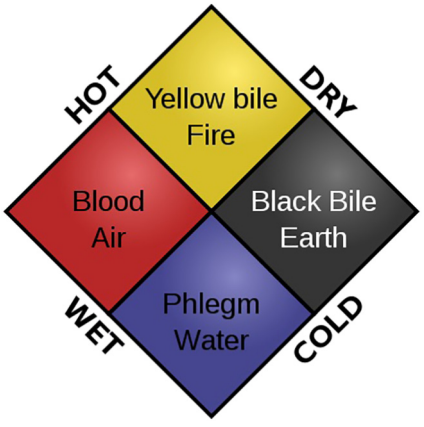

Fig. 2. Humoralism and humoral pathology: the four supposed humors and the assigned characteristics, effects on tissues (wetting/drying, cooling/heating) and their relationship to the four basic elements [9].

> "Atra bile vexati morbo comitiali corripi magna ex parte consuevere et morbo comitiali laborantes atra bile divexari. At horum utrumque magis accidit, prout ad alterutram partem morbus inclinarit. Etenim si in corpus, morbo comitiali laborant, sin vero in mentem, atra bile vexantur."

This is the famous critical citation targeted by modern neuropsychiatric authors, which points towards the mutual etiological relationship between epilepsy and depression ([1], p. 1):

> "melancholics ordinarily become epileptics, and epileptics, melancholics: of these two states, what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy".

Smith provided the following translation ([13], p. 289):

> "Melancholies tend to become epileptic generally and epileptics melancholic. Each of these develops more according to what the weakness inclines towards: if towards the body, epileptics, if towards the mind, melancholics."

Thus, in modern style, the more precise and up-to-date reference for this quotation should be: Smith WD. Hippocrates. Vol. VII: Epidemics, book 6, section 8, p. 288 (Greek), p. 289 (English) (The Loeb Classical Library). Cambridge/Mass., London 1994. — Source URL: https://archive.org/details/L477HippocratesVII.EpidemicsLoebClassicalLibrary, due July 13, 2018.

The cited sentences seem to suggest that melancholy is likely to convert into epilepsy and vice versa because one (single) underlying "weakness" (*gr.,* αρρωστημένος; *engl.,* sick, morbid) exists which determines a preference either for the one or the other condition, depending on whether it manifests in the body (*gr.* σώμα; *lat.* corpus) or the mind (*gr.* διάνοια; *lat.* mens). According to this quote, epilepsy and melancholy rather represent two different but mutually exclusive expressions of one single underlying "weakness" which either affects the body or the mind, respectively. Although the quotation suggests the conversion from one condition into the other, it does not fully exclude an interpretation in terms of developing the respective comorbidity — i.e., melancholics ordinarily *also* develop epilepsy, and epileptics, melancholia. This would certainly be more consistent with the intentions of modern neuropsychiatrists when citing this passage from Lewis [4]. From this point of view, the underlying "weakness" would start with a mental affection in terms of melancholy but then extend to a bodily affection in terms of epilepsy, or vice versa.

In the script "Epidemics", the term melancholia is also mentioned in other passages, which were not quoted or referenced by Lewis [4]. Paragraph 1 in section 5 of book 2 ([13], p. 75), which examines physiognomics (gr. φυσιογνώμικα) or the knowledge of natural signs, states:

> "However, those who lisp, who are bald, weak-voiced, or shaggy, have melancholic affections."

This statement relates invariant bodily features to melancholic affection, which seems more suggestive for melancholy as a personality trait. Book 7 of Epidemics ([13]) reports two lethal cases, one female servant of Conon and one male servant of Timochareus, who suffered from a condition which the writer characterizes as "melancholic" (pain in the head, delirious, shouting, crying with periods of quiet). Both also became "convulsive" before they died. In both cases, the term is rather used in its etiological meaning. Thus, these findings provide further examples of the term "melancholics" being used etiologically with reference to the entire group of melancholic diseases in the writing "Epidemics". However, as "melancholics" refers only to the mind in the famous quote by Lewis [4], the etiological interpretation can be excluded for those sentences.

Of interest, Smith translates another paragraph (89) from book 7 as follows ([13], pp. 389, 391):

> "Parmeniscus had previously been affected by depression and desire for death, and then again by optimism. … He was cured about the fourteenth day."

This condition strongly reminds of an acute episode of depression in its modern sense followed by an episode of "optimism". The Greek writer (p. 388) used the terms "αθυμία" (*engl.*, prostration, depression) and "ευθυμία" (exhilaration). The description reminds of bipolar disorder. Importantly, this acute episode of depressive mood is not referred to the concept of melancholia.

2.3. Coan Prenotions: Prænotion. 76 et seq., 313, pp. 44, 75

The phrases 76, 77 and what follows ("et seq."), and sentence 313 from the book "Coan Prenotions" (gr. κωάκαι προγνωσίες, *lat.*, prænotiones coacae) quoted by Lewis read as follows in the Ermerins' edition ([7], 76/77: p. 44; 313: p. 75):

> "(76) Dementiae, in quibus aegri fiunt tremuli, aut aliquid investigantium more sensim contrectant, aut palpant, phrenitim praenunciant. (77) Qui in febre assidua voce defecti iacent et oculis conniventibus nictantur, hi evadunt quidem, si post sanguinis e naribus fluxum ac vomitum ad loquelam et ad se ipsos redeant. Sin vero secus accidat, cum spirandi difficultate celeriter intereunt. … (313) Quae ex lumbis in cervicem et caput redundantia levis siderationis more resolutionis sensum inducunt, convulsionem ac mentis emotionem minantur. Videndumque est num talia convulsionibus solvantur. Ex his varie morbum trahunt eademque pati pergunt".

In the Greek–English edition by Potter, these phrases read as follows ([14], 76/77: p. 123; 313: p. 179):

> "(76) Patients with trembling, delirium, and groping with the hands are suffering from phrenitis; pains in their calves lead to a disturbance of their mind. (77) If patients in a continuous fever who lie speechless, closing their eyes and blinking, recover their voice after haemorrhaging from the nostrils and vomiting, and return to their senses, they are saved. If these things do not occur, their breathing becomes difficult and they rapidly succumb. … (313) In patients with pains of the loins, nausea but no vomiting, and a slight mental derangement toward the over-bold: are they likely to pass dark stools?"

Sentences following phrases 76 and 77 deal with fever and, more generally, signs indicating the upcoming of convulsions (i.e., seizures); also, "attacks of delirium" ([14], sentence 83, p. 123) are also referred to convulsion. It does not become totally clear why Lewis [4] cited these passages. These phrases may describe seizures with (secondary) mental affection (sentences 76, 83) as they might occur in a context of fever (i.e., inflammation); also, the possibility of convulsive states which do not terminate themselves (i.e., fatal status epilepticus) is mentioned (77) [14]. The last sentence (313) seems to refer to a hypomanic state. The term "phrenitis" indicates an inflammation of the mind itself (*gr.* φρένες, mind) whereas "delirium continuum cum febre" (*engl.*, chronic delirium with fever) was the standard Latin translation of this Greek term [15]. Of note, melancholia is not mentioned in this citation neither in terms of humoral etiology nor as a specific affective disorder.

No further use of the term "melancholia" was found in the writing "Koan Prenotions".

3. On the sacred disease

Lewis finally referred to sections xvii and xviii from the famous ancient treatise on epilepsy, "De Morbo Sacro", but once again, without a direct citation in the text body of his review. More precisely, Lewis referenced volume ii of the Greek–English edition by W. H. S. Jones which is also freely available in the Internet Archive (source URL: https://archive.org/download/hippocrates02hippuoft/hippocrates02hippuoft.pdf; due July 13, 2018) [10]. According to Jones ([16], p. 132), the author of the "Sacred Disease" is almost certainly not the writer of "Epidemics".

Also, it should be mentioned that some authors writing on epilepsy and depression also refer to Temkin (1945 or 1971) [17] in addition to citing Lewis [4]. For the purpose of the present paper, it is noteworthy that Temkin exclusively referred to "De Morbo Sacro" but not to other Hippocratic scripts.

The two sections referenced by Lewis [4] offer the following: (a) an unambiguous general hypothesis on the close relationship between mind and brain (section 17) and (b) a humoral etiological model for different personalities, acute epileptic seizures, and other mental disorders (section 18).

3.1. Section 17

Section 17 from the Jones edition reads as follows ([16], p. 175):

> "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. These things that we suffer all come from the brain, when it is not healthy, but becomes abnormally hot, cold, moist, or dry, or suffers any other unnatural affection to which it was not accustomed. Madness comes from its moistness. When the brain is abnormally moist, of necessity it moves, and when it moves neither sight nor hearing are still, but we see or hear now one thing and now another, and the tongue speaks in accordance with the things seen and heard on any occasion. But all the time the brain is still a man is intelligent."

The materialistic but nonreductionist theory of the irresolvable relationship between the mind and the brain, i.e., the brain functional basis of all mental states (both normal and pathological) could not be formulated more appropriately or beautifully than in this classical citation. In fact, this passage anticipates the (still) "astonishing hypothesis" as formulated by Nobel laureate Francis Crick (1916–2004) in 1994 [18]. Perhaps, it is not coincidental that this paragraph with its far-reaching and difficult-to-accept philosophical implications can be found in a treatise on epilepsy since also, most of our current knowledge about the human mind–brain can be attributed to clinical observations in people with epilepsy (e.g., Henry Molaison/memory; callosotomy & Wada tests/hemispheric specialization; electrocorticography/sensory and motor cortical homunculus; and so on). Importantly, this classical citation from the Hippocratic scripts provides the conceptual framework for the scientific (natural) understanding of the diverse and sometimes even contradictory bodily and mental semiological phenomena occurring during epileptic seizures (although the concept of humoralism is no longer accepted).

3.2. Section 18

Section 18 reads as follows ([16], pp. 175, 177):

> "The corruption of the brain is caused not only by phlegm but by bile. You may distinguish them thus. Those who are mad through phlegm are quiet, and neither shout nor make a disturbance; those maddened through bile are noisy, evil-doers and restless, always doing something inopportune. These are the causes of continued madness. But if terrors and fears attack, they are due to a change in the brain.

> Now it changes when it is heated, and it is heated by bile which rushes to the brain from the rest of the body by way of the blood-veins. The fear besets the patient until the bile re-enters the veins and the body. Then it is allayed. The patient suffers from causeless distress and anguish when the brain is chilled and contracted contrary to custom. These effects are caused by phlegm, and it is these very effects that cause loss of memory. Shouts and cries at night are the result of the sudden heating of the brain, an affection from which the bilious suffer but not the phlegmatic. The brain is heated also when the blood rushes to it in abundance and boils. The blood comes in abundance by the veins mentioned above, when the patient happens to see a fearful dream and is in fear. Just as in the waking state the face is flushed, and the eyes are red, mostly when a man is afraid and his mind contemplates some evil act, even so the same phenomena are displayed in sleep. But they cease when the man wakes to consciousness and the blood is dispersed again into the veins."

This section clearly states that seizures ("terrors and fears"; gr., δείματα και φόβοι) are caused by acute changes in the brain (instead of divine intervention as broadly believed at that time). Thereby, an abundance of phlegm (*gr.,* φλέγμα) cools the brain "contrary to custom" and causes its contraction which, in turn, results in distress, anguish, and memory problems (i.e., "minus symptoms"). In contrast, an abundance of (yellow) bile (*gr.,* χωλή) heats the brain leading to acute fear besetting the patient, as well as shouts and cries in the night (i.e., "choleric" behaviors or "plus symptoms") until the bile drains again via the veins. These groups of contrary ictal symptoms are presumed to be mutually exclusive due to their contrary etiology — which we know is actually not the case, e.g., in temporal lobe seizures with both ictal symptoms, preceding aura with fear/panic, and ictal/postictal impairment of memory. If the same humoral alterations persist over a longer period of time, personality disorders occur, namely phlegmatic vs. bilious/choleric temperaments.

3.3. Section 5

In section 5 from "De Morbo Sacro", which is not referenced by Lewis [4], the writer also argues in favor of epilepsy as an organic disease and against a divine or supernatural causation of epilepsy or seizures (which otherwise would constitute the sacred nature of this condition). In this section, the author states ([16], p. 153):

> "But this disease is in my opinion no more divine than any other; it has the same nature as other diseases …. It is also curable, no less than other illnesses, unless by long lapse of time it be so ingrained as to be more powerful than the remedies that are applied. Its origin, like that of other diseases, lies in heredity. … Another strong proof that this disease is no more divine than any other is that it affects the naturally phlegmatic, but does not attack the bilious. Yet, if it were more divine than others, this disease ought to have attacked all equally, without making any difference between bilious and phlegmatic."

Here, the author assumes an etiological relationship between a permanent abundance of phlegm in phlegmatic persons (usually inherited from their parents) and the likely occurrence of epilepsy in this population. Conversely, a bilious/choleric personality is believed to represent a protective factor against the development of epilepsy. The ancient author argues that such a correlation appears incompatible with divine intervention because divine punishment would similarly affect people of all characters.

Taken together, the author of the famous ancient treatise on epilepsy, "De Morbo Sacro", does not mention melancholia at all, neither as a possible etiological factor for epilepsy (i.e., surplus of black bile) nor as a specific mental condition. In contrast to aphorism 23 from section 6 of the book of "Aphorisms" which explained persistent fear and sadness by an abundance of black bile [9], section 18 from "De Morbo Sacro" attributes ictal fear and anguish to an acute abundance of either (yellow) bile or phlegm, respectively [16].

4. Further findings

In the Ermerins' edition [7], the Greek term μελανκωλικάι is also used in the writing "Predictions" (*lat.,* Praedictorum), liber 1, paragraph 123 (p. 25) and in the "Additamenta spuria" (i.e., non-Hippocratic scripts), paragraphs 16 (p. 337), 29 (p. 343), and 48 (p. 352). However, epilepsy is not mentioned in these passages.

In the edition of The Classical Loeb Library, the word "depressed" occurs in the English translation of the writing "Regimen in acute diseases" ([16], section 17, p. 99) within the context of iatrogenic adverse effects that can be caused by inappropriately changing the patient's diet (e.g., from fasting to gruel) during the course of a disease. However, the Greek edition uses the term περίλυπος (*German*, tief betrübt; *Engl.,* deeply saddened) instead of μελανκωλικός.

5. Conclusion

Modern neuropsychiatric authors may justifiably cite Lewis [4] in order to indicate that a mutual etiological relationship between epilepsy and melancholy was already known in ancient times. More precisely, a few restrictions and clarifications can be made. First, the critical quotation was taken from the 6th book of the Hippocratic work "Epidemics" (section 8, paragraph 31), and a more precise citation would refer to the Greek–English edition by Smith [13]. Furthermore, given the Hippocratic definition of melancholia as a persistent mental state of fear and sadness (aphorism 23 from section 6 of the book "Aphorisms"), the clinical picture seems to fit better with a dysthymic disorder, chronic depression, or depressive personality disorder than with episodic more acute depressive disorders. Of note, melancholia and depression were distinguished psychopathological entities until the introduction of the DSM-4 in 1994 [19], and the Hippocratic writings describe states of severely depressed mood without reference to the concept of melancholia [13,16]. Finally, as already denoted by Lewis [4], the term melancholia (i.e., surplus of black bile) is also used to indicate the shared humoral etiology of several diseases, including epilepsy ([9], aphorism 56 from section 6).

Obviously, the author of the ancient treatise on epilepsy, "De Morbo Sacro", was not aware of the considerations of a close etiological relationship between epilepsy and melancholy as proposed in the books "Aphorisms" and "Epidemics" which further confirms independent authorship. Interestingly, the author of "De Morbo Sacro" instead discusses an etiological relationship between epilepsy and (inherited) personality (or personality disorder), namely phlegmatic character as a risk factor for epilepsy and a bilious/choleric character as a protective factor against epilepsy. This notion is echoed by the epileptological and neuropsychiatric debate on the "epileptic personality" (or Geschwind syndrome) in the 19th and 20th century [20]. However, as regards this concept, it is safe to say that the current neuropsychiatric discussions are clearly dominated by other topics such as cognitive–mnestic impairments, affective and anxiety disorders but not personality alterations anymore, while up until the 1980s or so, personality disorder in epilepsy was a prevalent neuropsychiatric topic.

Finally, the famous section 17 of "De Morbo Sacro" [16] which emphasizes the irresolvable relationship between the mind and brain functioning makes it quite clear why the strict separation between neurology (i.e., brain diseases) and psychiatry (i.e., mental disorders proper *in the absence of manifest organic brain diseases*) must end in nothing. In fact, this separation has been outdated for two and a half millennia. In particular, those patients who are severely affected with epilepsy and comorbid psychiatric issues or psychogenic nonepileptic seizures are often underdiagnosed and thus, undertreated because of

the dualistic "either–or" misconception of the mind–brain or psyche–body relationship.

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