

## AN EARLY CONCEPTION OF INFLAMMATION IN THE HIPPOCRATIC TREATISE, *DISEASES I*

### ABSTRACT:

After a brief account of humoral theories, several of their commonly used terms are analyzed based on recent clinical translations of several Hippocratic texts. After applying the new definitions to the Hippocratic work, *Diseases I*, a nascent mechanistic understanding of inflammation is revealed, one that far exceeds in medical relevance the four descriptors of inflammation of Celsus. Furthermore, as the terms used in *Diseases I* were the same as those used in many humoral theories it is proposed that subsequent generations of physicians misappropriated them to accommodate a popular but grossly inaccurate explanation of body homeostasis that would receive much support thenceforth from Galen.

KEY WORDS: Hippocrates, humoral theory, inflammation

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### A. Introduction

There is a vast library of writings on humoral theories, including those originating from India, Egypt and the Middle East, and the variety of humors, their balance in maintaining bodily homeostasis, diseases caused by their imbalance, and therapies to restore balance have always been popular topics. Some trace aspects of humoral theory back to Empedocles (494-434 BC) who theorized there were four elements, indestructible, that composed all substances: water, fire, earth and air.<sup>1</sup> As a structural biological theory his four elements might be interpreted as representing fluidity (water), energy/metabolism (fire), tissue (earth), and oxygen (air or πνευμα [pneuma]). There is, however, no logical progression from the elements of Empedocles to a theory of health and disease. Instead, it is the 5<sup>th</sup> C BC Hippocratic treatise, *Nature of Man*, that provides a true humoral theory, one with characteristics inherent in man and comprising bile, phlegm, black bile, and blood.<sup>2</sup> Its components were within the body, whereas the Empedoclean components *were* the body. One of the supporting arguments for a humoral theory in *Nature of Man* is observational in that the ancient author had seen a sequential change in vomitus as induced by a potent (toxic) medicine, the initial appearance of the vomitus he interpreted as being bile, followed by phlegm, then black bile and finally blood, a valid observation if not deduction.<sup>3</sup>

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<sup>1</sup> W. H. S. Jones, in the Introduction to volume 4 of the Loeb Classical Library series of *Hippocrates*, Harvard University Press, Cambridge, 1931, p. xxvii.

<sup>2</sup> The Hippocratic treatises cited in this paper are from the presently twelve volumes of the Loeb Classical Library series of *Hippocrates*, Harvard University Press, Cambridge. *Nature of Man* in volume 4 (first published in 1931 and translated by Dr. Jones) is found on pp. 3-41. Chapters 1-8 discuss aspects of humors.

<sup>3</sup> *Ibid.*, *Nature of Man*, 6 (p. 17). The gastric response to a locally “toxic” substance could indeed have caused, in sequence, bilious (bile) and then mucoid (phlegm) emesis from gastric irritation which, if sufficiently erosive to gastric mucosa, could cause superficial bleeding which, if quickly digested by gastric acid, would have appeared in vomitus as the typical black “coffee-grounds” (presumably the “black bile”) of gastritis. Then, should deeper tissue destruction occur, there would be massive hemorrhage (red blood).

Like branches of a tree, humoral theories continued to emerge, as they do even today, for their geometric elegance and subtle intangibility are an open invitation to philosophic and biologic speculation.<sup>4</sup> A Hippocratic example of another humoral theory is found in *Diseases IV* in which the humors are phlegm, bile, blood and water (rather than black bile).<sup>5</sup> But this paper deals not with humoral theory *per se* nor with its varieties and legacies, instead being an analysis of the terminology commonly used in Greek humoral theories and specifically as used in *Diseases I*. This Hippocratic work discusses bile, phlegm, blood and black bile but does not cite them as humors. An analysis of *Diseases I* instead reveals a fundamental physiological process applicable to all human disease, the process of inflammation, at its most primitive stage of development. The motivation for this analysis stems from a recently compiled wordlist of terms useful in translating Hippocratic medical treatises.<sup>6</sup> When the new translations of some of its words were applied to *Diseases I* a plausible theory assumed the place of a fictive one.

## B. Hippocratic terminology

As background, Hippocratic physicians were unaware of the existence of microbes and had yet to apply available optics to the study of human tissues.<sup>7</sup> The cause of many diseases therefore wanted an explanation. A nosological framework was required for them to initiate a systematic organization of diseases that might be useful in prognostication and therapy. Thus, despite the known importance of the association of certain diseases with weather, season, and environment and in the absence of other obvious external physical threats, the idea of an internal source of disease was entertained. They considered that humans intrinsically carried what has been termed “promoters” of disease, especially the classical components “bile” and “phlegm,” these being translated terms applied by ancients and moderns alike to represent ancient Greek χολή and φλέγμα, respectively. But have these translations been accurate?

### a. Bile

Bile is highly irritating and its colors vary from dark green to yellow. The word “bile” is derived from the Latin *bilis*, used by the Roman playwright, Plautus (255-185 BC), in attributing a personality trait (or “temperament”) to “black bile” (*atra bilis*). This indicates that by that early date the Greek χολή as commonly employed and understood by the general educated population reflected one’s temperament. Χολή finds its root meaning in “wrath” and “bitter anger,” which also can be considered temperaments. In Homer’s *Iliad* its anatomic location is repeatedly stated to be in the chest (the source of Achilles’ wrath; 4.503) rather than the gall

<sup>4</sup> David Greaves, Biomedical, humoral and alternative systems of medicine, in *The healing tradition*, Radcliffe, Oxford, 2004, chapter 10, pp. 135-148.

<sup>5</sup> *Diseases IV* is found in volume 10 of the Loeb Classical Library series of *Hippocrates*, Harvard University Press, Cambridge, 2012. It is translated by Dr. Paul Potter who interprets the “imbalance” of four “moistures” as giving rise to disease.

<sup>6</sup> W. H. Adams, *The natural state of medical practice: Hippocratic evidence*, (Liberty Hill Publishing, Maitland [FL], 2019), pp. 522-623. The Hippocratic works translated included *Prognostics*, *Aphorisms*, *Prorrhetic I*, *The Epidemics*, *Oath*, an excerpt from Aretaeus’ work *On Diabetes*, and an excerpt from Thucydides’ *The Plague of Athens* as described in his *History of the Peloponnesian War*.

<sup>7</sup> In the Archeological Museum of Rhodes can be seen a series of graded 6<sup>th</sup> C BC quartz lenses that, while probably used by jewelers, could have (and I believe would have, given more time) been adapted for histological study. Rhodes is the largest of the twelve Dodecanese Greek islands, about sixty miles from Kos, the purported island home of Hippocrates.

bladder, and in the *Septuagint*, as translated into koine (common) Greek in the early 3<sup>rd</sup> C BC, it is used to describe hemlock, derived from a small flowering plant that had an “unpleasant” and “rank” smell and taste from which a greenish and poisonous drink was prepared. Linguistic investigation also indicates an Indo-European etymological association between χολή and χλοή, the latter being the color “yellow-green.” Furthermore, bile is not black, and yet the term “black bile” (μέλαινα χολή) was used to describe other disease states (discussed below). It is suggested, therefore, that Hippocratic χολή referred to the biliary system tangentially at best.

If reference to χολή as bile, the gallbladder fluid, was unintended by early Hippocratic authors, perhaps their use of the term was one of convenience, a euphemism for a substance that, while physically observable, was likened to a wrathful temperament; it was bitter and could cause pain or irritation. It also was tinted and accompanied many diseases. Green-to-yellowish matter is often seen in pus from wounds, drainage from abscesses, pharyngeal drainage from infected sinuses and purulent respiratory catarrhs, diarrheal stools with rapid transit times, jaundiced skin, and some urine and urine sediments in persons with urinary symptoms. It is proposed, therefore, that the Hippocratics impressed into service the word χολή to describe two categories of disease: (1) ξανθη χολή (usually translated as “yellow bile”) for diseases associated with purulence and (2) μέλαινα χολή (usually translated as “black bile”) for those that did not display purulence. Supporting arguments are given below. The names had nothing to do with bile. Indeed, the term χολή could be translated as something like “greenish-yellowish matter” or “purulence,” but because the term “bile” is brief and so engrained in our definitions it will remain in use in this paper.

#### **b. Phlegm**

“Phlegm,” the modern term for mucoid expectoration derived primarily from the respiratory tract, is the usual translation of φλέγμα even though the Greek noun and its verb φλέγω signify “fire/blaze.” The modern use of “phlegm,” however, comes from Late Latin describing it as moist and cold, those being classical characteristics of phlegm as one of the humors. Greek synonyms of φλέγμα include μύξα, from which “mucus” would later be derived, and βλεννα (blenna). With such alternatives why would the modern term “phlegm” be the translation of φλέγμα, a word derived from fire? Homer (active *ca.* 800 BC) had used φλέγμα to describe an unquestionably fiery “evil flame” in his *Iliad* (21.337). Perhaps φλέγμα was not like our “phlegm” and was perhaps not even mucoid. There are inconsistencies. Herodotus (484-425 BC), in his *Histories* (Bk. 4, 187) describes it in children as draining from the head, and in Hippocratic works it is described in *Aphorisms* (7.54) as reabsorbable, in *Nature of Man* 5 as something to be vomited, and in *Air, Water, and Places* (3, 10) as moist and flowing down from the head. Galen stated that Prodicus (465-395 BC) concluded there were two types of φλέγμα, one that was like mucus and the other was a denser “cooked” φλέγμα that represented the φλέγω, or fiery, component.<sup>8</sup> Aristotle (384-322 BC) in his *Metaphysics* (8.1044a, 20) describes it as “viscous” (or “oily,” λιπαρός). It is proposed here that the “fiery” attribution refers to the biting and bitter nature of, for example, a pathological postnasal drip, one that is often associated in viral catarrhs with a sore throat, with the acid reflux of gastric contents into the mouth, with pharyngeal drainage, cystic fluids of various pathological states and lesions including hydrocephalus and hydatid cysts, the non-purulent fluid sometimes present in chronic

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<sup>8</sup> David Wolfsdorf, Prodicus on the correctness of names: The case of ΤΕΡΨΙΣ, ΧΑΡΑ and ΕΥΦΡΟΣΥΝΗ, in *J. Hell. Stud.*, 131:131-145, 2011.

abscesses and pleural effusions, and transudates of wounds, blisters and eczemas. Thus, φλέγμα was a mix of exudates, transudates, and secretions whose common features were, compared to χολή, more fluid and not colorful. It is likely that φλέγμα was generally accepted as having physical characteristics of a mucoid substance by the time of Herodotus, abnormal in that its fiery nature was expressed in its association with disease, painful swelling, and perhaps in taste. This distinction from normal mucus was made in the Hippocratic work, *The Sacred Disease*, chapter 8 and by Prodicus as described above. Unlike χολή, it had no affiliation with a temperament. A unifying term is therefore proposed for φλέγμα, namely “tissue fluid,” for exudates, transudates and secretions can be considered intracellular alterations of tissue fluid, but “phlegm” is brief and familiar and so will be used herein.

### C. Inflammation

Using the text and context of *Diseases I* of the Hippocratic Corpus the clinical roles of χολή and φλέγμα in inflammation can now be addressed by referring to specific sections of that treatise as provided in the Loeb Classical Library series of *Hippocrates*.<sup>9</sup> What happened when either or both χολή (bile) and φλέγμα (phlegm) were in the blood? Both were liquids (Section 20g), soluble in and dispersed by the blood (Sections 7b and 26a). Both were considered cooler than blood (Section 23a) and thus were factors in causing chills. And when blood was cooled by them and returned centrally in the body to be heated, more heat energy than normal was required to bring the mixture up to the normal temperature. The mixture did then warm up, but perhaps the blood itself, being innately hotter at baseline, became overheated relative to bile and phlegm when they were present. Alternatively, maybe bile and/or phlegm triggered the body’s central heating mechanism to turn up the heat, thereby superheating the blood and activating bile and phlegm to promote the signs of inflammation to be discussed below. In either event, when the over-warmed blood was distributed throughout the body it gave rise to fever.

Of their site of production in the body *Diseases I* makes no comment. It is known that tissue fluid (another term is “interstitial fluid”) is found throughout the body and surrounds every individual cell (all 20,000,000,000,000 of them), whereas the ancient Greek φλέγμα seems to have become concentrated where there was a problem. There is, however, a suggestion that it was the normal systemic moisture, *i.e.*, tissue fluid and/or a transudate of blood plasma, that became phlegm when it was concentrated (Section 15e), but elsewhere (in the Hippocratic work, *The Sacred Disease*, chapter 8) it is an “impurity” although the same literary citation paradoxically states it was to be found even in a fetus. The Hippocratics were aware that bodily constituents required moisture to function, and perhaps they thought φλέγμα wasn’t necessarily bad. This makes sense, for one to two quarts of mucus are produced daily by mucous membranes of the respiratory and gastrointestinal tracts, much of which is involuntarily swallowed throughout the day. It seemed to become a problem only when it was excessive, either locally as in a swollen abscess, systemically if in all tissues (anasarca), or if it was concentrated, thickened, and thereby blocked anatomical passages. The same could be said of χολή (bile); when dispersed at low levels there was no problem (Section 20g), but when it became concentrated it produced pain, misery and heat. There was some logic, therefore, in the

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<sup>9</sup> Loeb Classical Library series on *Hippocrates*, (Harvard University Press, Cambridge [MA], 1988), volume 5, pp. 94-183, as translated by Dr. Paul Potter. Sections mentioned parenthetically in the text refer to the 34 divisions of *Diseases I*, and the accompanying lowercase letters refer to the alphabetically arranged paragraphs within a Section.

idea that by phlebotomy both of these agents could be lowered to less dangerous levels. It is unnecessary to postulate their removal as a mechanism to repair any “imbalance” of humors. It is proposed, therefore, that the Hippocratics thought that “bile” and “phlegm” were not necessarily noxious but could become so when locally concentrated and/or activated. In this sense they would be considered enablers of disease, now to be discussed.

Consider as an example a patient with an abscess on his neck. That abscess is caused by a pathogenic bacterium, often *Staphylococcus aureus*. The abscess is called the disease, the cause is the staphylococcus. But if there were no bodily defenses against bacteria the staphylococcus would proliferate exponentially, invade deeper, rapidly spread throughout the body, and kill the patient within hours before any obvious physical evidence of disease was apparent. The body, however, resists infection and its defenses include inflammation. There is a prompt release of mediators that dilate blood vessels and increase blood flow near the site of the bacterial invasion. Many substances are then released from the blood that fight the local infection, one being bradykinin, which dilates blood vessels, thereby increasing the redness of the surrounding area and also making it warm because blood from deeper tissues is shunted to the affected area. Bradykinin also makes blood vessel walls more permeable, thereby permitting easy passage of fluid out of the blood and into the affected area. While that fluid carries in it many proteins that help fight the developing infection the fluid itself leads to local swelling. Finally, some of those infection-fighting substances, especially bradykinin, trigger pain receptors and thus cause the developing lesion to be painful, the value of pain being that the patient now knows there is a problem with his neck and will attempt to avoid its further injury. Thus, the four classical features of inflammation identified by Celsus (25 BC – 50 AD), namely pain, swelling, redness, and heat, are, on the one hand an indication that the body’s defense mechanism is at work, but, on the other hand, in containing the infection it is producing an abscess which is generally considered the disease. Ask a patient with an abscess if he has a health problem and he will answer, “Yes, I have a bad infection,” and he will point to the abscess. And yet the “abscess” is not the infection; it is the body’s response to the infecting organism. We cannot blame the Hippocratic physician for considering an abscess a manifestation of a disease rather than its containment. We cannot blame him for thinking those agents that enabled clinical manifestations of disease, namely phlegm and bile, were the problem and should be the object of therapy when in fact they enabled the cure.

As bile and phlegm collected at a disease site the author of *Diseases I* concluded that the swelling, tenderness, heat and redness were the consequence of their presence. Thus, the Hippocratics not only identified the clinical features of inflammation (although they did not use a group name that combined those features in the manner of Celsus, *i.e.*, *inflammatio*, which is derived from *inflammare*, “to set on fire”) but they also designated mechanisms that produced them.<sup>10</sup> In proposing mediators of those actions (see Table), pain and heat were caused primarily by χολή (bile), swelling was caused primarily by φλέγμα (phlegm), and those two fluids were distributed by and squeezed out of the αἷμα (blood), with the latter, on becoming “thicker” (παχύνεται), presumably producing the redness (hyperemia) associated with inflammation. Importantly, the absence of any discussion of the three substances in the context of a humoral

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<sup>10</sup> Aulus Cornelius Celsus, *De Medicina*, in 8 books, a 1<sup>st</sup> C AD work first printed in 1478. The description of inflammation is found in Bk. 3, chap. 10. In the proemion of *De Medicina*, Bk. I, Celsus states that the Hippocratics used the term φλεγμὴ (phlegmone) as the equivalent of his *inflammatio*, but see p. 13 of *The natural state of medical practice: Hippocratic evidence* (ref. 6) for an opinion to the contrary, that φλεγμὴ is properly translated as a “localized soft-tissue swelling.”

theory relegates such theories to irrelevance at the time of, or in the mind of, the author of *Diseases I*. Furthermore, the idea of an imbalance is not raised in the text, although it is discussed in detail in another Hippocratic treatise, *Nature of Man*, where its importance to humoral theories was analyzed by Prof. Jacques Jouanna: “Good health is defined as the balance and mixture of humors, whilst their imbalance and separation is the cause of disease.”<sup>11</sup>

TABLE: The cardinal features of inflammation\*

| Celsus           | Hippocratic promoters of inflammation | Modern facilitators, examples    |
|------------------|---------------------------------------|----------------------------------|
| Dolor (pain)     | χολή (bile)                           | Bradykinin                       |
| Tumor (swelling) | φλέγμα (phlegm)                       | Histamine, vascular permeability |
| Calor (heat)     | αἷμα (blood)                          | Histamine, vascular dilation     |
| Rubor (redness)  | ”                                     | “                                |

\* As cited by Aulus Cornelius Celsus (25 BC-50 AD) and compared to Hippocratic promoters and modern facilitators of inflammation. The two components listed as bradykinin and histamine are often cited in simplistic descriptions of acute inflammation in the body’s response to bacterial invasion, but the entire mechanism of inflammation, including its cellular responses, is exceedingly complex, with components, stages, systems, and processes that are triggered, stimulated, regulated, retarded, and resolved, factors that number into the thousands and encompass the panoply of human disease.<sup>12</sup>

#### D. Black bile

Yet to be considered is the special case of the enigmatic “black bile.” Clinical effects of black bile have been viewed as of mysterious origin, one of the options posed by Prof. Vivian Nutton, or perhaps “black bile” was considered the ancient equivalent of today’s “idiopathic” as applied to diseases without a connection to any known cause, of which there are many.<sup>13</sup> The first mention of black bile as a humor in the Hippocratic corpus is in *Nature of Man*.<sup>14</sup> In *Diseases I*, however, μέλαινα χολή (black bile) is not identified as a humor but is associated with a noninflammatory disease. It is mentioned only once (Section 3e) where it is stated to be a

<sup>11</sup> Jacques Jouanna, The legacy of the Hippocratic treatise *The Nature of Man: The theory of the four humours*, in *Greek medicine from Hippocrates to Galen*, Brill, Leiden, 2012, pp. 335-359. This particular quotation is on p. 335.

<sup>12</sup> Jean-Marc Cavaillon and Mervyn Singer, editors, *Inflammation: from molecular and cellular mechanisms to the clinic*, a four-volume set, Wiley, Weinheim, 2018.

<sup>13</sup> For a scholarly review of the many and complex versions of humoral theory see: Vivian Nutton, *Ancient medicine*, (Routledge, New York, 2005), chapter 5, especially for the concept of “black bile.” Dr. Nutton also has documented the rise to prominence of humoral theory following the writings of Galen (130-210 AD); see: V. Nutton, Humoralism, in *Companion Encyclopedia to the History of Medicine*, edited by W. F. Bynum and Roy Porter (Routledge, London, 1993), pp. 281-291.

<sup>14</sup> χολή μέλαινα in the Loeb Classical Library series on *Hippocrates* is called “black bile” by Dr. Jones and “dark bile” by Dr. Potter, but in both the term refers to the physical appearance of something, e.g. diarrheal stool is declared a discharge of black bile. It is mentioned in *Nature of Man* where it is something that affects his being and is physically identifiable. It can be viewed, therefore, as a mechanism of disease as well as a consequence.

cause of stroke (mechanism, appearance and source not identified) with necrosis of part of the brain. The color was unlikely to have been black, however, and black/brown/sepia, colors of cephalopod inks, better cover the range if intended by the Hippocratics for damaged or dead non-purulent tissue. It may be no coincidence, therefore, that cephalopod ink is one of the translations for χολή as listed in the *Liddell and Scott Greek-English Lexicon*.<sup>15</sup> Some later translations consider lymph, the interstitial fluid around cells that drains into the lymphatic system, to be “black bile,” but lymph is a pale limpid yellow. There are several very dark, sometimes black, fluids associated with disease states: black tarry stools from major upper gastrointestinal bleeding, vomitus that contains material looking like coffee-grounds that is partially digested blood from serious upper gastrointestinal bleeding, black-brown urine in hemolytic anemias, and blackish growth on biological tissue such as the tongue surface by the fungus, *Aspergillus niger*. Infarcted tissue can also become blackened, as in dry gangrene. The common feature of “black bile” pathology, therefore, may be the absence of inflammation, whereas bile, phlegm, and blood are all mentioned in relation to diseases associated with signs of inflammation. Black bile could have included, in Hippocratic thinking, diseases due to ischemia or infarction (with secondary necrosis or gangrene). Black bile has been postulated to result from heating and drying of yellow bile, and perhaps the stiffening was thought sufficient to occlude blood vessels. Such is described in *Regimen in Acute Disease, Appendix 7* and implied in *Airs, Waters and Places, X*. Thus, although the author of *Diseases I* barely mentions black bile, from its brief reference plus information at hand from other Hippocratic sources it is tentatively proposed that the Hippocratics considered black bile to be the cause of what they considered noninflammatory diseases, with vascular occlusion (infarction) and its associated death of tissue an important mechanism. The lack of further discussion of the effects of black bile in *Diseases I* is further evidence that the association of bile, phlegm and blood in causation of disease was a “stand-alone” concept rather than their being components of a four-element humoral theory.

Black bile has also been associated with melancholy, although the latter is not mentioned in *Nature of Man* or *Diseases I*. Dr. Jouanna has clearly shown that “melancholy” the humor is a product of post-Galen scholarship, and a review of selected Hippocratic works confirms his conclusion that μελαγχολία does not occur outside a clinical context consistent with the modern term “depression,” a psychiatric illness.<sup>16</sup> Dr. Jouanna also considers melancholy as a

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<sup>15</sup> *A Greek-English Lexicon* (compiled by Henry George Liddell and Robert Scott), American Book, New York, 8<sup>th</sup> edition, 1897.

<sup>16</sup> The Hippocratic sources searched are those listed in ref. (6). The present definitive word on the subject is found in: Jacques Jouanna, At the roots of melancholy: Is Greek medicine melancholic?, in *Greek medicine from Hippocrates to Galen*, Brill, Leiden, 2012, chapter 12, pp. 229-258, translated by Neil Allies. Also see Keith Andrew Steward, *Galen's theory of black bile: Hippocratic tradition, manipulation, innovation*, (volume 51 in *Studies in ancient medicine*, Leiden, Brill, 2018). Both Jouanna and Steward consider Galen as central to the subsequent acceptance of black bile as a component of humoral theories. Dr. Jones, in volume IV of the Loeb Classical Library series on *Hippocrates* mentions “a melancholic temperament” in *Aph. IV, 9*, but the reference is to persons who are clinically depressed. And in *Epidemics VII, 89*, there is the association of μελαγχολία with suicidal ideation. Melancholy, the clinical illness, is defined as long-lasting in *Aphorisms 6.23*. As defined today, a major depressive disorder must last more than two weeks and include decreased interest/pleasure or depressed mood) and at least three of the following: significant weight change, significant change in sleep pattern, psychomotor agitation or retardation, feelings of worthlessness, loss of energy, decreased ability to think, concentrate or make decisions, recurrent thoughts of death or suicidal ideation. The Greek, μελαγχολία, is translated as melancholy by both Dr. Jones and Dr. Potter. There is no association in their use of that term with black bile or with a humor, although in *Epidemics III, Const., 14*, Dr. Jones has the translation “melancholic complexion.”

temperament to predate Hippocratic medicine. In contrast, μέλαινη χολή as black bile is frequently mentioned in Hippocratic works consistent with observable pathology. Thus, despite the seemingly common etymology the two terms are physiologically unrelated.<sup>17</sup>

There are also differences in translation of μέλαινη χολή. Dr. Potter refers to it as “dark bile” and Dr. Jones calls it “black bile.” Nevertheless, it is used only as a descriptive term for a physical finding except for the two instances mentioned above where the reference suggests causation of disease: *Regimen in Acute Disease, Appendix 7*, and *Diseases I, 3e*, in the former suggesting dark bile in some way is involved in blocking of blood vessels and leading to stroke, and in the latter it is associated with crippling diseases consistent with stroke. Although twelve categories of diseases are listed in proximity to the mention of black bile in *Diseases I, 3d,e*, as pointed out by Dr. Jouanna and as implied by the phrase in 3e of ἀπο τῶνδε, there is no clinical association that could have been intended by the ancient author.<sup>18</sup>

### E. An overview

There are other concepts hinted at in the Hippocratic descriptions in *Diseases I* relevant to inflammation. (1) Fever was triggered by the delivery to the body core of excess φλέγμα and χολή from the site of inflammation, similar to the modern view of exogenous pyrogens from bacteria at a peripheral site of infection being circulated to a central locus (the hypothalamus in the brain) which in turn induces fever. (2) Like bile and phlegm, a static collection of blood was thought to decompose and then evolve into purulence (Sections 14a, 17a, 19a), an indication that bile, phlegm, and blood can each be a focus of disease in certain situations, but only if they are concentrated and cannot be drained. This Hippocratic association of stasis with secondary infection remains an everyday consideration on surgical wards. (3) Most remarkably, mechanisms proposed by the author of *Diseases I* permitted the body to control and limit its own response to inflammation:

- (a) The heat resulting from the activation of or action by bile/phlegm served to evaporate the “phlegm” component (Sections 19c and 20c).
- (b) Blood flow delivered bile and mucus to a lesion, but, the flow being increased, it also could disperse excessive bile/phlegm throughout the body so that the diluted and cooled bile/phlegm levels that resulted were no longer pathogenic (Section 20d, e, f, g).
- (c) The blood, by dispersing a focus of bile throughout the tissues and under the skin, eliminated bile in the sweat (7b, 25a).
- (d) Bile was deemed irritating to the bowel, which shortened the transit time of bowel contents and leading to expeditious excretion (Section 15d).

The concept of feedback and self-limiting control mechanisms in biology is a relatively new, mainly 20<sup>th</sup> C, phenomenon, but it was hinted at in the mechanisms proposed by the author of

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<sup>17</sup> There is a joining of the two concepts (psychiatric and physical ailment) in the Hippocratic work *Affections* 36 where it is stated that the treatment for μελανχολία is to rid the body of black bile, although there is some controversy about the statement’s authenticity (Pilar Perez Canizares, The treatise *Affections* in the context of the Hippocratic Corpus, in *Ancient concepts of the Hippocratic*, Brill, Leiden, 2015, L. Dean-Jones and R. M. Rosen, editors, pp. 83-98). And in the earlier reference to Plautus the person with a bilious (black bile) temperament had skin lesions interpreted as being induced by black bile. Thus, physical and psychiatric confusion on this point did exist.

<sup>18</sup> See footnote 16, Jacques Jouanna, ref. 15, p. 234.



*Diseases I*: the increased heat led to a decrease in phlegm, one of the causes of the heat; the blood that transported bile and phlegm to the injured area could also transport them away from the area if their quantity became excessive because there was increased blood flow through dilated blood vessels; their pathologic concentration could thereby be reduced by peripheral dilution and excretion, thus mitigating their local effects; and the bowel, although adversely affected by either bile or phlegm, expedited their excretion.

In conclusion, by interpreting χολή and φλεγμά as “greenish-yellow matter” (or nascent “purulence”) and “tissue fluid,” respectively, rather than gallbladder bile and phlegm, a believable concept of inflammation has been exposed. This early Hippocratic physician was, purposefully or not, devising a framework, a work in progress, that supported a plausible explanation for his clinical observations of various disease states. He impressed familiar terms into service to explain their clinical observations. Concurrently, however, some of those same terms were being applied by others to theoretical constructs of human health and disease commonly referred to in the aggregate as humoral theory. Although *Diseases I* does not use the word “humor” (as χυμός), the four substances being discussed herein (bile, phlegm, blood, black bile) were in a fluid state at some point and their use in this sense could be considered an early form of humoral theory. Furthermore, as there is implied an optimal level of each of the four, there is even room for the idea of balance and imbalance if that balance is restricted to each them as an individual humor rather than a balance among humors. The focus of this paper, however, has been on individual substances and their locally observed responses to an inciting event (e.g., an infecting agent). In other words, the focus has been on local causation of disease, not systemic maintenance of health. In this fundamental sense the use of χολή and φλέγμα in *Diseases I* is inconsistent with a humoral theory. Finally, *Diseases I* provides additional confirmation that the distinguished reputation of Hippocratic medicine rests in no way on a humoral theory, and that subsequent promoters of such theories would have had no story to tell had they not appropriated the terminology of Hippocratic insights for the verbiage of humoral theory.