An Early Conception of Inflammation in the Hippocratic Treatise *Diseases* I

William H. Adams

A VAST LIBRARY OF WRITINGS exists 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 been perennially popular topics. Some trace aspects of humoral theory back to Empedocles who theorized there were four elements, indestructible, that composed all substances: water, fire, earth, and air.[1] As a structural biological theory his four elements might be interpreted as representing fluidity (water), energy/metabolism (fire), tissue (earth), and oxygen (air or πνεῦμα *pneuma*). There is, however, no logical progression from the elements of Empedocles to a theory of health and disease. Instead, it is the fifth century B.C. 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. Its components were within the body, whereas the Empedoclean components *were* the body. One of the supporting arguments for a humoral theory is observational in that the author of *Nature of Man* 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,

[1] W. H. S. Jones, *Hippocrates* IV (Cambridge [Mass.] 1931) xxvii. The Hippocratic treatises cited in this paper are from the twelve volumes of the Loeb Classical Library edition. *Nature of Man* is at IV 3–41; chapters 1–8 discuss aspects of humors.

Greek, Roman, and Byzantine Studies 64 (2024) 195–207
ISSN 2159-3159

and finally blood, a valid observation if not deduction.[2]

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.[3] 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). But this paper deals neither 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.[4] This Hippocratic work discusses bile, phlegm, blood, and black bile but does not cite them as humors. By the analysis offered here, a fundamental physiological process applicable to all human disease, the process of inflammation, is unmasked at its most primitive stage of understanding.

The motivation for this analysis stems from a recently compiled wordlist of terms useful in translating Hippocratic medical treatises.[5] When the new translations of some of its words were applied to *Diseases* I a plausible theory took the place of a fictive one.

[2] *Nature of Man* 6. 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' of gastritis and thus called "black bile." Then, should deeper tissue damage occur, there would be massive hemorrhage (red blood).

[3] David Greaves, "Biomedical, Humoral and Alternative Systems of Medicine," *The Healing Tradition* (Oxford 2004) 135–148.

[4] *Diseases* I and IV are in volumes V and X of the Loeb (1988, 2012), transl. Paul Potter, who interprets the "imbalance" of four "moistures" (X 101 ff.) as giving rise to disease.

[5] W. H. Adams, *The Natural State of Medical Practice: Hippocratic Evidence* (Maitland 2019) 522–623. The Hippocratic works translated include *Prognostics*, *Aphorisms*, *Prorrhetic I*, *The Epidemics*, *Oath*, an excerpt from Aretaeus' *On Diabetes*, and an excerpt from Thucydides' description of the plague in Athens.

Hippocratic terminology

As background: Hippocratic physicians had yet to apply available optics to the study of human tissues, and the cause of many diseases therefore wanted explanation.[6] 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 "promotors" of disease, especially the classical components "bile" and "phlegm," these being translations applied by moderns to represent Greek χολή *khole* and φλέγμα *phlegma*. But have these translations been accurate?

Bile:

Bile is highly irritating, and its colors vary from dark green to yellow. The word is derived from the Latin *bilis*, used by the Roman playwright Plautus in attributing a personality trait (or "temperament") to "black bile" (*atra bilis*, *Capt.* 596). This indicates that by the third century B.C. the Greek χολή as commonly employed and understood by the general educated public reflected one's temperament. χολή finds its root meaning in "wrath" and "bitter anger," which also can be considered temperaments. In the *Iliad* its anatomic location is repeatedly stated to be in the chest (the source of Achilles' wrath, 4.513) rather

[6] In the Archeological Museum of Rhodes can be seen a series of graded sixth century B.C. quartz lenses probably used by jewelers, but similar lenses could have (and I believe would have, given more time) been adapted for histological study. Examination of lesions and excreta with a lens is merely an observational extension of the physical examination, and lenses were at hand. Stone (λίθος) and glass (ὕαλος) describe burning lenses that were available at apothecaries (Aristophanes *Clouds* 766–767), and Pliny comments that physicians use crystals for cautery (*HN* 37.28 *urenda corporum*).

than the gall bladder, and in the Septuagint, translated into Koine Greek in the third century B.C., it is associated with bitterness and with a botanical component.[7] 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 only tangentially at best.

If reference to χολή as 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) ξανθὴ χολή (*xanthe khole*, usually translated as "yellow bile") for diseases associated with purulence and local irritation and (2) μέλαινα χολή (*melaina khole*, 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.

[7] χολή in the Septuagint has been translated as "gall" and is linked to bitterness. Deuteronomy 29:18 has it as a component of a root, and at 32.32 it is a component of a grape. Elsewhere the Hebrew term *rosh*, translated as χολή, refers to a bitter plant, including wormwood and hemlock.

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 "phlegm" include μύξα *muxa* from which "mucus" would later be derived, and βλέννα *blenna*. With such alternatives why would the modern term "phlegm" be the translation of φλέγμα, a word derived from fire? Homer had used φλέγμα to describe an unquestionably fiery "evil flame" (*Il.* 21.337). Perhaps φλέγμα was not like our "phlegm" and was perhaps not even mucoid. There are inconsistencies. Herodotus (4.187.2) describes it in children as draining from the head, and in Hippocratic works it is described in *Aphorisms* (7.54) as re-absorbable, in *Nature of Man* 5 as something to be vomited, and in *Air, Waters, Places* (3, 10) as moist and flowing down from the head. Galen states that Prodicus concluded there were two types of φλέγμα, one that was like mucus and the other a denser "cooked" φλέγμα called from πεφλέχθαι, "to be burned."[8] Aristotle describes it as "viscous" (or "oily," λιπαροῦ: *Metaph.* 1044a20).

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 juice 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 abscesses and pleural effusions, and transudates of wounds, blisters, and eczemas. Thus, φλέγμα was a mix of exudates, transudates, and

[8] *Vorsokr.* 84 B 4. Cf. David Wolfsdorf, "Prodicus on the Correctness of Names: The Case of τέρψις, χαρά and εὐφροσύνη," *JHS* 131 (2011) 131–145.

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* (8) and by Prodicus as described above. 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.

Inflammation

Using the text and context of *Diseases* I the clinical roles of χολή and φλέγμα in inflammation can now be addressed by referring to specific sections.[9] What happened when either or both χολή (bile) and φλέγμα (phlegm) were in the blood? Both were liquids (20, p.148: ἡ δὲ νοτίς ἐστιν ἀπὸ χολῆς καὶ φλέγματος), soluble in and dispersed by the blood or dilution (28, p.172: ἡ γὰρ φλὲψ, ὅσον ἔνι ἐν αὐτῇ χολῆς καὶ φλέγματος … μετὰ τούτου μεθίσησι τὸ πολὺ ἔξω, and ὑπό τε φαρμάκων ποτῶν διαχεῖται). Both were considered cooler than blood (24, p.162: ψυχρότατον γὰρ τοῦ ἀνθρώπου φλέγμα, θερμότατος δ' αἷμα, ψυχρότερον δὲ καὶ χολὴ αἵματος) 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 (24, p.164: καὶ γίνεται τὸ αἷμα θερμότερον αὐτὸ ἑωυτοῦ πολλαπλασίως). Whatever the mechanism, when the overwarmed blood was distributed throughout the body it gave rise to fever.

[9] The Loeb edition of Paul Potter, V (1988) 94–183, is cited by section and then page number.

Of their site of production in the body *Diseases* 1 makes no comment. It is now known that tissue fluid (another medical designation 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. The author indicates that it was the normal systemic moisture, i.e. tissue fluid, and fluid from blood (plasma) that became clinically important when it was concentrated (15, p.134: ἀποδιδοῖ πάλιν ἁλές τε καὶ παχύ), but elsewhere (*Sacred Disease* 8) it is an "impurity," although the same passage 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 was not 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 (generalized edema), 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 (28, p.172), but when it became concentrated it produced pain, misery, and heat. There was some logic, therefore, in the idea that by phlebotomy both of these agents could be lowered to less dangerous levels and improve a patient's status. 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 bac-

teria the staphylococcus would proliferate exponentially, invade deeper, rapidly spread throughout the body, and kill the patient within hours before any obvious localized 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 limit 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, 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 that 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, rather than the cause. 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, viz. *inflammatio*, which is derived from *inflammare*, "to set on fire") but they also designated mechanisms that produced them.[10] In proposing mediators of those actions, pain and heat were caused primarily by χολή (bile, or greenish-yellow matter), swelling was caused primarily by φλέγμα (phlegm, or tissue fluid), and those two fluids were distributed by and squeezed out of the αἷμα (*haima*, blood), with the latter, on becoming thicker (παχύνεται), producing the redness (hyperemia) associated with inflammation (20, p.148). Importantly, the absence of any discussion of the three substances in the context of a humoral 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 Jacques Jouanna: "Good health is defined as the balance and mixture of humors, whilst their imbalance and separation is the cause of disease."[11]

The cardinal features of inflammation named by Celsus can be compared to the equivalent Hippocratic 'promoters' of inflammation and to two major components of the inflammatory process identified by modern science:

[10] Celsus (1st cent. A.D.) *De medicina* 3.10 on inflammation. At proem. 15 he states that the Hippocratics used the term φλεγμονή *phlegmone* as the equivalent of his *inflammatio,* but see Adams, *The Natural State* 13, for an opinion to the contrary, that φλεγμονή is properly translated as a "localized soft-tissue swelling."

[11] 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* (Leiden 2012) 335–359, at 335.

Celsus:	*dolor*	*tumor*	*calor*	*rubor*
	(pain)	(swelling)	(heat)	(redness)
Hippocratics:	Bile	Phlegm	Blood	Blood
	(purulence)	(tissue fluid)	(heat)	(redness)
Modern:	Bradykinin	Histamine		
	(pain)	(increased vascular permeability and local blood flow)		

From this list it can be discerned that the terms provided by Celsus are descriptive, whereas the Hippocratic components are mechanistic. Modern mediators of inflammation are more specific and include bradykinin, which triggers pain receptors, and histamine, which causes increased vascular permeability and vascular dilation that increases local tissue fluid and increases blood flow that causes redness and warmth. Both bradykinin and histamine are often cited in simplistic descriptions of acute inflammation in the body's response to bacterial invasion, although the entire mechanism of inflammation, including its cellular responses, is exceedingly complex. The components, stages, systems, and processes that are triggered, stimulated, regulated, retarded, and resolved in the inflammatory process number in the thousands and encompass the panoply of human disease.

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 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.[12] The first mention of black bile as a humor in the Hippocratic corpus is in

[12] For a scholarly review of the many and complex versions of humoral theory see Vivian Nutton, *Ancient Medicine* (New York 2005), ch. 5, especially for the concept of "black bile." He also has documented the rise to prominence of humoral theory following the writings of Galen (130–210 A.D.) in "Humoralism," in W. F. Bynum et al. (eds.), *Companion Encyclopedia to the History of Medicine* (London 1993) 281–291.

Nature of Man. In *Diseases* I, however, μέλαινα χολή *melaina chole* is not identified as a humor but is associated with a non-inflammatory disease and is translated as "dark bile" by Potter. Furthermore, it is mentioned only once (3, p.104) where it is stated to be a 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/dead nonpurulent tissue. It may be no coincidence, therefore, that cephalopod ink is one of the translations for χολή listed in LSJ. The common feature of "black bile" pathology, therefore, may be diseased tissue in the absence of inflammation, whereas bile, phlegm, and blood are all mentioned in relation to diseases associated with signs of inflammation.

Thus, black bile could have caused, in Hippocratic thinking, diseases due to ischemia or infarction with secondary necrosis or gangrene. Its stiffening might have been thought sufficient to occlude blood vessels as is described in *Regimen in Acute Disease (Appendix)* 7 and implied in *Airs, Waters and Places* 10. Although twelve categories of diseases, including "melancholy" (μελαγχολία), are listed in proximity to the mention of black bile in *Diseases* I (3 p.104), as implied by the phrase ἀπὸ τῶνδε and as pointed out by Jouanna, there is no clinical association that could have been intended by the ancient author.[13] Although the author of *Diseases* I barely mentions black bile, from the brief reference plus information at hand from other Hippocratic sources it is tentatively proposed that the Hippocratics considered black bile to be a cause of what they considered non-inflammatory diseases, with vascular occlusion (infarction) and its associated death of tissue as one of its mechanisms.

Modern analogies

There are other concepts hinted at in the Hippocratic descrip-

[13] Jouanna, "At the Roots of Melancholy: Is Greek Medicine Melancholic?" in *Greek Medicine from Hippocrates to Galen* 234.

tions 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 (14, p.126; 17, p.136; 19, p.140), 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 today an everyday consideration on surgical wards. (3) Most remarkably, mechanisms proposed by the Hippocratics 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 could then enable their dispersion (20, p.146: σκίδναται ἀνὰ τὸ σῶμα πᾶν).

(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 (20d, p.146: ἕλκουσι γὰρ αἱ φλέβες μᾶλλον τῶν σαρκῶν).

(c) The blood, by dispersing a focus of phlegm and bile throughout the tissues and under the skin, eliminated them in the sweat, and local heat evaporated some so that their vapor could be eliminated in the breath (7, p.112; 25, p.164: καὶ σὺν τῷ πνεύματι μισγόμενον ἔξω χωρέει).

(d) There is an implication that a shortened transit time of bowel contents might lead to expeditious excretion of "pus" (15, p.134: τὸ πῦον τὰ ἐπιρρέοντα κακὰ ἢ τὰ ἀπορρέοντα).

The concept of feedback and self-limiting control mechanisms in biology is a relatively new, mainly twentieth-century, phenomenon, but it was hinted at in the mechanisms proposed by the Hippocratics: 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 of 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 pus, expedited its excretion.

In conclusion, by interpreting χολή and φλέγμα 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. Early Hippocratic physicians were devising a framework, a work in progress, that supported a plausible explanation for their clinical observations of various disease states. They 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. *Diseases* I does not use the word "humor" (χυμός), but three substances discussed herein (bile, phlegm, and blood) are fluid and thus might be considered a precursor of humoral theory. But in no sense are these substances in balance with one another. And in section 2a the author of *Diseases* I identifies only bile and phlegm as causative of internal disease, a further segregation of early Hippocratic thinking from humoral theory. Finally, the focus of this paper 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. What *Diseases* I makes clear is 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.

February, 2024

Cooperstown
whabooks@gmail.com