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Brief history of the clinical diagnosis of malaria: from Hippocrates to Osler

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Abstract

Since antiquity, malaria had a major impact on world history but this brief historical overview focuses on clinical features of malaria from Hippocrates to Osler. In antiquity, physicians tried to differentiate malaria from other acute fevers. The classic descriptions of malaria by Hippocrates in ancient Greece and Celsus in ancient Rome are excerpted here from the original Greek and Latin. Their clear clinical descriptions prove malaria was recognized in antiquity. In the modern era, it remains difficult to clinically differentiate malaria from typhoid fever. Since physicians used the term 'typhomalaria' to describe acute undifferentiated fevers a testimony to their lack of clinical acumen. Osler, the great clinician, by careful observation in clinical features and fever patterns was able to clearly differentiate malaria from typhoid fever as did the ancients.

Key words Celsus – clinical diagnosis of malaria – Hippocrates – malaria in antiquity – Osler – typhomalaria

"Sirius, harbinger of fevers (πυρετόζ), the evil star which dominates the night sky at harvest time".

Homer (Iliad, XXII)

Malaria in antiquity

In Hippocratic era, malaria was known simply as 'the fever' (πυρετόζ), to the Romans as 'intense burning heat' (*febris ardens*) or by its periodicity (*accessia*). In the modern era, malaria was known to the French by fever and chills (*fièvе äigue*) and to the English as 'seasonal fevers' (*ägues*). In Osler's time, because of its seasonal incidence malaria was also known as the fever of summer/fall (*estivoautumnal fever*).

Anopheles mosquitoes residing in dark/damp places during the day feed on animal/human blood at night. Mosquito's eggs are deposited in stagnant water, since moving water has an adverse effect on mosquito larvae. This is the reason, physicians and others have recognized and appreciated malaria with association with marshes since antiquity—'malaria', 'agues of the marshes' and 'marsh fever'.

In antiquity, *Plasmodium* species and vectors (anopheline mosquitoes) evolved together and became established in tropical Africa increased density of settled/migrating populations and in concert with agriculture. Since heterozygous sickle-cell gene (HbAS) individuals are less susceptible to *Plasmodium falciparum* malaria, *P. falciparum* has had a selective survival advantage in tropical Africa.

Over time, malaria spread from Africa along travel/shipping routes to Europe, India, China and Indone-

sia. It is unclear how/when malaria became established in the Americas.

The ability/efficacy of anopheline mosquitoes to transmit malaria varies greatly by species. Over 3300 different species of mosquitoes exist, and about 400 are of the *Anopheles* genus (Diptera: Culicidae). Among *Anopheles* sp about 70 species are potential vectors, but only about three dozen are important/efficient malarial vectors. In antiquity, the ineffectiveness of *An. atroparvus* as a vector of *P. falciparum* may explain its relative rarity in ancient Greece and Rome. By the end of the Roman Empire, efficient mosquito vectors from northern Africa (*An. labranchiae*) and Asia (*An. sacharovi*) were able to effectively transmit all *Plasmodia* sp including *P. falciparum*. Malaria clearly existed in the classical period, but did not have the devastating effect on armies/civilian populations that occurred after the fall of Rome[1–5]. This article highlights the clinical differentiation of malaria from typhoid fever from Hippocrates to Osler.

Acute fevers in antiquity: clinical differentiation

The ancients found it clinically difficult to differentiate malaria from other fevers. In the written accounts that have survived, it is often difficult to determine the infectious disease being described, malaria and typhoid fever were most likely to be confused with each other. There are several problems with ancient sources including interpretational differences in terminology between then and now. In spite of interpretational variability, fever (πυρετόζ), in ancient Greece specifically referred to malaria and not other fevers.

Hippocrates was the first to clearly describe the different types of malaria depending upon the periodicity of the fever—tertian and quartan fever patterns. He also described septans, nonanes, etc. as other malarial variants. The classic malarial fever patterns are clear in the writings of Hippocrates, and he appreciated the diagnostic significance of splenomegaly in malaria[6–10].

Hippocrates (460 BC – 370 BC) on malaria

The following is a translation from the ancient Greek of Hippocrates description of malaria from his *Epidemics* (Volume I)[11]. "*When the paroxysms fall on even days, the crises will be on even days; and when the paroxysms fall on odd days, the crises will be on odd days*. Thus, the first interval of those with crises on even days is on the fourth day, the sixth day, the eighth day, the tenth day, the fourteenth day, the twentieth day, the twenty-fourth day, the thirtieth day, the fortieth day, the sixtieth day, the eightieth day, and the one hundred and twentieth day. While those with crises on odd days, the first interval is on the third day, the fifth day, the seventh day, the ninth day, the eleventh day, the seventeenth day, the twenty-first day, the twenty-seventh day, and the thirty-first day. *Furthermore, it is necessary that one know that if crises fall on days other than those mentioned above, there will be a relapse, and this may be deadly. But it is essential to pay attention and know at which times the crises will lead to death and in which to recovery, or during which is there tendency to fair better or worse.* The intervals when crises occur in irregular fevers, quartans, quintans, septans and nonanes, should also be considered".

Malaria in ancient Greece

Hippocrates appreciated the relationship of malaria to the summer/fall, marshes outside Athens, and splenomegaly. He described the 'malarial paroxysm' (chills → fever → sweats → exacerbation), and the periodicity of malarial parasites. From his descriptions of malaria, it appears that *P. vivax* and *P. malariae* were the predominant species. *P. falciparum* may be recognized by its intensity, complications and lethality, but was not common at the time. Other plagues, not malaria, had devastating effects on battles/populations in ancient Greece.

Celsus (25 BC–54 AD) on malaria

Translated from the Latin of Celsus' description of

malaria from his *De Medicina* (Volume I)[12]. "But quartans are simpler. The fevers begin with shivering, then a heat erupts, and then, the fever having ended, the next two days are free of it. On the fourth day it returns. However, tertian fevers surely have two types. The one type beginning and ending in the same manner as a quartan, the other with only this difference; that it allows one day to be free of it, and returns on the third. The other type is far more insidious, for it always returns on the third day, and out of forty-eight hours, thirty-six of them (although sometimes less or more) are occupied by the paroxysm. Neither does it completely halt during remission, but only takes a lighter course. This type most physicians call semitertian".

"Quotidians, on the other hand, are surely varied and have many parts. For some begin immediately with a heat, others with a coldness, and still others with shivering. I call it coldness when the extremities of the body are cold; I call it shivering when the entire body trembles. *Again, some end with that, and a period free of symptoms follows; others end thusly, so that the fever diminishes somewhat, but nevertheless, some remnants of disease remain, until another paroxysm occurs*; and some often have no remission, and continue on. I say again, some have an intense fever, others a more tolerable one: some are the same everyday, other are different and, alternating, the fever is milder one day, more severe the next. Some return at the same time the next day, others either later or sooner; some take a day and a night to have paroxysm and remission, some take less time, others more. Some, when they remit, cause a sweat, others do not; and from the sweat some are free of their disease, but in others the body is only made weaker by it. *And the paroxysms sometimes occur only once during a single day, sometimes two or more times. Thus it often happens that everyday there are multiple paroxysms and remissions, as though each of the two answers its predecessor*" (Table 1).

Malaria in ancient Rome

The effect of malaria on ancient populations is dem-

Table 1. Characteristics of different fevers

Malarial species	Types of malaria	Duration of fever (hours)	Periodicity of malarial paroxysms (hours)	Days from initial fevers (onset) to next fever (Crisis)	Age of preferred human host	Age of parasitized RBCs
P. malariae	Quartan	9	72	4	All ages	All RBCs
P. vivax	Benign tertian	11	48	3	Young adults	Young RBCs
P. ovale	Ovale tertian	11	48	3	Young adults	Young RBCs†
P. falciparum	Malignant tertian*	40	48	3	Mature adults	Young RBCs†
Three parallel generations of *P. malariae* or Two parallel generations of *P. vivax, P. ovale*, or *P. falciparum*	Quotidian	6–12	24	2	Very young children	All RBCs
Mixed malarial species	Continuous	Continuous	Continuous	1	All ages	All RBCs

*Also known as pernicious tertian or semitertian malaria; †Reticulocytes (Adapted from reference No. 20).

onstrated by malaria in ancient Rome. The Romans recognized the relationship of stagnate water in the swamps surrounding Rome and the presence of fevers during the summer months. These fevers were initially ascribed to bad air—*mal aria*. They thought that the foul vapors emanating from the stagnate water and swamps was the cause of the disease, of course, this was incorrect, but at least it represented an appreciation of the importance of stagnate water being somehow related to the summer/early fall febrile illnesses among the Romans. Roman engineers, in appreciation of this relationship, designed extensive drainage systems which essentially eliminated malaria as a major problem in drained areas.

After the fall of Rome and the destruction of the Roman water drainage systems, the conquering barbarians became malarial victims[1,3,4,13]. Alaric, the first barbarian prince to conquer Rome (410 AD) perished himself from malaria. So many of his army succumbed to malaria that the few remaining survivors were forced to abandon the city[14].

Malaria in the modern era

Since antiquity, clinicians have had difficulty in differentiating typhoid fever from malaria because of some overlapping clinical features. Because the inability of physicians to clinically differentiate these two entities, since physicians used the term 'typhomalaria' as a diagnosis for acute fevers without localizing signs. The diagnosis of typhomalaria was used for decades by physicians and is still used in some areas today, e.g. Haiti[3,7,8,15].

Osler and typhomalaria

Osler clearly differentiated malaria from typhoid fever by clinical criteria alone. By recognizing and appreciating the characteristic clinical features, we were able to differentiate malaria from typhoid fever. Osler showed physicians without access to laboratory facilities how to differentiate these two infectious diseases. His observations remain valid and useful today[16–18].

Osler on malaria

Excerpts from Osler's 1897 article on malaria are excerpted here. "This form is *characterized by recurring paroxysms of what are known as ague, in which, as a rule, chill, fever, and sweat follow each other in orderly sequence*. The stage of *incubation* may be very short. Attacks have occurred within twenty-four hours after exposure. Usually the time of incubation is from seven to fourteen days. On the other hand, the ague may be, as is said, 'in the system', and the patient may have a paroxysm months after he has removed from a malarial region, though I doubt if this can be the case unless he has had the disease when living there".

Description of the paroxysm: The patient generally knows he is going to have a chill a few hours before its evident by unpleasant feelings and uneasy sensations, sometimes by headache. The paroxysm is divided into three stages—cold, heat, and sweating. Fever may rise during the chill to 105 or 106°F. *Of symptoms associated with the chill, nausea, and vomiting are common. There may be intense headache. The pulse is quick, small, and hard. The chill lasts for a variable time, from ten to twelve minutes to an hour, or even longer*.

The hot stage is ushered in by transient flushes of heat; gradually the coldness of the surface disappears and the skin becomes intensely hot. The contrast in the patient's appearance is striking: *The face is flushed, the hands are congested, the skin reddened, the pulse is full and bounding*, the heart's action is forcible, *and the patient may complain of a throbbing headache*. The rectal temperature may not increase much during this stage; in fact, by the termination of the chill the fever may have reached its maximum. *The duration of the hot stage varies from half an hour to three or four hours. The patient is*

intensely thirsty and drinks eagerly of cold water.

Sweating stage: Beads of perspiration appear upon the face and gradually *the entire body is bathed in a copious sweat. The uncomfortable feeling associated with the fever disappears, the headache is relieved and within an hour to two the paroxysm is over and the patient usually sinks into a refreshing sleep.* The sweating varies much. It may be drenching in character or it may be slight.

Types of the paroxysm: The periodicity of the paroxysms is one of the most striking features in malarial fever. They occur with regularity, either at the end of twenty-four, forty-eight, or seventy-two hours. Twenty-four hours the paroxysm is daily, hence the name quotidian. Paroxysm occurs at the end of forty-eight hours, it happens upon the third day; hence the term tertian applied to this form. This is the next most frequent form. Seventy-two hours the paroxysm is on the fourth day, hence the name quartan ague. This is rare.

Course of the disease: After a few paroxysms, or after the disease has persisted for ten days or two weeks, *the patient may get well without any special medication*. In cases in which we have been studying *the haematozoa I have repeatedly known the chills to stop spontaneously. Such cases, however, are very liable to recurrence.* Persistence of the fever leads to anaemia and a haematogenous jaundice, owing to the destruction of the red blood-disks by the parasites. *Ultimately, the condition may become chronic, and will be described under malarial cachexia*. Cases of intermittent fever yield promptly and immediately to treatment by quinine.

Symptoms: The disease may set in with a definite chill, or may be preceded for a few days by feelings of malaise. As seen in this latitude, the patient has either chilliness or a distinct rigor in the beginning. When seen on the second or third day of the disease he has a flushed face and looks ill. The tongue is furred, *the pulse is full and bounding, but rarely dicrotic*. The temperature may range from 102 to 103°F, or is in some instances higher. The general appearance of the patient is strongly suggestive of typhoid fever, a suggestion still further borne out by the existence of acute splenic enlargement of moderate grade.

The similarity of the cases at the outset to typhoid fever is most striking, more particularly the appearance of the facies, and the patient looks very ill. The cases develop, to, in the autumn, at the very time when typhoid fever occurs.

There are only two forms of these continued fevers in the South—the one due to *the typhoid*, and the other to the *malarial* infection. *The typhoid fever of Philadelphia and Baltimore presents no essential difference from the disease as it occurs in Montreal, a city practically free from malaria. Dock has show conclusively that cases diagnosed in Texas as continued malarial fever were really true typhoid.*

Osler pointed out that the fever curve in typhoid fever increases slowly stepwise over the first few days and is followed by a pulse temperature deficit as the infection progressed. Both typhoid fever and malaria are accompanied by a prominent headache. Both malaria and typhoid fever have few, if any localizing signs—rose spots (in typhoid fever). Splenomegaly is common to both infections.

Whereas malaria begins with multiple shaking chills, typhoid fever begins with a single morning shaking chill. In malaria, chills are followed by spiking fevers. Except for the initial shaking chill, chills are not comment with typhoid fever. In malaria, chills precede the fever followed by profuse diaphoresis and profound malaise followed by complete recovery between attacks.

Osler also appreciated the clinical features of malaria and typhoid fever using non-specific laboratory tests.

Whereas the WBC count in malaria is usually normal/elevated, typhoid fever is associated with a normal/slightly decreased WBC count. The platelet count in malaria is regularly decreased and thrombocytopenia is not a feature of early/uncomplicated typhoid fever. Mild elevations of serum transaminases may occur in both. An increased LDH clearly differentiates malaria (elevated) from typhoid fever (unelevated)[7,8,15,19].

Today, clinicians would be well served to review the original clinical descriptions of malaria by the ancients and Osler, who, with so little, saw so clearly.

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