Periodic pyrexia and malaria in antiquity

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Although malaria is today still an international scourge affecting 300 - 500 million people in mostly tropical and subtropical regions and causing approximately 2 million deaths per annum, evidence shows that it is an ancient disease. This study reviews its occurrence during antiquity and classical times, particularly in the Mediterranean areas.

Modern concepts

The name ‘malaria’ derives from ‘mal aria’ (bad air) in Italian and was probably first used by Carnaro in a publication of 1440. Theories regarding malaria’s miasmatic origins were only dispelled in the late 19th century when Manson (1877) described the malarial cycle with the mosquito as vector, and Laveran (1880) discovered the causative parasite in human blood. Of the four species of malarial parasite (Plasmodium) causing human malaria, P. ovale occurs only in West Africa, while P. falciparum, P. vivax and P. malariae were found in the Mediterranean basin until quite recently. DNA-sequencing studies show that P. falciparum originated 165 million years ago, probably in the Central Lakes area of Africa. Because of its intolerance of temperatures below 20°C, it probably migrated to the Mediterranean area only after termination of the last Ice Age, approximately 15 000 - 20 000 years ago. P. vivax and P. malariae probably originated in South-East Asia, and being tolerant of colder temperatures, possibly moved west at an earlier stage.

Humans are infected only through the bite of the female Anopheles mosquito, which breeds in well-aerated standing water. They can fly only a few kilometres in non-windy conditions, and characteristically enter dwellings to bite after dark. Anopheles mosquitoes are found in fossils of at least 26 - 38 million years old, and species like A. sacharowi and A. labranchiae, which caused Mediterranean malaria in modern times, probably existed there in Classical times and earlier.

Clinical picture

Because of the mosquito’s breeding requirements, malaria typically shows a seasonal incidence, highest in the warm and wet months. After entering the body and replicating in the liver
Pharaonic Egypt

If *P. falciparum* malaria originated in Central Africa and moved to the Mediterranean in post-glacial times, chances are that Egypt would have been infested on the way. The Nile, which regularly floods its banks, and terminates in the water-rich delta, would certainly have been conducive to the breeding of mosquitoes and other insects. Herodotus, a Greek historian who visited Egypt in the 5th century BC, tells us that the local inhabitants were indeed pestered by swarms of gnats (mosquitoes were not mentioned, but the Greeks often did not differentiate between gnats and mosquitoes). It is therefore surprising that our significant body of medical papyri dating back to the 3rd millennium BC reveals no convincing description of periodic fevers, reminiscent of malaria. Salla2 does suggest that intermittent fevers mentioned in the so-called magical papyri may perhaps point at malaria. However, immunological tests and DNA sequencing performed on tissues of mummies dating back to 3 200 BC have shown good evidence of *P. falciparum* infection.27

Greek era

At the dawn of Greek history, Homer (8th century BC) referred to the rising of the ‘Dog Star’ (Sirius), in late summer, as a time of ill health. In Classical times the connotation of suffering during the ‘dog days’ became commonplace. Malaria was probably part of this problem but we must accept that other diseases of the hot months, for instance waterborne intestinal disorders, would also have been at their height.2

The classical descriptions of periodic fevers in the Hippocratic corpus (5th and 4th centuries BC) almost certainly represent the first clear recordings of acute malaria.4 Kind suggests that a contemporary doctor, Diocles of Carystus (4th century BC), also recognised malarial fever patterns, but virtually all his writings are lost to us. Care should of course be taken not to read too much into terse aphorisms or elaborate descriptions of pyrexial illnesses, but it does seem most probable that the seasonal fevers (late summer, autumn), associated with marshy conditions and showing fever peaks (associated with rigor, hot and cold spells, sweating) on every third (tertiary) or fourth day (quartan fever), do represent malaria. We must remember that the Greeks counted their days from the day of onset of the illness – a fever 48 hours later would thus fall on their third day (thus tertiary fever). Hippocrates furthermore stated that quartan fever was the least serious disease but the most chronic, and could cause dropsy (presumably the nephrotic syndrome) of *P. malarie* infection mentioned above. Subterranean fever was the most serious fever, but it is not quite clear what is meant by the term ‘subterranean’. It would be tempting to equate it with the modern term ‘malignant tertian’. Other tertian fevers were said not to be fatal and to abate after the seventh fever peak. Quotidian (daily) fever is mentioned as a most serious condition, but it becomes difficult to be sure that these daily fevers do not represent other pyrexial illnesses (such as consumption) besides *P. falciparum* infection.

Historical malaria

Evidence of malarial infection in a specific community may be obtained through contemporary written records (describing the typical fever patterns), or through the detection of physical evidence of disease in human remains from the time period. Malaria leaves no pathognomic macroscopic lesions recognisable in the bodies of victims who died millennia ago. However, modern immunological tests for malarial parasites performed on human remains may produce conclusive evidence of malarial infection.7

Literature from antiquity will now be examined for evidence of malarial fevers. It is of course admitted that periodic fevers may occur in various diseases besides malaria, and infections like brucellosis (*Brucella abortus*) and relapsing fever (*Borrelia recurrentis*) did indeed exist in ancient times. However, the periodic fever patterns of these diseases, typically lasting 5 - 9 days at a time, are quite unlike the one-day spikes of malaria.2,4

*Phyto*parum* malaria* (malignant tertian malaria). Fever peaks recur every 48 hours; fever may not completely subside between peaks, and untreated, an attack may continue for months, with potentially fatal complications like cerebral malaria and acute renal failure (blackwater fever). With multiple episodes of different subspecies of *P. falciparum*, fever peaks may occur daily (quotidian fever). This is a most serious condition.

*P. vivax* (benign tertian malaria). Fever peaks also occur every 48 hours, the intervening period being fever-free, and untreated the condition may continue for many months – and it often relapses after apparent cure. Because it rarely causes death it is known as benign tertian malaria as opposed to the more serious *P. falciparum* infection.

*P. malariae* (quartan malaria). Fever peaks occur every 72 hours, and it is the most chronic of the three diseases. Death is uncommon, but it may cause a fatal nephrotic syndrome, characterised by gross oedema.

Chronic malaria. Typically found in endemic areas, is characterised by splenomegalia, degrees of malnutrition and weight loss, anaemia and secondary infections. In endemic areas acute malaria is commonest among children, and causes abortion in pregnant women. It is possible to develop a degree of immunity against acute attacks, which persists as long as the person is exposed to low-grade malaria.

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August 2006, Vol. 96, No. 8 SAMJ
Hippocrates’s description of a condition characterised by weight loss, splenomegaly and pot belly in people living in marshy areas and drinking stagnant water, could represent chronic endemic malaria – but a disease like chronic bilharzia, typically occurring in similar conditions, cannot be excluded. His mention of high fatality among children and women, but not older men, would fit the mortality patterns of endemic malaria.

Hippocrates also reports the case of Philiscus who developed a tertian fever, complicated by the passing of dark urine on the fourth day, delirium and loss of voice on the fifth and death on the sixth day. Could this be the first description of fatal cerebral malaria and blackwater fever complicating malignant tertian malaria?

In 413 BC during the Peloponnesian War the Athenian army encamped in a marshy area outside the walls of Syracuse and was decimated by an epidemic, which could well have been P. falciparum malaria. A good case can also be made for the suggestion that Alexander the Great’s death in Babylon in 323 BC was due to malaria, acquired in the marshy lower Mesopotamia.

Roman era

Roman history relates numerous instances where public health measures consisted of draining of marshy areas to relieve illness. Besides waterborne gastrointestinal disease, such diseases would certainly have included malaria. The agrarian, Columella, warned against the building of houses near marshes where mosquitoes were abundant. Interestingly enough, the architect Vitruvius distinguished between unhealthy and disease-free marshes – the stagnant Pontine marshes were pestilential, while the salty marshes of Ravenna and Aquilea, and the marshes of Alexandria (where Nile flooding regularly cleansed the waterways) were disease free.

Asclepiades (2nd century BC), while confirming the high incidence of periodic fevers in Rome, stressed the seriousness of quotidian fevers which often caused serious brain disease. In the 1st century the encyclopaedist, Celsus, again clearly described three kinds of periodic fevers which almost certainly were malaria, viz. quotidian, tertian and quartan fevers. In an extraordinary observation he mentioned that tertian fevers would be mild when days between fever peaks were apyrexial (benign tertian malaria), but more serious when fever never completely abated – malignant tertian malaria according to the classical description given above, and called hemitritaion (semi-tertian fever) by himself. He affirmed the benign nature of quartan fevers, stated that combinations of fever patterns could occur, and noticed that all fevers commonly relapsed after apparent cure. Perhaps the best description of malaria comes from Cicero’s correspondence with his friend Atticus. From these letters we learn that Atticus acquired quartan malaria in September 50 BC which persisted until December when his wife, Pilia, also contracted the disease. By February 49 BC Atticus was free of the fever bouts, but in March the fever relapsed. At the end of May husband and wife were permanently cured. According to Suetonius, Julius Caesar suffered from quartan fever early in his career. Writers like Martial, Terence and Horace often referred to periodic fevers. Galen (2nd century AD) also clearly described quotidian, tertary and quartan fevers, stating that quartan fever could last up to 2 years, and caused dropsy.

Others

It is probable that malaria also infested the rest of Europe in Roman times. P. vivax and P. malariae are less cold-sensitive than P. falciparum and are therefore more likely to have survived in the colder, northern regions. The consul Fabius Maximus acquired quartan fever while fighting German tribes in 121 BC, and a tombstone inscription from Hubitancum in Britain reflects a dedication to the goddess of tertian fevers. A remark by Julius Caesar that Gaul and Spain were healthier
in autumn than Italy could indicate that these regions were less malarious. The Greek geographer Strabo’s comment that the fertile regions of Sardinia were unhealthy in summer is interpreted by Sallares as indicative of malarial infestation, but factual evidence remains inconclusive. Josephus reported that summer fevers were rife around the Sea of Tiberias and that quartan fever hastened the death of the Jewish king, Alexander Jannaenus.\textsuperscript{15}

Evidence exists that fevers (probably malaria) were recorded in China as early as the 8th - 5th centuries BC. Unlike the Mediterranean people, they related the fevers to mosquito bites.\textsuperscript{7} The former blamed miasmic factors – toxic vapours that arose from marshy areas and caused illness. Varro and Columella did, however, talk of minute creatures that emanated from marshes and entered humans through their mouths and noses. Fevers were otherwise explained on the basis of reigning humoral theories and some considered it to be of divine origin; a Roman temple was dedicated to the goddess of fever.\textsuperscript{9}

### Discussion

We therefore have written evidence that at least Hippocrates, Asclepiades, Celsus and Galen recognised the typical periodic fever patterns compatible with various kinds of malaria: malignant tertian malaria with its significant mortality rate, benign (but chronic) tertian malaria, benign quartan malaria with its complication of nephrotic syndrome, and possibly even chronic endemic malaria. Reported quotidian fever is less comfortably associated with \textit{P. falciparum} infection. Treatment was acknowledged to be largely ineffective. Pliny the Elder\textsuperscript{2} summarised existing therapeutic regimens, including herbal remedies and magical procedures. In his long list of remedies he includes bizarre suggestions like the eating of bedbugs with eggs and wine, and Icatidas’s remedy of sleeping with menstruating women. Celsus felt that certain specific treatments could obviate death, and prescribed early venesection.\textsuperscript{7} Cato, the Roman autocrat who denounced anything Greek, treated splenomegaly (a sign of malaria) with aconite, a congenital eunuch and prominent Stoic orator, quoted Plato in repeating the ancient belief that an attack of quartan fever would terminate all other fevers and leave one a healthier person.\textsuperscript{15} At the turn of the 1st century Rufus of Ephesus also claimed that periodic fevers (probably malaria) had a beneficial effect on epilepsy, tetany, asthma, melancholia and certain skin diseases. He furthermore stated that certain African tribes used fever induced by the drinking of goat’s urine as a therapeutic manoeuvre in disease.\textsuperscript{17}

Although there is no modern explanation for this claim, it is nevertheless interesting that up to 40 years ago deliberate (controlled) infection with \textit{P. falciparum} was accepted therapy for forms of chronic neuro-syphilis.\textsuperscript{39}

Malaria was therefore a common and endemic disease in the Classical era.\textsuperscript{2} Scholars have debated its impact on the civilisations of antiquity. Jones\textsuperscript{3} proposed that malaria was indeed a decisive factor in the decline of Greek civilisation, but classicists such as Sallares\textsuperscript{5} disagree. Kind\textsuperscript{4} similarly posed the question whether the disease played a significant role in the decline of Rome, but it is again Sallares’s\textsuperscript{2} considered opinion that the hypothesis is not supported by available evidence.

However, as an agent of natural selection, malaria might well have had an important but less obvious impact. It is known that certain haemoglobinopathies (thalassaemia and sickle cell disease, in particular), deficiency of the enzyme glucose-6-phosphate-dehydrogenase (G-6PD) from red cells, and the presence of Duffy blood groups on erythrocytes, do protect against malaria. Carriers of these inherited characteristics would be better able to withstand malaria, and in endemic malarial areas they should indeed then gradually increase in numbers.\textsuperscript{24} We are unaware of an epidemiological study evaluating this possibility.