Malaria, a Journey in Time: In Search of the Lost Myths and Forgotten Stories

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Abstract: The saga of malaria parasites precedes the history of humans. Malaria has always been part of the rising and decline of nations, of wars and of upheavals. People of ancient times attributed the malarial manifestations to supernatural influences. Myths about demons responsible for fevers and efforts to bring them under control were often mentioned in ancient articles and attested archaeologically. More than 4 millennia were required until malaria was finally demystified. From the ancient Chinese Canon of Medicine to Ronald Ross' milestone discovery, the humanity struggled to face one of the most debilitating diseases of mankind. This essay assesses the history of malaria from ancient mysteries until it was demystified. Its sections describe the attempts of humans from different times to understand and defeat malaria through supernatural practices, religious rites and medicine, and also their efforts mirrored in art and literary masterpieces.

Key Indexing Terms: Malaria; Ague; Fevers; Marshes; Medical history. **[Am J Med Sci 2010;340(6):492–498.]**

The saga of malaria parasites precedes the history of humans.[1] Scientists demonstrated that malaria primarily emerged in our primate predecessors in Africa, in the Ethiopian region, and developed with humans and their continuously increased mobility. From the valley of the Nile, it spread into the Mediterranean region, then in Asia and to the north throughout Europe, where it played a significant role on different civilizations.[1–3] By the early 1800s, malaria was worldwide in its geographic distribution.[4]

Malaria has always been part of the rising and decline of nations; of wars and of upheavals. Kings, popes and military leaders were struck down in their prime by the disease. For centuries, it prevented any economic development in vast regions of the earth.[5]

This essay assesses the history of malaria from ancient mysteries until it was demystified. The sections below describe the attempts of humans from different times to understand and defeat malaria through supernatural practices, religious rites and medicine and also describe their efforts mirrored in art and literary masterpieces.

Historical Traces of Malaria

References to malaria from antiquity may be traced back according to its *sui generic* clinical signatures—recurrent periodic fevers and splenomegaly.[6] The 4 most important malaria parasitic species known to infect humans were historically correlated with the paroxysms as follows: *Plasmodium vivax*, *Plasmodium falciparum* and *Plasmodium ovale*—tertian periodicity, and *Plasmodium malariae*—quartan periodicity. References to semitertian fever could be considered as a combination of tertian and quotidian fevers. It was also suggested that many cases of both *P falciparum* and *P vivax* malaria would have taken a quotidian form in antiquity.[7]

The typical fever pattern associated with enlarged spleens and tendency to epidemic occurrence were referred to by the ancient Chinese Canon of Medicine (Nei Ching; 2700 BC) and afterward throughout the records of many other civilizations: Sumerian, Assyrian, Babylonian, Chinese, Egyptian, Indian, Greek, Roman or Arabic.[2,5,6,8,9] Numerous other ancient Chinese documents provided valuable information about the affection. Zuo Qiuming (c 500 BC) related the case of a minister who acquired the disease after the bite of an insect. Another 2 documents dating back as far as the period 476 to 221 BC mentioned that malaria was caused by mosquito bites, especially during the late summer and early autumn.[7] Writings from the Vedic period (1500–800 BC) refer to autumnal fevers as the "king of diseases" and describe the enlargement of the spleen, suggesting that malaria existed in India at that time.[4]

Malaria had appeared in the writings of the Greeks from around 500 BC. Hippocrates (460–377 BC) was the first physician who described the malarial paroxysm (including chills, fever, sweats and exacerbation) and the different clinical types of malaria depending on the periodicity of the fevers: "The most acute, most serious, most difficult and deadliest diseases were continuous fevers. The safest and easiest of all, but the longest in duration, was quartan fever . . . acute disease occurs in the fever called semitertian, which is more fatal than the others . . . exact tertian fever reaches its crisis rapidly and is not fatal."[7,10]

The disease used to be "for centuries . . . one of the determining factors of the demographic and socioeconomic evolution of a large part of the Italian peninsula" and the attention of numerous historians, scientists and politicians was focused on this topic.[7,11]

The falling agricultural and economic prosperity at the beginning of the 5th century AD facilitated the spread of malaria in the declining Roman Empire. Campagna Romana, the plain surrounding the city of Rome, was a favorable nest for malaria as a consequence of high temperatures: "The Tiber and its tributaries, which flow across it sunk into deep channels, have cut into the uneven surface of this plain, which is almost everywhere uncultivated, with only natural pastures, bare of trees and property, the home of malaria in summer." The presence of the vectors was also emphasized: "The very common fly and the mosquito . . . the one by day, the other by night, are the greatest nuisance to visitors to the Roman Campagna in summer."[7,12,13]

Pope St. Gregory I (c 540–604), also known as Gregory the Great, who suffered of malaria himself, described the great epidemic of fever, which occurred in Rome in 599 AD: "For every day I am weak and in pain and sigh, waiting for the remedy of death. Assuredly among the clergy of this city and people there are so many cases of lethargy and fever that hardly

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Submitted March 2, 2010; accepted in revised form May 14, 2010.

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a single free man or a single slave remains, who is fit for any office or ministry. However, from neighboring towns I receive reports every day of the carnage of death."[7,14]

Gaius Plinius Secundus (23–79 AD), better known as Pliny the Elder, reported on cases of tertian fever in Tungria (now southern Belgium and Holland) in the 1st century AD. Saint Gregory of Tours mentioned that malaria was common and familiar in France during the 6th century.[7]

Travelers to Rome were more severely affected by the disease than indigenous people. A possible explanation may be that survivors of malaria and those born of immune mothers had some acquired immunity. Alcuin of York (730/740–804), a scholar, ecclesiastic, poet and teacher from York, Northumbria, traveled from Britain to Rome where he acquired "the Roman fever" and exported the causative agent to northern Europe.[7]

Gervase of Canterbury (c 1141–1210), an English monk chronicler, reported a Roman epidemic because of the "bad air" in 1188 AD.[7] Beginning with the 16th century, the malady spread widely from the Mediterranean region up to northern Europe, in Britain, Denmark and Sweden.[15] In the 17th century, malaria reached Finland, and the years 1692 to 1693 were associated with severe fever. During the next century, many fatalities were registered in Finland's western parts.[16] In the Rhone-Alpes region in Eastern France, malaria was endemic during the 19th century shortening the life expectancy.[15]

Malaria became endemic in North America after the importation of slaves from Africa in the 16th and 17th centuries and reached a peak in 1875. Survey performed by Daniel Drake (1785–1852) in 1850 concluded that malaria was the main disease in Middle America. He referred to autumnal fever, described as "bilious, intermittent, remittent, congestive, miasmatic, malarial, marsh, malignant, chill fever, ague, fever and ague, dumb ague, and lastly the Fever."[17,18]

From Antiquity to the Middle Age, malaria took an active part in history. It dismissed leaders of any kind, from kings to churchmen and poets: Vespasian (9–79, Roman emperor), Titus (39–81, Roman emperor), Hadrian (117–138, Roman emperor), Constantine the Great (324–337, Roman emperor) and his son Constance (337–360), Alexander the Great (356–323 BC, ancient Greek king of Macedon), Alaric (c 370–410, king of the Visigoths), Gregory V (972–999, Pope), Alexius I Comnenus (1048–1118, Byzantine emperor), Dante Alighieri (c 1265–1321, Italian poet), Guido Cavalcanti (1255–1300, Italian poet), John VI Cantacuzenus (c 1292–1383, Byzantine emperor), Andronicus III Paleologus (1297–1341, Byzantine emperor), Francesco Petrarca (1304–1374, Italian scholar, poet and humanist), Leo X (1475–1521, Pope), Sixtus V (1520–1590, Pope), Urban VII (1521–1590, Pope) and Oliver Cromwell (1599–1658, English military and political leader).[3,8,19–21]

Different Names, Same Disease

The supposition of the miasmatic nature of the illness was widely spread until the first evidence of the causative parasites. The word "malaria" derives from the Italian words "mal'aria" meaning "bad air," "evil air" or "corrupted air." The first attested mention of the term "mal aere" can be found in Marco Cornaro's book "Scritture della laguna" published in Venice in 1440. "Malaria," the finally settled word for the disease, was used for the first time in Italy by Francesco Puccinotti in his book "Storia delle febbri intermittenti di Roma" published in Naples in 1838.[7,8,13,22]

Throughout the history, numerous synonyms were used to describe malaria in the affected regions: mal'aria, ague, paludisme, Wechselfieber, Dardag Kolle, triasuchka, likhoradka, the fever, febris ardens, accessia, paludal fever, fieve aigue, marsh fever, seasonal fevers, fever of summer/fall (estivoautumnal fever), autumnal fever, intermittent fever, periodical fever, the quakes, the Bailiff of the Marshes, Lord John's fever and Old Johnny Axey.[1,10,23,24]

Malaria, Armies and Warriors

Pontine Marsh was the main reservoir of infection from central Italy, and it was the subject of debate for historical personalities such as Julius Caesar (100–44 BC) and Napoleon (1769–1821). The first, once affected by quartan fevers, planned to drain the marsh and transform it in fertile agricultural land; the latter was very unpleased to hear that such an unhealthy swamp laid across the French Empire.[7]

Historians pointed out that malaria was the single major disease in Rome, which occurred as a result of the favorable ecologic conditions. Titus Livius (59 BC–17 AD), a Roman chronicler, known as Livy in English literature, mentioned the devastating effects of the disease on the Gallic military troops that attacked Rome. This may be the earliest attestation of malaria destroying foreign armies during a siege against Rome. Numerous and similar events followed that episode.[7]

A historical document (234 BC) revealed that Roman troops were decimated by the disease in Sardinia 4 years after the Roman Empire conquered the island. According to Strabo (63/64 BC–c 24 AD), a Greek historian, geographer and philosopher, the island that was an important source of grain for Rome, was unhealthy in summer. Consequently, Roman ships carried not only grain from Sardinia but also mosquitoes and people infected with malaria to the capital city.[7]

The army of Septimius Severus (145/146–211), a Roman general, was affected by the disease of the marshes in 208 AD in Scotland. A lost Roman inscription from Habitancum Roman fort, also known as Risingham, was supposed to be dedicated to the goddess of tertian fever. It has been suggested that *P vivax* was the source of infection. The remedy used in alleviation of malarial fevers was opium obtained from the opium poppy, which was cultivated on large scale in Eastern England.[7]

Alaric (c 370–410), the king of Visigoths, died from a disease contracted during an offensive against Rome, and Attila (406–453), the Emperor of the Huns, canceled his march on Rome in 452 AD probably motivated by the threat of pestilence.[7,10]

Otto von Freising (c 1114–1158), a German bishop and chronicler, described the decimation of the army of Frederick Barbarossa (1122–1190), king of Germany, by malaria in the year of 1155: "For the unhealthy climate and the heat at that time, especially around the city, had more power to hurt our men than the weapons of the Romans . . . all the air in the vicinity became dense with misty vapours arising from the neighboring swamps and caverns and the ruined places around the city, air that was pestilential and lethal for mortals to breathe. The citizens in the city, accustomed to take refuge in the mountains at that time of the year, and the soldiers in the camp, who were not accustomed to such bad air, were both afflicted with this disease . . . . As innumerable men developed very severe illnesses as a result of this corruption of the air . . . there were hardly any men left who were not debilitated by the seething heat and the bad air, and as many soldiers had also been injured."[7,25]

During the American War of Independence (1775–1783), malaria plagued both British and American troops. The siege of Yorktown (1781) was providential for the Americans despite the fact that their soldiers suffered by severe fevers. The disease was