Akhawaynī and the First Fever Curve

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By the time of Hippocrates the typical paroxysmal fever patterns of tertian (every 48 hours) and quartan (every 72 hours) fevers caused by malaria were known. Through the ensuing centuries, ancient Greek, Roman, and Persian physicians made additional contributions to the understanding of fevers. By the end of that era, there was a working definition of what constitutes a fever, the distinction between fever as a symptom and fever as a disease, an elaborate classification scheme for multiple types of fever, hypotheses as to the causes of fever, and methods for diagnosing and treating fevers. Based on the definition of fever at that time, the 10th century CE Persian physician Akhawaynī created fever curves hundreds of years before they were routinely used in the clinical setting. In Ḥidāyat al-Muta'allimin fī al-Tībb, Akhawaynī describes a system for fever curves and draws fever curves for tertian and quartan Fevers, as well as the double tertian, double quartan, and triple quartan fevers. In this work we examine the history of fevers in the ancient world and the first description of the fever curve.

By the mid-19th century, advances in thermometry and medicine enabled Wunderlich to produce his seminal 1868 work on clinical thermometry [1]. His work was based on approximately 1 million temperature measurements obtained in 25,000 patients during a 16-year period [2]. Wunderlich made use of graphs that plot temperature over time in normal and disease states (Figure 1), heralding the concept of “fever curves” that were to become one of the cornerstones of infectious diseases teaching and diagnoses for the next century. Although the understanding of fever has changed over the past millennia, the earliest use of fever curves dates to the 10th century Persian physician Akhawaynī. In this article, we examine the Hippocratic-Galenic concept of fever among Greek, Roman, and Persian physicians and describe the earliest known fever curve (see Supplementary Materials for the methods).

THE CONCEPT OF FEVER IN GREEK AND ROMAN TIMES

General Remarks and Etymology of Fever

The importance of febrile disorders as a cause of mortality was well known to the ancients. Thus, it is not surprising that the Romans envisioned a goddess of fever, Febris, who had the power to protect them from fever. Pliny the Elder (first century CE) states that “diseases and plagues are defined, in consequence of our anxious wish to propitiate them. It was from this cause that a temple was dedicated to Fever [Febris], at the public expense, on the Palatine Hill…” [3].

The Greek word for fever, pyrexia, derives from the word for fire, and the corresponding verb means “I’m on fire” [4]. In the lay literature, references to fevers are frequent. Aulus Gellius (second century CE), in describing his own illness, states, “I was confined to my bed by an attack of diarrhoea, accompanied by a high fever. When the philosopher Calvisius Taurus, and some others who were disciples of his, had come there from Athens to visit me, the physician who had been found there and who was sitting by me at the time, began to tell Taurus what discomfort I suffered and with what variations and intervals the fever came and went” [5]. Here we see that fever was considered an important part of the diagnosis and treatment of disorders, and particular attention was paid to its “variations and intervals.”

The Definition of Fever

Fever was (and is) readily apparent to both physician and patient. Early Greek texts did not distinguish between fever as a sign and fever as a symptom. Likewise, early on, there was an overlap between the sign or symptom of fever and Fever the disease, and scant attention was paid to the actual definition. Despite this, the many references to fever leave little doubt that the word was used to indicate body temperature higher than normal.
By the time of Galen (second century CE), it was thought of as such [6]. Galen regards fever as a “primary dyscrasia due to an excess of heat” [7]. Likewise, Palladius (sixth or seventh century CE) describes fever as “a preternatural heat, which begins in the heart, and is diffused by the arteries over the whole body, sensibly injuring the actions of the body” [8].

For physicians of that era, fever was conceptualized more in qualitative than quantitative terms. For example, Hippocrates (fifth century BCE) states that “Strong and continued headaches with fever, if any of the deadly symptoms be joined to them, are very fatal” and, “Those die whom the fever does not leave ...” [9]. In only a few instances is there use of words such as “strong” when describing fever, or “mild” when describing a resolving fever after treatment [8]. Physicians following Hippocrates likewise thought of fever mostly in qualitative terms. For example, Celsius (first century CE) cautions that “A woman after childbirth is in danger of death, if also oppressed by violent and persistent pain in the head along with fever” [10].

Herophilus (335–280 BCE) was the first to relate a change in the pulse rate in relation to fever. According to Marcellenius (third century CE), Herophilus built a water clock (adjusted to patient age) that measured the change in pulse with fever [11]. Although it is not clear how this apparatus worked, it represents the earliest example of an attempt to quantify fever. Unfortunately, none of Herophilus’ works have survived, and no other ancient writers substantially commented on his work.

Causes of Fever
Greek medicine subscribed to the humoral theory, which explained health and disease on the basis of interactions between 4 humors (blood, black bile, yellow bile, and phlegm). The specific sources of individual fevers remained elusive and controversial throughout the centuries, with different theories put forward based on the humoral theory. According to Hippocrates, “Fever comes about from the following: whenever bile or phlegm is heated, all the rest of the body is heated along with them, and this is called fever” [12].

Diocles (fourth century BCE) implied that fever was a symptom caused by a wound, tumor, or something hidden [13]. Erasistratus (304–250 BCE) espoused the surprisingly modern concept that fever was invariably caused by inflammation [14]. Erasistratus refuted overheating as a cause of fever, pointing out that only 4 of 1000 people attending a theater on a hot day are discomforted, and only 1 develops a fever [15]. Herophilus thought that fever preceded swelling and could occur without inflammation [16].

Later, Galen opposed Erasistratus’ claims, maintaining that fever occurred without inflammation. Although Galen thought that diseases causing local inflammation (in the lungs, for example) could cause the symptom of fever, he believed the disease Fever was not associated with inflammation [17]. Although this was implied in the older literature, Galen draws a clear distinction, thus separating the symptom of fever from the disease. In addition, Galen advanced the idea that many types of fevers arise from putrification of the humors.
Varieties of Fever
As noted above, the role of fever in disease was thought to be more complex than simply that of a sign or a symptom. By the time of Hippocrates, the typical paroxysmal patterns of tertian (every 48 hours), and quartan (every 72 hours) fevers caused by malaria were known [8]. Importantly, these occurred in malaria-endemic areas and had the characteristic paroxysms of febrile episodes corresponding to the release of merozoites and the symptom-free interlude (depending on the malaria species) between episodes. The description of these fevers and their treatments can be traced through other Greek (Archigenes, Palladius) and Roman (Celsius, Aetius, Galen) authors.

Galen broadened the classifications of fever. He believed that there were 3 main types of fevers: ephemeral, hectic, and those caused by corruption of humors [18]. Galen thought that ephemeral fevers lasted less than 1 day and could be brought on by many conditions (this was one reason he opposed Erasistratus). This category included overheating (modern day hyperthermia) as well as other causes of fever, such as fatigue and anger. Of fevers caused by corruption of humors, Galen believed that the intermittent fevers (quartan, tertian, quotidian, semitermian, and irregular) were caused by putrification of humors. Thus, quotidian Fever was linked to phlegm, tertian Fever to yellow bile, and quartan to black bile [19]. In addition to the above-mentioned fevers, there were many others, such as the continuous, ardent (or causus), hepialus, and leipryia fevers.

During the Roman era, there also developed the concept of more complex fevers. Celsius mentions instances in which a quartan Fever can change in to a quotidian Fever, worsening the patient’s prognosis [10]. Palladius and Galen thought that the semitermian Fever mentioned by the Greeks was actually a combination of quartan and tertian fevers [8]. Elsewhere, Celsius mentions a double quartan Fever, and Galen a double tertian [20]. These were overlapping fevers with 1 paroxysm per day. Thus, the double tertian would have a fever every day, and the double quartan a fever 2 of 3 days [20]. However, it should be noted that some fevers called “double” also meant that 2 paroxysms could occur in 1 day, with the regular fever-free day between paroxysms (a usage popular in the 18th and 19th centuries). This distinction will become important when considering Akhawayni’s fever curve.

CONCEPT OF FEVER AMONG PERSIAN PHYSICIANS

Historical Background
By the late Roman period, there was a definition for fever, hypothesis as to its cause, and a classification system. With the decline and fall of the Roman Empire, the scientific heritage of ancient Greece and Rome spread eastward with the translation of Greek and Roman texts into Syriac by Nestorian Christians. The contact between Nestorian Christians and Sassanid Persia began on the Eastern border of the Roman Empire (in cities such as Nisbis and Edessa) in the pre-Islamic era. Jun-disapur was the seat of some of this activity, and there are records of a major medical and philosophical conference held there in 610 ce [21]. After the rise of Islam and Arab conquest of Persia (651 ce), the new Arab ruling class encouraged renewed efforts to translate the ancient Greek and Roman texts into the Syriac language, as well as the new lingua franca, Arabic. Translations and new medicinal treatises were largely the work of non-Arab Muslims (Persians) and non-Muslims (Jews and Christians) [22], with the bulk of medical compendia being the work of the Persians (Tabari, Râzi [Rhazes], Majûsî [Haly Abbas], Ibn Sinâ [Avicenna], Akhawayni, and Jurjâni).

Concepts of Fever During this Era
During this period, most of the concepts espoused by Galen continued, with only a few exceptions. As most of the physicians of this era had similar ideas, we will quote Avicenna, whose work on fevers was detailed and eloquent (spanning 84 chapters and 200 pages) [23]. Avicenna defines fever as follows: “Fever is a foreign heat that starts in the heart and, with the flow of blood, spreads through the arteries and veins, and in the end the entire body becomes so hot that it can not perform its normal functions.”

Avicenna divided fever into 4 stages (the beginning, increasing fever, plateau, and fall), much as thermophysiologists do to this day. He describes the second stage as follows: “the second stage that we mentioned can be divided into two parts: the first part, or it is better to say the first part of the second stage begins when the patient’s pulse becomes faster, bigger, and more prominent, and the heat of the fever distributes evenly over the body. The second part of the second stage starts when the body heat, which is evenly distributed over the body, starts to increase moment by moment.”

Concerning the cause of fevers, Avicenna disagreed with Galen on the concept of putrification, instead advancing the Hippocratic idea of overabundance of humors [18]. Regarding inflammation and fever, Avicenna took a rational stance, stating, “Inflammation alone does not cause fever, it is the infection arising from the inflammation that leads to fever.” He goes on to say that it is infection (whether from inflammation or not) that causes fever. This debate would continue well into the 1800s [24].

One change from the past was an increase in the number of fevers described. Some of this was due to the description of new diseases (such as smallpox by Rhazes), as well as the placement of new fevers within Galen’s classification.
Physicians of this period were particularly interested in compound fevers, and references to this can be found from Tabari to Jurjānī, spanning almost 300 years.

Akhawaynī
On the life of Abū Bakr Rabīʿ ibn Ahmad Akhawaynī Bukhārī (Akhawaynī) not much is known other than what is found in Ḥidāyat al-Mutaʿallīmin fī al-Ṭībb [The Students’ Handbook of Medicine] [25, 26]. Akhawaynī was born in Bukhara (present-day Uzbekistan) during the 10th century CE and possibly spent some of his life in Tus (present-day Iran). This places him in the golden era of the Samanid Dynasty, which was among the first indigenous Persian political entities to arise after the defeat and dissolution of the Persian Empire at the hands of Arab Muslims. Thus, he was a contemporary of the great physicians Rhazes and Avicenna, as well as the poets Rūdaki and Ferdowsī. Akhawaynī, a famous physician in his day, was himself the student of a student of Rhazes. Because of Akhawaynī’s success in treating patients with psychiatric illnesses he was dubbed the “Physician to the Insane.”

Akhawaynī’s Ḥidāyat, the only of 3 known works to survive, was the first medical compendia to be written in Persian (rather than Arabic). Currently, only 3 copies are known to exist [26]. Akhawaynī’s text was written as a medical handbook for his son, and this is relevant in terms of interpreting his fever curve. In the introduction he states, “Presently, you who are my son, have asked me to write a medical book that is both short and simple to understand, to have something to remember me by and which will be beneficial to others. I have consented …”

Akhawaynī’s Treatise on Fever
Akhawaynī summarizes fevers in the following way: “Fever in Persian is derived from the words ‘burning’ and ‘fire,’ for the body becomes so hot that it can not perform its normal functions, and this is called fever. And the cause of this heating of the body is the heart, it becomes so heated that it heats the arteries along with the rest of the body such that it can not perform its normal functions … and there are two types of fever: one is not an illness by itself; rather, it is a symptom of another disease, and unless this disease is cured, the fever will not leave. And this fever is called an inflammatory fever and it is characterized by pneumonia and nephritis and cystitis, and others illnesses depending on its essence. And this [the second] Fever that is a disease in and of itself has three parts or kinds …”

Akhawaynī’s Fever Curve
Akhawaynī describes each of the fevers and their treatments in turn, including combination fevers. He states that up to 4 individual fevers can make up a combination. Fevers could be of at least 4 different subtypes, among which were 2 varieties (continuous or intermittent). Thus, in this scheme there were at least 8⁴ or 4096 different fevers. After describing the types of possible fevers in detail, he states, “And I will do a trick so that it will become apparent to you. I will draw lines corresponding to the number of days, and I will connect the tops together such as tertian Fever or quartan Fever so it will be apparent what I am saying. Now, for example, I will draw the lines like tertian Fever: 3[3]. Here, one day the fever comes and then the fever does not come, and those days that the fever comes I will connect the tops of the line so that you understand; again, if it is a double tertian all of the tops will be connected, and know that it has another cycle two days from now, and those two other days a turn, and the lines are as such: 3333. One turn is marked by aleph [the letter A, written as a straight line in Persian] and the other a period, now from the combination of these two tertians, a quotidian Fever appears. Now from the combination of three quarts a quotidian Fever comes, we measure it as such and I will draw the lines so you will understand: 3333. This is one quartan, and such we measure it that it comes one day and two days not, as you can tell by the tops of the lines. Now if two quarts come, then the tops of the lines are different, as such: 333333. Now it may happen that from two quarts one cycle combines to become like a quotidian and a tertian, and three quarts combine to become quotidian like this: 33333. And there is much to discuss about this subject but this much is sufficient.”

Akhawaynī set out to write a concise medical manual for teaching purposes, and the fever curve should be viewed in this context. Whereas the ancient Greeks, Romans, and Persians all recognized intermittent fevers caused by the various species of malaria, Akhawaynī was the first to document fever patterns with a fever curve. Quotidian, tertian, or quartan fevers were simple to understand and teach, as has been done through the millennia. However, Galen’s classification led to a number of increased combination fevers, so that even in Akhawaynī’s condensed manual, he describes a system with thousands of possible combinations. Akhawaynī thus describes a “trick” or a system, which plotted days versus the presence or absence of paroxysmal fevers. Although initially he demonstrated its use on simple fevers (tertian and quartan), it is clear that he intended to use his curves to characterize combination fevers to help students understand and diagnose these. His use of this system mirrors that by Wunderlich and others, who used the fever curve as a teaching tool. In modern times, an additional use of the fever curve was for in-hospital diagnoses. Likely, Akhawaynī’s fever curve was never used in this manner. Currently, the characteristic patterns of tertian and quartan fever curves are among the few that remain clinically relevant (along with Pel-Elbstein and saddleback fever curves) [27].

Although Akhawaynī’s Ḥidāyat continued to be used in Persia, it was soon superseded by more comprehensive works,
such as Avicenna’s *Canon* and Jurjāni’s *Zakhira-yi Khārazmshāhi* [3, 28]. Neither of these later works acknowledged Akhawaynī’s treatise on fever. Avicenna’s *Canon* would gain international recognition, being translated from Arabic into Latin and used in medical school across Europe as late as the 19th century. Meanwhile, Jurjāni’s medical compendia (written in Persian) became the standard reference for Persian physicians for many centuries and, like Akhawaynī’s work, was never translated into any European language. Much like the work of Herophilus, Akhawaynī’s fever curve, along with his other works, was eventually forgotten until these works were rediscovered during the 20th century.

**CONCLUSION**

Through the centuries, the ancient Greeks, Romans, and Persians made contributions to the understanding of fevers. By the end of that era, there was a working definition, an elaborate classification scheme, hypotheses for the cause, and methods for the diagnosis and treatment of fevers. An early attempt at quantifying fever based on change in pulse was made by Herophilus, whereas Akhawaynī created fever curves hundreds of years before they would routinely be used. In *Hidāyat al-Muta’allimin fi al-Tībb*, Akhawaynī describes a system for fever curves and draws fever curves for tertian and quartan fevers, as well as double tertian, double quartan, and triple quartan fevers.

**Supplementary Data**

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org) Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Note**

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