The Plague of Athens: Epidemiology and Paleopathology

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OUTLINE

ABSTRACT

In 430 BC, a plague struck the city of Athens, which was then under siege by Sparta during the Peloponnesian War (431-404 BC). In the next 3 years, most of the population was infected, and perhaps as many as 75,000 to 100,000 people, 25% of the city's population, died. The Athenian general and historian Thucydides left an eye-witness account of this plague and a detailed description to allow future generations to identify the disease should it break out again. Because of the importance of Thucydides and Athens in Western history and culture, the Plague of Athens has taken a prominent position in the history of the West for the past 2500 years.

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Despite Thucydides' careful description, in the past 100 years, scholars and physicians have disagreed about the identification of the disease. Based on clinical symptoms, 2 diagnoses have dominated the modern literature on the Athenian plague: smallpox and typhus. New methodologies, including forensic anthropology, demography, epidemiology, and paleopathogy, including DNA analysis, have shed new light on the problem. Mathematical modeling has allowed the examination of the infection and attack rates and the determination of how long it takes a disease to spread in a city and how long it remains endemic. The highly contagious epidemic exhibited a pustular rash, high fever, and diarrhea. Originating in Ethiopia, it spread throughout the Mediterranean. It spared no segment of the population, including the statesman Pericles. The epidemic broke in early May 430 BC, with another wave in the summer of 428 BC and in the winter of 427-426 BC, and lasted 4.5 to 5 years. Thucydides portrays a virgin soil epidemic with a high attack rate and an unvarying course in persons of different ages, sexes, and nationalities.

The epidemiological analysis excludes common source diseases and most respiratory diseases. The plague can be limited to either a reservoir diseases (zoonotic or vector-borne) or one of the respiratory diseases associated with an unusual means of persistence, either environmental/fomite persistence or adaptation to indolent transmission among dispersed rural populations. The first category includes typhus, arboviral diseases, and plague, and the second category includes smallpox. Both measles and explosive streptococcal disease appear to be much less likely candidates.

In 2001, a mass grave was discovered that belonged to the plague years. Ancient microbial typhoid (*Salmonella enterica* serovar Typhi) DNA was extracted from 3 skeletons. Because typhoid was endemic in the Greek world, it is not the likely cause of this sudden epidemic. *Mt Sinai J Med 76:456–467, 2009.* © 2009 *Mount Sinai School of Medicine*

Health and disease have played an important part in human religion and history. Although our conquest of disease has extended the modern lifespan to 78 years in the Western world versus 25 to 35 years in the ancient world, we are still frightened by and concerned with plagues. In the modern world, emerging strains of viruses and bacteria, such as influenza and acquired immune deficiency syndrome, cause much anxiety and millions of deaths on a yearly basis. These continuing tragedies are reminiscent of past centuries in which a husband and wife endured the deaths of half their children from infectious disease.[1] In addition to the normal patterns of disease in childhood, epidemics would often strike out of nowhere and carry off large percentages of the population. For example, a plague that occurred in the reign of Marcus Aurelius (AD 161–180), which was described extensively by Galen, killed a tenth of the population of the Roman Empire.[2,3] The bubonic plague struck in Byzantium in the 6th century and killed a substantial part of the city's population. This plague, named the Plague of Justinian after the sitting emperor, was extensively described in a contemporary account, modeled on the work of Thucydides, by the historian Procopius in *History of the Wars* (II 22–33). The worst plague in human history was the Black Death, which wiped out nearly half the population of Western Europe in the 14th century.[4,5] A contemporary literary account of the effects on society survives in Boccaccio's *Decameron*. Another famous literary account of a plague occurs in Daniel Defoe's *Journal of the Plague Year*, a semifictional account of the bubonic plague in London in the 17th century (1665).

Over the past 2000 years, we have learned much about infectious diseases, the existence of microorganisms, their causes, their symptoms, and how they are spread. Since its beginning, Western medicine has concentrated on the clinical aspects of disease. In the 19th century, epidemiology began to emerge as a scientific discipline, although its roots go all the way back to Hippocrates in the 5th century BC.[6–8] This new discipline has proved invaluable in learning the causes of diseases, thereby aiding modern medicine in formulating cures.

Despite some overlap, clinical medicine and epidemiology are distinct. Clinical medicine is the care and study of sick individuals, the examination of signs and symptoms present in sick persons, and attempts to treat the patient. Epidemiology has often been called the study of the distribution and determinants of disease in human populations; it seeks to determine who is infected, when, where, and why. It questions whether a disease strikes the young, the old, the sexually active, or those who smoke. Epidemiology, unlike clinical medicine, studies groups of people, not individuals. It also studies the well because those who do not contract a disease can often provide as many clues as those who do. A more modern definition of epidemiology is the study of the distribution and determinants of health events, including diseases, in human populations.

Ultimately, of course, the true test of public health, of which epidemiology is a component, is whether it can help us prevent disease. Arcane knowledge and intellectual formulations are of little use when the litmus test of lives saved and health improved stands visibly before us. Epidemiology has been less than successful in some of its applications. There is and perhaps always has been a tendency for epidemiology to become intellectualized, in part because of its complex and philosophical underpinnings.

However, consideration of the epidemiological approach with respect to the Athenian epidemic will have, I hope, some modest by-products. Among these are lessons in the approach to public health problem solving that can be applied to many new diseases that exist today and will be encountered in the future. What is needed is not only more technical knowledge about agents, hosts, and environments but also perspectives on and formulae for understanding the complex ways in which they interact, structures for assembling and synthesizing disparate facts, and approaches for deriving conclusions. Although this will not, in and of itself, create a healthier world, and the derived conclusions may not motivate human beings to change the behavioral risk components

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over which they theoretically have some control, it may at least assist us in creating a framework and a database structure from which to proceed in making public health decisions.

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sociological and demographic changes and to better understand how diseases work over centuries.[9]

THE PLAGUE OF ATHENS: THUCYDIDES' ACCOUNT

One disease that has particularly attracted the attention of both laymen and scholars alike is the Plague of Athens. Although this was not the most important plague in history in terms of mortality and political and socioeconomic consequences, the place of the 5th century BC Athenian historian, Thucydides, as one of the fathers of history has made his description one of the best known passages in Western literature and the history of medicine.

Thucydides presents a detailed description of the symptoms of the Plague of Athens that is marked by careful observation and is woven into a terse narrative about the devastation of war and disease. In his *History of the Peloponnesian War* (2.47–55), Thucydides[10] describes how the disease was accompanied by a pustular rash, high fever, and diarrhea and how it usually resulted in the death of the victim.

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He relates that it originated in Ethiopia and spread into Egypt and Libya and through the Near East before arriving at the Piraeus, the port of Athens. From the Piraeus, the epidemic moved rapidly into the city itself. Thucydides indicates that it was highly contagious and infected anyone who cared for the sick. He himself suffered from the plague but was one of the lucky ones who survived. Others were not so fortunate. Entire families were wiped out, and the dead became so numerous that corpses could not be buried and were left where they had died.

Thucydides (2.48.3) states that he will set down the nature of the disease and explain the symptoms by which it may be recognized if it should ever break out again. He was influenced by Hippocrates,[11,12] who lived at the same time, both in his description of the plague and also in his application of Hippocratic doctrine to his writing of history. In a sense, his account of the disease parallels the overall themes

of his work: history as an example and a force that repeats and the decay of Athens by both war and disease.

The political ramifications of the Plague of Athens were enormous because it struck Athens shortly after the Peloponnesian War (431-404 BC) between Athens and Sparta had begun (430 BC). Although Athens was devastated by the outbreak, Sparta was relatively unscathed because the epidemic did not penetrate the Spartan homeland in the Peloponnesus. The Plague of Athens carried off perhaps 75,000 to 100,000 people, about 25% of the population of Athens during the first few years of the Peloponnesian War. The Athenian leader Pericles perished of the disease in 429 BC. The plague was a major reason for the defeat of Athens in the Peloponnesian War. It was economically and socially devastating to Athens, both at the time and in the subsequent centuries. The combination of disease and war depopulated Athens and changed Greek history, which might have been very different had Athens won the war.

THE PLAGUE OF ATHENS: ANALYSES IN THE 20TH CENTURY

Numerous essays on the Plague of Athens appeared in the 20th century, attempting to identify the Athenian pestilence with 1 or more diseases. Because Thucydides provided the symptoms, the resultant studies were symptomatologies, which were correlated with a disease that presumably matched the ancient description. Two diagnoses became prominent in the modern literature on the Athenian plague. The first diagnosis was smallpox, which seemed to incorporate almost all of the Thucydidean details.[13]

The second most common retrospective diagnosis has been endemic typhus, as represented by Hans Zinsser,[14] who was one of the pioneers in the study of typhus and developed the first typhus vaccine in 1934. Two other frequently cited studies followed Zinsser's diagnosis, those of MacArthur[15] and Scarborough.[16] Scarborough especially called attention to Thucydides' description as accurate in its own context but incapable of accounting for any evolutionary shifts in the causative organisms. He argued that any modern diagnosis is flawed because of possible mutations over time. Although Scarborough might be correct if the disease described by Thucydides was caused by a microorganism that was prone to mutation (as typhus is), other microorganisms, such as smallpox, are very stable over time.

In 1994, Thomas E. Morgan[17] analyzed Thucydides' medical knowledge, or the lack of it. A

physician-classicist, Morgan argued that Thucydides desired to contrast the tragedy of war and the pathos of the disease with the lofty ideals presented by Pericles in the funeral oration. Thus, in his opinion, the descriptions of the plague are quite imprecise not only because the Hippocratic or other terminologies varied from those of modern epidemiology but also, more importantly, because Thucydides employed dramatic license in his account of the plague. The weakness in Morgan's argument is that his thesis is somewhat inconsistent with Thucydides' statement that he describes the symptoms so that the disease can be identified if it breaks out again.

Other possible candidates for the identification of the Plague of Athens have ranged from measles, typhoid fever, bubonic plague, anthrax, and ergotism to toxic shock syndrome with *Staphylococcus*, scarlet fever, Rift Valley fever, and arboviruses, but none of these possibilities has gained many adherents among students of ancient epidemics.[18,19] A number of these suggestions are diseases that may not have existed in the ancient world but appeared only in the 20th century. Lassa fever (1965) and Ebola fever (1976) are viral hemorrhagic fevers caused by RNA viruses. Rift Valley fever (1915) is a viral zoonosis whose vector is the bite of infected mosquitoes, typically the *Aedes* or *Culex* genera. Tularemia (1911) is bacterial with ticks as a vector. Each of these diseases has problems either in its symptomatology or in its epidemiology, as we will see later. For a full discussion of the various suggestions, see Morens and Littman,[19] Poole and Holladay,[20] Cunha,[21] Sallares,[22] and Bruce-Chwatt and de Zulueta.[24]

Beginning in the second half of the 20th century, new methodologies were developed that allowed fresh examinations of diseases, plagues, and pandemics in the ancient world. These methodologies were based on new academic disciplines, including forensic anthropology, demography, and epidemiology. Recent studies of the Plague of Athens reflect these developments in methodology. Although the emergence of modern medicine in the 19th century and the beginnings of the discipline of epidemiology led to a renewed interest in the Plague of Athens, it was not until 1992 that the first epidemiological approach to the disease was brought to bear by Dr. David Morens, now at the National Institute of Health, and myself[19,25] using such devices as mathematical modeling to look at various possibilities. Mathematical modeling allowed us to examine infection and attack rates based on the various candidates and to determine how long it takes a particular disease to spread in a city and how long it would be able to remain endemic. Several diseases, such as measles, had to be eliminated as possibilities because the population of Athens was too small to sustain an epidemic of them for more than a few months. Thus, the best possibilities were narrowed to typhus, typhus-like diseases, and smallpox.

EPIDEMIOLOGICAL INTERPRETATION

Person

A number of prominent people contracted the Plague of Athens. In the first outbreak, the historian Thucydides, who wrote a history of this period entitled *History of the Peloponnesian War*, contracted the disease. He survived and lived to write an account of it. The great Athenian statesman Pericles was less fortunate. He died in the first outbreak at the age of approximately 65, as did his sister, who was around 60, and 2 of his children, who were around 30 (Xanthippus) and 25 (Paralos; see Plutarch, *Life of Pericles*, 36.3-4).[23] The father of medicine, Hippocrates, according to legend, tried to combat the plague but in the end fled Athens so as not to contract it.[26] Thucydides (2:51) states that the epidemic "carried away all alike." Apparently, it spared no segment of the population. Thucydides relates that physicians had increased risk. The city of Athens was under siege, and the surrounding countryside was either burned or seized by the Spartans. Thucydides does not comment on the diet, although even with an unblockaded port, probably there were shortages of fruits and vegetables, with a possible concomitant deficiency of ascorbic acid (vitamin C). Vitamin A would have been obtained through fish and fish products.

Place

Thucydides (2.48.1) relates that the plague originated in Ethiopia and spread to Egypt and Libya and thence to the territory of the king of Persia (all of the Middle East and as far east as the Indus river). From there, it reached Athens, which was the hardest hit. The Roman historian Livy (*History of Rome*, 4.20–21, 4.25.3-4, and 4.30.8-10), writing many centuries later, reported that epidemics occurred in Rome in 433 and 438 BC. These outbreaks may well have been part of the same epidemic. The disease struck first at Athens' port, the Piraeus, one of the major ports of the Mediterranean. Premodern epidemics and pandemics of many diseases (cholera, dengue, plague, and smallpox) typically were spread by ships. Around July 430 BC, at the height of the epidemic, the Athenian general Hagnon took a naval expedition and sailed northward to Thrace with 4000 troops. The expedition was under sail for about 5 days, and by the time it had reached the city of Potidea, the

epidemic had struck. It killed about 25% of the army and infected the Athenian besiegers of Potidea. The city of Potidea itself, sealed shut by the invaders, was not afflicted by the epidemic.

Thucydides describes the directionality of spread when the disease first attacked Athens. It began in the port and spread inland into the area between the port and the city, which was encompassed by a defensive wall, and into the city itself. Thucydides is silent on the incidence rate (ie, number of new cases per population at risk per time), the high case fatality rate (proportion of those who died), and the rapidity of epidemic progression. He does say that the spread among the refugees in the city was caused by "poor ventilation," which is consistent with either airborne spread, poor hygiene and sanitation, crowding, or a combination of these. The water supply was probably uncontaminated. Potable water in the Piraeus came from cisterns and in Athens came from wells throughout the city. The city in addition had river-fed aqueducts from the Ilissus river and several springs. Thucydides mentions that despite frequent contact with the Spartan army, the disease did not spread much beyond the city. Thucydides (2.54.5) says that it did not enter the Peloponnesus to any extent and that its "full force was felt at Athens, and, after Athens, in the most densely populated of the other places." Perhaps the fact that the Peloponnesus was rather sparsely settled contributed to a lower epidemic rate.

Time

The epidemic broke out soon after the Spartans besieged Athens in early May 430 BC. There was another wave in the summer of 428 BC and in the winter of 427-426 BC. Apparently, the epidemic lasted around 4.5 to 5 years. The population of Athens,[27,28] with refugees from the invading Spartan army, amounted to around 300,00 to 400,000. According to Thucydides (3.87.3), the plague was uninterrupted, but with exposing outbreaks:

> The plague broke out among the Athenians for a second time. In fact, it had never entirely stopped . . . This second outbreak lasted for no less than a year and the first outbreak for two years.

Other Epidemiological Information

Thucydides portrays a virgin soil epidemic, which Thucydides confirms with his own words. It had a high attack rate and an unvarying course in persons of different ages, sexes, and nationalities. We cannot determine the incubation per- iod, attack rate, or case fatality rate. From July to August 430 BC,

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26% of an expedition of 4000 hoplites were killed in 40 days. Thucydides (3.87.3) records a final death toll of 4400 hoplites (34%) and 300 cavalry deaths (30%). This suggests that the first wave was the worst. Survivors did not contract the disease a second time. This implies an attack rate of more than 25 and a case fatality rate of greater than 25%. Thucydides (2.50.1-2) also suggests ambiguously that there might have been a zoonotic component:

> Though there were many dead bodies lying around unburied, the birds and animals that eat human flesh either did not come near them or, if they did taste the flesh, died of it afterwards. Evidence for this may be found in the fact that there was a complete disappearance of all birds of prey: they were not to be seen either round the bodies or anywhere else. But dogs, being domestic animals, provided the best opportunity of observing this effect of the plague.

Thucydides did not claim that anyone saw an infected dog or bird, but some scholars have used this to suggest epizootic involvement. However, Thucydides' description is so precise that if he saw an infected animal, he surely would have indicated it.

Thucydides' Text

Although Thucydides proposed to make a description that would allow others to identify the disease if it should break out again, he was not successful, although perhaps he was by ancient standards[17,29] Thucydides jumbled physical signs and symptoms, epidemiological observations, and historical facts. He was not a physician, and a technical medical vocabulary probably did not exist in the 5th century BC when he was writing.[30] He thus applied common words to signs and symptoms with the result that it is often difficult to figure out precisely what he meant. For example, Thucydides used the term *phlyktainai*, a word to describe blisters and spots on a loaf of bread. Scholars have translated this work with various terms, including blains, blebs, blisters, bullae, eruptions pimples, pustules, vesicles, and whelks. Hippocrates used the word to describe burns and contact dermatitis. Thus, questions of how to interpret the word have led scholars to develop theories suggesting smallpox, typhus, and syphilis. Trying to

reach a definitive conclusion from the clinical description alone has reached a limit of what it is able to achieve. Only when the clinical is melded with the epidemiological can more definitive conclusions be reached. Although the epidemiological approach cannot be definitive, it can clearly eliminate whole categories of disease and some specific diseases, such as measles.

Common Source Acquisition

Common source acquisition is not likely on the basis of Thucydides' description. Although ergotism has been suggested, it is difficult to see how all grain sources could have been contaminated.

Waterborne disease is also unlikely because there was no centralized water system that could have become contaminated. Also, the disease spread from the Piraeus uphill to Athens. There is no way for hundreds of Athenian wells to be simultaneously cross-contaminated. Also, common source acquisition of a single epidemic disease in 430-425 BC can be ruled out, including such diseases as cholera, dysentery, ergotism, shigellosis, scurvy, and typhoid fever. However, recent DNA investigations of skeletal remains from the plague years have suggested the presence of typhoid. We will return to a discussion of these results later.

Person-to-Person Transmission

Of the 3 main categories of person-to-person transmission, enteric and inoculation transmission can be ruled out. Most consistent with the symptoms and description of the disease is aerosol/respiratory transmission, as suggested by the high attack rate and rapid spread. However, most respiratory diseases rapidly die out in crowded populations, although some, such as tuberculosis, can become endemic. Thucydides records that the epidemic lasted 2 years or more. In addition, the besieging Spartan army was not infected to any degree.

Mathematical Modeling

Because epidemic diseases vary in incubation periods and in susceptible percentages of populations, the rate of disease spread varies. For example, if a disease takes 2 days to become contagious and becomes capable of transmitting the disease to a third party, it might spread faster than an infectious disease that takes 10 days to become contagious. Using mathematical models based on these factors, we can predict for any contagious disease mathematical patterns of occurrence over specified time periods for various

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population sizes and degrees of crowding. We can then apply such theoretical patterns to the Athenian epidemic.

The equation used to generate the epidemic curves is as follows[31]:

$$C_{t+1} = S_t(2 - qC_t)$$

where C_t is the number of cases of the disease at time t (the beginning of the epidemic), C_{t+1} is the number of cases of the disease at time $t + 1$, t is the chosen time interval (here the serial generation time), S_t is the number of susceptible persons at time t, and $q = 1 - p$ is the probability of adequate contact (ie, adequate to cause infection) between any 2 individuals per time interval t.

For each disease, the following assumptions are made:

1. There is universal susceptibility at the outset with infection either killing or conferring permanent immunity.
2. The serial generation time is assumed to be 4.5 days for influenza, 12 days for smallpox, 14 days for measles, and 19 days for streptococcal infections such as scarlet fever.
3. The total population of Athens was at least 100,000, and most likely during the war years, the population climbed to 200,000 to 400,000 as refugees poured into the city.
4. Adequate contact numbers are based on conservative estimates of the frequency of contact under conditions of known severe crowding.

The area of the Piraeus, connected by walls to the city of Athens, was about 4 square miles; this means a population density of 25,000 to 50,000 per square mile. Thirty percent of the square miles of Athens proper, not including Attica, was probably unoccupied.[32] This reflects a typical settlement pattern of cities with crowded populations; people are crammed into houses, rooms, and public places, while at the same time there are large pockets of unoccupied spaces. There were probably about 10,000 dwellings, each occupied by 10 to 40 persons during the siege.[33] Although the main outbreak of

the plague may give some ambiguity about onset, we have a clearer case with the expedition of Hagnon. The expedition would not have set out from the Piraeus with infected people on board. Among the 4000 hoplites in the force and the 3000 hoplites left in Potidea, the epidemic curve from the index case to extinction was about 6 weeks. The results of applying the aforementioned formula can be seen in Figures 1 to 3.

Discussion

Epidemiological analysis is consistent with (1) an animal or insect reservoir or (2) respiratory transmission combined with a reservoir-like mechanism of persistence. This is consistent with the fact that the besieging army of Spartans was not infected.

Respiratory Transmission

Diseases transmitted only by a respiratory route would not have "over-wintered" and would have spread rapidly through the population and lasted over 2 years. Within a very short period, all the population would have been exposed. For example, in 1918, influenza spread through and died out in Newark, NJ (population of 435,000) in 12 weeks.

Measles could not have persisted for 2 or more years: 300,000 to 500,000 people are considered to be necessary to sustain measles transmission. Measles would have been extinguished in several months.

Smallpox remains a strong possibility. In the mathematical modeling (see Figures 1–3), a 12-day serial generation time is assumed as well as 2 to 20 adequate contacts and a minimal base population of 100,000 people per 4 square miles. Under this model, with 2 contacts, the epidemic would last 11 months. Smallpox outbreaks in virgin populations tend to be brief. For example, in Aztec Mexico in 1530, between 3.5 and 15 million out of a population of 25 to 30 million died within 6 months.[34] However, in the case of smallpox, unlike other respiratory diseases, viruses in dried smallpox secretions can survive for at least several months in clothes or bed linen.[35] There is even a case of smallpox being used for biological warfare against the Indians in the French and Indian War, when the commander of British forces gave the Indians blankets contaminated with smallpox.[36] It is possible in Athens that smallpox was carried back to the countryside and dispersed in an indolent transmission among the population of Attica in the remote areas in which the Spartan army was not present, although most of the population had come within the city walls.[37]

Reservoir Transmission

The epidemiology of the epidemic is consistent with reservoir transmission (insect or animal vector). Anthrax might be a possibility because by a combination of inhalation, inoculation, and ingestion, it could be consistent with the clinical picture described by Thucydides. However, no large-scale anthrax epidemics are known to have ever occurred. Also, there is no easily identified reservoir in ancient Athens. Although sheep and cattle are very susceptible to anthrax, these animals were sent out of Attica to Euboea. Dogs, rodents, and birds remained in the city, but these are generally resistant to anthrax, although vultures and flies can spread the disease after feasting on contaminated carcasses, as is the case with dogs. Infected birds could contaminate the water supply, but Thucydides mentions the absence of birds. Anthrax is difficult to reconcile with these conditions.

Other reservoir diseases of epidemic proportion include various insect-borne diseases and diseases spread by various zoonotic reservoir hosts, such as malaria, plague, typhus, and various arboviral diseases (eg, dengue, yellow fever, and Rift Valley fever). All except Rift Valley fever are linked to war, refugees, and overcrowding. Dengue and Rift Valley fever both have explosive behavior consistent with the Plague of Athens. However, the clinical symptoms of both dengue and Rift Valley fever seem to differ greatly from Thucydides' description, especially in the nature of the rash.

Malaria is unlikely as a cause, particularly because it was not an unknown disease.[38] Although the ancient world did not distinguish between typhus and typhoid, it is clear that it was prevalent in ancient Greece and Rome. Hippocrates in the 5th century BC describes at least 6 cases in *Epidemics* I and II.[39]

Of the reservoir diseases, typhus is the best fit. It is classically associated with war and crowding, and some symptoms described in Thucydides are suggestive, such as gangrene (if in fact Thucydides is describing gangrene) and blindness. Also, the disease is persistent in crowded populations for prolonged periods. The main argument against typhus is the presence of bullae in the Athenian epidemic. Although not regular, they are seen occasionally in typhus,[15] and their occurrence in a mild form of the disease, rickettsial pox, might suggest that an ancestral rickettsial agent could have caused the Plague of Athens.

In summary, the epidemiological argument excludes all common source diseases and most respiratory diseases. By a process of elimination, the Plague of Athens can be limited to either a
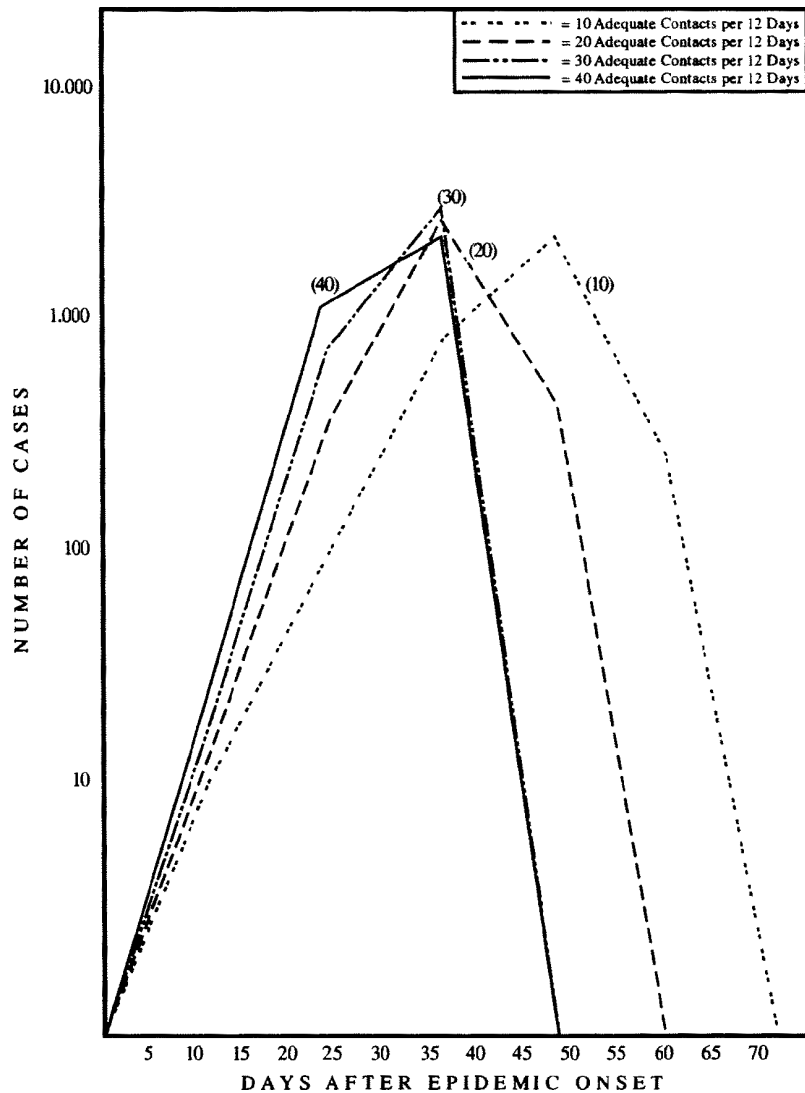
Fig 1. Theoretical epidemic curves of a transmissible respiratory disease with a 12-day serial generation time (eg, smallpox) in Hagnon's naval expedition to Potidea in 430 BC (a closed population of 4000 persons) according to the deterministic mathematical model of Maia. Four separate curves have been computed with adequate contact numbers of 10, 20, 30, and 40 per 12 days.

By a process of elimination, the Plague of Athens can be limited to either a reservoir diseases (zoonotic or vector-borne) or one of the respiratory diseases associated with an unusual means of persistence, either environmental/fomite persistence or adaptation to indolent transmission among dispersed rural populations. The first category includes typhus, arboviral diseases, and plague, and the second category includes smallpox. Both measles and explosive streptococcal disease appear to be much less likely candidates.

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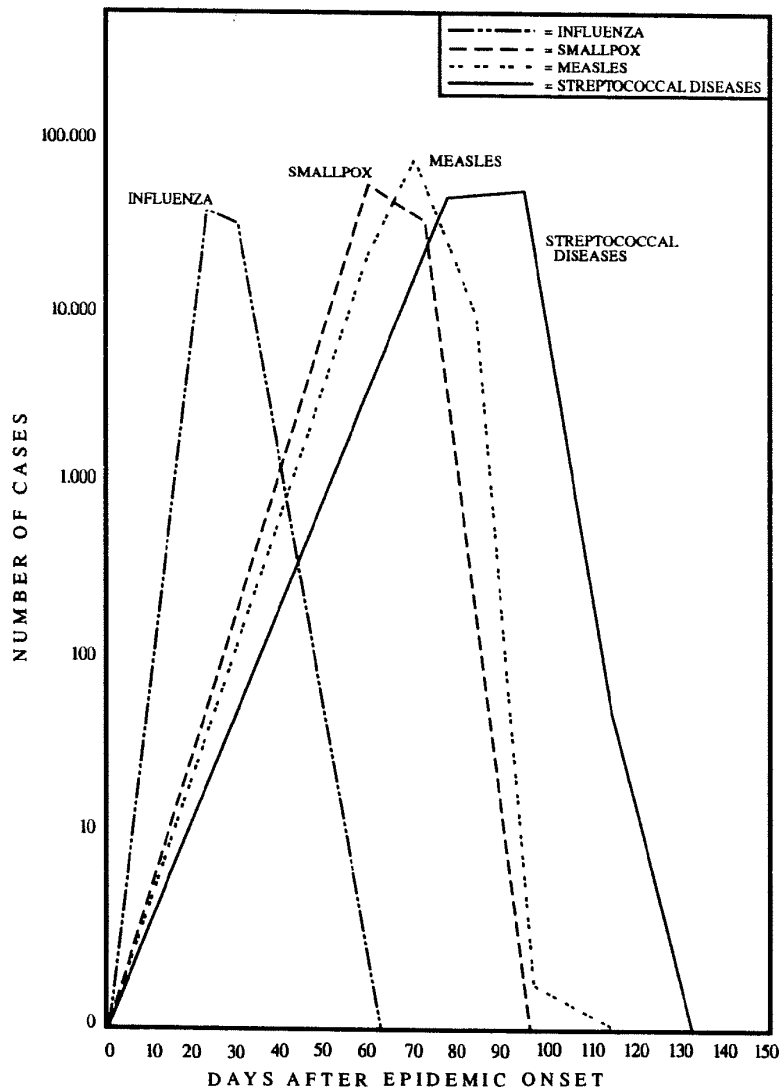
Fig 2. Theoretical epidemic curves of influenza A, smallpox, measles, and streptococcal disease in a closed population of 100,000 susceptible persons according to the mathematical model of Maia. The curves assume an adequate contact number of 10.

persistence or adaptation to indolent transmission among dispersed rural populations. The first category includes typhus, arboviral diseases, and plague, and the second category includes smallpox. Both measles and explosive streptococcal disease appear to be much less likely candidates.

PALEOPATHOLOGY

A challenge in historical epidemiology and the history of medicine is working with written history with little or no physical evidence. In some cases, particularly ancient Egypt, mummies provide actual physical evidence, as do skeletal remains. The new science of DNA analysis has opened new windows in the investigation of the past.

Beginning in the second half of the 20th century, new methodologies were developed that allowed fresh examinations of diseases in history. These methodologies were based on new academic disciplines, including forensic anthropology, demography, and epidemiology. Scientific discoveries and technology allowed us new insights into the very essence of life. Chief among these were the discovery of DNA and the ability to analyze it, magnetic resonance imaging, and computed axial tomography (ie, three-dimensional pictures of hard and soft tissue inside the human body). These disciplines, discoveries, and technology have been brought to bear on the
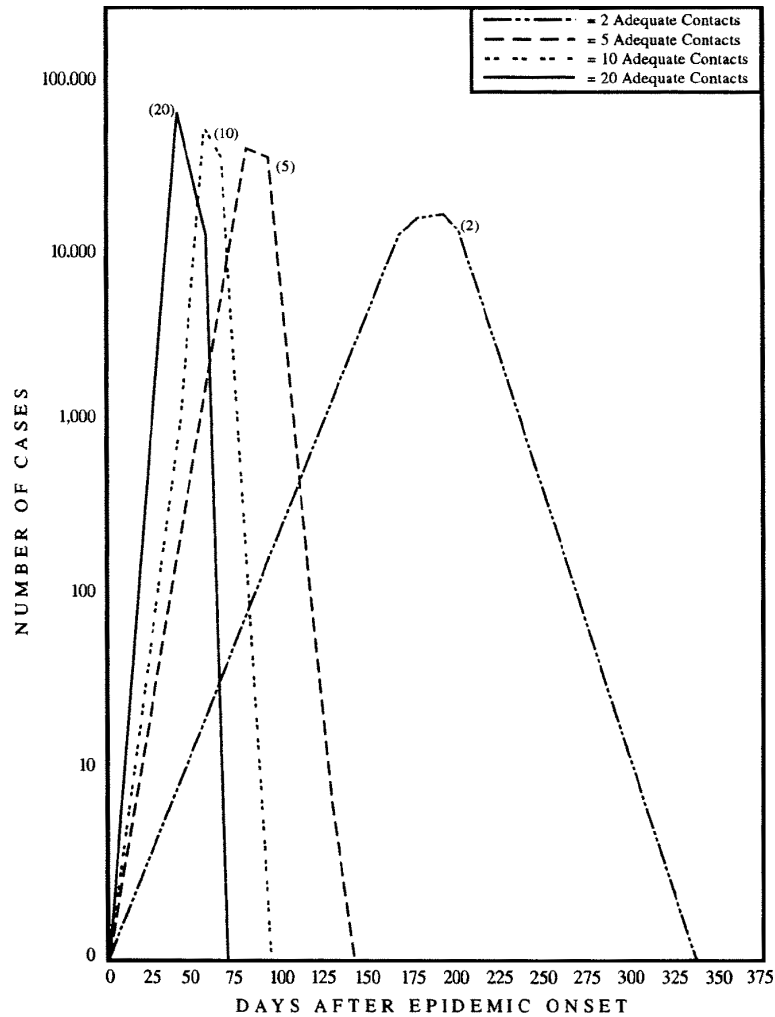
Fig 3.   Theoretical epidemic curves of smallpox in a closed population of 100,000 susceptible persons according to the mathematical model of Maia. The curves assume adequate contact numbers of 2, 5, 10, and 20 persons per serial generation time of 12 days.

study of diseases in antiquity, including the nature and impact of plagues and pandemics in the ancient world.

The study of ancient DNA has begun to provide new clues in studying plagues of antiquity. Ancient microbial DNA has been successfully extracted[40]; 400-year-old DNA of *Yersinia pestis*, the microorganism that causes bubonic plague, has been extracted from dental pulp.[41] The extraction of human DNA is more problematic. There are claims that Neanderthal DNA has been extracted, and other claims that it is not possible to extract DNA more than 800 years old. In any event, for both the Plague of Athens and other ancient diseases, microbial DNA might provide a useful tool.

In 2001, a mass grave was discovered at the cemetery of the Kerameikos, which belonged to the plague years. The excavation was conducted by Effie Baziotopoulou-Valavani,[42] a member of the Greek Archaeological Service. The study of the skeletal material was undertaken by Professor Manolis Papagrigorakis[43] of the University of Athens. He was able to extract ancient microbial typhoid (*S. enterica* serovar Typhi) DNA from the remains. He posited that the probable cause of the Plague of Athens was this disease. It is premature, however, to draw this conclusion. We know from Hippocrates that typhoid was most likely endemic in the Greek world. The presence of an endemic disease does not necessarily indicate that it was the cause of death. A second problem is that the sampling was extremely small: 3 skeletons. A third difficulty is that the analysis of Papagrigorakis has been challenged. Shapiro *et al.*[44] argued that Papagrigorakis reported a 7%

divergence between their sequences and *S. enterica* serovar Typhi and therefore by simple phylogenetic analysis the ancient sequence falls outside both *S. enterica* and *S. typhimurium*. Therefore, the obtained sequences do not allow an identification of typhoid in these skeletons, although it is possibly a related *Salmonella*. Shapiro *et al.* further suggested that the sequence might have come from soil surrounding the burial and that the analysis is therefore compromised. Papagrigorakis *et al.*[45] responded that soil wash was used as a negative control and that there was no contamination, a phylogenetic analysis of only 1 gene might be insufficient or misleading, and *Salmonella* species do not survive for long in soil. A DNA analysis of the skeletal materials is an intriguing start that one could anticipate will lead to new information about paleopathology and the plague years. Because the plague struck Egypt according to Thucydides, what we most hope for are Egyptian mummified remains of someone who died of the Plague of Athens.

DISCLOSURES

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