Hellenic Holocaust: A Historical Clinico-Pathologic Conference

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The traditional clinico-pathologic conference (CPC) begins with a case presentation. Next, a clinician analyzes the clinical information, illustrating the diagnostic process and proposing one "best-fit" diagnosis for the anonymous (and often dead) patient. Finally, a pathologist presents the actual autopsy or histologic findings, either validating or rejecting the clinician's diagnosis. This "historical" CPC differs from the traditional CPC in two ways: first, we have no all-knowing pathologist to deliver a final answer, and second, we are challenged to name the patient.

CASE PRESENTATION

Fever, headache, sore throat, and vomiting developed in a 65-year-old man. He had been in excellent health until approximately 1 week earlier, when he had sudden onset of headache, ocular erythema, and halitosis. On the third day of illness, he began to sneeze and cough, and noted bilateral pleuritic chest pain. On the sixth day, he developed projectile vomiting of dark, bilious fluid. At this time, he complained of fever so intense that he would not allow himself to be covered with even the lightest clothing. He also complained repeatedly of intense thirst. Although he drank copious amounts of water, his thirst persisted, worsened by frequent vomiting.

The patient had no history of major illnesses. He drank wine in moderation and did not use tobacco. He was taking no medications and had no known allergies.

The patient was a resident of Athens, where he had lived his entire life, except for brief excursions throughout the eastern Mediterranean. He spent his early years in military service. In recent years, he had devoted himself to politics. He was married and both of his children by this marriage, sons aged 30 and 25 years, had died recently of illnesses similar to his own. Another son (by his mistress), aged 10 years, was alive and well. The patient's father had died in battle at age 47 years; his mother's history is not known. His sister had recently died while in her mid sixties of an illness similar to that of the patient. The condition of his brother, who was approximately 60 years of age, is not known.

A similar illness simultaneously afflicted many of the patient's fellow Athenians. The epidemic began about a year earlier, 1 year after the outbreak of hostilities with a neighboring city. Although enemy forces had besieged Athens continuously during this period, their troops do not appear to have been affected by the illness. Refugees entering the city from the surrounding countryside, however, were quickly affected. The disease attacked all age groups and socioeconomic strata, with the highest incidence among physicians and other caregivers. The illness, which was reported to have originated in sub-Saharan Africa, had not been seen in Athens before the current epidemic. It was believed to have entered Athens through Piraeus, the city's port. Much of the eastern Mediterranean was also afflicted with the disease. The epidemic had waxed and waned since its appearance, with no apparent seasonality. Of those who contracted the disease, approximately one quarter died. Persons who recovered were immune to further attacks of the disease. Unfortunately, they were sometimes permanently disabled by residua of the disease, such as encephalopathy, blindness, or distal necrosis of extremities and sometimes the genitalia. Although there were reports of dogs and birds dying after feeding on the corpses of people who died of the illness, these reports are unsubstantiated.

The patient was alert, oriented, and extremely weak. He appeared well nourished, although moderately dehydrated. The pulse was rapid and thready. Respirations were deep. Although the patient complained of intense fever, his skin was moist and normothermic. The conjunctivae were injected. The oropharynx was red, inflamed, and covered with clotted blood. The breath was fetid. Diffuse rales, ronchi, and wheezes were present throughout both lungs. There was a generalized, erythematous maculopapular rash.

Supportive therapy consisting of cool baths was administered without relief. On the ninth day of illness, the patient developed profuse diarrhea, which was not examined for blood or inflammatory cells. Progressive dehydration and debilitation ensued. Cardiovascular collapse occurred on the 11th day of illness, and the patient died.

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Differential Diagnosis

Dr. David T. Durack. In working toward a diagnosis, I will first try a "pattern-recognition" analysis of the patient's symptoms. This unfortunate man was apparently in perfect health, busy with political affairs, when he was struck down by a mysterious disease. The illness began with fever, headache, conjunctivitis, and fetid breath. The patient's throat was markedly inflamed, with a coating of blood, pus, and (probably) ulcers. Later, bilateral pleuritic chest pain developed.

Many clinicians confronted with these symptoms in an epidemic setting would think first of influenza. Influenza is, of course, highly transmissible, and can be fatal. We learn later, however, that the fatality rate during this epidemic was as high as 25%—too high for influenza. Even during the most virulent influenza epidemic on record, the Spanish Flu of 1918 to 1919, the overall fatality rate was less than 1% (1). In other words, the millions of influenza deaths worldwide 1918 to 1919 resulted from an extremely high prevalence, not from an excessively high fatality rate (although it was higher than other influenza epidemics).

Influenza epidemics spread swiftly over wide areas, but they die out almost as quickly as they arise, within a matter of a few weeks. The Athenian plague waxed and waned for 3 years, an important point that was used by Littman and colleagues (2) to argue convincingly against proposals by others that influenza was the cause of the Athenian plague (3,4). The same argument repudiates theories postulating an influenza epidemic with secondary complications, such as toxic shock syndrome or Guillain-Barre syndrome.

In view of the pulmonary findings, other epidemic viral pathogens such as Hantavirus must be considered. Hantavirus can affect the lungs and cause a high fatality rate. Moreover, it might become epidemic in the face of social disorganization, crowding, and privation, all of which favor proliferation of its rodent vector.

The next symptoms to develop—retching, bilious vomiting, and unquenchable thirst—raise the possibility of a gastrointestinal infection, such as salmonellosis or typhoid fever, or perhaps a bacterial enterotoxin. The generalized, erythematous, maculopapular rash, however, would be difficult to reconcile with these diagnoses. The rash suggests another common, highly contagious, epidemic disease: measles. Could the death rate from measles be as high as 25%? The answer is yes, although such a high mortality rate has been recorded only rarely (5). The hemorrhagic fever viruses could easily cause high mortality, but prominent bleeding complications, which would have been obvious to all, were not recorded by Thucydides. In my view, this virtually eliminates Ebola (6) and other filoviruses as the cause of this epidemic.

Epidemic diarrhea and dehydration progressing to death must raise the possibility of cholera. But, of course, the other findings, especially the rash, do not fit this diagnosis. In fact, our patient manifests a number of findings that do not fit particularly well with the classic features of any common infectious disease. This is why we are discussing this case today, as many others have done before us.

Lacking a "perfect-fit" diagnosis, we must look for alternative ways to ferret out the cause of this patient's illness. Let us consider the characteristics of the epidemic. Four features make this outbreak unique: it occurred in Athens, its setting was wartime, it erupted within a besieged city, and it was associated with a mortality rate of nearly 25%. Only one recorded epidemic had all four of these features: the Great Plague of Athens (7–9).

How do we know so much about an epidemic that occurred in Athens in 431 BC? We owe most of what we know to the writings of Thucydides, a citizen of Athens during its war with Sparta, a historian—one of the greatest—and a survivor of the plague. His *History of the Peloponnesian War* is revered for its authority, accuracy, and literary style. Nevertheless, it is important to remember that Thucydides was not a physician and did not have access to formal medical terminology because it did not exist at the time. Furthermore, his personal observations on the Greek wars were written in retrospect; some parts of his great history were written as long as 20 years after the fact.

The main clinical findings described by Thucydides were "heat in the head, redness and burning in the eyes, inflamed throat and fetid breath, sneezing, hoarseness, then coughing" (7–9). As to the skin of afflicted patients, first it was "flushed and livid," and later it exhibited "pustules and ulcers" (7–9). But there is a critical issue of translation here: it is not entirely clear whether the words "pustules and ulcers" are an exact translation of the Greek terminology used by Thucydides. An alternative translation might be "blisters and sores." It is also possible that Thucydides was actually describing a papular rash.

Patients found that their burning skin was extremely uncomfortable to the touch, and they tossed off their sheets and clothing. One of the most striking observations of Thucydides was that patients often leaped into cisterns, water tanks, or wells in desperate attempts to slake their burning thirst and soothe their hectic fevers. This is an unusual behavior among febrile patients, with few parallels in the medical literature (5). Finally, in some victims, diarrhea and dehydration developed and death occurred, usually during the next 7 to 9 days.

Thucydides goes on to describe striking complications among the survivors: "If the patient recovered, symptoms appeared in the form of a seizure of the extremities and privy parts. The tips of the fingers and toes were attacked and many survived with the loss of these, others with blindness. Some rose from their beds with a total and immediate loss of memory" (7–9). Three specific compli-

Table 1. Theories on the Causes of the Plague of Athens (4–6, 18–24)

A.	A known infectious disease
	Anthrax
	Bubonic plague
	Cholera
	Dengue
	Ebola or Marburg virus
	Erysipelas
	Glanders
	Influenza
	Lassa fever
	Malaria
	Measles
	Meningitis
	Rift Valley fever
	Scarlatina maligna
	Scarlet fever
	Smallpox
	Sweating sickness
	Toxic shock syndrome
	Tularemia
	Typhoid fever
	Typhus fever
B.	A known infectious disease, more virulent in a "virgin-soil" population
C.	A known noninfectious disease
	Alimentary toxic aleukia
	Ergotism
	Scurvy
D.	Two known diseases occurring simultaneously
	Influenza complicated by Guillain-Barré syndrome
	Influenza complicated by toxic shock syndrome
	Typhus fever and bubonic plague
	Typhus fever and dysentery
	Typhus fever and yellow fever
	Yellow fever with scurvy
D.	A disease that has since changed beyond recognition
E.	A disease that has since disappeared

cations were peripheral gangrene, blindness, and amnesia. Again we must ask what disease causes such complications? Medical historians and diagnosticians have failed to reach a consensus on this question. Many theories have been advanced, strenuously supported, and just as strenuously opposed (Table 1).

So I shall return to the epidemiologic findings in search of further clues (3). The disease, like the acquired immunodeficiency syndrome (AIDS) of the present, came out of Africa into the developed world ("*ex Africa semper aliquid novi*"). From Africa the disease spread to the Persian Empire, finally reaching besieged Athens and sparking an explosive epidemic within the city walls. The epidemic began in the Port of Piraeus, thence spreading to the city proper, where some 250,000 and possibly as many as 400,000 persons were huddled within a 4-square-mile area. A population density of this magnitude is comparable with that of modern-day New York City. However, because there were no high-rise buildings in Athens at that time, its level of crowding was even greater—more like that of a concentration camp (2). Such extreme crowding would have caused serious sanitation problems and favored the proliferation of rodents and lice. Physicians were preferentially infected, as were other caregivers and family members. The case-fatality ratio was 20% to 25%. The initial epidemic lasted approximately a year (430 to 429 BC). Cases then continued to appear at an endemic level for 2 years (429 to 427 BC), only to reemerge in epidemic form for an additional year.

Several noninfectious etiologies (Table 1) have been proposed as the cause of the Plague of Athens, including alimentary toxic aleukia [which is caused by T-2 mycotoxins (10)], ergotism, and scurvy. However, Thucydides recorded that once patients recovered from the disease, recurrences were rare. Only an infectious agent is likely to induce such resistance to second attacks of an illness. I conclude that the natural history of this outbreak is incompatible with anything but an infectious disease.

Could this have been a common infectious disease that was unusually virulent because it had been introduced into a "virgin-soil" population? For that matter, is the concept that infections are more deadly in virgin-soil human populations valid? There are several well-documented examples of common infectious diseases exhibiting extraordinary virulence at the time of first introduction into a population (5). These include the epidemic of syphilis in Naples in 1494; the outbreak of smallpox in Mexico in 1530, with a death rate of almost 50%; and the outbreak of measles in Fiji in 1875, in which there was a case-fatality ratio of 25%. An interesting parallel between the latter epidemic and the Plague of Athens was a tendency for patients to seek relief from their discomfort by jumping into water (5).

There are several reasons why we might not be able to identify the infection responsible for the Plague of Athens today (11,12). The microbe responsible for the epidemic might have been highly virulent initially but evolved to become less deadly than its fearsome ancestor. Another possibility is that the disease no longer exists. A third possibility is that the Athenian plague was a composite of two or more diseases—for example, concurrent epidemics of typhus fever, typhoid fever, or bubonic plague. Perhaps a few hapless victims had two deadly diseases simultaneously. It would have been difficult or impossible for Thucydides, or any other observer, to distinguish between two or more such diseases at that time—we should recall that the distinction between typhus fever and typhoid fever was not made with certainty until 1837 (13).

When wrestling with a difficult differential diagnosis, I have found it useful to focus only on the information that is certain and put aside for the moment any findings, no matter how striking, unusual, or provocative, that are in

any way questionable. I believe that the certainties about the Plague of Athens are the following: it was a major outbreak of an infectious disease in time of war, privation, and crowding; the epidemic continued for several years, with fluctuating incidence during that period; patients developed a rash (although the precise nature of the rash is uncertain); some patients had gastrointestinal and respiratory symptoms; the case-fatality ratio during the epidemic was unusually high, up to 25%; the median time to death was 7 to 9 days; and some of those who survived the acute illness developed striking complications, including peripheral gangrene, blindness, and amnesia. I believe we should give special consideration to the complications because they would have been easily recognized by a lay observer such as Thucydides.

In my opinion, influenza and measles can be excluded as causes of the Plague of Athens on epidemiologic grounds. Of the diseases most consistent with the facts about which we are certain, I suggest three leading possibilities: Lassa fever or a similar arenavirus infection (perhaps transmuted over time), smallpox, and epidemic louse-borne typhus fever. Typhus has long been associated with war and privation, even more so than smallpox. The crowding that existed in besieged Athens would have favored proliferation of body lice, the vector for typhus. Rickettsiae, which cause typhus fever, Rocky Mountain spotted fever, and several other systemic infections, are specialized bacteria, highly adapted to the intracellular environment. They infect a wide variety of host cells, especially vascular endothelial cells. As they proliferate within endothelial cells, they damage blood vessels, causing vasodilatation, fibrin deposition, and localized hemorrhages. If the involved vessel lies within the skin, it swells and sometimes extravasates blood into the subcutaneous tissue, resulting in a macular, papular, or sometimes hemorrhagic rash. If the vessel lies within the brain, the inflammatory process can cause alteration of consciousness and amnesia. If vessels of the optic nerve are involved, blindness can result. And if the vasculitis is severe, involving large vessels of the extremities, peripheral gangrene can develop (Figure 1).

For these reasons, I believe epidemic louse-borne typhus is the most likely cause of the Plague of Athens. I recognize that the diagnostic fit is not perfect, and I cannot exclude smallpox or a vector-borne arenavirus infection such as Lassa fever. As to the identity of the patient, history tells us of a great Athenian statesman, orator, and soldier who died in the second year of the plague. His name was Pericles. He lived from 495 to 429 BC, a multitalented intellectual, patron of the arts, builder, general, democratic statesman, the preeminent figure of his time. I believe that Pericles is the subject of our historical clinico-pathological exercise, a great man who fell victim to a tiny insect that carried an even tinier pathogen.

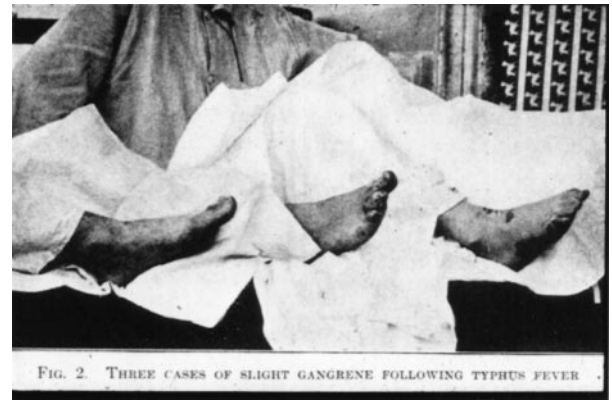

Figure. Peripheral gangrene in the feet of 3 patients with louse-borne typhus during an epidemic in the Balkans in 1918.

Dr. David T. Durack's Diagnoses

The disease. Epidemic louse-borne typhus fever.
The patient. Pericles, died 429 BC in the Great Plague of Athens.

HISTORICAL DISCUSSION

Dr. Robert J. Littman. The Golden Age of Greece, in the fifth century BC, was one of Western history's most creative periods, save for that of Renaissance Italy and our own 20th century. It was a time of immense productivity in philosophy, literature, medicine, and art, led by some of the greatest minds of western civilization—Socrates, Hippocrates, Aeschylus, Euripides, Sophocles, Herodotus, Thucydides, Pheidias, and others. In fact, it was the Golden Age of Athens, in that most of these men lived and worked in that city-state.

In 431 BC, the Peloponnesian War erupted between Athens and Sparta and soon embroiled the entire Greek world. The war, which lasted until 404 BC, was both a territorial and an ideological struggle. It pitted Athens, a democracy, against Sparta, an oligarchy, in a struggle for control of Greece. Each side, on conquering another city-state, imposed its form of government on the conquered citizenry.

The ruler of Athens at the time was the great general Pericles. Born to an aristocratic family 5 years before the battle of Marathon, he emerged as political leader in 463 BC. In 454 or 453 he became *strategos*, or general, and dominated Athenian politics thereafter until his death in 430 or 429, not only as political and military leader but also as cultural leader as well. Because of his influence, the Golden Age of Athens is frequently referred to as "Periclean Athens" (14–16). In 447 BC he initiated construction of the Parthenon. He surrounded himself with a circle of intellectuals, including the sculptor Pheidias, the philosopher Anaxagoras, and his mistress, Aspasia. When

war with Sparta threatened, he staunchly advocated an aggressive war policy, which became the Athenian strategy once war did break out in 431 BC.

In 430 BC the Spartans invaded Attica and besieged Athens. During the siege, plague struck, and in 2 to 3 years killed Pericles along with three members of his family and an estimated 25% of Athens' population. The epidemic had a devastating effect on the Athenian war effort. Victory in wars of fifth-century Greece hinged on the size of a city's army and the number of its ships. A smaller, well-trained force could defeat a larger force, as the Greeks demonstrated earlier in the century against the Persians. However, in the Peloponnesian War, which pitted well-trained Greek against Greek, the size of the army was critical to its success. By decimating Athens' population, the plague destroyed its fighting capacity. Had the plague not occurred, Athens might have won the war. Because Pericles was the city's leading statesman and its commander-in-chief, his death magnified the plague's effect, all the more because he was replaced by men of lesser military and political ability. Had Athens prevailed over Sparta, the creative impulse that gave us the Golden Age of Athens might have continued for another half century.

Our account of the Plague of Athens has been preserved in the writings of the Greek historian, Thucydides (8). Like Pericles, Thucydides (460 to 400 BC) contracted the plague. Unlike Pericles, Thucydides survived to describe the epidemic and the war whose course it influenced. He, too, was a general. However, after failing to save the city of Amphipolis from the Spartans, he was exiled. In 404 BC, some 20 years after the war with Sparta, he returned to Athens and died shortly thereafter. While in exile, he wrote his monumental history of the war.

Thucydides' account of the Peloponnesian Wars covers the conflict only to the year 411 BC, presumably because he died before he could complete his work. In contrast to earlier historians, Thucydides eschewed supernatural references in his historical account, devoting his efforts instead to an accurate description of events themselves and an objective analysis of the motives behind them. He recognized the plague as a critical event in Athenian history and took great pains to provide a detailed account of it, so "if it should break out again, it could be recognized." Interestingly, his account ignores the important fact that Pericles perished during the plague. We learn this from other sources.

In the fifth century, Greek medicine as we know it today was just beginning to emerge under the influence of Hippocrates. Hippocrates was a rationalist who ignored the prevailing belief that disease was the result of divine displeasure. He instead sought rational explanations based on careful observation. Thucydides' account, which reflects this same attitude, is the only contemporary source of information on the Athenian plague. However, additional information can be found in sources from the Roman period, 1 BC to 2 AD, which are almost certainly based on Thucydides' work and possibly contaminated by other sources.

Although Thucydides was a victim of the plague, and thus had first-hand experience to draw on in his description, his account is far from perfect. This is partly because his account was written before the maturation of Greek medical history and theory. Indeed, Hippocrates had just begun the work that would become the basis for medical theory and practice for over 2 millennia. Technical medical language was in its infancy (8), and even if it had been highly developed, it is unlikely that Thucydides, a layman, would have been conversant in it.

As a lay historian, Thucydides described signs and symptoms differently from modern-day clinicians. At times he stressed trivial signs and symptoms at the expense of important ones. His description of the rash is a case in point. He said nothing of its duration, its developmental stages, whether the *phlyctaenae* and *helke* existed simultaneously or sequentially, nor did he describe how the rash resolved. In an analysis of Thucydides' writings, Page (9) concluded that his medical terminology was standard for the fifth and fourth centuries. However, as Parry (17) demonstrated, much of this same terminology existed in the common everyday language of the Athens of Pericles' day.

Attempts to diagnose the disease described by Thucydides might take one of three approaches: a clinical, an epidemiologic, or a paleo-archaeologic approach. The clinical approach, which Dr. Durack demonstrated so well, examines the signs and symptoms of the disease in question, and by comparing them with those of other diseases, reaches a diagnosis on the basis of a "best fit." This method is most effective when the diagnostician has access to actual patients. When this is not possible, the diagnostician is at the mercy of the medical record. Clinical approaches to Thucydides' medical record have generated no fewer than 29 theories as to the cause of the plague of Athens (18–21).

The epidemiologic approach attempts to reach a diagnosis by examining the "who, when, where, and why" of the disorder. It focuses on the risk factors that determine who is affected by the disease within the population at risk. It studies groups of people, rather than individual patients, comparing those who contract the disease with those who do not in an attempt to understand the source of the disease and the means by which it travels within populations. Morens and I (2) used such an approach to formulate mathematical models for the spread of a disease having the characteristics of that described by Thucydides in a dense, premodern population of 250,000. Based on our analysis, we concluded that all common-source diseases and most respiratory diseases could be excluded in favor of either a reservoir disease (zoonotic or vector-borne) or one of the few unusually

persistent respiratory diseases. Of the diseases in the former category, typhus, an arboviral infection, and bubonic plague were felt to be the most likely. Smallpox was felt to be the strongest possibility among the diseases in the latter category.

Finally, there is the paleo-archaeologic approach, in which archaeologic material is examined using modern techniques to establish a clinical diagnosis. The possibility of applying such an approach to the question of the cause of the Plague of Athens emerged last year as a result of the discovery in Athens by the German School of Archaeology of 160 skeletons dating to 430 BC. If scientific analysis of these bones using molecular techniques such as the polymerase chain reaction is successful, we just might find the answer to a question that has perplexed medical historians for more than 2 millennia.

COMMENT

Dr. Philip A. Mackowiak and Dr. R. Michael Benitez. Why, after more than 2,000 years, do we continue to ponder the cause of the plague of Athens? We do so, as noted above, because of the epidemic's effect on Western history and because we are no closer to answering Thucydides' challenge to identify its cause than earlier generations we are inclined to dismiss as less capable.

As suggested by Dr. Durack, there are several possible reasons why the diagnosis has eluded recognition. One is that the disease was unique, arising de novo in a world long gone, never to be seen again. Alternatively, it might have changed during the course of the Athenian epidemic to such an extent that subsequent visitations have born little resemblance to the original syndrome. Although the preponderance of evidence suggests that evolution (of organisms, as well as the relationships between organisms) is an exceedingly tedious process, other examples of evanescent plague do exist, such as the sudden emergence and equally sudden disappearance of von Economo's encephalitis earlier this century. It is also possible that for all his talent as an historian, Thucydides was unequal to the task of crafting a sufficiently comprehensive and accurate clinical description of the plague of Athens to allow even the most sophisticated clinician to discern its cause. Modern-day clinicians who endeavor to do so are at the mercy not only of Thucydides and his case history, but also of subsequent translations of Thucydides' work as well. Nowhere are the limitations of Thucydides' case history and the translations that have followed more evident than in the description of the rash. In the 17th century translation used to prepare our case history (7), Thomas Hobbes (1589–1679), the well-known English philosopher, translated the critical passage describing the rash as "reddish livid, and beflowered with little Pimples and Whelks." Subsequent scholars have offered numerous translations of Thucydides' key descriptor, "*phlykainai*," including blain, bleb, blister, bulla, eruption, pustule, and vesicle (17), any one of which might form the basis for its own particular diagnosis.

For these reasons, clinical exercises such as this are not likely to provide a definitive answer to the cause of one of history's greatest medical mysteries. They can, nevertheless, give direction to those who might examine archaeologic specimens from the Hellenic holocaust, should they be uncovered. Dr. Durack has suggested that such examinations should probe for *Rickettsia prowazekii*. Others have suggested the need to search for evidence of smallpox (4,22,23), bubonic plague (24), scarlet fever, measles (5,9), typhoid (3), influenza (3,4), toxic shock syndrome, ergotism (3), and cerebrospinal fever (4). Until suitable archaeologic material has been obtained and analyzed successfully using modern molecular probes, Thucydides' challenge to future generations to name the disease that ended not only Pericles' life but his golden age as well will serve as a reminder of the limitations of medical knowledge.

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