Chapter 1
Great Plagues of the Past and Remaining Questions

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Abstract Due to the difficulty of obtaining tissue samples from victims of the ancient plagues, it is not always possible to utilise palaeomicrobiology techniques to determine the etiology of ancient infection. Therefore, it is often necessary to utilise other means to arrive at a likely diagnosis. The most helpful of these is the literary description of the disease. While this is often the best evidence available, working with such documents can prove difficult. Three great plagues of the ancient world, the Plague of Athens, the Antonine Plague, and the Justiniac Plague are described in either Latin or ancient Greek. The difficulties encountered when translating any ancient foreign language are compounded by the fact that so many words in these languages have a variety of meanings. This chapter reviews the three great plagues of antiquity from a clinical perspective.

1.1 Overview

There are numerous historical accounts of epidemics in ancient times. These accounts of epidemics or plagues describe infectious diseases ravaging ancient populations. Extant accounts of ancient plagues are limited. Certainly, many epidemics and outbreaks occurred in the ancient world that were not recorded or, if they were recorded, have been lost through the ages (Martin and Martin-Granel 2006). In the accounts that have survived, there are inherent difficulties of description and interpretation (Major 1978; Procopius 1981; Thucydides 1919). The descriptive terms used by the ancients are either not those that are we are familiar with today or, more problematic, multiple interpretations of terms are used to describe the physical findings in afflicted patients, which results in various possibilities and different assumptions are made according to translator variability and interpretation. Nevertheless, until recently, the only approach with which to try to determine the etiologies of ancient plagues has been examination of the relatively few written accounts that have survived over time. These accounts

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are variable and sometimes conflicting, and are dependent upon translator interpretation of the languages in which they were first described. Using the historical approach, there are other interpretational problems. The observers or recorders of the descriptions of ancient epidemics varied in their observational and descriptive capabilities as well as in their knowledge of medical terms used at the time (Page 1953; Parry 1969). All of these confounding variables make it difficult to determine the exact cause of the various plagues that afflicted the ancients (Brothwell and Sandison 1967; Cartwright 1972; Shrewsbury 1950).

In the absence of scientific proof, the historical method remains the backbone of an analytical approach to the problem of ancient plagues. Ancient descriptions provide at least some information about locale, season, descriptions of the findings, extent of the epidemic, mortality, and clinical sequelae. Although subject to interpretational difficulties, much has been learned by applying the historical method to determine the cause of widespread pestilence in earlier epics (Bollet 1987; Cunha 2004b; Cunha and Cunha 2006). Currently, methods are available to determine the actual cause of ancient plagues, but these methods depend on intact DNA for analysis, and are methodology dependent (Gilbert et al. 2003; Drancourt and Raoult 2005).

At the present time, sophisticated analytical methods are available to analyse ancient DNA in preserved tissue samples, permitting accurate identification of microorganisms present in samples from ancient animal and human remains (Cooper and Poinar 2000). As with the historical approach, there are problems with DNA-dependent technologies. The first difficulty using the scientific approach is to find suitably preserved samples to analyse. Just as there are problems with historical interpretation, so there are also problems with palaeomicrobiology (Hofreiter et al. 2001; Pääbo 1989). Firstly, there are relatively few geographical areas that have climatic conditions suitable for the preservation of tissue specimens in a state amenable to DNA analysis (Zink et al. 2002). The most likely situations in which DNA is likely to be preserved are in the dryness of the desert, in desiccated mummies, or tissues preserved in ice/glaciers (Jackson et al. 1998). DNA of microbial organisms or parasites from such specimens is likely to be well preserved and to lend itself readily to palaeomicrobiologic analyses (Arriaza et al. 1995; Li et al. 1999, Meers 1985; Reid et al. 2000, Rollo et al 2000; Spencer and Howe 2004; Taubenberger et al. 1997; Tumpey et al. 2004; Zink et al. 2002). Unfortunately, many of the ancient plagues that we are aware of from historical records did not occur in areas with favourable climatic conditions that would lend themselves to the preservation of analysable DNA samples (Antia et al. 2003; Brothwell and Sandison 1967; Cockburn 1971; Hofreiter et al. 2001; Zink et al. 2002). The ancient plagues of Egypt occurred in dry areas, but were not preserved in mummified remains.

The plagues of ancient Rome and ancient Athens occurred in climatic conditions that may not yield suitable specimens for palaeomicrobiologic identification (Kiple 1993; McNeill 1976). There are further problems with DNA specimen analysis, which has a corollary in contemporary clinical infectious diseases. In infectious diseases, one of the most fundamental determinations is to differentiate colonisation from infection. Similarly, in palaeomicrobiology, the mere recovery of an organism from an ancient preserved specimen does not necessarily implicate a role for this organism as the pathogen responsible for the demise of the individual whose remains

are being analysed. The recovery of *Salmonella typhi* in areas endemic for enteric fevers as well as malaria and a variety of other infectious diseases, does not necessarily imply that the organism was causally related to the patient's demise. For example, if a patient who has pulmonary tuberculosis dies of coronary artery disease, the presence of tuberculosis does not necessarily imply that tuberculosis was the cause of death. Nevertheless, the study of palaeomicrobiology has contributed greatly to our understanding of the ancient microbial milieu of humans and animals (Antia et al. 2003; Brothwell and Sandison 1967; Cockburn 1971; McNeill 1976).

The very fact that the presence of such organisms can be verified is of great scientific importance (Drancourt et al. 1998). The types of specimen that lend themselves most readily to analysis are those that are likely to survive the ravages of time, i.e. teeth, bone specimens, coproliths, etc. Palaeopathology, the study of pathological changes in ancient remains, has been very important in confirming the presence of various diseases in ancient times. Because palaeopathology depends upon observable pathological changes in ancient specimens, palaeopathology is most useful in identifying infectious diseases with observable pathological changes. Skeletal syphilis and tuberculosis are examples of infectious diseases that produce characteristic changes in bone, which are readily recognisable in palaeopathological specimens (Arriaza et al. 1995; Brothwell and Sandison 1968; Kiple 1993). Infectious diseases that kill rapidly leave no traces in teeth, bone, or coproliths, which is problematic. In the absence of permanently preserved specimens, how would scientists in the future determine the presence/lethality of severe acute respiratory syndrome (SARS) in tissue from cadaveric specimens from Asia? Palaeomicrobiology has been most successful in demonstrating bacteria, Rickettsia, and parasite ova (Drancourt and Raoult 2005).

Palaeopathology has also demonstrated non-microscopic parasites in tissue specimens. Such findings are interesting and add to our knowledge of the epidemiology of infectious diseases in the ancient world (Arriaza et al. 1995; Brothwell and Sandison 1967). Although epidemiological analyses provide the background for the endemic illnesses in ancient populations, they do not explain the causes of the various plagues described in the ancient world (Kiple 1993). Until there is incontrovertible proof based upon methodologically sound science, the best current and future approach of trying to determine the etiology of epidemics in the ancient world is to combine the epidemiological information from palaeopathology with the continuing advances made in palaeomicrobiology, and this information should be used in conjunction with historical analyses (Cunha 2004b; Cunha and Cunha 2006). This chapter will take a historical approach combined with what is currently known from palaeomicrobiological and palaeopathological information to review the likely causes of three key ancient plagues of the past.

1.2 Determination of the Cause of Ancient Plagues by Historical/Clinical Analysis

While palaeopathology is probably the best way to obtain a definitive diagnosis of an ancient disease, it is not always possible. Due to the difficulty of obtaining tissue samples from victims of the ancient plagues, it is not always possible to utilise the

technique of palaeomicrobiology to determine the etiology of ancient infection (Cooper and Poinar 2000; Drancourt and Raoult 2005; Hofreiter et al. 2001; Zink et al. 2002). Therefore, it is often necessary to utilise other means to arrive at a likely diagnosis. The most helpful of these is a primary literary description of the disease. While this is often the best evidence available, working with these sorts of documents can prove difficult. When it comes to discussing the three great plagues of the ancient world, the Plague of Athens, the Antonine Plague, and the Justiniac Plague, the descriptions are in either Latin or ancient Greek.

Therefore, The difficulties encountered when translating any ancient foreign language are compounded by the fact that so many words in these languages have a variety of meanings. Additionally, due to the precision required in medical documentation, any word or phrase that is interpreted in a way other than that intended by the original author can skew a description toward or away from the actual diagnosis (Cunha 2004b; Littman and Littman 1973; Major 1978; Procopius 1981). While Thucydides' chronicle of the plague is exquisitely detailed, variation in translation makes it impossible to definitively determine the causative agent (Page 1953; Parry 1969; Shrewsbury 1950; Thucydides 1919). Because of this, the only way to confirm a suspected diagnosis would be through the use of palaeomicrobiology (Drancourt and Raoult 2005). Indeed, a mass grave immediately outside Athens has been unearthed, but has not yet been analysed – until it is, debate will continue.

There is also an underlying assumption that the description was accurate to begin with and has been preserved intact (Major 1978). In the case of the Antonine plague, mere fragments of Galen's writings describing the course of the disease remain. Enough of the text is available to develop a clinical diagnosis, but this will need to be confirmed by palaeomicrobiological testing (Drancourt and Raoult 2005).

Obviously then, the best way to determine the cause of an ancient disease would be to combine palaeopathology with a literary clinical/historical analysis. This is the case with the Justiniac plague, which not only has a clear description that leads the reader to only one obvious conclusion, but also has evidence from mass graves from the era of the plague. These have been unearthed and genetic testing has confirmed the suspected etiology (Drancourt and Raoult 2002, 2004; Drancourt et al. 2004).

1.2.1 The Plague of Athens (430–426 B.C.): Determination of Etiology by Historical/Clinical Analysis

1.2.1.1 Historical Overview

Without doubt, Athens and Sparta were the two most powerful and influential civilisations on mainland Greece in the ancient world. By 431 B.C. the Peloponnesian War between Athens and Sparta had begun in earnest. Athens had only to survive the Spartan assault in order to claim victory, while the Spartans would have to conquer the city of Athens itself. Pericles, the leader of Athens, realised this and called for the Athenians to surrender their territory in Attica and to move all people in

Athens, and in the regions immediately surrounding it, into the city itself, which was protected by the great Themistoclean walls. These walls guarded the city proper, and provided a fortified connection with the harbour of Piraeus, 9 km from the city. Taking into account the Athenian's well-established naval superiority as well as their safe access to a protected port, it seemed as though taking Athens would be next to impossible for the Spartans. However, by 404 B.C., several events occurred that resulted in the total defeat of Athens and her allies. Most significant of these is the great Plague of Athens, described so accurately by Thucydides, the Greek historian. The plague struck Athens early in the conflict, during the summer of 430 B.C., and drastically reduced the population of the city, devastating Athenian society (Bollet 1987; Brothwell and Sandison 1967; Kiple 1993).

There has been much debate by both physicians and classicists as to the exact cause of the plague and neither group has come to a consensus. Although Thucydides was not a trained physician, he was most certainly an astute observer, and was careful to utilise the medical vocabulary of his era. Thucydides himself contracted and survived the plague, thus granting modern interpreters a precise and detailed account of the disease.

1.2.1.2 Thucydides' Clinical Description

It first began, so it is said, in ***Ethiopia above Egypt****, and then descended into Egypt and Libya and into most of the King's land. Suddenly falling upon Athens, it first attacked the population at Piraeus, so that they themselves said that the Peloponnesians had thrown poison into their cisterns: for there were, as yet, no wells there. But afterwards it came to the upper city as well, and from that time the deaths became much greater. Now, anyone, either physician or layman, can, by his own opinion, speak on its origins and the causes that produced so great a departure from normal conditions; but I shall talk about its course, and explain the symptoms, by which it could be recognised in the future, having knowledge of it beforehand. For I myself was ill and saw others suffer from it.*

That year, as agreed by all, had been unprecedentedly disease-free in respect to other sicknesses; but if anyone was suffering from anything at all before, all resolved into this. In other cases, there was no apparent cause, but suddenly, healthy men were seized first with ***mighty fevers in the head****, and* ***redness, and inflamed eyes,*** *and the inside, both the* ***throat and tongue****,* ***immediately became blood-red*** *and* ***emitted an atypical, foul breath****. After which came* ***sneezing and hoarseness****, and in not much time the pain descended into the chest, and produced a* ***severe cough****; and* ***when it fixed in the stomach, it upset it****, and* ***vomiting of bile*** *of every kind named by physicians ensued, accompanied by great suffering. In most cases* ***nonproductive retching*** *followed, giving way to* ***violent spasms****, which lessened, in some sooner, in others, not until much later. Externally, the body was* ***not very hot to the touch,*** *and was not pale,* ***rather, it was reddened, livid, and flowering with small blisters and wounds****. But* ***their insides burned so hotly, that the patients could not bare garments or fine cloths being laid on them, nor be anything but***

naked, and would have liked best to hurl themselves into cold water*, as in fact, many of those neglected did, throwing themselves into cisterns, tormented by unquenchable thirst. And it was the same whether they drank much or little. Also, they were ceaselessly tormented by the* ***inability to rest or sleep****. And the body, while the disease flourished, did not wither, but, contrary to expectations, withstood the ravages of the disease; so* ***that when they died, as most did, on the seventh or ninth day from the burning heat, they still had some strength****. But if they escaped this****, the disease descended into the bowels, resulting in a great ulceration****, and at the same time,* ***acute diarrhoea****. And many later* ***died from exhaustion*** *because of this.* ***For the disease, ran from above, in the head, where it first settled, throughout the whole body****, and if one survived the worst,* ***it left its mark on the extremities****.* ***For it fell upon the genitals, and the tips of the hands and the feet, and even having lost these parts, many survived,. Some also lost their eyes****. Others again were taken with a* ***complete loss of memory*** *after recovery, and they failed to know either themselves or friends.*

[Translation Thucydides (1919), bold/italics by Cheston B. Cunha].

1.2.1.3 Clinical Diagnostic Analysis

For over 2,000 years, physicians of every era have attempted to analyse Thucydides' writings and deduce the precise etiology of the Plague of Athens. Among the most likely diseases to have caused the plague of Athens are bubonic plague, typhoid fever, smallpox, measles, and epidemic typhus. All of these diseases were endemic to the ancient world and potentially fit the symptoms described by Thucydides (Longrigg 1980; McNeill 1976; Roberts and Manchester 2005; Shrewsbury 1950; Thucydides 1989). Unfortunately, the limitations presented by translation of the original Greek preclude a facile diagnosis, although it is possible to provide a satisfactory theory on the cause of the plague based upon the evidence provided by Thucydides. However, when carefully analysed, there is one disease that seems to fit the vast majority of symptoms more than the others (Kiple 1993; Osler 1876a, 1876b).

In modern times, whenever the word plague is mentioned to describe a disease, the most common thought is, of course, bubonic plague (Antia et al. 2003; Brothwell and Sandison 1967; Cockburn 1971). Boccaccio and others have passed down accurate descriptions of outbreaks of bubonic plague that occurred in Europe, and each resembles its fellows, but none of them bear a great likeness to Thucydides' account of the Plague of Athens. Indeed, the only symptoms of bubonic plague present in Athens during the plague years were fever and runny nose. Only if the Greek '*φλυκταιναις μικραις*' and '*ελκος*', meaning 'small blisters' and 'wounds', respectively, are interpreted as buboes, which is a linguistic stretch, would bubonic plague seem at all possible. However, none of the other features mentioned by Thucydides occur in bubonic plague outbreaks, suggesting that bubonic plague is a very unlikely cause of the Plague of Athens (Cunha 2004b; Page 1953; Shrewsbury 1950).

Typhoid fever is also an unlikely candidate. While the fever and diarrhoea are highly suggestive of typhoid, they are the only major symptoms that would indicate typhoid as the source of the plague. Typhoid fever requires fecal contamination of the water or food supply with *Salmonella typhi*, which could most definitely have occurred in the cramped, overpopulated conditions of wartime Athens. Even the rash, which is characterised by the presence of "rose spots", does not fit well with Thucydides' described rash. Additionally, typhoid usually causes death after 2–3 weeks, much longer than described by Thucydides. Also, typhoid fever does not confer complete immunity, while the Plague of Athens offered complete immunity in survivors. Finally, typhoid fever can be fatal, but usually does not approach a 25% mortality rate. It is for these epidemiological and clinical reasons that typhoid fever does not appear to be the cause of the Plague of Athens (Cunha 2004b; Cunha and Cunha 2006; Kiple 1993).

Smallpox is one of the diseased theorised to have caused the plague. This particular hypothesis, while put forward by many physicians over the years, was first suggested by the Persian physician Rhazes in 900 A.D. Thucydides' description has many features typical of smallpox. In particular, the rapid onset, fever, rash, and inflamed eyes all point to smallpox. Occurring in many forms, conventional smallpox or hemorrhagic smallpox is believed by some to be the most likely cause of the plague. Those who support the conventional smallpox hypothesis believe that the small blisters and wounds are indicative of the highly characteristic vesicles of smallpox. However, smallpox vesicles first appear as macules at the hairline and progress down from the face to the trunk, and that does not seem to be the rash that Thucydides describes. "Internal heat" has been mentioned in some smallpox cases, as has loss of vision, and gangrene of the extremities, but many other prominent symptoms are lacking. If hemorrhagic smallpox, the most lethal form of the disease, was the cause, then the vesicles of conventional smallpox would not develop, but rather a general petechial or purpuric rash, that is to say a rash characterised by small spots resulting from subcutaneous hemorrhage, would appear. Hemorrhagic smallpox bears a greater resemblance to Thucydides' description than the conventional form and would seem to be a very likely candidate for the cause of the plague. However, hemorrhagic smallpox never occurs independently of a conventional smallpox outbreak and, as such, Thucydides' description does not seem to be a description of a smallpox outbreak in Athens (Oldstone 1998; Osler 1876a, 1876b). In addition, the distribution of the rash and the lack of other symptoms all argue against smallpox being responsible for the plague of Athens (Aufderheide and Rodriguez-Martin 1998; Cunha 2002,; Cunha 2004a, 2004b; Fenner et al. 1988; Hopkins 2002; Osler 1876a, 1876b, 1892; Ricketts 1908).

One of the more likely causes, although one that is often overlooked due to the modern conception of the disease, is measles. When thinking of measles today, most conjure up the idea of a childhood disease, made less virulent by vaccination programs, incapable of inflicting the sort of damage witnessed in Athens in 430 B.C. However, when introduced to nonimmune populations, as happened on the Fiji Islands in 1875, mortality rates in all age groups approach the numbers described by Thucydides. Supporting measles as the cause of the plague are the

rash, respiratory symptoms, restlessness, and "internal heat". Indeed, victims of the Fiji epidemic were often reported to throw themselves into rivers to find respite from the sensation of intense internal heat, strikingly similar to what the Athenians did in an attempt to alleviate their unbearable "inner heat". All this would seem to lead to a diagnosis of measles as the cause. However, measles rarely, if ever, presents with diarrhoea or gangrene, and the fact that Thucydides mentions these suggests they were present in most cases, rather than being rare occurrences among the sick. Moreover, neurological complications are rare in measles, which further suggests that measles did not, in fact, afflict Athens during the Peloponnesian War (Brothwell and Sandison 1967; Cartwright 1972; Cunha 2004a, 2004b).

Thucydides' description suggests that epidemic typhus was very likely the disease that ravaged Athens. Carried by lice, typhus has historically struck during times of war when a large population is forced to live in a relatively confined space, something that certainly would characterise Athens during the Peloponnesian War. This would allow a lice-infested individual to enter Athens through the port of Piraeus, which was the lifeline of Athens, and infect the entire city, killing close to one-quarter of the population. Considering the wartime conditions in Athens, which undoubtedly eliminated the typically excellent hygiene of Athenians, replacing it with the unsanitary habits of those who dwelled outside the city, it is very likely that epidemic typhus could have quickly spread throughout the population. Typhus is typically characterised by fever, red eyes, a truncal rash, and respiratory symptoms. Neurological complications are common, and may have been responsible for the blindness and the memory loss described. However, the most compelling arguments supporting epidemic typhus as the cause are the diarrhoea and gangrene, both of which are common in epidemic typhus. Finally, exhaustion is characteristic of those who die of this disease, and this is a feature clearly described by Thucydides.

By analysing the clinical features described by Thucydides, it seems that it was in fact epidemic typhus that caused the great Plague of Athens (McNeill 1976; Osler 1892; Shrewsbury 1950; Tumpey et al. 2004; Table 1.1). However, a definite etiology cannot be determined with certainty by clinical/historical means alone. The difficulties in using the historical approach are best illustrated using the Plague of Athens as a prime example (Christie 1969; Cunha 2004b; Cunha and Cunha 2006; Page 1953; Shrewsbury 1953).

1.2.1.4 Historical Importance

The plague of Athens had many direct and indirect consequences on the ancient Greek world, the most obvious of which was the depletion of manpower in Athens, i.e. by the winter of 427 B.C., Athens' fighting forces had been reduced to approximately 75% of their original strength. Indeed, virtually the entire eastern section of the Peloponnese lost close to 25% of its population. The plague did not, however, travel far enough to affect the Spartans and most of their allies, leaving Athens' foes virtually untouched by disease (Bollet 1987; Cartwright 1972).

Table 1.1 Differential diagnosis of athenian plague (Adapted from Cunha 2004b and Cunha and Cunha 2006)

Clinical description by Thucydides	Time of appearance	Bubonic plague	Typhoid fever	Smallpox	Measles	Epidemic typhus[a]
Rapid onset	Early	•		•	•	•
Fever	Early	•	•	•	•	•
Red eyes	Early			•	•	•
Runny nose and sneezing	Early	•			•	•
Red throat and hoarseness	Early				•	•
Foul breath	Early				•	•
Retching and convulsions	Middle					•
Livid red rash	Middle	•		•	•	•
Blisters and sores	Middle				•	•
Sensation of "intense internal heat"	Middle			•	•	•
Insomnia	Late	•		•		
Diarrhoea	Late		•		•	•
Tracheal/laryngeal ulcers	Late					•
Red throat and hoarseness	Late			•	•	•
Death by haemorrhage	Late					•

[a]Most likely etiology based on clinical/historical analysis

The plague also had a significant impact on Athenian political leadership, most notably the death of Pericles due to plague, which left Athens without one of its greatest statesmen. As a result of Pericles' death, subsequent Athenian leaders, such as Cleon, Alcibiades, and Hyperbolus, were allowed to shift Athens away from the noble course upon which it had been set by Pericles, and towards its eventual demise (Kiple 1993).

By depleting the ranks of the Athenian army, removing one of Athens' greatest leaders, and eliminating a system of beliefs and ideals that distinguished Athens from other ancient societies, the great Plague of Athens effectively altered the outcome of the Peloponnesian War, and subsequent Hellenistic and Western history (Cunha and Cunha 2006; Soupios 2004).

1.2.2 The Antonine Plague (166–270 A.D.): Determination of Etiology by Historical/Clinical Analysis

1.2.2.1 Historical Overview

By the second century A.D., the Roman Empire had asserted itself as, perhaps, the greatest civilisation the world has ever known. Rome was the preeminent force in the ancient world in terms of her cultural, political, economic, and military power,

and Gibbon describes the reign of Marcus Aurelius, from 161–180 A.D., as "as the happiest and most prosperous period" in the history of humanity. This great empire stretched from the Iberian Peninsula to the Mid-East, and from Britain to North Africa, encompassing vast areas of the European continent.

When all of these grand achievements are viewed, it would seem as though a civilisation this splendid could never fall, and yet, by the third century, the Roman Empire was facing a period of crisis. This was in no small part due to the great plague that swept across the Empire in 166 A.D., which lasted for nearly a century. Later referred to as the Antonine Plague or the Plague of Galen, it decimated a large portion of the Empire's population and was a blow from which Rome never recovered (Bollet 1987; Brothwell and Sandison 1967; Cartwright 1972).

No great description exists for the Antonine Plague, unlike the earlier Plague of Athens. The only remaining documentation is in the form of several notes made by Galen, the great physician; an allusion to the epidemic by the emperor Marcus Aurelius in his writings, and two references by Lucian (Littman and Littman 1973; Major 1978). The plague originated in the Middle East and was brought to the Empire by Roman soldiers returning home after the Parthian War. Having thus been introduced into the Roman world, it spread rapidly, lasting until 270 A.D., claiming the lives of millions of Romans, including the Emperor Marcus Aurelius himself. Travelling via the Roman trade routes, there were even reports of the plague spreading as far east as China. So deadly was this pestilence that some sources suggest that, at one point during the plague years, over 2,000 people a day were dying in the city of Rome itself (Fears 2004; Gilliam 1961).

1.2.2.2 Galen's Clinical Description

Exanthem:

On the ninth day a certain young man was ***covered over his whole body with an exanthem****, as was the case with almost all who survived. Drying drugs were applied to his body.* ***On the twelfth day he was able to rise from bed****.*

On those who would survive who had diarrhoea, ***a black exanthem*** *appeared on the whole body.* ***It was ulcerated in most cases and totally dry****. The blackness was due to a remnant of blood that had putrefied in the fever blisters, like some ash which nature had deposited on the skin. "Of some of these which had become* ***ulcerated, that part of the surface called the scab fell away and then the remaining part nearby was healthy and after one or two days became scarred over****. In those places where it was not ulcerated,* ***the exanthem was rough and scabby and fell away like some husk*** *and hence all became healthy. In many cases where there was* ***no bloody colliquescences*** *(diarrhoea), the entire body was covered by a black exanthem. "And sometimes a sort of scale fell off, when the exanthem had dried and dissipated, little by little, over a period of many days after the crisis.*

Fever:

Those afflicted with plague ***appear neither warm, nor burning to those who touch them, although they are raging with fever inside****, just as Thucydides describes*.

Galen calls the plague a fever plague.

Black excrement *was a symptom of those who had the disease, whether they survived or perished of it. Colliquescence (diarrhoea) was first auburn, the yellowish red, later black, like fecal matter of blood. Colliquescence of evacuation was an inseparable symptom of the plague. In many who survived, black stools appeared, mostly on the ninth day or even the seventh or eleventh day. Many differences occurred. Some had stools that were nearly black; some had neither pains in their excretions, nor were their excretions foul smelling. Very many stood in the middle. If the stool was not black, the exanthem always appeared.* ***All those who excreted very black stool died***.

Vomiting:

Occurred in some cases.

Cough-Catarrh:

On the ninth day a young man had a ***slight cough***. *On the tenth day the* ***cough became stronger and with it he brought up scabs***. *After having catarrh for many days, first with a cough* ***he brought up a little bright, fresh blood****, and afterwards even part of the membrane which lines the artery and rises through the larynx to the pharynx and mouth*.

Internal Ulcerations and Inflammation:

On the tenth day a young man coughed and brought up a scab, which was an indication of an ulcerated area in the windpipe in the region of the trachea near the jugular vein. ***No ulcers were present in the mouth or throat*** *(there was no problem of ingesting food).* ***The larynx was infected, and the man's voice was damaged***.

Duration of the Disease:

The crisis appeared on the ninth to twelfth day. ***On the third day after the ninth the young man was able to rise from his bed.***

[Translation from Galen by Littmann and Littmann (1973), bold/italics by Cheston B. Cunha].

1.2.2.3 Clinical Diagnostic Analysis

Although what has remained of Galen's description of the Antonine Plague is not as detailed as Thucydides' Athenian plague description, Galen's precise account of the exanthem that characterises the plague makes it relatively easy to pinpoint its cause. The fact that the rash extends over the entire body rather than being concentrated in the form of buboes in the groin and armpit rules out bubonic plague as a cause. Similarly, typhoid fever lacks most of the symptoms Galen describes, and thus is not a very likely cause of the plague (Christie 1969; Kiple 1993).

The exanthem has the potential to be the rash that is seen in measles, epidemic typhus or smallpox. Indeed, the early stages of these diseases are very easy to confuse. Undoubtedly, since measles, typhus, and smallpox have many of the same characteristics found in Galen's plague descriptions, such as the "internal heat", and foul breath, the type of vesicles must be looked to in order to differentiate between the three most likely possibilities. However, Galen's statement that the exanthem was pustular and later became blackened is highly suggestive of the pustular stage of a smallpox rash most often seen in hemorrhagic smallpox. Because of this evidence, smallpox seems to fit; however, there is one problem with that diagnosis (Kiple 1993; Tumpey et al. 2004; Table 1.2) Smallpox confers complete immunity, which would seem to work against the plague's recurrences later in the third century. Nevertheless, it is possible, and very likely, that these recurrences were merely instances of the plague entering previously unaffected areas of the Empire, making smallpox a perfectly viable cause. Therefore, after considering all the information regarding the symptoms of the diseases, Galen's description of a pustular rash indicates that the Antonine Plague was, in fact, an outbreak of smallpox (Littman and Littman 1973; McNeill 1976).

Table 1.2 Differential diagnosis of antonine plague

Clinical description by Galen	Time of Appearance	Bubonic plague	Typhoid fever	Measles	Epidemic typhus	Smallpox[a]
Rapid onset	Early	•		•	•	•
Fever	Early	•	•	•	•	•
Foul breath	Middle			•	•	•
Livid red rash	Middle			•	•	•
Blisters and sores	Middle				•	•
Sensation of "intense internal heat"	Middle			•	•	•
Insomnia	Late	•		•		
Diarrhoea	Late		•		•	•
Tracheal/laryngeal ulcers	Late					•
Red throat and hoarseness	Late			•	•	•
Death by haemorrhage	Late					•

[a]Most likely etiology based on clinical/historical analysis

It is clear that the scope of the plague was enormous, and impacted all levels of Roman life. Indeed, for an Empire so dependent on manpower for its financial, agricultural and military infrastructure, the plague was a crippling event from which the Empire never truly recovered. Ultimately, it can be said that the Antonine Plague had a profound negative impact on the spiritual, political, economic, social, and military aspects of the Roman Empire. Together with military defeats at the hands of the German tribes, the Antonine Plague most definitely set Rome on her long decline to ruin (Fears 2004; Gilliam 1961).

1.2.3 The Justiniac Plague (542–590 A.D.): Determination of Etiology by Historical/Clinical Analysis

1.2.3.1 Historical Overview

As bleak as things appeared to be for the Roman Empire at the end of the third century A.D., during the time between 290 A.D. and 540 A.D., the Roman Empire was able to regain a certain degree of vitality. While the power of the western Empire slowly waned, the eastern part of the Empire maintained its presence and, with it, the spirit of the Roman Empire. When Justinian took power in the east, he brought with him a dream of resurrecting the old might of Rome by reuniting the eastern and western portions of the Empire, and he was almost able to accomplish this. After securing his northern and eastern borders, Justinian began his campaign in the west in 532 A.D. Initially he met with great success, retaking much of Rome's lost territory. The new emperor had recaptured North Africa, Carthage, Sicily, parts of Hispania, and even large sections of the Italian peninsula. Indeed, by 540 A.D. German resistance was collapsing, and Justinian hoped to launch an attack into Gaul and possibly Britain as well. It seemed as though the reign of Justinian would be one of renewed glory and vigour for the Roman Empire, but all that changed when the Justiniac Plague struck in 542 A.D. (Brothwell and Sandison 1967).

Most likely carried from Africa, where it originated, to Constantinople and the rest of the Empire in a shipment of grain from Egypt, it was easy for the disease to spread along the trade routes of Rome. The enclosed city of Constantinople, as was the case with Athens during the Peloponnesian War, would have provided ideal conditions for the proliferation of the disease throughout the city's population (Bollet 1987).

There are several descriptions of the Justiniac Plague, namely those of John of Ephesus, Evagrius Scholasticus, and Procopius. While all provide descriptions, it is Procopius' account that is considered to be the most accurate and certainly the most precise in describing the symptoms of the plague. Procopius was one of the principal archivists for the Emperor Justinian, and had travelled for some time on campaign with Justinian's great general, Belisarius. When the plague arrived in Constantinople, where Procopius was staying, he chronicled his account of the plague (Kiple 1993; Major 1978).

1.2.3.2 Procopius' Clinical Description

During this time there was a plague, by which all men were almost completely killed…

… For it did not come in a certain part of the world or to certain men, nor did it confine itself to any season of the year, so that from such circumstances it might be possible to find explanations of a cause, but it encompassed the entire world, and destroyed the lives of all men, although they differed from one another in the most obvious ways, respecting neither sex nor age.

For just as men differ with regard to the places in which they live, or in the manner of their daily life, or in natural disposition, or in active endeavor, or in whatever else man differs from man, in the case of this disease alone, the difference meant nothing. And it attacked some in the summer, others in the winter, and still others at other times of the year. Now let each one express his own opinion concerning the matter, both sophist and astrologer, but as for me, I shall proceed to tell where this disease originated and the manner in which it destroyed men.

***It came from the Egyptians who live in Pelusium**. But it split, and in one direction came toward Alexandria and the rest of Egypt, and in the other it came to Palestine bordering Egypt, and from there spread everywhere, always moving forward and going whenever time favoured it. For it seemed to move by a set plan and delayed in each land for a certain time, casting its blight leniently on none, but spreading in either direction right out to the ends of the world, as if afraid that some corner of the Earth might escape it. For it spared neither island nor cave nor mountain that had human inhabitants; and if it had passed over any land, either not affecting the men there or touching them in an inconsequential fashion, at a later time it still came back; then those who lived near this land, whom formerly it had most gravely afflicted, it did not touch at all, but it did not leave the place in question until it had given up its just and proper toll of dead, which corresponded exactly to the number killed at the earlier time among those who lived nearby. And this disease always **started on the coast and from there moved to the interior**. And in the second year it reached Byzantium in the midst of spring, where I happened to be staying at the time. And it came thusly. Many people saw the spirits of divine beings in human form of every kind, and, as it happened, those who encountered them thought that they were struck, in this or that part of the body, by the man they had met; and immediately seeing this apparition they were also seized by the disease. Now at first those who met these creatures tried to turn them aside by uttering the holiest of names and exorcising them in other ways as best each one could, but they accomplished absolutely nothing, for even in the sanctuaries, where the most of them fled for refuge, they were dying constantly. But later on they were unwilling to even listen to their friends when they called to them, and they shut themselves up in their rooms and pretended they did not hear, although their doors were being beaten down, fearing that he who was calling was one of those spirits. But in the case of some, the pestilence did not come in this way, but they saw a vision in a dream and seemed to suffer the very same thing at the hands of the creature who stood over them, or else to hear a voice prophesising that they were written down*

in the number of those who were to die. But with ***most it*** *happened that the disease seized them* ***without*** *being made aware of what would come* ***by a waking vision or a dream****. And they were taken as follows.*

They had a ***sudden fever****, some when they woke from sleeping; others while walking around; and still others while busy with other matters, regardless of what they were doing. But the body showed no change in its original color, neither was it as hot as expected when struck by the fever, nor did any inflammation occur, but the fever was of such a lethargic kind from its onset until the evening that it would not give any suspicion of danger either to the sick themselves or to a physician. Therefore, it was natural that none of those who had contracted the disease expected to die because of it. But in some cases on the same day, in others on the following day, and in the rest, not many days later, a* ***bubonic swelling developed****,* ***there in the groin of body, which is below the abdomen, but also in the armpit, and also behind the ear and at different places along the thighs****. Up to this point, then, everything occurred the same way with all who had taken the disease. But from then on very distinct differences developed for there ensued for some a deep* ***coma****, with others a* ***violent delirium****, but, in either case, they suffered the characteristic symptoms of the disease. For those who were under the spell of the coma* ***forgot all those who were familiar to them,*** *and seemed to lie, sleeping constantly. And if anyone cared for them, they would eat without waking, but some also were neglected, and these would die directly through lack of sustenance. But those who were seized with delirium suffered from* ***insomnia*** *and were victims of a* ***distorted imagination****; for they suspected that men were coming to them to destroy them, and they would become excited and rush off in flight, crying out at the top of their voices. And those who were attending them were in a state of constant exhaustion and had a most difficult time. For this reason everybody pitied them no less than the sufferers, not because they were threatened by the pestilence by going near it, for neither physicians nor other persons were found to contract this plague through contact with the sick or with the dead, for many who were constantly engaged either in burying or in attending those in no way connected with them survived in the performance of this service beyond all expectation, while with many others the disease came on without warning and they died immediately; but they pitied them because of the great hardships which they were undergoing. For when the patients fell from their beds and lay rolling on the floor, they kept putting them back in place, and when they were struggling to rush headlong out of their houses, they would force them back by shoving and pulling against them. And when water happened to be nearby, they wished to fall into it, not so much because of a desire for drink, for the most of them rushed into the sea, but the cause was to be found chiefly in the diseased state of their minds.*

They also had great difficulty in the matter of eating*, for they could not easily take food. And many perished through lack of any man to care for them, for they were either overcome by hunger, or threw themselves from a height. And in those cases where neither coma nor delirium came on, the bubonic swelling became worse and the sufferer, no longer able to endure the pain, died. And one would suppose that in all cases the same thing would have been true, but since they did not*

all have their senses, some were unable to feel the pain; for owing to the troubled condition of their minds they lost all sense of feeling.

In some cases death came immediately, in others, after many days; and with some the body broke out with ***black pustules*** *about as large as a lentil and these did not survive even one day, but all succumbed immediately*. ***Vomiting of blood*** *ensued in many, without visible cause, and immediately brought death. Moreover, I am able to declare this, that the most illustrious physicians predicted that many would die, who, shortly afterwards, unexpectedly escaped from suffering entirely, and physicians declared that many would be saved, who were destined to be carried off almost immediately. So it was that in this disease there was no cause that came within the realm of human understanding; for in all cases the issue tended to be something unaccountable*.

Now in those cases where the ***swelling rose to an unusual size and a discharge of pus had set in, it happened that they escaped from the disease and survived****, for clearly the acute condition of the swelling found relief in this direction, and this proved to be, in general, an indication of returning health; but in cases where the swelling maintained its former appearance, there ensued those troubles which I have just mentioned. And with some of them the thigh withered, in which case, though the swelling was there, it did not develop the least suppuration. With others who survived, the tongue did not remain unaffected, and they lived on either lisping or speaking incoherently and with difficulty*.

[Translation by H.B. Dewing from Procopius (1981), bold italics by Cheston B. Cunha].

1.2.3.3 Clinical Diagnostic Analysis

Unlike the Plague of Athens, after analysing the description of the symptoms and signs, the cause of the Justiniac Plague is apparent. The most notable of the symptoms described by Procopius is, of course, the bubonic swellings (*υσερον βουβων*), which developed in the groin and axilla of those who contracted the disease. Indeed, even without analysis of other signs and symptoms, this description is highly indicative of bubonic plague.

Perhaps the most unusual symptom described by Procopius was the visualisation of spirits that many infected individuals claimed to have seen. However, a common complication associated with a bubonic plague is encephalopathic. These visions may, in fact, be early manifestations of the neurological complications of the plague, i.e. encephalopathy, which may progress to coma and delirium in some. This type of neurological involvement is very different from epidemic typhus. Although typhus results in a loss of memory, hallucinations of the type described by Procopius occur only rarely. Similarly, while typhus presents with many of the features described by Procopius, it lacks many of the more critical symptoms, namely, the presence of buboes, and the development of coma (Christie 1969; Kiple 1993; Tumpey et al. 2004).

Similarly, measles also seems to lack the requisite symptoms and is unlikely to be the cause of the great Justiniac Plague. Both measles and typhoid fever show only a few basic features in common with the plague that descended on the Roman world in 542 A.D. The fever and diarrhoea of typhoid and the red throat of measles, when viewed by themselves, could be indicative of many infectious diseases, and do not provide enough commonality to warrant a diagnosis of either disease by description alone (Cunha 2004a, 2004b).

Finally, smallpox is a diagnostic possibility, but one that is not very likely when studied closely. As with the aforementioned diseases, the presence of buboes is not indicative of the type of rash seen in smallpox infections. Rather than the truncal, vesicular rash typical of variola, the swellings described concentrate in the primary lymphatic tissue of the groin, armpit, and neck (Christie 1969; Kiple 1993; Osler 1876a, 1876b, 1892). For this reason, along with the neurological and pulmonary complications often seen in plague, bubonic plague is almost certainly the cause of the Justiniac Plague (Bratton 1981a, 1981b; Tumpey et al. 2004; Table 1.3).

The damage resulting from the Justiniac Plague was both far reaching and disastrous for Rome. Although the precise numbers provided by Procopius and others who wrote about the plague are not always accurate, it can be safely assumed that well over one-third of the Roman world's population was eliminated by the conclusion of the sixth century A.D. Additionally, as Procopius describes, much of the surviving population of the Empire, who had become infected but did not perish, suffered from the debilitating and crippling neurological effects of the plague (Bollet 1987; Cartwright 1972).

Although Justinian sought to re-conquer much of Italy and the Western Empire, the plague effectively ended his plans of restoring much of what had been the old Roman Empire. These disastrous effects on the Roman Empire were compounded by the fact that the plague did not affect the less organised, "barbarian" societies

Table 1.3 Differential diagnosis of justiniac plague

Clinical description by Procopius	Time of appearance	Typhoid fever	Measles	Epidemic Typhus	Smallpox	Bubonic plague[a]
Rapid onset	Early		•	•	•	•
Slight fever	Early	•	•	•	•	•
Coma	Middle					•
Buboes	Middle					•
Delirium	Middle			•		•
Haematoemesis	Middle					•
Insomnia	Middle		•			•
Diarrhoea	Middle	•		•	•	
Red throat and hoarseness	Middle		•	•	•	•
Death by haemorrhage	Late				•	

[a]Most likely etiology based on clinical/historical analysis

outside of Rome's borders. This, in large part, was due to the fact that the highly developed internal structure of the Roman Empire actually facilitated the spread of bubonic plague along Rome's trade routes. The less centralised, foreign civilisations bordering the Roman Empire were, therefore, far less likely to have plague spread rapidly through their populations (McNeill 1976). It is, of course, impossible to claim that the eventual destruction of the Roman Empire was brought about solely by this plague, but it can be said that because of the Justiniac Plague, the Roman Empire lost any initiative it had recovered following the Antonine Plague. The plague so weakened the Eastern Roman Empire that it never truly recovered, and led to the eventual, complete collapse of the last remnants of the once mighty Roman Empire (Cunha and Cunha 2006; Kiple 1993).

1.3 Summary

The three great ancient plagues provide prime examples of the limitations and accuracy of clinical/historical analysis. Clinical historical analysis provides increasing diagnostic certainty going from the indeterminate certainty of the Plague of Athens, to more certainty with the Antonine Plague, and absolute certainty with the Justinian Plague. The challenges for the future are to find additional tissue samples that have sufficiently preserved microbiological DNA, which hopefully will provide definitive information on the cause of some of the ancient plagues (Drancourt and Raoult 2005). Mass burial sites that have previously remained uncovered may be found in the future, and analysis of such remains put in the correct clinical context can provide invaluable information regarding the infectious disease etiology of the causes of various ancient epidemics. Historical analysis will continue to be important because it provides the clinical descriptions of diseases, which may be the same as or different from current clinical descriptions of various infectious diseases (Brothwell and Sandison 1967; Kiple 1993). The historical approach is compounded by difficulties with infectious diseases that no longer exist, that occurred abruptly or more likely evolved over time, which created such mass devastation and then disappeared into the fog of history. Palaeomicrobiology is also of great importance in helping to sort out the evolution of infectious diseases on a microbe by microbe basis. A great breakthrough in palaeopathology has been the demonstration of microbial DNA in dental pulp specimens (Drancourt and Raoult 2002, 2004; Drancourt et al. 2005; Raoult et al. 2000). Bacteria early in bacteremia are trapped in dental pulp and preserved if the victim's teeth are preserved/found. To date, dental pulp DNA analysis is the only way to accurately identify microbial DNA from rapidly fatal infections of the past (Drancourt et al. 1998). Thus, although the future analyses of ancient plagues will still use the historical method as the foundation, as more well-preserved specimens are uncovered from ancient sites, and more DNA techniques are refined and standardised, ever more important information on the evolution of infectious disease agents as well as their role in ancient plagues will continue to interest and amaze us.

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