Dissecting Plague

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[See related article pp. 189 - 199]

Plague is an ancient infectious disease that has ravaged human society on three occasions during the past 2000 years. In Irwin W. Sherman's recent book, *The Power of Plagues*, the author chronicles the impact *Yersinia pestis* (the etiologic agent of plague) had on medieval society:

In Constantinople, the capital of the Roman Empire in the East, it was the first bubonic plague pandemic (542-543) that surely contributed to Justinian's failure to restore imperial unity. In 1346, the second pandemic began. By the time it dissipated in 1352, the population of Europe and the Middle East had been reduced from 100 million to 80 million people. This devastating pandemic, known as the Black Death, the Great Dying, or the Great Pestilence, put an end to the rise in human population that had begun in 5000 B.C.; it took more than 150 years for the population to return to its former size.¹

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Modern advances in living standards, coupled with a clearer understanding of infection transmission dynamics and the availability of antimicrobial therapy makes naturally occurring plague, on the scale seen in the Middle Ages, only a remote possibility. Nevertheless, sporadic infections due to *Y. pestis* still occur on a regular basis in rural areas of the western US as well as scattered areas in Africa, Asia and South America. For example, during 2003, nine countries reported 2,118 cases of plague associated with 182 deaths. The overwhelming majority of cases and deaths reported were from Africa². A real fear is that plague will resurface as localized epidemics, especially in those parts of the world with poor public health infrastructures due to poverty or civil unrest. Perhaps of equal or even greater concern is the threat *Y. pestis* poses as a potential agent of biological terrorism. These factors combined have made the plague bacillus an extremely important subject of biomedical research, especially with respect to elucidating the specific factors that have contributed to *Y. pestis* becoming such a successful human pathogen.

In this issue of *Clinical Medicine and Research*, Xiao-Zhe Huang and her colleagues from the Walter Reed Army Institute of Research review the tremendous progress that has been made in understanding the genetic basis of virulence in *Y. pestis* and the closely related human pathogens *Yersinia pseudotuberculosis* and *Yersinia enterocolitica*.³ This timely and comprehensive review underscores the impressive extent to which plague research has progressed in recent years, in large measure, due to the availability of complete genome sequences of multiple strains for comparison-based computational analysis. This approach, along with signature-tagged transposon mutagenesis, DNA microarrays and other sophisticated genomic approaches to virulence gene detection, has been highly productive and has resulted in the identification of numerous candidate genes that may be associated with enhanced virulence by *Y. pestis* in humans. As the authors correctly allude to in their review, dissecting virulence determinants takes medical science one-step closer to understanding the global regulatory systems that impact the pathogen's life cycle in humans and other hosts.

For practicing physicians it can often be difficult to see how this type of genetic information can be leveraged into practical interventions. On the human side, knowledge of virulence genes and gene products has a direct impact on areas such as developing diagnostic tests and choosing rational targets for antimicrobial agents and vaccines. Because plague and numerous other zoonotic infections cycle between animal reservoirs and arthropod vectors in natural settings, knowledge of virulence determinants could lead to novel approaches to disrupting disease transmission prior to the organism entering human hosts and thus, eliminating the threat of plague to modern human society.

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