Smallpox: Pathogenesis and Host Immune Responses Relevant to Vaccine and Therapeutic Strategies

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1. INTRODUCTION

Recently, smallpox has been a disease of only historical interest since the certification of its eradication by the World Health Organization on May 8, 1980.\(^1\) However, there is a growing awareness and apprehension regarding possible bioterrorist threats with these concerns escalating since the tragedy on September 11, 2001. Accordingly, there is an increased interest in understanding smallpox-induced pathogenesis as well as in the development of new vaccines and therapeutics. This chapter will discuss the history of smallpox infection and its eradication. Discovery of methods for protection against naturally occurring smallpox infection will also be discussed, as well as clinical and epidemiological features of infection, virus structure and pathogenesis as well as host defense and the immune response. An improved understanding of the disease is leading to new methods of prophylaxis and therapy that are discussed in this chapter. In addition, current vaccination strategies will also be reviewed since the development and licensure of novel smallpox vaccines.
that may be safely used to immunize those with exposure and/or risk factors is currently of high priority.

2. HISTORY OF SMALLPOX INFECTION AND ITS ERADICATION

Once prevalent throughout the world as an endemic infection, wherever concentrations of population were sufficient to sustain transmission, smallpox usually found its major reservoir in children because there is no animal reservoir for smallpox. Therefore, the virus had to spread continually from human to human to survive with epidemics occurring when travelers carried the agent to outlying populations that lacked immunity. Smallpox was first described in South Africa by de Korte in 1904 and in the United States by Chapin in 1913, and subsequently became prevalent throughout the United States, parts of South America, Europe as well as some areas of Eastern and Southern Africa.\(^2\) The first evidence that smallpox emerged as a pathogen was some time after the first human agricultural settlements, about 10,000 B.C., while the first scientific evidence for smallpox was identified in the mummified remains of the 18\(^{th}\) Egyptian dynasty and Ramses V.\(^3\) Written descriptions of smallpox typically did not appear until the fourth century A.D. in China and the tenth century in southwestern Asia. However, earlier descriptions, although rare, did appear such as the one by Thucydides in 430 B.C. in Athens.\(^4\) There is no Greek or Latin word for smallpox, although the name \textit{variola}, derived from the Latin \textit{varius}, meaning pimple was first used during the sixth century by Bishop Marius of Switzerland. By the tenth century, the word \textit{poc} or \textit{pocca}, a bag or pouch, was used to describe smallpox and the prefix \textit{small} was used to distinguish variola, the “small pox”, from syphilis, the “great pox”\(^5\).

The first immunization procedure was termed “variolation”, in which material from pustules or scabs from infected persons were deliberately inoculated into the skin, a method first carried out in India sometime before A.D. 1000.\(^6\) This method resulted in an infection that was usually less severe than an infection acquired naturally by inhalation of droplets. Importantly, the method of variolation was brought to England by Lady Mary Wortley Montague. She had been disfigured by smallpox in 1715 and while in Istanbul with her ambassador husband she became aware of the practice of variolation. She, in fact, had her son and daughter “variolated” which led to some acceptance of this method, which then spread throughout England. Although a small percentage of individuals “purposely” infected by the variolation method did not survive, the mortality was considerably lower than in those naturally exposed and infected with smallpox. In 1796, Edward Jenner discovered that infection with a more benign poxvirus caused by cowpox virus, prevented subsequent smallpox infection. He called the material \textit{vaccine}, from the Latin \textit{vacca}, meaning cow. The process of \textit{vaccination} then began to be employed widely in many countries of Europe, and within a decade, it had been transported to countries throughout