Modern Concepts of Hepatitis A

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INTRODUCTION

Recent developments in virology, immunology, and molecular biology have greatly expanded our knowledge of hepatitis A. These advances have the potential for leading in the foreseeable future to preventive measures for hepatitis A virus (HAV) infections and possibly even to treatments for people who are already infected. This chapter reviews hepatitis A by answering the major questions important to physicians interested in liver disease in general and in hepatitis in particular. Hepatitis A is often relegated to poor relative status among hepatologists who find that the complexities of hepatitis B, the uniqueness of delta hepatitis, and the mystery of non-A, non-B hepatitis all provide more grist for the intellectual mill. We hope that this chapter will provide not only useful information but will also spark heightened curiosity about what we believe is an interesting medical and virologic problem.

WHAT IS HEPATITIS A?

Hepatitis A is probably an ancient disease noted from time to time by political as well as medical historians. Hepatitis A has long been recognized as a problem during wars and at times of social or political upheaval. The modern era for viral hepatitis research began during World War II, when infectious hepatitis was a major cause of morbidity throughout the war among both Allied
and Axis forces. In some areas of the Pacific theater, the incidence of infectious hepatitis (presumed HA) exceeded 80 cases per 1000 per year. Such attack rates as well as the outbreak of hepatitis B related to the yellow fever vaccine, which had been stabilized with pooled human serum, prompted both the British and American armies to sponsor research in human volunteers aimed at determining ways to control the disease.

These studies accomplished several goals: (1) clearly separated infectious hepatitis from serum hepatitis, (2) showed that the infectious agent could pass bacterial filters, (3) demonstrated that the common route of transmission was fecal oral, and (4) defined the incubation period and the duration of infectivity. These wartime studies were followed by the pioneering work of Krugman, Giles, Ward, and colleagues at the Willowbrooke State School. The Willowbrooke studies were most important for the development of reagents known to contain infectious hepatitis A or B viruses or antibodies to them, and these greatly accelerated the development of diagnostic tests. In 1973 the virus particle of HA V was first identified, in 1979 HA V was first cultivated in vitro, and in 1983 the viral genome was molecularly cloned.

Although this is an exceptionally brief history, we believe it is important to understand that recent developments in hepatitis research, as with all of science, were possible because of a deep foundation laid by many investigators over a long period.

Hepatitis A is an acute infectious disease that exhibits varying degrees of symptomatology. Many infected persons experience no symptoms whatsoever, while in rare cases fulminant hepatitis, coma, and death may ensue. Age has been shown to be the single most important determinant of the clinical expression of illness. For instance, in the Greenland epidemic of 1970–1974, Skinhoj et al. reported that hepatitis was detected in only about 1% of susceptible children under 1 year of age but increased to about 24% in children 15 years of age. By contrast, a serologic analysis of the 1969 hepatitis outbreak among the Holy Cross football team indicated that all the young adults and adults at risk who had serologic evidence of HAV infection were jaundiced, while those who were asymptomatic or who had nonspecific symptoms such as nausea showed no serologic evidence of infection.

The incubation period for hepatitis A, defined as the time from exposure to the onset of symptoms, ranges between 15 and 50 days, with a mean of about 28 days. It is not known precisely what determines the duration of the incubation period, but in experimental infections of primates the incubation period has been shown to vary inversely with the dose of administered virus. We showed in marmosets that $10^8$ infectious doses administered intravenously produced evidence of liver disease in about 1 week, while one infectious dose resulted in disease in about 7 weeks (Fig. 1). The severity of illness, however, was not directly related to dose.