The natural history of viral hepatitis

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During the past three decades many outstanding investigators have attempted to adapt human hepatitis viruses to laboratory animals and tissue cultures. In spite of many initial successes subsequent attempts by others have failed to confirm the first observations. Although epidemiological evidence has indicated that chimpanzees may be carriers of human hepatitis viruses, efforts to infect these animals have failed. Today, man still remains the only established susceptible host. Knowledge of the natural history of viral hepatitis has been retarded by the absence of specific virus isolation and serological procedures.

Before the discovery of Australia or hepatitis-associated antigen (HAA) knowledge of the natural history of viral hepatitis stemmed in great part from human volunteer studies which were conducted by various investigators during the 1940s,[1-5] the 1950s[6-8] and 1960s.[9-11] This discussion of the natural history of viral hepatitis will be based in great part on our studies which have been in progress at the Willowbrook State School since 1956.[7-11] The more recent discovery of Australia antigen by Blumberg *et al*,[12-13] its association with viral hepatitis, type B by Prince[14] and by our group [15] and the development of tests for the detection of HAA and antibody (anti-HAA) by various investigators[16-19] provided the technology needed for further studies of the natural history of viral hepatitis.

Viral hepatitis has been endemic at the Willowbrook State School since 1949. The background and the justification of our studies on the natural history and prevention of hepatitis in this institution and the method of obtaining informed parental consent were described in detail in previous publications.[7-11] During the course of these studies we have had an opportunity to observe patients from the time of exposure, during the incubation period, after onset of clinical manifestations and for many months and years thereafter. The serial samples of serum and stool which were collected provided valuable materials for the characterization of the clinical, epidemiological and immunological aspects of the infection. These prospective observations were made on two types of viral hepatitis which have been endemic at Willowbrook: (1) classic infectious hepatitis caused by the MS-1 strain of hepatitis A virus and (2) classic serum hepatitis caused by the MS-2 strain of hepatitis B virus.

Course of viral hepatitis, type A

The typical course of infectious hepatitis is illustrated in the upper part of Fig.1. After an incubation period of approximately 32 days there is a spiking rise in serum glutamic oxaloacetic transaminase (SGOT). The period of abnormal SGOT is transient, rarely persisting for more than three weeks. Jaundice, when present, usually appears at the time of peak SGOT activity. In general, the disease in children is apt to be anicteric and milder than in the adult. The thymol turbidity is consistently abnormal in icteric and anicteric infectious hepatitis. As indicated in Fig.1, the thymol turbidity becomes abnormal after the rise in SGOT, and it returns to normal levels later. The immunoglobulin M (IgM) pattern is essentially the same as the thymol turbidity pattern; levels are increased. There is a striking correlation between rising thymol turbidity and rising IgM levels.

As indicated in Fig.2, HAA was not detected during the course of viral hepatitis, type A. This study indicated that the incubation period was not affected by the type of exposure; it was approximately 32 days after an oral as well as after a parenteral exposure.

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Course of hepatitis virus, type B

The typical course of serum hepatitis is illustrated in the lower half of Fig.1. After an incubation period of approximately 60 days there is a gradual rise of SGOT values which reach peak levels approximately 30 days later. Jaundice, if present, usually appears at this time. The duration of abnormal SGOT activity may persist for many months. As indicated in Fig.3, hepatitis B virus is infectious by mouth as well as by parenteral inoculation. Unlike hepatitis virus A infection, the incubation period of hepatitis virus B infection is dependent upon the route of infection; it is approximately 65 days following a parenteral exposure as compared with 98 days after an oral exposure.

The detection of HAA during the course of viral hepatitis, type B is shown in Fig.3. The antigen appears in the blood approximately 30 to 40 days after a parenteral exposure to MS-2 serum. It is usually detectable two

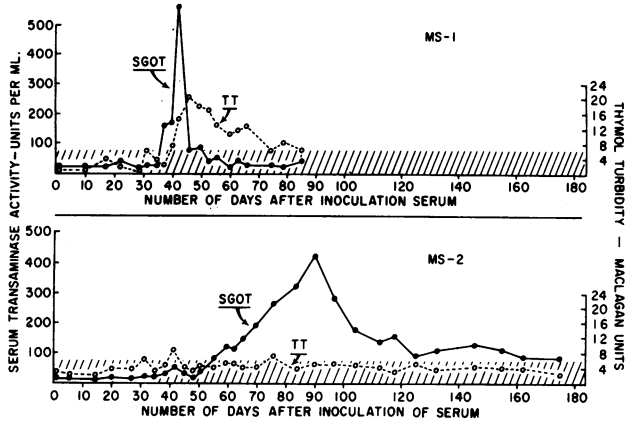

FIG. 1—Schematic illustration of serum glutamic oxaloacetic transaminase (SGOT) and thymol turbidity (TT) response following viral hepatitis type A (MS-1) and viral hepatitis, type B (MS-2). Jaundice when present is observed at time of peak SGOT. From Krugman S, Giles JP and Hammond J: *JAMA* 200:365, 1967.

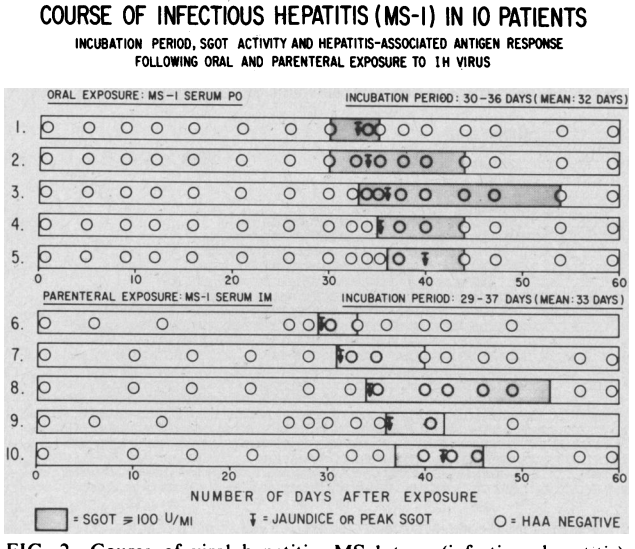

FIG. 2—Course of viral hepatitis, MS-1 type (infectious hepatitis) illustrating incubation period, SGOT activity, and HAA response in five patients following oral exposure (patients 1 through 5) and in five patients following parenteral exposure (patients 6 through 10) (PO signifies by mouth, IM signifies intramuscularly, ■ signifies SGOT value in 100 units/ml., ↓ signifies jaundice or peak SGOT value, O signifies HAA-negative). From Krugman S and Giles JP: *JAMA* 212: 1019, 1970.

Table I

Correlation of persistence of HAA with presence or absence of jaundice.

Total no. of cases	41
No. with transient HAA	25 (61%)
No. with persistent HAA	16 (39%)
No. of icteric cases	14
No. with transient HAA	13 (93%)
No. with persistent HAA	1 (7%)
No. of anicteric cases	27
No. with transient HAA	12 (44%)
No. with persistent HAA	15 (56%)

Transient = <120 days
Persistent = >120 days

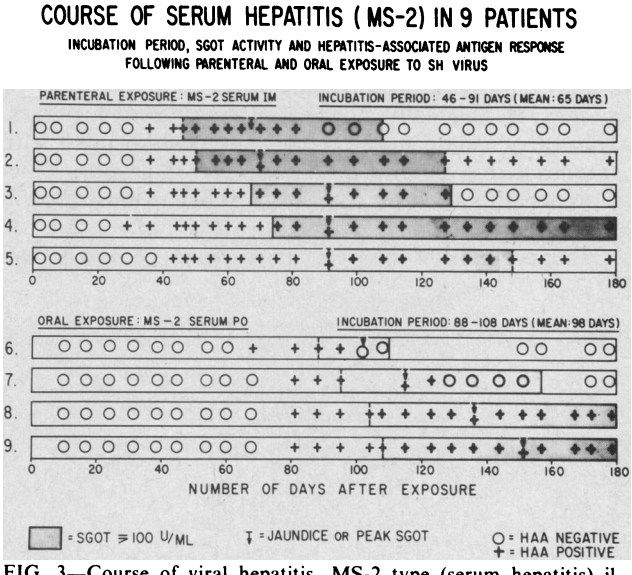

FIG. 3—Course of viral hepatitis, MS-2 type (serum hepatitis) illustrating incubation period, SGOT activity, and HAA response in five patients following parenteral exposure (patients 1 through 5) and in four patients following oral exposure (patients 6 through 9). IM signifies intramuscularly, PO signifies by mouth, ■ signifies SGOT in 100 units/ml., ↓ signifies jaundice or peak SGOT value, O signifies HAA negative, + signifies HAA positive. From Krugman S and Giles JP: *JAMA* 212:1019, 1970.

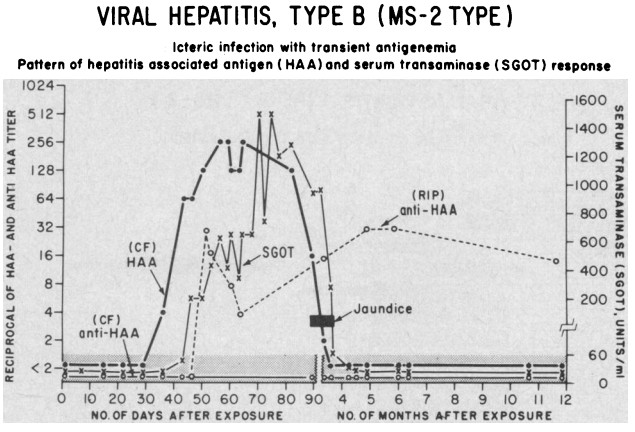

FIG. 4—Course of viral hepatitis, type B (MS-2 strain) illustrating (1) early appearance of HAA on day 36 and its persistence for three months; (2) subsequent rise in SGOT value on day 46, returning to normal at 3½ months; (3) absence of detectable complement fixation (CF) antibody (anti-HAA); (4) appearance of radioimmunoprecipitation (RIP) antibody on day 50; and (5) late appearance of jaundice at three months. Modified from Krugman S and Giles JP: *JAMA* 212:1019, 1970.

weeks to two months before evidence of abnormal SGOT activity. The occurrence of antigen in 49 of 50 (98%) consecutive cases of viral hepatitis, type B, MS-2 strain has confirmed the specificity of HAA for serum hepatitis.

The usual sequence of events following primary infection with hepatitis B virus is illustrated in Fig.4. The appearance of complement-fixing (CF) HAA precedes evidence of liver dysfunction as indicated by an elevation of the SGOT level approximately two weeks later. Jaundice is not detectable until day 90, shortly before CF HAA titres decrease to nondetectable levels. Complement fixing antibody has not been detectable following primary infection. As indicated in Fig.4, antibody is detectable when the more sensitive radioimmunoprecipitation (RIP) test is employed; RIP anti-HAA appears two weeks to two months after initial detection of HAA.

The duration of HAA in the blood is variable; it is usually transient, disappearing within several weeks or months. Occasionally, however, it may persist for years. This carrier state may or may not be associated with chronic active hepatitis. An example of primary anicteric hepatitis with persistence of HAA is illustrated in Fig.5.

The correlation between persistence of HAA and presence or absence of jaundice in children is illustrated in Figs.6 and 7 and summarized in Table I. The antigen was generally transient in icteric cases and more persistent in anicteric cases. The occurrence of persistent antigen in 39% of this group is unusual; it may represent a phenomenon related to the endemic conditions at the Willowbrook State School or to the large number of children with Down's syndrome in this group. In general, detectable HAA does not persist in adults who have had viral hepatitis, type B.

An extraordinary case of hepatitis infection without evidence of liver disease is illustrated in Fig.8. HAA has persisted for more than five years without evidence of abnormal liver function. This HAA-positive serum has been infectious for susceptible recipients.

Immunity to viral hepatitis, type A

Studies by Havens[20] and by our group[10] revealed evidence of homologous immunity following an attack of infectious hepatitis. However, there was no evidence of heterologous immunity. Hepatitis A infection did not protect against hepatitis B and hepatitis B infection did not protect against hepatitis A.

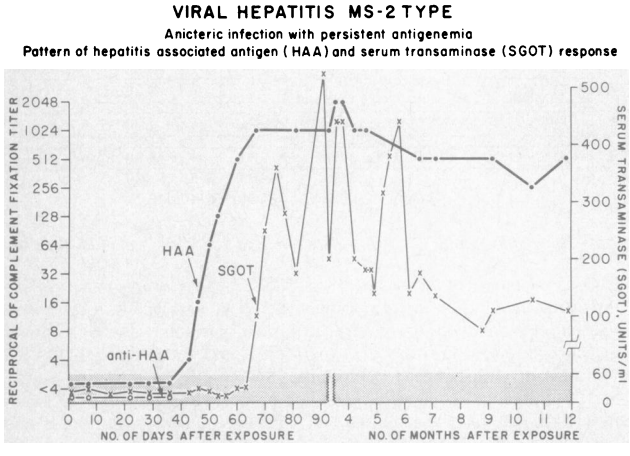

FIG. 5—Course of viral hepatitis type B (MS-2 strain) illustrating persistence of antigen and abnormal SGOT value for one year. From Krugman S and Giles JP: *JAMA* 212:1019, 1970.

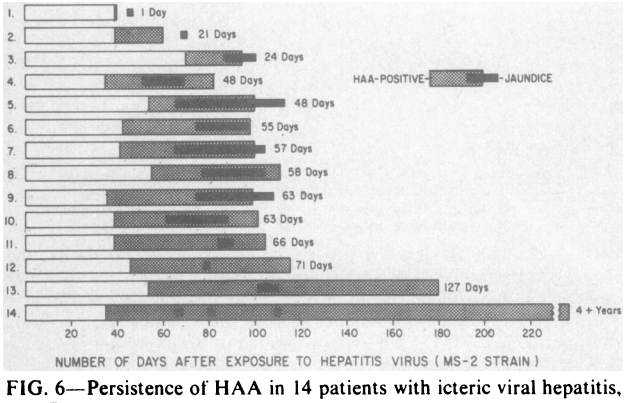

FIG. 6—Persistence of HAA in 14 patients with icteric viral hepatitis, type B.

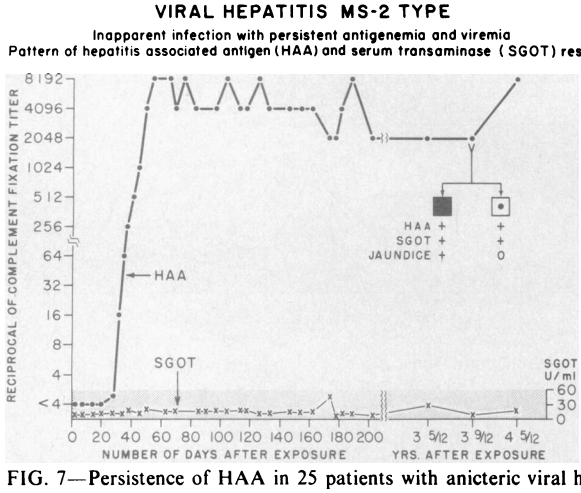

FIG. 7—Persistence of HAA in 25 patients with anicteric viral hepatitis, type B.

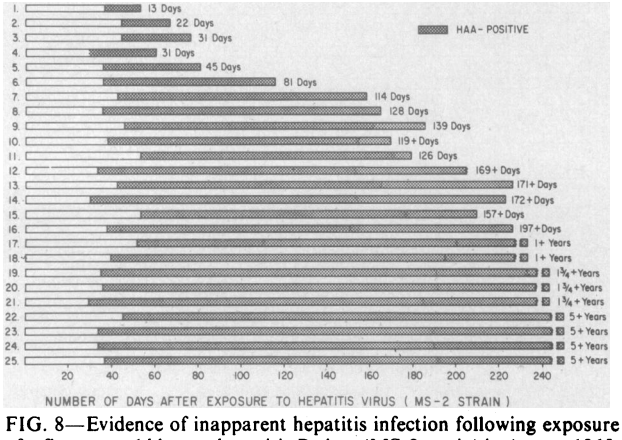

FIG. 8—Evidence of inapparent hepatitis infection following exposure of a five-year-old boy to hepatitis B virus (MS-2 strain) in August 1965. Antigen which was detected one month later persisted at very high levels for the four year, five-month period of observation. The child never had clinical or laboratory evidence of hepatitis. Serum obtained at 3¼ years was HAA-positive and caused hepatitis in two recipients, one icteric and one anicteric. From Krugman S and Giles JP: *JAMA* 212:1019, 1970.

Immunity to viral hepatitis, type B

In a recent report[11] we described studies which revealed evidence of homologous immunity following infection with hepatitis B virus, MS-2 strain. The results of these studies are illustrated in Fig.9. Exposure to infectious MS-2 serum on 12/23/68 was followed by typical hepatitis B virus infection with the appearance of HAA on day 36, abnormal SGOT on day 46 and anti-HAA on day 50. Re-exposure to the same dose of MS-2 serum one year later did not cause hepatitis infection. Consequently, homologous immunity to serum hepatitis was observed under the conditions of this study.

In a recent report[11] we described evidence of reinfection which was characterized by transient HAA of one week's duration, occurring 32 days and 137 days after an accidental inoculation of MS-2 serum; the SGOT was abnormal from day 137 to day 144. It was clear that the typical clinical manifestations of serum hepatitis were modified or prevented by immunity conferred by previous infection.

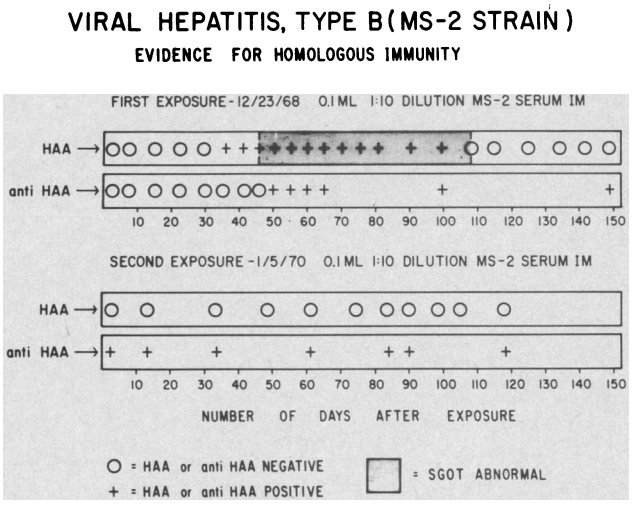

FIG. 9—Evidence for homologous immunity one year after first viral hepatitis, type B infection. First exposure to a parenteral inoculation of MS-2 serum was characterized by appearance of HAA on day 36 and abnormal SGOT on day 46. Second exposure to the same dose of infectious serum one year later revealed no evidence of HAA or abnormal SGOT. From Krugman S and Giles JP: *Tr Assoc Am Phys*, 83:133, 1970.

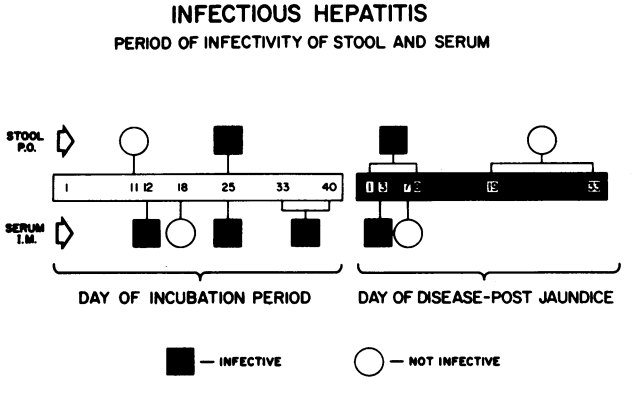

FIG. 10—Schematic illustration of the period of infectivity of serum and stool during the course of viral hepatitis, type A (infectious hepatitis).

Period of infectivity of patients with viral hepatitis

The period of infectivity of stool and serum during the course of viral hepatitis, type A is summarized in Fig.10. Virus was detected in the blood during the incubation period, two to three weeks before onset of jaundice. Viremia was also detected on the 12th day of the incubation period and on the third day but not on the seventh day after onset of jaundice. Virus was detected in the stools on the 25th day of the incubation period, two to three weeks before onset of jaundice and within the first eight days after onset of jaundice; it was not detected 19 to 33 days after onset of jaundice.

The period of infectivity of patients with viral hepatitis, type B is dependent upon the presence or absence of a carrier state. Detection of HAA in the serum is indicative of the presence of hepatitis B virus. Consequently, all secretions which are contaminated with blood or serum are potentially infectious. As indicated in Figs.3,4,5 and 8, HAA is detectable during the incubation period and for a variable period of time thereafter.

Conclusions

Studies of the natural history of viral hepatitis, types A and B, have been in progress during the past 15 years. These prospective observations were conducted in an institution where the disease has been endemic since 1949. The discovery of Australia antigen, its association with hepatitis B virus, and the development of tests to detect antigen and antibody provided the technology needed for the clarification of the clinical, epidemiological and immunological aspects of the disease. The studies described in this report provide background information which is needed to evaluate vaccines and immune serum globulin preparations for active and passive immunization.

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