Dr. Gocke reviewed his fairly recent experiences administering, intravenously, high-titered HB Ab plasma (1:2 to 1:4 by ACD) to patients with overwhelming viral hepatitis in stage three to four coma (this study did not include an untreated control group). All of the patients were probably also receiving corticosteroids, and some had received other overt measures, such as exchange transfus' · Five out of eight patients treated survived and in the survivals, th re no apparent untoward effects from the administration of antibody in orm given (i.e. plasma). Survival rate with antibody administration was ch greater than in a similar group of untreated patients with fulminant hepatitis. Dr. Prince raised the question of the absolute safety of administering type B antibody to antigen-positive subjects. He mentioned that he had seen what he had interpreted to be cardiac arrest in a chimpanzee with chronic HB Ag given somewhat inadvertently high-titered antibody (chimpanzee plasma).

Dr. Peters presented data that he and Dr. Schweitzer have collected in Los Angeles, having to do with the high rate of transmission of HB Ag infection from mothers to their infants. Overt antigenemia was observed in over 50% of the newborns whose mothers were antigen-positive very close to the time of delivery. The mother who was antigen-positive transiently early in the course of pregnancy seemed not to provide much risk to her child. All infants who were once positive have remained antigen-positive. An examination of histologic sections of nine biopsies from antigen-positive infants showed tissue which looked like unresolved or persistent viral hepatitis, with 24 nm particles demonstrable in the nuclei of about half of these biopsies. The incidence of antigenemia and hepatitis in infants was strikingly less when the mothers were chronic carriers of HB Ag than when the mothers had acute hepatitis B illness at the time of delivery. No globulin protection has been attempted.

Dr. Ward presented data from the study done in Chile on the effects of adding modified HB Ab gamma globulin (Swiss technique) to blood to be used in transfusion of young women. There was a definite and statistically significant reduction in the incidence of overt icteric hepatitis in patients receiving gamma globulin in comparison with patients receiving normal blood, although there was an equal amount of inapparent hepatitis in both treated and control patients.

Dr. Soulier presented his data on the clinical studies in France, using high-titered HB Ab globulin (no untreated controls were included in the study). In those patients who had received transfusions of blood containing HB Ag followed by a single 10 ml injection of HB Ab globulin after the transfusion, he found that only a small number of patients developed jaundice with or without antibody or antigen. Overt cases of hepatitis occurred in about 7 to 10% of the subjects who had received the HB Ab globulin. In the absence of controls of his own, he related this post-transfusion influence of gamma globulin administration on the incidence of overt hepatitis with other published studies of recipients of HB Ag-contaminated blood: With HB Ab gamma globulin administration, post-transfusion overt hepatitis was reduced to 1/4 - 1/3 the number of cases seen in untreated transfused patients. He also mentioned data from the Hospital Broussais (France): Among 21 untreated recipients of HB Ag and blood, 8 developed jaundice, where no jaundice was observed in 6 treated recipients of HB Ag and blood. When a single 5 ml injection of HB Ab gamma globulin was given to patients experiencing accidental parenteral exposure to hepatitis, no cases were observed and no subject became antigen-positive; some subjects did have a transient antibody rise. He concluded that 1) the HB Ab globulin that he was using was harmless in 117 subjects; it alone seemed to have no ill effects 2) prompt administration of high-titered HB Ab gamma globulin to "needle-stick" patients is effective in helping to eliminate hepatitis B illness.

In the future, the PHS regulations for the manufacture of biological products will have to include some standards for high-titered HB Ab gamma globulin, and Dr. Barker summarized some of the new issues being considered for future standards. Preparations of specific immune globulin must come from a pool of at least 10 donors. This gamma globulin must not transmit hepatitis B virus or cause immune-complex problems. Attenuation of the disease must not predispose the individual to chronic infection. HB Ab gamma globulin may have 14 ± 4% protein, and such gamma globulin preparations for intravenous use may have less than 10% protein. At least 80% of the protein must be monomeric globulins, preferably 5.5 - 7.5S. It is probable that future regulations for HB Ab gamma globulin will include restrictions on the content of isoagglutinin titers and transplantation antigen titers. Studies using HB Ab gamma globulin are just beginning, and the results of these studies will be used to determine potency and efficacy requirements. As knowledge is gathered on protective antibody or antibodies, standards on these parameters will be incorporated into the PHS regulations for HB Ab gamma globulin preparations.

Dr. Mosley reviewed his study on the effects of administering two forms of globulin (fragmented and unfragmented) to subjects with a household exposure to hepatitis A. All forms of gamma globulin gave some protection to hepatitis A and, interestingly, fragmented gamma globulin provided better protection when given late in the incubation period, compared to late administration of unfragmented globulin.

In summary, passive immunization is a feasible way to control both hepatitis A and hepatitis B infection in high-risk populations. As emphasized by Dr. Chalmers, initial trials of efficacy of high-titered HB Ab gamma globulin should be done in a double blind, random fashion.

III. Active immunization: The discussion on active immunization centered around a discussion of Dr. Krugman's Willowbrook studies on active immunization, using as the "vaccine" MS-2 serum (hepatitis B serum) that was diluted 1:10 and boiled for one minute. Live MS-2 material caused clinical hepatitis in 24 out of 25 cases. In a group of 10 patients receiving one dose of the "vaccine" followed by challenge with live MS-2 material four months later, only 5 out of 10 developed clinical hepatitis. A second group of 15 children received three doses of "vaccine" over a four-month period; this group was then challenged with live material four months after the last "vaccine" booster. Under these circumstances, 4 of the 15 subjects developed hepatitis marked by either antigenemia or transaminase rise; 11 of the 15 subjects developed only antibody (as detected by RIA or PHA techniques) or nothing. This "vaccine" schedule gave an apparent protection rate of 70%.

Dr. Soulier has also done some active immunization trials using undiluted HB Ag positive serum heated for 10 hours at 60°C. After heating, this material still maintained immunogenicity, and was able to produce an antibody rise, but it was also still infective, since one of seven recipients developed anicteric hepatitis with high-titered HB Ag and high level of transaminases.

The participants of this workshop noted that both human-type studies and animal model studies have important and different types of knowledge to give to the study of hepatitis B control. Human studies are necessary to test for the specific immunological aspects of the disease, while animal model studies will yield important information of the characteristics of the disease and disease agent. To develop a conventional hepatitis B vaccine for use in the general population might require growth of the hepatitis agent in a tissue culture system. Another logical approach to vaccine development would be to purify hepatitis B antigen, inactivate the purified material, and test this material in small groups of persons to see if it is as protective as the inactivated serum MS-2 "vaccine". A hepatitis animal model could be used to test potential hepatitis vaccines.

Dr. Raffel discussed immunological aspects of active and passive immunization. In view of Dr. Krugman's preliminary results with active immunization, of the fact that there seems to be ample HB-containing plasma stored, and of the disagreeable and dangerous nature of hepatitis and its high incidence in certain groups, the time may be ripe for carrying out controlled tests in high-target populations on the usual random selection basis, with relative incidence of disease in vaccinated and unvaccinated groups as the basis for obtaining further information. The work with primates has perhaps advanced sufficiently so that chimpanzees might be used as test animals for heat-inactivation of the infectivity of the serum used as vaccine. If the 20 nanometer particles are viral capsids, then purification of them might result in a purified subunit antigen which could be used as a vaccine. The possibility of immune complex disease, occurring from passive immunization, might be avoided by adding the HB Ab to the blood or blood product prior to administration, as described by Dr. Ward, or by treating the antibody and only administering the virus neutralizing fraction Fab_2. Lastly, more should be learned about the pathogenesis of the disease by doing specific cellular studies, e.g. tritium uptake, production of lymphotoxin, skin test, etc.

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HSM
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Bibliographic Notices

Participants are requested to send to the HSM a notation every time a manuscript on hepatitis research is accepted for publication. Notations may be sent, also, on pertinent publications by other authors.

HBN-199 - "Relationship of Milan antigen to abnormal serum lepoprotein" P. E. Taylor, J. D. Almeida, A. J. Zuckerman and J. M. Leach Amer. J. Dis. Child.,1972, 123: 329 - 333

To: HSM Participants

The Bibliographic Notices section has been included in the HSM since February 1971 and to date 199 publication citations have been received. Advice from a few hepatitis investigators indicates that the percentage of publications submitted to this section does not warrant continuation of this service in the HSM.

Before decision is made to delete the section, we invite comments from the HSM participants on the value of the Bibliographic Notices section and/or a greater contribution rate of publication citations. Comments can be sent to the Project Officer or submitted as a contribution to the HSM.

- Project Officer

June 1972
BSM – Annex

THE PUBLIC HEALTH IMPLICATIONS OF THE PRESENCE OF HEPATITIS B ANTIGEN IN HUMAN SERUM

A Statement By
The Committee[1] on Viral Hepatitis
of the
Division of Medical Sciences
NATIONAL ACADEMY OF SCIENCES – NATIONAL RESEARCH COUNCIL

Epidemiologic data for the United States since 1966 show steady annual increases in the incidence of type B hepatitis (serum hepatitis) and in its proportional representation among all reported cases of viral hepatitis, including type A (infectious) hepatitis. It is now recognized that, in addition to the well-established parenteral mode of transmission, type B hepatitis can be transmitted by other means. During the last few years, a clearer definition of the significance of type B hepatitis as a clinical and public health problem has arisen from the discovery, development, and widespread application of various serologic tests for the presence of an antigen, hepatitis B antigen[2] (HB Ag), that is associated with the disease.

The demonstration of the antigen in the serum of a patient or of an apparently healthy person raises questions not only of the presence of active liver disease but also of the potential risk of his transmitting the infection to others.

On the basis of information acquired from clinical and epidemiologic studies and from antigen testing programs, the Committee on Viral Hepatitis finds that:

1. A positive test is indicative of the presence of acute or chronic type B hepatitis or of the asymptomatic carrier state.

2. The presence of the antigen in the serum of a patient with acute type B hepatitis is usually transitory. If it persists for more than 3 months after the onset of illness, the person is likely to become a chronic carrier of the antigen.

3. The chronic carrier of the antigen may or may not have readily demonstrable evidence of related liver disease.

4. Although the infectiousness of patients with antigen-positive hepatitis apparently diminishes when the antigen is no longer demonstrable in the serum, they are not suitable as blood donors.

5. There is clear evidence that carriers should be prohibited from donating blood for transfusion.

6. There is insufficient knowledge of the extent to which chronic carriers can transmit type B hepatitis by non-parenteral routes.

The Committee recommends that:

1. When a person is found to have a positive test in the course of diagnostic studies, blood donor testing, or testing after exposure to a known risk of infection with type B hepatitis, he be so informed and the test be repeated promptly on a later sample of serum, and a person with a confirmed positive test be evaluated for the presence of liver disease and followed to determine whether the antigen persists.

2. Patients with acute antigen-positive hepatitis be considered infectious and control measures be taken with respect to potentially infectious materials such as blood and blood-contaminated secretions.

3. Testing be required of all blood donors, although, with respect to risk of transmission to others, there is no reason at this time to recommend routine testing of any specific professional or occupational group or of all hospital patients.

4. Until more complete knowledge of the significance of the antigen carrier state is acquired, particularly as to its prevalence and its relation to communicability, no routine precautions be instituted beyond those which apply to percutaneous routes of potential transmission.

5. Because standard Immune Serum Globulin (ISG) is of no demonstrable value in the treatment of carriers, it not be used for this purpose nor is there adequate evidence to recommend the use of standard ISG for prophylaxis among contacts.

6. An intensified effort be made to report hepatitis cases – on the basis of serologic test results, as well as epidemiologic characteristics – in order to improve surveillance on a national basis.

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This statement has been endorsed by the American Association of Blood Banks, the Committee on Transfusion and Transplantation of the American Medical Association, and the American National Red Cross.

[2] This antigen has been referred to as Australia antigen (Au Ag), hepatitis antigen (HA), serum hepatitis (SH) antigen, and hepatitis-associated antigen (HAA).