MEDICAL GRAND ROUNDS

July 21, 1977

University of Texas, Southwestern Medical School at Dallas

James Shorey, M.D.

THE HEPATITIS VIRUSES AND ASSOCIATED DISEASES: SOME ISSUES OF CURRENT INTEREST

THE VIRUSES

Hepatitis A Virus
Hepatitis B Virus
  Core Antigen and Antibody
  DNA Polymerase
  The e System
Non-A, Non-B Hepatitis Viruses

THE ROLE OF HEPATITIS VIRUSES IN ACUTE AND CHRONIC LIVER DISEASES

SOME SPECIAL PROBLEMS OF HEPATITIS VIRUS TRANSMISSION

Post-Transfusion Hepatitis
Maternal-Fetal Transmission
HBsAg-Positive Medical Personnel

SPECIFIC ANTIVIRAL THERAPY

Immunotherapy
Transfer Factor
Interferon

PREVENTION OF HEPATITIS VIRUS INFECTION

Passive Immunization
  Hepatitis A Prophylaxis
  Hepatitis B Prophylaxis
  Prophylaxis of Non-A, Non-B Hepatitis
Active Immunization

Since World War II it has been recognized that at least two different types of viral hepatitis exist. These diseases, identified as infectious and serum hepatitis, were distinguished primarily on the basis of epidemiologic evidence and were presumed to be due to two different viruses. When Blumberg's discovery of Australia antigen in the 1960's made it possible to identify one of these viruses, it became clear that diagnoses based on epidemiologic features were often incorrect. While some patients with post-transfusion ("serum-") hepatitis had the Australia antigen marker in their blood, many others did not. On the other hand, many hepatitis patients without a history of "parenteral exposures," considered to have infectious hepatitis, were Australia antigen (HBsAg) positive. For this reason the terms infectious- and serum hepatitis were replaced with the terms type A- and type B hepatitis, respectively, which MacCallum had proposed 30 years ago (1).

When, more recently, it became possible to identify the hepatitis A virus also, it became evident that one or more additional, and yet unidentified, "non-A, non-B" hepatitis viruses were important causes of liver disease.

A tremendous volume of literature concerning the hepatitis viruses has appeared in the past decade. Several issues which currently are of special interest are considered in this selective review.

TABLE I

THE TERMINOLOGY OF HEPATITIS VIRUSES AND ASSOCIATED ANTIGENS

The World Health Organization Expert Committee on Viral Hepatitis has recommended the following nomenclature for the hepatitis viruses (2).

HBV	Hepatitis B virus. The 42 nm double-shelled virus originally known as the Dane particle.
HBsAg	Hepatitis B surface antigen. The hepatitis B antigen found on the surface of the virus and on accompanying unattached 22 nm spherical particles and tubular forms.
HBcAg	Hepatitis B core antigen. The hepatitis B antigen found within the core of the virus.
HBeAg	The e antigen, which is closely associated with hepatitis B infection. The two e antigen subdeterminants are designated HBeAg/1 and HBeAg/2.
Anti-HBs	Antibody to hepatitis B surface antigen.
Anti-HBc	Antibody to hepatitis B core antigen.
Anti-HBe	Antibody to the e antigen.
HAV	Hepatitis A virus.
Anti-HAV	Antibody to hepatitis A virus.

THE HEPATITIS VIRUSES

Hepatitis A Virus

Much epidemiologic information about hepatitis A virus (HAV) infection has been gathered in the past three to four decades (3-5). The ability to study this agent was greatly advanced by the identification in 1973 of HAV by Feinstone and associates (6). Using the technique of immune electron microscopy (IEM), these investigators showed that serum of persons who had recovered from clinically documented hepatitis A caused the agglutination of 27 nm virus-like particles in extracts of feces from acute hepatitis patients. There was no viral agglutination by pre-inoculation serum from patients in two experimental hepatitis A studies, or by acute phase sera from patients of two naturally occurring outbreaks, but convalescent sera from each of these same patients caused HAV clumping, as observed by IEM. No such seroconversion was found in patients tested before and after an episode of acute type B hepatitis.

HAV is suspected to be an RNA virus, but this is unproven (7). There is no evidence for more than one serotype.

Experimental HAV infections have been induced in chimpanzees and marmosets (South American monkeys) (8). Unfortunately, chimpanzees are expensive and marmosets are very difficult to obtain. The virus has been identified in liver cell cytoplasm, serum, and bile, as well as in feces of experimentally infected animals.

Additional assay methods for HAV and anti-HAV have been developed, including complement fixation, immune adherence hemagglutination, and radioimmunoassay. Unavailability of suitable antigen preparations has confined the establishment of HAV assays to a small number of laboratories, but, according to rumor, a commercial HAV radioimmunoassay may become available in the near future.

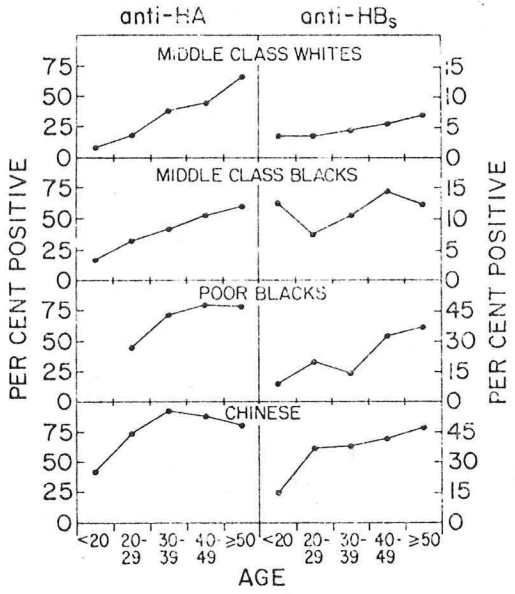
HAV is believed to be maintained in human populations by person-to-person transmission (9). The majority of infections are asymptomatic and unrecognized, as evidenced by the fact that the great majority of anti-HAV positive adults (over half of middle-aged and older persons; Figure 1) have no recollection of having had hepatitis (10).

There is no evidence that either healthy or diseased (*i.e.*, chronic hepatitis) viremic carriers of HAV exist (9). There may be occasional intestinal carriers (11), but they are not considered the source of a significant number of HAV infections (9).

Transient hepatitis A viremia occurs in the acute illness but is probably a brief event (a few days) which may partly explain the rarity of type A post-transfusion hepatitis (12-13).

The period of communicability by fecal contamination is also brief (Figure 2), and the virus typically disappears from the stool at about the time of peak transaminase levels (14)

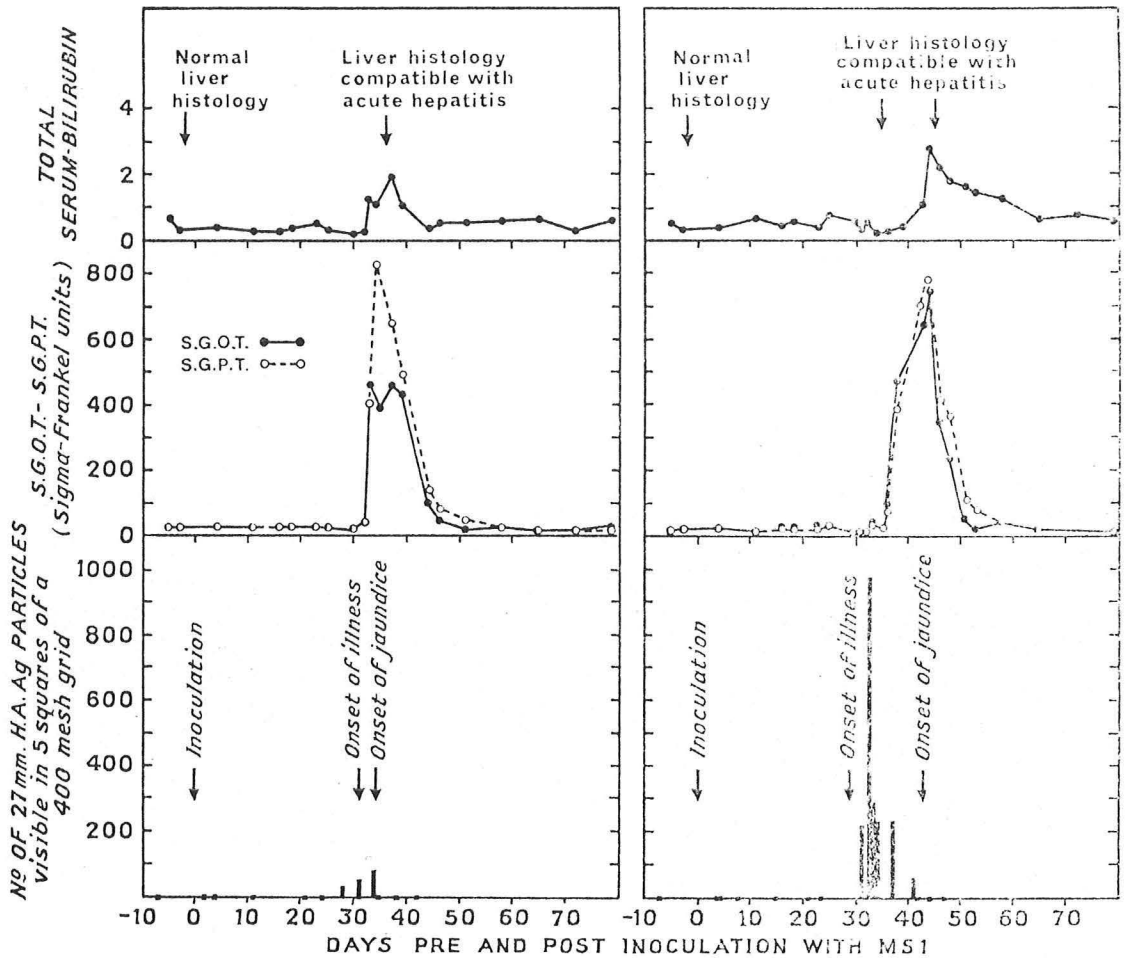
Figure 1 (Ref. 10)



Percentage Prevalences of Antibody against Type A Hepatitis (anti-HA) and Type B Hepatitis (anti-HB_s) According to Age in Four Populations from the Greater New York Metropolitan Area.

Anti-HB_s determination was done by passive hemagglutination in 8642 middle-class whites, 783 middle-class blacks, 178 poor blacks and 666 Chinese.[8] Note the different vertical scales used for anti-HA and anti-HB_s.

Figure 2 (Ref. 14)



Pattern of HAAg particle shedding in fæces and progress of clinical illness in case 1 and case 2.

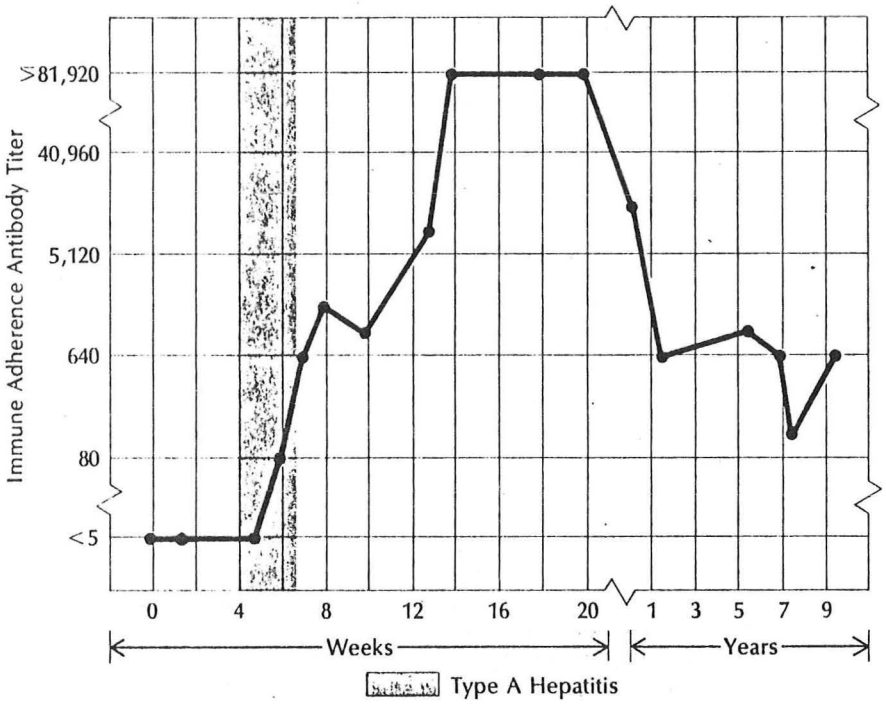
S.G.O.T. = serum-glutamic-oxaloacetic-transaminase. S.G.P.T. = serum-glutamic-pyruvic-transaminase.

Common source outbreaks of hepatitis A from fecally contaminated food or water are often well publicized but account for only a minor fraction of all HAV infection. Shellfish gathered from sewage-polluted waters are a significant hepatitis risk (15).

Since HAV infection is consistently followed by an anti-HAV response which lasts for many years (5) (Figure 3), surveys of anti-HAV prevalence provide useful information about the frequency of past exposure to this virus in different populations. The findings in such studies have been as might be expected - that the acquisition of anti-HAV positivity with age occurs more rapidly in lower socio-economic groups (Figure 4). Even in the most "advantaged" groups, however, immunity reaches about 75% by middle age (10,16) (Figure 1).

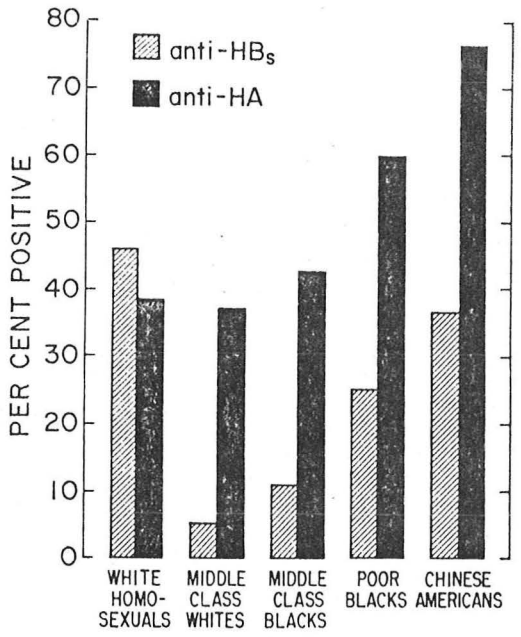
Recovery from hepatitis A confers essentially complete immunity to reinfection with this virus (17), and the presence of anti-HAV in serum is considered "proof" of such immunity.

Figure 3 (Ref. 5)



Graph shows response, over a decade, of one hepatitis A patient's serum to immune adherence (IA) antibody test. High titer of IA antibody was detectable within a month after onset of hepatitis A, and titer was still significantly high nine years later.

Figure 4 (Ref. 10)

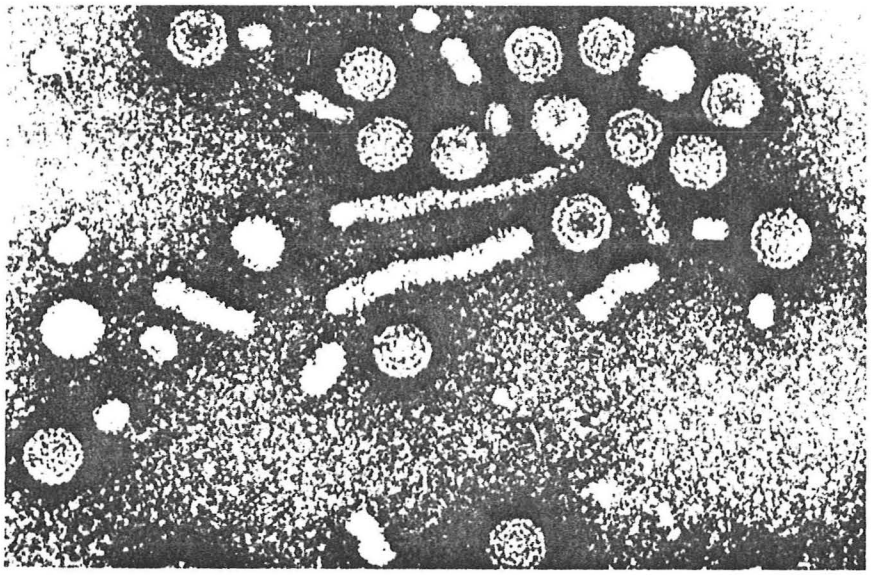


Sex-Age Standardized Prevalences (%) of Antibody against Type A and Type B Hepatitis in Five Population Samples from New York.

Hepatitis B Virus

The discovery of Australia antigen (18), for which Blumberg recently received the Nobel prize, is the critical event which led to identification of the hepatitis B virus. When Australia antigen positive serum was first examined by electron microscopy (19), numerous spherical particles averaging 22 nm in diameter were seen, and later, elongated tubular forms of the same diameter were found. In 1970, Dane and associates identified a 42 nm spherical, double-shelled particle, sometimes containing a dense core in some Australia antigen positive serum specimens (20). It is now almost certain that this Dane particle is the actual hepatitis B virus (HBV) (Figure 5). The small spherical forms (sometimes called Australia particles) and the tubular forms share common antigens with the envelope protein of the Dane particle. As a group, these antigens are called hepatitis B surface antigen or HBsAg. HBsAg includes an antigen common to all different species of the virus, the a antigen, as well as several subgroup-specific antigens designated d, y, w, r, *etc.* by which different viral subtypes can be identified. Antibody to HBsAg (anti-HBs) with anti-a and sometimes anti-subdeterminant specificity develops in most persons who have recovered from HBV infection, and may be present in very high titer in persons, such as hemophiliacs, who have had repeated HBV exposures from blood transfusion.

Figure 5 (Ref. 5)



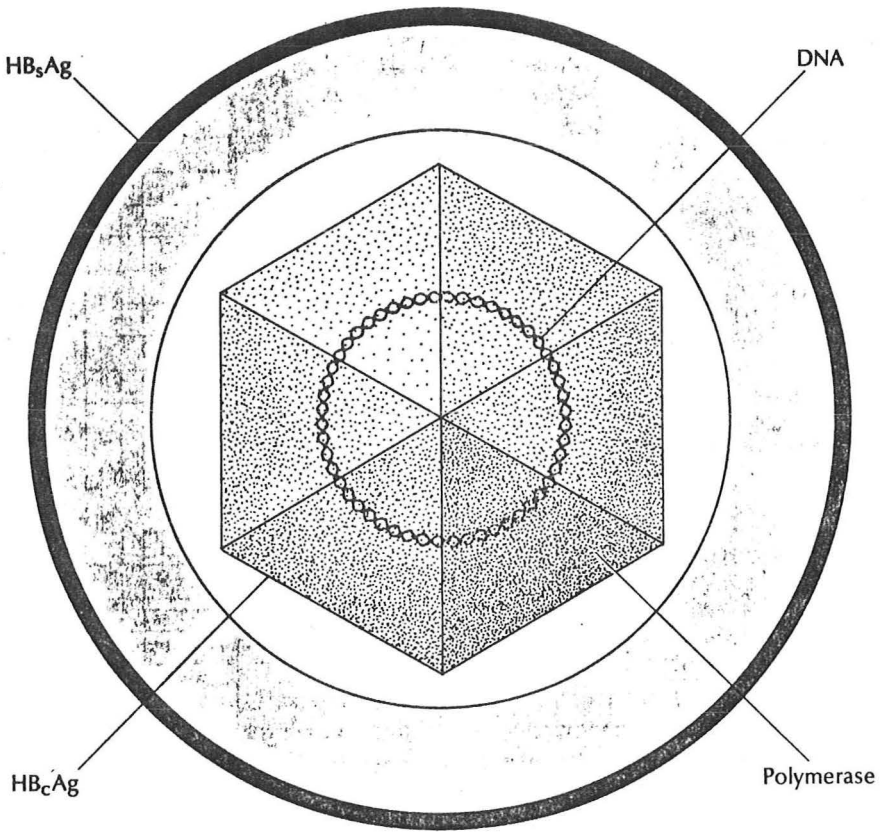
Three morphologic forms of hepatitis B antigen (below) are seen in electron micrograph made by Dr. June D. Almeida, Wellcome Foundation Ltd. Research Laboratories, Beckenham, England. The large round form is the 42 nm Dane particle (the virus); the small round and elongated forms are hepatitis B surface antigen.

Another antigen, hepatitis B core antigen (HBcAg), is specifically located on the core of the Dane particle, and antibody to HBcAg (anti-HBc) is found in serum during and after HBV infection (21).

e antigen and anti-e constitute the third antigen/antibody system associated with HBV (22). These reactivities are further discussed below.

Dane particle cores may be found in large numbers in the nuclei of infected liver cells where they are presumed to be synthesized. The HBsAg-protein is produced in the cytoplasm where some is applied to Dane cores as the HBV envelope, while other HBsAg, produced in great excess, is released directly into the circulation (Figure 6).

Figure 6 (Ref. 5)



Structure of hepatitis B virus (Dane particle) is visualized by Drs. R. H. Purcell and J. L. Gerin, National Institutes of Health, as having outer and inner rings (cf bottom micrograph, p. 40) and hexagonal core containing polymerase and circular DNA.

It is now evident that HBV is a DNA virus (23). The small (mw 1.6 million) circular, double-stranded DNA is located in the core of the Dane particle, and a specific DNA polymerase has also been identified in purified cores. The character

of Dane core DNA and the incorporation of DNA polymerase into the viral nucleocapsid (core) are features sufficiently unique to indicate that HBV is not a member of any known group of viruses (24).

It is important to recognize that the HBV infectious potential of serum or other biologic materials is probably a reflection, primarily, of the quantity of Dane particles in that material. HBsAg tests measure the total quantity of HBsAg protein in serum. The bulk of this HBsAg protein is in the form of Australia (22 nm) particles and tubular forms which contain no DNA and so are noninfectious. Dane particle coat HBsAg constitutes only about 1/1000th part of the total amount of circulating HBsAg protein (25). The ratio of Dane particles to Australia particles plus tubules may vary greatly so that some serum specimens with high concentrations of HBsAg may have very small numbers of Dane particles and accordingly may be of low infectious potential. Since the infectious risk of a particular HBsAg-positive individual is believed to parallel the titer of Dane particles in his serum, it may be of considerable importance to be able to measure serum concentrations of Dane particles. This information can be obtained from direct visualization of the particles by electron microscopy, or by measurement of HBcAg, or DNA polymerase. But these determinations are difficult and require expensive equipment. Essentially the same information is provided by measurement of e antigen, an HBV associated factor of uncertain nature. Because Dane particles, e antigen, HBcAg, and DNA polymerase all tend to occur in parallel (26,27) and, among these indicators of infectivity, e antigen is the most easily measured, the clinical significance of these factors is discussed below only with reference to e antigen.

Core Antigen and Antibody

HBcAg can be identified in serum containing Dane particles, but this requires, first, the separation of the Dane particles from anti-HBc which is usually also present in the serum, and then the splitting of the Dane particle envelope by detergent to expose HBcAg on the core. Failure to first remove endogenous anti-HBc leads to its prompt binding to-and obscuration of the core HBcAg, making it undetectable by immunoassay (28). These cumbersome methodological requirements make routine assay of HBcAg in serum impractical.

HBcAg can be identified by immunofluorescence in the nucleus of HBV-infected liver cells where Dane particles are being synthesized (29).

Sensitive assays - complement fixation (30) and, especially, radioimmunoassay (24,31) - have been developed for detection of anti-HBc. In early studies (30), anti-HBc was identified in each of 100 chronic HBsAg carriers but in only two of 200 HBsAg negative blood donors. Anti-HBc occurred regularly in the course of acute type B hepatitis, first appearing four to ten weeks after the appearance of HBsAg and before the onset of clinical hepatitis (32).

In 1974, Krugman (33) and Hoofnagle (34) reported data suggesting that anti-HBc positive donor blood which was HBsAg negative might carry a risk of transmitting type B hepatitis and that routine screening of donor blood for anti-HBc in addition to HBsAg might be advisable. Noting the rapid "disappearance" (as measured by complement fixation) of anti-HBc after resolution of acute hepatitis B, and its

persistence in chronic HBsAg carriers and chronic hepatitis patients, they proposed that anti-HBc, even without coexistent HBsAg, might be evidence of HBV replication. The absence of further reports supporting this idea, even with the availability of sensitive radioimmunoassays, is implicit evidence that anti-HBc cannot necessarily be considered indicative of active HBV infection.

DNA Polymerase

Hirschman first described a DNA polymerase specifically associated with HBsAg positive serum (35). He regarded this as an RNA-dependent enzyme because its activity appeared to be sensitive to RNAase treatment. Kaplan, Robinson, Greenberg and associates at Stanford have done extensive work with this enzyme (24, 36,37,38) and have convincingly demonstrated that this is actually a DNA-dependent DNA polymerase and that the circular ds-DNA of the Dane core is a primer-template for the enzyme.

DNA polymerase activity is demonstrable in serum containing intact Dane particles but is enhanced after detergent treatment which removes the HBsAg shell from the Dane core. The same enzyme is identified in naked Dane cores which can be extracted from the nuclei of HBV-infected liver cells.

Recent evidence suggests that the DNA polymerase integrated into the Dane core structure is a repair enzyme, rather than the enzyme primarily responsible for synthesis of the viral DNA (38).

The e System

In 1972 Magnius reported the occurrence of precipitin lines between certain pairs of HBsAg-positive serum specimens being tested by agar gel diffusion and designated these reactants e antigen (HBeAg) and anti-e antibody (anti-HBe) (22).

While the precise nature of e antigen is still uncertain, it is clear that:

1. e antigen and (with rare exception) anti-e are found only in HBsAg-positive serum specimens (39).

2. e antigen is physically separate from the HBsAg-bearing particles (39,40).

3. e antigen is distinct from core antigen (HBcAg) (41) and is not the immunologic representation of DNA polymerase (42).

4. Despite early contrary evidence (43), e antigen and anti-e are not associated with any particular subtype of HBV (44).

5. There are at least two separate e antigens, designated e_1 and e_2 (HBeAg/1 and /2), which may appear in the same serum specimen, or independently (40).

6. There is a close association between e antigen, Dane particles (45-47), and DNA polymerase (46,48,49) and each of these factors relates to the infectious risk of the patient, as is described below.

It is still not known whether e antigen is produced by the host in response to HBV infection or if it is a product of the virus itself.

The methodology for identification of e antigen remains rather primitive, being limited to agar gel diffusion and counterelectrophoresis. Several investigators have tried to develop red cell agglutination tests and radioimmunoassays for e antigen/anti-e but, thus far, such efforts have been unsuccessful. The sensitivity, and perhaps even specificity, of the assays currently used in various laboratories may differ considerably. Data collected up to the present time may undergo revision when better tests are available.

TABLE II

e ANTIGEN IN HBsAg-POSITIVE PATIENTS: COMBINED DATA*

DISEASE	NUMBER OF PATIENTS TESTED	NUMBER OF PATIENTS e POSITIVE	PERCENT e POSITIVE
Healthy HBsAg Carriers	211	2	1
Acute Hepatitis	676	82	12
**Chronic Hepatitis	289	113	39
Chronic Hemodialysis	71	45	63

*References 22,44,45,47,50,52,55,59,62,70
**Includes chronic persistent- and chronic active hepatitis.

Clinical Significance of e Antigen and Anti-e

There are three important areas where knowledge of e antigen/anti-e status may be of value to the clinician:

First, there is evidence that the persistence of e antigen in patients with acute type B hepatitis may be the first indication of progression to chronic hepatitis (45,50). Such information would be especially important if, in the future, the means become available to prevent such progression to chronicity. Lam, *et al.*, showed that early in the course of acute hepatitis B, the majority of patients were e antigen positive, but in most the antigen had disappeared by the time the transaminase value reached its peak (51,52). Overall, about 10% of patients with acute type B hepatitis progress to chronic disease (53). Nielsen (45) observed that 11 of 19 acute hepatitis patients who were e antigen positive later developed chronic hepatitis, as did seven of 13 e positive patients in Fay's series (50). In exception to these observations, however, of 11 e antigen positive acute hepatitis patients followed by Thamer, chronic disease developed in only one (54).

Second, among chronically HBsAg-positive persons, e antigen is associated with the presence of liver disease, *i.e.*, chronic persistent- or chronic active hepatitis (45,47,50,52,55-58). By contrast, anti-e is usually found in "healthy" carriers of HBsAg who have normal liver function tests and normal liver histology (55,59). Hemodialysis patients may be exceptional in this regard; Nordenfelt found e antigen in serum of all 17 HBsAg-positive patients in one dialysis unit and five of the 17 had normal liver biopsies (60). Although there is tentative evidence that HBsAg-positive chronic active hepatitis patients may respond less well to therapy than HBsAg-negative patients (61), preliminary data suggest that the e antigen negative hepatitis B patients do, in fact, respond to treatment (62, 63).

Third, and perhaps most importantly, e antigen is a marker of HBV infectivity, and anti-e indicates a relative lack of infectivity. There is a high incidence of e antigen positivity among HBsAg-positive hemodialysis patients and among chronic hepatitis patients (see Table II). Patients in both of these groups are known to be at considerably increased risk of transmitting HBV to their contacts (64). Although anti-e positive serum, in sufficient quantity, has been proven infectious (65,66), the risk is relatively low. In a retrospective survey of 95 recipients of blood donated by 10 anti-e positive HBsAg carriers, Magnius failed to identify any cases of overt post-transfusion hepatitis (52). Others have noted the "incomplete" infectiousness of HBsAg-positive donor blood (67). Serum of "donors" and "recipients" of positive blood who were enrolled in the VA Cooperative Needlestick Study were tested for e antigen and DNA polymerase (68). Of 20 DNA polymerase positive donors, 18 were also e antigen positive, and hepatitis B developed in 14 persons exposed to the blood of these donors. No hepatitis occurred among 11 recipients of e antigen/polymerase negative blood. In a similar study sponsored by the NIH (NHLI), 62 of 104 (60%) persons with e antigen positive needlestick exposures developed hepatitis B (or anti-HBs), whereas this occurred in 31% of persons receiving e negative inocula (69).

Non-A, Non-B Viruses

Certain evidence indicates that many cases of non-B hepatitis cannot be attributed to hepatitis A infection either. That evidence includes the following observations.

First, the infrequency of secondary cases associated with adult non-B hepatitis patients (9); unless gamma globulin has been administered prophylactically, type A hepatitis is readily transmitted to family members and other close contacts.

Second, the occurrence of two or more separate episodes of non-B hepatitis in individual patients (71) despite the essentially complete immunity to re-infection which regularly follows recovery from type A hepatitis (5).

Third, the frequency of non-B hepatitis cases with incubation periods exceeding 50 days; the maximal incubation period of hepatitis A is about 45 days (72,73).

Finally, with the advent of specific serologic tests for hepatitis A, the recognition of patients with acute hepatitis in whom the involvement of HAV, HBV, CMV, and Epstein-Barr viruses can all be specifically excluded (12, 13).

Identification of Non-A, Non-B Viruses

Despite the efforts of several investigators, no non-A, non-B agent has yet been identified either by direct visualization (electron microscopy) or by immunologic methods. The elusiveness of this virus is suggested by the experience of Purcell and associates at the NIH and Bureau of Biologics (74). They examined a collection of serum specimens obtained from prisoner volunteers studied by Murray, *et al.*, over 20 years ago (75). The prisoners had been inoculated with serum from persons known previously to have transmitted hepatitis by means of blood transfusion. More recent studies of the stored donor- and recipient serum specimens have shown that two of the donors were HBsAg positive; all recipients of their serum showed serologic evidence of HBV exposure (HBsAg antigenemia, anti-HBc, and/or primary or secondary anti-HBs responses), and several developed clinical hepatitis. The four remaining donors were HBsAg negative. The serum of one of these four donors caused clinical hepatitis in seven of 15 recipients. There was no serologic evidence of either hepatitis A - or hepatitis B virus infection in any of these 15 prisoners (76). Purcell's group examined the donor serum, "proven" to contain non-A, non-B virus in these human transmission studies, by electron microscopy and were unable to identify viral particles. Chimpanzees inoculated with this serum failed to develop hepatitis (74).

The failure of such sophisticated investigations to identify non-A, non-B virus may not be surprising when one considers the circumstances of the discovery of the type A and type B viruses. Hepatitis B virus (as Australia antigen) was first identified using agar gel diffusion, a very insensitive method. This was possible because of a unique and peculiar property of the hepatitis B virus - *i.e.*, the production of excess viral coat protein (HBsAg) in tremendous quantities and the release of this material into the circulation. If only the infectious virus (Dane particle) were present in the blood this might escape detection by even the most sensitive of current HBsAg assays. Similarly, the relatively great quantities of hepatitis A virus shed into the GI tract enabled its identification in the feces.

Presuming that the failure to identify non-A, non-B viruses in serum (or feces?) reflects the absence of these advantageous properties which characterize type A and type B viruses, the next area in which to search for such new agents would be in the liver of patients with non-A, non-B hepatitis. A single report of the possible demonstration of viral particles in the liver of such a patient has appeared (77). It would seem logical to examine hepatitic liver tissue by immunofluorescence also, using the serum of multiply transfused (*e.g.*, hemophiliac) persons as the presumptive source of "anti-HCV" antibody.

Clinical features of acute non-A, non-B hepatitis, in comparison with acute hepatitis B, are summarized in Table III.

TABLE III

COMPARISON OF TYPE B AND TYPE NON-A, NON-B ACUTE VIRAL HEPATITIS

Reference	Number of Cases		Incubation Period Weeks	Maximal Bilirubin mg/dl	Maximal Transaminase	Other Data
					SGOT (iu)	Number Hospitalized
Gocke (67)	Type B	35	-----	9.0	1159	23/35
	Non-B	17	-----	1.7	414	1/17
				(% icteric)	SGPT (ku)	Duration SGOT > 60 (weeks)
Prince (72)	Type B	15	10.4 ± 4.9	47%	318	8.9
	Non-B	36	8.0 ± 2.7	39%	259	10.5
					SGPT (iu)	Progression to Chronic Hepatitis
Alter (73)	Type B	4	14.5 (8-23)	7.8 (0.6-24)	857	1/4
	Non-B	8	9.4 (6-22)	1.3 (0.4-5.3)	470	1/8
					SGPT (mu)	Overt Hepatitis
Knodell (78)	Type B	4	-----	2.2 (0.7-5.1)	151	1/4
	Non-B	30	-----	1.6 (0.1-10.0)	256	7/30
					SGOT (mu)	Hospital Stay (Days)
Sandler (79)	Type B	42	-----	12.0 (1.5-58)	2360 (75-8720)	24 (9-52)
	Non-B	113	-----	8.4 (1.0-33)	1460 (80-8000)	10 (3-63)

THE ROLE OF HEPATITIS VIRUSES IN ACUTE AND CHRONIC LIVER DISEASES

Since 1966 the US Public Health Service (CDC) has reported hepatitis incidence data in terms of "infectious-" (later type A) and "serum" (type B) acute hepatitis. These diagnoses are made by the reporting physicians and originally were based entirely on epidemiologic information. More recently, the diagnosis of type B hepatitis presumably has been made on the basis of a positive HBsAg test. Since January, 1974, the third category of "type unspecified" has been included (Figure 7). For the first 26 weeks of 1977, 29,407 cases of acute hepatitis were reported to the CDC, among which 60% were considered type A, 25% type B, and 15% type unspecified (80). It is likely that when specific tests for hepatitis A virus infection become generally available many cases now considered hepatitis A (which often is simply a guess) will be moved into the type unspecified category as more accurately defined "non-A, non-B" cases.

The majority of adult sporadic hepatitis cases are probably due to either HBV or to the non-A, non-B viruses, with relatively few cases caused by hepatitis A virus (71). With the availability of HAV assays this point should become more certain in the near future.

The clinical features of type B and non-A, non-B hepatitis are discussed in several reports (16,17,67,71-73,78,79,81,82). Some of these studies are summarized in Table III. The data are limited and are so variable as to demand conservative interpretation. In general, it appears that acute non-A, non-B hepatitis is less severe than hepatitis B and has a slightly shorter mean incubation period. Preliminary data (53,73) suggest that both diseases have a similar propensity for progression to chronic hepatitis (Figure 8). It is also probable that non-A, non-B viruses can cause fulminant hepatitis (Table IV).

Figure 8 (Ref. 53)

ACUTE VIRAL HEPATITIS:
FOLLOW-UP STUDIES

Acute Hepatitis No. Patients	Chronic Hepatitis	%
Hepatitis B		
134	13	9.7
Hepatitis non-B		
93	13	12.2
Type unknown		
705	85	12

Frequency of persistent hepatitis during 18-month follow-up period (hepatitis B and non-B) and during a 1-9 year follow-up (type unknown).

Figure 7 (Ref. 154)

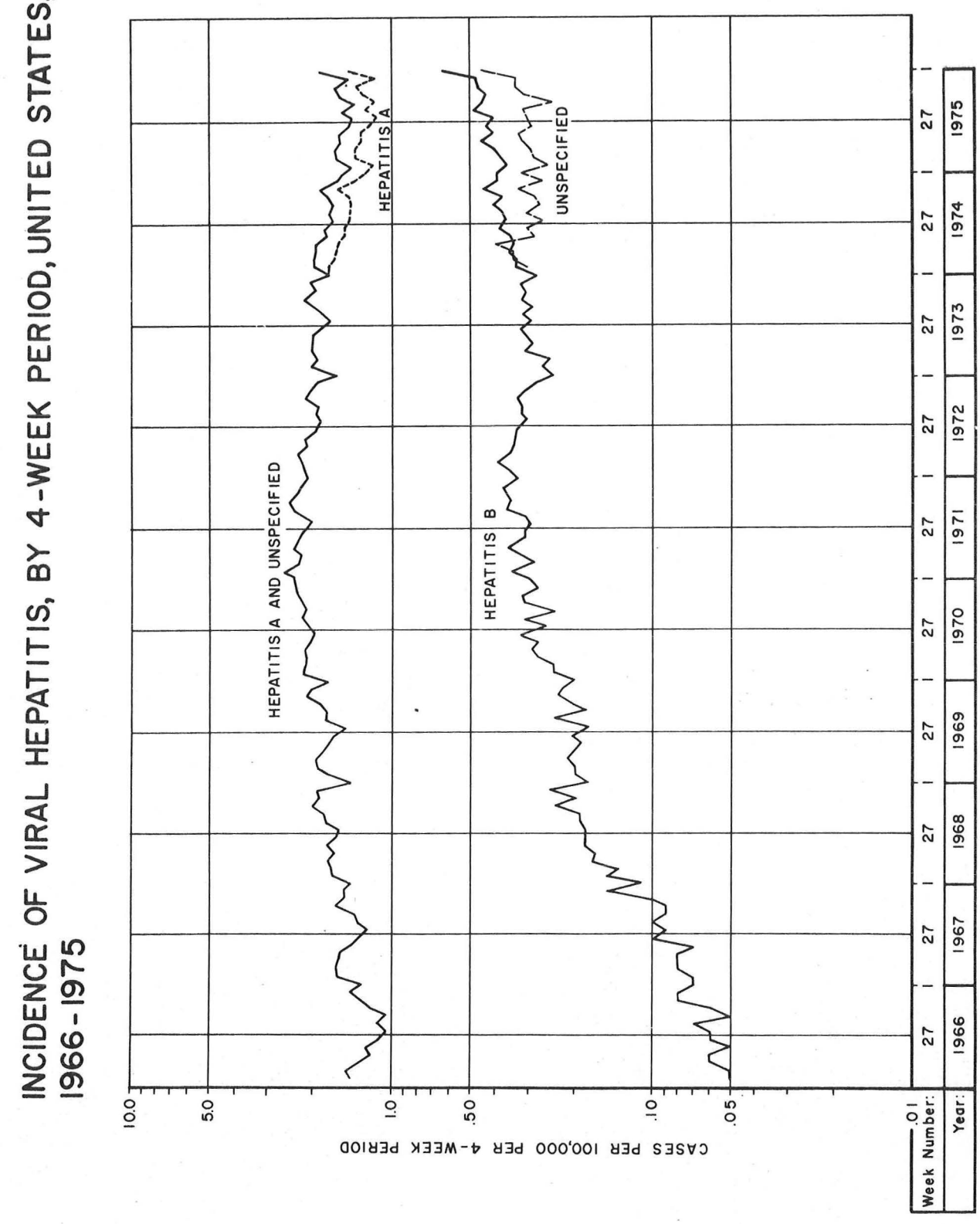


TABLE IV

ETIOLOGY OF FULMINANT HEPATITIS IN THE UNITED STATES

July 1975 to June 1977*

Etiology	Number of Cases	(%)
Hepatitis B Virus	39	(45)
Halothane	7	(8)
Other Drug Hepatotoxicity	9	(11)
Unknown (Possibly Non-B Viral)	31	(36)
TOTAL	86	(100)

*Cases reported by 18 hospitals to the Corticosteroid Study Coordinating Center, Acute Hepatic Failure Study Group, American Association for the Study of Liver Disease.

SOME SPECIAL PROBLEMS OF HEPATITIS VIRUS TRANSMISSION

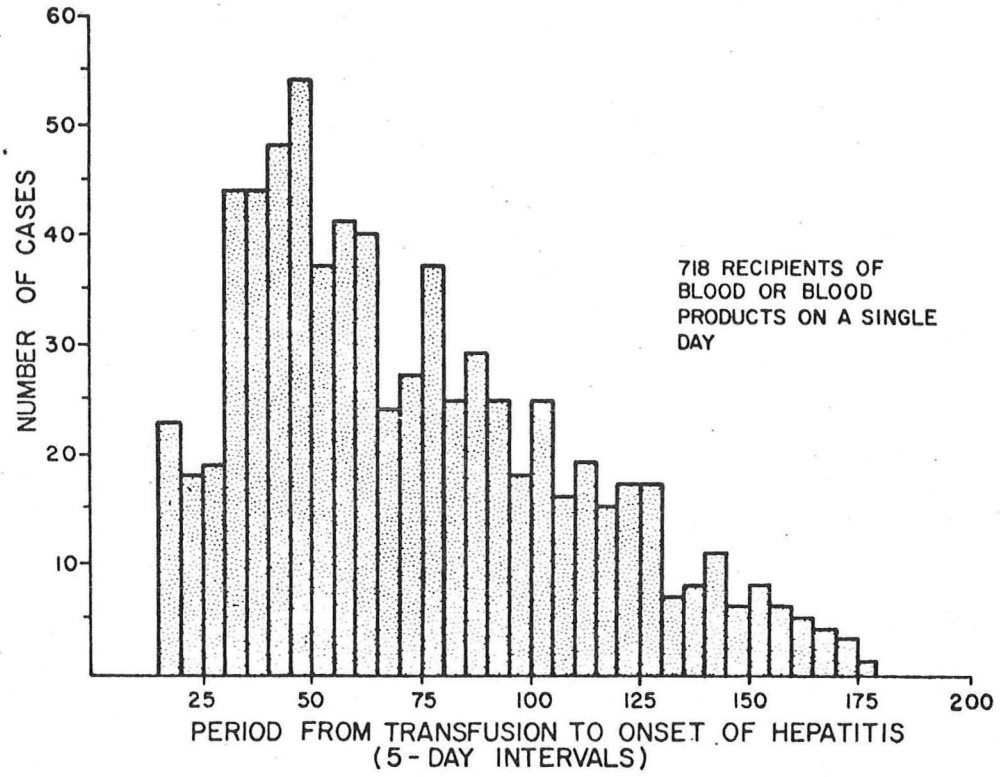
Post-Transfusion Hepatitis

Etiology

For many years post-transfusion hepatitis (PTH) was generally regarded as being due to a single agent, the virus of "serum hepatitis." When HBsAg was identified, it was considered to be a marker of that virus, and one of the early names applied to this agent was "SH-antigen" (83). When patients with PTH were tested for HBsAg, however, it became clear that roughly half were HBsAg negative (84). The natural assumption at that point was that the latter patients were infected with HAV, and the possibility of parenteral transmission of this virus had been well documented (85). But this was an uncomfortable assumption for several reasons: first, it was believed (more or less correctly) that the majority of PTH patients, many being middle-aged or older persons, were already immune to HAV infection because of earlier exposure (Figure 1) (it was recognized that the predictable efficacy of gamma globulin in preventing HAV infection indicated a high prevalence of anti-HAV antibodies in the general population). Second, persons with non-B PTH usually did not transmit infection to their close contacts. Third, it had been known since at least 1962 (86) that the

distribution of incubation periods for PTH cases, instead of forming a bimodal curve with a trough at about 45 days (the maximal incubation period of "infectious-" or type A hepatitis, and the minimal incubation period for type B "serum" hepatitis) was actually unimodal, with its peak at just this 45-50 day time, with many non-B cases developing after 50 days (Figure 9).

Figure 9 (Ref. 87)



Incubation periods of transfusion-associated viral hepatitis among 718 recipients of blood or blood products on a single day.

Finally, while gamma globulin was known to be highly protective against HAV infection, its value, if any, in preventing PTH was slight (See Seeff (88) - his references 9-21).

Considering such observations, the failure to find serologic evidence of HAV infection in any of 22 non-B PTH patients studied by Feinstone, *et al.*, (12) and in only two of 24 patients studied by Hollinger, *et al.*, (13) may not be surprising. It is evident from several studies that, while cytomegalovirus (CMV) and, less often, Epstein-Barr virus may be the cause of a few PTH cases, the majority of non-B cases are due to viruses yet to be identified (72).

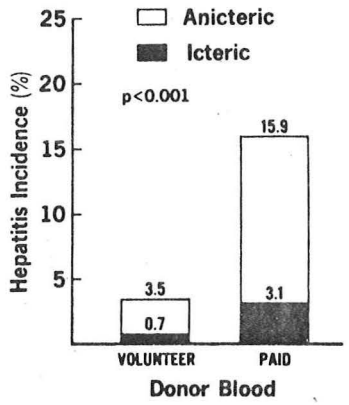
With the high sensitivity of current screening tests resulting in the exclusion of most HBsAg-positive blood donors, it is estimated that nearly 90% of PTH cases are now due to non-A, non-B viral infections (88).

Post-transfusion hepatitis (PTH) is an especially important disease because it represents a late therapeutic complication in patients who may already be suffering from serious diseases. These patients often are of advanced age and less able to tolerate hepatitis. Potentially, PTH is the most preventable form of hepatitis.

The major risk factors for PTH include:

1. *Source of donor blood.* It has been recognized for many years that the risk of hepatitis following transfusion of commercial donor blood was several-fold greater than for blood of volunteer donors (Figure 10). This remains true despite general use of sensitive HBsAg screening tests for exclusion of HBsAg-positive donors (88). Obviously, it is not the exchange of money which makes commercial blood dangerous, but the fact that many paid donors are vagrants, indigent alcoholics, and other destitute persons, among whom hepatitis carriers are clearly more common. This point is emphasized because, whether donors are paid or not, the ideal donor pool is a "biologically tested" closed population of persons who serve as repeating donors. Using such a donor group, appropriate follow-up studies of the blood recipients (certainly a laborious task) could identify carriers of non-A, non-B hepatitis viruses, as well as HBV carriers who are HBsAg negative. The present trend in this country is rapidly toward the establishment of an all volunteer donor system.

Figure 10 (Ref. 153)

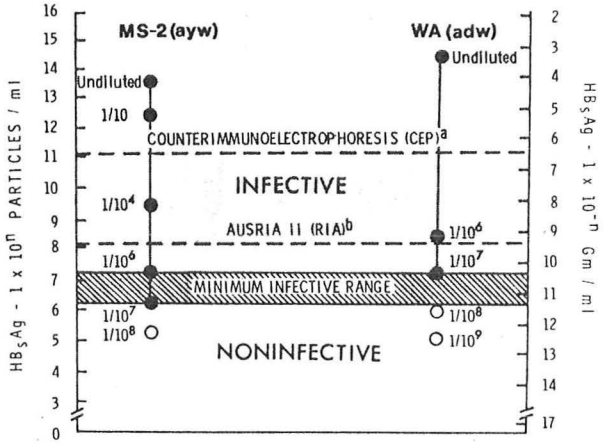


2. *Effectiveness of HBsAg screening tests.* The use of "third generation" screening tests, *i.e.*, hemagglutination or radioimmunoassay, is currently mandated by the Bureau of Biologics, FDA. While exact data are not available, it is certain that even these highly sensitive tests fail to identify some HBV-carrier donors (90,91). It can be estimated that at present roughly 5-15% of PTH cases (and probably even fewer in some areas)

in this country are due to HBV infection (88,91). This underestimates the number of missed HBV carriers, however, since a number of transfused patients show serologic evidence of HBV exposure (HBsAg, anti-HBc, anti-HBs seroconversion, or anamnestic response) without developing hepatitis (88).

Why some HBV carriers are not detected is uncertain, but this could be due simply to insufficient sensitivity of present assays. It has been shown that dilutions of infectious HBsAg-positive serum beyond the detection limits of the most sensitive tests are still capable of causing infection, although the severity of illness diminishes as extremely low concentrations are reached (93,94) (Figure 11).

Figure 11 (Ref. 92)



Approximate number of HB_sAg particles and amount of antigen in dilutions of pedigreed human sera infective in chimpanzees (data adapted from Barker and co-workers, 1975). ● = Injection of 1 ml. of dilution caused infection in chimpanzees. ○ = Injection of 1 ml. of dilution was noninfectious in chimpanzees. a = approximate sensitivity of CEP assay. b = approximate sensitivity of Ausria II RIA.

The development of more sensitive HBsAg tests and, perhaps, of simpler and more sensitive screening tests for HBV-related DNA polymerase and e antigen may result in the eventual elimination of type B post-transfusion hepatitis.

There has been discussion of the need to screen donor blood for anti-HBs and possibly to eliminate antibody positive donors (95), which constitute 10% or more of the general donor population (96,97). Blood banks regularly exclude donors with a history of hepatitis. Anti-HBs is considered proof of past HBV infection. Anti-HBs in sufficient quantity can prevent detection of coexistent HBsAg.

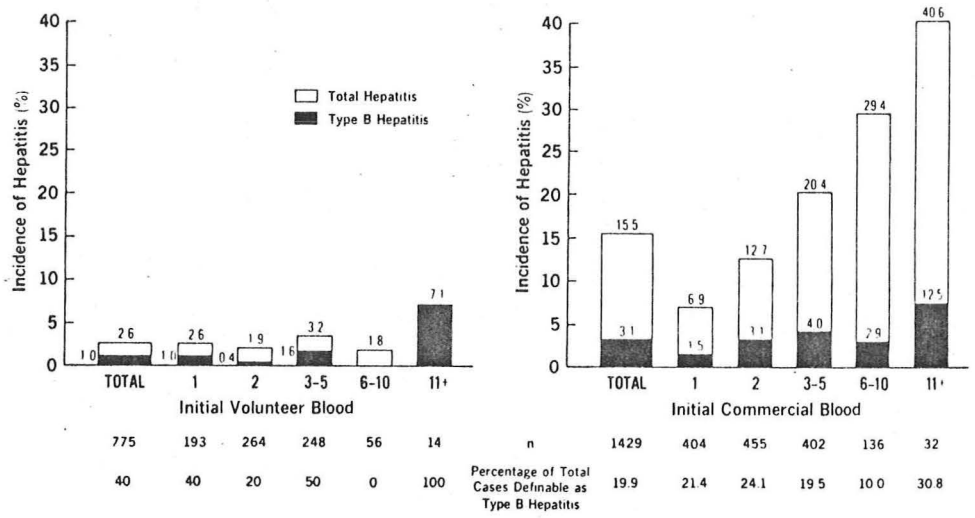
Most available studies fail to support the idea that anti-HBs positive blood carries an increased potential for hepatitis B transmission (73,88,98, 99). Curiously, two studies (88,100) showed that recipients of anti-HBs positive blood did develop hepatitis more often, but the difference was entirely attributable to non-B hepatitis cases. In the VA Cooperative Study

(88), the increased risk was apparently a reflection of the "commercial" source of the donor blood (Figure 10). Neither type B nor non-B hepatitis occurred more frequently in persons receiving anti-HBs positive volunteer donor blood. Although the possible value of screening donor blood for anti-HBc was suggested a few years ago, the absence of confirmatory reports suggests that this is not useful (see above) (33,34).

3. *The prevalence of immunity to hepatitis in recipient populations.* Approximately 10-20% of persons in this country are anti-HBs positive (96,97), and such persons are relatively immune to HBV reinfection (88,99). This may be a partial explanation for the low frequency of PTH-B observed in some areas after transfusion of HBsAg-positive blood (101,102). The prevalence of immunity to non-A, non-B viruses is unknown.

4. *The quantity of blood transfused.* As might be expected, the more blood transfused, the greater the risk of consequent hepatitis (Figure 12)(86,103, 104,105). In some studies (86), a plateau of incidence and possibly even some decline in risk was observed with transfusion of more than 10-15 units of blood.

Figure 12 (Ref. 88)



Incidence of total and type B hepatitis according to source and number of administered transfusions.

Maternal-Fetal Transmission of Hepatitis B Virus Infection

Prior to the identification of Australia antigen transmission of hepatitis virus from mother to infant was rarely recognized.

Studies of this problem in Western countries (106-111)(Table V) have been in general agreement and have demonstrated the high risk of viral transmission to infants by mothers with acute hepatitis B in the third trimester and during the first two postpartum months (Table VI). On the other hand, the risk was minimal for infants of

women with acute hepatitis in the first and second trimesters or for babies of healthy HBsAg carrier women. In one series, only four infants of 89 born to healthy HBsAg carrier mothers became HBsAg positive (107).

TABLE V (Ref. 113)

FREQUENCY OF TRANSMISSION OF HBV FROM HB_s Ag CARRIER MOTHERS TO INFANTS IN VARIOUS GEOGRAPHIC AREAS

Investigator	Geographic Area	Patients Studied	% Vertical Transmission
Beasley	Taiwan	158	40
Papaevangelou	Greece	15	6.5
Punyagupata	Thailand	14	0
Schweitzer	USA	36	16.5
Skinhoj	Denmark	36	0

TABLE VI (Ref. 113)

ONSET OF MATERNAL HEPATITIS B RELATING TO HB_s Ag POSITIVE INFANTS

Onset of Maternal Hepatitis	Women with Viral Hepatitis B	HBV Infected Infants	Percentage HBV Infected Infants
Trimester I	10	0	6.2
Trimester II	6	1	
Trimester III	19	13	70
0-2 Months Post-partum	8	6	
TOTAL	43	20	

The exact means by which HBV passes from mother to infant is still uncertain. Antepartum transmission might occur by transplacental passage of the virus or its transferral directly into amnionic fluid from maternal plasma (HBsAg has been identified in amnionic fluid (112)). Infection could be an intrapartum event with maternal serum reaching the infant through placental breaks, or by direct exposure of the infant to maternal blood by ingestion or through trivial cutaneous or mucosal injuries. Infection following birth might occur by exposure to maternal saliva (170) or breast milk.

HBsAg, along with Dane particles, is frequently identified in cord (fetal) blood when the mother is HBsAg positive, indicating current or past transplacental infection (171-175), but this correlates poorly with the infant's subsequent risk of developing HBs antigenemia (113) (Figure 13). HBsAg and Dane particles have also been detected in breast milk, but it is doubtful that this is an important mode of transmission (111,114,115).

Figure 13 (Ref. 113)

31 MATERNAL CARRIERS WHERE CORD BLOODS WERE AVAILABLE AND HB_S Ag AND ANTI-HB_S RESPONSE IN THEIR INFANTS

	Cord Bloods	Babies HBsAg+ in 1-3 Months	Babies with Marked anti-HBs Response
Positive	17 (1+ CEP)	2*	1*
Negative	14	1	1

* same baby HBsAg+ followed by marked anti-HBs response

In marked contrast to the situation in Western countries, the vertical HBV transmission rate from healthy carrier mothers in Taiwan is about 40% (116), and this is also true in the Japanese population (117). This becomes especially important when one considers the extremely high percentage of HBsAg carriers in the Formosan population - approximately 15% - as compared with 0.1 to 0.5 % in Western countries (118). The recognition that so many HBV infections in Far Eastern countries may be congenitally acquired may make active immunization against hepatitis B less effective in those areas.

It was further noted in the oriental studies that the pattern of vertical transmission, or lack of transmission, remained consistent for all children born to a particular mother. Although certain factors such as the maternal HBsAg titer and the presence of HBsAg in cord blood were thought to be indicators of "transmitter" mothers (116), other factors such as maternal anti-HBc titer and viral subtype were shown to be unimportant (119,120).

A major advance in the understanding of vertical HBV transmission came with the recognition that the risk of transmission was closely related to the e antigen Ag/anti-e status of the mother. Skinhoj found that in a group of 17 HBsAg carrier women in Copenhagen, one was e Ag positive and she transmitted HBV infection to both of her children and possibly to her husband who was anti-HBs positive. The remaining 16 carrier mothers were anti-e positive. None of their 29 children and five husbands tested were HBsAg positive (119).

Even more remarkable are the data of Okada and associates (120) (Tables VII and VIII). These authors studied 23 Japanese women who were healthy HBsAg carriers and their children. As shown in Table VII, all 10 infants born to e Ag positive women acquired HBV infection, while this occurred in none of the infants of anti-e positive women. In keeping with the impression (see above) that e Ag is a marker for the presence of infectious viral particles in the serum, Dane particles were found by electron microscopy in each of the six e Ag positive sera examined but in none of five anti-e positive specimens. In subsequent studies (121) this group has confirmed the further association of HBV-related DNA polymerase with e Ag and Dane particles. They found DNA polymerase activity in the serum of the two women of their original group who were e Ag/anti-e negative but who had transmitted HBV to their babies. The four non-transmitting e Ag/anti-e negative women had no DNA polymerase activity in their serum.

TABLE VII (Ref. 120)

e Antigen — anti-e System in the Serum of Asymptomatic Carrier Mothers and Vertical Transmission of Hepatitis B Surface Antigen (HB_s Ag) to Their Children.

Group	Mothers' Serum Samples		Children's Samples	
	Finding	Number	HB_s Ag (+)	HB_s Ag (−)
A	e Ag	10	10	0
B	anti-e	7	0	7
C	—*	6	2	4
Totals		23	12 (52%)	11 (48%)

*Neither e antigen nor anti-e detected by immunodiffusion.

TABLE VIII (Ref. 120)

Hepatitis B Core Antigen (HB_c Ag) and Dane Particles in the Serum of Asymptomatic Carrier Mothers with (Group A) and without (Group B) Vertical Transmission of HB_s Ag to Their Children.

	Case No.	Titer of HB_c Ag*	Dane Particles†
Group A:			
	1	128	+
	2	8	+
	3	16	+
	6	16	+
	7	64	+
	8	64	+
Group B:			
	13	ND‡	−
	14	ND	−
	15	ND	−
	16	ND	−
	17	ND	−

*Serum samples were separated from anti-HB_c, concentrated 20-fold & determined for HB_c Ag by IAHA.'

†Serum samples were partially purified & concentrated by density-gradient centrifugation, & tested by electron microscopy.

‡Not detected.

Fate of HBsAg Positive Infants

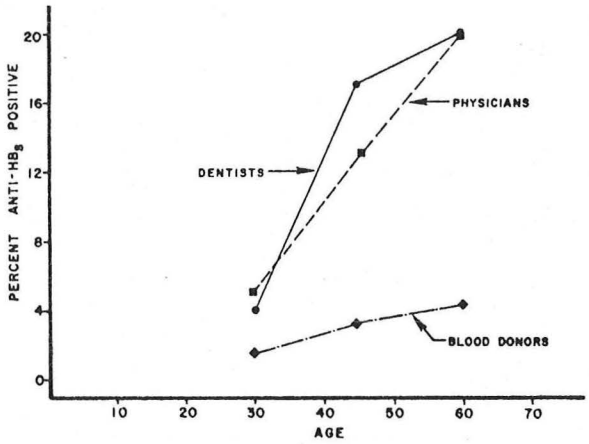
A small percentage of children infected with HBV in infancy have a brief period of antigenemia, sometimes with evidence of mild acute hepatitis, followed by clearing of the antigen and development of anti-HBs (122). Of interest are the rare instances of neonatal fulminant type B hepatitis, reported in the children of three women (123-125). Oddly, these women were all (occidental) healthy carriers of HBsAg. It is even more intriguing, though tragic, to note that each of two infants born to two of the three women died of fulminant hepatitis B (124,125).

The majority of children infected in infancy become chronically antigenemic (113). The eventual fate of these children is not fully determined. An uncertain number have significant chronic active liver disease (126,127), and, in the Orient at least, these chronically HBV-infected persons may be at increased risk of developing hepatocellular carcinoma later in life (128).

The Risk of HBsAg-Positive Medical Personnel to Patients

There is abundant evidence that health care personnel are at increased risk of developing hepatitis B virus infection (129, 130-132) (Figure 14) and, as a result, are probably more likely to become chronic carriers of this virus.

Figure 14 (Ref. 132)



Prevalence of antibody to hepatitis B surface antigen (anti-HB$_s$) in dentists, physicians, and socioeconomically comparable first-time volunteer blood donors.

Transmission of HBV infection from two dentists (133,134), a nurse (135), and a respiratory therapist (136) to their respective patients has been credibly documented. The two "donor" subjects tested for e antigen were both positive (134, 136).

In the cases of the respiratory therapist and the two dentists, the mode of transmission was presumably from minor cuts on their hands to breaks in the skin (arterial punctures in the case of the respiratory therapist) or buccal mucosa of the recipients.

The appropriate counseling and regulation of HBsAg-positive health care personnel is a very uncertain matter. Much more information is needed concerning the relative risks involved according to the type of HBV carrier ("healthy" vs chronic hepatitis, e antigen/DNA polymerase positive or negative), the type of patient contact, and the value of protective measures such as wearing of gloves, masks, *etc.* There is an urgent need to clarify these issues before public pressure on insufficiently informed government officials leads to the indescriminate prohibition from practice of all HBsAg-positive health care personnel, some of whom probably offer no risk to their patients. At least one such project, a VA cooperative study of the risk of HBsAg-positive dental personnel, is now in preparation.

Recently, a position paper concerning these issues was prepared by the National Academy of Sciences Joint Committee on Viral Hepatitis and the Public Health Service Advisory Committee on Immunization Practices (137). The following conclusions were made:

> Health care personnel observed to be HBsAg-positive should not be restricted from patient contact solely on the basis of this serologic finding. Rather, their personal procedures and practices should always reflect an awareness of the potential for transmitting HBV and include rigorous efforts to reduce any chance that transmission might occur. Knowing that contact with blood or serum containing HBV is a likely cause of hepatitis B infections, scrupulous aseptic technique, avoidance of personal hand injuries, and use of gloves in office-based minor surgery, dental procedures, and wound dressing, *etc.* have obvious value.
>
> Health care personnel clearly associated epidemiologically with HBV transmission obviously pose a greater risk for patients and associates and must be evaluated carefully with respect to continuing risks. In these instances, more restrictive measures (*e.g.*, limiting or eliminating some types of procedures or contact with patients) may be needed. Obviously, each such episode will have to be dealt with separately and recommendations and control measures tailored to the specific conditions.

SPECIFIC ANTIVIRAL THERAPY

Immunotherapy of HBV Infections with Anti-HBs

Although one would not expect that antiviral antibodies would have an effect on viral proliferation within the liver cell, it is believed that the infection may be sustained within the liver by passage of virus from infected to uninfected cells. It was hoped that specific antibody might interrupt such cell-to-cell transfer.

Immunoglobulin preparations containing high titers of anti-HBs have been used to treat patients with type B chronic active hepatitis but without evidence of beneficial effect (138-140).

In uncontrolled studies in 1971, Gocke (141) reported the survival of five of eight patients with fulminant type B hepatitis treated with anti-HBs containing plasma. In a similar study in 1974, Opolon reported six of 19 survivors (142).

In a multi-center controlled study involving a total of 63 patients with fulminant type B hepatitis, treated with either anti-HBs immune globulin especially prepared for intravenous administration, or with a placebo, it was concluded that anti-HBs was of no benefit (143).

Despite the administration, in these studies, of anti-HBs to patients with circulating HBsAg, no convincing evidence of immune-complex mediated complications was observed.

Transfer Factor Therapy of Chronic Active Viral Hepatitis

Several isolated case reports describe attempts to treat type B- and non-B chronic active hepatitis with transfer factor (TF) (139,140,144,145-148). Trepo carried out similar studies in HBsAg carrier chimpanzees (149). In almost all cases, the donors from whom TF-producing leukocytes were obtained were persons who had recovered from type B hepatitis if the recipients were to be HBsAg-positive patients. In Shulman's studies, non-B chronic hepatitis patients were included, and they received TF from donors who had recovered from non-B acute hepatitis (147). In several of these studies, cell-mediated immunity to HBsAg and to other antigens such as PPD, mumps, and streptokinase/streptodornase was induced in the recipient subjects by TF. Several patients manifested brief and modest rises in transaminase levels after TF therapy suggesting (perhaps) increased cell-mediated cytotoxicity against virus-infected liver cells. Shulman is currently conducting a controlled study of TF therapy for type B and non-B chronic hepatitis patients (147) and reports that each of three HBsAg-positive patients treated with TF has shown a favorable response as judged by clinical, biochemical, and histologic criteria, but neither of two saline-placebo control patients has responded. No further details are given in this preliminary report.

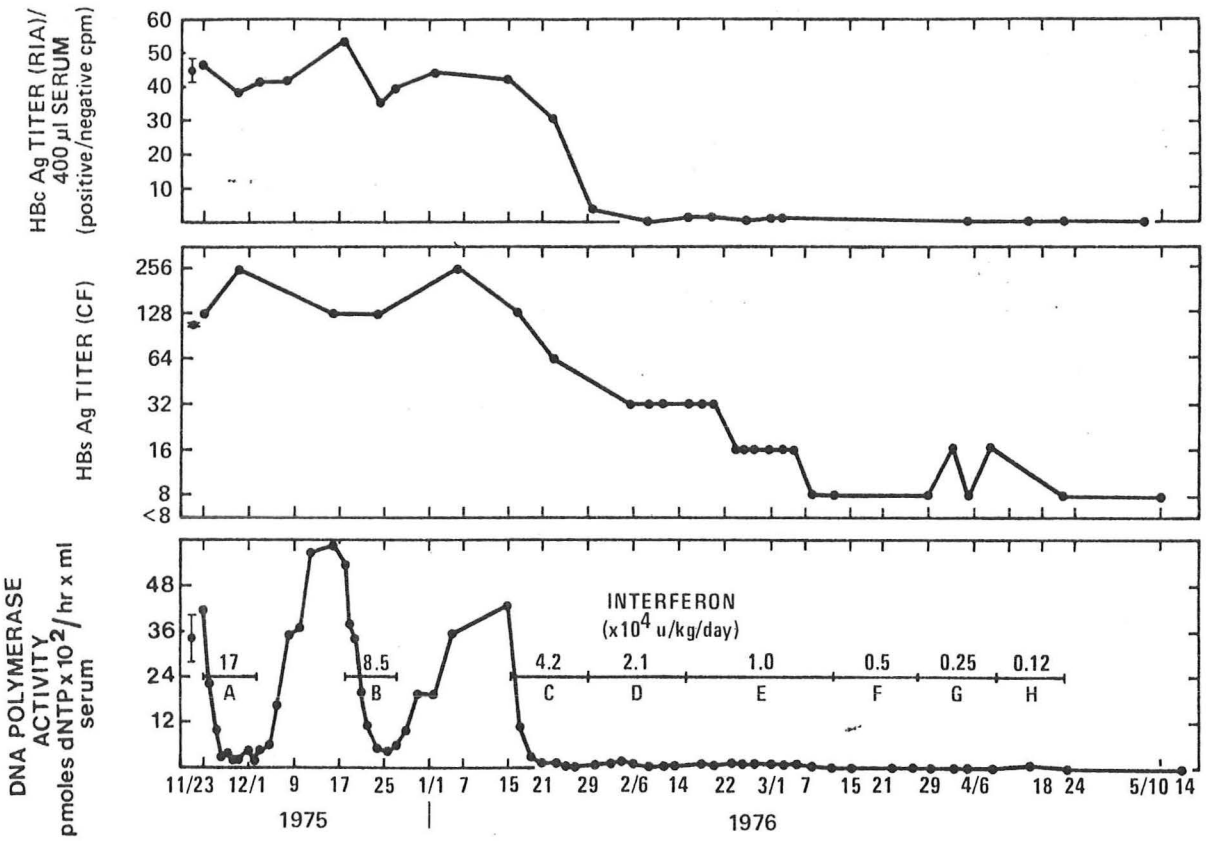
None of the several other case reports provide any convincing evidence of a beneficial effect of transfer factor therapy on type B chronic active hepatitis.

Interferon Therapy

The use of interferon for treatment of chronic HBV infection has been evaluated in three recent studies (150-152). These studies, using both human and chimpanzee subjects, and different forms of interferon - endogenous, produced in response to an interferon inducer (150), and exogenous, of human leukocyte (151) or human fibroblast (152) origin, all provided evidence of HBV suppression, as reflected in reduced titers of DNA polymerase, e antigen, and HBsAg in serum (Figure 15) and of HBsAg and HBcAg in liver cells. In all cases the response,

while tending to persist for the duration of therapy, was a temporary one, with return to basal status after completion of treatment.

Figure 15 (Ref. 151)



Effect of Three Separate Courses (A, B and C–H) of Human Leukocyte Interferon on Dane-Particle-Associated DNA Polymerase, HB_s Ag (by Complement Fixation) and HB_c Ag (by Radioimmunoassay) in Case 1.

ϕ denotes mean and 2 standard deviations of a minimum of four separate values in serum samples obtained at regular intervals during the two months before study. Letters A through H denote individual interferon treatment courses at specific dosages with the units of interferon per kilogram per day × 10^4 as shown.

The results of these studies are encouraging since this is the first form of therapy shown to have any influence on HBV viremia. Certain important problems must be resolved, however, before more intensive use of interferon therapy is possible. The first is the problem of possible toxicity; the use of P.I.C.L.C., considered the most satisfactory of available interferon inducers, was associated with anemia (reduced red cell production) and transient hepatotoxicity in Purcell's chimpanzee study (150). Human leukocyte interferon caused marrow suppression with a fall in white blood cell, platelet, and reticulocyte counts among Greenberg's chronic hepatitis B patients (151). A moderate febrile response was the only side effect observed with use of human fibroblast interferon in Desmyter's one human subject (152); the two chimpanzees in that study showed no ill effects.

The second problem is the difficulty, and therefore the expense, of producing the quantities of interferon which seem to be required for these treatment regimens. Again, human fibroblast interferon appeared to be the most promising in this regard since it was produced by cells which potentially are available in unlimited quantities.

Even if interferon proves incapable of completely eradicating an HBV infection, its impressive capacity to reduce DNA polymerase and e antigen levels suggests its potential value in lowering the infectious risk of DNA polymerase/e antigen positive HBsAg carriers. Since the titers of these markers, and therefore presumably the degree infectious risk of these patients, fluctuates considerably over time, intermittent courses of interferon therapy might be sufficient.

PREVENTION OF HEPATITIS VIRUS INFECTION

Passive Immunization

Early studies showed that type A hepatitis was effectively prevented by immune serum globulin (ISG; gamma globulin) administered prior to the onset of clinical illness. By contrast, ISG was considered relatively ineffective in preventing "serum" hepatitis resulting from blood transfusion. The more recent demonstration that ISG may prevent hepatitis B under some conditions appears to conflict with these earlier impressions. The impotence of ISG in past studies of transfusion-associated hepatitis is better understood when one considers that prior to 1972 many lots of commercially prepared ISG contained minimal amounts of anti-HBs (162) (Table IX). Furthermore, it is now evident that the volume of infectious virus transfused in a unit of HBsAg-positive blood can be so great that manageable doses of ISG, even those containing anti-HBs in very high titer (designated hepatitis B immune globulin or HBIG), might be insufficient to neutralize all the infused virus.

TABLE IX (Ref. 162)

Prevalence of Anti-HB_s Positive Lots of Immune Globulins by Manufacturer and Year of Submission to the Bureau of Biologics*

Manufacturers	1962-1963 (%)	1964-1965 (%)	1966-1967 (%)	1968-1969 (%)	1970-1971 (%)	1972 (%)	1973-1974 (%)
A	35 (9/26)	60 (24/40)	24 (8/34)	22 (2/9)	13 (2/16)	50 (1/2)	89 (34/38)
B	9 (3/35)	0 (0/42)	0 (0/40)	6 (2/35)	13 (5/40)	81 (17/21)	100 (19/19)
C	97 (35/36)	100 (40/40)	99 (35/40)	92 (36/39)	63 (20/32)	85 (17/20)	100 (27/27)
D	90 (26/29)	94 (17/18)	53 (17/32)	50 (14/28)	72 (21/29)	85 (17/20)	100 (18/18)
E	23 (9/40)	28 (10/36)	41 (16/39)	3 (1/29)	20 (6/30)	95 (19/20)	100 (34/34)
F					11 (3/27)	0 (0/11)	87 (34/39)
Others	81 (47/58)	95 (19/20)	0 (0/1)	0 (0/19)	56 (14/25)	30 (3/10)	74 (26/35)
Total	58 (129/224)	56 (110/196)	41 (76/186)	35 (55/159)	35 (71/199)	71 (74/104)	91 (192/210)

*A titer of $\geq$ 1:8 on passive hemagglutination was considered positive.

Hepatitis A Prophylaxis

Close contacts of hepatitis A patients should receive gamma globulin in a dose of 0.01 ml/lb body weight, or 2 ml, whichever is larger (administered at the City or County Health Department at physician's request). "Close contact" refers to exposures in the household, and/or to persons sharing toilet facilities. Generally, classmates or co-workers are not considered sufficiently at risk to require ISG prophylaxis. Larger doses of ISG (0.01 ml/lb/month, administered every 4-6 months) provide more prolonged protection for persons working in areas where hepatitis A is highly endemic.

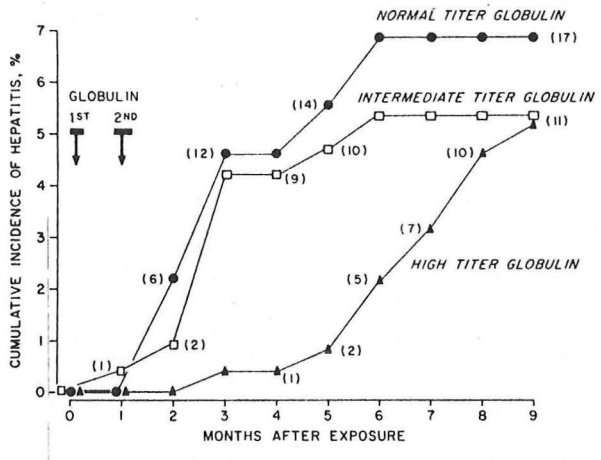
Hepatitis B Prophylaxis

Results of the several studies of passive prophylaxis against HBV infection may be summarized as follows:

First, ISG containing anti-HBs is capable of preventing some cases of clinical hepatitis B, at least those likely to develop after small volume exposures such as needlestick accidents (155,156), close personal contacts (157), and hemodialysis exposures (158,159). It remains to be proven that HBIG can prevent type B post-transfusion hepatitis (88,160). Infusion of a unit of HBsAg-positive blood constitutes the administration of millions of infective doses of virus and prophylaxis likely would require very large (possibly impractical) doses of HBIG.

Second, part of the apparent advantage of HBIG over ISG which contains anti-HBs in lower titers may be due simply to prolongation of the hepatitis B incubation period by the larger doses of antibody (161). Such an effect may have been demonstrated in at least one HBIG study (156) (Figure 16).

Figure 16 (Ref. 156)



Cumulative Incidence of Viral Hepatitis among Medical Workers Who, after Accidental Exposure to Infective Serum, Received One of Three Gamma-Globulin Preparations Containing Anti-HB_S of Normal, Intermediate, or High Titer, Respectively.

Each person received two injections of globulin, one during each of the periods indicated by the bars. Onset time, as defined in the text, was observed in the earliest case at 29 days and in the latest at 270 days.

Third, passive-active immunity may result from the prophylactic use of anti-HBs; patients may develop sustained levels of endogenous anti-HBs after the disappearance of the administered anti-HBs, without the occurrence of clinical hepatitis (155). It should be emphasized that the development of such active immunity, a desirable phenomenon, has been more common among recipients of ISG with modest or low anti-HBs titers than among recipients of HBIG. It is speculated that HBIG completely prevents viral replication and resultant active immunization, while smaller amounts of anti-HBs merely prevent clinical illness.

Finally, early concern about converting what might otherwise be a self-limited HBV infection into a chronic carrier state or chronic hepatitis has not been realized in the extensive studies cited.

Local policy for the treatment of persons who have had needlestick - or comparable exposure to hepatitis patients - has been essentially the same as the approach recently recommended by Grady (163) (Table X). The major exception is

TABLE X (Ref. 163)

MANAGEMENT OF NEEDLESTICK - OR OTHER HEPATITIS VIRUS EXPOSURES

1. Verify the nature of the exposure.

   a. "Donor" is HBsAg positive and/or has acute or chronic viral hepatitis.

   b. Significant exposure

and, <u>if possible</u>,

2. Determine that "recipient" is HBsAg-negative.

3. Obtain blood from "recipient" for later anti-HBs testing.

If exposure was "significant," and "recipient" is HBsAg-negative, administer 10 ml ISG, i.m.

that our "recipients" have not been tested for HBsAg before receiving gamma globulin. Grady's recommendation for such testing reflects his concern that administration of anti-HBs to an HBsAg-positive person might produce an anaphylactic response. A "significant exposure" for which ISG prophylaxis would be indicated consists of inoculation injuries, accidental splashing of contaminated blood into

eyes, nose, mouth, or over large areas of skin, and the accidental swallowing of pipetted blood. Remarkably, such things actually do happen. The donor should be HBsAg positive or have acute or chronic non-B hepatitis (ISG may also prevent non-A, non-B hepatitis; see below). The recipient's blood is drawn before ISG is given, to be tested, if possible, for preexistent anti-HBs. If the recipient is already anti-HBs positive, knowledge of such immunity may be reassuring. Locally, we have routinely administered 5 ml of gamma globulin from two different lots of ISG (either from different manufacturers or of different lot numbers if from the same manufacturer). This is done to insure that at least one of the two simultaneously administered doses will contain a reasonable titer of anti-HBs. About 90% of lots currently available contain anti-HBs (162) (Table IX).

Prophylaxis of Non-A, Non-B Hepatitis

It is of considerable interest that two recent studies showed that when ISG was administered at the time of blood transfusion there was a reduction in the incidence of non-A, non-B post-transfusion hepatitis (PTH) (88,164). This is curious in view of the numerous earlier studies showing little or no effect of ISG on transfusion-associated hepatitis (See Seeff's references 9-21 (88)). A possible explanation for this situation is that prior to routine HBsAg testing a large proportion of PTH cases were due to HBV infection, against which the ISG of that time, with its generally low levels of anti-HBs, was very likely ineffective. Now the percentage of HBV cases has been substantially reduced due to HBsAg screening of blood donors and the proportion of PTH cases due to non-B viruses has increased accordingly. Any prevention of such non-B cases by the use of gamma globulin in the early studies may have been "buried" among the non-responding type B cases.

On the basis of these observations, and recognizing that non-A, non-B infection may progress to severe chronic liver disease, we advise the prophylactic use of ISG for persons "significantly" exposed to non-B hepatitis patients, as discussed above.

Active Immunization Against HBV Infection

Several years ago it was recognized that recovery from "serum" hepatitis (presumably type B hepatitis) led to permanent immunity against reinfection (165). The first specific demonstration of immunization against HBV was provided in the study of Krugman (166) in which susceptible recipients were inoculated with heat inactivated(98°C for one minute) MS-2 serum known to contain infectious HBV. Among 25 children who had received one to three inoculations of inactivated serum, subsequent challenge with unheated MS-2 serum caused hepatitis in 12; all 25 nonimmunized control subjects became infected after a similar challenge.

Efforts to develop an HBV vaccine have been impeded by the inability to propagate the virus in tissue culture. This problem has been circumvented, however, by the use of noninfectious, but immunogenic, Australia (22 nm) particles purified from the serum of healthy HBsAg carriers as the immunogen (167-169). Large quantities of such vaccine have now been prepared, and in chimpanzee studies have been shown to be noninfectious, free of side effects, antigenic, and capable of producing immunity to

HBV challenge. Human field trials have been initiated and preliminary results from the study of Maupas, *et al.*, in France (169) have been encouraging.

Once effective vaccines become generally available, certain high-risk groups should be among the first to be considered for immunization; these include renal disease patients, cancer patients, diabetics, health care personnel, and employees of plasma fractionation plants.

REFERENCES

1. MacCallum FO: Paper presented at the International Conference of Physicians. *Lancet* 2:435, 1947
2. Terminology of hepatitis viruses and antigens. *Weekly Epidemiol Record* 51: 365, 1976
3. Mosley JW: Type A hepatitis. *Med Clin North Am* 59:831, 1975
4. Maynard JE: Hepatitis A: perspectives and recent advances. *Am J Pathol* 81: 683, 1975
5. Krugman S: Hepatitis: Current status of etiology and prevention. *Hosp Prac*: 39, November, 1975
6. Feinstone SM, *et al.*: Hepatitis A detection by immune electron microscopy of a virus-like antigen associated with acute illness. *Science* 182:1026, 1973
7. Provost PJ: Physical, chemical and morphologic dimensions of human hepatitis A virus strain. CR 326 *Proc Soc Exp Biol Med* 148:532, 1975
8. Purcell RH, *et al.*: Relationship of hepatitis A antigen to viral hepatitis. *Am J Med Sci* 270:61, 1975
9. Mosley JW: The epidemiology of viral hepatitis: An overview. *Am J Med Sci* 270:253, 1975
10. Szmuness W, *et al.*: Distribution of antibody to hepatitis A antigen in urban adult populations. *N Engl J Med* 295:755, 1976
11. Stokes J, *et al.*: The carrier state in viral hepatitis. *JAMA* 154:1059, 1954
12. Feinstone SM: Transfusion-associated hepatitis not due to viral hepatitis type A or B. *N Engl J Med* 292:747, 1975
13. Hollinger FB, *et al.*: HBcAg, anti-HBc, and DNA polymerase activity in transfused recipients followed prospectively. *Am J Med Sci* 270:343, 1975
14. Dienstag JL, *et al.*: Faecal shedding of hepatitis-A antigen. *Lancet* 1:765, 1975
15. Dienstag JL, *et al.*: Mussel-associated viral hepatitis, type A: serological confirmation. *Lancet* 1:561, 1976
16. Villarejos VM, *et al.*: Sero-epidemiologic investigation of human hepatitis caused by A, B and a possible third virus. *Proc Soc Exp Biol Med* 152:524, 1976
17. Dienstag JL, *et al.*: Non-A, non-B post-transfusion hepatitis. *Lancet* 1:560, 1977
18. Blumberg BS, *et al.*: Australia antigen and hepatitis. *JAMA* 207:1895, 1969
19. Bayer ME, *et al.*: Particles associated with Australia antigen in serum of patients with leukemia, Down's syndrome, and hepatitis. *Nature* 218:1057, 1968
20. Dane DS, *et al.*: Virus-like particles in serum of patients with Australia antigen-associated hepatitis. *Lancet* 1:695, 1970
21. Almeida JD, *et al.*: New antigen-antibody system in Australia antigen-positive hepatitis. *Lancet* 2:1225, 1971
22. Magnius LO, *et al.*: New specificities in Australia antigen-positive sera distinct from the Le Bouvier determinants. *J Immunol* 109:1117, 1972
23. Kaplan PM: Personal communication (*Hepatitis Scientific Memoranda)*, January, 1974
24. Robinson WS: DNA and DNA polymerase of a virus-like particle in hepatitis B. *Dev Biol Stand* 30:23, 1975
25. Bond HE, *et al.*: Separation and purification of HAA into morphological types by zonal ultracentrifugation. *J Infect Dis* 125:263, 1972

26. Purcell RH, *et al.*: Modification of chronic hepatitis B virus infection in chimpanzees by administration of an interferon inducer. *Lancet* 2:757, 1976
27. Greenberg HB, *et al.*: Effect of human leukocyte interferon on hepatitis B virus infection in patients with chronic active hepatitis. *N Engl J Med* 295:517, 1976
28. Miyakawa Y: Determination of HBcAg and anti-HBc by immune adherence hemagglutination and association of HBcAg with e antigen. *Bibl Haematol* 42:70, 1976
29. Brzosko WJ, *et al.*: Duality of hepatitis B antigen and its antibody. *J Infect Dis* 127:424, 1973
30. Hoofnagle JH, *et al.*: Antibody to hepatitis B virus core in man. *Lancet* 2:869, 1973
31. Purcell RH, *et al.*: Radioimmunoassay for the detection of the core of the Dane particle and antibody to it. *Intervirology* 2:231, 1974
32. Hoofnagle JH: Antibody to hepatitis B core antigen. *Transmissible Disease and Blood Transfusion*, page 43, 1975
33. Krugman S, *et al.*: Viral hepatitis, type B, DNA polymerase activity and antibody to hepatitis B core antigen. *N Engl J Med* 290:1331, 1974
34. Hoofnagle JH, *et al.*: Antibody to hepatitis B core antigen: a sensitive indicator of hepatitis B virus replication. *N Engl J Med* 290:1336, 1974
35. Hirschman SZ, *et al.*: DNA polymerase in preparations containing Australia antigen. *Lancet* 1:1099, 1971
36. Robinson WS: DNA polymerase in the core of the human hepatitis B virus candidate. *J Virol* 13:1231, 1974
37. Kaplan PM, *et al.*: DNA polymerase associated with human hepatitis B antigen. *J Virol* 12:995, 1973
38. Hruska JF, *et al.*: Structure of hepatitis B Dane particle DNA before and after the Dane particle DNA polymerase reaction. *J Virol* 21:666, 1977
39. Magnius LO: Characterization of a new antigen-antibody system associated with hepatitis B. *Clin Exp Immunol* 20:209, 1975
40. Williams A, Le Bouvier G: Heterogeneity and thermolability of "e." *Bibl Haematol* 42:71, 1976
41. Trepo C, *et al.*: (Letter) Detection of e antigen by immunofluorescence in cytoplasm of hepatocytes of HBsAg carriers. *Lancet* 1:486, 1976
42. Neurath AR, *et al.*: Evidence against the postulated identity of e-Ag with DNA polymerase associated with hepatitis B virus. *Intervirology* 7:356, 1976
43. Magnius LO, *et al.*: A new antigen complex co-occurring with Australia antigen. *Acta Path Microbiol Scand* 80 (B):335, 1972
44. Norkrans G, *et al.*: e antigen in acute hepatitis B. *Br Med J* 1:740, 1976
45. Nielsen JO, *et al.*: Incidence and meaning of the "e" determinant among hepatitis B antigen positive patients with acute and chronic liver diseases: Report from the Copenhagen hepatitis acuta progamme. *Lancet* 2:913, 1974
46. Nordenfelt E: Dane particles, DNA polymerase and e-antigen in two different categories of hepatitis B antigen carriers. *Intervirology* 5:225, 1975
47. El Sheikh N, *et al.*: e antigen-antibody system as an indicator of liver damage in patients with hepatitis B antigen. *Br Med J* 4:252, 1975
48. Nordenfelt E, *et al.*: Dane particle-associated DNA polymerase and e-antigen: relation to chronic hepatitis among carriers of HBsAg. *J Infect Dis* 134:85, 1976
49. Alter HJ, *et al.*: Type B hepatitis: the infectivity of blood positive for e antigen and DNA polymerase after accidental needlestick exposure. *N Engl J Med* 295:909, 1976

50. Fay O, *et al.*: The e antigen as an index of chronic hepatitis B virus infection (abstract). *Gastroenterology* 68:1081, 1975
51. Lam KC, *et al.*: e antigen of hepatitis B virus in relation to phase of acute illness (abstract). *Gastroenterology* 71:917, 1976
52. Magnius LO, *et al.*: A new antigen-antibody system: Clinical significance in long-term carriers of hepatitis B surface antigen. *JAMA* 231:356, 1975
53. Redeker AG: Viral hepatitis: Clinical aspects. *Am J Med Sci* 270:9, 1975
54. Thamer G, *et al.*: (Letter) e antigen: Prognostic marker in acute viral hepatitis B? *Lancet* 2:577, 1976
55. Eleftheriou N, *et al.*: Incidence and clinical signficance of e antigen and antibody in acute and chronic liver disease. *Lancet* 2:1171, 1975
56. Vogten AJ, *et al.*: Behavior of e antigen and antibody during chronic active liver disease: Relation to HB antigen-antibody system and prognosis. *Lancet* 2:126, 1976
57. Maynard JE: Hepatitis A. *Yale J Biol Med* 49:227, 1976
58. Trepo CG, *et al.*: Detection of e antigen and antibody: Correlations with hepatitis B surface and hepatitis B core antigens, liver disease, and outcome in hepatitis B infections. *Gastroenterology* 71:804, 1976
59. Feinman SV, *et al.*: e antigen and anti-e in HBsAg carriers. *Lancet* 2:1173, 1975
60. Nordenfelt E: The relationship between hepatitis B antigen, e antigen, and liver pathology in patients treated with dialysis. *Scand J Urol Nephrol* 9:277, 1975
61. Schalm SW, *et al.*: Responsiveness of HBsAg-associated chronic active liver disease to corticosteroid therapy. *Ann Clin Res* 8:221, 1976
62. Weinreb A, *et al.*: Response to therapy in e-Ag-positive and e-Ag-negative patients with chronic active hepatitis (abstract). *Gastroenterology* 71:1147, 1977
63. Vogten AJ, *et al.*: Behavior of e antigen and antibody during chronic active liver disease: Relation to HB antigen-antibody system and prognosis. *Lancet* 2:126, 1976
64. Heathcote J, *et al.*: Role of hepatitis B antigen carriers in non-parenteral transmission of the hepatitis B virus. *Lancet* 2:370, 1974
65. Schweitzer IL, *et al.*: (Letter) e antigen in HBsAg carrier mothers. *N Engl J Med* 293:940, 1975
66. Berquist KR, *et al.*: (Letter) Infectivity of serum containing HBsAg and antibody to e antigen. *Lancet* 1:1026, 1976
67. Gocke DJ: Prospective study of transfusion hepatitis. *JAMA* 219:1165, 1972
68. Alter HJ, *et al.*: Type B hepatitis: the infectivity of blood positive for e antigen and DNA polymerase after accidental needlestick exposure. *N Engl J Med* 295:909, 1976
69. Relation of e antigen to infectivity of HBsAg-positive inoculations among medical personnel (editorial). *Lancet* 2:492, 1976
70. Thamer G, *et al.*: Das e-antigen. *DMW* 101:1573, 1976
71. Mosley JW, *et al.*: Multiple hepatitis viruses in multiple attacks of acute viral hepatitis. *N Engl J Med* 296:75, 1977
72. Prince AM, *et al.*: Long-incubation post-transfusion hepatitis without serological evidence of exposure to hepatitis B virus. *Lancet* 2:241, 1974
73. Alter HJ, *et al.*: Clinical and serological analysis of transfusion-associated hepatitis. *Lancet* 2: 838, 1975
74. Purcell RH: Personal communication, November, 1976
75. Murray R: Viral hepatitis. *Bull NY Acad Med* 31:341, 1955
76. Hoofnagle JH, *et al.*: (Abstract) *Gastroenterology* 71:911, 1976
77. Kendrey G, *et al.*: Intranuclear virus-like particles in HBsAg and IHxAg-negative acute hepatitis (type C?) (Preliminary report). *Acta Morphol Acad Sci Hung* 23:173, 1975

78. Knodell RG, *et al.*: Etiological spectrum of post-transfusion hepatitis. *Gastroenterology* 69:1278, 1975
79. Sandler SG, *et al.*: Type B and non-B viral hepatitis in Jerusalem. *Bull WHO* 54:193, 1976
80. *Morbidity and Mortality Weekly Report* 26:218, 1977
81. Villarejos VM, *et al.*: Evidence for viral hepatitis other than type A or type B among persons in Costa Rica. *N Engl J Med* 293:1350, 1975
82. Knodell RG, *et al.*: Efficacy of prophylactic gamma-globulin in preventing non-A, non-B post-transfusion hepatitis. *Lancet* 1:557, 1976
83. Prince AM: Relation of Australia-and SH antigens. *Lancet* 2:462, 1968
84. Gocke DJ, *et al.*: Hepatitis antigen: Correlation with disease and infectivity of blood donors. *Lancet* 1:1055, 1969
85. Krugman S, *et al.*: Viral hepatitis - new light on an old disease. *JAMA* 212: 1019, 1970
86. Allen JG, *et al.*: Serum hepatitis from transfusion of blood. *JAMA* 180:1079, 1962
87. Mosley JW: New patterns of transfusion-associated hepatitis. *Epatologia* 12: 527, 1966
88. Seeff LB, *et al.*: A randomized, double-blind controlled trial of the efficacy of immune serum globulin for the prevention of post-transfusion hepatitis: A Veterans Administration cooperative study. *Gastroenterology* 72:111, 1977
89. Feinstone SM, *et al.*: Transfusion associated hepatitis not due to viral hepatitis type A or B. *N Engl J Med* 292:767, 1975
90. Goldfield M, *et al.*: The consequences of administering blood pretested for HBsAg by third generation techniques: A progress report. *Am J Med Sci* 270: 335, 1975
91. Alter HJ, *et al.*: The emerging pattern of post-transfusion hepatitis. *Am J Med Sci* 270:329, 1975
92. Johnson AJ, *et al.*: Removal of hepatitis B surface antigen from plasma fractions. *J Lab Clin Med* 88:91, 1976
93. Barker LF, *et al.*: Transmission of serum hepatitis. *JAMA* 211:1509, 1970.
94. Barker LF, *et al.*: Viral hepatitis B detection and prophylaxis. *Transmissible Disease and Blood Transfusion*, page 85, 1975
95. Mullis CH, *et al.*: Hepatitis B antigen in corresponding antibodies following multiple blood transfusions. *Schweiz Med Wochenschr* 104:1053, 1974
96. Lander JJ, *et al.*: Frequency of antibody to hepatitis A associated antigen as measured by a new radioimmunoassay technique. *J Immunol* 106:1166, 1971
97. Peterson MR, *et al.*: Detection of antibody to hepatitis-associated antigen in hemophilia patients and in voluntary blood donors. *Vox Sang* 22:66, 1973
98. Hollinger FB, *et al.*: Limitations of solid-phase radioimmunoassay for HBAg in reducing frequency of post-transfusion hepatitis. *N Engl J Med* 289:385, 1973
99. Alter HJ, *et al.*: Post-transfusion hepatitis after exclusion of commercial and HBAg positive donors. *Ann Intern Med* 77:691, 1971
100. Aach RD, *et al.*: Risk of transfusing blood containing antibody to hepatitis B surface antigen. *Lancet* 2:190, 1974
101. Cherubin CE: Risk of post-transfusion hepatitis in recipients of blood containing SH antigen at Harlem hospital. *Lancet* 1:627, 1971
102. Szmuness W, *et al.*: Familial clustering of hepatitis B infection. *N Engl J Med* 289:1162, 1973
103. Egoz N, *et al.*: Viral hepatitis in Israel: Transfusion associated hepatitis. *Transfusion* 12:12, 1972

104. Katz R, *et al.*: Transfusion hepatitis: Effect of modified gamma globulin added to blood *in vitro*. *N Engl J Med* 285:925, 1971
105. National Transfusion-Hepatitis Cooperative Study: Risk of post-transfusion hepatitis in the United States. *JAMA* 220:692, 1972
106. Skinhoj P, *et al.*: Hepatitis A antigen in pregnant women and their newborn infants. *Am J Dis Child* 123:380, 1972
107. Schweitzer IL, *et al.*: Factors influencing neonatal infection by hepatitis B virus. *Gastroenterology* 65:277, 1973
108. Merrill DA, *et al.*: Neonatal onset of hepatitis A associated carrier state. *N Engl J Med* 287:1280, 1972
109. Cossart YE, *et al.*: Australia antigen and the human fetus. *Am J Dis Child* 123:376, 1972
110. Papaevangelou G, *et al.*: Transplacental transmission of hepatitis B virus by symptom-free chronic carrier mothers. *Lancet* 2:746, 1974
111. Boxall E: (Letter) Vertical transmission of hepatitis B surface antigen. *Lancet* 2:1211, 1975
112. Matsuda S, *et al.*: Australia antigen in amnionic fluid. *Lancet* 1:1117, 1972
113. Schweitzer IL: Vertical transmission of hepatitis B surface antigen. *Am J Med Sci* 270:287, 1975
114. Linnemann CC, *et al.*: (Letter) HBAg in breast milk. *Lancet* 2:155, 1974
115. Beasley RP, *et al.*: Evidence against breast-feeding as a mechanism for vertical transmission of hepatitis B. *Lancet* 2:740, 1975
116. Stevens CE, *et al.*: Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med* 292:771, 1975
117. Okada K, *et al.*: Hepatitis B surface antigen in the serum of infants after delivery from asymptomatic carrier mothers. *J Pediatr* 87:360, 1975
118. Tong MJ, *et al.*: Hepatitis A associated antigen and hepatocellular carcinoma in Taiwan. *Ann Intern Med* 75:657, 1971
119. Skinhoj P, *et al.*: Transmission of hepatitis type B from healthy HBsAg-positive mothers. *Br Med J* 1:10, 1976
120. Okada K, *et al.*: e antigen and anti-e in the serum of asymptomatic carrier mothers as indicators of positive and negative transmission of hepatitis B virus to their infants. *N Engl J Med* 294:746, 1976
121. Mayumi M: (Letter) *N Engl J Med* 295:171, 1976
122. Papaevangelou G, *et al.*: Transplacental transmission of hepatitis B virus by symptom-free chronic carrier mothers. *Lancet* 2:746, 1974
123. Kattamis CA, *et al.*: Australia antigen and neonatal hepatitis syndrome. *Pediatrics* 54:157, 1974
124. Dupuy JM, *et al.*: Severe viral hepatitis type B in infancy. *Lancet* 1:191, 1975
125. Fawaz KA, *et al.*: Repetitive maternal-fetal transmission of fatal hepatitis B. *N Engl J Med* 293:1357, 1975
126. Wright R, *et al.*: Cirrhosis associated with the Australia antigen in an infant who acquired hepatitis from her mother. *Br Med J* 4:719, 1970
127. Schweitzer IL, *et al.*: Viral hepatitis in neonates and infants. *Am J Med* 55: 762, 1973
128. Ohbayashi A, *et al.*: Familial clustering of asymptomatic carriers of Australia antigen and patients with chronic liver disease or primary liver cancer. *Gastroenterology* 62:618, 1972
129. Feldman RE, Schiff ER: Hepatitis in dental professionals. *JAMA* 232:1228, 1975
130. Mosley JW, *et al.*: Viral hepatitis as an occupational hazard of dentists. *JADA* 90:992, 1975

131. Lewis TL, *et al.*: Comparison of the frequency of hepatitis B antigen and antibody in hospital and non-hospital personnel. *N Engl J Med* 289:647, 1973
132. Smith JL, *et al.*: Comparative risk of hepatitis B among physicians and dentists. *J Infect Dis* 133:705, 1976
133. Levin ML, *et al.*: Hepatitis B transmission by dentists. *JAMA* 228:1139, 1974
134. Rimland D, *et al.*: Hepatitis B outbreak traced to an oral surgeon. *N Engl J Med* 296:953, 1977
135. Garibaldi RA, *et al.*: Hospital-acquired serum hepatitis. *JAMA* 219:1577, 1972
136. Snydman DR, *et al.*: Nosocomial viral hepatitis B: A cluster among staff with subsequent transmission to patients. *Ann Intern Med* 85:573, 1976
137. *Morbidity and Mortality Weekly Report*, Supplement, May 7, 1976
138. Reed WD, *et al.*: Infusion of hepatitis B antibody in antigen-positive active chronic hepatitis. *Lancet* 2:1347, 1973
139. Kohler PF, *et al.*: Immunotherapy with antibody, lymphocytes, and transfer factor in chronic hepatitis B. *Clin Immunol Immunopathol* 2:465, 1974
140. Tong MJ, *et al.*: Failure of transfer factor therapy in chronic active type B hepatitis. *N Engl J Med* 295:209, 1976
141. Gocke DJ: Fulminant hepatitis treated with serum containing antibody to Australia antigen (Letter). *N Engl J Med* 284:919, 1971
142. Opolon P, *et al.*: Passive immune therapy in HBsAg-positive fulminant hepatitis (Abstract). *Gastroenterology* 66:891, 1974
143. Failure of specific immunotherapy in fulminant type B hepatitis. *Ann Intern Med* 86:272, 1977
144. Shulman S, *et al.*: Transfer factor therapy of chronic active hepatitis. *Lancet* 2:650, 1974
145. Grob PJ, *et al.*: Therapeutic use of transfer factor. *Eur J Clin Invest* 5:33, 1975
146. Jain S, *et al.*: Failure of transfer factor therapy in chronic active type B hepatitis (Letter). *N Engl J Med* 295:504, 1976
147. Shulman ST, *et al.*: Transfer factor in treating hepatitis B (Letter). *N Engl J Med* 295:898, 1976
148. Sano M, *et al.*: Transfer factor in treating hepatitis B (Letter). *N Engl J Med* 296:53, 1977
149. Trepo CG, *et al.*: Attempted immunotherapy with dialyzable transfer factor in hepatitis B carrier chimpanzees: Induction of delayed hypersensitivity to hepatitis B surface antigen. In Acher MS, *et al.* (editors), *Transfer Factor: Basic Properties and Clinical Applications*, page 449, 1976
150. Purcell RH, *et al.*: Modification of chronic hepatitis B virus infection in chimpanzees by administration of an interferon inducer. *Lancet* 2:757, 1976
151. Greenberg HB, *et al.*: Effect of human leukocyte interferon on hepatitis B virus infection in patients with chronic active hepatitis. *N Engl J Med* 295:517, 1976
152. Desmyter J, *et al.*: Administration of human fibroblast interferon in chronic hepatitis B infection. *Lancet* 2:645, 1976
153. Sceff LB, *et al.*: VA cooperative study of post-transfusion hepatitis. *Am J Med Sci* 270:355, 1975
154. *CDC Hepatitis Surveillance Report*, Number 39, February, 1977
155. Seeff LB, *et al.*: Efficacy of hepatitis B immune globulin after accidental exposures: Preliminary report of the Veterans Administration cooperative study. *Lancet* 2:939, 1975
156. Grady GF, *et al.*: Hepatitis B immune globulin - prevention of hepatitis from accidental exposure among medical personnel. *N Engl J Med* 293:1067, 1975.
157. Redeker AG, *et al.*: Hepatitis B immune globulin as a prophylactic measure for spouses exposed to acute type B hepatitis. *N Engl J Med* 293:1055, 1975

158. Prince AM, *et al.*: Hepatitis B "immune" globulin: Effectiveness in prevention of dialysis-associated hepatitis. *N Engl J Med* 293:1063, 1975
159. Desmyter J, *et al.*: Hepatitis B immunoglobulin in prevention of HBs antigenaemia in haemodialysis patients. *Lancet* 2:376, 1975
160. Kuhns WJ, *et al.*: A clinical and laboratory evaluation of immune serum globulin from donors with a history of hepatitis: Attempted prevention of post-transfusion hepatitis. *Am J Med Sci* 272:255, 1976
161. Wanters JP, *et al.*: Delayed hepatitis after treatment with hepatitis B immune serum globulin. *Br Med J* 2:19, 1976
162. Hoofnagle JH, *et al.*: Antibody to the hepatitis B surface antigen in immune serum globulin. *Transfusion* 15:408, 1975
163. Grady G: Passive immunotherapy (passive immunization) against viral hepatitis. Postgraduate Symposium on Viral Hepatitis, AASLD, November 3, 1976, page 15-1
164. Knodell RG, *et al.*: Efficacy of prophylactic gamma globulin in preventing non-A, non-B post-transfusion hepatitis. *Lancet* 1:557, 1976
165. Neefe SR, *et al.*: Homologous serum hepatitis and infectious (epidemic) hepatitis. *Am J Med* 1:3, 1946
166. Krugman S, *et al.*: Viral hepatitis type B (MS-2 strain): Further observations on natural history and prevention. *N Engl J Med* 288:755, 1973
167. Purcell RH, *et al.*: Hepatitis B subunit vaccine: A preliminary report of safety and efficacy tests in chimpanzees. *Am J Med Sci* 270:395, 1975
168. Hilleman MR, *et al.*: Purified and inactivated human hepatitis B vaccine: Progress report. *Am J Med Sci* 270:401, 1975
169. Maupas P, *et al.*: Immunization against hepatitis B in man. *Lancet* 1:1367, 1976
170. Villarejos VM, *et al.*: Role of saliva, urine and feces in the transmission of type B hepatitis. *N Engl J Med* 291:1375, 1974
171. Schweitzer IL, *et al.*: Hepatitis and hepatitis associated antigen in 56 mother-infant pairs. *JAMA* 220:1092, 1972
172. Fujita K, *et al.*: Materno-fetal transport of Au/Sh antigen and antibody. *Lancet* 2:378, 1972
173. Papaevangelou G, *et al.*: Hepatitis B antigen and antibody in maternal blood, cord blood and amniotic fluid. *Arch Dis Child* 49:936, 1974
174. Boxall EH, *et al.*: (Letter) Dane particles in cord blood. *Lancet* 2:1513, 1974
175. Beasley RP, *et al.*: (Letter) Breast-feeding and hepatitis B. *Lancet* 2:1089, 1975