Current Concepts of Viral Hepatitis and A Peek into the Future

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New information has prompted revision of the conceptual framework for considering the epidemiology and virology of viral hepatitis. The means are now at hand to identify infections due to either Hepatitis A or B, as well as to implicate other etiologic agents in hepatitis. Immunologic evidence of variation in the antigens associated with Hepatitis B, and possibly in Hepatitis A, may explain some well known epidemiologic phenomena and has important implications in immune serum globulin prophylaxis. The ambiguous relationship of antigenemia and viremia in Hepatitis B is explored in relation to the hepatitis hazard of blood products, to trials of immune serum globulin, and to the potential role of the carrier-health worker in hepatitis transmission. The emerging concept of non-parenteral transmission of Hepatitis B is reviewed and future developments in the production of hepatitis vaccines and in experimental viral hepatitis in non-human primates is briefly discussed.

Since we last reviewed the epidemiology of viral hepatitis (1) there have been a number of advances in our knowledge of the agents responsible for this illness and a greater appreciation of the diverse modes of transmission by which hepatitis may be spread. Despite, or in some instances because of, these new observations in both the laboratory and the field, the conceptual framework within which one might consider the epidemiology of viral hepatitis has become more rather than less complex. The available voluminous literature dealing with the Hepatitis B surface antigen (HBsAg) will not be discussed in detail since this has been the object of a number of recent reviews. I would prefer to emphasize in these brief remarks a few selected areas of continuing controversy in which conceptual turnabouts are likely to occur, and others which have not yet received adequate attention but will certainly be the subject of future investigations.

AGENTS RESPONSIBLE FOR VIRAL HEPATITIS

The Hepatitis B virus (HBV) is now believed to contain antigenic material in its core (HBeAg) as well as on its surface (HBsAg). Detection of HBeAg, anti-
body to this surface antigen (anti-HB$_s$), and antibody to the core antigen (anti-
HB$_c$) (2, 3) has permitted specific identification of HBV infections even in the
absence of overt clinical disease. The use of sensitive tests to identify these Hepatitis
B antigens and antibodies has provided a great deal of information about the fre-
quency of infection, range of possible incubation periods, and variations in the clini-
cal manifestations of HBV infections, and has permitted identification of chronic
HB$_c$.Ag carriers who may be potential sources of infection.

The recent identification of different virus-like particles with antigenic properties
in the stools of patients with acute Hepatitis A (4, 5, 6), and the demonstration
of seroconversion by immune electron microscopic techniques (5) will provide the
means to gather more information on the epidemiological attributes of this infection
as well.

It seems likely that this newly acquired ability to positively identify both A and
B infections may shed light on an old problem, the frequency of non-A or B viruses
as the cause of hepatitis. The suggestion that hepatitis may be a complication of
infection with viral agents that usually produce manifestations of disease which
are more prominent than hepatic involvement can now be tested in both sporadic
infections and in epidemiologically related groups of cases. Although CMV, herpes
simplex, Coxsackie, reovirus, and adenovirus (7) as well as other known agents,
have been isolated from occasional patients with clinical hepatitis, their epidemi-
ologic importance has not been clear. Whether they are responsible for outbreaks
of hepatitis has been a difficult question to resolve. It seems possible that some
agents may be more important in this respect than others. At least one such agent
has been associated with an outbreak of anicteric hepatitis occurring in a hemodi-
alysis unit. In that episode approximately 25% of dialyzed patients developed the
disease with a mean incubation period estimated to be 25 days, an appropriate
interval for Hepatitis A. Serologic studies provided convincing evidence that EB
virus was the responsible agent (8).

In addition to infection with known viruses, the existence of unidentified hepatitis-
inducing agents may now be approached by means of exclusion. It would appear
likely that hepatitis viruses other than A and B, e.g., C, D or E, may exist and
may be more commonly encountered than was previously believed. The observation
that the incidence of transfusion-associated hepatitis has remained nearly constant
despite implementation of screening of blood donors, albeit imperfectly, for
HB$_c$.Ag, during a period in which Type A hepatitis has not increased in frequency
(9) provides circumstantial evidence that much post-transfusion hepatitis is due
neither to A nor B, but rather is related to other hepatitis viruses.

Another important area which is now amenable to investigation is concerned
with the existence of different strains of Hepatitis A and B viruses. The identifica-
tion of several subtypes of HB$_c$.Ag has provided immunologic evidence for varia-
tions in the Hepatitis B antigens. (10, 11) It has already been demonstrated that
these determinants are related to different subtypes of HBV. Subtype HB$_c$.Ag/ayw
is predominant in drug-addict associated viral hepatitis, while HB$_c$.Ag/adw is the
predominant subtype in carriers identified among North American and Northern
European blood donors. These antigenic subtypes could have important implica-
tions in both vaccine development and potential efficacy of hyperimmune globulin
for prophylaxis in exposed susceptible populations. In addition, the well known
frequency of multiple episodes of acute viral hepatitis in parenteral drug users may
now also be explained by infection with immunologically distinct variants, or
strains, of Hepatitis B, A, or other hepatitis agents. Until recently, there was scant sero-epidemiologic evidence to support the concept of immunologic variation in HAV. However, laboratory studies involving nonhuman primates have now provided the first evidence of immunologic differentiation in HAV (12). In these studies direct cross-challenge experiments have indicated the existence of at least two strains of HAV. Confirmation of these exciting investigations is awaited.

ANTIGENEMIA AND VIREMIA

Much confusion abounds concerning the possible equation of antigenemia with viremia or infectivity. HB,Ag is a marker of HBV but it is by no means certain that the presence of HB,Ag indicates that HBV is present at the same time. That is, it is not clear that de novo synthesis of the virion of Hepatitis B occurs in parallel with the synthesis of antigenic subunits of the outer viral coat. In fact, there is little reason to believe that these events are synchronous. Nonparallel production of viral antigens and infectious virus has been described following inoculation into human amnion cells of the infectious canine hepatitis virus (13). It would appear that the HB,Ag is the coat material of the true Hepatitis B virion. Although HB,Ag may be released from infected cells concurrently with infectious particles early in the course of infection, host or viral factors which determine or may modify the sequence of production and release are not presently understood.

It is not yet known whether infectious virions are released constantly, intermittently, or rarely, if at all, in individuals recognized to be chronic carriers of HB,Ag. This issue is extremely important not only to virologists and immunologists but also to clinical epidemiologists, hepatologists, and practitioners who are concerned with the risks of exposure to chronic or transient carriers of HB,Ag.

Of specific interest is the potential risk of Hepatitis B infection following exposure by accidental tissue-penetration with equipment contaminated with blood or blood products containing HB,Ag. Two nationwide cooperative trials (14, 15) designed to evaluate the efficacy of high titer anti-HB,s gamma globulin in such situations are currently underway. Although neither code has yet been broken a most striking feature in both studies has been the very low attack rate of icteric
or anicteric hepatitis among exposed subjects. The demonstration of HBsAg in heat-treated human serum albumin preparations (16) is similarly of interest since this product is not known to have transmitted hepatitis. These observations provide circumstantial support for the notion that the presence of HBsAg does not necessarily signal the existence in the same material of infective doses of HBV.

It might be appropriate, at this point, to raise some cautionary questions concerning trials in which immune serum globulin containing high titers of anti-HBs is being administered. Although preliminary studies have suggested that such material may be effective, (17, 18) the titer of anti-HBs may not be the best indicator of whether a specific preparation contains that immunoglobulin which will effectively neutralize infectious virus. A number of trials of so-called conventional immune serum globulin have provided conflicting evidence of efficacy in the prevention or modification of transfusion-associated hepatitis (7). Methodological differences, such as lack of randomization, unblinded observations, and variable follow-up techniques, may account for some of the variability in reported effectiveness. However, inherent differences in the immune serum globulin employed in these trials may be even more crucial. When some of these materials were tested recently for anti-HBs, no correlation between titer and reported efficacy could be demonstrated (19). This observation suggests that effective neutralizing antibody may not have been measured. Clearly, further information must be sought for other specific antibodies, e.g., anti-HBc, and their relationship to antibodies present in the materials used in therapeutic trials. The recently demonstrated failure of high titer anti-HBc to modify fulminant hepatitis due to HBV may be a case in point (20), although other explanations for its lack of efficacy may be more appropriate in this situation.

The role of the health worker in the spread of HBV is presently a subject of intense interest. It is reasonably clear that medical and paramedical personnel are at higher risk for acquiring viral hepatitis than is the general population, (7, 21, 22). Recognized and unrecognized parenteral exposures, and contact-transmission-involving asymptomatic or anicteric cases, may be responsible for epidemics and sporadic cases among health workers, particularly in hemodialysis and transplantation units where a very high risk of developing hepatitis exists (23). The role of the health worker in transmitting disease to the general population or to specific intra-hospital populations, is less well understood. Although a number of instances have been described in which physicians and dentists have been responsible for outbreaks in their patients because of faulty sterilization techniques, spread by contact transmission (24) although possible, is more controversial. Recent studies designed to determine the prevalence of HBsAg in medical workers have not defined the nature of the risk existing for individuals exposed to such carriers by personal contact. Since the presence of circulating HBsAg may not necessarily indicate the presence of infectious virus, it is exasperating to attempt to make intelligent recommendations curtailing the professional activities of documented carriers. Future studies undoubtedly will be directed to this perplexing problem.

NON-PARENTERAL TRANSMISSION OF HEPATITIS B

The implications which have been drawn from equating antigenemia with infectivity also have permeated many of the interpretations of recent investigations of possible non-parenteral transmission of HBV. The detection of HBsAg in saliva, duodenal fluid, urine, semen, and other body fluids has permitted a wide range of speculation concerning mechanisms of person-to-person transmission of Hepa-
tis B. The precise role of these materials in the transmission of non-percutaneous infection remains to be defined, although there is no doubt that nonparenteral transmission can occur. Experimental evidence of successful transmission of Hepatitis B by the feeding of a large inoculum of infectious serum was demonstrated several years ago (25). Thus, it seems reasonable that blood or blood contaminated body fluids can be infective by the oral as well as parenteral route. Observations of high prevalence rates of HB,Ag and anti-HB, among mentally retarded individuals in large institutions are also compatible with contact transmission of HBV, presumably by fecal-oral spread (18). It should be noted, however, that HB,Ag has not been found with any consistency in a number of studies directed at examination of fecal samples from HB,Ag carriers. Unfortunately, available data from institutions for the mentally retarded do not entirely exclude inapparent percutaneous or parenteral modes of transmission. Furthermore, as previously indicated, the notion that the presence of HB,Ag indicates the concomitant presence of HBV remains to be proved.

The wide spread use of tests for HB,Ag in sporadic cases of hepatitis in adults living in urban areas of this country has revealed a surprisingly large proportion of patients with serologic evidence of HBV infection in whom no history of parenteral exposure was obtained. (26). Studies of apparently healthy blood donors have also revealed the presence in 6–30% of anti-HB, (27). Both pieces of data suggest that inapparent HBV infection is not uncommon, and that infection had been acquired by contact with asymptomatic infected cases or carriers. Further circumstantial evidence, often cited to support the concept of person-to-person fecal-oral HBV infection, is the high prevalence rate of HB,Ag and anti-HB, in certain tropical and subtropical developing populations (28). It has been assumed, because of generally low levels of hygiene and population crowding in these nations, that HBV infection has been acquired by fecal-oral spread.

These interpretations are difficult to reconcile with previous observations that HBV infections are not readily spread from person to person, except by means of shared needles. It is noteworthy and unfortunate that much of the data on sporadic hepatitis in adults has been collected during the recent international epidemic of parenteral drug abuse, and the value of the absence of parenteral exposure history must, in at least some instances, be questioned. Whether parenteral spread, by repeated use of scarification needles, lancets, vaccination equipment, or mechanical transmission by biting insects, is important in developing countries must be clarified in future studies. The role of minor breaks in the integument and mucous membranes in the transfer of infection, as distinct from personal contact, requires further exploration. This mechanism of transmission of Hepatitis B was apparently responsible, some years ago, for a large outbreak of hepatitis among trackfinders who suffered multiple lacerations, scratches, and abrasions of their uncovered skin (29).

In contrast to Hepatitis A, available data have failed to incriminate HBV in either food or water-borne epidemics of hepatitis. A special case may exist for shellfish-associated hepatitis which has been described in both epidemic and endemic forms (1). The recent recovery of HB,Ag from clams (30) has implications which may yet alter our concepts of HBV infection through common vehicles. Whether this is a real epidemiologic entity in the spread of HBV is unknown.

Non-parenteral epidemics of Hepatitis B are most unusual. Only two such contact-associated large outbreaks have been adequately described to date. The first
of these occurred among U.S. Navy personnel inoculated with plasma in a study of the efficacy of influenza vaccine (31). 36% of this group developed hepatitis after a mean incubation period of 79 days, consistent with Hepatitis B infection. Three percent of uninoculated personnel also contracted hepatitis, mainly at the end of the epidemic in inoculated individuals. Allergic symptoms, now recognized as probably related to the formation and deposition of immune complexes of HB,Ag and anti-HB, occurred with equal frequency in both inoculated and uninoculated hepatitis cases. The exact mode of transmission of Hepatitis B from inoculated to uninoculated cases was not defined in this outbreak but contact spread was postulated. The second epidemic of Hepatitis B attributed to person-to-person transmission occurred in a region of Costa Rica with a high background prevalence rate of HB,Ag (32). The occurrence of an outbreak of Hepatitis A some 3 years later provided an opportunity to compare and contrast these two episodes. In the outbreak attributed to HBV all age groups were affected, the disease spread rather slowly, and the secondary attack rate was very low. In contrast, in the epidemic attributed to Hepatitis A cases were concentrated in children, the disease appeared to have been rapidly disseminated within the community, and secondary attack rates were about 4 times greater than in the Hepatitis B outbreak.

Although the existence of these two contact-associated epidemics of Hepatitis B cannot be dismissed, the frequency of person-to-person transmission of HBV and the precise means of spread remain ill defined in general populations. A number of specific questions have not yet been answered. For example, is the risk of acquiring HBV infection confined to contacts of carriers or to those exposed to acutely infected individuals? Are skin lesions both a site of entry and exit of virus? What is the role of shared razors, toothbrushes, drinking glasses, etc.? Is there a real risk of venereal transmission? The role of the latter mode of transmission has been re-evaluated recently in view of some new observations in selected populations. A higher prevalence rate has been found among some homosexual groups than in the general population (33). Furthermore, in a study of secondary attack rates of HBV infection among household contacts of hemodialysis patients, marital partners were affected 14 times more frequently than children and non-spouse adults (34). Although sexual transmission may explain these differential rates, it is also possible that spouses were more intimately exposed to blood in dialysis procedures than were other household members. The recent failure to demonstrate a difference in HBV infection rates in female prostitutes compared to nuns (35) also suggests that venereal transmission may not be as important as has been suggested by some investigators. Further investigation of the venereal mode of transmission is required.

HEPATITIS VACCINES

Although we are undoubtedly closer now to vaccine development for the prevention of both Hepatitis A and B than ever before, a number of formidable problems remain before this goal can be realized. Preliminary trials of heat-inactivated preparations of serum containing HB,Ag have provided evidence of protection in limited studies (36, 37). Whether this technique will prove reproducible and efficacious in larger trials is not yet known. The inability to propagate and isolate either virus A or B in tissue culture systems to date suggests that much work will be required before the development of an attenuated live virus vaccine is feasible. Once these agents are grown in tissue culture systems, it is still likely that at least
5 years and probably 10 years will elapse before a specific hepatitis vaccine is commercially available.

EXPERIMENTAL VIRAL HEPATITIS

One of the most important developments in viral hepatitis research has been the transmission of both Hepatitis A and B to non-human primates. As recently outlined (38), exploitation of these experimental models should provide new information concerning 1) host factors which determine the localization of hepatitis viruses in the liver, 2) biochemical pathology of viral liver disease, 3) modification of the response to infection by immunological, humoral, and genetic factors, 4) the potential role of antiviral chemotherapy in hepatitis, and 5) the role of immune mechanisms in recovery from or perpetuation of viral induced liver disease. These areas will be fertile grounds for new investigations.

CONCLUSION

One may conclude by noting that exciting information has become available in recent years and that knowledge of viral hepatitis will certainly continue to expand. Although a number of challenges lie ahead, the complexities of the virology and epidemiology of viral hepatitis will eventually be unraveled and there will ultimately be no necessity for frequent revisions of the conceptual framework within which we attempt to understand this group of diseases.

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