Non-A, Non-B Hepatitis: Evolving Epidemiologic and Clinical Perspective

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More than a decade has elapsed since non-A, non-B (NANB) hepatitis entered our lexicon. After all this time, after the publication of hundreds of articles, after the emergence and maturation of now well-stated controversies over the agents and the disease, our understanding of NANB hepatitis is still unsettled and evolving. What began as the concept of a single agent transmitted exclusively by transfused blood has been broadened to accommodate the recognition of potentially two blood-borne agents transmitted, like hepatitis B, in a variety of epidemiologic settings. Incubation periods vary and may be surprisingly brief. There is even a type of NANB hepatitis that appears to resemble type A hepatitis epidemiologically and clinically. Frustration persists over our inability to identify the agents of NANB hepatitis definitively; however, by observing the disease for more than a decade, we have gained insight into its natural history and its unusual pattern of insidious, silent progression. Strikingly clear is just how much we do not know about NANB hepatitis.

Often overlooked in considerations of NANB hepatitis is how imprecise a diagnosis it is. This fact alone may account for much of the inconsistency among reports from different investigators. In certain population groups with a high frequency of chronic hepatitis B infection, cases of superimposed NANB hepatitis may be overlooked. Alternatively, superinfections of hepatitis B carriers with the delta agent or spontaneous reactivations of chronic hepatitis B may be attributed mistakenly to superimposed NANB hepatitis and the frequency of NANB hepatitis overestimated. Occasionally, conventional serologic markers of hepatitis B cannot be readily detected, or historical and biochemical information about other potential hepatotoxins and metabolic derangements cannot be elicited, as in cases of fulminant hepatitis. Recently, a deletion mutant of hepatitis B virus (HBV) was described that, lacking a segment of the S gene coding for hepatitis B surface antigen (HBsAg), cannot produce HBsAg.1 Conceivably, infection with this agent could be classified incorrectly as NANB hepatitis. Although this exceptional case hardly invalidates conventional understanding of serologic events associated with HBV infection, its existence adds to the potential difficulty in making a diagnosis of NANB hepatitis.

Rarely, other viruses and even nonviral agents that cause systemic infections can cause mild hepatocellular inflammation and necrosis. On the other hand, carefully done epidemiologic investigations in transfusion recipients and experimental serial transmission studies in chimpanzees have documented conclusively the existence of cases of viral hepatitis devoid of indicators of infection with HBV, hepatitis A virus (HAV), or any other known agents. These well-pedigreed cases provide the most compelling evidence for the existence of NANB hepatitis agents.

In this article we will present an overview of the epidemiologic and clinical features of NANB infection. For more detail, there are available several more extensive treatments of the subject.2-4 An assessment of putative NANB hepatitis agents appears elsewhere in this issue of Seminars.

EPIDEMIOLOGY

Thought originally to be a disease limited to transfusion recipients, NANB hepatitis is now recognized in many other epidemiologic settings. The type of NANB hepatitis prevalent in the United States and Western Europe resembles type B hepatitis in that transmission occurs efficiently and primarily by percutaneous routes, but by apparently nonpercutaneous routes as well.5

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Percutaneous Transmission
Transfusion-Associated Hepatitis

Transfusion-associated hepatitis (TAH) remains the most commonly recognized form of NANB hepatitis. Despite use of blood from volunteer donors that has been screened for HBsAg by highly sensitive third-generation immunoassays, the residual frequency of TAH is now approximately 7 to 10% of multitransfused patients or 3 to 6 cases per 1000 units transfused; 75 to 95% of these cases throughout the world can be classified as NANB hepatitis, and in the United States, where 200,000 to 300,000 cases are estimated to occur annually, the proportion attributable by serologic exclusion to NANB hepatitis exceeds 90%. More than any single other intervention, conversion from a blood donor population, including paid, "commercial" donors to an all-volunteer donor population has had the most dramatic impact on reducing the frequency of hepatitis after transfusion. Before the exclusion of paid donors, the frequency of post-transfusion hepatitis was on the order of three- to fourfold higher than it is today. Voluntary self-exclusion of blood donors in high-risk groups for the acquired immunodeficiency syndrome (AIDS) will probably further reduce the frequency of TAH, but quantitative studies to document the extent of this effect have not as yet been reported.

Intravenous Drug Users

Multiple attacks of acute hepatitis after self-injection in drug addicts had been recorded as early as the 1950s and provided one of the earliest clues to the existence of at least one and probably more than one NANB hepatitis agent. The application of sensitive serologic tests for HAV and HBV infection to cases of acute hepatitis in drug addicts led to reports in which approximately 40 to 50% of the cases were classified by serologic exclusion as NANB hepatitis. Similarly, isolated cases in drug addicts have been included in reports of sporadic NANB hepatitis; in some of these reports, drug addicts accounted for a majority of sporadic NANB hepatitis cases. The fact that so many intravenous drug users have serologic evidence of current or previous infection with HBV makes difficult an accurate assessment of the contribution of NANB hepatitis to the liver disease in this population. Therefore, reports of observed frequencies of NANB hepatitis in drug addicts almost certainly underestimate the contribution of NANB hepatitis agents to both their acute and chronic liver disease.

Hemodialysis and Renal Transplantation

Since the introduction of effective measures to prevent the spread of HBV infection in hemodialysis units, NANB hepatitis has become the most common cause of acute hepatitis in patients and staff of these units. Discrete outbreaks as well as sporadic, isolated cases of acute NANB hepatitis have been reported from dialysis units in several countries. In addition, studies have been undertaken to define the prevalence and incidence of NANB hepatitis in hemodialysis units. Fifteen percent in one study and 16% in another of chronically hemodialyzed patients had persistently elevated serum alanine aminotransferase (ALT) activity in the absence of serologic markers of identifiable viruses known to cause hepatitis. Moreover, the annual incidence of net acute NANB hepatitis averages between 3 and 6% in patients and approximately 1% in staff of hemodialysis units. In some studies, but not others, the risk in dialysis patients was associated with recent transfusion, whereas the risk in dialysis staff was associated with recent needlestick.

Organ transplant recipients are also at high risk of acquiring NANB hepatitis, and the consequences can be devastating. Although drug hepatotoxicity, overdose resulting from multiple transfusions during pretransplantation hemodialysis, and infection with other viral agents account for some cases of hepato-cellular dysfunction in renal transplant recipients, NANB hepatitis can be implicated by exclusion in a substantial proportion of cases of acute and chronic hepatitis in these patients. Ware et al attributed 71% of 38 cases of chronic liver disease in renal transplant recipients to NANB hepatitis. More than half experienced progressive deterioration; cirrhosis, transition from chronic persistent (CPH) to chronic active hepatitis (CAH), and death resulting from liver failure were observed. Similarly, LaQuaglia et al found that NANB hepatitis developed after renal transplantation in 6.5% of patients and that chronic hepatitis developed in as many as 93% of those affected. Furthermore, these investigators found that mortality within the first 3 years after transplantation was significantly increased in patients with hepatitis. Death in approximately 5% of the fatal cases, however, was related not to liver failure, but, instead, to bacterial or fungal sepis. Even among survivors, the frequency of life-threatening extrahepatic infections was significantly more common in the hepatitis patients. This higher frequency of infection plus the higher graft survival observed in the group of renal transplant recipients with hepatitis suggest that, like other systemic viral infections, infection with a NANB hepatitis agent has an immunosuppressive effect.

Whereas the early morbidity and mortality in renal transplant recipients with NANB hepatitis may be related to nonhepatic sources, the late consequences shift to hepatic decompensation. After 5 to 10 years of asymptomatic low-level elevations of aminotransferase activity, patients may present with new-onset complications of end-stage liver disease, such as ascites.
hepatic encephalopathy, or bleeding from esophageal varices.22 This slow, insidious, late deterioration is also being observed currently 5 to 10 years after the onset of transfusion-associated NANB TAH in immunocompetent persons (see later).22

Recipients of Multiple and Pooled Blood Products

NANB hepatitis has been reported in persons with hereditary and acquired coagulation disorders after infusion of antihemophilic factor (AHF), Factor IX concentrates, cryoprecipitate, and fibrinogen,24-25 as well as in thalassemics who require life-long blood transfusion therapy.26,27 The occurrence of NANB hepatitis in hemophiliacs varies widely as a function of the age and duration of exposure, the type of Factor VIII replacement therapy, and the donor source of plasma derivatives. Single and multiple episodes of acute hepatitis with incubation periods as brief as 1 to 4 weeks have been observed in hemophiliacs treated with commercial or even volunteer donor Factor VIII concentrates28-29 and even with cryoprecipitate prepared from the plasma of a single volunteer donor.30 Similarly, heat-treated Factor VIII concentrates that failed to transmit NANB hepatitis to chimpanzees have been responsible for the transmission of NANB hepatitis to patients with hemophilia.31 Annual NANB hepatitis attack rates of 2 to 6% have been reported in hemophiliacs,32,33 and in a recent study of patients with hemophilia and von Willebrand's disease treated for the first time (or for the first time in 6 months in a few cases) with Factor VIII or IX concentrates obtained from small pool volunteer donor plasma, NANB hepatitis developed in as many as 65% during the first 1 to 12 weeks after infusion.34 Although the cause of the chronic liver disease so prevalent in multiply infused hemophiliacs cannot be characterized definitively, a substantial proportion are probably cases of chronic NANB hepatitis.

Even immune globulin, long considered one of the safest blood products, has been implicated in the transmission of NANB hepatitis. Recent reports have appeared in which short incubation NANB hepatitis followed by chronic liver disease occurred in agammaglobulinemic persons who were treated with intravenous globulin.35,36 Still, immune globulin (IG) is considered a safe product; the cases of NANB hepatitis appear to have resulted from an aberration in the manufacturing process of intravenous globulin.37

Occupational and Nosocomial Transmission

Clinically apparent NANB hepatitis has been observed in health workers exposed to patients and their blood, primarily after accidental needlestick, but even in the absence of such an identifiable incident.32,34 Similarly, occupationally acquired cases have been included in reports of sporadic NANB hepatitis and in hemodialysis units.38-40 In a report from Denmark, 40% of hepatitis cases among nurses were categorized by serologic exclusion as NANB hepatitis.41 Several outbreaks of nosocomial NANB hepatitis in oncology units and plasmapheresis centers have been described,42 and in several reports recent hospitalization was the only risk factor identifiable in a proportion of sporadic cases of NANB hepatitis.43 The frequency of NANB hepatitis after surgery without transfusion has been found to range between 0.2 and 2.1%.44,45

Nonpercutaneous Transmission

Although percutaneous or transmucosal inoculation appears to be the most efficient mechanism for the spread of NANB hepatitis, so-called nonpercutaneous routes (including covert percutaneous inoculation) have also been implicated.

Sexual Transmission

Although the role of sexual activity in the spread of NANB hepatitis is not known, sexual transmission probably does occur. Among prospectively followed homosexual men, a 2.9% annual attack rate of acute NANB hepatitis was found,44 and homosexual men account for a proportion of reported cases of sporadic NANB hepatitis.32,33,46 Still, homosexual transmission of NANB hepatitis appears to be relatively less frequent than homosexual transmission of HBV and HAV infection, and the proportion of sporadic NANB hepatitis cases that involve homosexual men is quite small. In addition, secondary spread of NANB hepatitis to heterosexual partners of patients with transfusion-associated or hemodialysis-associated NANB hepatitis is rare.47 Taken together, these observations suggest that sexual transmission of NANB hepatitis is inefficient and uncommon.

Perinatal Transmission

Perinatal transmission from mother to offspring has been observed in infants born to mothers with acute NANB hepatitis during the third, but not the second, trimester of pregnancy.48 The extent of such perinatal transmission remains to be defined.

Sporadic Cases

A substantial proportion of isolated, sporadic cases of hepatitis occurring in the absence of a defined outbreak or epidemic have been attributed to NANB hepatitis. Surveys of patients presenting with acute hepatitis for medical care, primarily at large urban hospitals, have shown that the distribution of NANB
hepatitis is worldwide and that these agents account for 6 to 46% of sporadic cases of viral hepatitis in urban areas. The extremes in this range reflect biases of selection and definition, particularly differences in the proportion of persons included with an antecedent history of percutaneous exposure. In the recent sentinel study conducted by the Centers for Disease Control, all reported cases of viral hepatitis occurring in a 10 to 20 month period among five American counties were characterized; 26% of cases were labeled as NABN hepatitis, ranging from 18 to 37% among the different counties. In general, in developed countries, HBV and HAV are not highly endemic, and in the absence of an emphasis on percutaneously transmitted cases, NABN hepatitis agents account for approximately 15 to 30% of sporadic cases of acute hepatitis in urban adults, perhaps half that frequency in children. The fact that as many as 25 to 50% of patients with sporadic acute NABN hepatitis fail to recall any percutaneous exposure suggests that NABN hepatitis, like hepatitis B, can be transmitted both by covert percutaneous routes and by nonpercutaneous mechanisms.

**Person-to-Person Spread**

The proportion of sporadic cases of NABN hepatitis without identifiable percutaneous exposure raises the question of whether NABN hepatitis can be transmitted by person-to-person spread. Such a mechanism is the likely explanation for limited observations of NABN hepatitis transmission within families and institutions. Two secondary cases were identified in a study of 34 household contacts of persons involved in a plasmapheresis center outbreak of NABN hepatitis; however, other than these few cases, cases of NABN hepatitis have not been observed in household contacts of patients with TAH or dialysis-associated NABN hepatitis.

**Fecal-Oral Spread (Epidemic NABN Hepatitis)**

The predominant and most easily recognized forms of NABN hepatitis in the United States and western Europe appear to be transmitted predominantly through percutaneous exposures, are rarely, if ever, associated with secondary cases, and, like hepatitis B, are not spread by the fecal-oral route. In contrast, what appears to be a distinct type of water-borne NABN hepatitis has been described in India, Burma, northern Africa, and Asia. A notorious epidemic in 1955 and more limited outbreaks and isolated cases described recently all share several common features: occurrence in populations universally immune to HAV; fecal-oral spread traced to contamination of water supplies by sewage; rarity of secondary cases in house-
imately one-quarter of patients with NANNB TAH are icteric, and ALT levels are moderately elevated, ranging between mid-200 and mid-600 U/L. A clinical feature quite characteristic of NANNB hepatitis is the episodic, fluctuating pattern of ALT and aspartate aminotransferase activity; periods of elevated enzyme activity alternate with periods of near normal or normal enzyme activity. Because periods of intervening normal enzyme activity may last many months between episodic elevations, determining convalescence accurately is difficult. Such episodic exacerbations of protracted NANNB hepatitis are easily confused with occurrences of multiple, distinct bouts of acute hepatitis presumed to result from infection with different NANNB hepatitis agents.

Despite its usually benign course, acute NANNB hepatitis may be severe and even fulminant. Fulminant cases often occurred among patients with transfusion-associated hepatitis B. In contrast, fulminant cases of NANNB hepatitis have rarely been encountered in studies of TAH. Still, one very severe outbreak of NANNB TAH has been described in patients undergoing cardiovascular surgery in Japan; one of the 65 patients had fulminant hepatitis. In addition, fulminant cases of percutaneously transmitted NANNB hepatitis have been observed in patients with underlying chronic liver disease, immunodeficiency, or malignancy, and fulminant cases of sporadic NANNB hepatitis have been described in previously healthy persons. In addition, in surveys of fulminant hepatitis in the United States and Europe, 25 to 44% of cases have been attributed by serologic and historical exclusion to NANNB hepatitis agents, and survival in these so-called NANNB hepatitis cases was less likely than in cases of fulminant hepatitis A or B. Confident exclusion of non viral causes and of the role of HBV in many of these cases is difficult to establish, however. The one form of NANNB hepatitis associated with an unusually high frequency of fulminant hepatitis and death in 10% is the epidemic, water-borne type described in India and Asia (see before).48

Extrahepatic manifestations of viral hepatitis, such as arthritis, rash, glomerulonephritis, and periarteritis nodosa, have been associated unequivocally with acute and chronic hepatitis B; rare instances of postdromal arthritis have been described in patients with acute NANNB hepatitis. In addition, transient agranulocytosis and aplastic anemia have been both observed in patients with NANNB hepatitis; in fact, most cases of hepatitis-associated aplastic anemia have been classified as NANNB hepatitis.

Descriptions of the histologic features of acute NANNB hepatitis in humans suggest that, in addition to the classic features of acute viral hepatitis, these cases may have a number of unusual morphologic findings. These include irregular eosinophilic clumping of the cytoplasm, microvesicular steatosis, marked acti-
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NANB hepatitis is now only 10 years, we may find increasing NANB hepatitis-related morbidity and mortality occurring in this patient population over the next decade and beyond. The same trend is being appreciated in immunosuppressed patients with chronic NANB hepatitis (see before).

The progression to chronic NANB hepatitis cannot be predicted from the clinical or biochemical severity of the acute illness. Anicteric cases are just as likely as icteric cases to have an untoward outcome. Similarly, the proportion of patients with acute NANB hepatitis who recover completely is difficult to ascertain, because of the generally asymptomatic nature of the illness, the characteristic fluctuations in serum aminotransferase levels, and the frequent occurrence of prolonged intervals of normal aminotransferase values, which are followed by distinct elevations indicating persistent liver disease. Korets et al determined that the cumulative probability of spontaneous resolution of NANB hepatitis after transfusion was no higher than 0.47.

Thus, one decade after the classification of NANB hepatitis as a distinct form of viral hepatitis, collected observations indicate that biochemical evidence of chronic hepatitis develops in approximately 50% of cases related to transfusion; that among those with chronic ALT elevations who are biopsied, approximately 60% have CAH, cirrhosis, or both; that overall, 10 to 20% of those with chronic ALT elevations have cirrhosis on initial or repeat biopsy; and that among cases described in published reports, of 20 patients in whom cirrhosis was documented to have developed after transfusion, five have now died of liver failure. Assuming a 5 to 10% frequency of acute NANB hepatitis after transfusion, a 50% likelihood of chronic hepatitis after TAH, and the ultimate detection of cirrhosis in 20% of those with chronic NANB hepatitis after transfusion, we can calculate that cirrhosis will develop eventually in 0.5 to 1% of all transfused patients. Thus, of the 3 million patients transfused annually in the United States, cirrhosis can be expected to develop ultimately in approximately 15,000 to 30,000. The accuracy of such a prediction remains to be substantiated. Prospective evaluation of newly developing NANB hepatitis cases and continued long-term follow-up of existing cases is essential to define more precisely the chronic consequences of NANB hepatitis.

In most studies, the frequency of chronicity is more likely in NANB hepatitis cases associated with transfusion and other percutaneous modes of exposure (40 to 60%) than in cases occurring sporadically in the absence of identifiable percutaneous inoculation (10% or less). The only exception to this generalization comes from a study of sporadic hepatitis in Baltimore, Maryland. Although the study involved a large proportion of drug addicts and transfused pa-
patients, 47% of 32 patients with NANN hepatitis who had no antecedent blood transfusion or who denied intravenous drug use had elevated ALT activity at 6 months. Chronic hepatitis has not been documented to occur after the water-borne type of "epidemic" NANN hepatitis.

Acute NANN hepatitis is likely to be followed not only by chronic hepatitis, but also by an asymptomatic carrier state. In one study, serum and plasma collected over the course of 6 years from a single donor remained persistently infectious for chimpanzees. A disconnecting statistic is the highest estimated frequency of the NANN hepatitis carrier state. Based on the frequency of NANN hepatitis in recipients of single-unit transfusions, the asymptomatic NANN hepatitis carrier rate in the general population of the United States may be as high as 3 to 7%. A lower frequency of 1 to 2% has been calculated based on the incidence of NANN hepatitis after transfusion divided by the average number of units transfused per recipient of multiple-unit transfusions. Because the relationship between donor units transfused and the frequency of hepatitis in recipients of volunteer blood is not linear, the calculated frequency of infectious donors based on multiple-unit transfusions may not be as true a reflection of the NANN hepatitis carrier rate as that based on single-unit transfusions.

**Chronic NANN Hepatitis in Hemophiliacs**

The significant chronic consequences of NANN TAH are well documented in the hemophiliac population. Infectivity studies performed in chimpanzees have shown that most lots of AHF contain the agent or agents of NANN hepatitis, and it is clear that virtually every hemophiliac patient requiring repeated transfusion of either AHF or cryoprecipitate has been exposed to the NANN hepatitis agent. In this population, elevated ALT levels persisting longer than 6 months were found in 19 to 53% of patients in studies reported between 1977 and 1980. In a more recent study by Hay et al., persistently abnormal aminotransferase levels were found in 56 of 79 (71%) hemophiliacs. Although patients with hemophilia also have a very high prevalence of HBV markers, indicating almost universal past exposure to HBV, only about 2% of those with persistent ALT abnormalities are chronic HBsAg carriers; therefore, the major proportion of chronic hepatitis in these patients is believed to related to NANN hepatitis rather than to HBV.

Despite the difficulties in performing liver biopsies in hemophiliac patients, there is now a substantial body of histologic data. These data have been collected by an ad hoc hemophilia study group. Biopsy or autopsy-derived hepatic histologic examination was done on 155 patients with either Factor VIII (80%) or Factor IX (17%) deficiency; 3% were from autopsy specimens antedating the time when specific factor assays were available. In this study, liver biopsies were read under code by four independent pathologists and a final diagnosis was established by consensus. Because in cases with mild to moderate hepatitis there was some disagreement as to whether they should be classified as CPH or mild CAH, the investigators chose to classify the chronic hepatitis cases into four categories: (1) trivial, mild, and moderate; (2) severe; (3) cirrhosis; (4) other. Among the 155 patients, 64% were classified in category one, 7% had severe CAH, and 15% had cirrhosis. Twelve patients in this analysis had more than one liver biopsy. In the varying interval between biopsies, five remained unchanged, three improved, and four showed progressive lesions, including the development of severe CAH in two and cirrhosis in one.

Although 40% of cases with severe lesions and 61% of those with cirrhosis were HBsAg positive, the committee of pathologists believed that in many of these cases the chronic hepatitis was related more likely to NANN hepatitis than to HBV. This was based on histologic features suggesting NANN hepatitis and on the absence of ground glass hepatocytes. However, the exact proportion of HBV-related and NANN virus-related chronic liver disease could not be ascertained. Although the majority of liver biopsies indicated a relatively benign form of chronic liver disease, nonetheless, cirrhosis had developed in 15%, an alarming percentage and one similar to that obtained in non-hemophiliac transfused populations. Of interest in this study was the fact that the frequency of severe liver disease in patients receiving pooled clotting factor concentrates was no greater than in patients treated principally with cryoprecipitate or plasma.

Although chronic hepatitis in hemophiliacs has been reported to be nonprogressive, a more recent study demonstrated the presence of severe, progressive liver disease in a large number of patients. Among 79 patients enrolled in the latter study, 56 (71%) had persistently abnormal ALT levels. Of these, 34 underwent initial liver biopsy, that showed CPH or chronic lobular hepatitis in 62%, CAH in 26%, and micronodular cirrhosis in 12%; one of the four patients with cirrhosis was believed to have alcoholic liver disease. None of these patients had histologic or serologic evidence to indicate that they were chronic HBV carriers, and most had histologic findings compatible with NANN hepatitis. Nine of these 34 patients had a second liver biopsy, and progressive disease was found in the majority, unexpectedly including those with CPH as the initial histologic diagnosis. Of six patients with CPH on initial biopsy, two were stable, but two progressed to CAH, and cirrhosis developed in two others during the 8-year period of observation. Among four patients with CAH on initial biopsy, one improved subsequently, but in two, histologically-confirmed cirrhosis developed, and, in another, unequivocal evidence...
of portal hytention developed, but no biopsy was obtained. Five of the nine patients with cirrhosis had radiographic evidence of esophageal varices. Two of the patients with cirrhosis died as an immediate result of intracerebral hemorrhage.

Overall, a large number of hemophiliacs have persistently or intermittently elevated ALT levels, suggesting chronic viral hepatitis. Although some of these cases are HBV-related, the histologic, clinical, and serologic pattern suggests that most are associated with NANB hepatitis infection. Of those biopsied on a single occasion, 12 to 15% had cirrhosis, a dramatic figure and one similar to that obtained in prospectively followed nonhemophilic transfusion recipients.

Although there is a divergence of opinion as to the progressive nature of these histologic abnormalities in hemophiliacs, a substantial proportion of these patients end up with cirrhosis, an unequivocal histologic diagnosis that leaves little room for argument; in at least one series, 26% of those biopsied on one or more occasions had cirrhosis, and among 10 patients biopsied serially during an 8-year observation period, cirrhosis developed in 50%. Thus, the experience in patients with hemophilia confirms the accumulating evidence in other transfused populations, namely, that NANB hepatitis leads to chronic hepatitis in more than 50% of patients and that 10 to 20% of those with chronic hepatitis will progress to cirrhosis.

NANB Hepatitis and Hepatocellular Carcinoma

Seropidemiologic data demonstrating concordance between areas of high HBV endemicity and areas of high incidence for primary hepatocellular carcinoma (HCC) established the initial etiologic link between HBV infection and the development of this lethal tumor. In most cases of HBV-associated HCC, cirrhosis is an antecedent or concomitant finding. The high frequency with which NANB hepatitis eventuates in cirrhosis (see before) suggests that this agent might also play an etiologic role in the development of HCC. Unfortunately, the lack of specific serologic markers for NANB hepatitis precludes the necessary seropidemiologic surveys. Despite this, indirect evidence for an association between NANB hepatitis and HCC is beginning to accumulate. Resnick et al. described a single case of HCC occurring in a woman with well-documented chronic NANB hepatitis after blood transfusion. The interval between the acute onset of NANB hepatitis and the development of HCC was 17 years. A similar case was reported by Kiyosava and coworkers in 1984. In a 39-year-old man in whom NANB hepatitis developed 2 months after transfusion, chronic aminotransferase elevations led to five serial liver biopsies that documented progression from CPH to CAH to cirrhosis and finally to HCC. The interval from transfusion to the diagnosis of HCC was 18 years. The patient had no history of alcoholism, had no serum markers of HBV infection, and showed neither HBsAg nor core antigen (HBeAg) by immunoperoxidase staining of liver tissue. Similarly, Gilliam et al. described a well-documented case of NANB TAIH that culminated in HCC 9 years after the transfusion episode.

In a retrospective analysis, Okuda et al. studied 113 nonalcoholic patients with HCC; 55 were HBsAg positive, 55 were HBsAg negative, but had anti-HBc, anti-HBe, or both, and 23 were negative for all HBV seromarkers. There was no apparent nonviral cause for the HCC, and it was inferred that chronic NANB hepatitis antedated the HCC in many of these cases. NANB hepatitis is felt to be responsible for 70% of the chronic hepatitis and nonalcoholic cirrhosis in Japan. Okuda et al. postulated that NANB hepatitis played at least an indirect role in hepatocarcinogenesis and that NANB hepatitis agents may have been responsible not only in the 23 seronegative cases, but also in the 55 cases who had serologic evidence of pHBV infection, but who were HBsAg negative. To support the latter, they cite the classic study of Beasley et al., which showed that HBsAg-positive Taiwanese men were at a markedly increased risk of developing HCC, whereas HBsAg-negative persons with anti-HBs or anti-HBe were not at high risk for HCC. Thus, in patients with chronic NANB hepatitis and markers of past HBV infection, the development of HCC, may be more likely to be related to NANB hepatitis than to HBV, but this cannot be proved at this time.

DETECTION OF NANB HEPATITIS AGENTS

Although much has been learned about the NANB hepatitis viruses in the past decade, there has been no significant advance in the development of a specific detection system for this agent or group agents. Instead, there have been innumerable false leads and unfilled expectations. There are more than 40 published reports of specific NANB hepatitis assays, many of which have been reviewed. Not a single test, however, has been reproducibly and independently confirmed, not a single test has successfully distinguished proved NANB hepatitis infectious sera from control sera when tested under independent codes, and not a single test has moved from the research laboratory to the point of practical application.

The failure of such test development has severely impeded characterization of the agent, definition of epidemiologic patterns, and detection of the NANB hepatitis carrier blood donor. There are probably several elements that account for the difficulty in developing a specific NANB hepatitis assay and for the apparent false-positive reactions. It is probable that
the amount of circulating NAB hepatitis-related antigen is low and perhaps unmeasurable within the sensitivity limits of existing immunoassays. Chimpanzee transmission studies indicate that most NAB hepatitis-containing sera have infectivity titers of less than 10^3 chimpanzee infectious doses per ml (CID/ml) and, indeed, most are less than 10^3 CID/ml; the highest known titer is 10^5 CID/ml (see Bradley elsewhere in this issue of Seminars). If this agent does not follow the defective pattern of HBV, in which antigen is produced in massive excess of complete virions, then it is probable that the number of antigenic particles will be considerably less than 10^6 /ml and therefore not detectable by the techniques used to detect HBsAg. In addition to the anticipated low level of NAB hepatitis antigen, it is likely that antibody to this agent is either not present in serum or present in insufficient titer to serve as a reliable reagent with which to probe for antigen. This inference is based primarily on the inordinately high frequency of chronicity after acute NAB hepatitis infection (see before). Recovery from NAB hepatitis infection and the associated development of convalescent antibody may be an unusual occurrence. Failure to identify NAB hepatitis convalescent antibody after a decade of intense effort makes it increasingly unlikely that such antibody exists. Perhaps a more realistic hope is that an antibody will be identified that can coexist with virus, such as anti-HBe in chronic HBV infection and the antibody associated with HTLV-III infection. The recent finding by Shimizu et al100 of apparent NAB virus-specific antibody in the supernatant of cultured lymphocytes from NAB hepatitis-infected chimpanzees is exciting in this regard. In this study the Epstein-Barr virus (EBV)-transformed lymphocytes from chimpanzees convalescent from NAB hepatitis infection produced an IgM antibody that reacted with NAB virus-infected chimpanzee liver in an indirect immunofluorescence assay; control liver from HBV-infected or uninfected chimpanzees did not react in this system.100 Whether this antibody is directed against a NAB hepatitis agent or against a component of chimpanzee liver, perhaps activated by the virus, is currently unknown. Efforts are in progress to identify the implicated antigen. This finding, although exciting, may not have direct applicability to human disease. It is possible that this system will parallel the finding of the cytoplasmic tubular structures that are relatively specific for NAB hepatitis infection in the chimpanzee and are very useful in chimpanzee inoculation studies, but that are not directly applicable to the development of specific serologic assays.

As indicated by Bradley elsewhere in this issue of Seminars, it has been suggested that the NAB hepatitis agent might be a retrovirus detectable by the measurement of serum reverse transcriptase (RT) activity.103 However, many laboratories have been unable to confirm the finding of RT activity in well-purified NAB hepatitis sera, and coded panels from several sources have demonstrated that the measurement of serum RT activity cannot distinguish proved and presumed NAB hepatitis infectious sera from appropriate controls. Other accumulating data, particularly filtration studies (see Bradley), indicate that the small size of the NAB hepatitis agent is inconsistent with its being a retrovirus.

Although most reported NAB hepatitis assay appear to be internally consistent and appropriately controlled, it is now apparent that the observed actions are often nonspecific. Several studies have shed light on the mechanism of false positivity. Suh et al104 demonstrated that a putative NAB hepatitis antigen, which was identified by gel diffusion and which was immunologically identical with that reported by others, represented instead a complex in which the putative antibody was not an immunoglobulin. Hoofnagle105 also showed that the "antibody" reactant in his gel-based system was not an immunoglobulin. Zhuang et al106 identified an abnormal lipoprotein that precipitated in agar and that became detectable in serum with a temporal relationship to the development of NAB hepatitis. Working with an enzyme-linked immunoassay, Roggendorf and coworkers110 demonstrated that a rheumatoid factor-like material present in NAB hepatitis sera could simulate the presence of a NAB hepatitis antigen. Similar findings were reported by Shiraishi et al,112 who found that apparent NAB hepatitis reactivity by radioimmunoassay coincided with an aberrant, high molecular weight IgM that had rheumatoid factor activity but that was not detected in standard rheumatoid factor assays; by reacting with immunoglobulin in presumed NAB hepatitis convalescent sera, this rheumatoid factor gave the appearance of being a NAB hepatitis antigen.

In the absence of a specific NAB hepatitis assay, two indirect tests have been proposed as a means to detect NAB hepatitis carrier blood donors. The Transfusion Transmitted Viruses Study group (TTVS) was the first to report a significant association between elevated serum ALT levels in the donor and the development of NAB hepatitis in the recipient.114 This association was apparent in multitransfused cardiac surgery patients and, importantly, was also seen among recipients of only single blood units. Hepatitis risk increased with the number of elevated ALT units transfused. The TTVS predicted that the exclusion of blood units with elevated ALT might have prevented 40% of TAH (30% after correction for the hepatitis risk of blood units with normal ALT). Alter et al107 reported a similar relationship between donor ALT and recipient NAB hepatitis. The predicted efficacy of ALT donor exclusion in this study was 29%, with a projected loss of 1.6% of the donor population. Based on these studies, a small number of blood centers adopted rou.
tine ALT testing; however, none performed a randomized controlled trial to determine if actual efficacy confirmed the predicted efficacy. Investigators at the NIH compared hepatitis incidence after ALT testing with that of identically followed historical controls. The efficacy of the ALT test could not be substantiated, but hepatitis incidence was declining before initiation of the study, and the number of study participants may have been too small to demonstrate significant differences at the relatively low hepatitis rates that prevailed.

Subsequently, these same two investigative groups have analyzed the impact of testing donors for the presence of anti-HBc. Paradoxically, it was demonstrated that this HBV marker in the donor correlated strongly with the development of NANB hepatitis in the recipient. Presumably, this test is detecting a cohort of high-risk donors that have been exposed to both HBV and NANB hepatitis. The relationship may not be that simple, however, for donor anti-HBs, another marker of past HBV infection, did not correlate with recipient NANB hepatitis. Whatever the reason for the association, the statistical relationship between donor anti-HBs and recipient NANB hepatitis is even stronger than that for ALT, and the predicted efficacy is in the range of 40%. Both these indirect assays have the disadvantage of relatively low sensitivity and specificity (both in the range of 60%) and a very low positive predictive value (12% in the NIH study). If adopted, the anti-HBs test will result in the initial loss of 4 to 8% of the donor population and the sustained loss of probably 2 to 4%. Cost and time are other detrimental elements to the adoption of either or both of these nonspecific assays. Despite these negative features, however, the accumulating data that chronic NANB hepatitis leads to cirrhosis in 10 to 20% of cases has served as compelling evidence for the need to rely on indirect assays as an interim measure until such time as specific NANB hepatitis assays are developed. The major components of the blood delivery complex are currently considering the adoption of either the anti-HBc test or both the ALT and the anti-HBs test. Because of the cost and significant donor loss engendered, and because of recent introduction of mandatory screening of all donor blood for antibody to HTLV-III, adoption of yet another one or two donor-blood screening tests represents a very complex and difficult decision. Nonetheless, increasing documentation of the chronic sequelae of NANB hepatitis and the continued high incidence of this disease after transfusion have tipped the balance in favor of adopting indirect assays for NANB hepatitis carrier detection.

Evidence for Multiple Agents

Although a specific NANB hepatitis agent has not been identified, considerable evidence exists for the presence of more than a single agent. This includes the occurrence of two or more distinct bouts of NANB hepatitis in drug addicts, hemodialysis patients, and hemophiliacs; cross-challenge studies in chimpanzees demonstrating that different inocula from different sources can induce two immunologically distinct episodes of NANB hepatitis in the same animal; and studies that appear to distinguish a chloroform-sensitive agent that is derived from a Factor VIII concentrate and that induces cytoplasmic tubular changes in chimpanzee hepatocytes (tubule-forming agent, or NANB-I) from a chloroform-resistant agent that is derived from a Factor IX concentrate and that does not induce cytoplasmic tubular changes in chimpanzee hepatocytes (NANB-II). Even these distinctions are not accepted universally, however. Most cases of TAH studied in the United States appear to be caused by a single agent, indistinguishable from the NIH Hutchinson strain. Furthermore, Brotman et al have demonstrated that immunity to this agent may be overwhelmed in chimpanzees by reexposure with a high titer of the same strain of virus. Conceivably, then, cross-challenge experiments demonstrating second NANB hepatitis infections in chimpanzees may represent reexposure with or reactivation of the same NANB hepatitis agent rather than infection with two distinct agents. Therefore the existence of more than a single blood-borne agent is not established with absolute confidence. On the other hand, the water-borne type of NANB hepatitis almost certainly represents yet another NANB hepatitis agent distinct from blood-borne agents.

THERAPY AND PREVENTION

Specific therapy for either acute or chronic NANB hepatitis is not available. Neither corticosteroids nor antiviral agents have had any demonstrable beneficial effect. In the absence of effective treatment, the need for prevention assumes even greater import. Unfortunately, the effectiveness of immunoprophylaxis has not been established. Three placebo-controlled trials of IG in the prevention of TAH have generated conflicting results. Suffice it to say that administration of IG after transfusion of volunteer donor blood has no demonstrable effect on reducing the incidence of acute or chronic hepatitis. In the one study in which IG was effective in preventing both acute and chronic NANB hepatitis after transfusion, the globulin was administered before transfusion, which may have accounted for its efficacy. On the other hand, the transfused blood was derived from military volunteer donors, which have been shown in other studies to be the equivalent, in terms of hepatitis risk, of civilian commercial blood. Despite the apparent, albeit controversial, effectiveness of IG in reducing the severity of NANB hepatitis after transfusion of com-

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merical blood, the same effect can be achieved by relying exclusively on volunteer blood donors. Therefore Ig is not recommended for routine prophylaxis of TAH. Hepatitis B immune globulin (HBIG) has been used as well in attempts to prevent NABN hepatitis. In a 3-year study of repeated HBIG injections among hemodialysis patients, NABN hepatitis occurred in only 2 of 67 (3%) patients who received globulin, compared with 31 of 83 (37%) who did not. In contrast, in a controlled trial of HBIG among 415 patients undergoing cardiac surgery and exposed to transfused blood, no significant reduction in the frequency of NABN hepatitis cases occurred in the treated group, compared with un inoculated controls. Therefore HBIG is not recommended either.

There are no studies that address the issue of specific guidelines for the prevention of NABN hepatitis after categories of exposure besides transfusion. Conceivably Ig, whose efficacy in preventing TAH is equivocal at best, might be more effective in the setting of a smaller inoculum, such as might accompany accidental needlestick or transmucosal penetration, sexual contact, or neonatal exposure. Therefore some authorities recommend prophylaxis with 0.06 ml/kg intramuscularly of Ig for such exposures (or 0.5 ml for neonates). Less intense types of exposures, such as between family members other than sexual partners, are too unlikely to transmit NABN hepatitis; secondary cases within households are very rare, indeed. Therefore in such cases the risk is insignificant and prophylaxis is not suggested. For the water-borne type of epidemic NABN hepatitis, the effectiveness of Ig prophylaxis has not been demonstrated.

Until a specific NABN hepatitis viral agent can be identified, neither effective globulins nor a vaccine are likely to be developed. Therefore prevention of NABN hepatitis after transfusion must rely on the interim on such nonspecific measures as minimizing the volume of transfused blood and blood products, avoiding pooled blood derivatives, identifying and deferring blood donors with known or presumed infectivity, establishing the use of indirect screening tests (ALT or anti-HBe), or institution of physical or chemical inactivation procedures, should effective measures be developed.

SUMMARY

Evidence for the existence of human hepatitis agents besides HAV and HBV is compelling. Transmitted predominantly by transfusion and percutaneous inoculation, the type of NABN hepatitis encountered most frequently is epidemiologically similar to type B hepatitis. NABN hepatitis accounts for more than 90% of TAH, but can be transmitted by nonpercutaneous routes as well. Approximately 15 to 30% of sporadic hepatitis cases are attributable by serologic exclusion to NABN hepatitis agents, and, in addition, there is an epidemic form of NABN hepatitis that resembles hepatitis A epidemiologically in its transmission by the enteric route. Clinical features of the predominantly percutaneously transmitted forms of NABN hepatitis are similar to those of hepatitis B, but tend to be less severe during acute illness, on the one hand, but to lead more frequently to chronic hepatitis, on the other; 40 to 60% of patients with TAH have chronic elevations of aminotransferase activity, often in an episodic, fluctuating pattern. CAH can be identified histologically in a majority of patients with chronic NABN TAH. Despite a relatively quiescent course, progression of such chronic cases may be quite insidious; cirrhosis occurs in 10 to 20% of patients with chronic hepatitis after acute TAH. The frequency of chronic liver disease after nonpercutaneously acquired sporadic NABN hepatitis tends to be lower, on the order of 10% or less, and chronic hepatitis has not been recorded after the epidemic type of NABN hepatitis. Evidence supports the existence of an asymptomatic chronic NABN hepatitis carrier state that is several-fold more frequent than the chronic HBV carrier state. Neither viruses nor virus markers have been described that fulfill accepted criteria reproducibly for a specific causal association with NABN hepatitis; on the other hand, evidence suggests (but does not prove) the existence of two different blood-borne NABN hepatitis agents and, in addition, an enterically transmitted NABN hepatitis agent. Effective therapy for and immunoprophylaxis against NABN hepatitis are lacking. Until specific screening tests are developed, interim screening based on indirect, nonvirus-specific tests may be the only practical approach to minimizing the frequency of NABN hepatitis after transfusion. Identification of virus-specific serologic markers remains a high priority.

REFERENCES

6. Cazaja AJ, Davis GL: Hepatitis non A, non B. Manifestations

Supplied by The British Library - "The world's knowledge"
11. Alter HI, Holland PV, Purcell RH, et al: Post-transfusion hepatitis after exclusion of commercial and hepatitis-B anti-
17. Galbraith RM, Dienstag JL, Purcell RH, et al: Non-A, non-B hepatitis associated with chronic liver disease in a bact-
30. Papazoglou G: Non-A, non-B hepatitis in Greece. In: Ger-
32. Rickard KA, Batey RG, Dotty P, et al: Hepatitis and hae-
37. Tabor ER, Gerety RJ, Drucker JA, et al: Transmission of non-
43. Meyers JD, Dienstag JL, Purcell RH, et al: Parenterally ter-
46. Aach RD, Landier JS, Sherman LA, et al: Transfusion-trans-

Supplied by The British Library - "The world's knowledge"
NON-A, NON-B HEPATITIS—Dienstag, Alter 79


