Non-A, Non-B Hepatitis. I. Recognition, Epidemiology, and Clinical Features

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The concept widely accepted a decade ago that there are only two hepatitis viruses is now obsolete. Application of sensitive serologic tests for identifying infection with hepatitis A and B viruses unearthed hepatitis cases with incubation periods and modes of spread characteristic of an infectious disease, but without serologic evidence for infection with known hepatotropic human hepatitis viruses. Once the existence of these hepatitis agents distinct from hepatitis A virus (HAV) and hepatitis B virus (HBV) became apparent, an exhaustive investigative effort was launched. As a result, progress has been made in characterizing the clinical and epidemiologic features of these newly recognized agents, convincing transmission of disease to experimental animals has been demonstrated, and methods have been identified that have the potential to reduce the frequency of infection with these agents after transfusion. Despite these advances, however, efforts to identify specific virus particles, antigens, and antibodies have met with limited, if any, success. Contemporary investigators, unsuccessful after a decade's work, might appear impatient when measured against investigators of a generation ago, who bore witness to the 20-30 yr that elapsed between the intensification of hepatitis research in the 1940s and the identification and characterization of HBV and HAV in the 1960s and 1970s. Their frustration, however, is not without justification. During the last decade, an impressive array of sophisticated immunologic, biochemical, and biophysical tools was applied to the identification and characterization of HAV and HBV; therefore, optimism was high that one or more of these advanced techniques would be used successfully in the search for this new category of hepatitis agents. The eagerly anticipated breakthrough, however, has not materialized, and we still know more about what these agents are than we know about what they are. This uncertainty and the high likelihood that there is more than one such hepatitis agent are reflected in the awkward but accurate label, "non-A, non-B hepatitis," chosen tentatively to designate these agents.

The fact that there are no accepted serologic tests for non-A, non-B (NANB) hepatitis may come as a surprise to those who have read the several dozen supposedly definitive reports describing antigen-antibody systems and virus particles associated with putative NANB or "hepatitis C" agents. These reports to the contrary notwithstanding, none of the antigen-antibody tests or viruslike particles that have been described have withstood critical analysis or the test of time. Still, much has been learned about these elusive agents and their clinical and epidemiologic features, many of which would not have been predicted. The high calculated frequency of asymptomatic chronic NANB hepatitis carriers, the high rate of progression to chronic liver disease, the unusually brief incubation periods observed in some cases, and the existence of a category of enterically transmitted NANB hepatitis are just a few of the enigmatic characteristics of NANB hepatitis that have piqued the interest of both clinicians and investigators.

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Recognition of Non-A, Non-B Hepatitis

Non-A, non-B hepatitis is not a new disease; clues to the existence of hepatitis agents other than HAV and HBV had been overlooked for several decades. In the 1940s and 1950s, one of the most carefully documented features of the so-called "infectious" and "serum" hepatitis viruses was the homologous, but not heterologous, immunity acquired after infection with each agent (1). Even then, however, drug addicts with more than two bouts of acute hepatitis were described (2-4), and similar instances of multiple attacks of acute hepatitis have been reported more recently in hemophiliacs (5). Certainly, the existence of more than two hepatitis agents should have been suspected. Little weight was given, either, to the observation in the 1960s that the mode incubation period for transfusion-associated hepatitis was --7 wk (0-9), intermediate between the modes for HAV infection (3-4 wks) and for HBV infection (12-14 wk), precisely the length of the incubation period observed currently for posttransfusion NANB hepatitis. Had transfusion-associated hepatitis been related even then to the known types of viral hepatitis, the distribution of incubation periods would have been quite different from the unimodal pattern observed.

Other clues to the existence of NANB hepatitis agents emerged after serologic markers to identify HBV infection were developed. Serologic analyses of transfusion-associated "serum" hepatitis with early-generation tests for hepatitis B surface antigen (HBsAg) failed to implicate HBV in as many as 50%-75% of cases (10,11). Even as the sensitivity of tests to detect HBsAg in donor blood improved, and as HBsAg screening of donor blood by radioimmunoassay was introduced into blood banking, the impact of this much-heralded advance was relatively limited. Although the frequency of posttransfusion hepatitis B was reduced by 50% (12), the overall frequency of posttransfusion hepatitis was reduced by only 25% (13,14). Even as new serologic markers of HBV infection were discovered and HBV diagnostic sophistication improved, few additional cases of transfusion-associated hepatitis could be attributed to HBV. Despite the fact that even currently available HBsAg screening tests cannot detect HBsAg when present at levels below 10^8-10^9 particles/ml (15) (0.2-0.5 ng/ml), HBV accounts for no >5%-10% of cases of transfusion-associated hepatitis (16-22), and posttransfusion hepatitis B occurs in no >0.4% of patients transfused with HBsAg-negative blood obtained from volunteer blood donors (23). Moreover, as Holland et al. (24) showed, antibody to HBsAg (anti-HBs), known to correlate with immunity to HBV, when present in a recipient's blood before transfusion, did not protect that recipient from hepatitis after transfusion.

An additional observation providing compelling evidence for the existence of transfusion-transmitted hepatitis agents other than HBV was the reduction in the frequency of not only type B but also type non-B hepatitis after transfusion as a result of elimination of commercially obtained donor blood. In fact, the measure that has had the largest impact on minimizing the occurrence of posttransfusion hepatitis has not been HBsAg screening of blood donor units, but conversion from commercial donors, generally derived from lower socioeconomic strata and in poorer health, to volunteer blood donors (7,14,18,20,25-27).

Once it became clear that diagnostic tests for HBV infection were sensitive enough to detect almost all cases of type B hepatitis and that serologic evidence of HBV infection was lacking in most cases of transfusion-associated hepatitis, it became fashionable to implicate HAV in these non-B cases of hepatitis after transfusion. This assumption, however, became untenable once serologic tests to identify HAV infection were developed in the early 1970s. Several serologic studies demonstrated convincingly that HAV plays no role in transfusion-associated hepatitis (16,17,19,21,22,28,29), and in the decade since the availability of serologic tests for HAV, only 4 cases of posttransfusion hepatitis have ever been serologically attributed to HAV (30-33). This was the privy revelation that focused attention on the existence of and initiated the search for NANB hepatitis agents. In retrospect, however, HAV was the far more attractive candidate for the agent of transfusion-associated hepatitis. In most cases, the incubation period of posttransfusion hepatitis exceeds the 3-4-wk incubation period of type A hepatitis cases, and secondary cases, common after acute type A hepatitis, rarely follow acute NANB cases. Moreover, the viremia of acute HAV infection is very limited in concentration and duration, and there are no chronic HAV carriers (34), features that reduce the likelihood of transmission to blood recipients remote. Even more, most of the elderly patients in whom posttransfusion hepatitis develops after cardiac surgery have antibodies to HAV (anti-HAV) (35) and are immune to reinfecction, and chronicity of liver disease, alarmingly frequent after posttransfusion hepatitis (see following discussion), is not associated with HAV infection (36).

Although designated as NANB hepatitis, such cases of hepatitis after transfusion appear to be unrelated to other potential causes, both infectious and noninfectious, of acute and chronic hepatocellular injury besides HAV and HBV. In the early studies of posttransfusion NANB hepatitis, patients were ex-
cluded from consideration if their liver dysfunction could be attributed even inerratically to hepatotoxic drugs, passive congestion of the liver associated with right ventricular failure, biliary tract disease, sepsis, shock, anesthetic agents, or alcohol. Metabolic causes of liver disease are easily excluded in most of these transfusion-associated cases as well. In addition, a host of infectious agents can involve the liver both in otherwise normal and in immunosuppressed persons. Bacterial, mycobacterial, spirochetal, fungal, rickettsial, and parasitic infections occasionally involve the liver, but these are easily excluded, and NANB agents have been shown to be filterable agents, too small to be a microorganism larger than a virus (37). Viral infections with yellow fever virus, rubella, rubella, varicella, coxsackie, and herpes simplex viruses, as well as infection with such exotic agents as Marburg, Lassa, Ebola, and Rift Valley fever viruses, are potential cause of posttransfusion hepatitis, but are easily excluded serologically or clinically. Although an isolated case of hepatitis has been associated with one of these agents in a few instances, clinical and serologic evidence of infection with these organisms is lacking in patients with posttransfusion hepatitis. Before the identification of HAV and HBV, a variety of enteroviruses, adenoviruses, myxoviruses, parvoviruses, mycoplasmas, and uncharacterized agents were isolated from patients with hepatitis (38); however, evidence to support a role for any of these agents in hepatitis is lacking.

Two viral agents that merit more serious consideration are the two herpes viruses, Epstein–Barr virus (EBV) and cytomegalovirus (CMV), both of which can be transmitted by transfusion and can cause hepatitis as part of a more generalized systemic illness (39). Infection with EBV has been reported after transfusion (40–43), and this agent was incriminated serologically in a hemolytic-angina-associated outbreak of hepatitis (44). A substantial role for EBV in cases of posttransfusion hepatitis is unlikely, however. Most patients receiving transfusions have antibodies to EBV before transfusion, and do not have heterophile antibody or the clinical features of infectious mononucleosis. In addition, no serologic association with EBV has been demonstrated in several large studies of transfusion-associated hepatitis (11,14,17,19,21,28).

The role of CMV in posttransfusion hepatitis has been more difficult to evaluate and remains controversial. In the studies of posttransfusion hepatitis reported before 1981, the role of CMV was discounted. Interpretation of serologic findings, obtained in these studies by complement fixation, was complicated by the frequency of anticomplementarity in serum samples, fluctuating titers of antibodies to CMV (anti-CMV) in normal persons, poor reproducibility of the test, and the existence of multiple, partially related CMV serotypes (45). Infection with CMV is transmitted regularly by blood transfusion (46,47) with a frequency proportional to the volume of blood transfused (46), and convincing evidence has accumulated for the occurrence of CMV-induced liver disease in immunosuppressed renal transplant recipients (48–50). In most patients with transfusion-associated hepatitis, however, studies reported until recently failed to demonstrate serologic evidence of CMV infection or to show a temporal association between CMV seroconversion and hepatitis (11,14,17,19,21,28,46,51).

Additional doubt about the role of CMV in transfusion-associated hepatitis arose from the equal frequency of serologic evidence of recent CMV infection in transfused patients in whom hepatitis did and did not develop and by the detection of CMV seroconversions in patients with posttransfusion type B hepatitis (11,46,51). Based on these early observations made with complement fixation assays for anti-CMV, investigators concluded that CMV did not play a substantial role in transfusion-associated hepatitis. Recently, however, a more reliable, sensitive, and reproducible indirect hemagglutination (IHA) test for anti-CMV was applied to the serologic evaluation of posttransfusion hepatitis cases. Alter et al. (52) found, in contrast to earlier reports, that anti-CMV seroconversions, detected by IHA, were significantly more common among transfused patients in whom hepatitis developed than in transfused patients in whom hepatitis did not. In their most recent series of posttransfusion hepatitis cases, Alter et al. (52) attributed 15% of the cases to CMV on the basis of IHA serologic studies. Although CMV infection was documented in a few cases with clinical characteristics of NABN hepatitis (i.e., presumed simultaneous CMV and NABN hepatitis infections), the mild clinical features of most of the CMV cases were distinct from those seen in the NABN hepatitis cases. Their incubation periods were briefer, none became icteric, their alanine aminotransferase (ALT) levels were only marginally elevated (mean peak ALT 177 IU/L, never exceeding 300 IU/L), and chronic hepatitis did not develop in any of the CMV cases. In fact, the clinical and biochemical features of the CMV hepatitis cases were often equivocal.

Even considering other potential causes of posttransfusion hepatitis, we remain unable to identify the agent(s) of >80%–90% of all cases. The fact that a majority of such cases conform to an easily recognized clinical pattern and the successful serial transmission of these agents in experimental animals, as reviewed in part 2, provide the most compelling evidence for the existence of NABN hepatitis agents.
Epidemiology

Transfusion-Associated Hepatitis

Despite the use of volunteer rather than commercial blood, and despite the adoption of third-generation screening of donor blood for HBsAg, the residual frequency of posttransfusion hepatitis, including asymptomatic acute cases, is 7%–10% of transfused patients, or 3–6 cases/1000 U transfused (14,17,18,21). As previously reviewed, several reports published in the mid-1970s focused attention on the existence of NANB hepatitis agents by excluding HAV as the agent responsible for HBsAg-negative posttransfusion hepatitis (17,19,28,29). These and subsequent studies (16,20–22,51–54), as discussed earlier, have shown that ~85%–95% of cases of posttransfusion hepatitis are caused by these unidentified, so-called NANB agents.

Described in initial reports among transfused patients, NANB hepatitis was thought, erroneously, to be transmitted exclusively by blood transfusion. Recently, however, epidemicologic modes besides transfusion have been implicated in its transmission. Unfortunately, current understanding of the modes of spread and distribution of NANB hepatitis agents is limited by reliance on epidemicologic observation and historic/serologic exclusion of other potential hepatotropic viruses and hepatotoxins. Currently, there are no satisfactory methods to identify persons who are susceptible to, immune to, or carriers of NANB hepatitis. Therefore, precision in defining the modes of spread for these agents and their current and previous distribution in populations will not be achieved until reliable serologic markers become available. Despite these limitations, a wealth of epidemicologic information has accumulated to suggest that NANB hepatitis, like hepatitis B, is spread by both percutaneous and apparently nonpercutaneous routes of transmission.

Nontransfusional Percutaneous Transmission

As previously mentioned, multiple episodes 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 NANB agents (2). The possibility that unidentified viruses were involved in some of these cases was suggested by the description of three or more bouts in reports predating the availability of serologic markers for HBV infection (2–4) or two non-B acute episodes in reports after the introduction of serologic testing for HBV (55–57). Shortly after serologic testing for HAV infection became available, Mosley et al. (58) reported serologic confirmation (by exclusion) of NANB hepatitis in drug addicts. They characterized 30 episodes among 13 drug addicts who had had multiple bouts of acute hepatitis widely spaced in time. Of all episodes, HAV accounted for 7%, HBV for 40%, and CMV and EBV for none. The 16 (53%) remaining cases, therefore, were classified by exclusion as NANB hepatitis. Moreover, and suggesting the existence of more than one NANB agent, three of the addicts had two or more bouts of NANB hepatitis. In retrospect, a 1973 report by Irvinson et al. (4) also appears to have emphasized a category of hepatitis in Swedish drug addicts that probably contained NANB cases. Evaluating 39 bouts of acute hepatitis among 27 addicts who injected themselves intravenously with drugs, these investigators described 15 cases (38%) who lacked HBsAg, had normal serum IgM levels, had only minimal bilirubin elevations, and most of whom (9 of 12 evaluated) had a histopathologic pattern on liver biopsy, which was distinctively different from that observed in the other cases. The possibility that these cases included patients with NANB hepatitis is supported by the similarity between their morphologic lesions (marked sinusoidal cell activation but subdued lymphocytic infiltration) and the characteristic NANB hepatitis lesions observed recently in humans and experimentally infected chimpanzees (see later discussion). A report from the same group in which the experience after 1973 is described confirms the contribution of NANB hepatitis to frequent bouts of hepatitis in Swedish drug addicts. Of 71 episodes among 32 drug addicts, 25% were defined by serologic exclusion of type A (32% of cases) and type B hepatitis (42% of cases) as NANB episodes; 1 patient had two discrete episodes of NANB hepatitis (59,60). An additional description of NANB hepatitis in drug addicts was reported by Gust et al. (61), and cases in drug addicts have been included in reports of sporadic NANB hepatitis as well (62–78).

Although the most important agent in the chronic liver disease of drug addicts appears to be HBV (79,80), accurate estimates of the contribution of NANB agent(s) remain to be defined. In a recently followed cohort of 725 drug addicts institutionalized for rehabilitation, 14 (2%) had elevated levels of serum ALT in the absence of HBV serologic markers (81). In all likelihood, the contribution of NANB hepatitis agent(s) is higher: 70 of these addicts with elevated ALT (another 10%) had anti-HBs in their serum. Most of these probably had HBV infection in the past. These preliminary results, therefore, suggest that as many as 12% of drug addicts with chronically elevated ALT levels have NANB hepatitis.

As the risk of HBV infection in hemodialysis units has declined, the contribution of NANB agents to
hepatitis among staff members and patients in these units has attracted attention. Galbraith et al. (82) described two outbreaks of acute HBsAg-negative hepatitis involving 29 hemodialysis patients, including 7 who had two discrete episodes and 8 in whom chronic liver disease developed. Originally labeled as type A hepatitis (83), these cases were shown retrospectively to be NANB hepatitis cases. Similarly, sporadic cases and outbreaks of acute NANB hepatitis have been reported from other hemodialysis units (84–87).

Recently, studies have been undertaken to define the prevalence and incidence of NANB hepatitis in hemodialysis units. A preliminary survey in a dialysis unit at a metropolitan teaching hospital in the United States revealed that among patients dialyzed in an HBsAg-free unit, 15% had persistently abnormal ALT activity in the absence of serologic markers for current infection with HAV, HBV, or CMV (81). During a follow-up period of 29 mo in a newly opened HBsAg-free hemodialysis unit in Paris, the incidence of new acute NANB hepatitis was 11% (or 4.6% per yr) (88). In a similar prospective surveillance study, the annual incidence of NANB hepatitis among 460 chronically hemodialyzed patients was 5% (89). In the latter study, there was no relationship between acquisition of NANB hepatitis in patients and their receipt of blood transfusions.

In another, more extensive, multicenter study, however, transfusion was found to be an important risk factor for NANB hepatitis in dialysis patients (81). Among 2070 patients and 1629 personnel of 13 hemodialysis units followed prospectively for 3 yr, the average annual attack rate of acute NANB hepatitis was 5.8% (range 0%–16.1%) for patients and 0.8% (range 0%–2.3%) for staff. For patients, the risk of NANB hepatitis was associated significantly with recent transfusion, while, for staff the risk factor that correlated with NANB hepatitis was recent needlestick. The importance of these modes of transmission and the absence of secondary cases among family members of affected patients and staff provide compelling evidence for predominantly percutaneous transmission of NANB hepatitis in dialysis units and the requirement of percutaneous exposure for efficient transmission of NANB hepatitis (81). As is the case for HBV infection in dialysis units, severity of acute NANB hepatitis was found to be more pronounced, jaundice more frequent, and likelihood of chronicity lower in staff than in patients (81).

Another potential cause for hepatic inflammation and fibrosis in chronically hemodialyzed patients, "spallation" and migration of silicone from dialysis machine tubing, has been described by Leong et al. (90), who cited confirmatory brief reports from two other hemodialysis units. In dialysis patients with chronic liver dysfunction, these investigators identified silicone particles, often associated with granulomas, in the liver as well as in other organs. The likelihood that this phenomenon accounts for a substantial proportion of dialysis-associated NANB hepatitis appears to be small, however. The statistical association with transfusion (81), the occupationally acquired cases in dialysis staff (81), and the absence of silicone and granulomas in histologic material from patients in other centers with dialysis-associated NANB hepatitis (91) all argue in favor of a transmissible infectious agent rather than of a foreign body reaction.

Non-A, non-B hepatitis can cause appreciable morbidity and even mortality in renal transplant recipients. Warren et al. (90) described 72 episodes of acute hepatitis or abnormal liver tests among 62 (38%) of 162 renal transplant recipients. Drug hepatotoxicity and infection with CMV, HBV, EBV, or varicella zoster accounted for as many as 74% of the 34 cases of acute hepatitis. On the other hand, 27 (71%) of the 38 cases of chronic liver disease in these patients were attributed by exclusion to infection with NANB agent(s). Sixteen of the patients with chronic liver disease (at least 12 of whom had NANB hepatitis) had "progressive" deterioration; cirrhosis developed ultimately in 11, 4 experienced a transition from chronic persistent hepatitis to chronic active hepatitis, and 1 succumbed to liver failure after 1 yr of liver disease. Whereas the liver disease of renal transplant recipients has been attributed by some investigators primarily to hemodialysis-acquired events before transplantation (92), analyses by others have shown that hepatitis in renal transplant recipients is acquired after transplantation. In a report by LaQuaglia et al. (93), the 10-yr experience of 405 consecutive renal transplant recipients was reviewed. Among these patients, who received frozen, washed red blood cells as their exclusive source of transfused blood, biochemical or clinical evidence of acute hepatitis developed after transplantation in 10.4%, 62% of whom (or 6.5% of the total) were categorized by exclusion as having NANB hepatitis. Because all five type B hepatitis cases occurred during the first 3 yr evaluated, 1970–1973, the relative proportion of NANB cases during the last 7 yr was even higher. Both chronicity, mortality, and mortality were high in patients with hepatitis. Chronic hepatitis developed in 93% of those acquiring hepatitis during the first posttransplant year and in 84% of those affected after the first year. Those with hepatitis had a significantly higher mortality rate (45% vs. 15%) than patients without hepatitis. Surprisingly, death in ~60% of the fatal cases was due not to liver disease—only 1 patient died of liver failure—but to infection of systems besides the liver.
Similarly, even among survivors, life-threatening extrahepatic infections were significantly more common in hepatitis patients than in patients without hepatitis (52% vs. 20%) and a substantial cause of morbidity. The frequency of serious infections in hepatitis patients and the significantly higher 1-yr allograft survival observed in the group (79% vs. 50% for patients without hepatitis) suggested that NANC hepatitis infection, like CMV infection, had an immunosuppressive effect on transplant recipients. Non-A, non-B hepatitis, including fatal cases, is being recognized with increasing frequency in renal transplant units (94). Similarly, a case of severe acute NANC hepatitis progressing to cirrhosis and death has been reported in a liver transplant recipient (95).

Non-A, non-B hepatitis has been appreciated as well in such patients requiring repeated administration of blood and pooled blood products as thalassemics, hemophiliacs, and others with coagulopathies. In thalassemic children, evidence for the occurrence of NANC hepatitis derives from the observation that serologic markers of HAV and HBV infection are absent in a proportion of such children who have had clinically apparent episodes of acute hepatitis (96). More recently, Papaevangelou (97) reported that 78% of cases of acute hepatitis in multiply transfused thalassemic children were caused by NANC agents. Non-A, non-B hepatitis has been transmitted by infusions of fibrinogen (98) and other clotting factors (99–105). In hemophiliacs, serologic evidence of exposure to HBV is almost universal, and HBV-related chronic elevations of serum aminotransferase activities are common. In addition, both acute and chronic hepatitis, attributable to NANC agents, have been observed in hemophiliacs. Single and multiple episodes of short-incubation (1–4 wk) acute hepatitis in hemophiliacs treated with commercial (or noncommercial) factor VIII concentrates have been described (5,100–103,105–109). In one report, five discrete episodes of short-incubation (7–16 days), transient acute hepatitis occurring over the course of 3 yr in 1 hemophiliac were attributed to an allergic reaction to an antigenic protein in the factor VIII concentrates (110). On the other hand, there is compelling evidence that clotting factor concentrates can harbor NANC agents. Both factor VIII concentrates in hemophiliacs and factor IX concentrates in patients with the coagulopathy of chronic liver disease have been implicated in cases of acute hepatitis and have been documented to contain serially transmissible NANC agents by experimental inoculation of chimpanzees (99,102,111–114).

In a study of 103 clotting factor-requiring hemophiliacs, Kim et al. (103) detected a high frequency of current or previous HBV infection, as well as a 6% incidence of new acute NANC hepatitis over a 3-yr observation period, i.e., an annual attack rate of 2%. In a similar 4.5-yr survey of 243 Australian hemophiliacs treated with clotting factors from voluntary donors (i.e., no commercial products), and often with cryoprecipitate obtained from a single donor, acute NANC hepatitis developed in 66, for an annual attack rate (incidence) of 6% (109). Of the hemophiliacs described with acute NANC hepatitis, at least half had persistently elevated aminotransferase activity lasting >6 mo, a feature quite typical of NANC hepatitis [see later discussion] and characteristic of the chronic liver disorder in hemophiliacs with NANC hepatitis (115). As in patients with chronic NANC posttransfusion hepatitis, hemophiliacs with chronic NANC hepatitis have been found to have morphologic lesions of chronic persistent hepatitis, chronic active hepatitis, and, in a small proportion, cirrhosis (116–119). Overall, from 20% to 60% of hemophiliacs have been reported to have chronically elevated ALT levels (103,108,115,118,119), but the cause of this chronic liver disease is not understood. Although some hemophiliacs with serum anti-HBs (presumably immune to HBV) have evidence of ongoing intrahepatic HBV replication (120), there is little doubt that the outbreaks and sporadic cases of acute hepatitis being reported with increasing frequency in hemophiliacs after clotting factor concentrate infusions are related to NANC hepatitis agents. Cases of acute (including fulminant) NANC hepatitis have been reported to occur in patients with chronic liver disease treated for coagulopathy with factor IX concentrates (99). Similarly, acute NANC hepatitis developed in 8 of 8 cardiac surgery patients treated with coagulation factors concentrated from pooled plasma (104).

Other percutaneous routes have been implicated in the spread of NANC hepatitis. Occupational contact with patients and their blood has resulted in NANC hepatitis in health care workers (63) and investigators, most often after percutaneous inoculation with a blood contaminated instrument (121–123), but even without such an identifiable incident (124). Usually, however, there has been contact with blood or plasma, and the likelihood is high that most occupationally acquired NANC hepatitis cases result from overt or covert percutaneous transmission. Most outbreaks of nosocomial NANC hepatitis involve percutaneous routes and blood products. Several such outbreaks, originally thought to be caused by HAV infection, have been reevaluated with new serologic tests for anti-HAV and been reclassified as instances of NANC hepatitis. An example is a nosocomial outbreak reported in a Seattle oncology unit. Acute hepatitis developed, presumably as a result of contamination of blood components during fraction-
Smallpox vaccination of Bremen shipyard workers could have been NANB hepatitis.

Nonpercutaneous Transmission

Although percutaneous transmission appears to be the most efficient mode of spread for NANB agents, presumably nonpercutaneous routes have also been implicated. In fact, most cases of sporadic hepatitis, that is, individual hepatitis cases occurring in the absence of a defined epidemic or outbreak, are not associated with identifiable percutaneous exposures, and a substantial proportion of such cases have been attributed to NANB hepatitis. One of the earliest descriptions of NANB hepatitis unassociated with transfusion was reported from Costa Rica, where 11 NANB (non-CMV) cases were identified among 103 cases of sporadic hepatitis. Person-to-person spread was incriminated in several cases, including 4 cases occurring in one family (134).

Surveys of patients with hepatitis presenting for medical care have shown that the distribution of NANB hepatitis agent(s) is worldwide and that these agents account for 6%–48% of sporadic hepatitis cases in urban areas (63–79, 81, 135–144). Unfortunately, most of these surveys are too dissimilar to be comparable, with some weighted heavily toward adults, others toward children; some restricted to hospitalized cases only, others including all community acquired—both hospitalized and nonhospitalized cases; some with a high proportion of intravenous drug users, transfusion recipients, or homosexual males. Moreover, criteria for the diagnosis of NANB hepatitis by exclusion are not equally rigorous among these studies. The extremes in the 6%–48% range reflect these biases of selection and technique. In general, however, in developed countries where HAV and HBV are not highly endemic, and in the absence of an emphasis on percutaneously transmitted cases, NANB agent(s) account for ~15%–30% of sporadic cases of acute hepatitis in urban adults; and perhaps half that frequency in children. In most epidemiologic studies of sporadic hepatitis cases, a substantial proportion of patients with NANB hepatitis report having been exposed by such percutaneous routes as transfusion and intravenous drug injection, or by exposure to blood, such as occurs in health care workers. On the other hand, as many as 25%–50% of patients with sporadic acute NANB hepatitis cannot recall any percutaneous exposure, suggesting that NANB hepatitis, like hepatitis B, is spread by covert percutaneous routes or by nonpercutaneous mechanism (see following discussion).

If the spread of NANB hepatitis is similar to that for hepatitis B, a likely “nonpercutaneous” route for
the transmission of NANN hepatitis is through sexual contact. Although little information exists to define the role of heterosexual activity in the spread of NANN hepatitis, sexual transmission of infection among homosexual men has been recorded. Homosexual contact accounts for a small percentage (<10%) of NANN cases in several reports of sporadic acute hepatitis (76,77,81,145): both types B and A hepatitis in homosexuals overshadow the NANN cases (146,147). The incidence of NANN hepatitis in homosexual men was determined during a study of the efficacy of hepatitis B vaccine. The annual attack rate of NANN hepatitis in 1093 homosexual men, as determined by the life-table method, was 1.13 for placebo recipients and 2.80 for vaccine recipients (148). The crude attack rate for all participants was 2.9% annually. Thus, as deduced from studies of sporadic hepatitis, NANN hepatitis can be transmitted in a setting of frequent sexual encounters with many different partners; however, the risks of type B and type A hepatitis under these conditions are higher. In the hepatitis B vaccine trial previously cited, the crude incidence of HAV infection was 5.2% annually (4.03% in placebo and 6.26% in vaccine recipients, by life-table method) (148); the life-table annual attack rate in this population for hepatitis B without prophylaxis (placebo recipients) was 18% when clinically severe hepatitis cases were considered and as high as 38% when all HBV events, including asymptomatic seroconversions, were counted (148).

Perinatal transmission from mother to offspring, another of the modes of hepatitis B spread classified as nonpercutaneous, is probably the single most important factor in the perpetuation of HBV in its human reservoir. Although the contribution of perinatal transmission to the maintenance of NANN hepatitis has not been defined, maternal-neonatal transmission has been recorded in 8 of 12 infants born to women with acute NANN hepatitis during the third trimester of pregnancy (149). Another report of maternal-fetal transmission of non-B hepatitis, which proved fatal to both mother and child, was probably related to a NANN agent as well (150).

The role of person-to-person spread of NANN hepatitis is not understood. In some surveys, personal contact with hepatitis patients was never observed in cases of NANN hepatitis (63,64,70), while in others, as many as 6%–20% of NANN patients gave a history of such contact (69,74,76,145,151). Person-to-person spread is the likely mechanism for the observations, though limited, of NANN hepatitis within custodial institutions for the mentally retarded (152) and the 4 cases identified by Villarejos et al. (134) within a family in Costa Rica. Other than these data, however, there have been no reports of sizeable clusters of NANN hepatitis within institutions or families. Two secondary cases occurred in 34 household contacts of plasmapheresis donors with acute NANN hepatitis (129), but, other than this, cases have not been observed in household contacts of patients with percutaneously acquired or dialysis-associated NANN hepatitis (81). No evidence has been provided either that infection can be transmitted by direct contact with fomites contaminated by saliva from a patient with NANN hepatitis (153).

The question remains whether NANN hepatitis can be transmitted by the fecal-oral route. In several studies of sporadic hepatitis, patients with NANN hepatitis had a history of recent shellfish ingestion or foreign travel to areas of the world in which hepatitis is considered endemic, epidemiologic features of enterically transmitted infections (64,65,74,76,78,145). On the other hand, the predominant forms of NANN hepatitis currently being seen in the United States and Europe appear to be transmitted primarily through percutaneous exposure, are not associated with secondary cases, and, in all likelihood, are not spread by the fecal-oral route. In contrast, what appears to be a distinct type of water-borne NANN hepatitis has been described in India, Burma, and Asia. The most notorious outbreak of this type was a water-borne, common source epidemic of 35,000 hepatitis cases beginning in December 1955, in Delhi, India. For 25 yr, the Delhi epidemic was assumed to have been caused by HAV; however, a number of features atypical of type A hepatitis characterized these cases. The mean incubation period, 40 days, was longer than expected for hepatitis A; the distribution was shifted toward a population that by virtue of its age (20–40 yr) and of the extent standards of environmental hygiene should have been immune to HAV infection; there were no secondary cases; cholestasis was a prominent histologic feature; and the case fatality rate, especially in pregnant women (for whom it reached 10%), was unusually high for type A hepatitis (154). The suspicions based on these peculiarities that this outbreak was unrelated to hepatitis A were recently confirmed by serologic testing of stored serum samples. Neither HAV nor HBV could be implicated (155,156). Similar water-borne outbreaks and endemic cases occurring in the mid-to-late 1970s have been described in Ahmedabad, Pune, and Kashmir, in India, and in Mandalay, Burma (156,157). Tin KM, Khin MM, personal communication, 1977). Each of these instances share many of the features of the Delhi outbreak (158), and, like the Delhi cases, have been serologically characterized by exclusion as NANN hepatitis but, in addition, have been associated with secondary cases. Although the criticism has been raised that such...
cases represent contamination of water with a hepatotoxict substance rather than a viral agent, the long incubation period and the occurrence of secondary spread in recently described cases suggest that this type of water-borne hepatitis is caused by an infectious agent. It is unlikely, however, that those water-borne agents are the same as those responsible for the type(s) of percutaneously transmitted NANB hepatitis. This water-borne type of hepatitis in the Indian subcontinent is different from the percutaneously transmitted type, not only in its focal-oral route of spread, but also in its lack of progression to chronic hepatitis (159) (see following discussion). Although this form of NANB hepatitis has not been observed in North America and Europe, potentially these enterically spread agents could account for the cases of person-to-person transmission or sporadic cases described for which no percutaneous or intimate contact has been identified.

Thus, although the types of NANB hepatitis that have received the most attention resemble hepatitis B epidemiologically, a new category of NANB agents has been identified that is similar epidemiologically to hepatitis A.

Clinical Features

Although overlap in clinical features occurs among the three types of viral hepatitis, trends have emerged that provide a clinical profile of NANB hepatitis. Because of uncertainty in the diagnosis of NANB hepatitis, the most reliable information about clinical characteristics derives from studies of carefully pedigreed patient groups rather than from individual cases. Unfortunately, recent studies rely on more sophisticated diagnostic criteria than earlier studies, and diagnostic criteria of exclusion are not equally rigorous among reported series. In arriving at a diagnosis of NANB hepatitis, a clinician should attempt to exclude infection with HAV, HBV, CMV, EBV, as well as other viruses rarely associated with hepatitis; infection with the HBV-associated delta agent (see part II, to be published next month in Gastroenterology); toxic and drug-induced liver injury including alcoholic liver disease; circulatory abnormalities associated with congestive heart failure, shock, or sepsis; biliary tract disease; metabolic liver disease, such as Wilson’s disease; and hepatitis associated with bacterial, spirochetal, rickettsial, or other nonviral microorganisms. The differential diagnosis of NANB hepatitis is rendered even more difficult by the occasional occurrence of new acute hepatitis in chronic HBsAg carriers or by the early disappearance of HBsAg or unconventional absence of serum markers in patients with HBV infection. Still, thorough serologic analysis, especially when repeated several times during illness, and clues from the epidemiologic setting are helpful in establishing a diagnosis of NANB hepatitis. Series of such relatively well-characterized patient populations have shown that NANB hepatitis clinically resembles type B hepatitis but tends to be milder during acute illness and, even more frequently than type B hepatitis, progresses to a chronic disorder. Because of the overlap in clinical features among the several viral hepatitides, however, reliance on clinical features alone to arrive at a diagnosis is unreliable.

Incubation Period

Posttransfusion NANB hepatitis occurs after a mean incubation period of 7.8 wk, shorter by 4 wk than the mean incubation period of 11.8 wk for posttransfusion hepatitis type B (Table 1) (14,17,20–22,51–53,160–162). The mean incubation period of NANB transfusion-associated hepatitis resembles closely the 7-wk mode incubation period recorded in the 1960s for all cases of transfusion-associated hepatitis (6–9), suggesting that, even before HBsAg screening of donor blood, most posttransfusion hepatitis was the NANB type. Although the incubation period for NANB hepatitis after transfusion has ranged from 1 to 26 wk, 80%–90% of cases occur within 5–12 wk after transfusion (21,52). In other epidemiological settings, however, shorter incubation periods for NANB hepatitis have been recorded. In a nosocomial outbreak of NANB hepatitis among plasma and platelet donors and recipients, the mean incubation period was only 27 days (125). Incubation periods as short as 1–2 wk have been reported in

<table>
<thead>
<tr>
<th>Table 1. Incubation Period of Posttransfusion Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type B hepatitis</td>
</tr>
<tr>
<td>Investigator</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Alter (14)</td>
</tr>
<tr>
<td>Prince (91)</td>
</tr>
<tr>
<td>Alter (17)</td>
</tr>
<tr>
<td>Purcell (160)</td>
</tr>
<tr>
<td>Seeff (20)</td>
</tr>
<tr>
<td>Alter (21)</td>
</tr>
<tr>
<td>Aich (22)</td>
</tr>
<tr>
<td>Serafini (161)</td>
</tr>
<tr>
<td>Seeff (53)</td>
</tr>
<tr>
<td>Alter (52)</td>
</tr>
<tr>
<td>Cossart (162)</td>
</tr>
</tbody>
</table>

Total 140 11.8* 550 7.9*

* Weighted mean = (ΣA × B)/ΣA, where A = number of cases studied and B = mean incubation period reported.

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Table 2. Clinical Features of Posttransfusion Hepatitis

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Type B</th>
<th>Type non-A, non-B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. studied</td>
<td>Mean peak SGPT (IU)</td>
</tr>
<tr>
<td>Prince (51)</td>
<td>15</td>
<td>318</td>
</tr>
<tr>
<td>Alter (17)</td>
<td>4</td>
<td>637</td>
</tr>
<tr>
<td>Parcell (160)</td>
<td>12</td>
<td>768</td>
</tr>
<tr>
<td>Schef (20)</td>
<td>52</td>
<td>448</td>
</tr>
<tr>
<td>Alter (21)</td>
<td>3</td>
<td>1160</td>
</tr>
<tr>
<td>Ach (22)</td>
<td>10</td>
<td>628</td>
</tr>
<tr>
<td>Schef (53)</td>
<td>4</td>
<td>395</td>
</tr>
<tr>
<td>Alter (52)</td>
<td>4</td>
<td>1050</td>
</tr>
<tr>
<td>Cossart (162)</td>
<td>3</td>
<td>—</td>
</tr>
</tbody>
</table>

SGPT = Serum glutamic pyruvic transaminase.

patients in whom NANB hepatitis developed after percutaneous inoculation with contaminated blood products administered for experimental purposes or reinfused during plasmapheresis (128,132). Short incubation hepatitis has been observed with the greatest regularity in hemophilias in whom NANB hepatitis developed after factor VIII therapy. Incubation periods as brief as 4 days–2 wk have been recorded in this setting; most cases occur within 1–4 wk after factor VIII administration (100,103,106,107). Whether the differences in incubation period (short vs. long) reflect different NANB agents or different doses of the inoculum remains to be determined; however, the length of the incubation period has been reported to “broad true” in experimentally infected chimpanzees (see discussion in part 2) (102,103), and at least two distinct NANB agents, one short-incubation, the other long-incubation, have been transmitted experimentally in chimpanzees (see discussion in part 2) (112,114).

Clinical Course of Acute Illness

The clinical features of acute NANB hepatitis are indistinguishable from those of the other viral hepatitis, except that, as a rule, acute illness tends to be less severe in NANB cases. For example, serum glutamic pyruvic transaminase (SGPT) is <800 IU in >50% of cases and >2000 IU in <10% of posttransfusion NANB hepatitis cases (21). In comparisons between posttransfusion type B and type A hepatitis, with rare exceptions, peak serum amino-transferase activities are lower and the proportion of asymptomatic and anicteric cases is higher for the NANB group (Table 2) (17,20–22,51–53,160,162). In many patients with posttransfusion hepatitis, because the frequency of asymptomatic or mild disease is so high, the illness is likely to remain undetected unless liver tests are monitored regularly or abnormal tests are discovered coincidentally during evaluation for other medical problems. Reports of sporadic hepatitis and hepatitis occurring in non-transfusion settings include patients with more severe, easily recognized hepatitis. Illness in these patients is sufficiently severe to warrant medical attention and, frequently, hospitalization. Even at this end of the spectrum, however, the typical immunocompetent person with NANB hepatitis unrelated to transfusion has lower serum amino-transferase activity and less severe acute disease than his/her counterpart with type B or type A hepatitis (Table 3) (63,66,71,151,164). This is not to say that fulminant hepatitis and fatalities do not occur in patients with NANB hepatitis. Fatalities have been reported in isolated instances of sporadic (59,63,165), renal transplant-associated (50,93), perinatally acquired (150), and nosocomial hepatitis in immunodeficient patients (126). In an outbreak of NANB hepatitis in

Table 3. Clinical Features of Acute Sporadic Hepatitis

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Non-A, non-B hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. studied</td>
<td>Mean peak SGPT (IU)</td>
<td>Mean peak bilirubin</td>
</tr>
<tr>
<td>Dienstag [63]</td>
<td>20</td>
<td>875</td>
<td>5.5</td>
</tr>
<tr>
<td>Berg (71)</td>
<td>67</td>
<td>525</td>
<td>—</td>
</tr>
<tr>
<td>Kell [151]</td>
<td>112</td>
<td>721</td>
<td>5.1</td>
</tr>
<tr>
<td>Norkrans [66]</td>
<td>80</td>
<td>1025</td>
<td>7.1</td>
</tr>
<tr>
<td>Warrnambool [164]</td>
<td>23</td>
<td>1750</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Table 4: Cause and Outcome of Fulminant Hepatitis

<table>
<thead>
<tr>
<th>Study</th>
<th>No. cases</th>
<th>HAV Survival (%)</th>
<th>HAV + HBV Survival (%)</th>
<th>Drug Survival (%)</th>
<th>Non-A, Non-B Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (165)</td>
<td>108</td>
<td>2</td>
<td>33</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Demark (157)</td>
<td>22</td>
<td>18</td>
<td>25</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>England (95, 168)</td>
<td>73</td>
<td>31</td>
<td>43</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

* Drug-induced cases excluded in this series. HAV = hepatitis A virus. HBV = hepatitis B virus.

platelet and plasma donors and recipients (126). jaundice occurred in 0 of 9, ascites in 2 of 8, and death from acute hepatic failure in 3 of 8. Immunity to HBV was achieved in 6 of 8 post-transplant recipients. In contrast, all of the 27 immunocompetent donors affected had mild hepatitis and survived (126). Similarly, underlying chronic liver disease may predispose to increased severity of superimposed acute NANB hepatitis. Wyko et al. (99) described fatal acute fulminant hepatitis in 3 of 4 patients with preexisting cirrhosis and coagulopathy in whom acute NANB hepatitis developed after factor IX concentrate therapy.

The contribution of NANB hepatitis to fulminant hepatitis cannot be assessed accurately because of the absence of reliable serologic tests; however, several estimates have been made by reliance on serologic and historic exclusion criteria. In studies from the United States, Scandinavia, and Great Britain, NANB hepatitis accounted for 27%–44% of a total of 203 cases of fulminant hepatitis, and survival—9%–13%—was less likely for these NANB cases than for cases of fulminant hepatitis A or B (Table 4) (95,166–168). Actually, 27%–44%, rather than an accurate reflection of the contribution of NANB agents to fulminant hepatitis, represents the maximal proportion of cases potentially attributable to these agents. Not unlikely, included in this group are cases of fulminant hepatitis B in which HBsAg has become undetectable (109–174). In addition, many of these patients are comatose and, especially among fatalities, incapable of providing historic details; therefore, the apparent NANB group probably includes cases of drug toxicity for which historic verification is unavailable. Ultimately, a more accurate estimate of the contribution of NANB agents to fulminant hepatitis must await the development of serologic markers of infection. In general, however, severe acute and fulminant NANB hepatitis are rarely encountered. No deaths associated with acute NANB hepatitis were observed in any of the 515 patients with posttransfusion hepatitis cited in Table 2. Similarly, when sensitive serologic tests to detect HBsAg were introduced in blood donor screening programs, there was a fivefold-to-eighthfold decrease in fatalities resulting from posttransfusion hepatitis.

![Figure 1: Serial determinations of serum glutamic oxaloacetic transaminase (SGOT) activity in a patient with occupationally acquired chronic non-A, non-B hepatitis. Note the waxing and waning SGOT levels and the long duration of biochemical abnormalities.](image-url)
patients with acute NANB hepatitis and found monophasic enzyme elevations in 76%, biphasic or multiphasic elevations in 24%. In the report by Tateda et al. (54), patients with monophasic aminotransferase elevations had more severe disease but of relatively limited duration. In contrast, those with biphasic and plateau patterns of enzyme elevation tended to have more protracted hepatitis. Similarly, among patients in other studies who demonstrated fluctuating aminotransferase levels, biochemical abnormalities persisted for many months (see chronicity, discussed later). Because periods of intervening normal enzyme activity may also last many months between episodic elevations, determining true convalescence is difficult. Care must be taken not to confuse these instances of episodic exacerbations of protracted NANB hepatitis with occurrences of multiple, distinct bouts of acute hepatitis, separated by long intervals of normal liver function and histology, as described in drug addicts (56). Unfortunately, the distinction is not always possible.

**Histology**

Because few patients with acute hepatitis undergo liver biopsy, descriptions of the histologic features of acute NANB hepatitis in humans are limited. Recent studies, however, suggest that acute NANB hepatitis after transfusion is characterized by distinctive hepatic morphologic features that are unusual for types A and B hepatitis. Although, in many cases, the classic histologic features of acute viral hepatitis are found, approximately half of the acute NANB hepatitis cases in a study of 64 patients by Dienes et al. (179) had unusual morphologic findings. These included irregular eosinophilic clumping of the cytoplasm; microvesicular steatosis; marked activation of sinusoidal lining cells, which in some cases may be the only manifestation; a less intense portal and parenchymal inflammatory response than in types A and B hepatitis, with a paucity of lymphocytes; and a large number of acidophilic bodies, out of proportion to the degree of hepatocytic degeneration and inflammation (Figures 2–4) (179). The cytoplasmic eosinophilic changes appeared in biopsy specimens in which ultrastructural nuclear changes were observed by electron microscopy (see part II). In this study, cholestasis was rare, erosion of the limiting plate occurred in one-third of the cases but was never conspicuous or associated with bridging necrosis, folliculolike clusters of lymphocytes appeared rarely in portal tracts, and no bile duct lesions were seen (179). In several other smaller-scale studies of sporadic and post-transfusion acute NANB hepatitis cases, fatty changes were common, eosinophilic clumping was

---

**Figure 2.** Photomicrograph of a liver biopsy from a patient with acute NANB hepatitis showing diffuse eosinophilic granulation of the cytoplasm, intensification of star-shaped cells (straight arrow). Sinusoidal cells are increased in places (curved arrows) (hematoxylin and eosin, ×240). This photograph was kindly provided by Dr. Hans Popper and is reproduced from Hepatology 1982:2:562–71 (179) with permission.
Figure 3. Photomicrograph of a liver biopsy specimen from a patient with acute posttransfusion NANB hepatitis. The cytoplasm shows eosinophilic granulation and microvesicular steatosis. In addition, many acidophilic bodies (arrows) can be seen (hematoxylin and eosin, ×240). This photograph was kindly provided by Dr. Hans Popper and is reproduced from Hepatology 1982:2:562–71 (179) with permission.

Figure 4. Photomicrograph of a liver biopsy specimen from a patient with acute NANB hepatitis. The portal tract is markedly enlarged and densely infiltrated by mononuclear cells. Acidophilic bodies (curved arrows) are present, and there is diffuse microvesicular steatosis. Hepatic vein tributaries (left upper corner) are uninvolved, and, in contrast to other studies (160–165), bile ducts (straight arrow) are intact (hematoxylin and eosin, ×100). This photograph was kindly provided by Dr. Hans Popper and is reproduced from Hepatology 1982:2:562–71 (179) with permission.
not described, but distinctive bile duct lesions were observed (65, 138, 180–185). Bile ductular cells appeared to be piled up in the lumen without any interruption in the basement membrane—a lesion described previously (see following discussion) in patients with chronic NANB hepatitis (128) and originally described by Poulsen and Christoffersen (186) in patients with chronic active hepatitis. In one study (184), the presence of this bile duct lesion during acute illness was associated with a high likelihood (85%) of progression to chronic disease, and, therefore, this lesion was felt to have prognostic importance. Because it appeared in 29% of acute NANB cases, but in only 1 of 30 patients with acute type A or B hepatitis, this bile duct change was felt to be a useful diagnostic feature as well (184). As previously mentioned, pleocellular necrosis was not conspicuous and bridging necrosis was not observed in the study by Dienes et al. (179), but others (138, 182–185) have detected pronounced pleocellular necrosis and bridging. In hemophiliacs with factor VIII-associated acute NANB hepatitis, the most impressive histologic feature observed has been sinusoidal cell activation, often with normal hepatocytes (179). Still different is the morphologic pattern observed in cases of water-borne NANB hepatitis, as in the Delhi epidemic of 1955–1956 (157, 175). Although features of classic viral hepatitis appear in many of these cases as well, the most prominent morphologic characteristic of the water-borne type of NANB hepatitis is cholestasis.

Based on the finding of a paucity of lymphocytes, Dienes et al. (179) have postulated that hepatocytolysis in NANB hepatitis is not the result of lymphocyte-mediated injury, but instead involves a direct cytopathic effect of the virus on the liver cell. Episodic recurrences of such cytotoxic alterations, they go on to postulate, could account for the fluctuating aminotransferase patterns frequently observed in NANB hepatitis. Although attractive, evidence to buttress this speculation is lacking.

Table 5. Frequency of Chronic Elevation of Serum Aminotransferase Activity After Acute Posttransfusion Types B and Non-A, Non-B Hepatitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Type B hepatitis</th>
<th>Non-A, non-B hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) with</td>
<td>No. (%) with</td>
</tr>
<tr>
<td></td>
<td>elevated ALT*</td>
<td>elevated ALT*</td>
</tr>
<tr>
<td></td>
<td>studied ≥6 mo</td>
<td>≥6 mo</td>
</tr>
<tr>
<td>Purcell (160)</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Alter (21)</td>
<td>3</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Arch (22)</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>Alter (22)</td>
<td>10</td>
<td>30 (55)</td>
</tr>
<tr>
<td>Arch (22)</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>Kiyotaka (187)</td>
<td>20</td>
<td>70 (45)</td>
</tr>
</tbody>
</table>

* Alanine aminotransferase.

Chronicity

Despite its relatively mild, often asymptomatic and anicteric presentation during acute infection, posttransfusion NANNB hepatitis has a disturbing tendency to progress to a chronic stage, perhaps even more frequently than transfusion-associated type B hepatitis (Table 5) (21, 22, 52, 100, 187). As shown in Table 6, there is a broad spectrum in the frequency of chronic liver disease after acute NANB hepatitis, measured by persistently elevated aminotransferase activity (18, 20–22, 52–54, 59, 60, 76, 83, 93, 100, 103, 107, 109, 125, 126, 128, 129, 131, 132, 134, 136, 159, 178, 182–184, 187–193). Most patients in these studies had persistently elevated ALT levels for at least 6 mo–1 yr, often lingering for several years. In most studies, the frequency of chronicity is more likely in NANB hepatitis cases associated with transfusion and other percutaneous modes of transmission, 40%–60% (16, 21, 22, 52), than in cases occurring sporadically in the absence of identifiable percutaneous inoculation, ≤10% (59, 66). Still, these distinctions are not absolute, as shown in Table 6. Moreover, even in cases of person-to-person spread in an endemic area, originally reported as invariably self-limited (134), Villarejos et al. (194) recently observed progression to chronicity in 5 cases.

Acute NANB hepatitis is likely to be followed not only by chronic hepatitis, but also by an asymptomatic carrier state. The fact that normal blood donors transmit NANB hepatitis to recipients suggests that there is an asymptomatic NANB carrier state, and transmission of NANB hepatitis from asymptomatic persons to volunteers (131, 132) and to experimental animals (121, 163, 177), even in the absence of elevated ALT in the inoculum, proves the point. In one study, serum and plasma from a single donor collected over the course of 6 yr remained persistently infectious in chimpanzees (195). What is most disconcerting is the high estimated frequency of the NANB carrier state, which can be derived from the frequency of NANB hepatitis in recipients of single-unit transfusions. Posttransfusion hepatitis (80% type NANB) occurred in 3% of 193 recipients of a single unit of volunteer blood and in 7% of 404 recipients of a single unit of commercial blood in a Veterans Administration cooperative study (20), and NANB hepatitis occurred in 7% of 275 recipients of a single unit of primarily volunteer blood, but also including commercial or commercial-equivalent blood, in the Transfusion-Transmitted Viruses Study (196). Thus, if 3%–7% of American blood donors are asymptomatic NANB hepatitis virus carriers, the frequency of the NANB carrier state is 15- to 70-fold higher than the 0.1%–0.2% frequency of the hepatitis B carrier state in the United States.
A disquieting feature of the chronic liver disease associated with NANB hepatitis is the fact that, at least in transfusion-associated cases, the liver morphology in most patients is compatible with chronic active hepatitis (Table 7) (50,52,68,83,107,138, 178,181-184,186,189,191,192,197). More reassuring is the lower frequency of severe morphologic lesions in patients with chronic NANB liver disease unassociated with transfusion (Table 7). Furthermore, in most of the chronic active hepatitis cases, the disease is relatively benign, and the prognosis for the group, as a whole, of patients with chronic NANB hepatitis is, ultimately, good. With the exception of immuno-suppressed renal transplant patients (50), patients with chronic NANB hepatitis have qualified for the morphologic designation of chronic active hepatitis on the basis of piecemeal necrosis, i.e., erosion of the limiting plate of hepatocytes surrounding the portal tract. Bridging necrosis, described in the liver of patients with acute NANB hepatitis (138,179,181-185), has not been observed in immunocompetent patients with chronic active NANB hepatitis (59,83,178,186,189,191,192,198,199). In fact, most patients with chronic NANB hepatitis are asymptomatic or only mildly so, despite fluctuating levels of aminotransferase activity. In one of the earliest descriptions of the chronic sequelae of posttransfusion NANB hepatitis, Berman et al. (178) reported sponta-

Table 6. Differences in Frequencies of Chronicity of Non-A, Non-B Hepatitis Based on the Epidemiologic Setting of Acute Infection

| Epidemiologic setting | Report | No. studied | No. (%) with elevated ALT ≥ 500
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion</td>
<td>Seeff (20)</td>
<td>207</td>
<td>~10%*</td>
</tr>
<tr>
<td></td>
<td>Tateo (54)</td>
<td>116</td>
<td>19 (16)</td>
</tr>
<tr>
<td></td>
<td>Knodell (188)</td>
<td>44</td>
<td>10 (23)</td>
</tr>
<tr>
<td></td>
<td>Goldfield (18)</td>
<td>26b</td>
<td>7 (25)</td>
</tr>
<tr>
<td></td>
<td>Seeff (53)</td>
<td>115</td>
<td>31 (26)</td>
</tr>
<tr>
<td></td>
<td>Purcell (100)</td>
<td>21</td>
<td>7 (33)</td>
</tr>
<tr>
<td></td>
<td>Alter, Berman (21, 178)</td>
<td>26</td>
<td>12 (46)</td>
</tr>
<tr>
<td></td>
<td>Rakela (180)</td>
<td>13</td>
<td>7 (54)</td>
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<tr>
<td></td>
<td>Omata (180)</td>
<td>24</td>
<td>13 (54)</td>
</tr>
<tr>
<td></td>
<td>Goodson (100)</td>
<td>13</td>
<td>7 (54)</td>
</tr>
<tr>
<td></td>
<td>Asch (22)</td>
<td>65</td>
<td>30 (55)</td>
</tr>
<tr>
<td></td>
<td>Goldfield (18)</td>
<td>26c</td>
<td>17 (51)</td>
</tr>
<tr>
<td></td>
<td>Koretz (191)</td>
<td>47</td>
<td>28 (02)c</td>
</tr>
<tr>
<td></td>
<td>Kiyosawa (187)</td>
<td>70</td>
<td>45 (64)</td>
</tr>
<tr>
<td></td>
<td>Alter (52)</td>
<td>96</td>
<td>30 (65)</td>
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<td></td>
<td>Readl (183)</td>
<td>21</td>
<td>14 (67)</td>
</tr>
<tr>
<td></td>
<td>Koretz (100)</td>
<td>65</td>
<td>46 (70)</td>
</tr>
<tr>
<td>Homodialysis</td>
<td>Galbraith (93)</td>
<td>29</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Renal transplant</td>
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<td>Bamber (107)</td>
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<tr>
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<td>Muller (193)</td>
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</tr>
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<td>Altorf (138)a</td>
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<td>Alter (78)</td>
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<td>Schmid (184)c</td>
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<tr>
<td>Water-borne</td>
<td>Khuro (159)</td>
<td>30</td>
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</table>

* Patients with type non-A, non-B (predominantly) and B combined. a Volunteer donors. b Commercial donors. c Alanine aminotransferase not done, presence of chronic liver disease determined by persistent symptoms, signs, and fluctuation/turbidity tests. d Children. e Although these were sporadic cases, a substantial proportion had percutaneous exposures.
Table 7. Hepatic Morphologic Findings in Chronic Non-A, Non-B Hepatitis

<table>
<thead>
<tr>
<th>Epidemiologic setting</th>
<th>Study</th>
<th>Nonspecific or slowly resolving hepatitis</th>
<th>Chronic persistent hepatitis*</th>
<th>Chronic active hepatitis</th>
<th>Cirrhosis (x CAH)</th>
<th>% with CAH and/or cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion</td>
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<tr>
<td></td>
<td>Bablor (101)§</td>
<td>6</td>
<td>0</td>
<td>2</td>
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CAH = chronic active hepatitis. § Includes chronic lobular hepatitis. ‡ Primarily non-A, non-B cases but includes type B hepatitis (50, 193) or cytomegalovirus infection (50). * One patient died of liver failure after 1 yr of disease. At autopsy her liver was infiltrated with fat.

CAH is a proportion with percutaneous inoculation.

Neous biochemical improvement in all such patients with chronic active hepatitis and histologic remission within 1–3 yr in 4 of 12 such patients for whom follow-up liver biopsy was available. In contrast, more recent reports have focused attention on cases of chronic NAB hepatitis with less benign outcomes. J. Avarson et al. (1986) described 2 patients with severe chronic active hepatitis with fibrosis, 1 of whom responded biochemically, but not histologically, to immunosuppressive therapy, and the other of whom ultimately succumbed to liver failure after 3 yr. Similarly, severe cases of chronic active hepatitis with rapid progression have been described by others (59, 181, 183, 192), including fatal cases (50, 183, 189). Koret et al. (200) reported spontaneous and medically induced remission from chronic active to chronic persistent hepatitis in a limited number of patients but progression of disease in others, both among those treated with immunosuppressive therapy and those untreated. By actuarial analysis of their patients' outcomes, these investigators calculated that only 54% of patients with posttransfusion NAB hepatitis would experience a spontaneous biochemical remission within 3 yr (192). Severity of disease has prompted others to treat their patients with chronic active hepatitis with immunosuppressive therapy and have achieved poor success in some series (201) and dramatic improvement in others (183, 202), with 4 of 6 improving histologically in one series (183). Adequately controlled trials of immunosuppressive therapy for chronic active NAB hepatitis, however, have not been undertaken, nor has the natural history of this disease been evaluated adequately. In any event, whether most patients experience spontaneous remissions (178) or progressive disease (183, 198), optimism about the prognosis of chronic NAB hepatitis must be tempered by the occurrence of cirrhosis in a proportion of cases. In reports of chronic active hepatitis after acute transfusion-associated NAB hepatitis, at least 1 patient with cirrhosis has been identified in every series, ~10%–20% of all cases (Table 7) (52, 178, 182, 183, 186, 189, 191, 192). In one report (59), cirrhosis was detected as early as 4 mo and in others (198, 199, 203, 204) as early as the first year after the onset of acute illness, and in several cirrhotic cases, death resulting from liver failure was observed (50, 183, 189, 192, 198). Progression to cirrhosis can occur insidiously in the absence of symptoms (204, 205) and becomes more frequent as the duration of follow-up increases (183, 204). Realdi et al. (183) found cirrhosis in only 1 of 8 patients who underwent biopsy within 1–2 yr after acute NAB hepatitis, but in 4 of 6 patients undergoing the procedure 2–4 yr after acute NAB hepatitis. In another series of 23 cirrhotic patients seen at a
referral center, cirrhosis in cases of chronic NANB hepatitis was detected a mean of 2.6 yr (range, 6 mo–11 yr) after transfusion, and 5 of the 23 experienced such complications as encephalopathy, bleeding from esophageal varices, and ascites (203). Non-A, non-B hepatitis probably accounts for a proportion of cases of chronic active hepatitis (187,206,207) and cirrhosis (187) without hepatitis B markers or autoantibodies, but the precise contribution of NANB hepatitis agents to these groups of chronic liver disease will not be known until NANB serologic markers are available.

Aside from the rarity of bridging necrosis in patients with chronic active NANB hepatitis, histologic features of chronic NANB hepatitis resemble those identified in the livers of patients with acute NANB hepatitis: steatosis, sinusoidal cell activation, eosinophilic granules, and a paucity of lymphocytes (179). In addition, the bile duct lesion—piling up of ductular epithelial cells in the duct lumen without a break in the basement membrane—originally described by Poulsen and Christoffersen (186) in patients with chronic active hepatitis and noted in some patients with acute NANB hepatitis (138, 180,181,184) has been observed by some investigators in the livers of patients with chronic active NANB hepatitis (128,181). This lesion, however, has not been observed by other investigators who have accumulated a large experience in evaluating the morphologic features of chronic NANB hepatitis. Characteristic ultrastructural changes have been observed in the livers of experimental animals and humans with chronic NANB hepatitis; these are discussed in part 2.

Few clinical, biochemical, or morphologic features of acute illness can be relied upon to predict the development of chronic NANB hepatitis. Among the features found in some studies to be associated with ultimate chronicity were receipt of large transfusion volumes (188), receipt of commercial rather than volunteer blood (18,20), having experienced symptoms of malaise, nausea, vomiting, and anorexia during acute illness (188), having had an anicteric rather than an icteric acute illness (189), having achieved a peak ALT level of >300 IU, at least among anicteric patients (178), having had a mild rather than severe acute illness (138), having had a slow rise in and multiple peaks of aminotransferase activity (182), having had bile duct lesions demonstrable histologically during acute illness (184), and having had erosion of the limiting plate, ballooning hepatocellular degeneration, and "poor regenerative capacity" demonstrable histologically during acute hepatitis (182). Each and every one of these factors, however, was found to have no effect on the outcome in other studies (52,76,164,178,183,192). What is apparent and worth reiterating is the importance of not ignoring anicteric and asymptomatic acute NANB hepatitis, which has been shown in many cases to progress silently to chronic active hepatitis and cirrhosis (204,205).

Miscellaneous Clinical Features

Extrahepatic features, such as arthritis and rash, are rare in patients with NANB hepatitis. Martini et al. (208) observed urticaria and purpura in 1 of 34 patients in a plasmapheresis-associated outbreak of NANB hepatitis, and Koff et al. (151) detected rash in 5% of sporadic NANB cases. In 1 case of acute NANB hepatitis, Perrillo et al. (209) reported the occurrence of a serum sickness-like syndrome associated with circulatory immune complexes. Except for these observations, despite the frequency of circulating immune complexes in patients with NANB hepatitis (210), symptoms and signs attributable to deposition in tissues of immune complexes are rarely identified.

Aplastic anemia has been associated with acute hepatitis, but until recently, no one type of hepatitis was implicated. Contemporary serologic analyses, however, indicate that most instances of aplastic anemia after hepatitis are attributable to NANB hepatitis (211).

Hepatocellular carcinoma (HCC) has been linked to HBV. Because, like HBV, NANB is associated with chronic hepatitis and an asymptomatic carrier state, and because, like HBV, NANB can be transmitted during the perinatal period, the question arises whether NANB can participate in the pathogenesis of HCC. Although the evidence linking NANB to HCC does not compare with the plethora of data supporting the association between HBV and HCC, HCC cases have been described in patients in whom tentative diagnoses of NANB hepatitis were made (212). In several series of patients with HCC, 5%–28% had no serum markers of HBV (213–217), and the non-B cases were a mean of 8–10 yr older than cases associated with HBV (216,217). In two of these series (216,217), 17%–33% of these patients had a history of having received blood transfusions, and 17%–28% had HCC in the absence of cirrhosis. Kobayashi et al. (213) described 9 cases of HCC in patients who had had NANB posttransfusion hepatitis 13–30 (mean 21) yr earlier, and 4 of whom had cirrhosis. In a report from Nigeria, Ayoola et al. (214) followed 35 patients with acute NANB hepatitis for 5 yr and identified 2 patients in whom HCC developed after 2 and 4 yr, respectively. Unfortunately, these are only fragmentary data which do not provide convincing evidence for an association. Moreover, HBV deoxyribonucleic acid (DNA) has been detected.
in the genome of tumor cells even in some patients with HCC in the absence of all HBV serum markers (218,219). Additional study will be required to assess the role, if any, of NANB hepatitis in HCC.

Immunologic Features and Pathophysiology

Because of the many similarities between NANB hepatitis and hepatitis B, presumably both of these types of hepatitis share similar pathophysiologic mechanisms. Immunologically mediated hepatocyte injury has been postulated to account for hepatitis type B (220), and, presumably, immunologic responses to NANB virus(es) and virus-infected hepatocytes, rather than a directly toxic effect of the virus on liver cells, play a role in the initiation and/or perpetuation of liver injury in NANB hepatitis. Data to support this hypothesis have yet to be generated, and even for HBV, with its many easily identifiable serum and tissue markers, the immunopathogenesis of the disease has not been established.

A limited number of immunologic observations have been made in patients with NANB hepatitis. As discussed in part 2, several antigen-antibody systems have been described in serum of patients with NANB hepatitis, but none of them have proven to be universally accepted, and some represent nonimmunologic precipitins (52,221,222). Acute NANB hepatitis is associated with normal serum IgM (67,74,223–226) and normal (74,223,224,226) or elevated serum IgG levels (ratio of IgG to IgM > 6 in 82% of patients) (225); routine autoantibodies are rarely present in the serum of patients with acute NANB hepatitis (181,223) but have been observed in a proportion of patients with chronic NANB hepatitis (178,186,202,223). Among the immunologic findings described in patients with reasonably well-documented NANB hepatitis are the following: anticomplementary activity and immune complexes in serum (11,210), the presence in serum of rosette inhibitory factor (227), a normal rise in interferon levels in patients with self-limited acute disease but defective interferon production in patients with fulminating hepatitis (228), no consistent pattern of antibodies to single-stranded DNA (229), the presence of "liver-specific" antigen in serum of a third of acute cases (230), antibodies to "liver-specific protein" ranging from absent or rare in cases of acute and chronic hepatitis (231) to present in approximately one-third of acute cases (232,233), lymphocyte sensitization to "liver-specific protein" in two-thirds of early acute cases (234), absence of liver membrane autoantibody in acute cases (235), enhanced spontaneous and antibody-dependent cytotoxicity by lymphocytes from patients with chronic NANB hepatitis for Chang cells (236) but no increase in spontaneous (natural killer cell) cytotoxic activity for the HbsAg-expressing PLC/PRF/5 cell line (237,238), and normal T- and B-cell numbers (239). Little uniformity exists among studies of immunoregulatory balance in NANB hepatitis. Mitogen-induced suppressor cell function was normal in one group of patients with chronic active NANB hepatitis (240), but in another series of studies of patients with chronic NANB hepatitis, a multiplicity of different defects in spontaneous suppressor and helper T-cell function and in B-cell responses, rather than a uniform immunoregulatory abnormality, was found (241,242). In contrast, studies of immunoregulatory T-cell phenotype in patients with chronic NANB hepatitis have identified a uniform decrease in the ratio of helper to suppressor T cells. This shift in immunoregulatory balance favoring suppressor influences, it has been speculated, may limit both the humoral immune response to the virus and the aggressor lymphocyte response to virus-infected hepatocytes (243). A clinical counterpart to this laboratory finding is the exaggerated generalized immunosuppression in renal transplant patients with chronic NANB hepatitis, reflected by increased graft survival and an increase in fatal and nonfatal infections (93).

Most of these immunologic abnormalities are not unique to NANB hepatitis and appear with similar frequency in other viral and nonviral hepatitides. Moreover, such immunologic features may be secondary to the disease process rather than primarily involved in its pathogenesis. In fact, as noted earlier, Dienes et al. (179) have postulated that unlike HBV, which is believed to lead to immunologically mediated hepatocyte injury, NANB hepatitis is directly cytotoxic for liver cells. Although the relative paucity of intrahepatic lymphocytes in NANB hepatitis supports this view, the many other similarities between hepatitis B and NANB, including the occurrence of asymptomatic carriers, suggests that neither agent is directly cytotoxic to hepatocytes.

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