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Non-A/Non-B Hepatitis: A Review and Interim Report of an Ongoing Prospective Study

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INTRODUCTION AND HISTORICAL SUMMARY

Although the introduction of sensitive assays for HBsAg and the exclusion of high risk commercial donors have resulted in a marked reduction in the incidence of posttransfusion hepatitis[1,2], there remains a significant base of residual hepatitis cases[3-7]. Serologic analysis of these residual cases revealed that virtually none were due to the HAV, the cytomegalovirus (CMV) or the Epstein-Barr virus (EBV) and that only 10 to 30% were due to the HBV. It thus appears that there is at least one additional human hepatitis virus and this postulated virus has been tentatively designated, "non-A/non-B."

Perhaps the earliest clue to the existence of more than two human hepatitis viruses was the observation by Mosley[8] that the incubation period of viral hepatitis did not depict the expected bimodal cure, but rather presented a unimodal cure as if there was hepatitis-like illness with an incubation period intermediate between that of the epidemiologically well defined short incubation HA ("infectious") and the long incubation HB ("serum"). Such epidemiologic observations were of limited impact, however, until serologic methods were developed which allowed for accurate characterization of individual hepatitis cases. The landmark discovery of the Australia antigen (HBsAg) by Blumberg and coworkers[9] and the linking of this antigen to viral hepatitis[10] provided the cornerstone for the rapid acceleration in our understanding of viral hepatitis in general, and posttransfusion hepatitis in particular. Additional studies by Prince[11] and Krugman et al.[12] demonstrated that HBsAg was specifically related only to viral HB, and that HA was a serologically and immunologically distinct entity. The application of increasingly sensitive tests for the HBsAg and its corresponding antibody made it clear that a large proportion of posttransfusion hepatitis cases could not be classified as HB. It was assumed that many of these cases represented HA and that the remainder were HB cases that were not serologically detected because of inadequate sampling or inadequately sensitive assays. It was not until Feinstone et al.[13] demonstrated by immune

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electron microscopy a HA antigen and antibody that the final groundwork was prepared for the definition of non-A/non-B hepatitis. Using this serologic marker, Feinstone and coworkers[14] demonstrated that none of 22 cases of non-B hepatitis represented HA. Similarly, Prince et al.[3] demonstrated on epidemiologic grounds that it was very unlikely that non-B hepatitis represented HA. This conclusion was based on an incubation period distinct from that of classic HA and on the epidemiologic pattern of disease transmission. To date, the existence of an infectious agent(s) as the cause of non-A/non-B hepatitis has not been proved since no associated particle has been observed, no growth in tissue culture has been documented, and no specific immunologic test has been developed. In the face of elevated hepatic enzymes, the diagnosis of non-A/non-B hepatitis can only be made by the serologic exclusion of other known hepatitis viruses and by the clinical exclusion of other causes of hepatocellular injury. Nonetheless, there is a rising groundswell of evidence that substantiates the existence of at least one human hepatitis virus distinct from HAV and HBV, and some of this evidence will be presented below.

NON-A/NON-B: 1975-1977
1975 SYMPOSIUM

In May 1975, a symposium on viral hepatitis was sponsored by the National Academy of Sciences and held in Washington, D.C. The section on posttransfusion hepatitis (PTH) was marked by a striking unanimity of opinion among four independent investigators performing prospective studies of posttransfusion hepatitis. The results of these studies by Alter et al.[15], Goldfield et al.[16], Hollinger et al.[6] and Seeff et al.[2] can be summarized as follows:

1. The hepatitis risk of commercial donor blood, even when tested for HBsAg by radioimmunoassay, was markedly higher than that of volunteer donor blood similarly tested. The incidence of hepatitis was 5 to 20 times higher among recipients of commercial as compared with volunteer donor blood. It was estimated in two reports[2,15] that exclusion of commercial donors even without HBsAg testing would account for approximately 75% reduction in PTH.

2. Among recipients of volunteer donor RIA-tested blood, approximately 90% of the hepatitis which occurred was serologically unrelated to the HBV. The remaining cases were due to the HBV despite HBsAg screening. Virtually no cases were due to the HAV, cytomegalovirus or Epstein-Barr virus.

3. The institution of RIA testing resulted in a significant decrease in HB (an approximate 50% reduction)[6] and fivefold decrease in fatalities[16], but, because of the preponderance of non-B disease, did not profoundly affect the overall frequency of PTH.

4. Non-A/non-B hepatitis was commonly anicteric and frequently associated with prolonged enzyme abnormalities.

POSTTRANSFUSION HEPATITIS

Since the 1975 symposium, the published literature has continued to confirm these findings and has focused on four major areas: *1.* the incidence of non-A/non-B hepatitis following blood transfusion; *2.* the incidence of non-A/non-B hepatitis among patients without prior transfusion; *3.* the relationship of non-A/non-B hepatitis to chronic liver disease; and *4.* possible means of detecting donors at high risk of transmitting non-A/non-B hepatitis.

The occurrence of non-A/non-B hepatitis after transfusion is depicted in Table 32-1. In the study of Alter et al.[4], recipients received only volunteer blood which was initially screened by counterelectrophoresis, but retrospectively tested by RIA. Had RIA-positive, CEP-negative donors been excluded, 89% of the hepatitis which occurred would have been classified as non-A/non-B. The study of Goldfield[17] not only demonstrated that 93% of hepatitis cases were non-A/non-B, but also that the introduction of routine HBsAg screening of blood donors resulted in a fourfold decrease in overt hepatitis cases and an eightfold decrease in hepatitis fatalities. This suggests that HB is acutely more severe than non-B hepatitis. The investigation of Koretz et al.[18] is not strictly comparable to the others in Table 32-1 in that consecutive transfusion recipients were not followed. Rather, the investigators selected patients who had received blood which retrospectively was found to be HBsAg-positive either by RIA and/or by reversed passive hemagglutination (RPHA). They also followed a control group which received only blood HBsAg-negative by these sensitive assays. The primary purpose of the study was to evaluate the significance of blood HBsAg-negative by CEP but positive by RIA or RPHA. The control population of 42 patients can, however, also be used to evaluate the incidence of non-B hepatitis in recipients of blood HBsAg-negative by third generation tests. The observed incidence (63%) is lower than in the other studies probably because of the very high percentage

Table 32-1. Non-A/Non-B Hepatitis After Transfusion: 1975–1977

Study/Yr. [Ref]	Donor Source/Test	No. in Study	% Hepatitis	%Hepatitis Non-B
Alter '75 [4]	V/CEP (RIA)[c]	108	11	75 (89)[a,b]
Goldfield '75 [17]	18% C/RIA	563	13	93
Koretz '75 [18]	80% C/RIA	42	45	63
Knodell '76 [19]	V/CEP (RIA)[a]	279	17	94 (96)[a,b]
Seeff '77 [5]	65% C/CEP	2204	11	78
TTV[c] '77 [20]	V, C/RIA	359	13	80[b]

Abbreviations: V = volunteer, C – commercial, CEP = counterelectrophoresis, RIA = radioimmunoassay.

a: Initially screened by CEP, but subsequently retested by RIA. Results in parentheses indicate expected percentage had RIA-positive, CEP-negative donors were excluded.

b: Also proven non-A hepatitis.

c: Transfusion Transmitted Virus Study Group.

of commercial blood utilized (80%) and the probable high frequency of subdetectable carriers of HB virus in such a donor population.

The study of Knodell et al.[19] was designed to test the effect of immune serum globulin (ISG), HBIG and an albumin placebo on the incidence of PTH. The conclusion of this study was that ISG and HBIG were equally effective in reducing the incidence of both anicteric and icteric non-A/non-B hepatitis as compared with control recipients. It is not the purview of this synopsis to further discuss the complexities of clinical trials to evaluate gamma globulin prophylaxis for preventing PTH, but merely to cite that 94 to 96% of the hepatitis which occurred in this trial was classifiable as non-A/non-B.

The investigation of Seeff et al.[5] represents a double-blind, randomized, controlled trial in 11 VA hospitals to compare ISG with an albumin placebo for the prevention of PTH. The only significant effect of ISG was to reduce the incidence of icteric non-B hepatitis, but further analysis showed the same effect could have been achieved by decreasing the use of commercial blood. The primary point to be made is that, in this very large prospective study, 78% of hepatitis cases were unrelated to the HBV. This proportion would probably have been even higher had HBsAg testing of donors been performed by RIA.

The data from the Transfusion Transmitted Virus (TTV) study[20] represents the pilot phase of a large multihospital study which has been published only in abstract form. Eighty percent of the observed hepatitis was classified as non-A/non-B.

NON-A/NON-B WITHOUT PRIOR TRANSFUSION

There is increasing evidence that the mode of transmission of non-A/non-B hepatitis parallels that of HB. Transmission via blood products has been clearly documented as noted above, but accumulating data also attest to nonpercutaneous spread and to spread by needlestick without associated transfusion. Evidence reported since 1975 is presented in Table 32-2. Villarejos et al.[21] studied 103 cases of endemic hepatitis in Costa Rica and classified 12% as non-A/non-B. Mosley and coworkers[22] investigated 30 episodes of heptatitis occurring in 13 patients, each of whom had at least two episodes of acute hepatitis. Seven percent of the 30 episodes were serologically related to HAV, 40% to HBV and 53% were classified as non-A/non-B. Of particular interest were three patients who had two distinct bouts of non-A/non-B hepatitis suggesting that more than one agent may be responsible for this disease. Dienstag et al.[23]investigated 417 patients who had a hospital discharge diagnosis of viral hepatitis: 50.4% were HBsAg-positive. Sufficient sera were available for comprehensive serologic testing of only 40 of the remaining 49.6%. Fifty percent of these had HA and 50% non-A/non-B hepatitis. Thus, overall, of patients hospitalized for viral hepatitis approximately 50% had HB, 25% HA and 25% non-A/non-B. Myers et al.[24] reinvestigated a nosocomial outbreak of hepatitis in an oncology unit. This outbreak was originally thought to be due to the HAV, but testing of acute and convalescent

Table 32-2. Non-A/Non-B Hepatitis Without Transfusion

Study/Yr. [Ref]	Setting	No. Hepatitis Cases Studied	% Hepatitis Non-A/Non-B
Villarejos '77 [21]	Endemic Hepatitis: Costa Rica	103	12
Mosley '77 [22]	Sporadic Hepatitis: Multiple Episodes	30 (13)[a]	53
Dienstag '77 [23]	Hospitalized HBsAg-neg Hepatitis	40	50
Myers '77 [24]	Nosocomial Outbreak	15	100
Hoofnagle '77 [25]	Human Volunteer Studies	9	100

a: 30 episodes occurring in 13 patients.

phase sera by sensitive assays for exposure to HAV and HBV resulted in reclassification of this epidemic as non-A/non-B.

Although it represents a parenteral inoculation, I have included the study of Hoofnagle et al.[25] in this section because it did not involve therapeutic transfusion. This study involved a serologic reevaluation of volunteer studies performed in the early 1950s. Three HBsAg-negative inocula were icterogenic in 10 to 47% of recipients. Recipients did not develop serologic evidence of exposure to HBV, HAV, CMV or EBV and hence were designated non-A/non-B hepatitis. These recipients were immune to rechallenge by the same inoculum suggesting immunity to the non-A/non-B agent. Clinically, non-A/non-B hepatitis was milder than HB, but it more frequently resulted in chronic hepatitis.

Other Parameters of Non-A/Non-B Hepatitis

It had been previously reported that persistent and fluctuating enzyme abnormalities were common in non-A/non-B hepatitis[26]. Two additional studies have now focused on the relationship of non-A/non-B hepatitis to chronic liver disease. Koretz et al.[27] reported that among 49 cases of PTH (only three of which were HBsAg-positive), 29 (59%) had ALT abnormalities for greater than 20 weeks. Liver biopsies were performed in 15 of these 29 patients and revealed CAH in 60%, CPH in 13% and unresolved hepatitis in 27%. In 1977, Knodell and coworkers[28] reported that 10 of 44 (23%) of patients with non-A/non-B hepatitis had persistent ALT abnormalities for greater than one year. Liver biopsy revealed cirrhosis in one, CPH in one and CAH in eight. This study, which involved a comparison of ISG, HBIG and albumin for the prevention of posttransfusion hepatitis, also indicated that

there was significantly less progression to chronic liver disease in those who received either gamma globulin preparation.

Two studies have examined the correlation between anti-HBs in the donor and non-A/non-B hepatitis in the recipient. In one[29] there was no positive association, but in the other[30] it was suggested that recipients of anti-HBs-positive blood were at higher risk of developing non-A/non-B hepatitis. However, recipients of anti-HBs also received a greater number of transfusions, and it is more likely that the observed association was due to this factor rather than to the presence of anti-HBs.

A finding of potentially great practical import was the observation in the TTV study[20] that 30% of patients with non-A/non-B hepatitis received one or more blood units with an ALT of greater than 60 International Units/liter (I.U./1). This raises the possibility that donor screening for ALT might prevent some cases of non-A/non-B hepatitis, but it must be remembered that 70% of non-A/non-B cases received only blood with normal ALT and that 3% of blood units with elevated ALT did not result in hepatitis. This observation has vast implications for blood banks in that it will increase the time and cost of donor screening and will exclude a significant number of donors who probably do not represent a hepatitis risk. Nonetheless, it is a provocative finding which must be further analyzed on a much larger scale.

ONGOING NIH PROSPECTIVE STUDY

Study Design

Consecutive patients over 18 years of age undergoing open heart surgery were prospectively followed for 9 months. Patients with HBsAg or trans-aminase elevations prior to surgery were not followed. Samples were obtained weekly or biweekly during the first 3 months posttransfusion, monthly for the next 3 months and then again at 9 months. All donors were volunteers and were screened for HBsAg by solid phase RIA (Ausria II). Hepatitis was diagnosed when, between 2 and 26 weeks posttransfusion, the ALT exceeded 2½ times the upper limit of laboratory normal and when a repeat sample one week later was at least two times the upper limit of normal. Other causes of transaminase elevation had to be reasonably excluded. Icteric hepatitis was diagnosed when the serum bilirubin exceeded 2.5 mg/dl.

ALT, AST and HBsAg were measured on all samples. The pretransfusion and 3-, 6-, and 9-month posttransfusion samples were tested for anti-HBs by RIA (Ausab, Abbott Laboratories). The pre-, 3- and 6-month samples were also tested for anti-HBc by solid phase RIA (Corab, Abbott Laboratories) and, where indicated by elevated ALT, tested for antibody responses to CMV (complement fixation), EBV (fluorescence) and HA (immune adherence). Aspiration liver biopsies were performed only when serum ALT was abnormal for longer than 6 months. Biopsies were kindly read under code by Dr. Kamal Ishak of the Armed Forces Institute of Pathology.

Hepatitis Incidence and Serology

As indicated in Table 32-3, 388 patients completed at least 6 months of follow-up. Of these, 30 (7.7%) developed hepatitis. Based on an average transfusion number of 15.7 per patient, this represents a hepatitis risk of .49% or 4.9 cases per 1,000 units transfused. The incidence of icteric hepatitis was 2.8%, which represents an icteric hepatitis risk of .17% per unit or 1.7 cases per 1,000 units transfused.

Of the 30 hepatitis cases, only three were HB; 90% of the observed cases could be classified as non-B. Further serologic analysis revealed that none of the non-B cases were due to the HAV or EBV. One case, however, demonstrated a definite development of antibody to cytomegalovirus, and also differed from the other cases in that fever was the prominent feature of the disease. There were thus 26 cases (87% of the total) which could be classified as non-A/non-B hepatitis. Lastly, in addition to the three HB cases, there were five patients who demonstrated serologic evidence of HBV infection, but who did not have enzymatic changes consistent with viral hepatitis.

Clinical Analysis

Table 32-4 depicts the clinical presentation of non-A/non-B hepatitis and compares this with the HB cases. In general, HB had a longer mean incubation period, a higher ALT, a higher mean peak bilirubin and a higher percentage of icterus. However, there was considerable overlap in all these parameters and the number of type B cases was so small that these comparisons may not be meaningful. Several clinical features of non-A/non-B hepatitis merit particular consideration. First, although the incubation period (as measured to the first ALT to exceed twice the upper limit of normal) ranged from 5 to 20 weeks, only one case exceeded 12 weeks and 92% fell between 5 and 10 weeks. The median incubation period was 7 weeks and the mean 8.2 weeks. Second, although the clinical severity was generally mild as judged

Table 32-3. Hepatitis Incidence and Serology

Total patients	388	
Av. No. Transfusions	15.7	
Total Hepatitis	30 (7.7%)	
Hepatitis B		3 (10%)[a]
Non-B Hepatitis		27 (90%)
HA		0
EBV		0
CMV		1
Non-A/non-B Hepatitis		26 (87%)

a: Five patients without hepatitis had evidence of HBV infection.

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Table 32-4. Hepatitis Cases: Clinical Analysis

	Hepatitis B	Non-A/Non-B
No. cases	3	26
Mean incubation (range)	16.6 wks (7–28)	8.2 wks (5–20)
Mean peak ALT (range)	1,168 I.U./l (800–1900)	744 I.U./l (132–2322)
No. Icteric	3 (100%)	8 (31%)
Mean Peak Bil (range)	7.3 mg/dl (4.3–12)	2.8 mg/dl (0.2–10.8)
Chronic hepatitis	1 (33%)	12 (46%)

both by symptoms and the magnitude of ALT elevation, 31% of cases were icteric and 35% had a peak ALT in excess of 800 I.U./l; 7.7% had an ALT in excess of 2,000 I.U./l. Third, a higher proportion of non-A/non-B cases progressed to chronic liver disease (see below).

Chronic Hepatitis

Twelve of the 26 patients (46%) with non-A/non-B hepatitis had an abnormal ALT for greater than 9 months. Three of these 12 have not yet been followed for 1 year, but in the remainder these abnormalities have persisted beyond one year. It is of considerable interest that in four patients who have had abnormal enzymes for from 1 to 3 years, there has been a return to normal values. It is too early to be certain whether this normalization represents a true remission or whether it is part of the fluctuating enzyme pattern commonly observed in non-A/non-B hepatitis[26].

Eight of the 12 patients were biopsied 6 months to 1 year after the onset of their hepatitis. A striking feature in seven of the eight patients was the histologic appearance of CAH; in one of these there was early evidence of cirrhosis. None of the patients with CAH had bridging necrosis. The eighth patient had chronic persistent hepatitis with an associated fatty metamorphosis. One patient with CAH was rebiopsied 1 year after the initial procedure and the second biopsy was interpreted as chronic persistent hepatitis. This improved histologic picture was paralleled by a gradual return to normal ALT values.

Of the 12 patients with chronic hepatitis, three were icteric in the acute phase and nine were anicteric. Interestingly, among the anicteric cases, one could prognosticate the trend toward chronicity based on the peak ALT. Among nine anicteric cases whose peak ALT was less than 300 I.U./l, eight went on to complete recovery and one developed CAH. Among nine anicteric cases whose peak SGPT exceeded 300 I.U./l, only one recovered completely and eight developed chronic hepatitis (seven, CAH). The outcome in these two groups was so diametrically opposed that the differences were highly significant despite the relatively small number of patients (chi square = 8, P .005).

Donor Transaminase and Recipient Hepatitis

Based on the provocative findings of the TTV group[20] and on our own donor recall which, retrospectively, found a donor with elevated enzymes in two of four cases of non-A/non-B hepatitis, we recently initiated a prospective program which tests donors for ALT on a sample obtained at the time of donation. Since the significance of these values is unknown and since the results are not returned to us for approximately 1 week, these tests are not currently used to interdict donors with elevated values. Indeed the initial findings, though limited, do not substantiate the correlation between donor transaminase elevation and recipient hepatitis. As seen in Table 32-5, one of seven patients with non-A/non-B hepatitis received blood from a donor with a transaminase above the upper limit of normal (45 I.U./l). In contrast, six of 20 patients who did not develop hepatitis received at least one unit of blood from a donor with elevated ALT. Were these ratios to be maintained as this study expands, one would have to conclude that the exclusion of donors with elevated ALT would result in an inordinate loss of donors without a commensurate decrease in non-A/non-B PTH.

ANIMAL TRANSMISSION STUDIES

The concept that only two viruses, HAV and HBV, were primarily responsible for human hepatitis has become so thoroughly ingrained in our diagnostic thinking that the idea of a third or possibly more viruses has been slow to gain acceptance. Transaminase elevations observed following transfusion which could not be attributed to HAV or HBV have been considered by some to be coincidental or due to some unusual host response rather than to a new transmissible agent. However, there are now several lines of evidence that support the existence of a transmissible agent, presumably a virus, as the cause of non-A/non-B hepatitis. First, non-A/non-B hepatitis occurs ten times more frequently after commercial as compared with volunteer donor blood[3]. This relationship to donor source strongly implies that non-A/non-B hepatitis is related to an infectious agent carried by the donor, rather than to some unusual response in the recipient. More direct evidence comes from the retrospective analysis of sera obtained during human volun-

Table 32-5. Relationship of Donor Transaminase to Recipient Non-A/Non-B Hepatitis

	Hepatitis	No Hepatitis
All donor ALT < 45	6	14
Donor ALT >45	1	6
Total	7	20

ALT = alanine aminotransferase (SGPT).

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teer studies conducted in the early 1950s[25]. As noted above, these studies demonstrate the transmission of icteric non-A/non-B hepatitis by serum obtained from three HBsAg-negative implicated donors. More recently, we have transmitted non-A/non-B hepatitis to five of five chimpanzees inoculated with sera obtained from four patients and one donor participating in the ongoing open-heart surgery study reported herein[31]. Of the five chimpanzees inoculated, three had unequivocal biochemical and histologic evidence of hepatitis with peak ALT values of 265, 212, and 219 I.U./l.. Two additional chimpanzees had only modest elevations of ALT (70 and 62 I.U./l), but even these values were distinctly elevated as compared with multiple baseline determinations and with an uninoculated control. In addition, these animals had mild histologic evidence of hepatitis. Of particular interest was the fact that non-A/non-B hepatitis was transmitted by serum obtained in either the acute or chronic phase of non-A/non-B hepatitis. This provides strong evidence for a chronic carrier state for the non-A/non-B agent. The existence of such a carrier state is essential to account for the large number of non-A/non-B hepatitis cases which derive from seemingly healthy donors. Two other studies,[32,33] which will be described in more detail in other reports in the proceedings of this meeting, have also confirmed transmission of non-A/non-B hepatitis to chimpanzees.

SUMMARY

Non-A/non-B hepatitis: *1.* accounts for approximately 90% of PTH following volunteer donor, RIA-screened blood; *2.* can also occur without prior transfusion; *3.* has a moderately well-defined incubation period, most commonly 5 to 10 weeks; *4.* tends to be acutely mild, but about one-third of cases are icteric with ALT in excess of 800 I.U./l; *5.* frequently progresses to chronic liver disease (CLD), particularly CAH, but may regress with time, (anicteric cases with ALT in excess of 300 I.U./l are at greatest risk of CLD); and *6.* is caused by a transmissible agent which can persist and remain infectious over a prolonged period of time.

ACKNOWLEDGEMENTS

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