International Forum

Vox Sang. 32: 346–363 (1977)

'How Frequent is Posttransfusion Hepatitis after the Introduction of 3rd Generation Donor Screening for Hepatitis B? What is its Probable Nature?'

Harvey J. Alter. There are three aspects to the question broached in this International Forum. First, has the introduction of third generation testing specifically reduced the frequency of type B post-transfusion hepatitis (PTH)? second, has it significantly reduced the overall frequency of PTH? and third, what causes the residual hepatitis which occurs despite third generation tests? I will attempt to answer these questions using data derived primarily from an ongoing series of prospective studies among patients undergoing open-heart surgery at the Clinical Center, National Institutes of Health.

Patients in these studies were tested for hepatitis B surface antigen (HB_sAg), hepatitis B surface antibody, and hepatic enzyme abnormalities every 1–2 weeks during the first 3 months posttransfusion and then monthly for an additional 3 months. Patients who developed elevations of SGPT suggestive of hepatitis were followed more frequently and for longer periods. When other causes of SGPT elevation were reasonably excluded, a diagnosis of hepatitis was made if between 2 and 26 weeks posttransfusion, a patient had an SGPT value greater than 2.5 times the upper limit of normal and, at least 1 week later, a value greater than twice the upper limit of normal.

Since the initiation of these studies in 1965, the most dramatic decrease in PTH occurred in 1970 when we simultaneously excluded all commercial donors and began screening donor blood for HB_sAg prior to transfusion, at first by agar gel diffusion (AGD), and later, by counterelectrophoresis (CEP) [1]. This dual exclusion resulted in an 83% reduction in hepatitis incidence as compared with previous studies utilizing unscreened blood from mixed voluntary and commercial sources. The exclusion of the commercial donor was judged to be more significant in reducing hepatitis than was HB_sAg testing, but both parameters were important.

In a subsequent study [2], we continued to screen donors by CEP but were able to retain donor sera for retrospective testing by solid phase radio immunoassay (RIA, Ausria I). This study, involving 108 patients, clearly showed the efficacy of RIA in preventing type B posttransfusion hepatitis. Of twelve patients who developed hepatitis following open-heart surgery, four were HB_sAg-positive. Retrospective testing revealed an RIA-positive, CEP-negative donor in 3 of these 4 cases, whereas no such RIA-positive blood was administered to the 8 patients who developed non-B hepatitis or to 96 patients who did not develop hepatitis; conversely, all three RIA-positive, CEP-negative units resulted in hepatitis. These data, as well as that accumulated in other laboratories [3], convinced us that RIA was a valuable adjunct to donor screening and had a significant impact on reducing the frequency of type B post-transfusion hepatitis. We were impressed not only by the increased sensitivity of RIA, but also by its inherent objectivity. Interpretive error was a significant cause of false negative results in the CEP technique and remains a problem in such third generation tests as reversed passive hemagglutination.

Based on these data, we instituted pretransfusion HB_sAg screening by RIA in 1973. This study has not been completed, but we have thus far followed 252 patients for at least 4 months following their open-

Table I. Incidence of type B posttransfusion hepatitis as related to the method of HB_sAg donor screening

Study period	Type of donor	Method of donor screening	Type B hepatitis No. cases/ No. studied, %
I	volunteer	AGD/CEP	6/126 (4.8)
II	volunteer	CEP	4/108 (3.7)
III	volunteer	RIA	2/252 (0.8)

heart surgery. Table I depicts the incidence of type B posttransfusion hepatitis in these three consecutive studies and relates this to the HB_sAg test method employed. The three studies are comparable in the type of patient followed, in the number of transfusions given, and in the intensity of posttransfusion follow-up. The observed hepatitis incidence is high because of the large number of transfusions given (average of 17 U/patient) and because of the close prospective follow-up resulting in the detection of many anicteric, asymptomatic cases. As shown in the table, there has been a progressive decrease in type B hepatitis with increasing sensitivity of the test method. The difference in hepatitis frequency between recipients of RIA tested blood (0.8%) and CEP tested blood (3.7%) is not statistically significant, but the difference between RIA tested blood and the combined CEP and AGD/CEP tested blood (4.3%) is significant ($p<0.05$). We believe the failure to demonstrate more impressive statistical differences is related to the relatively small number of patients involved. This is confirmed in a much larger study by *Seeff et al.* [4] in which adoption of the RIA method resulted in a significant decrease in type B PTH as compared with CEP.

Combining available data, there is little doubt that RIA-positive, CEP-negative donors exist and that such donors transmit type B hepatitis. The exclusion of these donors has resulted in a definite decrease in type B hepatitis, and this form of hepatitis is now a relatively rare posttransfusion event. Nonetheless, some type B hepatitis occurs despite RIA testing, and there is need for a still more sensitive detection method.

The impact of RIA testing on type B hepatitis has not been paralleled by a significant reduction in the overall incidence of PTH. This has been true in our studies and in those conducted in the Veterans Administration hospitals [4]. The failure to demonstrate a significant reduction in PTH as a whole is not totally explained, but is due, in large measure, to the fact that the major portion of PTH is caused by an agent(s) other than the hepatitis B virus (see below). Tests for HB_sAg, no matter how sensitive they become, will not prevent hepatitis due to other viral agents.

The same technologic advances which have helped to identify and partially eradicate type B hepatitis have served to define non-B hepatitis. It had originally been assumed that non-B hepatitis was due to the hepatitis A virus, but both epidemiologic [5] and serologic [2, 6] investigations have demonstrated that the type A hepatitis virus is not a significant cause of posttransfusion hepatitis. These same serologic studies have failed to implicate the cytomegalovirus or Epstein-Barr virus as a major cause of non-B PTH. This disease, tentatively termed 'non-A, non-B' hepatitis, currently accounts for 70–90% of PTH [2, 5]. Non-A, non-B hepatitis, is an ill-defined entity diagnosed by the serologic exclusion of other agents known to cause viral hepatitis; there are currently no serologic markers for non-A, non-B hepatitis, no electron microscopic observation of viral particles and no documented transmission to an animal host. Nonetheless, non-A, non-B hepatitis is a repeatedly observed phenomenon and has been the most prevalent form of hepatitis in several prospective studies [2, 4, 5, 7]. While its viral nature has not been proved, the fact that non-A, non-B hepatitis is much more common following commercial rather than volunteer donor blood suggests that it is due to an agent transmitted by the donor rather than a host-related phenomenon. Indeed, it may be due to several different viral agents.

Although non-A, non-B hepatitis is, on the average, less acutely severe than type B hepatitis, it can cause severe acute disease and, more disturbing, it appears to have considerable propensity to progress to chronic hepatitis. The major thrust of posttransfusion hepatitis research must now be directed at developing detection methods for the non-A, non-B agent(s) or developing some reliable method of viral inactivation or removal which would be independent of testing.

References

1 Alter, H. J.; Holland, P. V.; Purcell, R. H., et al.: Post-transfusion hepatitis after exclusion of Com-