Indirect Tests to Detect the Non-A, Non-B Hepatitis Carrier State

Elsewhere in this issue, Stevens and associates (1) have detailed the second major finding of the Transfusion-Transmitted Viruses (TTV) Study, showing a significant correlation between the presence of antibody to the hepatitis B core antigen (anti-HBc) in donors, and the occurrence of non-A, non-B hepatitis in recipients of their blood. Previously, the TTV study had shown a similar correlation between donor alanine aminotransferase (ALT) and recipient hepatitis (2).

The TTV study was a superbly conducted, controlled, prospective study of transfusion-associated hepatitis. The criteria for assessing hepatitis were valid and patient follow-up was excellent. As a result, the data generated for this observation, the one favored by the TTV group is that persons exposed to the hepatitis B virus are also more likely to have been exposed to the non-A, non-B virus and, hence, that a marker for one is indirectly a marker for the other. This assumption would be more tenable if the same association could be shown for antibody to hepatitis B surface antigen (anti-HBs) because anti-HBs is an equally good indicator of past exposure to hepatitis B virus. However, in the TTV study, recipients of only anti-HBs positive blood were not at higher risk for non-A, non-B hepatitis, and in three previous studies (3-5) no significant association between donor anti-HBs and recipient hepatitis was demonstrable. Stevens and associates (1) attribute the lack of association with anti-HBs in previous studies to insensitive tests, the nonspecificity of low-level anti-HBs, and inadequate sample size, but the fact remains that there is an apparent dichotomy between anti-HBs and anti-HBc.

An alternate explanation for the association between anti-HBc and non-A, non-B hepatitis is that the non-A, non-B hepatitis agent may be a variant of the hepatitis B virus as has been previously suggested by molecular hybridization studies (6); the presence of anti-HBc in transmitters of non-A, non-B hepatitis infection would then represent further evidence for the link between the hepatitis B virus and the non-A, non-B hepatitis virus. However, the possibility that non-A, non-B hepatitis and hepatitis B viruses are related remains speculative. By definition, no cases of non-A, non-B hepatitis develop serologic markers for hepatitis B virus during the course of their infection. Further, hepatitis B virus and non-A, non-B hepatitis virus have been repeatedly shown to be immunologically distinct in cross-challenge studies in chimpanzees and in humans with sequential episodes of hepatitis. In addition, well pedigreed inocula from patients with non-A, non-B hepatitis administered to chimpanzees have never been shown to induce serologic markers for hepatitis B virus in either serum or liver. Whatever the reason for the association between donor anti-HBc and recipient non-A, non-B hepatitis,
the fact that such an association exists has been clearly established by both the TTV data and studies in our laboratory (7).

Before consideration of the major issue of whether indirect tests to identify non-A, non-B carriers would be effective in preventing the occurrence of transfusion-associated non-A, non-B hepatitis, two minor issues in this study need to be discussed.

If both the tests for ALT and anti-HBc are indirect indicators of the non-A, non-B hepatitis carrier state, one by detecting subclinical liver disease and the other by indicating the likelihood of virus exposure, then both tests should detect the same non-A, non-B hepatitis carrier population. In fact, the tests do not: Of 121 donors with elevated ALT in the TTV study only 15% were anti-HBc positive, and of 220 donors with anti-HBc only 8.6% had elevated ALT. These tests are identifying two different, seemingly high-risk populations. This dichotomy is disturbing, suggesting either that the tests are not really detecting carriers of non-A, non-B hepatitis and that their apparent association with non-A, non-B hepatitis is a statistical artifact, or that they are detecting two different carrier populations perhaps harboring different agents for non-A, non-B hepatitis. The latter possibility has considerable implications. If both tests detected the same carrier population, then one could select the most practical test for routine donor screening. However, if each test detects a different carrier population for non-A, non-B hepatitis and if, as shown, the predicted efficacy of each is similar, it will be difficult to choose one test in preference to the other. The justification for one test would serve as justification for the other and both would have to be adopted at considerable expense and at a donor loss in excess of 7.5%.

Data are presented in the TTV study that hepatitis cases associated with blood positive for anti-HBc have more severe biochemical abnormalities than cases associated with anti-HBc negative blood. This finding is important. However, it is not the acute severity of non-A, non-B hepatitis that is generally relevant but rather its chronic sequelae; these manifestations are equally likely to follow acutely mild disease as they are to follow biologically severe disease (8).

The key question in this study is test efficacy: How effective would anti-HBc testing of donors be in preventing cases of transfusion-associated hepatitis? Unfortunately, true efficacy cannot be determined from this study or from the previous studies of ALT because none were randomized, controlled trials that compared tested blood with untested blood. Thus, efficacy determinations in these studies are predictions of what might have occurred if blood positive for anti-HBc or with elevated ALT levels had not been transfused. Such predictions require assumptions that may or may not be valid. Depending on the assumptions made, the predicted efficacy can be quite variable. The TTV study analysis provides three different estimates of efficacy for anti-HBc testing ranging from 21.4% to 34.9%, depending on various adjustments for the incidence of hepatitis in recipients of HBV marker-negative blood and the incidence in non-transfused controls.

To derive a predicted efficacy, the TTV analysis imposed two corrections upon the observed incidence of hepatitis. One correction was for the hepatitis rate associated with anti-HBc negative blood and the other correction was for the 3.3% background hepatitis incidence in their untransfused control population. The validity of the latter correction needs to be scrutinized further. In their analysis, the TTV group corrects their hepatitis incidence by multiplying the number of recipients in each study arm by 3.3% and then subtracting this number from the number of observed cases of hepatitis in each group. This correction has a marked influence on their calculated efficacy and a disproportionate influence because there were more recipients in the anti-HBc negative group. There were 69 cases of hepatitis among the 953 recipients of anti-HBc negative blood. The correction factor imposed by the TTV analysis assumes that 31 cases (3.3% of 953) would have occurred even without transfusion and these 31 cases are omitted from their efficacy calculations. A lesser number (6.5) are omitted among recipients of anti-HBc positive blood because there were only 198 recipients in this category. By considerably reducing the total number of cases of hepatitis and by disproportionately reducing the number in the anti-HBc negative group, this correction has a profound effect in raising the calculated efficacy. We are concerned with any adjustment of the data that excludes from analysis 31 cases of hepatitis, or almost half of the cases in one study arm.

The important point is not which calculation of efficacy is correct, but that these calculations deal with predicted efficacy rather than true efficacy. The calculations are attempts to determine, in retrospect, what might have happened if the study had been randomized. Such attempts require data adjustments, which may or may not be valid, and are subject to differing interpretations. Such analyses cannot be equated with a randomized, prospective study that allows for a direct determination of efficacy. These same considerations pertain to data on ALT testing. Although the predicted efficacy of ALT testing of donors is 30%, one study that excluded all donors with elevated ALT and prospectively followed recipients showed no impact of ALT testing when the incidence of transfusion-associated hepatitis was compared with that of historical controls (9).

At the very best, anti-HBc testing of donors may prevent 33% of transfusion-associated hepatitis. It is more likely that actual efficacy will be less and may be as low as 22%. This test is therefore of very low sensitivity. In addition, according to the TTV and National Institutes of Health studies, the test has very low specificity in that 80% of anti-HBc positive donors are not associated with the transmission of viral hepatitis. Lastly, the test will have a major impact on blood delivery because it will result in the loss of at least 5% of the donor population.

We wish to reemphasize that the TTV study is one of the best studies of transfusion-associated hepatitis ever done. We do not question the accuracy of the data gener-
ated, but the interpretation of data and the recommendations based on that interpretation.

There are three options in regard to anti-HBc and ALT testing (9). The first is to decide that existing data are inconclusive, and that in view of problems of nonspecificity, diagnostic uncertainty, responsibility to the donor, test standardization, cost, and donor loss, it is best not to adopt routine donor anti-HBc or ALT testing at this time.

The second option would be to decide that, although the data relating to anti-HBc and ALT efficacy are not definitive, they are scientifically valid and, overall, are sufficiently compelling to warrant universal donor testing at this time. Implicit is the assumption that if an interpretive error is to be made, it is best to err on the side of recipient safety and that to withhold such testing is ethically unjustified.

The third option is that existing data are inconclusive, but are sufficiently compelling that a definitive answer must be sought. Implicit is the assumption that efficacy based on predictions from a nonrandomized study is not the same as efficacy established by a randomized, controlled trial. Also implicit is the concern that the improper assumption of efficacy is not benign and may do considerable disservice to the donor, to the blood delivery complex, and even to the recipient who would then have less blood available at higher cost. Although it may be construed as unethical to withhold a given interventional measure, history has shown that it may be equally unethical to withhold the proper study; a randomized, controlled study should be instituted as rapidly as possible.

It is our opinion that the third option is the most tenable alternative. Had this controlled study been done 3 years ago when first proposed, a definitive answer would be at hand. Instead, the same uncertainties persist. A multicenter, randomized, controlled trial could be completed in 1.5 years, address both the ALT and anti-core issues, and provide a definitive and rational basis for making these complex decisions. Even at this late date, such a study should be done, lest 2 years from now we find ourselves still far from the core (or the ALT) of this issue. (Harvey J. Alter, M.D.; National Institutes of Health, Bethesda, Maryland; and Paul V. Holland, M.D.; Sacramento Medical Foundation, Sacramento, California)

Addendum

While this editorial was in press, the Office of Biologics, Food and Drug Administration (10) reported finding reverse transcriptase activity in the sera of patients with both transfusion-associated and sporadic non-A, non-B hepatitis and not in the sera of appropriate controls. The reverse transcriptase activity, banded at a density of 1.14, is consistent with the hypothesis that the agent of non-A, non-B hepatitis may be a retrovirus. Thus far, viral particles have not been seen in sera that had reverse transcriptase activity nor have retroviruses been isolated in culture. In addition, serial sera from persons infected with non-A, non-B hepatitis have not yet been tested to establish that the appearance of reverse transcriptase activity is coincident with the appearance of clinical, biochemical, or histologic evidence of non-A, non-B infection.

The finding of reverse transcriptase activity in patients with non-A, non-B hepatitis has thus far not been independently confirmed. Nonetheless, the evidence that the agent of non-A, non-B hepatitis may be a retrovirus represents by far the most exciting finding in this field to date. If confirmed, it will dramatically change the direction of research and will hold the potential for eradication of this prevalent form of transfusion-associated infection.

The finding of a specific agent should permit identification of an antigen or antibody for non-A, non-B hepatitis that could be used in assays to detect carriers of the virus. The reverse transcriptase assay will probably not be a practical measure for routine blood bank use. The development of a specific assay would, of course, ultimately negate the need for indirect measures such as the ALT or anti-HBc tests. However, these indirect assays may still be useful as an interim measure because, even if a retrovirus is confirmed as the cause of non-A, non-B hepatitis, a specific, licensed assay would not be available for several years. Whether the agent for non-A, non-B hepatitis is a retrovirus should be answered rapidly as investigators throughout the world apply this initial lead to the study of their own patient populations. If a retrovirus etiology is confirmed, then considerations of ALT or anti-HBc testing will be narrowed to their potential usefulness as an interim screening measure. If the existence of a retrovirus as the cause of non-A, non-B hepatitis is not substantiated, then this possibility will have been an exciting, but inconsequential interlude in the decision to adopt indirect measures for the detection of non-A, non-B hepatitis carriers.

References
