Penrose Inquiry

Surrogate testing for NANB hepatitis

Statement (4) by Professor Juhani Leikola

1. After the testing for hepatitis B surface antigen (HBsAg) turned out to be successful in the early 1970's in eliminating most of the posttransfusion hepatitis B cases, the non-A, non-B hepatitis (NANBH) remained the main problem for safety of transfusion. Two studies in the US, the so called TTV study (Aach RD, Szmuness W, Mosley et al. Serum alanine aminotransferase of donors in relation to the risk of non-A, non-B hepatitis in recipients. The transfusion-transmitted viruses study. N Engl J Med 304:989-994, 1981) and NIH study (Alter HJ, Purcell RH, Holland PV el al. Donor transaminase and recipient hepatitis. Impact on blood transfusion services. JAMA 246:630-634, 1981), raised world-wide interest. They showed an association between elevated donor ALT and NANBH of the recipient. Before a specific assay for hepatitis C virus antibodies was developed and published in April 1989, there was a vivid discussion in different parts of the world whether or not to start routine ALT testing, and later also anti-hepatitis B core (anti-HBc) testing as surrogate markers for the then unknown hepatitis agent. After the anti-HCV became commercially available in early 1990 the question of introduction of surrogate marker testing became obsolete.

2. When there is a recognized risk for disease transmission through transfusion, and when the infective agent is not known, the only means of reducing the risk are selection of donors and judicious use of products. If clear risk factors are identified for the given infection, the donors with those risk factors can be asked to refrain from donation as was the case with AIDS. This policy is likely to be more effective with voluntary unpaid donors in general population than with paid donors. The second possibility is to use laboratory tests (surrogate tests) that could identify donors with risk factors.

3. The use of surrogate markers to reduce posttransfusion infections has been a controversial issue. If a surrogate marker identifies only a small proportion of infective donors, it is unlikely to affect the infection incidence in the recipients, and hence is ineffective as a public health policy. Furthermore, if the surrogate marker is positive in a large proportion of the donor population, it is mostly identifying wrong people. This has two consequences: It may seriously reduce the number of eligible blood donors, and the donors found to be positive need to have a plausible explanation so that the test results should not raise unwarranted anxiety in the donor. A voluntary unpaid donation system underlines the obligation for the transfusion service to arrange for an appropriate counselling system.

4. Different countries with different cultural backgrounds and different history of transfusion-transmitted infections perceive transfusion safety differently. This, combined with the fact that the infection incidence varies in different populations, usually means that a careful study has to be made in a given population and in a given society before introduction of a new test, especially of an unspecific surrogate test. Much depends also on the prevalence of the marker and on the incidence of the infection.

5. A third factor has to be taken into account. Once a test has been introduced to routine screening, it is psychologically and politically difficult to stop even if a specific test would have made it obsolete. To my knowledge, ALT testing for surrogate purposes was not started anywhere after the specific

test for HCV became available.

6. Hepatitis was a well-known transfusion complication before any of the hepatitis viruses were known. In Germany, in April 1965 at a Congress of Hospital Hygiene it was suggested that blood donors should be tested for liver enzymes to prevent transfusion-transmitted hepatitis. In the same month, the German Society of Surgery recommended the same measure. The German Society of Blood Transfusion first considered such mandatory testing of all donors be premature, especially in the light of losing many regular donors, but yielded the following year to the growing pressure. A general ALT testing was started in Germany in 1966. Many blood banks in Italy had introduced ALT testing already in 1960.

7. The example was not followed in other countries. Japan started ALT testing of donors in 1975, but this was part of the "Biochemical Testing Service" package offered to Japanese donors in order to enhance the recruitment process.

8. The German transfusion doctors remained sceptical about the efficacy of the ALT screening. Professor Siegfried Seidl, the then leading German expert in the field of blood transfusion, wrote to Deutsche Medizinische Wochenschrift in January 1983 and reviewed the American TTV and NIH studies. He mentioned that the ALT screening had not decreased the incidence of NANBH in the Federal Republic of Germany. He concluded that there were still too many open questions to be solved before routine donor ALT screening could be recommended. Instead, the efforts should be directed towards finding a specific marker for NANBH.

9. The TTV and NIH studies had in 1981 shown a correlation between donor ALT and recipient NANBH, even though this finding was not confirmed in all donor populations. The American Association of Blood Banks established an ad hoc committee on ALT testing. The committee concluded in 1982 that "while we share the desire of the entire medical community to reduce the incidence of transfusion-associated hepatitis, we believe that the currently available evidence does not justify either universal testing of donor blood for ALT or the rejection of donors who have elevated levels". Still in 1985, four years after the two important studies on donor ALT had appeared, Dr. Harvey J. Alter, the leading transfusion-transmitted hepatitis expert in the US wrote: "The question of whether of not the ALT test should be routinely adopted for donor screening was widely debated and currently remains an essentially unresolved issue". In the same article he mentions that the New York Blood Center had initiated such testing but that they did not accumulate additional efficacy data. Dr. Alter had also started ALT testing of donors at the NIH blood bank in order to obtain more information, but "there was no significant decline in hepatitis incidence after ALT testing. This is even more striking since transfusion volume declined over this time period". The same sceptical view on routine ALT testing was presented in a review article of Transfusion which appeared in April 1985.

10. In 1986 the American opinion changed. In the re-examination of the old TTV study data the authors had found out that there was also a correlation between donor anti-HBc and recipient NANBH, but ALT and anti-HBc identified different donor groups. It is interesting that Dr. Alter in his article of 1985 was already aware of this fact but that his conclusion is different: "One would then have to predict that if both ALT anti-HBc testing were instituted, we might expect an approximate 60% reduction in PTH. It is highly unlikely that such would be the case and I think it points out the fallacy of this type of predictive reasoning".

11. Later in 1986 the major American blood transfusion service organizations recommended routine ALT and anti-HBc testing of all donations. It is notable that this was never required by the US health authorities. However, the usefulness of this testing remained controversial.

12. From a European perspective it was difficult to determine the reasons underlying the change in American thinking. At the meeting of the Council of Europe Expert Committee in May 1987 the consensus of opinion was that the American decision had been influenced by non-scientific reasons. It appeared that, in the litigation-prone atmosphere of the United States the professional organisations decided that objective, scientific reasoning was not enough, but to protect the transfusion community from further financial or legal consequences it was better to start routine surrogate testing despite the fact that the efficacy of such testing was unproven and was based, in Dr. Alter's words, on fallacious predictive reasoning.

13. The American development was keenly followed also in Europe. In the early 1980's the conclusion by the AABB ad hoc committee was considered reasonable, and there was no move in Europe to introduce surrogate testing. It was recognized that the incidence of NANBH varied from country to country and in different donor populations. In northern parts of Europe there were less cases of NANBH than in the south, and there were also differences between urban and rural populations. Australia was considered to belong to the lowest prevalence countries, similar to Northern Europe and dissimilar to the United States.

14. There was a general feeling that more information was needed of the possible correlation between screening for surrogate markers and prevention of NANBH. The journal Vox Sanguinis published in 1983 nine short articles with the title "Based on your analysis of the benefits and costs of routine donor screening for ALT-GPT to reduce the incidence of post-transfusion non-A, non-B hepatitis in your blood services region, what action would you recommend on this matter?" (International Forum. Vox Sang 44:48-64, 1983). All contributors took a cautious view on ALT screening. Even Dr. Aach, the principal investigator of the TTV study, admitted that the cost-benefit ratio of surrogate testing could not be assessed at the time, and that a decision should be made to either perform a properly designed randomized study or to set a "target date for routine ALT testing for those donor populations in which an association with the NANBH PTH has been identified".

15. The American finding that anti-HBc correlated with NANBH was disturbing and could not be explained. Correlation with ALT was much more natural since the definition of NANBH was based on elevated ALT values, and there the question was about the efficacy of the test in identifying donors at risk of transmission of hepatitis. There were soon reports appearing, notably from France, the Netherlands and the United Kingdom showing that in the European donor populations studied anti-HBc did not correlate with recipient NANBH. The pattern was clearly different from the American donors: Incidence of NANBH much less and anti-HBc meaningless as surrogate marker. There was some association between elevated donor ALT and recipient NANBH, but its efficacy as a possible surrogate screening test was considered weak. This view was supported by the negative findings of NANBH incidence after that ALT screening in Germany on one hand and in the New York Blood Center and at the NIH on the other.

16. After the American organizations decided to recommend the introduction of routine ALT and anti-HBc testing it was necessary to decide also in European countries whether or not to follow the suit.

There was a consensus among the scientific and blood transfusion expert community that prospective studies were urgently needed before a decision could be taken. This is clearly reflected in the minutes and other documents of the Council of Europe Committee of Experts meeting in May 1987.

17. It was not only a question of whether or not to introduce surrogate testing but also which tests should be used. There were reports from Japan indicating that the enzyme guanase would be a better indicator of liver damage, and other markers such as carcinoembyogenic antigen and serum bile acids had been suggested as better tests than ALT. The main goal for the European countries was to find out the true incidence of transfusion-transmitted NANBH. Ideally, in these trials the donors and recipients should also be tested for other candidate markers to signify the possibility for the presence of the transmissible agent of NANBH.

18. Most countries that I know elected in 1987 not to blindly follow what the Americans did but to first find out the situation in their own donor population. Thus, the attitude towards surrogate testing was not negative per se, but before making a decision in Europe the expert community wanted to know whether the concept would really produce results. A different matter was the ALT testing that was started by some plasma fractionators (e.g. in Sweden, Switzerland and later also Finland) because it was needed for product export.

19. The first news of a probable causative virus of NANBH, the hepatitis C virus, was published in May 1988 in the prestigious journal Nature. Thereafter it was quite natural that the decisions concerning commencement of routine surrogate testing with doubtful efficacy should be postponed until a specific test was available.

20. In Europe, France was one of the few countries which decided to go for surrogate testing any way. ALT testing became mandatory in April 1988. In the aftermath of the "tainted blood affair" (HIV contaminated blood) the decision is understandable. It was not motivated by the scientific knowledge but by the political necessity. Something had to be done, whether or not it truly reduced the risk of NANBH transmission by blood. Northern countries with low NANBH incidence such as the Netherlands, Denmark, Norway, Sweden and Finland decided not to introduce surrogate testing before more was known of the efficacy in the respective donor populations. There were many articles published by UK authors in the Lancet and in Vox Sanguinis advising against a hasty introduction of surrogate testing (Anderson CC, Contreras M, Barbara JAJ et al. Surrogate testing for non-A, non-B hepatitis. Lacet i:912, 1987. Dow BC, Mitchell R, Follett EAC. Non-A, non-B hepatitis surrogate testing of blood donations. Lancet i:1366, 1987. Gillon J, Hussey AJ, Howe SP et al. Post-transfusion non-A, non-B hepatitis: Significance of raised ALT and anti-HBc in blood donors. Vox Sang 54:148-153, 1988). These opinions in the prestigious medical journals were not without influence in the international community.

21. We decided in 1979 at the Finnish Red Cross Blood Transfusion Service to undertake a prospective study to determine the prevalence of post-transfusion hepatitis (PTH) in Finland (Lagestedt A, Leikola J, Merikallio E et al. Post-transfusion non-A, non-B hepatitis in Finland: a prospective study. Scand J Clin Lab Invest 42:567-570, 1982). The study was carried out in 1980-1981. It was a relatively small study involving 65 patients and 652 transfusions. Three cases of NANBH were found. The main conclusion was that NANBH was, indeed, present also in Finland but its incidence was lower than e.g. in the United States. In one of the implicated donors there was elevation of ALT

in one sample, but this finding did not warrant surrogate testing. In the discussion part of the article it was concluded, that "elevated ALAT [ALT] in blood donor samples are often associated with NANB hepatitis in the recipients, and screening of all blood donors for transaminase levels has been taken into consideration. – However, the magnitude of the problem varies in different parts of the world, and it seems that, in this respect, blood transfusion is safer in Finland than in many other countries, even with an all voluntary, non-remunerated blood donor programme".

22. The decision in the USA in 1986 prompted a new discussion on the value of surrogate testing also in Finland. Since in Finland, as in other countries, the AIDS risk had resulted in new donor selection criteria in 1983-84, which influenced also the incidence of PTH, it was decided in 1987 to undertake a new study "to determine the current incidence and types of post-transfusion hepatitis among open-heart surgery patients from all parts of Finland. The second objective was to obtain donor samples for future evaluation of possible preventive strategies" (Ebeling F, Naukkarinen R, Hanhela J et al. Post-transfusion hepatitis after open-heart surgery in Finland - a prospective study. Transfusion Medicine 1:103-108, 1991). This policy decision was also reported at the meeting of the Council of Europe expert committee in May 1987. The study was commenced in the beginning of December 1987 and lasted for one year. It involved all the five Finnish university hospitals. There were 685 patients and transfusion of 8,436 units of blood products. Several candidate markers for surrogate testing were also investigated (Ebeling F. Alanine aminotransferase, gamma-glutamystransferase, antibodies to hepatitis B core antigen and antibodies to hepatitis C virus in blood donor screening. Vox Sang. 60:219-224, 1991).

23. Preliminary evaluation of our study had indicated that there could be some correlation between elevated ALT values in the donors and PTH in the recipients, but the correlation was weak. There was no correlation between anti-HBc and PTH. The conclusion was: "Based on this material, ALT does not seem to be a useful test in the primary screening of blood donors. In secondary screening of anti-HCV-ELISA-positive donors raised ALT seems, however, to be associated with chronic viraemia and infectivity" (Ebeling, F: Post-transfusion hepatitis in Finland. Academic dissertation, Finnish Red Cross Blood Transfusion Service, Helsinki 1991).

24. After the introduction of routine screening of anti-HCV in 1990, additional surrogate screening was not seriously considered any more. Later experience has confirmed that surrogate testing after starting anti-HCV testing does not bring about any additional value.

25. Comments on specific questions.

On the basis what was known at the time, was it reasonable for the UK not to introduce surrogate testing of blood donors for NANBH?

It was known at the time that the surprising American finding of anti-HBc as surrogate marker for NANBH could not be validated in some other populations in the US as well as in most European populations. Therefore, introduction of anti-HBc to donor screening would have been improbable. ALT as surrogate marker is more logical. However, it is not an on-off test but there is a linear scale. At the time it was used in some countries, not because of scientific basis and logical reasoning but because of public pressure. I believe it was reasonable for the UK not to introduce surrogate testing for NANBH.

On the basis of what is known now (including, in particular, that when screening for HCV was introduced in September 1991, ALT levels above upper limit of normal were found in 59% of donors in Scotland infected with HCV), should surrogate testing have been introduced in the UK and, if so, when?

Crawford et al. (SNB.008.2088) found that of the donors with positive anti-HCV test a majority had elevated ALT values. This finding does not say much about the possible usefulness of ALT screening of all donors, since anti-HCV negative donors were not included and thus, we do not know how many donors in general would have had elevated ALT value at the time of donation. I believe still now that not introducing ALT screening as surrogate test in the UK for NANBH was correct.

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