ALANINE AMINO-TRANSFERASE (ALT) AND HEPATITIS B-CORE (ANTI-HBc) SCREENING OF BLOOD DONATIONS

INTRODUCTION

Recent proposals by the American Association of Blood Banks (AABB) and the American Red Cross concerning the introduction of ALT and anti-HBc screening of blood donations as a means of reducing the incidence of transfusion associated non-A, non-B (NANB) hepatitis have brought attention to the consideration of implementing such a policy in the U.K.

The purpose of this paper is to summarize the investigations which have led to the proposals from the U.S.A. blood collection agencies and to use the paper as a discussion document for recommendations to the D.H.S.S. with respect to the possible introduction of such tests in the U.K.

INCIDENCE OF TRANSFUSION ASSOCIATED NANB HEPATITIS

Several hepatotropic viruses have specific markers, i.e. hepatitis A and B, EB virus and cytomegalovirus. After the exclusion of these causes of hepatitis, and those drugs which may affect liver function, there remains a group of patients who develop transfusion associated hepatitis and these have been attributed to NANB agents. It is thought that there may be at least two distinct infectious agents and that these are almost certainly of virus origin. Despite considerable investigation a specific marker test for NANB hepatitis has not been found.

Clinically, transfusion associated NANB hepatitis runs a milder acute course than hepatitis B and many patients are anicteric; currently it is diagnosed by at least two consecutive two fold elevations of ALT levels occurring in patients with or without jaundice during a time interval of 2 to 26 weeks after transfusion (1). Exclusion of specific markers for other types of hepatitis, drugs and underlying clinical disease are implicit in making the diagnosis.

The incidence of transfusion associated hepatitis in the U.S.A. has been stated as 5.4% to 27.1% (2, quoted by Deloris et al (3)) and of these cases it is estimated that greater than 90% are due to NANB (4). From this it may be deduced that of the three million blood recipients, 150,000 may develop NANB hepatitis. Although the disease is mild there is a tendency towards chronic liver damage and it has been estimated that there may be as many as 7500 cases of cirrhosis induced per year by transfusion (3).

The incidence of transfusion associated NANB hepatitis varies widely from Country to Country. It has been reported to be 13.8% in Italy, 18.9% in Sweden, 30.4% in Japan and 3.4% in the Netherlands (quoted by Collins et al (5)).

It is more difficult to estimate the incidence of transfusion associated NANB hepatitis in the U.K. In the MRC study (5), 768 patients were prospectively studied between 1969 and 1971. Eight patients were judged to have developed icteric or anicteric jaundice, four of whom remained HBsAg negative (0.5%). In addition 35 patients had significant or sustained rises of ALT although in 19 a possible cause for this was put forward (HB, CMV, EBV). Thus, it is possible that the remaining 16 (2%) may have suffered NANB hepatitis, giving an overall incidence of 2.5%. This figure agrees well with the conclusions of Collins et al (6) who found an incidence of 3.2% presumed NANB hepatitis in a prospective study of 248 patients undergoing cardiac surgery who received an average of just over six units of blood each.

From this data, the incidence of NANB hepatitis in the U.K. could be half that of the lowest estimate for the U.S.A.

ALT SCREENING

The first indication that a relationship existed between raised ALT in blood donors and the risk of transmitting NANB hepatitis was reported in the Transfusion Transmitted Viruses Study (TTV) (7). The study comprised a prospective investigation of 1513 recipients of 5564 units of blood. In approximately 40% of the cases of NANB hepatitis asociated with the transfusions there was an association with an ALT value over 45 iu/l which corresponded to the upper 3% of the distribution. If a correction is made for the substitution of units with ALT values less than 45 iu/l with respect to the NANB hepatitis risk, it could be calculated that one might expect a 31% decrease in the incidence of NANB hepatitis in recipients receiving more than one donation of blood if blood with ALT values less than 45 iu/l were used.

These findings were confirmed in a second study by Alter et al (8) in which 283 transfused cardiac surgery patients were followed; 12.7% developed hepatitis of which 97% was assessed to be NANB. Using an ALT exclusion value of 53 iu/l (2.25 standard deviations of the mean log of the donor population) it was estimated that 29% of transfusion associated NANB could be prevented with a loss of 1.6% donor units. In a more extensive study by the same group of workers (3) a correlation was again found between ALT values and the incidence of transfusion associated NANB hepatitis ($p = \sim 0.01$).

I am not aware of any study in the U.K. which links ALT levels in donors to the development of NANB hepatitis in recipients. However, screening of donor bloods for ALT has been carried out in various countries and the results are reported below.

(a) **Mijovic V, Patapion H and Barbara J.A.J. (1982)**

Study carried out in 1973

1004 donors in North London
Mean ALT (35°) 16.5 iu/l S.D. 8.4
(Male donors had a wider spread of ALT values than females and were more likely to have elevated ALT values).

At cut-off value	35 iu/l	3.1% donations lost
	40 iu/l	1.8% donations lost
	45 iu/l	0.9% donations lost
	50 iu/l	0.7% donations lost

It is not possible to accurately determine 2.25 x SD log values from the data available but I calculate that it will be in the region of 47.5. Therefore, the donation rejection rate will be in the order of 0.7-0.9%.

(b) Dow B.C., (1986)

5464 donors in West of Scotland
No. 2.25 x SD log values over log mean: 41 (0.75%)
(484 donors had a history of previous jaundice and 6 (1.2%) were above 2.25 x SD over log mean).

ANTI-HBc

There have been suggestions for several years that anti-HBc might act as a non-specific marker for NANB hepatitis transmission (9). However, the definitive study has been recently performed by Deloris et al (3), in which the relationship between the presence of anti-HBc in 6293 donors and the development of transfusion associated hepatitis in 481 recipients between 1973 and 1980.

Their results can be summarized as follows:

1. Of 193 recipients receiving at least one unit of blood positive for anti-HBc, 23 (11.9%) developed NANB hepatitis compared with 12 (4.2%) of 288 recipients of only anti-HBc negative blood ($p < 0.001$).

2. There was no statistically significant difference in the incidence of hepatitis B or serological markers for hepatitis B among recipients having anti-HBc positive or negative blood.

3. Within the anti-HBc categories the presence or absence of anti-HBs was not significantly associated with transfusion associated hepatitis.

4. Eighty-eight per cent of recipients of blood positive for anti-HBc did not develop NANB hepatitis; the predictive value of the test is, therefore, 11.9%.

5. A dose response relationship is unlikely.

6. There was a lack of association between donor ALT levels and anti-HBc status. The two tests appeared, therefore, discriminating to unrelated donor populations and the two non-specific markers appeared to act as independent variables.

7. The receipt of anti-HBc positive blood did not correlate with the biochemical severity or persistence of the hepatitis.

8. Both ALT and anti-HBc have a high level of false positivity; 70-88% of recipients of blood with high ALT levels or anti-HBc positive do not develop NANB hepatitis.

9. The incidence of anti-HBc in the donor population studied was 103/2549 (4%). In other studies this has been as high as 8% (7,8).

10. It was estimated that approximately 40% of transfusion associated NANB hepatitis could be prevented by routine screening of donations for ALT and anti-HBc.

No comparable study to the above has been carried out in the U.K. Some screening has taken place for anti-HBc ~~has taken place~~ in two RTC's in England and one in Scotland.

At the Bristol RTC the incidence of anti-HBc in donors in a limited study in the mid 1970's was 0.5% (Fraser, personal communication). A series of 1853 British born new blood donors attending the Edgware RTC who had not lived or worked in Countries where HBV infection was common and who were HBsAg negative were tested for anti-HBV markers; 25 (1.4%) were anti-HBc positive (10). Of these, 18 were positive for anti-HBs and/or anti-HBc. In a second similar series at the same RTC carried out in 1983/4 an incidence of 0.82% was found. (Howell and Barbara, personal communication). Of 395 donors from the general public in the West of Scotland, 4 were found to be anti-HBc positive (1%), three

small number.

of whom were also positive for anti-HBs. This compared with an incidence of 6% in a prison population (11).

In 1985 the Manchester R.T.C. carried out anti-HBc tests on 6163 random donor samples and found 27 positive for anti-HBc only and 7 positive for anti-HBc and anti-HBs (0.6%).

MATTERS FOR CONSIDERATION

1. **Incidence of Transfusion Associated NANB Hepatitis in the U.K.**

   The best estimate of incidence from published data is 3%. If one assumes that the 2.3 million donations in the U.K. are transfused to 750,000 recipients annually, (possibly a more accurate assessment should and could be made), then one would expect 22,500 icteric or anicteric cases of NANB hepatitis each year. If the morbidity pattern of the disease is similar to that in the U.S.A. then one might expect half of these patients to have chronic ALT elevation and 10%, i.e. 2250, to develop cirhosis.

2. **Projected value of ALT and anti-HBc screening in prevention of transfusion associated NANB Hepatitis**

   If 30-40% of NANB hepatitis could be prevented by the use of the above tests, then the reduction in the number of cases would be 6750-900 per year and by extrapolations; 675-900 cases of cirhosis.

   Some qualifications should be made to (1) and (2) above.

   (a) The course of the chronic disease in NANB hepatitis is mild and, therefore, many cases probably remain undiagnosed even when cirrhotic changes occur. This, I feel certain is why we have not been aware of what appear to be quite serious statistics. Of course, one must also bear in mind that approximately 50% of patients die of their primary disease within one year of transfusion, and this presumably applies in the U.S.A.

   (b) The incidence of NANB hepatitis has been determined in the U.S.A. often with multiply transfused patients and in the TTV there was clearly dose relationship. Even in the two U.K. studies the patients in the second one (6) received an average of 6.28 units each.

   (c) The data from the U.S.A. is from transfusions administered in the 1970's and early 1980's and even the more recent studies in the U.K. were undertaken before attempts to encourage self-selection of donors.

   (d) One must question, therefore, whether the incidence of transfusion associated NANB hepatitis is as high now as the estimates suggest.

3. **Effect of ALT and Anti-HBc Screening on Blood Collection**

   From the evidence available in the U.K. one might expect that ALT screening will cause the loss of 0.7-0.9% of donations and anti-HBc in the order of 1%.

   Presumably there will be some overlap in the ALT and anti-HBc results but one might expect a loss of donations of approximately 1.5-1.75%.

Again, some qualifications need to be made:

(a) The data is largely from the time period before self-exclusion of donors for HIV infection and it is important to determine in a new study, perefably carried out in three Centres in England - Bristol,

Edgware and Manchester have been suggested, by the routine screening of 3000-4000 donations in each Centre how many donations are rejected. Preferably, also one Centre in Scotland should join the study.

All Centres should work to a common protocol and analysis of the results should yield information from which a prediction of loss of donations throughout at least England and Wales, can be estimated.

(b) The method for ALT estimation must be clearly defined and the means of determining the lower cut-off determined. (Note the AABB and the American Red Cross recommend the lower cut-off to be determined as:

antilog (log mean + (2.25 x SD log values).

Other topics for discussion:

(1) The cost of implementing ALT and anti-HBc screening

(2) The effect of screened donations in lessening the occurrence of NANB hepatitis from fractionated products derived from pooled plasma.

(3) If routine screening was introduced how would donors be managed?

H.H. GUNSON
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ADDENDUM

Since this report was prepared the following data has been received:

ALT Testing:

1. North London RTC

ALT levels in 319 plasmapheresis donors

			%
ALT normal		233	73
ALT raised	10%	60	18
ALT raised	50% occasions	12	3.8
ALT raised	100% occasions	14	4.2

ALT levels of the 86 donors above:

31-35 iu/l	22
36-40	20
41-45	6
46-50	12
51-55	2
46-50	2
51-55	1
56-60	3
61-65	7
66-70	4
-71	7

Upper limit of normal - 30 iu/l

2. Manchester RTC

ALT levels on 535 plasmapheresis donors

ALT normal	496	
ALT raised	39	(7.2%)

Upper limit of normal - 40 iu/l

3. North London RTC

1986 ALT testing on 2023 random donors

Conclusions:
(i) there is a skewed distribution with a long tail
(ii) there would appear to be a need for a lower cut-off for females compared with males
(iii) taking the U.S. cut-off of 45 iu/ml (for both females and males), 65 males and 8 females were above this level, i.e. 73 out of 2023 (3.6%).

30 randomly selected donations with raised ALT levels were screened for anti-HBc - 2 were positive.

4. South London RTC

1985-1986 ALT testing on 1257 plasmapheresis donors

ALT normal (i.e. 50 iu/l)	1213	
ALT raised	44	(3.6%)

These figures indicate that there would be a high rate of rejection of donations than indicates by the U.K. data given on page 2 of the report.

Anti-HBc Screening

North London RTC (March 1985)

6000 unselected donors:

first time donors anti-HBc positive	-	9 out of 1200	(0.75%)
established donors anti-HBc positive	-	27 out of 4800	(0.6%)
	Total	36 out of 6000	(0.6%)

These figures are identical to those found at the Manchester RTC (page 4 of the report).

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