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2nd November, 1987.

Dr. W. D. Forbes,
Chief Scientist Office,
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EDINBURGH,
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Dear Bill,

You asked me to write to you with more details about my assessment of the grant application relating to Alanine Aminotransferase and hepatitis B core antibody; screening of blood donations in a multicentre study.

I have had some opportunity to consider this study further and feel that although my original critical comments can still be justified, I am somewhat uncertain whether all the data necessary to make a really thorough appraisal of the scientific merits of the application is available to us. In a sense this is an academic point because any such deficiency will also certainly relate to the authors of the application.

It seems to me that the principal objective of this study (namely to determine the distribution of ALT levels in the donor population and determine whether the presence of an abnormal ALT is significant as a risk indicator of future hepatitis in recipients) cannot be achieved with the present study design. In this I agree with the comments of your other external referee - (C du V F); the principal reason being that they do not propose to follow-up and examine the recipients of the donated blood and determine the attack rates for different levels of ALT (and/or the presence of anti-HBc).

However, my main comments related to the difficulty of confirming their assertions that in general there would be a reduction in non-A non-B hepatitis of 31% if donors with an ALT value of greater than 45 IU/1 were screened out. First, I confirm their reporting of the assertions by Alter et al that a reduction of 29% could be achieved by screening. However I could not find a reference to the figure of 31%, although the paper by Aach et al comments that "the observations in this report suggest that about 40% of the cases of post-transfusion hepatitis could have been prevented by discarding units with an ALT level in the upper 3% of the distribution, i.e. greater than 45 IU/1".

When I first read the papers, I formed the opinion that they had confused the total amount of risk attached to high ALT values with the attack rate in these sub-groups; I think I was wrong in making this assertion although not absolutely sure. Secondly, it seemed possible that they had simply examined the proportion of cases contributed by donors with high ALT levels on the basis of the total number of cases occurring in the recipients. Again this seems possible, though I would certainly give them the benefit of the doubt. I turned again to the problem of trying to identify exactly how the comments made by Aach et al might have been formulated. I examined the three tables on page 991 of their paper. First turning to Table 2, this shows the relation between the highest ALT level of the donors contributing to a recipient's transfusion. As can be seen, the average number of units transfused for each recipient was 4. Refer to my Figure 1 for relevent observations which might be derived from this Table. On the basis of the observed prevalence of ALT greater than 45 IU/1 in this population (10.5%), the relative risk of hepatitis is 5.3 and the population attributable risk (or "preventable fraction") is 31%.

It seems, therefore, that the applicants may be correct in making this assertion although the authors of the original paper do not appear to have done so. The latter may be referring to the proportion of cases which are "contributed" by high ALT levels, which I made to be 38.5%. However, as I said in the Committee, this is an unsatisfactory index of the preventable fraction of hepatitis because it is dependent first on the observed prevalence of high ALT levels (which they were going to measure in the British population but not associate it with hepatitis in the recipients - a crucial step in establishing causality and opportunities for prevention). Secondly, it is crucially dependent on the fact that these recipients received around 4 units of blood. In such a population it seems to me that the high risk donations are concentrated in relatively few patients. I wonder if the assessment of the value of screening in prevention of hepatitis should not be based, at least in part, on the preventable fraction which accrues when we examine recipients of single units. This data is in fact provided in Table 3 (my Figure 2). Although the numbers here are much smaller and therefore the precision of the estimates weaker, the preventable fraction is estimated at only 23%. The majority of cases of transfusion hepatitis are related to lower risk donors. If existing donations were spread more widely and associated with smaller transfusions (which seems at least possible through changes in clinical practice) then it seems that the preventable fraction will be much less than estimated from the overall current figures.

There may be other ways of examining the data available form these publications, though they are not entirely clear to me. I applied the same 2 x 2 table mathematics to Table 1 of the paper by Aach et al, making the tacit assumption that the hepatitis was a characteristic of the donors rather than the recipients. I am sure that there are all kinds of objections which could be raised to this approach, but I think it may have some validity. It is somewhat closer to the notion of trying to estimate what the preventable fraction would be if the donations were spread more widely than is currently standard clinical practice. My Figure 3 provides the relevant data. It suggests that the preventable fraction is around 8.3%. It is interesting in any case to note that from this Table the proportion of cases of hepatitis "contributed" by the high ALT donors is only 11%.

I made a similar but less thorough examination of the data from Alter et al and my Figures 4 and 5 present some of this. Figure 4 is perhaps the most useful, in which the preventable fraction appears to be about 28%, close to the figure of 29% quoted by the authors. The interesting feature of this study is the apparently much higher average number of units transfused in all the ALT level bands. The prevalence of a "raised ALT" in this paper is much lower than in the other study because of the higher cut-off point. It is difficult to be certain about this (because the data are not published in sufficient detail) but I suspect that the overall prevalence of high levels of ALT is considerably lower in this population. The so-called high ALT donors only contributed 56 cases altogether in a total population of 3,359. Calculating a preventable fraction in this group (that is using the whole donor population and the numbers associated with hepatitis in the recipients) gives a preventable fraction of only 1.8%.

In conclusion, I feel I may have been a little hard on this paper in Committee, but not much. I am left with a feeling that the authors may not fully understand the nature of the research approach which is needed to identify the benefits of screening in terms of the proportion of cases which will be prevented. At best it seems it would be difficult for them to have made a proposal about this in any detail by using the published data. I think one might get a little closer to this by doing more work on the published data but suspect that the output to input ratio would not be worth the time and effort. Furthermore, if as seems likely, the risk in British donors, in terms of ALT levels and other indicators, turns out to be lower than in the American population then the preventable fraction which accrues from screening will also predictably be lower. Whatever the details of the final outcome it is probably fair to say that only a minority of cases will be prevented by this approach. The risk factors may of course be very different in a British population.

I am sorry it has taken so long to come back to you on this; if you think I can be of any further help please let me know.

Kindest Regards

Yours sincerely,

(A. J. Hedley)

Encs.

Figure 1:

ALT and Hepatitis in 1513 Recipients
Aach et al 1982

ALT of Donor	Recipients with Hepatitis +	-	
⩾ 45	60	100	160
⩽ 45	96	1257	1353
	156	1357	1513

Relevant observations

1 Overall attack rate = 156/1513 = 10.3%

2 Proportion of cases "contributed" by ALT ⩾ 45 = 60/156 = 38.5%

3 Prevalence of ALT ⩾ 45 in this study = 160/1513 = 10.5%

4 Relative risk of hepatitis associated with ALT ⩾ 45

$$= \frac{60/160}{96/1353} = \frac{.375}{.071} = 5.28\%$$

5 Population attributable risk of ALT ⩾ 45

$$= \frac{.105(4.28)}{1 + .105(4.28)} = \frac{.4494}{1.4494} = 31\%$$

Figure 2:

ALT levels and Hepatitis in Recipients of Single Units

	Hep	No Hep	
≥ 45	5	7	12
< 45	14	249	263
	19	256	275

Relevant observations

1 Overall attack rate = 19/275 = 6.9%

2 Proportion of cases "contributed" by ALT ≥ 45 = 5/19 = 26.3%

3 Prevalence of ALT ≥ 45 in this study = 12/275 = 4.4%

4 Relative risk of hepatitis = $\frac{5/12}{14/263} = \frac{.42}{.053} = 7.86\%$

5 Population attributable risk (preventable fraction) = $\frac{.044(6.86)}{1 + .044(6.86)} = \frac{0.302}{1.302} = 23\%$

Figure 3:

ALT levels and donors associated with hepatitis

	Donors associated with hepatitis +	-	
≥ 45	71	101	172
< 45	567	4825	5392
Total	638	4926	5564

Relevant observations

1 Overall attack rate = 638/5564 = 11.4%

2 Proportion of cases "Contributed" by ALT ≥ 45 = 71/638 = 11.1%

3 Prevalence of ALT ≥ 45 = 172/5564 = 3.09%

4 Relative risk of hepatitis $= \frac{71/172}{567/5392} = \frac{.412}{.105} = 3.92\%$

5 Population attributable risk (preventable fraction) $= \frac{.309(2.92)}{1 + .309(2.92)} = \frac{.0902}{1.0902} = 8.3\%$

Figure 4:

ALT and Hepatitis in Recipients
From Alter et al 1981

	Hepatitis +	Hepatitis -	
ALT +	15	37	52
Cut-off 53 -	21	210	231
	36	247	283

Relevant observations

1 Overall attack rate = 36/283 = 12.7%

2 Proportion of cases "contributed" by ALT ⩾ 53 I.U = 15/36 = 42%

3 Prevalence of ALT ⩾ 53 in this study = 52/283 = 18.3%

4 Relative risk of hepatitis associated with ALT ⩾ 53

$$= \frac{15/52}{21/231} = \frac{.288}{.091} = 3.169\%$$

5 Population attributable risk, in this population

$$= \frac{.183(2.169)}{1 + .183(2.169)} = \frac{.3967}{1.3967} = 28.4\%$$

Figure 5:

ALT and Hepatitis Associated with Donors
Alter et al 1981

		Hepatitis Associated +	-	
ALT > 53	+	16	40	56
	-	439	2864	3303
Total		455	2904	3359

Relevant observations

1 Overall attack rate = 455/3359 = 13.5%

2 Proportion of cases "contributed" by ALT ⩾ 53 = 16/455 = 3.5%

3 Prevalence of ALT ⩾ 53 in this study. = 56/3359 = 1.67%

4 Relative risk of hepatitis associated with ALT ⩾ 53 = $\frac{16/56}{439/3303} = \frac{.285}{.133} = 2.14\%$

5 Population attributable risk = $\frac{.0167(1.14)}{1 + .0167(1.14)} = \frac{.019}{1.019} = 1.8\%$