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Dr W. Forbes,
Scottish Home and Health Department,
Chief Scientist Office,
St. Andrew's House,
EDINBURGH EH1 3DE

Dear Bill,

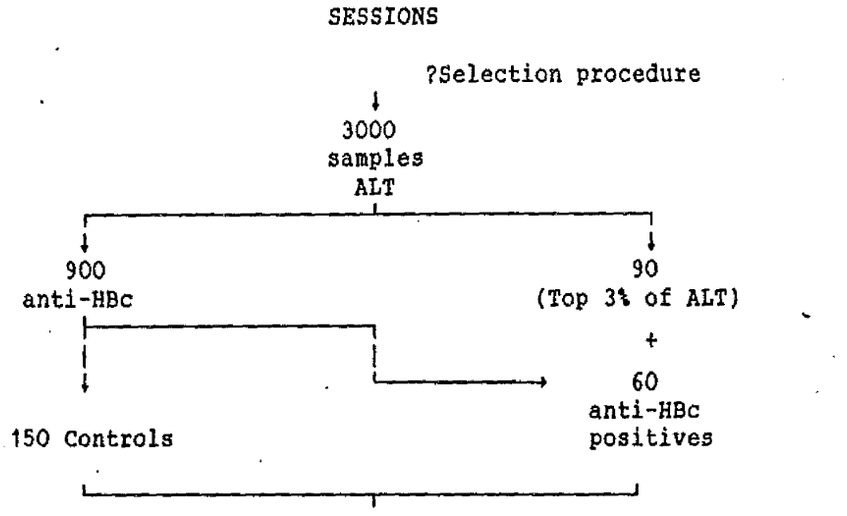
REF V/18B - GRANT APPLICATION
BY DR J. GILLON AND DR D. B. L. McCLELLAND

Thank you very much for sending me this application for comment. I can only give comments on the epidemiological aspects of the project and presume that you will be getting other advice on the various blood tests.

The applicants propose to take part in a multi-centre investigation of the value of screening blood donors using tests for Alanine Amino-Transferase (ALT) and hepatitis B core antibody (anti-HBc). In the introduction they point out that a study in the United States has shown that in approximately 40% of cases of NANB hepatitis associated with transfusions the donors had an ALT level greater than 45 IU/l. They want to see whether this relation holds in the UK before recommending that screening be introduced routinely.

There are four aims, namely: to describe the distribution of ALT and anti-HBc levels in a cohort of blood donors; to relate these levels to further tests and to the clinical state of the donor; to evaluate the economics of routine testing; and to determine effects that routine testing would have on blood donor panels.

I have drawn a little sketch of the method of data collection on the next page. Although little is said about the session at which blood is collected it is from these that 3,000 individuals will be selected. All 3,000 will have ALT measured but a random sample of 900 will have the anti-HBc evaluated. Donors whose ALT values are within the top 3% will be invited for an interview, clinical examination and to provide blood for further tests. Of the 900 donors whose blood is tested for anti-HBc, all those who are positive will also be invited for interview, exam and testing. An equal number of controls will be drawn from the remainder of the 900 whose blood was tested for anti-HBc. It is expected that there will be 150 donors who are positive for ALT or anti-HBc and 150 controls.



There are three problems that arise from this design, although I believe that they can all be dealt with by slight alterations in the protocol.

The first is that the sampling of donors through sampling sessions is not described. It is important that the 3,000 donors who are selected for the study are representative of all donors if the impact of routine screening is to be assessed properly. This part of the sampling process needs to be much more clearly defined.

The second problem arises from the selection of donors who have ALT values in the top 3% of the distribution. It will not be possible to describe the distribution until all 3,000 samples have been tested. This would leave too short a time available for the examination of the donors, given that the full duration of the study is only 8 months. It would seem more reasonable to set a cut-off point based on previous work and test donors who have their ALT values above this.

Although an equal number of controls will be selected, they are not chosen in any way to ensure matching with the affected group. Many, if not all of the blood tests may be unrelated to age or sex, but the clinical examination may be affected by those two factors and possibly others. The applicants should consider whether or not the controls should be more carefully chosen.

The underlying hypothesis which has been tested by this project is that the some outcome is dependent upon the value of the ALT and anti-HBc tests. The outcome that has been chosen by the applicants is clinical status. No description of what this means is given. It is also possible that the outcome is

measured in terms of the tests made during the donor recall session. Neither of these outcomes however addresses the real problem of transmission of virus. It would seem prudent to determine to what extent recipients of the donor blood contract evidence of infection since this is the outcome which the use of the tests is expected to avoid. This will need a detailed protocol for follow-up, but if omitted will leave the key question unanswered.

The protocol raises an ethical question which needs more discussion than the one line at the bottom of the page describing the plan of investigation. If it has already been shown that raised ALT levels are an indicator of increased NANB incidence in recipients, is it ethical to permit blood known to have been provided by a donor with high levels of ALT to be made available for issue to hospitals? A statement of the uncertainty of the value of the test needs to be made to justify the study.

Although the third aim is described as assessing the economics of ALT and anti-HBc screening, there is no discussion whatsoever of how this will be done. I get the impression that this is thrown in for good measure and has not received adequate thought for an effective evaluation to be made. This part of the protocol needs expansion, particularly since a decision on whether or not to implement routine screening will depend not only on the benefit to recipients but also on the cost of providing the benefit.

Finally, but probably the most important of all the comments is that the size of the problem is never described. What is the incidence of NANB hepatitis in recipients in the UK? How many cases would be prevented if there were a 40% decrease in the incidence? All these things are hinted at in the introduction but there is no clear statement as to the size of the problem.

I believe the study could certainly be done but it would benefit from a great deal more consideration of the practical steps to be taken, what is the real outcome against which and anti-HBc should be measured and what would be the expected benefit of routine screening based on what is already known about the tests and the incidence of hepatitis in recipients.

I hope this will be of some value to you.

My best wishes.

Yours sincerely,

Charles du V. Florey, M.D.