B23/94A

N CONFIDENCE - NOT FOR PUBLICATION

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Note of a meeting held at Alexander Fleming House on 20 July 1970 to discuss the problems of the Hepatitis Associated Antigen in relation to Blood Transfusion and associated matters.

Present: (Chairman)

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opened the meeting by saying that its purpose was to seek advice, in general terms, on what the Department could do now, in the light of present knowledge, about hepatitis associated antigen (HAA), (i) to lessen the risk of transmitting hepatitis by blood and blood derivatives and (ii) to lessen the risk to which persons associated with transfusion work were exposed.

1. Screening of blood donations for the presence of HAA antigen

introducing this item, said that there seemed to be two main points of view about the screening of blood donations.

One was that screening should be introduced as and when possible even though methods and reagents were not uniform. The other was that attempts to institute screening should not be pressed until much more was known about HAA antigen and methods of testing for it and that routine screening should not be introduced except on a national scale with uniform methods of testing, reagents etc. This point of view regarded the subject as largely one for research.

Unavoidable facts were the great scarcity of suitable antisera, the varying quality of those there were and the lack of reference standards of antidody and antigen.

He said that at present about 1.5 million blood donations were collected annually in England and Wales. -- ---------- , in his paper, had estimated that the use of this blood might cause some 1500 cases of serum hepatitis per year. Using the results of previous surveys and assuming 3 donations per transfusion, gave an estimate of 1000 cases. Assuming there were five times as many anicteric as icteric cases, there might therefore be between 6000 and 9000 cases occuring per year. The current MRC Post-Transfusion Hepatitis Survey was expected to yield information about the actual incidence of anicteric cases.

said that at least five methods were being used to detect the presence of HAA antigen in blood. This antigen had been shown to be very closely, but not necessarily causally, associated with the form of viral hepatitis known as serum hepatitis. He thought that three methods might be considered at the present time for use for large scale screening:-

Gel diffusion test
Complement fixation test
Immuno-electrophoresis

The existing methods were constantly being improved and other methods developed. It was therefore difficult to select the best method. Of the present tests he thought that immunoelectrophoresis was probably best for large scale screening: it was reasonably sensitive and relatively easy to adapt for large numbers of specimens. This method would detect strongly positive sera in a few hours, but required 48 hours to show up weakly reacting sera. It had the disadvantage of using relatively large volumes of antisera.

The gel diffusion method used the least antiserum, but was less sensitive and required several days. The CFT was sensitive but expensive in antiserum and

complicated by the occurrence of anti-complementary sera in up to 5 per cent of donors (in USA).

He said the present opinion was that testing by gel diffusion and excluding positive bloods would reduce the risk of contracting hepatitis by about 25 per cent, so that although exclusion of such donations would diminish the transmission of serum hepatitis, it would not eliminate it. He pointed out that donations containing antibody should also be excluded because the presence of antibody indicated previous exposure to HAA and because antigen and antibody could both be present in the blood at the same time.

In the present state of knowledge donors whose blood contained antigen or antibody or both should probably be excluded permanently. He said it could not be too strongly emphasized that a negative gel diffusion test for HAA did not necessarily mean that donations would not transmit serum hepatitis.

said that plasma fractions should be screened, unless they had been prepared from "negative" blood. He said it should be borne in mind that it is, of course, possible that fractionation procedures may concentrate the antigen.

He said that among 1500 donations used in the MRC Post-Transfusion Hepatitis Survey at Central Middlesex Hospital, which had been screened for HAA, 6 had been positive by gel diffusion (confirmed by electronmiscroscopy).

thought that testing of donations for the presence of HAA should be started in laboratories that had the staff and equipment, even though antisera were scarce and, at present, unstandardized and there were no uniform methods of testing.

said that antigen had been detected in one donor among 1000 tested by gel diffusion at Manchester.

thought that testing should be started in a limited number of centres to test the feasibility of routine screening and to determine the cost in staff, equipment and materials, At Oxford, using gel diffusion only, he had not detected HAA in any of 600 specimens from healthy individuals without a history of drugs or multiple injections. He had detected HAA in cases of hepatitis. He had found only one antibody carrier (a haemophiliac) among multiply transfused patients. Four other haemophiliacs had only a low titre of antibody and were not capable of supplying useful quantities of blood.

_ said he was screening on a limited scale in connection with the haemodialysis unit at Birmingham. He thought that it might be possible to mechanize testing, using a CF test, when supplies of antisera were adequate. A national screening programme might then be feasible.

_____n thought that the institution of testing should not await the perfection of testing methods and materials. In Edinburgh they were using the gel diffusion test to screen all staff associated with the haemodialysis unit or with renal transplantation, and all the patients and blood donations concerned. They were beginning to attempt to raise antibody in guinea pigs. He thought one should not delay testing for antigen, even if one could start only on a small scale. The extent of screening would grow as facilities and antisera became available.

____ _ pointed out that there was probably a 50 per cent chance that a patient who received HAA positive blood would develop clinical or subclinical hepatitis. The Department should, therefore, consider carefully the medico-legal implications that would almost certainly arise if screening, even in a small way, were not started. She said the work of __ suggested that more than one antigen associated with viral hepatitis was detectable. If this observation were confirmed, screening programmes would have to be designed to take account of it.

Methods of selecting "safe" donors were briefly discussed.

_____ thought a history of previous donations unassociated with hepatitis was not enough and that each donation should be tested for HAA. It was pointed out that the latter test did not detect all unsafe donors and that the results of antigen testing would not always be available before donations had to be used. Several members considered that a clean history alone was of value, but agreed that ideally the history should be clear and the antigen test negative.

_____ said that positive donor found by his centre had given 12 previous donations, all of which had, as far as he knew, been used without hepatitis occurring. Investigations are continuing.

_____ asked if separate notification of serum hepatitis would help.
_____ agreed this would be useful; analysis of notifications of jaundice

might then follow the line already taken in respect of notifications of acute meningitis. _____ indicated that the Oxford Public Health Department investigated all notifications of infective jaundice. Edinburgh also did this. The value of the results would depend on the completeness of notification.

. mentioned the potential icterogenicity of fibrinogen which, labelled with iodine, was being used increasingly for the localization of deep venous thrombosis. _____ informed the meeting that the Department was arranging the formation of two panels of "safe" donors (clear histories and negative antigen tests) whose plasma would be used for the preparation of labelled fibrinogen. In time fibrinogen, antihaemophilic globulin and Christmas Factor concentrate would be prepared from "safe" donors but this could not be done until screening was widespread. Immmunoglobulin, as prepared, was not-icterogenic. Albumin and plasma protein fraction were rendered non-icterogenic by heat treatment.

_____, summarizing the discussion, said that the meeting appeared to agree that, in the light of present knowledge of HAA, the Department should facilitate, in every way it could, the testing of blood donations for the presence of HAA and its antibody. As long as antisera for testing were scarce it would not be possible to organize testing on a national scale. The Department might therefore consider starting testing in a few centres, as suggested by _____ to test the feasibility of routine screening and gauge the requirements in staff etc. It was agreed that each donation from a given donor should be tested and that the donor should be excluded if antigen or antibody were found. At present it seemed that such a donor should be permanently excluded.

2. <u>The need to test medical and other staff in hospitals and laboratories and patients in haemodialysis units.</u>

There was general agreement that it was desirable to screen, for the presence of HAA and antibody, (i) all staff working in units in which blood or blood products were collected, prepared, tested, stored or issued (eg Regional Transfusion Centres, hospital transfusion laboratories) and haemodialysis units and (ii) all patients in haemodialysis units and patients with chronic renal disease who are potential candidates for such units.

_____ reported that up to 3 per cent of staff in some transfusion laboratories in Europe had been found to carry antibody. _____ reported that in a sample of 1080 such staff in European laboratories the incidence of HAA was 1 : 270. The incidence of antibody in this group was 1 : 97, but it was not known whether HAA

was also present in these antibody carriers.

_____ thought that all staff in haemodialysis units should be tested at intervals of 2 to 3 months and that "positive" staff should be removed from possible contact with patients in the unit. ___ said that "positive" staff dealing with blood and blood products should likewise be taken off such work. He thought "positive" staff should be treated in the same way as "positive" donors, whose removal from the donor panel no-one seemed to question.

_ thought that one should examine staff other than in those units mentioned above, eg operating theatre staff who might be involved in renal transplantations. He said he considered that, as far as hepatitis in haemodialysis units was concerned, it was unwise to assume, as often seemed to be done, that the disease as it occurred in different units was necessarily caused by the same virus. The mode of spread might also differ.

_____ doubted whether agreement to undergo such testing should be a condition of employment. ____ mentioned two members of his own staff who had refused to be tested unless they were given a written assurance concerning their jobs, should positive results be obtained. The RHB had felt unable to give such an assurance, so that this staff was not tested.

The meeting discussed what should be done with staff found to be positive for antigen or antibody. The difficulty of deciding to ban staff from work at which they were skilled was stressed by several members of the meeting. _____ pointed out that it was now known that serum hepatitis could also be spread by the faecal-oral route and that this fact would have to be taken into account when deciding what to do with "positive" staff.

_____, summarizing the discussion, said all members of the meeting apparently agreed that the staff under discussion should be tested for the presence of antigen and antibody. There were differing views on the frequency with which such testing should be done and on whether it was necessary to test such staff as secretaries, clerks and drivers. There seemed to be a majority view that "positive" staff should be put on other work, but there was no agreement as to what this work might be. Likewise, the majority view seemed to be that all the staff concerned should be tested as a condition of their employment. He said the Department would consider these points.

3. Categories of patients to whom priority should be given in distributing such blood donations as can at present be tested for the presence of HAA and antibody.

_____ said that with the present very limited potential for screening donations of blood, this problem was a very difficult one and the advice of those present would be most valuable. There were three categories of patients for whom it might appear desirable to provide "negative" blood:

Patients undergoing haemodialysis or renal transplantation
Those receiving chronic transfusion therapy
Those undergoing cardiac surgery

and invited discussion on these and other categories.

There was general agreement that patients on haemodialysis were probably the most important group to cover. _____ thought that patients on high doses of immunsupressive drugs should be included. _____ sought to widen this to include all patients in whom the immune response was depressed; this group would include all the leukaemias. After further discussion it was agreed that, after haemodialysis patients, the next most important category was those patients in whom the capability for an immune response had been reduced, either as a result of the disease itself or of the effects of treatment. The case for according a high degree of priority to patients undergoing cardiac surgery and those patients already suffering from a condition which involved some degree of liver damage was not supported.

_____ asked that all patients with chronic renal disease, each of whom was a potential candidate for haemodialysis, should be regarded as a priority category.

The problem of haemophiliac patients was also considered, but in view of the vast amount of material which was required for their treatment (in terms of numbers of donations) it was agreed that their inclusion as a priority category was impossible at the present time.

_____ summarized the discussion by saying that the order of priority suggested by the meeting was:-

(i) Patients undergoing haemodialysis or renal transplantation
(ii) Patients with diminished immunological competence, whether this was a result of the disease or of immunosuppressive therapy.
(iii) Patients with chronic renal disease.

4. Organisation and methods of testing and supplies of reagents

Introducing this item, _ said that the opinion of the meeting would be welcome on the view expressed in some countries, that testing should be done in virology laboratories, at least until more was known about HAA, the antibody, testing methods and reagents. The meeting might also care to express a view regarding the need for a special reference laboratory. With regard to reagents, he said the assistance of the members of the meeting in locating antibody carriers would be most welcome. Experience so far suggested that such individuals in UK were much less numerous than in USA. He informed the meeting that a human serum containing antibody to HAA had been obtained which seemed suitable for use as a working reference antiserum with which other human antisera and also animal antisera could be compared. The use of such a preparation would make possible more accurate comparison of results. He said the views of the meeting on animal antisera were also sought by the Department.

Opening the discussion, _____ thought that any organization for screening which was evolved should allow for local flexibility. _ said the actual tests were not complicated and a reasonably competent laboratory should be capable of undertaking them, but so far testing had largely been confined to specialist laboratories, and on some occasions had not been successful when attempted in routine laboratories. On the whole, the meeting thought that these tests could be done in regional transfusion centres.

There was general agreement that a reference laboratory would be necessary to which problems concerning HAA could be referred and that this was properly a function of the PHLS Dr Macrae agreed that there might be a need for a reference laboratory, but doubted whether the existing PHLS Virus Reference Laboratory could deal with this work on any scale, although to some extent they were discharging this function at the present time.

_____ said that antibody was available commercially in the USA. Mention was made of the various projects, involving commercial firms and others, for producing antibody in animals. cautioned against the too ready acceptance of animal sera, until these had been fully characterised and shown to have the same specificity as human antisera. It was known that some animal antisera did not react with all the HAA-containing sera detected by human antisera. Even if animal antisera were adopted, human antisera would be needed for reference purposes. He thought that some of the antisera

available commercially abroad were of doubtful specificity.

_____ suggested that the Department might consider, as a bridging operation and in order to gain time, the purchase of supplies of antisera, from abroad.

5. Protection of staff who come into contact with material that may contain HAA.

_____ said that the Central Pathology Advisory Committee had formed a Working Party to examine health hazards in laboratories and the risk of contracting hepatitis through handling infective material was undoubtedly one which they would consider.

said that the essential need was basic education of all laboratory staff in handling potentially infective specimens; he thought standards were lax outside bacteriology laboratories and that most staff soon forgot the principles and techniques learnt whilst working in bacteriology. Application of the same standards in other laboratories would do much to reduce the risk. The meeting agreed with this view and _____ suggested that the enforcement of such standards and techniques was the responsibility of the Consultant in charge of the laboratory and that there was a case for appointing a senior technician in each laboratory as safety officer with responsibility for seeing that the precautions laid down were strictly observed.

_____ stated that attention was now being given to the development of disposable items for use in laboratories - eg absorbent tissue coated with plastic on one side to prevent soiling of the fingers - and to the sterilization of complex equipment such as autoanalysers. _____ emphasized the urgent need for specimen containers which could be opened without contaminating the hands.

The meeting discussed briefly the prophylactic value of human normal immunoglobulin against serum hepatitis. _____ said that the results of a recently completed double blind clinical trial undertaken in USA to test the value of immunoglobulin suggested that it was of little value for preventing serum hepatitis. Hepatitis had been observed in 3.1 per cent of 2000 transfused patients given immunoglobulin; in 2000 comparable patients not given immunoglobulin the incidence was 3.4 per cent (O'Grady et ol. J Amer med Assoc: in press) _____ said that, while he agreed with Professor Sherlock that there was little or no evidence that immunoglobulin prevented infection, experience in Manchester and in Edinburgh tentatively suggested that the severity and normality of the disease might be

modified by proplylactic administration of immunoglobulin. Consequently policy in Edinburgh was to give staff who had had an accident 20 ml immunoglobulin immediately followed by 10 ml four weeks later.

6. thanked the members of the meeting for their helpful advice.