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Your reference Our reference **11 December 1980**

ADVISORY GROUP ON TESTING FOR THE PRESENCE OF HEPATITIS B SURFACE ANTIGEN AND ITS ANTIBODY

Dear Members of the Advisory Group

Dr Jenkins has asked me to distribute the final draft of the Group's report for your approval. He would like to submit the agreed report to the Department as soon as possible and I would be grateful therefore if you could let me have your comments (if any) by the end of this month.

Members are invited to supply details of the entries which they would wish to have made against their names. Reference to the previous report of the Advisory Group may be helpful as an indication of what was set out at that time.

> Yours sincersly, GRO-C

Dr Phyllis M Furnell

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FIFTH DRAFT NOV. 1980

THIRD REPORT OF THE

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ADVISORY GROUP ON TESTING FOR

THE PRESENCE OF HEPATITIS B SURFACE

ANTIGEN AND ITS ANTIBODY

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Chapter I

INTRODUCTION

1. A meeting convened by the Department of Health and Social Security on 20 July 1970 to discuss the problems of what was then known as Australia (hepatitis-associated) antigen in relation to blood transfusion and associated matters recommended that the Department should give any assistance it could "in the institution of testing blood donations for the presence of Australia (hepatitis-associated) antigen and its antibody".

2. In the light of this recommendation, in September 1970 the Advisory group on Testing for the Presence of Australia (Hepatitis-Associated) Antigen and its Antibody was appointed jointly by the Department of Health and Social Security, the Scottish Home and Health Department and the Welsh Office with the following terms of reference :-

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- (i) the organisation of and responsibility for testing blood donations and other specimens of blood for Australia (hepatitis-associated) antigen and its antibody in the hospital service;
- (ii) the provision of reagents, choice of methods and whether, and if so, what kind of, training facilities are required;
- (iii) the scale of accommodation, staffing equipment and other services necessary to implement the group's proposals.

3. The Group's Revised Report ⁽¹⁾ published in May 1972, recommended, inter alia, that Regional Transfusion Centres (RTCs) should begin, at the earliest possible date, to test all blood donations for the presence of Australia (hepatitis-associated) antigen and its antibody using, initially, an immunoelectroosmophoretic method of testing. The Group pointed out, however that knowledge of all aspects of the Australia (hepatitis-associated) antigen was accumulating very rapidly and that its recommendations should therefore be regarded as interim and subject to modification at a later date.

4. The Group, under a slightly amended title, was reconvened 6 December 1973 and in its Second Report ⁽²⁾ published in September 1975, recommended that reversed passive haemagglutination (RPH) should be adopted by all RTCs in place of counterimmunoelectrophoresis (CIE) to screen every blood donation for the presence of Hepatitis B Surface Antigen (HBsAg). It also recommended that the practice of excluding donors with a history of jaundice be discontinued provided that HBsAg was not detected and the donor had not suffered from hepatitis or jaundice during the previous 12 months. Attention was drawn, as had been done in the 1972 Revised Report, to the rapidity with which information on the subject was ' umulating and the need not to regard its recommendations as final.

5. In November 1979 the Group was reconstituted and reconvened to consider whether any alterations in the methods used for testing donations were desirable as a consequence of developments in knowledge and technique which had occurred in the intervening 5 years. The Group was asked by the Department of Health and Social Security (DHSS) on this occasion to restrict its recommendations to matters directly connected with testing.

Chapter 2

SCREENING BLOOD DONATIONS FOR HBsAg

1. The general principles of testing were considered in Chapter 2 of the Second report and do not need to be repeated. At that time the Group recommended reverse passive haemagglutination (RPH) as the method of choice for screening blood donations. Since then more sensitive tests have become widely used and we have considered whether any of these should replace RPH.

As screening tests have become more sensitive progressively fewer additional Hepatitis Surface Antigen (HBsAg) positive donations have been found. The change in the testing method from counterimmunoelectrophoresis to RPH introduced 5 years ago resulted in a 30% to 40% increase in the number of HBsAg positive donations found, whereas a further change from RPH to radioimmunoassay (RIA), the most sensitive test currently available, has resulted in only a 5% to 10% increment in the United Kingdom (3).

3. Of the more sensitive screening tests available for the ptection of HBsAg we considered the following:-

Radioimmunoassay (RIA) Enzyme-linked immunoassay (ELISA) Reverse passive haemagglutination (RPH)

Rodioimmunoassay

The quality of commercial RIA kits has improved over the 4. past 5 years and more laboratories in the U.K. are now familiar with this type of test. The delays caused in the past by the use of single-well gamma radiation counters have disappeared with the introduction of 12- and 16- well counters, though the potential hazards involved in handling the radio-isotope I-125 Several commercial RIA kits and also an RIA test remain. developed by Blood Products Laboratory (BPL), Elstree ⁽⁴⁾ for its own use were compared in the laboratories of members of the A isory Group. Differences in the detection sensitivity of the various tests were small and likely to be of little practical significance. Factors such as cost, assurance of continuity in supply and the ease with which a test could be put up are likely to be of more importance in determining choice between the various RIA tests. It is noted that the BPL test employs considerably less rodioactivity than the other tests.

Enzyme-linked immunoassay

5 Though ELISA tests for HBsAg have so far proved slightly less sensitive than RIA tests they have the advantages that radio-isotopes are not used, the reading of results is more simple, and the reagents have a longer shelf life.

<u>Reverse passive haemagglutinotion tests</u>

6. The RPH test most widely used by Regional Transfusion Centres (RTCs) has been inexpensive, fast and simple to read but it has been less sensitive than some of the other commercially available RPH tests. Some RTCs have used a modified RPH which has reduced costs and increased sensitivity (5,6), but generally RPH tests have been less sensitive than ELISA tests.

7. At the present time RTCs are finding between 1 in 500 and in 1,000 new donors to be HBsAg positive, but because of previous screening, the overall incidence in blood donors is between 1 in 3,500 and 1 in 5,000. The 5% to 10% increment in the number of HBsAg positive donations found which could be expected to follow a change to RIA screening might mean an additional 1, 2 or 3 HBsAg positive donations found in every 100,000 tested. Fewer than half of any undetected HBsAg positive donations issued are likely to cause icteric post transfusion hepatitis (PTH)^(7,8). The benefits of changing from the present RPH method of screening to a more sensitive method are thus likely to be small in the context of routine hospital blood banking. However, in relation to plosma () ducts they will be greater (see below).

8. The safety of blood products such as Factor VIII made from large pools (3 - 5,000 donations) of plasma increases as more sensitive HBsAg screening methods are used for testing the individual donations. To minimise the hazard of contamination of the large pools it is desirable to test individual donations by a technique detecting at least 2 British Standard Units/ml. (B.S.U./ml.) of antigen (see Chapter 4). Donor units despatched to NHS Fractionation Centres not tested at this level of sensitivity would have to be retested; this would result in duplication of testing with double standards. For this reason, it is desirable that a suitably sensitive test be carried out at RTCs.

9. We recommend that all donations destined to contribute to protein fractionation at NHS Fractionation Centres be tested by techniques with a sensitivity of at least 2 B.S.U./ml. of HBsAg. With the increasing need for plasma, this would imply all donations collected for transfusion purposes at RTCs.

Sensitivity of Testing Methods

10. It is only possible to lay down approximate guidelines for the sensitivity of tests. RIA or ELISA tests should be able to detect 2 B.S.U./ml. of HBsAg or less. In addition tests must how broad reactivity against a suitable panel of low titre HBsAg positive sero. RPH tests are likely to be of lower sensitivity, but should detect 100 B.S.U./ml. of HBsAg or less.

Chopter 3 OTHER SCREENING TESTS

Tests for anti-HBs

1. Donations containing high titre anti-HBs are required for the production of hepatitis B immunoglobulin (HBIG). Only one in several thousand donors has suitable levels of this antibody and an anti-HBs screening programme is therefore required to satisfy the demand for HBIG. RTCs using RPH can employ a simple "nhibition test to identify donors with high titre anti-HBs which -e-uses the serum dilutions and test cells already used in the screening test for HBSAg ⁽⁶⁾. A simple blocking test for high titre anti-HBs will be available for RTCs using the BPL RIA test for HBsAg. We recommend that RTCs should screen as many new donors as possible for anti-HBs.

2. Donors identified as possessing high titre anti-HBs are likely to retain a useful level of antibody for many years and therefore panels of suitable donors can be built up.

It is desirable that the quality of anti-HBs donations supplied to NHS Fractionation Centres should be controlled by the issue of an appropriate minimum standard anti-HBs serum to RTCs.

Tests for unti-HBc

4. Blood donations which are negative for HBsAg by RIA and negative for anti-HBs, but positive for core antibody (anti-HBc) may occasionally transmit hepatitis B. Some of these donations are from donors recovering from unrecognised hepatitis B infections who still have minute but undetectable amounts of virus in their blood. At the present time there is no evidence that this type of donation causes more than a few cases of postansfusion hepatitis (PTH) in the U.K.

5. Screening all donations for anti-HBc would be costly and result in discarding many harmless donations from immune donors unless tests for anti-HBs were also carried out.

6. We recommend that there should be no general screening of donations for anti-HBc, but that all donors implicated in cases of PTH should be tested at reference centres for anti-HBc as well as for other hepatitis markers so that more information can be obtained on the dangers of HBsAg negative, anti-HBs negative, ti-HBc positive donors.

Tests for non-A, non-B hepatitis viruses

7. Non-A, non-B hepatitis viruses are a common cause of PTH in the United States and are thought to have been responsible for some cases of PTH in the U.K. Hepatitis due to these viruses is common among haemophiliacs and follows the administration of imported, and occasionally of British, Factor VIII and Factor IX. There is some evidence for the occurrence of sporadic cases of non-A, non-B hepatitis in the general adult population and in association with cryoprecipitate therapy in the U.K.

8. There are at the present time no screening tests for detecting non-A, non-B hepatitis viruses in blood donations.

9. We recommend that research is undertaken in the U.K. to determine the extent and severity of PTH due to non-A, non-B hepatitis viruses. Unless this is done we will not have the knowledge on which to base any possible future recommendations about screening blood donations for these viruses. Regional Transfusion Directors should encourage hospital haematologists to report all cases of post-transfusion jaundice and where these rould be due to non-A, non-B hepatitis, the facts should be reported the appropriate Adviser in Blood Transfusion at the Department of Health and Social Security (DHSS) or Scottish Home and Health Department (SHHD).

Liver Function Tests

10. Several categories of people are found to have raised blood transaminase levels which are not associated with viral hepatitis. Some 3% of new donors may be excluded if the criteria of one raised transaminase level is applied. In addition to the need for confirtory transaminase testing there would also be a problem of responsibility to apparently healthy donors found to have raised transaminase levels. Therefore, we advise against these tests in screening blood donors.

11. Sporadic cases of apparent post-transfusion hepatitis due to the hepatitis B virus will continue to occur despite the most rigorous screening of donor blood samples because there are routes of infection other than transfusion; by coincidence, a transfusion may appear to have been responsible.

Chapter 4

A BRITISH STANDARD PREPARATION OF HBsAg

1. For several years there has been a need for an HBsAg standard preparation so that results in one laboratory could be compared with those from another. Any standard preparation of HBsAg has certain obvious disadvantages. For example the surface antigens produced by different strains of hepatitis B virus vary even though all share one common antigen. The elative numbers of the three morphological types of hepatitis B particle in different serum samples is another variable factor. However, we considered that provided its limitations were recognised there were many occasions when reference to a standard would be useful and in co-operation with the National Institute for Biological Standards & Control, we have prepared one.

2. We chose a high titre HBsAg positive donation, sub-type <u>ad</u>, which was positive for anti-HBe. This was diluted 1 in 4 in vater and heated at 60°C for 10 hours to reduce infectivity. The preparation is then further diluted, aliquoted and freeze-dried.

.3. We recommend that the Standard preparation of HBsAg be made available only to laboratories familiar with safety aspects of testing for HBsAg and that these laboratories make their own working standard by comparison with a freshly re-constituted ampoule of the British Standard.

Chapter 5

QUALITY CONTROL OF ROUTINE SCREENING TESTS

1. We recommend that the Division for Microbiological Reagents and Quality Control (DMRQC), Central Public Health Laboratory, Colindale continues to distribute panels of antigens to RTCs and that these should contain samples of a strength appropriate to the standard of testing. RTCs should make available to the DMRQC any low titre HBsAg positive donations which they find and which might be suitable for inclusion in one of these panels.

• NHS Fractionation Centres receive many fresh frozen plasma donations, as well as 5-litre packs of plasma from time-expired blood donations, for the manufacture of blood products. We recommend that quality control testing of this plasma be continued at Fractionation centres.

3. We recommend the establishment of a committee of experts to assess the suitability of any new tests for hepatitis markers which may have implications in the preparation of large pool blood products and in the testing of blood donations.

4. The Second Report ⁽²⁾ recommended that HBsAg positive donations found by RTCs should be confirmed as positive by Reference Centres. Because of the growing experience at RTCs we now recommend that they should carry out their own confirmatory tests on all screen test positive donations. However, they should continue to send samples of donations which they confirm as positive to Reference Centres for additional verification. Suitable methods for confirmation testing by RIA have been described ⁽⁹⁾

5. Samples of donations which a) are HBsAg positive, or
b) give equivocal results in confirmation tests, or
c) give repeatable false positive screen tests should be
sent to the Fractionation Centres for their quality assurance
programmes.

Training of Staff

6. The full value of screening donations by RIA and other sensitive tests will not be achieved unless staff are properly trained. We recommend that the Blood Transfusion Service has its own training programme, which should be organised by the NHS Fractionation Centres because of their special interest in high quality screening of donations for pooled products.

Summary of Principal Recommendations

- (i) All donations destined to contribute to protein fractionation at NHS Fractionation Centres should be tested by techniques with a sensitivity of at least 2 B.S.U./ml. of HBsAg.
- (ii) The British Standard of HBsAg should be made available by the National Institute of Biological Standards & Control only to laboratories familiar with safety aspects of testing for HBsAg.
- (iii) The Division of Microbiological Reagents and Quality Control of the Central Public Health Laboratory Service, should continue to distribute self-assessment panels of known HBsAg positive samples. Regional Transfusion Centres should make available any low titre HBsAg positive donations for this purpose.
 - (iv) All Regional Transfusion Centres should screen as many new donors as possible for anti-HBs. Panels of suitable anti-HBs donors should be built up and NHS Fractionation Centres should issue an appropriate minimum standard anti-HBs serum to Regional Transfusion Centres.
 - (v) Regional Transfusion Centres should now undertake their own confirmation tests as a preliminary to sending confirmed positives to reference centres for more detailed analysis.

- (vi) There should be no general screening of donations for anti-HBc. Donors implicated in cases of post transfusion hepatitis should be comprehensively tested at reference centres.
- (vii) Liver function tests should not be used for general screening of blood donors.
- (viii) Hospitals should be encouraged to report all cases of post transfusion jaundice and where these could be due to non-A, non-B hepatitis, the facts should be reported to the appropriate Adviser in Blood Transfusion at the D.H.S.S. or S.H.H.D.

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- (ix) Research should be undertaken in the U.K. to determine the extent and severity of post transfusion hepatitis due to non-A, non-B hepatitis viruses.
- (x) A committee of experts should be established to assess the suitability of any new tests for hepatitis markers.
- (xi) The National Blood Transfusion Service should set up its own training programme for staff engaged in HBsAg testing. Such programmes are best organised by the NHS Fractionation Centres.

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- Revised Report of the Advisory Group on Testing for the 1. Presence of Australia (Hepatitis Associated) Antigen and its Antibody. 1972, DHSS. Second Report of the Advisory Group on Testing for the 2. Presence of Hepotitis B Surface Antigen and its Antibody. 1975, DHSS. 3. A Comparison of Different Methods of Screening Blood Donations for HBsAg. J.A.J. Barbara, D.R. Howell, T.E. Cleghorn, C.H. Cameron, Moya Briggs and D.S. Dane. Vox Sang. 32: 4-9 (1977). 4. A Sensitive Immunoradiometric Assay for the Detection of Hepatitis B Surface Antigen. C.H. Cameron, B.S. Combridge, D.R. Howell, J.A.J. Barbara. Journal of Virological Methods (in press). 5. An improved hoemagglutination technique for the detection of hepatitis Bs antigen. A.C. Archer. Med. Lob. Sci. 34: 345-350 (1977). 6. A sensitive single reverse passive haemaglution test for detecting both HBsAg and anti-HBs. J.A.J. Barbara, P.J. Harrison, D.R. Howell, T.E. Cleghorn, D.S. Dane, Moya Briggs and C.H. Cameron. J. Clin. Poth. 32: 1180-1183 (1979). 7. A randomized, double blind controlled trial of the efficacy of immune serum globulin for the prevention of post-transfusion hepatitis. L.B. Seef, H.J. Zimmerman, E.C. Wright, J.D. Finkelstein. P. Garcia-Pont, H.B. Greenlee, A.A. Dictz, C.M. Leevy, C.H. Tamburro, E.R. Schiff, E.M. Schimmel, R. Zemel, D.S. Zimmon and R.W. McCollum. Gastroenterology 72: 111 (1977). 8. Unpublished report. Moya Briggs, C.H. Cameron, D.S. Danc, Jennifer Dorman, J. Blagdon and W.J. Jenkins. (1974). Confirmation of specificity by neutralisation in immunoradio-9. metric assay for hepatitis B Surface antigen.
 - C.H. Comeron and Moya Briggs. J. Virol. Methods 1: 113 (1980).

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APPENDIX

REFERENCE CENTRES FOR RADIOIMMUNOASSAY

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