DRAFT (February 1971)

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

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CHAPTER 1

INTRODUCTION

1. A meeting convened by the Department 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, we were appointed in September 1970 as an advisory group 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:-

"To advise the Health Departments on:-

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. In the Report which was published in May 1972 we recommended, inter alia, that Regional Transfusion Centres 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. We pointed out, however, that knowledge of all aspects of Australia (hepatitis-associated) antigen was accumulating very rapidly and that our recommendations should therefore be regarded as interim and subject to modification at a later date.

4. We reconvened on 6 December 1973 and have met on five occasions during which we reviewed our earlier recommendations in the light of new information which has become available since our previous Report. Our members include Consultant

Virologists, Directors of Regional Transfusion Centres and a Senior Technical Officer of the Public Health Laboratory Service. We considered papers from a wide variety of sources at home and abroad including WHO, but did not feel it necessary specifically to invite evidence. We thought it sufficient, where necessary, for individual members to make their own contacts with experts in a particular field.

5. Australia (hepatitis-associated) antigen is now known as Hepatitis B surface antigen. As in the case of our previous Report, we have not included the details of the methods of testing we recommend or a description of the detailed scientific background of the subject. The World Health Organisation Memorandum (1970) and WHO Technical Report Series No 512, 1973 and No , 1975 and the papers to which they refer may be consulted by those responsible for testing for hepatitis B surface antigen and its antibody.

6. Information about this subject continues to accumulate very rapidly. Although we are satisfied that our present recommendations reflect the state of existing knowledge they cannot necessarily be regarded as final.

CHAPTER 2

GENERAL PRINCIPLES OF TESTING

7. Hepatitis B surface antigen is the name now used to describe the antigen previously known as "Australia antigen", "Australia (hepatitis associated) antigen", "hepatitis-associated antigen", "SH antigen", "Australia-SH antigen", "Au/SH" and "hepatitis antigen". In this report we use the term hepatitis B surface antigen (abbreviation, HB_sAg) to describe the antigen and hepatitis B surface antibody (abbreviation, anti-HB_s) to describe the antibody to the antigen.

8. Infection with the virus, or at least one of the viruses of type B hepatitis, is associated with the appearance in the serum of a specific antigen, HB_sAg, and its homologous antibody. A second antigen-antibody system, the hepatitis B core, appears to be intimately related to the infection.

9. There is now substantial evidence that the 42 nm double-shelled spheroidal particle is the human hepatitis B virus, the core being the nucleocapsid and hepatitis B antigen the surface coat containing glycoprotein, lipid and other substances.

10. The surface antigen displays complex reactivities. The group specific antigen has been named a and there are at least four phenotypes adw, adr, ayw and ayr. There may be other subdeterminants. The a antigen complex is associated with molecules distinct from particles of HB_sAg. The a system is postulated to be related in some way to the infectivity of the virus and to the pathogenesis of liver damage, but the precise relationships to the virus are not yet established.

11. The core antibodies are produced in response to replication of the virus in the liver and they appear during or immediately after hepatitis B antigenaemia and well before the appearance of anti-HB_s. Neither antibody signal recovers from infection and each persits with slow decline in titre. Core antibodies do not correlate with resistance to re-infection. They are not boosted by re-exposure to serum containing HB_sAg and they are present in persistent carriers of HB_sAg.

12. The association between the presence of HB_sAg in donor blood and the occurrence of hepatitis in the recipients after an incubation period of 40-180 days is established. Blood and blood products can also transmit infective hepatitis which does not appear to be associated with the presence of HB_sAg.

13. The presence of HB_sAg can be detected by various serological tests which are described in Chapter 3. Among 214,552 blood donors being tested for the first time by differing techniques of counter immunoelectrophoresis at 15 Regional Transfusion Centres (RTCs) in England and Wales in the period January 1973 - June 1974, 182 donors (1 in 1179) were found to be HB_sAg positive and 247 (1 in 869) to be anti-HB_s positive.

14. The case incidence of ictoric hepatitis after transfusion of whole blood in a survey in 1954 was observed to be 0.2 per cent (Medical Research Council 1954). A prospective survey of the occurrence of icteric and anicteric hepatitis among transfused patients in a hospital before the general introduction of HB_sAg screening revealed a case incidence of 1.0 per cent among 768 patients observed for 6 months after blood transfusion. The morbidity and mortality were equivalent to 27 cases, including eight deaths, per 10,000 units of blood transfused in patients receiving blood only, (Medical Research Council, 1974).

15. Several surveys in USA have shown that exclusion of HB_sAg - positive donors diminishes the incidence of hepatitis B in transfused patients. Although comparable surveys in UK have not yet been reported, it seems likely that exclusion of HB_sAg-positive donors here will also be associated with a diminution in the number of cases of hepatitis B transmitted by blood and blood products and that, in general, the more sensitive the method used to detect HB_sAg the greater will this reduction be.

16. Since publication of our previous Report in May 1972 (under cover of HM(72)33) a great deal of work has been done on methods for detecting HB_sAg and anti-HB_s and on the natural history of the disease. Published reports show that the incidence of hepatitis B in recipients of antibody positive blood is no greater than that of recipients of blood in which neither HB_sAg nor anti-HB_s is demonstrable. Therefore, while confirming the recommendation in our previous Report that all blood donations should be tested for HB_sAg and that those donors whose blood is HB_sAg positive should be permanently excluded from the panel and their donations rejected for clinical use, we now recommend that donors whose blood contains anti-HB_s may be retained on the panel and their donations used clinically.

17. We have given much thought to the problem of donors with a history of jaundice but in whom neither HB_sAg nor anti-HB_s is detected. We are not aware

of any evidence that a relationship exists between a history of jaundice in donors and the occurrence of hepatitis or post-transfusion hepatitis in recipients of their blood. We therefore recommend that the practice of permanently excluding from the panel donors with a history of jaundice should be discontinued provided that HB_sAg is not detected by one of the tests described in Chapter 3 and that the donor has not suffered from jaundice during the previous 12 months.

18. We recommend that blood donations should continue to be tested in RTCs. The results of the testing are usually needed within 24 hours of collection of the blood at the latest and it would therefore not be practicable for the tests to be done in other laboratories on behalf of RTCs. We further recommend that specimens of the antigen required for testing should not be introduced deliberately into hospital pathology laboratories, unless there is a consultant microbiologist on the staff. We also recommend that at hospitals which organise donor panels and which do not have a consultant microbiologist specimens of locally collected donations should be sent for testing to the appropriate RTC or Public Health Laboratory Service (PHLS) Laboratory.

19. Where it is not possible to complete testing before a donation is issued the clinician should be told that the donation has not been tested for the presence of HB_sAg and the donation should be so marked. This practice is similar to that followed for many years regarding donations transfused before syphilis-testing has been completed.

20. In May 1974 a sub-group of the Advisory Group considered the problem of certain groups in the population in whom the incidence of antigenaemia is known to be high. The report of the sub-group is at Appendix 1.

CHAPTER 3

METHODS OF TESTING

21. A number of methods are available for detecting HB_sAg and anti-HB_s; others are being developed. Appropriate reference preparations of antigen and antibody are not yet available. It is stressed that a negative result for antigen and antibody, by even the most sensitive of the available methods, does not necessarily imply absence of an infective agent or agents.

22. The following seven methods of testing are at present suitable for large scale screening for the presence of HB_sAg and anti-HB_s:-

Immunodiffusion (ID)
Complement fixation (CF)
Counterimmunoelectrophoresis (CIE)
Inert particle agglutination
Passive haemagglutination - inhibition and passive haemagglutination
Reversed passive haemagglutination (RPH)
Radioimmunoassay (RIA)

These methods are described briefly below; detailed descriptions are to be found in WHO Memorandum (1970) and WHO Technical Report Series No 512, 1973 and No , 1975.

Immunodiffusion

23. This was the first technique used to detect HB_sAg and anti-HB_s. It is simple and can be used to demonstrate specificity, but it is slow and lacks sensitivity. Various modifications improve sensitivity but even so ID is less sensitive than the more rapid electrophoretic and agglutination techniques.

Complement fixation

24. This method, which may be automated, is more sensitive for detection of antigen than CIE (see next paragraph) but it is technically more difficult to carry out except in experienced laboratories. The sensitivity for measuring antibody is approximately equivalent to that of CIE. It should be noted, however, that some types of precipitating antibodies do not fix complement. CF testing may detect a/ab complexes which are missed by the ID and CIE methods in some sera. Anticomplement activity may result from a number of causes; it should not be regarded as being specifically associated with hepatitis.

Counterimmunoelectrophoresis

25. This is at present the most widely used technique for large-scale screening for HB_sAg and anti-HB_s. The method is relatively simple and sensitive and can be used to demonstrate specificity. A discontinuous buffer system increases the sensitivity and ease of reading precipitin lines. Weak precipitin lines may be seen by careful examination by oblique illumination in a darkened room and by staining with protein stains. The technique has been employed to detect simultaneously antigen and antibody, but this requires careful positioning of the wells. False positive reactions result from the crossing-over of one of the reagents leading to the formation of a precipitin line between the two reagents. Another source of false positive reactions is the presence of other precipitating antigen-antibody systems, such as antiruminant antibodies, red cell and lipoprotein alloprecipitins. The sensitivity of the technique is influenced dramatically by the quality of the reagents and technical skill. Overall the method is perhaps as many as three times more sensitive than ID.

Inert particle agglutination

26. Detection of antigen by latex particles, coated with anti-HB_s prepared in animals, is a rapid and simple, albeit somewhat deceptive, screening procedure which is usually slightly more sensitive than CF. Some false positive reactions are obtained but better reagents have diminished their occurrence. Anti-HB_s has been detected by its ability to inhibit latex agglutination. Detection of antigen by charcoal particle agglutination-inhibition has been reported. Despite the false positive reactions the technique appears to be particularly useful for preliminary rapid screening purposes. We consider that its manual use should be restricted to such occasions and that it should be used only in laboratories able to verify results by RPH (paragraph 28).

Passive haemagglutination-inhibition and passive haemagglutination

27. Passive haemagglutination-inhibition for detection of HB_sAg is comparable in sensitivity to, but is not as simple as, the CF test. Passive haemagglutination is very sensitive for the assay of anti-HB_s. The technique is relatively easy to perform but the preparation of red cells coated with pure antigen is difficult and expensive.

[A revised text to cover Dr Cash's paper is being prepared]

Reversed passive haemagglutination

28. Erythrocytes from various species coated with IgG fractions of anti-HB_s provide a simple and sensitive technique for detection of HB_sAg. Comparative tests indicate sensitivity greater than that of CF and passive haemagglutination-inhibition and some 50% greater than that of CIE. For example while CIE can be expected to disclose about 20 HB_sAg positives among 20,000 new donors the number disclosed by RPH is about 30. The sensitivity of RPH test systems varies but in general it approaches that of radioimmunoassay (see next paragraph). Although in experienced hands the number may be few, nonspecific false-positive results on screening are inherent in the method due to species-specific red cell agglutinins. Confirmatory tests are therefore required, but appropriate reagents are available. RPH tests can be performed rapidly, the results are easy to read and the technique may be semi-automated with simple equipment. (The tests should lend themselves to full automation but an automated method suitable for routine use has not yet been developed).

Radioimmunoassay

29. RIA techniques include assays in which antigen-antibody complexes are separated from unbound reagents by chromatoelectrophoresis, precipitation with antibody, attachment to a solid phase or sandwich methods. Double antibody, solid phase and sandwich systems are the most widely used and are the most sensitive methods available for detecting HB_sAg and anti-HB_s. Non-specific reactions have been found with a commercially available sandwich-type RIA technique for detection of HB_sAg. It is essential therefore to carry out routinely neutralization tests on positive samples in the presence of normal human serum and a broad spectrum hepatitis B antibody. Results are confirmed as positive only if neutralization tests with human hepatitis B antibody show specific blocking. The technique is relatively slow, is tedious to carry out on a large scale and is subject to variable performance. The capital equipment is expensive to install and maintain and is subject to breakdown. The cost of reagents is high. There are also hazards associated with the handling of radioactive isotopes.

Other methods

30. Other methods of testing include immuno-electronmicroscopy which, in experienced hands, is a valuable method of confirming doubtful positive results. It is not, however, applicable to large scale screening.

The core and its antibody

31. The core antigen may be demonstrated in the nuclei of liver cells by the direct immunofluorescent antibody technique, by thin-section electron microscopy and by immune electronmicroscopy. Antibody to the core has been measured by CF and RIA. Other techniques are under development.

Recommended method

32. In the light of the developments which have occurred since the publication of our last Report we no longer consider that CIE should be the recommended technique for routine screening by RTCs for HB_sAg. The choice for a replacement method lies, in our view, between RPH and RIA. Compared with RIA, RPH is simpler and quicker for RTCs to perform, is less expensive and does not have the technical and staff problems associated with the use of radioactive materials. RIA is, admittedly, more sensitive than RPH, but even so cannot be relied upon to detect every case of HB_sAg. In our opinion the extra degree of sensitivity which RIA affords is outweighed by the considerable advantages which RPH offers in other, no less important, respects. RPH represents a significant improvement in testing which can be brought into immediate use by RTCs with comparitive ease and at relatively little cost. We therefore recommend that RPH should be introduced as soon as possible into all RTCs in place of CIE to screen every blood donation for the presence of HB_sAg but that both systems of testing should be used in parallel for at least 5,000 tests on new donors before RPH is adopted as the routine method.

CHAPTER 4

STAFF AND TRAINING

STAFF

33. In view of the importance and potential hazards of the work and because of the problems which may arise in dealing with donors, patients and others found to be antigen positive a consultant should be responsible for the organization and direction of the testing laboratory in any laboratory in which testing for the presence of HB_sAg and anti-HB_s is performed.

34. The laboratory where these tests are carried out should be in the immediate charge of someone in a senior grade, who should preferably have had experience in bacteriology or virology. It is important to have a capable second in command to take control of the special laboratory during absences of the head of the laboratory.

35. Although it is difficult to foresee accurately all the implications of the introduction of more sensitive methods of testing, the screening of all blood donations imposes a considerable work load on RTCs. The prevalence of presumptive positive reactions for HB_sAg may well be at least 1 per cent of the total screened. It is essential that these reactions are verified by further tests at RTCs. The number of staff must be sufficient not only to provide a regular and continuing service, but also to reduce the risk of accidents. Overloading and overcrowding tend to cause technical and clerical errors, and may give rise to added hazards to staff handling infective material. It is important to bear in mind that, because of the continuing flow of work, testing begun on a particular day should be completed on that day.

36. Having regard to the volume of work, to the need to verify positive results and to potential hazards and problems that arise in such a laboratory, it is important to have well-trained and sufficient members of staff. The numbers should also be enough to cover holidays and sickness. It is not possible to say how many technicians will be needed in a particular RTC, but if a medical laboratory technician is put in immediate charge he should be of the grade of Chief Technician and should be supported by a Senior Technician, or other individual of equivalent grade and experience, and assisted by qualified technicians. Laboratory assistants (or aides) should be employed for the preparation and disposal of equipment. There is no objection to the employment of Junior Laboratory Technicians or laboratory assistants for the work in the laboratory provided there is adequate supervision. Additional technical staff will be required if the RTC also screens donations for anti-HB_s.

Training

37. The principles employed in haemagglutination methods are familiar to medical laboratory staff. However, proper training in these tests for the detection of HB_sAg is essential and staff in RTCs about to introduce RPH should therefore be seconded for training to laboratories which already have experience in the use and quality control of this technique.

CHAPTER

ACCOMMODATION

Regional Transfusion Centres

38. We base our recommendations concerning space required for testing in RTCs on the following assumptions; (a) that the method use for detecting and titrating HB_sAg will be RPH, (b) that other techniques may be used to confirm some results, to titrate antigens and to detect the presence of antibodies in selected sera and (c) that testing for syphilis will be carried out elsewhere in the building. The testing laboratory should be isolated from the remainder of the RTC building but we do not consider that isolation in a separate building is necessary.

Tissue Typing

39. RTCs and other laboratories which undertake tissue typing and histocompatibility testing should ensure segregation of known HB_sAg positive specimens and take precautions against infection similar to those taken when testing blood donations for HB_sAg.

General Serology Laboratory

40. We envisage that the separation of each specimen into portions for blood-grouping, syphilis testing and for tests for HB_sAg will be done in the general serology laboratory. One in slightly more than a thousand of these sera, equivalent to about one specimen every day or so in some centres, is likely to be HB_sAg positive. Some of the precautions recommended below for the testing laboratory would be required here, including provision of wash-hand basins and of floors and benches which can be washed down with disinfectants. Centrifugation probably creates the main specific hazard and the area occupied by centrifuges, benches, floors and walls in the area should be easy to clean. As testing for HB_sAg will be carried out in the special hepatitis laboratory extra space for preparing specimens for testing will not be needed in the general serology laboratory.

Testing Laboratory

41. We recommend that at least two rooms should be provided for HB_sAg testing: an ante-room and a testing laboratory. The ante-room should connect the corridor or exterior to the testing laboratory. It should be used for the receipt of specimens, for changing into and out of protective clothing and for keeping stocks of such clothing, reagents and other supplies. It must have a wash-hand basin and also, if possible, a WC and a shower.

42. The testing laboratory should be accessible only from the ante-room. To avoid overcrowding of staff it should be not less than 400 sq ft in area and have a bench run of 16 feet for a work-load of 400 tests per day with proportionally more for larger work-loads. It must have at least one wash-hand basin. The doors must be lockable. There should be a warning light over the door of the testing laboratory or laboratories. The international BIOHAZARD sign should be displayed on each door and be accompanied by red KEEP OUT or DANGER signs. The surfaces of the walls and woodwork must be painted with a gloss paint, such as an epoxy paint, which is resistant to a variety of disinfectants (including glutaraldehyde hypochlorite solution) and withstands scrubbing. Flooring should be waterproof and resistant to disinfectants and made, for example, of asphalt, rubber or vinyl sheeting. Electric power points at 4ft intervals along the benches are essential and gas points at 8ft intervals are desirable. Preferably an autoclave should also be provided and there should be easy access to an incinerator outside the laboratory.

Additional Accommodation

43. We have considered whether in hospitals where there are renal units and where biochemical and haematological tests must be carried out on "high risk" specimens an additional room should be provided so that these specimens are not tested in the routine laboratory. We have concluded that this is not necessary and that the appropriate way of meeting this problem is to ensure that the accommodation and procedures in the routine laboratory comply with the standards recommended in "Safety in Pathology Laboratories" and "The Prevention of Laboratory Acquired Infection".

Virus Reference Centres

44. The work in these laboratories consists of the investigation by various techniques of specimens referred from all sources and the space requirements will vary according to the type and volume of the work undertaken.

CHAPTER 6

SAFETY IN LABORATORIES

45. Available evidence suggests that the prevalence of hepatitis among laboratory workers is not high. We consider, however, that the risk to laboratory staff will be minimised by the adoption, wherever possible, of the principles and techniques used in microbiological laboratories for dealing with blood specimens, together with a warning system for "high risk" specimens described in paragraph 48 below. Recommendations on practice in laboratories are given in detail in "Safety in Pathology Laboratories" and "The Prevention of Laboratory Acquired Infection" and all staff should make themselves familiar with these handbooks. Some points are particularly to be emphasised.

46. All staff should be informed of the potential risks and of the need for care when handling specimens of blood or blood products and the need to maintain a high standard of personal hygiene. Sufficient wash-hand basins and disposable towels should be provided. Especial care should be taken to avoid spilling blood; if blood is spilled it should be cleaned up thoroughly with swabs soaked in disinfectant (see paragraph 51 below).

47. Smoking, eating, drinking, licking of labels and mouth pipetting must be banned in areas of laboratories where specimens of blood or blood products are dealt with.

"High Risk" Specimens

48. Blood specimens from patients known to be HB_sAg positive should be labelled as such. Specimens from the following categories of patient should be labelled "high risk" at the time of collection:

i. patients in renal units for repeated haemodialysis or transplantation;
ii. patients suffering from diseases of the liver;
iii. patients with defective or altered immunological competence, eg with leukaemia or Downs syndrome;
iv. patients in other "at risk" groups, eg drug addicts.

Patients in categories (i) to (iv) should, if possible, be tested for HB_sAg before specimens are sent for testing elsewhere. There is evidence that body fluids from cases of hepatitis B or antigen carriers may be infective and such specimens should be appropriately labelled and handled as though they were infective.

49. Labelling of specimens as "high risk" does not imply that other samples, not so labelled, are "safe"; it merely indicates that the specimens are known to come from potentially infective sources.

Transmission of "High Risk" Specimens

50. Special arrangements should be made for the transport of "high risk" specimens. They should be placed in glass containers fitted with a rubber-lined screw cap. We suggest that the containers should be placed in self sealing plastic bags. Stapling should on no account be used. The accompanying request form must not be placed in the same plastic bag as the container. The specimens should be opened only by the staff who are to process them. Hospitals should inform RTCs, or other receiving laboratories, if a specimen is from a "high risk" patient or area or if there is any local code of practice for identifying or transporting such specimens.

Disinfection

51. As the infective agent(s) causing hepatitis has not been isolated, the effects of disinfectants upon it cannot be examined, and our recommendations are based upon the known effects of disinfectants upon enteroviruses. We suggest that hypochlorite solution (eg Chloros) is the disinfectant of choice when HB_sAg may be present. It is usually supplied as a 10 per cent solution containing 100,000ppm available chlorine. For general disinfection it should be diluted 1:100 to give 1,000ppm available chlorine. Where blood has been spilt, or for disinfecting of equipment soiled with blood, a 1:10 dilution to give 10,000ppm available chlorine should be used. The available chlorine in a solution gradually diminishes; a hypochlorite solution should not be used unless it turns starch iodide paper dark blue (ie available chlorine is not less than 200ppm). Glutaraldehyde (2 per cent) and warm formaldehyde gas are also effective. For disinfection of the fixed parts of centrifuges or aluminium rotor heads glutaraldehyde or formaldehyde gas should be used as hypochlorite solution may cause corrosion. Contaminated buckets and other removable parts (other than aluminium rotors) should be soaked in glutaraldehyde and then autoclaved. If hands have been contaminated with blood they should be disinfected with hypochlorite solution and then thoroughly washed with soap and water. If, however, they have not been directly contaminated thorough washing with soap and water is sufficient. Disinfection and washing must be done before leaving the laboratory. Sudol and chlorhexidine (Hibitane) are not considered effective against the causative agent(s) of hepatitis.

Accidents

52. A full record must be kept of each incident in which exposure to the causative agent(s) may have occurred. This should include, at least, the name of the member of the staff involved, the reference number of the specimen to which he may have been exposed, the date and time of the incident and a brief description of it, the names of witnesses and details of any treatment given. Incidents such as the following should be recorded; the list is not exhaustive:

(a) a cut or other skin penetration caused by any needle, instrument or equipment contaminated with blood, blood components or body fluids;

(b) the aspiration or ingestion of blood, blood components or body fluids;

(c) splashing of blood, blood components or body fluids on to the face, particularly the lips or the eyes;

(d) extensive splashing with blood, blood components or body fluids over large areas of unprotected body surfaces;

(e) the contamination by blood, blood components or body fluids of a skin surface which is visibly broken, eg dermatitis or previous cuts, and which has not been covered by protective clothing.

Immunoglobulin in Prophylaxis

53. A few reports of the attenuation of hepatitis B by human normal immunoglobulin have been published. This effect has subsequently been shown to be due to the use of normal immunoglobulin which happened to contain anti-HB_s. Human normal immunoglobulin as prepared in the United Kingdom contains neglible amounts of, or no, anti-HB_s. On the other hand human normal immunoglobulin will attenuate hepatitis A and should be accessible if exposure to this disease is suspected.

54. The preventive and curative value of anti-HB_s immunoglobulin, separated from plasma containing anti-HB_s is being investigated. The evidence available suggests that this specific immunoglobulin may have some protective value. Advice on its use may be obtained from the Central Public Health Laboratory, Colindale.

55. In view of our recommendation that blood donations containing anti-HB_s may be used clinically (paragraph 16) it will no longer be necessary, on clinical grounds, to screen all donations for anti-HB_s. However, we consider it most important that plasma containing appropriate titres of anti-HB_s from which this specific immunoglobulin is separated should continue to be provided. We therefore recommend that arrangements should be made to continue the detection of anti-HB_s at RTCs to the extent necessary to obtain sufficient plasma of appropriate titres for the preparation of human anti-HB_s immunoglobulin. These arrangements should be reviewed from time to time as knowledge of the clinical value of this specific immunoglobulin develops.

CHAPTER 7

ANTIBODY AND ANTIGEN AS REAGENTS FOR TESTING

56. Reagents for the detection of HB_sAg by the RPH technique are now obtainable from commercial sources. RTCs will also require further reagents for use in tests to confirm a positive result by RPH and for the detection of anti-HB_s. Although anti-HB_s sera may be obtained commercially, RTCs may prefer to select all they require from anti-HB_s detected during routine tests of donors. It is important that selected anti-HB_s should have a wide spectrum of reactivity. The required sensitivity should be assessed in tests performed in the routine manner with a number of antigens of different specificities and potencies. Panels of such antigens are issued twice yearly by the Standards Laboratory for Serological Reagents, Central Public Health Laboratory, Colindale to RTCs and reference laboratories. Before issue the titres and specificities of these antigens are determined in a variety of tests in six nominated laboratories. These panels of antigens may also be used by laboratories to control the sensitivity of their methods of routine screening for the presence of HB_sAg.

57. Reagents selected by RTCs as suitable for use in tests for the detection of anti-HB_s may be submitted to the Standards Laboratory for confirmation before they are used for routine testing.

CHAPTER 6

REFERENCE CENTRES

58. Following the publication of our previous Report a number of reference centres, supported by the Virus Reference Laboratory of the Central Public Health Laboratory, Colindale, were established by the PHLS Board. By providing a reference service these centres play an essential part in the testing for HB_sAg and we recommend that the PHLS Board should be invited to arrange for them to continue to do so. The centres should also continue to undertake diagnostic work for hospitals which do not have a consultant microbiologist, examine positive samples referred, after local verification, from RTCs, undertake survey work, (eg in renal units and hospitals for the mentally handicapped), assess and develop new scientific techniques and characterise preparations of antibody and antigen used for routine testing for HB_sAg and anti-HB_s. They should be in a position to apply any of the methods of testing used by RTCs and other laboratories which may refer specimens for confirmation.

Reference Centres in England and Wales

59. In England and Wales there are reference centres at the following PHLS laboratories

Birmingham	Exeter	Newcastle
Bristol	Leeds	Oxford
Cambridge	Liverpool	Portsmouth
Cardiff	Manchester	Sheffield

The Virus Reference Laboratory of the Central Public Health Laboratory, Colindale, acts as local centre for the four Thames Regions and also as the central reference laboratory.

Reference Centres in Scotland

60. In Scotland reference centres have been established in Edinburgh and Glasgow. In Edinburgh the centre is in the Department of Bacteriology, University Medical School, and offers a service in the detection of HB_sAg and anti-HB_s by various techniques including radioimmunoassay and electron microscopy. Monitoring of high risk areas, epidemiological survey work and research are also carried out. In Glasgow the centre is at the Virus Laboratory, Ruchill Hospital. This centre at present undertakes routine testing and confirmation of positive results found

in other laboratories. Arrangements are being made to provide a range of routine and reference facilities similar to those offered at the Edinburgh centre. It is also proposed to carry out development and epidemiological research.

61. The addresses of the centres referred to in the two preceding paragraphs are given in Appendix 2.

Radioimmunoassay Centres

62. A reference radioimmunoassay service is provided by the hepatitis reference centres at Birmingham, Cardiff, Colindale and Edinburgh, by the Department of Virology, School of Pathology, Middlesex Hospital and by the WHO Collaborating Centre for Reference and Research on Viral Hepatitis at the London School of Hygiene and Tropical Medicine.

The addresses of these centres are at Appendix 3.

Central Reference Work

63. Since the publication of our previous Report the PHLS Board has arranged for three laboratories at the Central Public Health Laboratory, Colindale, to be involved in work on HB_sAg. The Virus Reference Laboratory investigates "difficult" specimens and subtypes samples; the Standards Laboratory prepares, stores and distributes reference preparations of antibody and antigen and undertakes validation work on reagents; the Epidemiological Research Laboratory investigates the natural history of hepatitis in the United Kingdom and includes the result of testing in the Communicable Disease Report. This work is essential and we recommend that the PHLS Board should be invited to arrange for it to continue.

64. We regard as most important close collaboration and exchange of information between reference centres and RTCs. In particular the reference centres should report to RTCs all cases of hepatitis (whether HB_sAg positive or not) which may have been caused by blood or blood products, so that the recipients of other donations from the donor(s) concerned can be followed up and so that the donor(s) can be re-examined for the presence of HB_sAg or anti-HB_s.

CHAPTER 9

HEPATITIS B SURFACE ANTIGEN POSITIVE SUBJECTS

65. We define a "positive subject" as one in whose blood hepatitis B antigen has been detected. Positive findings should, after local verification by the laboratory of origin, be sent for confirmation to one of the reference centres listed in Appendix 2. For this purpose a second sample of blood should be obtained from the subject or, in the case of a donor, a sample of plasma should be taken from the donation itself to ensure that no error in identification of the blood donation has occurred. The specimen should be tested by at least two techniques in the reference centre which should be told whether the specimen is of serum of plasma.

Donors

66. A donor whose blood is positive on the first screening should be suspended from the panel, and the donation concerned should be destroyed, unless required for the preparation of reagents. The donor's certificate booklet should not be endorsed with this information.

67. We recommend that when a donor is permanently excluded from the panel (following confirmation of a positive result by a reference laboratory) a letter should be sent to him by the Director of the RTC informing him of the finding and inviting him to give the name of his family doctor. If he does so the Director should write to the family doctor pointing out that the implications of a positive test to the individual concerned are not yet clear, suggesting that liver function tests be undertaken and, should the results prove abnormal, advising reference to a consulting physician who has an interest in diseases of the liver. Suggested drafts of the two letters are at Appendices 4 and 5.

Staff

68. Epidemiological evidence of transfer of antigen within transfusion laboratories (other than by accidental parental injection) is meagre. Evidence of transfer of infection from staff to blood or blood products is difficult to obtain and we know of none. There is some evidence of transfer of infection from blood to staff but the number of known cases is small.

69. There are, however, good reasons for testing staff for HB_sAg. These, not necessarily in order of importance, are (a) to avoid the risk however slight, of contaminating blood or blood products, (b) to monitor the effectiveness of the methods used to protect staff, (c) to permit the early institution of treatment of staff found HB_sAg positive and (d) to obtain information which might be valuable in the study of the epidemiology of hepatitis. We have therefore concluded that we should reaffirm the recommendation made in our previous Report that all applicants for posts in the Blood Transfusion Service should be tested for HB_sAg as a condition of appointment and that all staff in post should be offered tests, which they should be urged to accept, at intervals of three to six months.

70. There are some sections of a transfusion centre where an HB_sAg-positive person could work without danger of his contaminating blood or blood products. These are prepared in closed systems or by use of aseptic procedures so that, theoretically, they should not be contaminated even if such a person assisted in their preparation. Nevertheless we recommend that, until more is known about the epidemiology of hepatitis B a member of staff found to be HB_sAg-positive should not, so long as he remains positive, assist in the preparation, by an open process, of blood or blood products intended for clinical use. He should also be referred to his family doctor.

71. The problems associated with the general antigen testing of medical and para medical staff are discussed in the Report of the WHO Expert Committee on Viral Hepatitis.

CHAPTER 10

SUMMARY OF PRINCIPAL RECOMMENDATIONS

72. We summarise our principal recommendations as follows:-

i. all blood donations should be tested for the presence of hepatitis B surface antigen (HB_sAg); donors whose blood is HB_sAg positive should be permanently excluded from the panel and their donations rejected for clinical use; however, donors whose blood contains hepatitis B surface antibody (anti-HB_s) may be retained on the panel and their donations used clinically (paragraph 16).

ii. the practice of excluding from the panel donors with a history of hepatitis should be discontinued provided that HB_sAg is not detected by one of the tests described in Chapter 3 and that the donor has not suffered from jaundice during the previous 12 months (paragraph 17);

iii. blood donations should be tested at Regional Transfusion Centres (RTCs); specimens of the antigen required for testing should not be introduced deliberately into hospital pathology laboratories unless there is a consultant microbiologist on the staff; otherwise specimens of locally collected donations should be sent for tesing to the appropriate RTC or Public Health Laboratory Service (PHLS) laboratory (paragraph 18).

iv. reversed passive haemagglutination (RPH) should be introduced as soon as possible into all RTCs as the method of testing in place of counterimmunoelectrophoresis (CIE) but both methods should be used in parallel for at least 5000 tests on new donors before RPH is adopted as the routine method (paragraph 32);

v. in matters concerning staff, training, accommodation and safety, RTCs should be guided by the advice given in paragraphs 33-36, 37, 38-44 and 45-52 respectively;

vi. arrangements should be made to continue the detection of anti-HB_s at RTCs to the extent necessary to obtain sufficient plasma of appropriate titres for the preparation of human anti-HB_s immunoglobulin; these arrangements should be reviewed from time to time as the knowledge of the clinical value of this specific immunoglobulin develops (paragraph 55);

vii. the PHLS Board should be invited to arrange for the reference centres established since our previous Report to continue to undertake the reference work arising from testing at RTCs and the diagnostic work for laboratories without a consultant microbiologist (paragraph 58);

viii. the PHLS Board should also be invited to continue the arrangements by which three laboratories at the Central Public Health Laboratory at Colindale are involved in work on HB_sAg (paragraph 63);

ix. when a donor is permanently excluded from the panel, following confirmation by a reference laboratory that his blood is HB_sAg positive, a letter should be sent to him by the Director of the RTC informing him of the finding and inviting him to give the name of his family doctor; if he does so the Director should write to the doctor suggesting certain action in the donor's interest (paragraph 67);

x. all applicants for posts in the Blood Transfusion Service should be tested for HB_sAg as a condition of appointment; all staff in post should be offered tests, which they should be urged to accept, at intervals of three to six months (paragraph 69);

xi. a member of staff found to be HB_sAg positive should not, so long as he remains positive, assist in the preparation, by an open process, of blood or blood products intended for clinical use (paragraph 70).

APPENDIX 1

CONSIDERATION OF CERTAIN CATEGORIES OF POTENTIAL BLOOD DONORS

A Sub-Group of the Advisory Group met on 23 May 1974 to consider what groups of donors can be identified whose blood should be given special consideration and whether any group can be identified whose blood should be rejected.

2. The Sub-Group reached the following conclusions:-

i. A high frequency of hepatitis B surface antigen (HB_sAg) occurs in people who were born or who have lived in certain countries which are (or were) designated by WHO as endemic malarious areas. People from these areas are preponderantly coloured.

ii. There is a much greater risk of transmitting hepatitis through blood from donors described in (i) than from donors born in the UK.

iii. The risk at (ii) is not confined to coloured donors because, with certain exceptions, HB_sAg occurs with high frequency in all countries. The exceptions are Australia, Canada, New Zealand, the United States of America and some parts of Europe. However, in Europe HB_sAg also occurs with high frequency in those countries, other than France, which have a Mediterranean littoral. Thus, for example, the blood of a person born in Greece or Turkey must be considered to be at 'high risk' of transmitting hepatitis no less than the blood of a coloured person born, say, in Jamaica.

iv. The currently recommended test for the routine testing for the presence of HB_sAg (counterimmunoelectrophoresis) should be replaced as soon as possible by one of the more sensitive tests (reversed passive haemagglutination or radioimmunoassay) at present being considered by the Advisory Group. No test can be completely reliable but the risk of HB_sAg not being detected by either replacement test is small and is regarded as acceptable.

v. The whole blood or concentrated red cells of donors found to be HB_sAg negative by either of the more sensitive tests mentioned at (iv) above and which are otherwise medically acceptable may be used for normal transfusion purposes irrespective of the donors' ethnic group or country or origin.

vi. The red cells of all donors who were born or have resided in an endemic malarious area must continue, as at present, to be discarded because of the danger of transmitting malaria. However, the plasma from these donations providing they are negative for HB_sAg by either of the more sensitive tests mentioned at (iv) may, as now, continue to be used to prepare immunoglobulin and albumin.

vii. To ensure that donors are not needlessly 'disqualified' on grounds of malaria it will be necessary to ask all donors whether they were born outside the UK and whether they have lived in an endemic malarious area (see (i) above). These enquiries must be carefully phrased and suitable explanations given in order to avoid accusations of discrimination on grounds of race or colour. Donors from malarious areas should be told that their red cells cannot be used because they may transmit malaria but that their plasma is valuable as a source of plasma fractions.

Prisons

3. There is a relatively high risk of hepatitis being transmitted by the blood of prisoners. But there is probably an equally high risk in other groups of the population, eg drug addicts, who are not so easily identified in advance as prisoners. It is not necessary to discontinue the collection of blood at prisons and similar institutions provided all donations are subjected to one of the more sensitive tests referred to at 2(iv) above.

APPENDIX 2

REFERENCE CENTRES FOR HEPATITIS B SURFACE ANTIGEN

BIRMINGHAM	Dr T H Flewett Regional Virus Laboratory East Birmingham Hospital Bordesley Green East Birmingham B9 5ST	021-772-4021
BRISTOL	Dr S M R Clarke Public Health Laboratory Myrtle Road Kingsdowne Bristol BS2 8EL	0272-291326
CAMBRIDGE	Dr J Nagington Addenbrooke's Hospital Hills Road Cambridge CB2 2QW	0223-42111
CARDIFF	Dr A D Evans Public Health Laboratory Institute of Pathology 3rd Floor Royal Infirmary Cardiff CF2 1SZ	0222-755944
EDINBURGH	Professor B P Marmion Department of Bacteriology University Medical School Teviot Place Edinburgh EH8 9AG	031-667-1011
EXETER	Dr R J C Hart Public Health Laboratory Church Lane Heavitree Exeter EX2 5AD	0392-51251
GLASGOW	Virus Laboratory Ruchill Hospital Bilsland Drive Glasgow G20 9NB	041-946-6491
LEEDS	Dr M H Hambling Public Health Laboratory Bridle Path York Road Leeds LS15 7TR	0532-645011

LIVERPOOL	Dr C C Turner Rathbone Hospital Lower Lane Liverpool L9 7AL	051-5252323
LONDON	Dr Y M Gossart Virus Reference Laboratory Central Public Health Laboratory Colindale Avenue London NW9 5HT	01-205-7041
MANCHESTER	Dr D M Jones Public Health Laboratory Withington Hospital Manchester M20 8LR	061-445-2416
NEWCASTLE	Dr J H Hale Public Health Laboratory Institute of Pathology General Hospital Westgate Road Newcastle upon Tyne NE4 6BE	0632-38811 Ext 297
OXFORD	Dr F O MacCallum United Oxford Hospitals Radcliffe Infirmary Oxford OX2 6HT	0865-49231/2
PORTSMOUTH	Dr J V T Gostling Public Health Laboratory St Mary's General Hospital East Wing Milton Road Portsmouth PO3 6AQ	0705-22331
SHEFFIELD	Dr M A M Wilson Public Health Laboratory Northern General Hospital Herries Road Sheffield S5 7AU	0742-387253

APPENDIX 3

REFERENCE CENTRES FOR RADIOIMMUNOASSAY

BIRMINGHAM	Dr T H Flewett Regional Virus Laboratory East Birmingham Laboratory Bordesley Green East Birmingham B9 5ST	021-772-4031
CARDIFF	Dr A D Evans Public Health Laboratory Institute of Pathology 3rd Floor Royal Infirmary Cardiff CF2 1SZ	0222-755944
EDINBURGH	Professor B P Marmion Department of Bacteriology University Medical School Teviot Place Edinburgh EH8 9AG	031-667-1011
LONDON	Dr Y E Cossart Virus Reference Laboratory Central Public Health Laboratory Colindale Avenue London NW9 5HT	01-205-7041
	Dr D S Dane Department of Virology School of Pathology Middlesex Hospital Medical School Riding House Street London W1P 7LD	01-636-8333 Ext 7393
	Professor A J Zuckerman WHO Centre London School of Hygiene and Tropical Medicine Keppel Street (Gower Street) London WC1E 7HT	01-636-8636

APPENDIX A

SUGGESTED LETTER TO DONOR WHO IS HBsAg POSITIVE DONOR

Dear Mr/Mrs/Miss

As a (regular) blood donor you may perhaps be aware that there is a risk that patient receiving a transfusion of blood from a donor who has had hepatitis (a disease of the liver sometimes accompanied by jaundice) may himself develop hepatitis.

Hepatitis may occur in such a mild form that it is not recognised; jaundice does not appear and the person concerned may feel quite well or only slightly indisposed. Tests have, however, been devised which identify a healthy person whose blood may transmit hepatitis even though he may be unaware that he has ever had this disease.

I am writing to let you know that your blood has recently been found positive by these tests. I am sure you will understand that the Blood Transfusion Service cannot accept a donation from anyone whose blood is capable of transmitting hepatitis to a patient. I regret therefore that we shall have to remove your name from our panel of donors and you should not be a blood donor in the future.

I think we ought to let your own doctor know about this finding, since he may wish to discuss with you the need for further testing, and I should be glad if you would agree to our doing this. If you would kindly send me his name and address, I will then write to him. You should let your dentist know, or show him this letter at your next visit.

We are grateful to you for all the help you have given this vital service in the past and are very sorry indeed that we can no longer call upon you. May I offer you my warmest thanks.

Yours sincerely

APPENDIX I.

SUGGESTED LETTER TO THE GENERAL PRACTITIONER
(TO BE SENT ONLY AFTER THE DONOR HAS AGREED)

Dear Dr.

Your patient (name and address) is a blood donor and routine testing has shown that his/her blood is at present Hepatitis B surface antigen (Australia antigen) positive. He/She has been informed of this and told that because of the risk of transmitting hepatitis to a patient receiving a transfusion of his/her blood he/she cannot be a blood donor in the future. He/She has agreed that we may give this information to you.

Although the implications for your patient of the result of the test are not at present entirely clear may I suggest that it would be desirable to have liver function tests done as he/she may possibly be incubating disease, and that you should consult the pathologist at your local hospital about these tests. If a specimen of blood is sent to the laboratory it should be clearly marked "Hepatitis B - positive sample" and be most carefully collected, handled and packed. If the liver function tests show any abnormalities suggesting some form of hepatitis, you might be interested to know that Dr ..... of ..... Hospital, who is specially interested in diseases of the liver, is willing to see such individuals should you think it necessary to refer your patient to him/her or is willing, as a matter of interest, to follow-up all such patients, even though their liver function tests might be normal and to all intents and purposes they appear to be healthy individuals.

Your patient has been advised also to inform his/her dentist at the next visit of the findings of the test. Perhaps you would be good enough to remind him/her of the need to do so.

Yours sincerely