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STANDING MEDICAL ADVISORY COMMITTEE

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

NOTE BY SECRETARY

Members are invited to endorse the Advisory Group's Second Report in which the Group have confirmed a number of their earlier recommendations and made several new ones. Subject to this and the approval of Ministers the Department proposes to enter into consultations with outside bodies with a view to issuing guidance to Health Authorities about giving effect to the Report.

Of the new recommendations the most important relates to the method of testing for the presence for Hepatitis B Surface Antigen (HB<sub>s</sub>Ag) as it is now generally known. The Group consider that counter-immunoelectrophoresis should no longer be the recommended technique for routine screening for HB<sub>s</sub>Ag and that it should be replaced as soon as possible by reversed passive haemagglutination.

Other changes in procedure recommended by the Advisory Group which may be of interest to members include the following:-

- i. while blood donors whose blood is HB<sub>s</sub>Ag positive must continue to be permanently excluded from the panel and their donations rejected for clinical use, donors whose blood contains hepatitis B surface antigen (anti-HB<sub>s</sub>) may be retained on the panel and their donations used clinically; however, the detection of anti-HB<sub>s</sub> should be continued to the extent necessary to obtain sufficient plasma for the preparation of human anti-HB<sub>s</sub> immunoglobulin;
- ii. the practice of permanently excluding from the panel donors with a history of jaundice should be discontinued provided that HB<sub>s</sub>Ag is not detected by reversed passive haemagglutination (or a test of equal sensitivity) and that the donor has not suffered from hepatitis or jaundice during the previous 12 months.

October 1975

J G H  
Department of Health and Social Security

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 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, 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 our Revised 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. Our members include Consultant Virologists, Directors of Regional Transfusion Centres and a Senior Technical Officer of the Public Health Laboratory Service. We have reviewed the recommendations in our previous Report in the light of new information which has since become available and have considered papers from a

wide variety of sources in this country and elsewhere, including WHO. We have not felt it necessary specifically to invite evidence but have 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 570, 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 reasonably 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<sub>s</sub>Ag) to describe the antigen and hepatitis B surface antibody (abbreviation, anti-HB<sub>s</sub>) to describe the antibody to the antigen.

8. Infection with the virus of type B hepatitis is associated with the appearance in the serum of a specific antigen, HB<sub>s</sub>Ag, 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 some evidence that the 42 nm double-shelled spheroidal particle (the Dane 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<sub>s</sub>Ag. 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<sub>s</sub>. Neither antibody signals recovery from infection and each persists with slow decline in titre. Present evidence suggests that core antibodies are not protective; they are not boosted by re-exposure to serum containing HB<sub>s</sub>Ag and they are present in persistent carriers of HB<sub>s</sub>Ag.

12. The association between the presence of HB<sub>s</sub>Ag in donor blood and the occurrence of HB<sub>s</sub>Ag positive hepatitis in the recipients after an incubation period of 40-180 days is established. Blood and blood products can also transmit other forms of hepatitis which do not appear to be associated with the presence of HB<sub>s</sub>Ag.

13. The presence of HB<sub>s</sub>Ag can be detected by various serological tests which are described in Chapter 3. Among a total of 255103 general public and factory blood donors tested for the first time by differing techniques of counterimmunoelectrophoresis at 12 Regional Transfusion Centres (RTCs) in England in 1973 and 1974, 216 donors (1 in 1181) were found to be HB<sub>s</sub>Ag positive and 282 (1 in 905) to be anti-HB<sub>s</sub> positive. Because of the insensitivity of the techniques used and possible geographical variations in the incidence of antigen these figures are not reconcilable with those in the succeeding paragraph.

14. The case incidence of icteric 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<sub>s</sub>Ag screening revealed a case incidence of about 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<sub>s</sub>Ag 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<sub>s</sub>Ag positive donors here will also be associated with a diminution in the number of cases of hepatitis B transmitted by blood and blood products.

16. Since publication of our previous Report in May 1972 much work has been done on methods for detecting HB<sub>s</sub>Ag and anti-HB<sub>s</sub> and on the natural history of the disease. Published reports show that the incidence of hepatitis B in recipients of antibody positive is no greater than that of recipients of blood in which neither HB<sub>s</sub>Ag nor anti-HB<sub>s</sub> is demonstrable. Therefore, while confirming the recommendation in our previous Report that all blood donations should be tested for HB<sub>s</sub>Ag and that those donors whose blood is HB<sub>s</sub>Ag 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<sub>s</sub> may be retained on the panel and their donations used clinically.

17. Although we no longer consider it necessary, on clinical grounds to screen all donations for anti-HB<sub>s</sub>, it is, in our view, most important that plasma containing adequate titre of anti-HB<sub>s</sub>, from which anti-HB<sub>s</sub> immunoglobulin is

prepared, should continue to be provided. We therefore recommend that arrangements should be made to continue the detection of anti-HB<sub>s</sub> at RTCs to the extent necessary to obtain sufficient plasma of adequate titre for the preparation of human anti-HB<sub>s</sub> immunoglobulin. These arrangements should be reviewed from time to time as knowledge of the clinical value of this specific immunoglobulin develops.

18. We have given much thought to the problem of donors with a history of jaundice but in whom neither HB<sub>s</sub>Ag nor anti-HB<sub>s</sub> is detected. We are not aware of any evidence that a relationship exists between a history of jaundice in donors and the occurrence of icteric or anicteric 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<sub>s</sub>Ag is not detected by reversed passive haemagglutination or a test of at least equal sensitivity described in Chapter 3 and that the donor has not suffered from hepatitis or jaundice during the previous 12 months.

19. We recommend that blood donations should continue to be tested in RTCs. The results of the testing are usually needed within 24 hours, at the latest, of collecting the blood and it would therefore not be practicable for the tests to be done in other laboratories on behalf of RTCs. We also recommend that positive findings should be verified at RTCs and, upon verification, should be referred for confirmation to a reference centre (see Chapter 5).

20. We recommend that specimens of the antigen required for testing should not be introduced deliberately into hospital pathology laboratories unless there is a consultant microbiologist responsible for the testing and that at hospitals which do not have a consultant microbiologist specimens should normally be sent for testing to the appropriate Public Health Laboratory Service (PHLS) Laboratory in England and Wales or Virus Laboratory in Scotland. However, where ante-natal specimens are sent to the RTC for blood grouping they may also be tested there for HB<sub>s</sub>Ag if the Director of the RTC agrees.

21. We recommend that 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<sub>s</sub>Ag 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.

## CHAPTER 3

### METHODS OF TESTING

22. Several methods are available for detecting HB<sub>s</sub>Ag and anti-HB<sub>s</sub>; others are being developed. Appropriate reference preparations of antigen 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.

23. The following methods can be used to detect the presence of HB<sub>s</sub>Ag or anti-HB<sub>s</sub> and, in most cases, of both:-

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

The suitability of these methods for large scale screening is briefly discussed below; detailed descriptions are to be found in WHO Memorandum (1970) and WHO Technical Report Series No 512, 1973 and No 570, 1975.

#### Immunodiffusion

24. This was the first technique used to detect HB<sub>s</sub>Ag and anti-HB<sub>s</sub>. It is simple and can be used to demonstrate specificity, but it is slow and lacks sensitivity. Various modifications improve sensitivity but are not suitable for use in large-scale screening.

#### Complement fixation

25. 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. 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 antigen/antibody complexes that are missed by ID and CIE in some sera. Anticomplement activity may result from a number of causes; it should not be regarded as being specifically associated with hepatitis.

#### Counterimmunoelectrophoresis

26. This is at present the most widely used technique for large-scale screening for HB<sub>s</sub>Ag and anti-HB<sub>s</sub>. The method is relatively simple but comparatively insensitive 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 using 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 may result from the electrophoresis or diffusion of one of the reagents past the nearest well to form a precipitin line with the reagent from another well. Another source of false positive reactions is the presence of other precipitating antigen-antibody systems, such as antiruminant antibodies, blood group 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

27. Detection of antigen by latex particles, coated with anti-HB<sub>s</sub> prepared in animals, is a rapid and simple, though somewhat unreliable, 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<sub>s</sub> 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 rapid screening in emergency. We consider that its use should be restricted to such occasions and that it should be used only in laboratories able to verify results by RPH (see paragraph 30) or a test of at least equal sensitivity.

#### Passive haemagglutination-inhibition and passive haemagglutination

28. Most passive haemagglutination-inhibition methods for the detection of HB<sub>s</sub>Ag appear to be comparable in sensitivity to the simpler CF test (WHO 1973). The method described by Hopkins and Das (1973) has been used in the RTCs at Edinburgh, Dundee and Inverness and has proved to be a simple, rapid, economical and highly sensitive test for screening blood donations for the presence of HB<sub>s</sub>Ag.

29. Passive haemagglutination is very sensitive for the assay of hepatitis B surface antibody. The technique is relatively easy to perform, but the preparation of suitable HB<sub>s</sub>Ag-coated red cells may be difficult and expensive

and raises problems of special accommodation, equipment and quality control. However Hocking and Dor (1973) using tanned red cells have found the preparation of reagents straight forward.

#### Reversed passive haemagglutination

30. Erythrocytes from various species coated with IgG fractions of anti-HB<sub>s</sub> provide a simple and sensitive technique for detection of HB<sub>s</sub>Ag. Comparative testing indicates sensitivity greater than CF, CIE and passive haemagglutination-inhibition. Thus while CIE may be expected to disclose about 20 HB<sub>s</sub>Ag positives among 20,000 new donors the number disclosed by RPH may be about 30. The sensitivity of RPH test systems varies but in general it approaches that of radioimmunoassay (see next paragraph). Nonspecific false positive results on screening are inherent in the method due, for example, to species-specific red cell agglutinins although the number may be few. Confirmatory tests are therefore required. RPH tests can be performed rapidly, the results are easy to read and the technique may be semi-automated with simple equipment. The tests by their nature lend themselves to full automation and a semi-automated method suitable for routine use is being developed.

#### Radioimmunoassay

31. 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<sub>s</sub>Ag. Non-specific reactions have been found with a commercially available sandwich-type RIA technique for detection of HB<sub>s</sub>Ag. 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 and tedious to carry out on a large scale. 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

32. Other methods of testing include immune 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

33. Core antigen may be demonstrated by immune electronmicroscopy and in the nuclei of liver cells by the direct immunofluorescent antibody technique or by electron microscopy of thin sections. Antibody to the core has been measured by CF and RIA and may be demonstrated by immune electron microscopy. Other techniques are under development.

#### Recommended method

34. 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 the presence of HB<sub>s</sub> Ag. The choice for a replacement method lies, in our view, between RPH and RIA. Compared with RIA, RPH is simpler and quicker 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 HB<sub>s</sub> Ag in every donation in which it is present. 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 comparative ease and at relatively little cost. We therefore recommend that RPH should be adopted as soon as possible by all RTCs in place of CIE to screen every blood donation for the presence of HB<sub>s</sub> Ag but that both systems of testing should be used, in each RTC, in parallel for at least 5,000 tests on new donors before RPH becomes the routine method. We see no objection to the use of passive haemagglutination-inhibition, in place of RPH, in those RTCs with the required experience which either can make the reagent or have access to supplies.

CHAPTER 4

HEPATITIS B SURFACE ANTIGEN POSITIVE SUBJECTS

35. We define a "positive subject" as one in whose blood hepatitis B antigen has been detected and have recommended in paragraph 19 that positive findings should, after local verification by the laboratory of origin, be sent for confirmation to a reference centre. 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 or plasma.

Donors

36. We recommend that a donor whose blood is positive on first screening should be suspended from the panel. The donor's certificate booklet should not be endorsed with this information until confirmation of a positive test has been received. Before an antigen positive donation is destroyed its use for the preparation of reagents or other materials should be considered (paragraph 52).

37. We recommend that when a positive test for antigen has been confirmed by the reference laboratory the donor should be permanently excluded from the panel and that a letter should be sent to him by the Director of the ETC 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 entirely 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 1 and 2.

Staff

38. 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.

39. There are, however, good reasons for testing staff for HB<sub>s</sub>Ag. These, not necessarily in order of importance, are (a) to monitor the effectiveness of the methods used to protect staff, (b) to permit the early institution of treatment of staff found HB<sub>s</sub>Ag positive, (c) to obtain information which might be valuable in the study of the epidemiology of hepatitis, and (d) to maintain public confidence in the safety of blood and blood products although the risk of transfer of infection from staff to blood or blood product is apparently very remote. 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 the presence of HB<sub>s</sub>Ag 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.

40. There are some sections of a transfusion centre where an HB<sub>s</sub>Ag 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<sub>s</sub>Ag 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.

41. At present there is no evidence that HB<sub>s</sub>Ag carriers among medical or paramedical staff constitute a hazard to those with whom they come into contact in pursuit of their duties. WHO Technical Report Series No 570, 1975 recommends that such carriers should "take special precautions in their professional activities". Only one survey of the health of the professional and other contacts of such carriers has to our knowledge been published. It showed that such carriers were not a danger to those with whom they come into contact. (Alter et al 1975). Further investigations will be necessary to demonstrate whether and, if so, under what conditions, they transmit infection and we recommend that the Health Departments should examine the feasibility of undertaking of such investigations.

CHAPTER 5

REFERENCE WORK AND NOTIFICATION

Reference Centres in England and Wales

42. Following the publication of our previous Report reference centres, supported by the Virus Reference Laboratory of the Central Public Health Laboratory, Colindale, were established by the PHLS Board 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.

These centres provide a reference service for the detection of HB<sub>s</sub>Ag and anti-HB<sub>s</sub>. assess and develop new scientific techniques and characterise preparations of antibody and antigen used for routine testing for HB<sub>s</sub>Ag and anti-HB<sub>s</sub>. They also undertake diagnostic work for hospitals which do not have a consultant microbiologist and do survey work, eg in renal units and hospitals for the mentally handicapped.

Central Reference Work in England and Wales

43. The PHLS Board has also arranged for three laboratories at the Central Public Health Laboratory, Colindale, to be involved in work on HB<sub>s</sub>Ag. The Virus Reference Laboratory investigates "difficult" specimens and subtypes samples; the Standards Laboratory prepares, stores and distributes panels of antigens and undertakes validation work on reagents; the Epidemiological Research Laboratory investigates the natural history of hepatitis in England, Wales and Northern Ireland and includes the result of testing in the Communicable Diseases Report.

Reference Centres in Scotland

44. In Scotland reference centres have been established in Edinburgh and Glasgow. In Edinburgh the centre offers a service for the detection of HB<sub>s</sub>Ag and anti-HB<sub>s</sub> by various techniques including radioimmunoassay and electron microscopy. Monitoring of high risk areas, epidemiological survey work and research are also carried out.

The centre in Glasgow at present undertakes routine testing and confirmation of positive results found in other laboratories. Arrangements are being made to provide a range of other routine and reference facilities similar to those offered at the Edinburgh centre.

#### Central Reference Work in Scotland

45. In Scotland the investigation of "difficult" specimens and arrangements for subtyping are made through the reference centres in Edinburgh and Glasgow. Epidemiological work in Scotland is effected partly through these centres and partly through the Communicable Diseases (Scotland) Unit, Ruchill Hospital, Glasgow, which also collates the results of HB<sub>s</sub>Ag testing in all laboratories in Scotland and includes them in the Communicable Diseases (Scotland) Weekly Report.

46. The work described in the four preceding paragraphs is an essential part of the arrangements for testing for HB<sub>s</sub>Ag and anti-HB<sub>s</sub> and we recommend that the PHLS Board in England and Wales and the Common Services Agency and the appropriate Health Boards in Scotland be invited to arrange for it to continue.

47. The addresses of the centres referred to in paragraphs 42-45 are given in Appendix 3.

#### Radioimmunoassay Centres

48. A reference radioimmunoassay service is provided by the hepatitis reference centres at Birmingham, Cardiff, Colindale and Edinburgh, by the Middlesex Hospital, London, and by the WHO Collaborating Centre for Reference and Research on Viral Hepatitis at the London School of Hygiene and Tropical Medicine. We recommend that this service should continue and be increased as necessary in accordance with demand. The addresses of these centres are at Appendix 4.

#### Collaboration between Reference Centres and Regional Transfusion Centres

49. We regard as most important close collaboration and exchange of information between reference centres and RTCs. We recommend that reference centres and RTCs should notify each other of all cases of hepatitis (whether HB<sub>s</sub>Ag 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<sub>s</sub> Ag or anti-HB<sub>s</sub>.

Differential Notification

50. WHO Technical Report Series No 570 (1975) recommends that national government health services and statistical agencies should endeavour to obtain complete reporting of hepatitis by age and sex and to institute differential notification of hepatitis as hepatitis A, hepatitis B or hepatitis type unspecified. We are aware of the difficulties in achieving valid differentiation of hepatitis by type in a national notification scheme but consider that the more widespread testing for the presence of HB<sub>s</sub> Ag and anti-HB<sub>s</sub>, now practised, may have lessened these difficulties sufficiently to make such a scheme possible. We therefore recommend that the Health Departments should again consider whether differential notification of hepatitis, as suggested in the WHO Report, is now practicable.

CHAPTER 6

QUALITY CONTROL OF ROUTINE SCREENING TESTS

51. There are wide variations in results obtained in the same serological tests performed in different laboratories. The performance of quality control tests enables the extent of these variations to be assessed so that measures may be taken to correct discrepancies and to obtain more uniform results. Panels of antigens for quality control tests and for assessing the quality of locally selected reagents have been distributed by the Standards Laboratory for Serological Reagents, Central Public Health Laboratory, Colindale, to RTCs and reference centres since CIE became the routine screening test. We recommend that the PHS Board should be invited to arrange for the Standards Laboratory to continue to distribute panels of antigens, to analyse the results of quality control tests submitted to it and to report the findings to the participants. The composition of the panels will vary with current knowledge and needs. To begin with they should contain HB<sub>s</sub>Ag of different potencies and specificities, other agents which may cause false positive reactions and HB<sub>s</sub>Ag negative specimens.

52. Potential working reagents selected by RTCs as suitable for use in CIE tests, which may still be required, may be submitted to the Standards Laboratory for confirmation before they are used for routine tests.

## CHAPTER 7

### STAFF AND TRAINING

#### STAFF

53. 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 any laboratory in which testing for the presence of HB<sub>s</sub>Ag and anti-HB<sub>s</sub> is performed.
54. Such a laboratory 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 during absences of the head of the Laboratory.
55. 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<sub>s</sub>Ag may well be at least 1 per cent of the total screened and these reactions must be 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.
56. Because of the volume of work, the need to verify positive results and the potential hazards and problems that arise, 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. 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<sub>s</sub>. (see paragraph 17)

Training

57. The principles employed in haemagglutination methods are familiar to medical laboratory staff. However, proper training in these tests for the detection of HB<sub>s</sub>Ag 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 8

### ACCOMMODATION

#### Regional Transfusion Centres

58. We base our recommendations concerning space required for testing in RTCs on the following assumptions; (a) that the method used for detecting the titrating HB<sub>s</sub>Ag 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.

#### General Serology Laboratory

59. We envisage that the separation of each specimen into portions for blood grouping, syphilis testing and for tests for HB<sub>s</sub>Ag will be done in the general serology laboratory. One in about 1100-1200 of these sera, equivalent to about one specimen every day or so in some centres, is likely to be HB<sub>s</sub>Ag positive. Some of the precautions recommended below for the testing laboratory will be required in the general serology laboratory, including provision of wash-hand basins and of floors and benches that can be washed down with disinfectants. Centrifugation probably creates the main specific hazards and the area occupied by centrifuges, benches, floors and walls in the area should be easy to clean. As testing for HB<sub>s</sub>Ag 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

60. We recommend that at least two rooms should be provided for HB<sub>s</sub>Ag 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, preferably also, a WC and a shower.

61. The testing laboratory should be accessible only from the ante-room. To avoid overcrowding of staff it should have an area of not less than  $37.2\text{m}^2$  (400 sq ft) and a bench run of 6.1m (20ft) 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 wood work must be painted with a gloss paint, such as an epoxy paint, which is resistant to disinfectants (including glutaraldehyde and hypochlorite solution) and withstands scrubbing. Flooring should be water-proof and resistant to disinfectants and made, for example, of asphalt, rubber or vinyl sheeting. Electric power points at 1.2m (4ft) intervals along the benches are essential and gas points at 2.4m (8ft) intervals are desirable. There should be easy access to an autoclave and an incinerator.

#### Additional Accommodation

62. We have considered whether in hospitals 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 (see paragraph 68 below). We have concluded that this is not necessary and that the best way of meeting this problem is to arrange that, except in emergency, "high risk" patients are first tested for the presence of HB<sub>s</sub>Ag and 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

63. 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 9

SAFETY IN LABORATORIES

64. The risk to laboratory staff of contracting hepatitis in the course of their work 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 such as that described in paragraph 68 below. Recommendations on practice in laboratories are given in detail in "Safety in Pathology Laboratories", "The Prevention of Laboratory Acquired Infection" and the Report of the Working Party on the Laboratory Use of Dangerous Pathogens and all staff should make themselves familiar with these handbooks. Some points are particularly to be emphasised.

65. All staff must 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 must be provided.

66. 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. 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 71 below).

"High Risk" Specimens

67. Blood specimens from patients known to be HB<sub>s</sub>Ag positive should be labelled as such. 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. Specimens from patients with hepatitis B or from HB<sub>s</sub>Ag carriers should be tested under hepatitis laboratory conditions.

68. 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 infective, or suspected infective, 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, except in emergency, be tested for HB<sub>s</sub> Ag before specimens are sent for testing elsewhere. (see paragraph 62).

69. 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

70. 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

71. As the infective agent(s) causing hepatitis has not been isolated, the effects of disinfectants upon it cannot be examined. Our recommendations are based upon the known effects of disinfectants upon small viruses. We suggest that hypochlorite solution (eg Chlorox) is the disinfectant of choice when HB<sub>s</sub> Ag 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. When 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) or Formalin BP 10% (v/v) (containing Formaldehyde 4% v/v) 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.  
Articles should be exposed to the disinfectant for at least one hour. Some  
commercial glutaraldehyde preparations may not be free of corrosive activity  
for aluminium alloys. After disinfection rotor heads should be rinsed in water  
and carefully dried. Hands contaminated with blood 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

72. 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 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

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

74. The preventive and curative value of anti-HB<sub>s</sub> immunoglobulin, separated from plasma containing anti-HB<sub>s</sub>, is being investigated. The evidence available suggests that this specific immunoglobulin may have some protective value. Advice on its use may be obtained from a reference centre (see paragraph 42), from the Central Public Health Laboratory, Colindale, (see paragraph 43) or from the RTCs of the Scottish National Blood Transfusion Service.

CHAPTER 10

SUMMARY OF PRINCIPAL RECOMMENDATIONS

75. We summarise our principal recommendations as follows:-

- i. all blood donations should be tested for the presence of hepatitis B surface antigen (HB<sub>s</sub>Ag); donors whose blood is HB<sub>s</sub>Ag 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<sub>s</sub>) may be retained on the panel and their donations used clinically (paragraph 16);
- ii. arrangements should be made to continue the detection of anti-HB<sub>s</sub> at RTCs to the extent necessary to obtain sufficient plasma of adequate titre for the preparation of human anti-HB<sub>s</sub> immunoglobulin; these arrangements should be reviewed from time to time as the knowledge of the clinical value of this specific immunoglobulin develops (paragraph 17);
- iii. the practice of excluding from the panel donors with a history of jaundice should be discontinued provided that HB<sub>s</sub>Ag is not detected by reversed passive haemagglutination or a test of at least equal sensitivity described in Chapter 3 and that the donor has not suffered from hepatitis or jaundice during the previous 12 months (paragraph 18);
- iv. blood donations should be tested at Regional Transfusion Centres (RTCs); positive findings should be verified at RTCs and, upon verification, should be referred for confirmation to a reference centre (paragraph 19);
- v. specimens of the antigen required for testing should not be introduced deliberately into hospital pathology laboratories unless there is a consultant microbiologist responsible for the testing; at hospitals which do not have a consultant microbiologist specimens should normally be sent for testing to the appropriate Public Health Laboratory Service (PHLS) Laboratory in England and Wales or Virus Laboratory in Scotland; where ante-natal specimens are sent to the RTC for blood grouping they may also be tested there for HB<sub>s</sub>Ag if the Director of the RTC agrees (paragraph 20);

vi. 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<sub>s</sub>Ag and the donation should be so marked (paragraph 21);

vii. reversed passive haemagglutination (RPH) should be adopted as soon as possible by all RTCs in place of counterimmunoelectrophoresis (CIE) to screen every blood donation for the presence of HB<sub>s</sub>Ag but both systems of testing should be used in parallel for at least 5000 tests in each RTC on new donors before RPH becomes the routine method; there is no objection to the use of passive haemagglutination-inhibition, in place of RPH, in those RTCs with the required experience which either can make the reagent or have easy access to supplies (paragraph 34);

viii. a donor whose blood is positive on the first screening should be suspended from the panel; the donor's certificate booklet should not be endorsed with this information until confirmation of a positive result has been received; before an antigen positive donation is destroyed its use for the preparation of reagents or other materials should be considered (paragraph 36);

ix. when a donor is permanently excluded from the panel, following confirmation by a reference centre that his blood is HB<sub>s</sub>Ag 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 37);

x. all applicants for posts in the Blood Transfusion Service should be tested for the presence of HB<sub>s</sub>Ag 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 39);

xi. a member of staff found to be HB<sub>s</sub>Ag 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 40);

xii. the Health Departments should encourage investigation of the role of HB<sub>s</sub>Ag positive carriers among medical and paramedical staff in transmitting hepatitis B (paragraph 41);

- xiii. the PHLs Board in England and Wales and the Common Services Agency and the appropriate Health Boards in Scotland should be invited to continue to provide a reference service for testing for HB<sub>s</sub>Ag and anti-HB<sub>s</sub> and to undertake the related central reference and epidemiological work (paragraph 46);
- xiv. the reference radioimmunoassay service should continue and be increased as necessary in accordance with demand (paragraph 48);
- xv. reference centres and RTCs should notify each other of all cases of hepatitis (whether HB<sub>s</sub>Ag positive or not) which may have been caused by blood or blood products (paragraph 49);
- xvi. the Health Departments should again consider whether differential notification of hepatitis is now practicable (paragraph 50);
- xvii. the PHLs Board should be invited to arrange for the Standards Laboratory for Serological Reagents, Central Public Health Laboratory, Colindale, to continue to distribute panels of antigens to RTCs and reference centres after the introduction of RPH, to analyse the results of quality control tests submitted to it and to report the findings to the participants (paragraph 51);
- xviii. in matters concerning staff, training, accommodation and safety, RTCs should be guided by the advice given in paragraphs 53-56, 57, 58-63 and 64-74 respectively.

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APPENDIX 1

SUGGESTED LETTER TO THE HEPATITIS B SURFACE ANTIGEN POSITIVE DONOR

Dear Mr/Mrs/Miss

As a (regular) blood donor you may perhaps be aware that there is a risk that a 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.

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

ENDIX 2

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 antigen 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 disease 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.

Yours sincerely

APPENDIX 3

REFERENCE CENTRES FOR HEPATITIS B SURFACE ANTIGEN

BIRMINGHAM	Dr T H Flewett Regional Virus Laboratory East Birmingham Hospital Bordesley Green East Birmingham B9 5ST	021-722-4311 Ext <b>GRO-C</b>
BRISTOL	Dr S K 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	Professor N R Grist 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 G C Turner Fazackerley Hospital Lower Lane Liverpool L9 7AL	051-5252323
LONDON	Dr Y E Cossart 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: GRO-C
OXFORD	Dr J O'H Tobin United Oxford Hospitals Radcliffe Infirmary Oxford OX2 6AH	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 4

REFERENCE CENTRES FOR RADICIMMUNOASSAY

BIRMINGHAM

Dr T H Flewett  
Regional Virus Laboratory  
East Birmingham Hospital  
Bordesley Green East  
Birmingham  
B9 5ST

021-772-4311

Ext **GRO-C**

CARDIFF

Dr A D Evans  
Public Health Laboratory  
Institute of Pathology  
3rd Floor  
Royal Infirmary  
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0222-755944

EDINBURGH

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Department of Bacteriology  
University Medical School  
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031-667-1011

LONDON

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Central Public Health Laboratory  
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Middlesex Hospital Medical School  
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01-636-8333

Ext **GRO-C**

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and Tropical Medicine  
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01-636-8636