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Blood Transfusion and Transmissible Disease

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During the past 30 years great advances have been made in preventing what were the commonest forms of adverse transfusion reactions: namely pyrogenic reactions, circulatory overloading, haemolytic reactions and bacterial contamination of donations. This has been achieved by the combined efforts of transfusion centres, hospital laboratories and clinical users of donor blood to promote safer transfusion practices. In particular, care in collecting and storing blood, the performance of sensitive grouping and matching tests and attention to the volume and rate of transfusion have helped to reduce the incidence of adverse reactions. One result of this achievement has been to focus attention on the need to prevent the transmission of infective agents by transfusion.

Maycock (1972) stated that the transmission of viral hepatitis was the most serious complication of the use of blood and blood products. That emphatic statement was made at a time of great concern arising from the many serious outbreaks of viral hepatitis in chronic renal dialysis and transplant surgery units. Measures for the prevention of hepatitis in patients with chronic renal failure were discussed in detail (Department of Health and Social Security, 1972a) and practical recommendations were made to avoid the transmission of hepatitis by transfusion (Department of Health and Social Security, 1972b). The most important preventive measure against the transmission of communicable diseases is the avoidance of unnecessary transfusions.

A single donation may be used to provide as many as six different blood components. Thus an infective agent in one donation may be disseminated into multiple blood products. Similarly, because blood products are prepared from a large number of pooled donations, a recipient may be exposed to infective agents from multiple blood donors. Recipients may not have normal immune competence because of the primary disease or immunosuppressive therapy. The severity and consequences of adverse transfusion reactions depend in part on the clinical condition and immune state of the host.

Consideration of the transmission of communicable diseases must be seen against this background of preventive measures, sophisticated blood component therapy and the state of the patient. In transfusion therapy it is

important to consider the individual patient, but in respect of the transmission of disease the implications are much wider. A recipient who acquires an infective agent from a transfused blood component may expose contacts and attendants to the risk of infection. Nursing, medical and laboratory staff are at risk, as well as household and domestic contacts. Furthermore, an immunosuppressed recipient may become a chronic carrier of an infective agent, thus increasing the circulation of the infective agent in the community.

TRANSMISSION OF COMMUNICABLE DISEASES

In theory many communicable diseases might be transmitted by transfusion provided: (1) the infective agent is present in the blood of the donor at the time of blood collection; (2) the infective agent survives in the donation or its components during processing and storage; and (3) the recipient is susceptible to the infective agent. The safe and proper practice of transfusion involves the care of the donor, of the donation and of the recipient. If the transmission of disease is to be prevented, or at least reduced in incidence, donors must be carefully selected, appropriate tests must be performed on the donation and specific prophylactic or therapeutic measures undertaken in the recipient. The monograph entitled *Whole Human Blood* in the British Pharmacopoeia (1973) refers to disease transmissible by blood transfusion. In particular donor blood should not be obtained from a human subject: (1) who is known to be suffering from or has suffered from syphilis; (2) whose blood has not been tested with negative results for evidence of syphilitic infection; or (3) whose blood has not been tested with negative results for the presence of Australia (hepatitis-associated) antigen and its antibody—now known as the hepatitis B surface antigen (HB_sAg) and its antibody (anti-HB_s). In addition every donor should, as far as can be ascertained by a registered medical practitioner after inspection or simple clinical examination and consideration of his medical history, be free from disease transmissible by blood transfusion.

Viraemia occurs in systemic viral diseases, and a donor with symptoms will either not volunteer or will be excluded by the medical practitioner at the donor session. The 'dangerous' donors are those with asymptomatic viraemias, which may occur in the following situations:

1. during the incubation period of a specific infection, prior to the onset of symptoms
2. in association with an inapparent infection in which no obvious symptoms or signs are present
3. in the prolonged viraemias of persistent carrier states in apparently healthy persons.

Thus a simple medical examination and consideration of the medical history may not detect the donor with an asymptomatic viraemia. The volunteer who is a persistent carrier of a virus may not have had an overt illness.

Viral hepatitis

Mollison (1972) emphasises the prime importance of · l hepatitis among the diseases transmitted by transfusion. Specific virus infections which may cause

hepatitis are infectious mononucleosis (Epstein–Barr virus), cytomegalovirus, Q fever, coxsackie A, coxsackie B, yellow fever, herpes simplex, congenital rubella and adenovirus. When the term 'viral hepatitis' is used without qualification, it is usually taken to mean either viral hepatitis type A (formerly called infective, epidemic or short incubation hepatitis) or viral hepatitis type B (formerly called serum or long incubation hepatitis). There are no reliable biochemical or histological features to help distinguish between type A and type B hepatitis. The main clinical difference is in the incubation period, type A having an incubation period of 15 to 50 days and type B 30 to 160 days. A serological marker for recognising infection with or carriage of the virus of type B hepatitis has been discovered (Blumberg et al, 1967). This serum antigen was formerly called the Australia antigen, but is now known as the hepatitis B surface antigen (HB_sAg). An antigen described by Del Prete et al (1970) has been called the epidemic hepatitis associated antigen (EHAA) because of its prevalence in the sera of patients suffering from acute viral hepatitis type A. This antigen however is also found in the sera of patients with various other liver diseases, and is an abnormal lipoprotein associated with hepatocellular damage. A serum antigen specific for the infective agent of type A hepatitis has not yet been convincingly described.

Both type A and type B hepatitis can be transmitted by transfusion. The term post-transfusion hepatitis is often taken to imply only the transmission of type B hepatitis, but should include type A infections and hepatitis associated with cytomegalovirus and Epstein–Barr virus (Stern, 1972). Clinical manifestations of hepatitis include inapparent infection, anicteric illness, acute icterus and chronic liver disease. Studies of hepatitis B infection among volunteers and those naturally infected with the virus suggest that a greater proportion of individuals who have had a mild or inapparent infection become chronic carriers of HB_sAg than those who have had a more severe illness (World Health Organization, 1973). The existence of a chronic carrier state following hepatitis A infection has not been proved and many doubt that it exists. The viraemic phase of acute hepatitis A infection is brief, and for this reason exclusion of donors with a clinical history of hepatitis A infection may not materially diminish the frequency of hepatitis among recipients.

Similarly the exclusion of a donor with a history of close contact with a case of hepatitis during the previous six months is probably a wise precaution in our present state of knowledge, but it is doubtful if such exclusions reduce the incidence of post-transfusion hepatitis. Type A hepatitis is usually spread by the faecal–oral route. Epidemics of type A hepatitis tend to occur among children in families, schools and residential institutions. The contacts at greatest risk of acquiring the infection are close contacts in the household or institution, and the majority of adult contacts probably already have an active immunity to type A hepatitis. Anicteric hepatitis is common, so that adults who are unaware of ever having had a childhood illness characterised by jaundice may still have an active immunity. Type B hepatitis is usually associated with parenteral transmission, for example by transfusion, inadequately sterilised needles, razors, dental instruments and tattooing needles. Heathcote and She: k (1973) have however produced evidence suggesting that contact with cases of hepatitis or with HB_sAg carriers is the single most

important factor in the spread of acute type B hepatitis in a large, urban, cosmopolitan community. These authors emphasised that contact needs to be close and transmission is most likely to occur between sexual partners. Blood donors should be questioned about close contacts with patients with hepatitis, but it is probably necessary to exclude temporarily only those volunteers who have had a close contact during the past six months.

Alter, Holland and Schmidt (1970) noted that transfusion-associated viral hepatitis resulted in 30 000 cases of serious overt illness and 1500 to 3000 deaths each year in the United States. Since five subclinical cases appeared to occur for each instance of overt disease, the actual incidence of post-transfusion hepatitis in the United States probably exceeded 150 000 cases a year. Against that background it was estimated that the introduction of a relatively insensitive screening test which detected only 25 per cent of the carriers of HB_sAg would prevent approximately 40 000 cases of transfusion transmitted hepatitis in a year. In the United Kingdom post-transfusion hepatitis seemed to be a far less serious problem. Spurling, Shone and Vaughan (1946) found six (0.7 per cent) cases of jaundice among 891 recipients of blood, but doubt was expressed about the infective agent being transmitted by transfusion. Lehane et al (1949) observed 22 cases (0.8 per cent) in 2796 patients transfused with blood. A joint survey (Medical Research Council, 1954) reported four cases (0.16 per cent) of jaundice among 2538 recipients in England and Wales and five cases (0.36 per cent) among 1387 recipients in Scotland. In these three series within the United Kingdom there were no deaths attributable to the transfusion of blood. The frequency of anicteric hepatitis in the United Kingdom was investigated in a small series in Birmingham (Somayaji, Stone and Glover, 1967). This was a prospective study in which 45 patients were observed for 22 weeks after transfusion. Only two recipients had a transient rise in the level of serum transaminases. The authors concluded that none of the 45 recipients developed hepatitis. A recent detailed study (Medical Research Council, 1974) reported eight cases (1.0 per cent) of hepatitis among 768 recipients of blood in the London area. Five of these eight patients had icteric hepatitis, and two died from acute hepatic necrosis.

This report (Medical Research Council, 1974) compared the low incidence of icteric and anicteric hepatitis (1.0 per cent) in the United Kingdom with reported incidences from Japan (65 per cent), United States (18 per cent) and Germany (14 per cent). If the difference is real, it may be associated with a lower incidence of carriers of HB_sAg among British blood donors, with differences in the patient populations studied or with the criteria used in diagnosing hepatitis. The incidence of post-transfusion hepatitis in Britain may have been slightly underestimated in that towards the end of the survey, patients were receiving blood which had been found negative for HB_sAg by an immunodiffusion test. In the United Kingdom all donors are unpaid, and evidence from the United States has indicated that the incidence of HB_sAg is much higher in paid than in unpaid donors. The use of paid donors may account in part for the high incidence of post-transfusion hepatitis in some countries. An important reason for the reported differences in incidences of post-transfusion hepatitis may however be differences in the criteria used to establish a diagnosis of anicteric hepatitis. In the recent British series (Medical

Research Council, 1974) alanine transaminase (ALT) was estimated and values greater than 30 iu/l were regarded as abnormal. However, if other factors were present which might have caused the enzyme rise, these patients were not considered to be suffering from viral hepatitis. These other factors included underlying hepatobiliary disease and the administration of potentially hepatotoxic drugs. This rigid exclusion of all patients having other possible causes for their liver damage may have contributed to the low incidence (1.0 per cent) of post-transfusion hepatitis in the British study. It should be noted however that although the incidence of post-transfusion hepatitis was low, there was a morbidity and mortality equivalent to 27 cases of hepatitis and eight deaths per 10 000 units of blood transfused. One fatal case occurred towards the end of the survey, by which time donations were being tested for HB_sAg.

This last observation raises the important aspect of the reduction in the incidence of post-transfusion hepatitis achieved by the total screening of donations for the presence of HB_sAg. Alter, Holland and Schmidt (1970) stated that with the techniques then used to detect HB_sAg the exclusion of antigen positive donors would prevent no more than 25 per cent of transfusion-associated hepatitis. This inability to prevent 75 per cent of cases of transfusion-transmitted hepatitis was multifactorial:

1. The techniques used for detecting HB_sAg were mainly immunodiffusion (ID) or counter-immunoelectrophoresis (CIEP) which are relatively insensitive. It was also suspected that HB_sAg was not homogeneous and that different antigenic determinants existed (see below).
2. Infective agents other than that of type B hepatitis might be transmitted by transfusion. These other infective agents include type A hepatitis, cytomegalovirus (CMV), Epstein–Barr virus (EBV) or some other hepatitis virus not yet isolated.
3. The use of freshly donated blood not tested for HB_sAg.
4. A route of transmission other than transfusion.

Although the introduction of disposable syringes and needles has helped to prevent transmission from one patient to another there are still other potential portals of entry, for example haemodialysis, cardiac catheterisation, tuberculin testing (Heaf gun), paracentesis and electromyography.

Detection and measurement of HB_sAg

The morphology of the hepatitis B antigen is sufficiently characteristic for electron-microscopy to be used for direct detection. Three types of particle may be seen. Small round forms about 16 to 18 nm diameter are most numerous. Long forms about 20 nm diameter, but of variable length, are usually present. A third type called the Dane particle may be present. It is a double-shelled or 'doughnut' form about 45 nm diameter, the inner shell or core being approximately 20 nm diameter. The Dane particle may be the intact hepatitis B virus, while the small round particles and the long forms are derived from the surface coating of the virus. Antigenic determinants are present in the coat protein of the hepatitis B virus, and are now termed the hepatitis B surface antigen (HB_sAg). The dense core of the Dane particle is

antigenically distinct and is called the hepatitis B core antigen (HB_cAg). Visualisation of the particles by electron-microscopy or serological techniques for the identification of HB_sAg may be used for detection. Wallace, Barr and Milne (1975) report the results of a four-year programme of screening 438 937 donations for HB_sAg by the technique of counter-immunoelectrophoresis (CIEP). A comparative trial of the techniques of CIEP, reversed passive haemagglutination (RPHA) and radioimmunoassay (RIA) was conducted on 27 487 of these donations.

The serological method used for the detection of HB_sAg in blood donors should be simple, rapid, sensitive and specific. Available techniques are discussed in a special report (World Health Organization, 1973) in which CIEP is recommended as a desired minimum for testing blood donations. The most sensitive method is RIA. Each method has advantages and disadvantages, but the successful detection of HB_sAg depends as much on the meticulous performance of the chosen test as on its relative sensitivity. A large transfusion centre may require to test 500 or more donations each day. It is therefore important to employ a screening procedure which is simple and rapid, and at the same time sensitive without being oversensitive to the extent of giving a large number of non-specific or false positive reactions.

The sensitivity of the technique and specificity of the reagents used for screening donations obviously influence the rate of detection of HB_sAg. However, according to the World Health Organization (1973), most apparently healthy carriers of HB_sAg have a high titre of circulating antigen that is readily detectable by insensitive methods such as CIEP. This special WHO report indicates that CIEP screening of blood donations might be expected to prevent approximately 30 per cent of cases of post-transfusion hepatitis, and the effect of introducing more sensitive techniques is unlikely to be great. However, Ling and Overby (1972) reported that RIA detected ten times as many HB_sAg positives among clinically well donors in the United States as did CIEP. A similar observation was made by Prince et al (1973) who noted, however, the occurrence of false positive reactions by RIA. In only 21 per cent of sera which were RIA positive but CIEP negative, was the RIA positivity specific for HB_sAg, as shown by clearcut neutralisation by anti-HB_s.

Wallace, Barr and Milne (1975) tested 27 487 Scottish donors and found the number of HB_sAg positives to be 27 by CIEP, 39 by reversed passive haemagglutination (RPHA) and 41 by RIA. These findings indicate an increased detection rate of 44 per cent by RPHA and of 52 per cent by RIA compared with the CIEP screening method. Nine recipients of these 14 donations giving false negative reactions by CIEP were traced: two died soon after transfusion, one remained well, two developed anicteric and four icteric hepatitis type B. One patient with icteric hepatitis died from acute hepatic necrosis. There seems to be no doubt that the replacement of CIEP by haemagglutination inhibition (Hopkins and Das, 1973) or by RPHA or RIA will detect more carriers of HB_sAg. It is especially important to use a sensitive test for donors who are suspected of being potential carriers of HB_sAg. Groups known to have a high prevalence of antigenaemia include immigrants or returned travellers from tropical areas, drug addicts, male homosexuals, prisoners, the tattooed and the sexually promiscuous.

From a carefully controlled study Koretz et al (1973) were uncertain whether post-transfusion hepatitis was related to the presence of HB_sAg or to other infective agents in the donations. The practical importance of infective agents other than virus B in the causation of post-transfusion hepatitis was illustrated in a report by Prince et al (1974). In a detailed prospective study of 204 cardiovascular-surgery patients, an agent other than virus B seemed to be the cause of 36 (71 per cent) of 51 cases of overt post-transfusion hepatitis. The sera of these 36 cases showed by sensitive tests no evidence of the HB_sAg or anti-HB_s response which would have been expected in a hepatitis type B infection. Incubation periods and clinical and epidemiological features were inconsistent with short incubation infective or type A hepatitis. Cytomegalovirus (CMV) seroconversion was no more common among the HB-negative cases than among either HB-positive cases or patients who did not develop hepatitis. It was concluded that CMV was not responsible for the HB-negative cases of post-transfusion hepatitis. The possible role of Epstein–Barr virus (EBV) in the aetiology of HB-negative hepatitis was also considered, but the serological evidence indicated that it was unlikely that EBV played an important role in post-transfusion hepatitis. While in the series of 204 patients only 15 (29 per cent) of the 51 cases of overt post-transfusion hepatitis were HB-positive, another 25 patients had serological evidence of exposure to HB_sAg without developing hepatitis. However Prince et al (1974) suggest that a large proportion of long incubation post-transfusion hepatitis is unrelated to hepatitis type B and that control of post-transfusion hepatitis will require identification of a hepatitis virus type C.

Another concept of the causal agents of post-transfusion hepatitis is elaborated by Sutnick et al (1973) following a prospective study. The HB_sAg screening of donations was performed at first by ID and later by CIEP. At the outset of the study HB_sAg-positive donations were not withdrawn from use, but later all positive units were excluded. Patients admitted to the study included those who had no history of prior transfusion, hepatitis contact, heavy alcohol intake, drug addiction, exposure to hepatotoxic agents or drugs, including halothane, and no history of past or present liver disease, malignancy or sickle-cell disease. Of the 24 recipients who developed post-transfusion hepatitis, 12 had received at least one unit of HB_sAg-positive blood, while the remaining 12 had received only blood in which HB_sAg was not detected. The absence of HB_sAg from donations given to the latter group of 12 recipients was confirmed by retesting the donors by RIA. These two groups of recipients who developed hepatitis had similar clinical symptoms and signs, and there was no difference in the median incubation period. It was concluded that there were no distinguishing features between the hepatitis occurring in recipients of HB_sAg-positive blood and that occurring in recipients of HB_sAg-negative blood in respect of incubation period, symptoms, physical signs, clinical course, laboratory findings, histological features and severity of disease. An apparently paradoxical finding was the occurrence of HB_sAg in the serum of recipients of HB_sAg-negative donations. Among the 12 recipients of HB_sAg-positive blood who developed hepatitis, seven were HB_sAg-positive by ID and eight by RIA. None of the 12 recipients of HB_sAg-negative blood developing hepatitis were HB_sAg-positive by ID, but nine were positive by RIA. Having

found no distinguishing features between hepatitis in recipients of HB_sAg-positive and HB_sAg-negative donations, and an equivalent frequency of HB_s antigenaemia in each of these two groups of recipients, it was suggested that there was one major aetiological agent for human viral hepatitis. Differences in host response to this single infective agent might be responsible for the clinical differences in the disease.

Even if there is only one major type of viral hepatitis, namely type B of which HB_sAg is a marker, there is no doubt about the complexities of the antigenic structure of HB_sAg (Nature, 1974). All examples of HB_sAg share a common antigen *a*, but differ in the possession of a second antigen which may be either *d* or *y*. Thus there are two antigenic subtypes *ad* and *ay*. Among symptomless carriers of HB_sAg the subtype *ad* predominates in northern Europe and in North America, whereas there is a preponderance of the subtype *ay* in Pakistan, the Middle East and Mediterranean countries. However regional differences in the prevalence of these subtypes may occur in blood donors within a country. In general both *ad* and *ay* subtypes are encountered in patients with acute hepatitis type B, but the *ay* subtype has been detected frequently among drug addicts and in hepatitis outbreaks in renal units. Investigations by Iwarson et al (1973) showed that Swedish donors of subtype *ad* usually had normal liver function and presented little risk of transmitting hepatitis, whereas donors of subtype *ay* commonly had signs of acute or chronic liver disease, and their donations often caused post-transfusion hepatitis. This difference may, however, have been associated with the fact that there were some drug addicts among the *ay* donors as well as some non-addicts who were incubating type B hepatitis. New antigenic subtypes designated *w* and *r* have been described. Four phenotypes of HB_sAg, namely *adw*, *adr*, *ayw* and *ayr* have now been recognised (Nature, 1974). An epidemiological study on these new subtypes in 63 Canadian blood donors who are persistent carriers of HB_sAg has been reported (Feinman et al, 1973). Most of these donors who had the subtype *adw* were born in Canada, China, Germany and the West Indies, whereas most donors who had the subtype *ayw* were from Mediterranean countries. All eight donors with the subtype *adr* were from China. No examples of the subtype *ayr* were found among these Canadian donors. The phenotype *ayr* seems to be found only in the Far East. In the Canadian study evidence of abnormal liver function was equally common in the three phenotypes, *adw* (30 per cent), *adr* (25 per cent) and *ayw* (26 per cent), which contrasts with the Swedish study in which donors of subtype *ad* usually had normal liver function (Iwarson et al, 1973).

The serological complexities of the hepatitis B antigen system were increased by the observations of core antibody (anti-HB_c) directed against core antigen (HB_cAg), the inner component of the Dane particles. Persistent anti-HB_s which is directed against the surface antigen HB_sAg is found in only a proportion of cases of type B hepatitis. Anti-HB_s is found more frequently in those repeatedly exposed to antigenic stimuli from HB_sAg, for example nurses, hospital laboratory staff, drug addicts, haemophiliacs and those who live in situations in which HB_s antigenaemia is common. Although anti-HB_s tends to appear only transiently after type B hepatitis, Hoofnagle, Gerety and Barker (1973) showed that all patients with type B hepatitis developed anti-

HB_c. Furthermore, all HB_sAg carriers had anti-HB_c in their sera, indicating that they were neither immunologically tolerant nor unresponsive to HBAg. It was observed that one per cent of unpaid donors and five per cent of commercial donors in the U.S.A. had anti-HB_c in the absence of HB_sAg and anti-HB_s. This finding may reflect insensitivity in the detection of HB_sAg and anti-HB_s, but persistent anti-HB_c may represent a sensitive marker of continuing viral replication and of potentially dangerous blood donors. It has already been noted that cases of type B hepatitis have occurred after transfusion of apparently HB_sAg negative donations. Perhaps tests for anti-HB_c will be useful for screening blood donations to prevent the transmission of post-transfusion hepatitis.

At present in Britain all donations are tested not only for HB_sAg, but also for anti-HB_s. Screening for anti-HB_s provides reagents for the detection of HB_sAg and donations of plasma for the production of the specific immunoglobulin anti-HB_s. The British Pharmacopoeia (1973) states that donor blood should not be obtained from a human subject whose blood has not been tested with negative results for the presence of HB_sAg and anti-HB_s. There has been considerable controversy over the rejection of donors whose serum contains anti-HB_s. Apart from the provision of reagents such donations have been used hitherto in the U.K. to prepare only the specific immunoglobulin anti-HB_s. It is generally accepted that human immunoglobulins, IgG, prepared by chemical precipitation do not transmit viral hepatitis. In some other countries donor plasma containing anti-HB_s has also been fractionated to provide albumin or plasma protein fraction, because solutions of these albuminoid fractions can be pasteurised at 60°C for 10 hours to inactivate viral agents. The finding of anti-HB_s in a donation is evidence that the donor has been exposed to HB_sAg, and it is known that antigen–antibody complexes may occur. Furthermore, it has been the practice in Britain for the past 20 years to reject as donors, volunteers with a history of viral hepatitis. Opinions on the risk of transfusing blood containing anti-HB_s are however changing, as are views on the rejection of volunteers with a history of hepatitis.

Aach et al (1974) followed recipients who were considered to be susceptible to the infective agent of hepatitis type B in that prior to transfusion the recipients' sera contained neither HB_sAg nor anti-HB_s. Approximately half of these susceptible patients received at least one unit of donor blood containing anti-HB_s; the remainder did not receive donations containing anti-HB_s. All donations were HB_sAg negative. There was no significant difference between these two groups of recipients in the development of biochemical or overt hepatitis type B. It was concluded that blood containing detectable anti-HB_s carried no increased risk of transmitting type B hepatitis compared with donations which lack this antibody. This conclusion was reached also by Dane (1975) following a controlled study in London of recipients of donations containing anti-HB_s. A forthcoming report from the World Health Organization (Zuckerman, 1975) is likely to recommend that donations containing anti-HB_s can be used for normal transfusion purposes, provided the donation is HB_sAg negative by a sensitive method of testing. Maycock (1975) considers that the following three modifications should be made to the present policy in Britain: (1) that all donations should be tested for HB_sAg by reversed

passive haemagglutination (RPHA) or by an alternative technique with a sensitivity at least equal to RPHA; (2) that donations containing anti-HB_s can be used normally, provided the donation is found to be HB_sAg negative by a sensitive method of testing; and (3) donors with a history of hepatitis may be accepted provided the illness was not within the previous 12 months; any donation from such a donor must not however be used until it has been shown to be HB_sAg negative. If these recommendations are adopted it will no longer be obligatory to test every donation for the presence of anti-HB_s. It will however be necessary to screen some donations, because plasma containing anti-HB_s will be required for the production of specific immunoglobulin. Once donors with anti-HB_s have been identified it would be advantageous to encourage and persuade these donors to give large volumes of anti-HB_s plasma by plasmapheresis. The amount required is uncertain, because the prophylactic value of the specific immunoglobulin is not yet proven. Spread of viral hepatitis type A in the community cannot be prevented, but when special protection is required human normal immunoglobulin (HNI) is of proven value (Public Health Laboratory Service Report, 1968). This suppresses the overt features of type A hepatitis, although infection may still occur. It is doubtful if HNI attenuates viral hepatitis type B, but the effectiveness of HNI probably depends on the anti-HB_s content of the particular preparation of HNI. Experience in the West of Scotland has shown that 0.2 per cent of donors tested for the first time have anti-HB_s using the CIEP technique. The incidence rises to approximately 1.0 per cent with the more sensitive haemagglutination method. Since the current practice in Britain is to screen all donations for anti-HB_s, and to use the high titre anti-HB_s detected by CIEP for the production of specific immunoglobulin, the HNI currently in use has a lower anti-HB_s content than formerly. If Sutnick et al (1973) are correct in postulating only one infective agent for viral hepatitis, the current HNI may be less effective than earlier batches in attenuating infection. Limited amounts of human specific immunoglobulin (HSI) anti-HB_s are available, and use should be carefully controlled (Kerr, 1973). Genuine accident situations are a clear indication for use. For example accidental self-inoculation with material which is definitely known to contain HB_sAg or the transfusion of blood which is HB_sAg positive constitutes an indication for the immediate use of HSI anti-HB_s. The dosage is empirical, but for the present the recommended dose is 0.5 g IgG given by deep intramuscular injection. Until international units for anti-HB_s are established the dose is expressed gravimetrically, the IgG fraction having been prepared from selected high titre plasma. Another situation in which HSI anti-HB_s may be of value is in chronic renal dialysis units. Szmuness et al (1974) report encouraging initial results in a pilot study of the prophylactic value of anti-HB_s in haemodialysis centres, but significant results must await the outcome of a larger controlled trial now being conducted in the U.S.A. Another clinical situation in which passive HSI anti-HB_s may be of value is the protection of infants born to mothers who are symptomless carriers of HB_sAg.

The most important preventive measure against post-transfusion hepatitis is the avoidance of unnecessary transfusions. Albu[illegible]noid fractions can be heated at 60°C for 10 hours to inactivate viral agents. IgG fractions prepared

by chemical precipitation appear to carry no risk of transmitting viral hepatitis. The transfusion of red cells recovered from a frozen bank rarely causes hepatitis. However the prevention of parenterally transmitted viral hepatitis type B depends primarily on the recognition of symptomless carriers of HB_sAg. Persistent carriers must be excluded from panels of blood donors and from haemodialysis units. Experience in the West of Scotland has shown that 0.13 per cent of donors tested for the first time by the CIEP technique are chronic carriers of HB_sAg. When the more sensitive RIA method is used the incidence rises to approximately 0.2 per cent. Such screening for HB_sAg has however created new problems in deciding what should be done for blood donors and indeed for all asymptomatic and apparently healthy individuals found to be HB_sAg positive. This problem has been reviewed (British Medical Journal, 1974). Clinical examination and liver function tests should be undertaken to exclude liver disease. The healthy carrier must be told that he must not donate blood, but that at present there is no epidemiological evidence to justify other restrictions (Turner, 1973). Existence of HB_s antigenaemia should be reported to practitioners who may then take special precautions. For example, a dentist treating a patient with known HB_s antigenaemia may use gown, face-mask, eye protection and rubber gloves.

Hepatitis transmitted by cytomegalovirus (CMV) and Epstein–Barr virus (EBV)

CMV and EBV infections of the liver are reviewed by Stern (1972). Yellow fever, hepatitis type A and hepatitis type B are the only viral infections of man which consistently have hepatitis as the main clinical manifestation. Other viruses that cause hepatitis tend to do so rather as a complication of their more usual clinical picture. The most important of this group are CMV and EBV. CMV is an important cause of Paul–Bunnell negative infectious mononucleosis, while EBV is the cause of Paul–Bunnell positive infectious mononucleosis.

An illness resembling infectious mononucleosis is a complication of open-heart surgery and of other procedures requiring large transfusions of fresh blood from multiple donors. This illness, often described as the post-perfusion syndrome, is reviewed by Kantor and Goldberg (1971). It is a systemic disorder associated with fever, hepatosplenomegaly and atypical lymphocytosis. The finding of increasing serum antibody titres to CMV and the isolation of this virus from patients with the post-perfusion syndrome have clearly established CMV as the aetiological agent in this disorder. Liver function tests are nearly always abnormal and some patients develop severe icteric hepatitis.

A recent study (Medical Research Council, 1974) found that 270 (38 per cent) of 712 recipients had no detectable CMV antibodies before transfusion. Of these susceptible recipients 24 (nine per cent) acquired CMV antibodies after transfusion, but only four had biochemical abnormalities suggesting a CMV primary infection with anicteric hepatitis. CMV antibody booster responses occurred in 13 (2.9 per cent) of the 442 recipients who had antibodies at the time of trar[illegible]sion. Only one of these patients with a booster response was considered to [illegible]ave anicteric hepatitis. Thus in this series of 712 recipients

five cases of CMV-associated anicteric hepatitis occurred: four were examples of primary CMV infection, and the remaining case was an example of CMV reinfection.

Most adults have EBV antibodies, but since EBV may be carried in a latent form in the circulating leucocytes of healthy persons possessing EBV antibodies, infection can also be transmitted by blood transfusion. In turn, however, few adult recipients lack EBV antibodies, and the incidence of post-transfusion EBV infections is low compared with CMV infections. Of 712 recipients only 55 (7.7 per cent) had no EBV antibodies before transfusion and only four of these showed primary seroconversion after transfusion (Medical Research Council, 1974). An EBV booster response occurred in only one of the 657 patients who had EBV antibodies before transfusion. Thus there was serological evidence of post-transfusion EBV infection in five of 712 recipients, but no clinical illness or disturbed liver function associated with the EBV infection.

This frequency of CMV and EBV antibodies in the hospital population studied is similar to that found previously for the same age groups in London. Although the risk of post-transfusion infection with these viruses is greater with fresh blood, infection can be transmitted by blood stored for several days. Although most of these infections are primary in patients without specific viral antibodies, reinfections or reactivations of latent infections do occur, particularly in patients with low titres of pre-existing antibody. Nearly all of these infections are symptomless and both CMV and EBV infections transmitted by transfusion are essentially benign conditions. However, transfusion can be a hazard for patients on immunosuppressive therapy and for pregnant women. There is currently no established method for preventing the transmission of these viruses by transfusion. Preventive measures might include the screening of blood donors for evidence of infection, utilising stored rather than fresh blood when possible, or adding antiviral agents to potentially infected blood products (Kantor and Goldberg, 1971). Screening of donors for the absence of EBV antibodies is unlikely to be productive, because relatively few adults are without these antibodies. A similar screening procedure may help to prevent the transmission of CMV infections, although it will be difficult to detect the occasional donor undergoing primary infection at the time of giving blood (Stern, 1972).

Syphilis

In the United Kingdom it is not customary to question donors directly about syphilis, but a serological test for syphilis is performed on each donation. If a clinician insists on transfusing absolutely fresh blood he is advised by the transfusion service that no serological test for syphilis has yet been performed on the donation. In such circumstances it is desirable to use blood from a volunteer who has given blood on several previous occasions and has been consistently seronegative. Should the results of the subsequent serological tests on the donation be positive, then the recipient must be given a course of antibiotic therapy.

Transfusion transmitted syphilis is not a serious problem with the voluntary

unpaid donor service in Britain. The incidence of confirmed positive reactions for syphilis in donors is low, being less than one in 10 000 in the West of Scotland. Routine serological testing is not by itself a complete safeguard, since it is known that approximately 35 per cent of persons with primary syphilis are seronegative. It is possible that a donor incubating secondary syphilis might have spirochaetes in the blood and be seronegative. Although syphilis is an uncommon disease in voluntary blood donors it is advisable to have confidential communications between the transfusion service and practitioners in special clinics for the sexually transmitted diseases. Patients attending these clinics should be asked routinely about blood donations. During the past 30 years five cases have come to light in the West of Scotland of donations probably having been given during the seronegative phase in the incubation period of syphilis. The recipients were followed up and investigated thoroughly, but no evidence of syphilitic infection was found. Even if the five donations contained spirochaetes, the storage conditions of donations would have been unfavourable for the survival of these infective agents. Each of the five donations of whole blood had been stored for at least five days prior to transfusion. Blood stored for four days or more at +4°C is virtually safe as far as transmitting syphilis is concerned (Mollison, 1972). The majority of donations transfused have been stored for at least four days, and even blood stored for 24 hours is in this respect probably much safer than fresh blood. Apart from the use of platelet concentrates prepared from freshly donated blood, it is now unusual in Britain to use donations which have not been stored for at least 24 hours. This practice allows the performance of laboratory tests not only for syphilis but, more important, for the detection of HB_sAg (see above). Each of the five recipients of potentially infective blood had been given penicillin for the primary clinical condition. A large proportion of patients ill enough to require transfusion also receive antibiotic therapy, and this is a further safety factor in preventing the transmission of syphilis by transfusion.

Most transfusion services in the U.K. rely on only one serological test for syphilis as a screening procedure. The number of tests performed each day is likely to be at least 400 and often greater. There is therefore a growing tendency to use an automated procedure such as an automated VDRL test or an automated Wassermann reaction. These sensitive screening tests may detect some biological false positive reactions in apparently healthy donors. It is clearly important not to make a firm diagnosis of syphilis on the basis of a single serological test. Sera giving presumptive positive reactions should be referred to a laboratory which undertakes a battery of serological tests for syphilis. If the results of the confirmatory tests suggest that the donor has or has had a syphilitic infection, then the donor should be advised to consult his general practitioner.

Brucellosis

In the United Kingdom this is largely an occupational disease, more than 70 per cent of cases occurring in farm workers. Other hazardous occupations are veterinary surgeons and workers in abattoirs. The number of reported cases of brucellosis clearly transmitted by transfusion is small. Mollison (1972)

quotes three cases. Only one definite case is known to have occurred in the West of Scotland in the past 30 years. There appears to be a long incubation period in transfusion transmitted brucellosis, symptoms and signs not being evident until three months after transfusion. When a recipient develops a febrile illness several weeks or months after transfusion, the possibility of brucellosis transmitted by transfusion should be considered and investigated. If the diagnosis is confirmed by specific serological tests, all the donors involved should be traced.

Toxoplasmosis

There is a possibility of transmitting this infection by transfusion. Parasitaemia may occur asymptomatically in an apparently healthy person and the organism may retain its viability in blood stored at +4°C. However, the only reported cases of transmission by transfusion have occurred in special circumstances. The recipients suffered from acute leukaemia and were given leucocyte transfusions from 'donors' with chronic myeloid leukaemia (Siegel et al, 1971). It is suggested that transmission of toxoplasmosis by transfusion may occur when large numbers of infected leucocytes are given to recipients with impaired immune responses.

BLOOD TRANSFUSION AND TROPICAL DISEASES

The growing importance of this subject has been emphasised (Lancet, 1973). All over the world there is an increasing demand for donor blood and this has created in some countries problems in recruiting suitable donors. In such a situation donations may be accepted from apparently healthy volunteers whose history should have excluded them, because of the danger of transmitting disease. The increase in exotic diseases imported from tropical areas into countries with temperate climates is closely related to the rapidity of international travel. It must be emphasised that donations from volunteers whose visits overseas were of only short duration may transmit certain tropical diseases.

The high incidence of HB_s antigenaemia in tropical areas has already been noted, and viral hepatitis is undoubtedly the most common and the most serious infection transmitted by transfusion. Sporadic cases of brucellosis, kala-azar, relapsing fever, syphilis and African trypanosomiasis transmitted by transfusion have been described. However the two tropical diseases proper which are of the greatest importance in this context of transmission by transfusion are malaria and American trypanosomiasis (Chagas' disease).

Malaria

The accidental transmission of malaria by transfusion was recognised soon after the first attempts at direct transfusion. Records covering the period 1950 to 1968 and based on data from 35 countries showed 655 cases of transfusion malaria (Bruce-Chwatt, 1971). More than one half of these cases were associated with *Plasmodium malariae* infections; the remainder were due to

P. vivax, *P. falciparum* and *P. ovale* in decreasing order of frequency. Such occurrences were probably more common because of failure to diagnose or to report. The number of cases of transfusion malaria in the past 30 years reported in the U.K. was only eight (Dike, 1970). This small number probably reflected the careful selection of blood donors, but constant vigilance is needed.

Thus Bruce-Chwatt, Southgate and Draper (1974) describe a case of transfusion malaria due to *P. falciparum* which occurred in Britain. The donor was a visitor from Africa and his donation was intended to be used only for the preparation of plasma, but by mischance was transfused as whole blood. Fortunately the recipient had only a mild pyrexia with low parasitaemia and spontaneous recovery. Malaria should be suspected in any patient with pyrexia of uncertain origin who has had a blood transfusion up to three months prior to the onset of fever. In 1971 there was an outbreak in Spain of 54 cases of malaria (*P. vivax*) due to the indiscriminate use of previously infected donors.

Transfusion services in temperate zones should not use a donation of whole blood or the red cells from a volunteer who has had malaria in the past or has lived until recently in an endemic malarious area. Plasma from these donors may be used for the preparation of fractions. Malaria can be transmitted by fresh whole plasma if it contains a few intact red cells which contain parasites. This type of screening of volunteers by history is most effective, provided it is strictly applied. Two other preventive measures which should be considered in relation to transfusion transmitted disease are a screening test for the detection of the infective agents and the effect of blood storage conditions on infective agents. In the case of malaria the detection of the infective agent in an apparently healthy donor is difficult since asymptomatic parasitaemia is usually very scanty. Thus microscopic examination of blood films is of little value. In addition the need to prepare for each donor a minimum of at least three thin films and three thick films free from even small amounts of foreign matter renders this form of screening a large number of volunteers impractical. The method of indirect diagnosis of malaria by the use of immunofluorescence tests offers the best possibility of routine screening of donors for latent malaria infections.

Bruce-Chwatt et al (1972) studied a group of potential blood donors in the London area by application of the indirect fluorescent antibody (IFA) test to detect malaria antibodies. These potential donors numbered 880 adults, all British-born, who had lived or travelled extensively in tropical areas. Some gave a clear history of malaria, while others had only a vague recollection of an undiagnosed febrile illness during their stay abroad. Only 209 (24 per cent) were found to have a positive IFA test. In the remaining 671 (76 per cent) with negative IFA test, either past malaria was unlikely or their infection was eliminated, and thus their donations of whole blood or red cells might have been used for transfusion. It was shown that the highly sensitive IFA test can detect malaria antibodies as long as 20 years after the last exposure to malaria.

All known species of malaria parasites may survive for at least 14 days in blood stored at +4°C. For example quartan malaria (*P. malariae*) has been accidentally transmitted by blood stored for five days, and malignant tertian

malaria has been transmitted by a donation stored for 14 days. Thus the problem of preventing the accidental transmission of malaria by transfusion cannot be solved by using only stored blood. In temperate zones the best solution is to avoid transfusing the red cells from a person who has previously resided in an area in which malaria was endemic. The selection of non-infected donors is impracticable in tropical countries where malaria is prevalent and the best method of prevention is the prophylactic administration of anti-malarial drugs, for example a single intramuscular injection of chloroquine (600 mg) to all recipients immediately following transfusion.

American trypanosomiasis (Chagas' disease)

Chagas' disease is prevalent between northern Argentina and southern Mexico; over 7 million people are infected and 35 million are exposed to the risk of infection (Lancet, 1973). In Latin America blood transfusion constitutes the second most important way of transmitting Chagas' disease. The parasites survive well in stored blood. Addition of crystal violet (125 mg) to a unit of stored blood kills the parasites, but does not damage the red cells. However toxicity tests are needed particularly in recipients of multiple units of donor blood so treated.

ACCIDENTAL INTRODUCTION OF INFECTIVE AGENTS

Patients with malignant disease are susceptible to common and exotic infections because their defences are compromised as a consequence of the primary disease and intensive chemotherapy. Frequently these patients are given supportive transfusion therapy which creates a portal of entry for infective agents. The prevention and treatment of infection in states of immunosuppression have been reviewed by Levine et al (1974). Particular mention is made of the introduction of infective agents through intravenous catheters, contaminated infusion fluids and infected blood products.

The possibility of transmitting malignant disease by transfusion is raised by Molnar and Gitnick (1974) with specific reference to carcino-embryonic antigen (CEA) which is an immunological marker associated with many malignancies, especially those of the gastrointestinal tract. CEA has been found in 20 per cent of donations. The hazard of transfusing CEA may not become evident for many years, but the need for a large collaborative long-term follow-up of recipients of blood products containing CEA is indicated.

Indeed, close collaboration is essential if the incidence of transfusion-transmitted disease is to be reduced. The safest and most efficient hospital transfusion service is achieved when there is regular consultation and good communication between the clinician in charge of the patient, the hospital haematologist and the medical director of the transfusion service. It is particularly important to have a rapid exchange of information about any alleged case of the transmission of a communicable disease. In this way 'dangerous' donors can be identified and potentially infected blood products isolated. Constant vigilance is necessary to prevent the transmission of infective agents by transfusion.

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13

Massive Blood Transfusion

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The massive transfusion of blood is required to sustain the life of the exsanguinating patient. This situation represents a most severe challenge to blood banking as a science and as an art, because any shortcomings in supply, distribution, storage, preservation and administration will produce disastrous results.

Because of the desperate clinical circumstances, detailed studies in patients undergoing massive transfusion have been very rare. Much of our hard data are therefore fragmentary, poorly controlled and even anecdotal. However, there have been enough new observations in this field in the last ten years to warrant a reconsideration and a redefinition of some of these problems. This chapter will deal mainly with those problems of massive transfusion that can be categorised as metabolic and related (Table 1).

MATHEMATICS OF EXCHANGE TRANSFUSION

If a number of simplifying assumptions are made, the mathematics of exchange transfusion are rather straightforward (Wiener and Wexler, 1946; Marsaglia and Thomas, 1971). These are that mixing in the recipient is instantaneous and complete; that the blood volume at completion equals the initial blood volume; that the transfused blood is constant in composition; and that the recipient is a closed system so that no substance in question is otherwise added or removed during the exchange and that only the blood volume is involved in the exchange. Formula (1) applies when exchange is performed in equal stepwise or incremental manner, with the volume infused equaling the volume withdrawn for each step, beginning with withdrawal.

$$X_n = X_o \left(1 - \frac{b}{v}\right)^n \qquad (1)$$

where X_n = the amount or concentration of the substance in question remaining in the recipient's blood after n units of blood; X_o = the amount or concentration of the substance in question in the recipient's blood before transfusion; b = the volume of a unit of blood; v = the recipient's blood volume; n = the number of units of blood transfused.