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Viral Infections Transmitted by Blood and Its Products

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Hepatitis B virus (HBV) is the traditionally important example of a virus transmitted by blood transfusion. In part, this observation led to the name 'serum hepatitis' by which HBV was previously known. In recent years a number of other agents have been identified whose mode of transmission is similar. The transmission of some of these agents has become apparent only since the introduction of supportive therapy for highly immunosuppressed patients; in addition the widespread use of blood products produced from plasma pools derived from several thousands of donors has increased the chances of transmitting infectious agents. Since one contaminated pool may represent the raw material for hundreds of doses of product, 'biological amplification' of a single infectious donation can occur. This is particularly true in the case of products like factor VIII concentrate, where little antibody is included in the product. Even in the presence of high levels of antibody which might be expected to diminish viral infectivity, certain viruses, for example HBV and the human parvovirus, transmit effectively.

Recent changes in medical practice have also exacerbated the problem. Transplant recipients, immunosuppressed to prevent graft rejection, and cancer patients receiving chemotherapy are often given cellular blood components; these patients can then act as sensitive 'sentinels' for viruses like cytomegalovirus (CMV). As a result, the replacement therapy of these patients whose underlying illnesses, directly or indirectly, cause impaired immune responses is at the cost of an occasional overwhelming and sometimes fatal infection. Nevertheless, not all infections will manifest themselves clinically, a fact amply demonstrated by HBV infection in the immunosuppressed.

The characteristics of agents lending themselves to transmission by blood or blood products centre around their presence in blood, or its components, which has been taken from *apparently healthy donors*. Thus these agents often will have a combination of a long incubation period with a prolonged and high-level viraemia. A propensity for causing a mild, often subclinical, infection would also predispose to transmission by blood transfusion. Add to this the ability to develop an expressed carrier state (e.g. HBV) or a latent

infection in cells (e.g. CMV), then, provided the agent is stable in stored blood or blood products, transmission by transfusion becomes likely.

For a virus present in a donation to infect the recipient, it is necessary for the recipient to be susceptible to that agent. Where the prevalence of immunity varies with age, obviously the age of the recipient will influence the outcome of exposure. For example, transfusion of an infant or child could well lead to a primary Epstein–Barr virus (EBV) infection but would be unlikely to do so in an adult who would almost certainly be immune.

Consideration also must be given to the expected prevalence of immunity to any agent in patients from different parts of the world. Just as this may vary with age, equally so in certain areas of the world the antibody prevalence may vary. For example, although blood from this centre has on one occasion transmitted hepatitis A to a 33-year-old female British patient (Barbara et al, 1982), it is unlikely that this would have been the outcome if the same unit had been given to, say, an Indian or African patient, who would almost certainly have been immune. It must be noted too, that the prevalence in any donor panel of donors whose blood might be infective for a particular agent may vary greatly from area to area in the world.

THE NATURE OF THE VIRAL AGENTS

Depending upon the nature of the infection in the blood, virus transmission by transfusion can be associated either with the cellular components of blood (usually the white cells) or with the plasma alone (see Table 1).

It is possible that other viruses may have rarely been transmitted by transfusion and the infection gone undetected. The table lists, *not* in order of significance, those of greatest importance to transfusion practice. The agents transmitted by transfusion have been reviewed recently by Tabor (1982) and Barbara (1983). The policy of screening blood for evidence of viral infections, where one can screen either for the agent and its antigens (e.g. HBsAg for HBV) or for the presence of antibody as evidence of past infection with a concomitant chance of latency (e.g. anti-CMV for CMV), will be discussed later.

Table 1. *Viruses transmitted by blood or its products*

Cell-free viraemia
HAV(hepatitis A, rarely)
HBV(hepatitis B) and delta agent
NANB(hepatitis non-A, non-B)
HPVLV(parvovirus)
Cell-associated viraemia
CMV(cytomegalovirus)
EBV(Epstein–Barr virus)
HTLV(Human T-cell leukaemia virus) type I
Agent of AIDS-HTLV-III

CELL-FREE VIRAEMIA (PLASMA-RELATED AGENTS)

Hepatitis B virus (HBV)

This agent will be considered first since it serves as a model when considering transfusion-transmitted infections. It has been until recently one of the most frequent clinical infections transmitted by blood transfusion. Certain characteristics both of the virus and of the infection that it causes are 'tailor made' to enhance its infectivity by this route.

Apart from being a very stable virus (Bond et al, 1981) many of the infections in adults are subclinical. With an incubation period of around three months, there can be a prolonged symptomless viraemia before the illness and, even if there were not a carrier state, hepatitis B would be a considerable transfusion problem. Fortunately it is relatively easy to identify donors who are likely to transmit HBV by identifying hepatitis B surface antigen (HBsAg) in their serum. The potential of this virus to cause a persistent expressed infection in otherwise well donors (termed 'carriers') and the potential severity of hepatitis B in recipients have provided HBV with a major role in transfusion microbiology. Carriers may be divided broadly into two categories of differing infectivity, depending upon the presence in their serum of another antigen, hepatitis B e Ag (HBeAg) or its antibody (anti-HBe). About one in four carriers have HBeAg in their serum. It is likely that they will have recently become carriers and their blood will be highly infectious. In contrast, the more commonly identified carriers will have anti-HBe in their serum and will be at a later stage of the chronic infection. The inference of this is that the HBsAg-positive carrier will later become an anti-HBe-positive carrier; they do, at a rate of about 5–10 per cent per year. Although anti-HBe carriers are far less infectious, they may nevertheless transmit infection by transfusion. For this reason all HBsAg-positive individuals must be excluded from giving blood for transfusion.

The most reliable method for preventing HBV transmission is screening blood donors for the presence in their serum of the major coat-protein of the virus, HBsAg. This is now mandatory in the UK and it is a matter of routine for all blood donations to be screened for HBsAg. Although exclusion of epidemiologically identifiable 'high risk' groups is possible, the detection of HBsAg remains the method of choice (Barbara, Tedder and Briggs, 1984).

In some situations testing for antibody to the core of the virus (anti-HBc) may provide some additional advantages, since it may lead to the identification of the donor recently recovered from an HBV infection who may still be infectious (Barbara and Briggs, 1982). Many of these donors will be in the diagnostic window, i.e. sero-negative for HBsAg and not yet sero-positive for anti-HBs. In addition the occasional donor with high levels of anti-HBc as the sole marker of HBV infection will also be identified. Some of these may transmit HBV. However, as anti-HBc testing does not detect donors early in an acute infection when they are likely to be quite infectious (Barbara, Tedder and Briggs, 1984) it will never replace HBsAg screening. Apart from increased costs, anti-HBc testing has other drawbacks. Many HBV-immune donors will

be identified and there will be a problem of deciding which anti-HBc-positive donors are likely to be infectious. Many donors will also have anti-HBs present in their serum and will represent no risk of infection. Deciding on a 'safe' level of anti-HBs for allowing transfusion of their blood will be largely arbitrary and testing for anti-HBs will itself involve further costs. Nevertheless donors from certain 'high-risk' groups would be identified by the anti-HBc test. This could be an advantage, although a proportion would not be in groups whose lifestyles were associated with increased risk of transfusion-transmitted infections (see AIDS section).

A novel approach to HBV screening is a single assay testing jointly for HBsAg and anti-HBc. A trial of one such test produced by Abbott Laboratories (Chicago, Illinois, USA) has been reported by Wylie and colleagues (1983). The results were encouraging, indicating similar sensitivities for the combined test compared with either of the single tests, although there was a significantly higher rate of false-positive screen results for HBsAg detection by the combined test. Cost may well be a factor but results of large-scale trials will be interesting.

In order to define the 'best' method of screening blood donors for HBsAg, it is necessary to consider test sensitivity, ease of use and cost. Some blood products such as those obtained in 'part-open' systems have a short shelf life and will require a rapid test for HBsAg before release. On the other hand plasma destined for pooling will require as sensitive a test as possible to avoid contamination of a large plasma pool with HBV, which could then be disseminated widely.

It is customary to rank HBsAg tests in categories by 'generation' (Table 2). The basis of this is historical, though in fact earlier test systems (first generation) are invariably less sensitive than the most recent ones (third

Table 2. *Comparison of some tests for HBsAg*

	Type of test	Sensitivity (approx. ng/ml HBsAg detected)	No. of HBsAg-positives detected per 'unit' donor panel, taking EIOP as reference method
EIOP		1000	100
RPHA	Hepatest[a] 1% test cells; 1 in 8 screen dilution	100	140 (40)[b]
	Hepatest[a] 0.1% test cells; 1 in 8 screen dilution	10–20	147 (47)
RIA	Middlesex Hospital or Blood Products Laboratory reagents	<0.5	154 (54)

[a] Wellcome Reagents, Beckenham, Kent.
[b] Percentage increase in absolute number of HBsAg-positive donors identified.

generation). The tests range from immunodiffusion and its electrophoretic modifications to solid-phase assays including reverse passive haemagglutination (RPHA), radioimmunoassay (RIA; perhaps more correctly called immunoradiometric assay, IRMA), enzyme-linked immunosorbent assays (ELISA) and fluorescent immunoassays (FIA). Some of the more recent developments include enzyme amplification to enhance the sensitivity of ELISA (or to reduce test times) and chemiluminescence assays. The old argument over the merits of different methods for tagging the tracer antibody continue, covering safety, convenience, speed and sensitivity. Although time-resolved fluoroimmunoassay (TR-FIA) may combine some of the better features of both RIA and ELISA (Siitari et al, 1983) it has not achieved the same increase in sensitivity as enzyme amplification systems.

The sensitivities of different tests and the HBsAg detection rates obtained by them have been reviewed elsewhere (Barbara, 1983).

The different sensitivities of HBsAg assays are shown in Table 2. It can be seen that tests of increasing sensitivity do not detect proportionately more HBsAg-positive donors. Thus, a one-hundred-fold increase in sensitivity from RPHA to RIA results in a 10 per cent increase in detection rate at the most.

The exact test chosen will depend on the individual requirements and constraints mentioned earlier. The ultimate effectiveness of the HBsAg-detection assays used will be reflected in the amount of transfusion-associated hepatitis (TAH) that occurs. Figure 1 analyses the reports of TAH made to the North London Centre (NLBTC) over the last 13 years.

The efficiency of retrospective reporting of TAH depends very much on the efficiency with which hospitals monitor TAH and then inform the centres supplying them. Grindon and Rosvoll (1980) showed an alarming six-fold increase in the reporting rate by sending a six-month follow-up postcard to the physician of every patient receiving blood; similarly the 1981 increase in TAH reported to NLBTC (mainly due to non-B hepatitis) followed attempts to

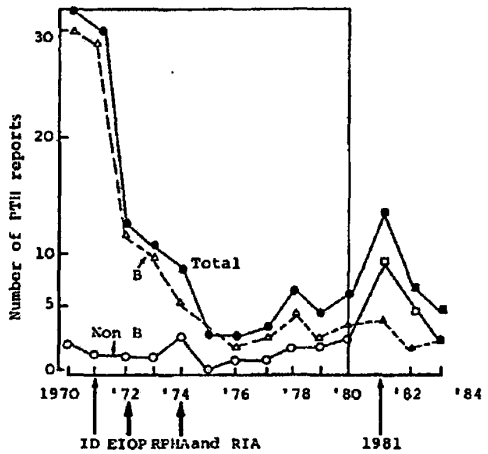

Figure 1. Post-transfusion hepatitis in North London. Note the increase in 1981 following the campaign to encourage hospitals to report PTH. (Reproduced with kind permission of the editor of *Medical Laboratory Science*.)

increase awareness in the hospitals supplied by NLBTC. In prospective studies in the USA roughly 1 in 10 transfusions appear to cause TAH, of which 90 per cent is due to non-A, non-B hepatitis. Currently in the UK most of the transfusion-associated hepatitis B is in fact caused by the administration of clotting factor concentrates prepared from large pools of plasma. For example, hepatitis B infection rates between 7 and 9.5 per cent per annum were reported in Edinburgh from 1971 to 1979 in patients with haemophilia A (Stirling et al, 1983). Haemophiliacs are even more likely to be infected with non-A, non-B hepatitis after receiving blood products and most show evidence of infection with at least one of the NANB viruses (see below).

Delta agent

Another transfusion-transmitted hepatitis virus is the delta agent, first described by Dr Mario Rizzetto and his colleagues (1977). This defective agent can replicate only in HBV-infected hosts and consists of viral RNA coated in HBsAg produced by HBV, its 'helper' virus. Chronic delta infections are mostly commonly found in HBsAg carriers of Southern Italian origin, but have also been identified in HBsAg carriers who are drug addicts. In the UK chronic infection is rare among British blood-donor HBsAg carriers though not uncommon in HBsAg-positive drug addicts (Tedder, Briggs and Howell, 1982). Acute co-infections of HBV and delta are commonly seen in drug addicts in Ireland (Shattock, Fielding and Kelly, 1982).

Delta infection may increase the severity of both acute and chronic hepatitis B infections and also probably partially suppresses HBV replication. The possibility of an acute delta hepatitis should be considered in cases of acute hepatitis in B carriers. Although there is some evidence that hypertransfused patients demonstrate a higher prevalence of delta markers, most delta infections associated with transfusion will be prevented by exclusion of HBsAg-positive donors. Since it is very rarely found in HBsAg-positive donors in the UK, delta infection should not be a problem with British blood products.

Hepatitis A virus (HAV)

Most adult infections with this virus are clinically apparent, leading to donor self-exclusion. Its short incubation period (about 4–6 weeks), the resulting short viraemia, the lack of a carrier state and the high prevalence of immunity in recipients will lead to an extremely low rate of transmission by transfusion (Conrad, 1981). By all standards it is a very rare occurrence. Nevertheless a few well-documented cases of transfusion-associated hepatitis A have occurred. Reports of transmission by transfusion have come from Sweden (Seeberg et al, 1981), London and Birmingham in the UK (Barbara et al, 1982 and Skidmore, Boxall and Ala, 1982) and the USA (Hollinger et al, 1983).

Non-A, non-B hepatitis (NANB)

When a diagnosis of hepatitis A or hepatitis B has been excluded in a patient with hepatitis, the possibility of non-A, non-B (NANB) hepatitis must be

considered. The transfusion aspect of NANB has been considered in the February 1984 issue of *Clinics in Haematology* (Bayer, Tegtmeier and Barbara, 1984) and by Hopkins (1983), and has also been the subject of a book edited by Gerety (1981).

There are a number of different patterns of NANB disease. There is an epidemic waterborne acute NANB which has an epidemiology similar to that of HAV. By contrast, although transfusion-associated NANB can be divided into short and long incubation types with incubation periods of between 1–5 weeks and 7–12 weeks respectively, these diseases do not seem to cause secondary cases. The existence of at least two transfusion-associated NANB viruses is also indicated by multiple episodes of acute hepatitis in treated haemophiliacs and in chimpanzee studies. Most NANB infections are inapparent and are detected by mild elevation of transaminase levels. Less than one quarter of patients develop jaundice. In prospective studies, NANB hepatitis associated with transfusion has usually been defined by transaminase levels 2.5 times the upper limit of normal on two or more separate occasions, though such minimal elevations could be due to a variety of causes, many of which may be non-microbiological. If a virological cause is thought likely, hepatitis B (and A), cytomegalovirus (CMV) and Epstein–Barr virus (EBV) must be eliminated as causes before NANB is considered. For example, it has been suggested that CMV infection may account for up to 15 per cent of TAH (Alter et al, 1981). Factors such as drugs, including alcohol, obesity and medications could all cause elevated transaminase levels.

It has been suggested that exclusion of donors with elevated serum transaminase levels might reduce the prevalence of TAH-NANB. The cost effectiveness of alanine aminotransferase (ALT) screening is difficult to assess because of major uncertainties about the medical consequences of non-A, non-B hepatitis (Hornbrook et al, 1982). It is not even certain that this policy would necessarily reduce post-transfusion NANB. This matter has been discussed in an International Forum feature in *Vox Sanguinis* (1983), where it was pointed out that an appropriate ALT exclusion level could be chosen to prevent 29 per cent of the TAH cases at a loss of 1.6 per cent of donor units. Using similar exclusion levels at NLBTC as many as 10 donors a day would be disqualified (Mijovic, Patapiou and Barbara, 1982). With the high proportion of 'false positive' and 'false negative' results involved when ALT is used as an index of NANB infectivity and with the geographical variations in ALT levels reported in other studies, routine ALT screening was not considered feasible in North London. The additional question of appropriate advice to donors would also be enormous. Such considerations also led the American Association of Blood Banks to advise against routine ALT screening of donors. A British prospective study in cardiac surgery patients reported an incidence of 2.4 per cent acute short-incubation NANB hepatitis after transfusion (Collins et al, 1983). This rate for acute transfusion-associated NANB compares with 4 per cent reported from the 1971 MRC study and 1.7 per cent reported from an Australian study (Cossart, Kirsch and Ismay, 1982).

Because of the 'bio-amplification' of large blood pools the risk of developing NANB hepatitis after infusion with pooled blood products is very much higher. Most haemophiliacs develop NANB hepatitis after their first

treatment with factor VIII concentrate and may do so more than once (Craske et al, 1978; Fletcher et al, 1983). The usually mild acute NANB infections in the haemophiliac would have little significance but for their possible association with the development of chronic hepatitis. However, even this is frequently self-limiting and resolves within two years in most cases. Blood transfusion has been performed for many years, hence a simple way to determine the correlation of transfusion with the risk of developing chronic hepatitis is to determine the proportion of chronic liver disease patients who have a history of prior transfusion. The study in Boston conducted by Koff, where the proportion of chronic liver disease patients with a history of transfusion was less than 15 per cent, has been reviewed elsewhere (Bayer, Tegtmeier and Barbara, 1984).

As yet, there is no satisfactory specific serological test for NANB that is generally available (see Hopkins, 1983); there is little reason to expect NANB agents to be as obliging as HBV in producing an excess of a marker antigen. It may be that some assay for virus-specific nucleic acid may be necessary, but until an agent is characterized this is unlikely to be forthcoming. As an alternative there is some evidence that it may be possible to define donors belonging to 'high-risk populations'. In this manner we have noted at NLBTC an increased prevalence of anti-HBc-positive donors in panels associated with post-transfusion NANB. Even so it is questionable if the approach of using anti-HBc as a marker for high-NANB-risk donors would be generally applicable.

Parvovirus (HPVLV)

The serum parvovirus-like virus (SPLV) of humans has also been shown to be transmitted in clotting-factor concentrates, but not in transfused blood (Mortimer et al, 1983). Although virus may be present at a high level the viraemia is only transient (see Chapter 10). This probably explains transmission by concentrates prepared from pools but the failure of transmission by cryoprecipitate or whole blood, each of which comes from single donors. Although the significance of such transmission is uncertain, the fact of its occurrence must be borne in mind when considering putative transmission of other agents.

CELL-ASSOCIATED AGENTS

Cytomegalovirus (CMV)

Transmission of this virus by transfusion of blood or components containing white cells is assuming increasing importance in patients with severely impaired immunity who require supportive therapy. This topic was considered in detail in the February 1984 issue of *Clinics in Haematology* (Bayer, Tegtmeier and Barbara, 1984). It is also to be the topic for an 'International Forum' in a recent volume of *Vox Sanguinis* and therefore will only be summarized in this section.

A review of 1845 patients from 15 different studies (Bayer, Tegtmeier and Barbara, 1984) showed an average infection rate of 13 per cent following transfusion to immunocompetent recipients, with most infections being asymptomatic. The presence of pre-transfusion CMV antibody in the recipient affords protection from a primary CMV infection but will not prevent reactivation of the latent infection. Immunosuppressed patients (either due to underlying disease or to therapy) have an increased risk of morbidity and mortality from CMV infections, particularly if this is a primary infection. These include recipients of kidney and heart transplants, but those patients at most risk of severe disease are bone marrow recipients. Children with leukaemia and premature infants of less than 1200 g birthweight also fare badly and fatal infections have been reported. This may be because the infection in these patients is likely to be a primary one. In practice the greater the degree of immunosuppression, the more likely the patient is to suffer from a CMV infection, be it primary or reactivation, and the more chance there is that these infections will be clinically apparent.

Between one in four to one in 40 CMV antibody-positive donations seem capable of transmitting the virus. There are a variety of tests that could be used to identify donors whose blood might be infectious. Direct testing for the virus antigen is not appropriate in a transfusion context. CMV antigen detection would be unlikely to identify all donors capable of transmitting CMV infection. Since CMV is a member of the herpes group and exhibits latency, the level of virus expression in donor blood cells could be very low indeed. The alternative and probably the simplest approach is to identify the donor who has serological evidence of previous CMV infection. The presence in serum of anti-CMV is a reliable marker of infection and can be used to identify these donors.

Reports of morbidity and mortality due to transfusion-associated CMV in certain high-risk patients has prompted serious efforts to provide convenient anti-CMV screening methods for transfusion centres. The prevalence of anti-CMV in the blood-donor population varies with age and geographical location, ranging from 40 up to 100 per cent. The prevalence in British blood donors is between 50 and 60 per cent. Identification of anti-CMV-positive donors and their exclusion from certain uses could increase the safety of blood transfusion for certain high-risk patients. However, the constraints for the transfusion services are those of simplicity, economy and speed, especially where cellular components are concerned. Although Booth and colleagues (1982) found passive haemagglutination (PHA) the least satisfactory of those methods tested, others have obtained more favourable results (Hunt et al, 1984). The commercially available reagents (Cetus, Berkeley, California) in a modification in Terasaki plates provided a very economical if not very robust test. Current trials at NLBTC with reagents from the same suppliers, both in standard format (70p per test) and in a diluted-cells test (at 7p per test) using plate centrifugation, are underway to evaluate the use of PHA testing for anti-CMV before release of blood and its products. Alternatively the complement-fixation test can be made acceptably sensitive (Ronalds, Hardiman and Griffiths, 1983). Although the overnight incubation step required might preclude its use in the transfusion centre if pre-release testing is

required, it is possible to use the CF assay to identify an accredited anti-CMV-negative donor panel. These donors may be used for quick release of CMV-negative blood products and their serum tested subsequently at each attendance. The frequency of seroconversion of antibody-negative individuals would be some 1–2 per cent per year. Hence if this strategy were to be used, the incidence of transfusing a CMV-positive unit in unselected blood taken every six months from a CMV-negative donor panel would be an acceptable 0.5–1.0 per cent of all donations from the panel. A choice of 'panel' or 'rapidly tested' options is thus open for centres.

One additional advantage of anti-CMV testing could be the identification of suitable donors for CMV immunoglobulin. Hyperimmune globulin ameliorates symptoms in bone marrow and renal transplant recipients. Although this blood product is clinically useful, one caveat is that certain of these donors may be homosexual males. It has been shown in the USA that plasma for CMV-specific immunoglobulin production may come selectively from this section of the general donor panel (Ikram, Prince and Baker, 1983) and many homosexual men display high titres of CMV antibody. The problem of AIDS risk in these donors and indeed in donors selected for anti-HBs has to be considered. At present, it is generally considered that as long as the selected plasma donations for hyperimmune immunoglobulins are appropriately flagged these donations should continue to be collected. Further, provided the immunoglobulins are only prepared for intramuscular use by Cohn II fractionation incorporating standard protocols for freeze drying of the cold ethanol slurry, there seems to be no risk of AIDS transmission. Certainly, starting with Cohn II fractions contaminated with NANB and HBV, this procedure can be shown to have a virucidal effect. The specific nature of this effect remains uncertain.

Epstein–Barr Virus (EBV)

Although EBV, another of the herpes virus group associated with white cells, can be transmitted by blood transfusion (McMonigal et al, 1983) this virus does not cause as much of a problem in blood recipients as does CMV. This is probably because approximately 90 per cent of adult patients already have protective neutralizing antibodies in their sera. This has two effects. Firstly, most recipients will be immune and, secondly, where multiple transfusions have been given, antibody present in one or more of the donations may have a protective effect.

If infection is transmitted, this can be confirmed by detecting anti-EBV IgM, rises in anti-EBV titres and the presence of heterophile antibodies.

Human T-cell lymphotropic virus (HTLV)

There are three closely related viruses in the HTLV group. Two that are well characterized are the human T-cell leukaemia viruses, type 1 and 2 (HTLV I, HTLV II). At present, of these two, only HTLV I is considered a problem for the transfusion microbiologist.

HTLV I. The association of a group of human retroviruses (the HTLV group) with overt malignant lymphoma/leukaemia raises the concern of possible 'transmission' of neoplasia by blood transfusion. This agent is associated with a condition which has been long recognized as a specific clinical entity, the acute adult T-cell leukaemia. HTLV exhibits a variable prevalence of infection and in certain parts of the world as many as one in four adults will show serological evidence of infection. It seems likely though that few of these adults subsequently develop neoplasia since patients with leukaemia represent only a small proportion of the total, sero-positive pool. The virus is usually cell-associated and it is not surprising that blood transfusion transmission has been documented only for whole blood and cellular components (Okochi, Sato and Hinuma, 1984). Clearly in those parts of the world where this infection is common, e.g. Japan and the Caribbean, consideration may need to be given to identification and exclusion of infected donors. Fortunately in the UK, preliminary surveys at NLBTC indicate that the prevalence of HTLV I-positive donors is very low indeed.

HTLV III and acquired immune deficiency syndrome (AIDS). The implications of AIDS in blood transfusion, a topic that has overshadowed NANB, has been reviewed recently (Bayer, Tegtmeier and Barbara, 1984; Sandler and Katz, 1984) and the infectious complications have been considered elsewhere in this issue (see Chapter 12). Two haemophiliacs with AIDS, one of whom has died, have been reported in the UK and 21 haemophiliacs with AIDS have been identified in the USA up to November 1983 (Morbidity and Mortality Weekly Report, 1983). In addition, 18 American patients have been identified who are thought to have acquired AIDS following transfusion of whole blood, packed cells, fresh-frozen plasma or platelets (Curran et al, 1984). Most of the transfusion-associated cases occurred in those areas of the USA which had the highest incidence of AIDS in the population. Overall, these recipients had received five times the average number of units per patient usually given to transfusion recipients in the USA as defined in national USA surveys of transfusion. By the end of 1983, AIDS in patients receiving transfusions (and with no other risk factors) accounted for only 1 per cent of the 3000 cases reported to the Communicable Disease Center in Atlanta. The mean period between transfusion and diagnosis was 27 months (ranging from 15 to 57 months).

The transmission of AIDS by pooled clotting factor concentrates is less controversial. Since, as a group, haemophiliacs are well studied, it is unlikely that there should have been an illness like AIDS unrecognized before 1980. Little significance should be attached to reports of abnormal lymphocyte profiles in haemophiliacs; nevertheless there is no doubt that there have been deaths of haemophiliacs due to AIDS in the absence of other established risk factors and that, unlike those associated with transfusion, these cases were scattered throughout the USA. In addition there is a report which seems to have identified the transmission of AIDS from a haemophiliac (asymptomatic at that time) to his wife (Pitchenik et al, 1984).

The initial isolation of a T-lymphotropic retrovirus from an AIDS-risk patient (Barre-Sinoussi et al, 1983) strengthened the belief that such an agent

might be aetiologically linked to AIDS. Subsequently sera from AIDS patients were demonstrated to contain low level antibody to HTLV I but at a prevalence which made a causal relationship unlikely. Very recently two groups, one in France (Vilmer et al, 1984) and one in America (Popovic et al, 1984) have described simultaneously a new member of the HTLV family. The viruses isolated in France, called Lymphadenopathy-Associated Virus (LAV) or Immunodeficiency-Associated Virus (IDAV), are probably similar, if not identical, to the American viruses, Human T-cell Lymphotropic Virus III (HTLV III). It appears that at least 80 per cent of AIDS patients and an even higher proportion of lymphadenopathy patients have anti-HTLV III in their serum. Although HTLV III should be considered only as a candidate virus, it seems very likely that it will turn out to be the unique infective cause of AIDS. What is not known at present is the proportion of anti-HTLV III-positive persons who will subsequently develop AIDS.

There are no commercially available specific tests for HTLV III. The exclusion of donors in high-risk groups (i.e. homosexuals with promiscuous or multiple sexual partners and intravenous drug abusers) remains at present the only practical method for reducing the possibility of AIDS transmission by transfusion. In Britain this exclusion is achieved largely by self-selection and a pamphlet with AIDS information for donors is available at donor clinics. Non-specific tests fall into two broad groups. Firstly there are those, like anti-HBc and anti-treponemal antibodies, which would indicate that the donor is in one or other high-risk category. Secondly there are tests for markers such as β-2-microglobulin, α-interferon and α-1-thymosin which might identify the affected, hence infectious, donor. All these assays remain to be evaluated.

In our experience at NLBTC, evidence of previous HBV infection identifies donors at a significantly higher risk of transmitting NANB and at a marginally higher risk of transmitting HBV. At present it is not known whether this would be a suitable or effective screen for donors who constitute a high-risk of transmission of AIDS. An economical modification of the passive haemagglutination test for anti-HBc (Corecell, Green Cross Corporation, Osaka, Japan) is under evaluation at NLBTC. *Treponema pallidum* haemagglutination tests, as opposed to cardiolipin screens for syphilis antibody, may also be of value in detecting donors in high-AIDS-risk groups, especially as most new cases of syphilis in Britain occur in males.

Other approaches for prevention of transmission of infectious agents by blood transfusion

Apart from exclusion of high-risk donor populations, chemical or physical treatments of blood products or the addition of antibody (possibly even monoclonal antibody eventually) are being investigated in attempts to reduce the infectivity of blood or its products. Some of these treatments may reduce the biological activity of products and thereby raise the unit cost and all may be difficult to standardize. The preparative methods used when producing some blood components have in themselves a beneficial effect by reducing contamination. Washed red cells (or 'frozen' red cells, which also require

washing to remove the cryoprotectant) will reduce contamination by agents in the plasma. Cellular components are also removed in some processes by filtering and transmission of cell-associated organisms is thereby reduced. Obviously the problems remain when the blood products are inappropriate for treatment or when cellular components are the ones required!

Susceptible patients may be considered for vaccination prior to transfusion provided that suitable vaccines are available. However, this is rarely the case for a number of reasons. In some instances the agents responsible have not been identified (e.g. hepatitis NANB); in others either the efficacy of available vaccines has not been proven (e.g. CMV) or no vaccines are available at present (HPVLV, HTLV, AIDS). With HBV, although efficient vaccines are currently available, their cost makes this approach untenable. The alternative, that of passive protection of recipients, has so far also proven unsatisfactory. Probably, until safe and efficient substitutes for blood and its components are available (e.g. improved oxygen-carrying substances, monoclonal antibodies and gene-cloned and expressed factor VIII), the most significant single factor in the provision of blood with minimal risk of transmitting infection remains careful selection of donors and avoidance of those comprising high-risk populations. This, coupled with routine screening of donations, currently by antigen–antibody interaction, perhaps in the future by assays for specific nucleic acid, remains the mainstay of the effort to provide safe blood, free of extraneous infectious agents.

SUMMARY

Modern transfusion practice is associated with an increased risk of transmitting viral agents because of the changing nature of the patients and of the therapeutic blood products. More immunosuppressed patients are receiving blood released faster and with more elaborate blood components.

In addition to the classically recognized importance of hepatitis B virus (itself disseminated most efficiently by contamination of products derived from large pools of plasma containing many donations) other agents are assuming increasing importance. They frequently display one or more of the predisposing characteristics of prolonged viraemia, inapparent infections and a carrier or latent state. Some of these infections like cytomegalovirus and the human T-cell leukaemia virus are transmitted only by the cellular component of blood. Others like B and non-A, non-B hepatitis and the putative agent(s) of the newly recognized acquired immune deficiency syndrome can also be transmitted in the plasma or its products. Not all the agents transmitted cause severe illness, however; human parvovirus appears to cause no clinical illness when transmitted by transfusion and infections with non-A, non-B hepatitis are largely detected only by elevations in transaminase levels.

Screening tests for the presence of these agents in donor blood or for evidence of infection by them in donors continue to be studied. Other approaches, related in particular to the selection of donors, are becoming increasingly important where serological screening tests are not available.

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