Second Edition

AHG and bovine AHG, are potent freeze-dried powders. Only porcine factor VIII (Hyate:C) is now made by Speywood Laboratories in Wales. Hyate:C is an interesting product with great potential. The old pig VIII concentrate caused a fall in platelets in the recipient's blood; the new product does not. The old concentrate caused resistance in the recipient about a week after a course was started. The new product does not appear to do this on every occasion. If the cause of resistance, which results in a failure to raise the level of active factor VIII, can be identified and overcome the porcine material will be a viable and potentially safer product for the treatment of haemophilia A. At present it holds a well-deserved place in the management of people with factor VIII antibodies (see Chapter 12).

Platelets

These are prepared from fresh blood either by cell separator or by spinning the blood in a centrifuge at the correct speed and withdrawing the fraction of plasma known to contain the greatest number of platelets. As there is no way of storing platelets for more than 3 days, fresh supplies must be made on demand.

White cells

Sufficient active white cells can only be obtained using a cell separator. Transfusion into the recipient must be immediate.

Red cells

It is possible to store red cells for longer than 5 weeks in liquid nitrogen. However, the process is uneconomic.

Artificial blood

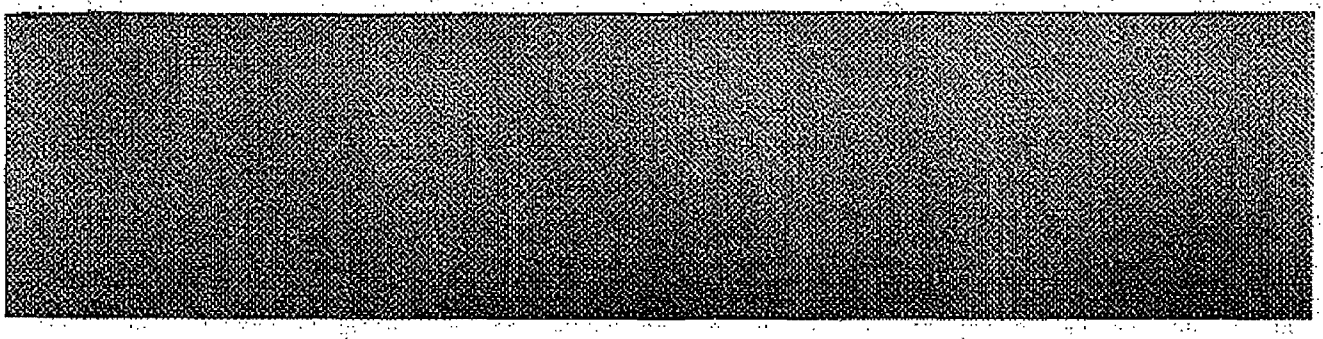
This is a chemical mix developed by the Green Cross commercial company in Japan. The name 'artificial blood' is a misnomer; all it does is to carry oxygen from the lungs to the tissues. It could be a very useful alternative to red cells, especially in times of war or natural disaster.

JEHOVAH'S WITNESSES

Whilst members of this faith have deep convictions against the transfusion of whole blood and some of its constituents, they do not prohibit the use of anti-haemophilic preparations. Reference to this topic may be found in the *Journal of the American Medical Association*, 1981, vol. 246, pp. 2471–2.

ADMINISTRATION OF BLOOD PRODUCTS AND SIDE-EFFECTS

All the blood products described must be injected intravenously (into a vein) so that they enter the bloodstream directly. The technique of placing a needle in the vein is called venepuncture. With modern transfusion equipment the



procedure is virtually painless, but occasionally minor side-effects of the injection are experienced. These seldom amount to more than a little discomfort and soon disappear; they should, however, be reported. Most people feel the fluid, which is usually colder than their body temperature, flowing into the vein. Sometimes the vein becomes a little reddened for a while. Occasionally a rise in temperature or a fleeting rash may be experienced, and very rarely shortness of breath, headache or backache occur. With some products, numbness or a tingling sensation is felt in the lips, and there may be a metallic or salty taste in the mouth. These immediate effects are frequently associated with the rate of injection, and can be reduced by giving the blood product more slowly. Those patients who continue to experience immediate allergic-type side-effects may be prescribed an anti-histamine to give intravenously (page 112).

Hepatitis

One of the most important side-effects of blood transfusion is hepatitis, or inflammation of the liver. The liver becomes inflamed when it is infected by one of a number of viruses. If the infection is marked enough jaundice may result. The liver is unable to remove a naturally occurring pigment from the bloodstream, and the build-up in pigment stains the skin and the whites of the eyes yellow. The urine becomes darker and, because pigment is no longer being excreted from the liver into the bile, the faeces become pale. We know that many liver infections are not severe enough to result in the appearance of jaundice; they show themselves as mild, transient periods of feeling unwell, or only as changes in liver function measured in the laboratory. One of the reasons for following up people with haemophilia carefully is to monitor these changes.

Jaundice does not always mean that the liver has become infected. It occurs when red blood cells break down too rapidly, and when the passage of bile from liver to bowel is blocked. Usually the underlying disorder can be determined fairly easily by examining the blood and urine, but more sophisticated tests may sometimes be necessary. These include ultrasound, computerized tomographic (CT) or radioisotope scans of the liver and the spleen, X-rays which show up the bile passages, and liver biopsy. This last test involves taking a minute piece of liver tissue to examine under the microscope. The procedure is done under local anaesthetic, using a special needle. The same precautions that are used for any surgical procedure in haemophilia must be observed; factor replacement is given before and for 3 days after the biopsy.

Three types of viral hepatitis are known. They are called hepatitis A, hepatitis B, and hepatitis non-A, non-B (NANB).

Hepatitis A is the common, short-lived, flu-like illness which is also called 'infectious hepatitis'. It is not spread by blood transfusion, and does not cause chronic liver disease.

Hepatitis B is also called 'serum hepatitis', because it is spread through contact with serum, other blood constituents, and some body secretions. Despite the introduction of increasingly sophisticated techniques for its detection, hepatitis B remains a transfusion hazard.

Hepatitis non-A, non-B results from infection with one of at least three viruses, none of which has, at the time of writing, been positively identified in the laboratory; hence the name. NANB viruses are transmitted by blood transfusion, and now account for most cases of transfusion hepatitis.

Hepatitis B

Hepatitis B is one of the most widespread infections known to man; an estimated 200 million of the world's population carry the disease. It is important for someone with haemophilia to appreciate this because occasionally the finding of the B viral markers in a patient results in too much alarm and despondency. You are not alone!

When a virus attacks the body it is recognized as an invader or antigen, and the recipient reacts by producing antibody against it. The antigen now called hepatitis B surface antigen (HB_sAg for short) was originally discovered in 1965 in the blood of an Australian aborigine, and named the 'Australia antigen'. Intense work on the virus responsible has since revealed more about its structure, how it affects liver cells, and how it can be controlled. The understanding of hepatitis B is one of the success stories of contemporary medicine.

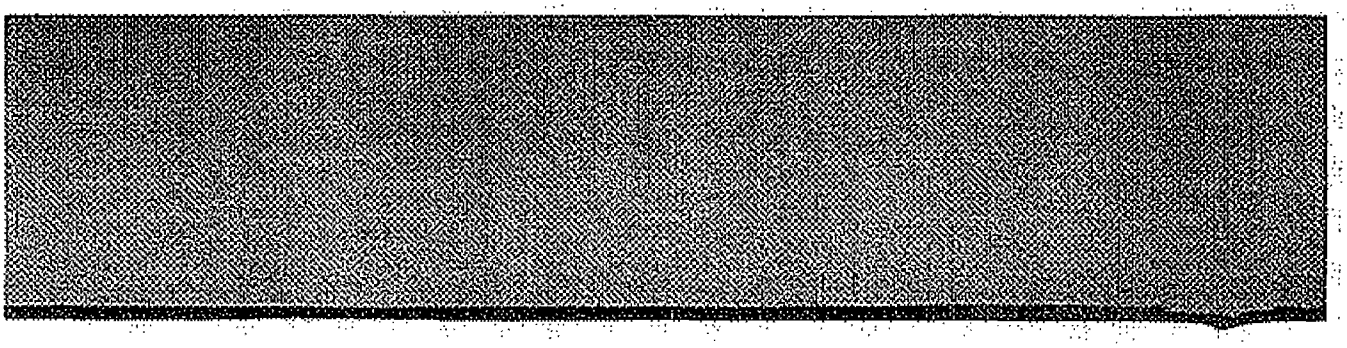
As the term HB_sAg implies, the first antigenic or 'recognition' points of the virus were found on the surface. Beneath lies a core, and it was not long before markers were found which identified this structure too; they are called hepatitis B core antigen, or HB_cAg. Within the core was found yet another marker which was called the 'e' antigen' or HB_eAg, and it is now known that this particular antigen is associated with infectivity.

Thus, the original Australia antigen has been taken apart by the researchers and has revealed itself to be like a nest of Russian dolls. Each of the antigens found has an associated antibody. Hence we have anti-HB_s (or HB_sAb), anti-HB_c and anti-HB_e. Their recognition, together with the liver function tests, allows the course of serum hepatitis attack to be plotted, and gives an indication of when vaccination is needed to protect contacts.

Whenever someone with haemophilia is shown to have experienced hepatitis B the information is passed to the blood product manufacturer so that identification of the infected donor can be attempted. This time-consuming and difficult job depends entirely on knowing the precise details of the blood product used within the past 6 months (the incubation period for hepatitis B). This is why the recording of batch or lot numbers *every* time a blood product is given is a vital part of haemophilia care, wherever the transfusion takes place.

Vaccination against hepatitis B is now available. Considerable resources were needed to develop and test the vaccine, consequently it is expensive. Hopefully its widespread introduction will bring the price down and allow its use in many of the poorer nations where hepatitis B is a major cause of ill health. At present it is indicated in haemophilia practice:

(1) For severely affected children who have either not yet been exposed to large-pool concentrates, or can be shown by testing not to have acquired immunity already.



(2) For the close relatives of someone with haemophilia whose blood is shown by testing to be potentially infective.
(3) For those who participate in the treatment of someone with haemophilia; this may mean some family members or friends, as well as hospital staff.

Vaccination involves three intramuscular injections, the second 4 weeks and the third 6 months after the first.

Temporary protection against hepatitis B following accidental exposure may be provided by an injection of specific immunoglobulin.

Hepatitis non-A, non-B

The incubation periods for these agents appear to be short, in some cases only a matter of days. There is evidence that haemophiliacs have multiple episodes of NANB hepatitis, most going unnoticed, although the first attack is sometimes accompanied by the appearance of jaundice. The NANB agents are important because, as with hepatitis B, the infection they cause can lead on to chronic liver disease. No way of protecting recipients from NANB hepatitis is known. Manufacturers are trying the effects of heat and chemicals on blood products, but no foolproof method of inactivating NANB viruses has been found. Vaccination is not yet possible.

Chronic liver disease

It is extremely rare for someone with haemophilia to become very ill as a result of hepatitis itself, whatever the cause. Usually the patient with hepatitis will be ill for a while, will feel nauseated and off his food and cigarettes, and be a bit depressed for some weeks after the attack. He should be nursed at home rather than in hospital, and should refrain from drinking alcohol because of its effect on the liver. His family doctor will give advice about hygiene within the home.

The worry about viral hepatitis is that it can lead on to more permanent changes in the structure of the liver. These changes have become more defined in recent years, and are grouped under the headings:

(1) chronic persistent hepatitis,
(2) chronic active hepatitis, and
(3) cirrhosis.

Thankfully most cases of prolonged liver disease in haemophilia are of chronic persistent hepatitis in which the outlook is excellent. No treatment is indicated.

Occasionally chronic active hepatitis complicates haemophilia, and may rarely lead on to cirrhosis of the liver. Although no specific treatment is yet available for chronic active hepatitis patients with persistent jaundice or illness, they may benefit from treatment with steroids (page 24). The decision to use steroids depends on the individual, the laboratory tests and, most probably, on the results of the liver biopsy. Hopefully it will not be long before specific anti-viral medicines become available.

Chronic active hepatitis appears to follow a mild course and be of little relevance to the haemophiliac unless cirrhosis develops.

Cirrhosis of the liver

In this condition normal, fleshy liver tissue becomes scarred and unable to function properly. Cirrhosis results from many different disorders, including viral hepatitis. Probably the best known cause is long-standing alcohol abuse. No one treatment is available for people with cirrhosis, although several ideas are being explored in an attempt to switch off the process that results in scar, or fibrous tissue formation. The main hope lies in preventing the disease in the first place. The technique of liver transplantation is now feasible for a minority of patients.

Alcohol and the liver

Before concluding this account of liver disease the question of the effect of alcohol on the liver has to be faced. As a doctor concerned with the many difficulties of haemophilia, including the joint pain experienced by the older generations of patients, I am loath to suggest the withdrawal of one of life's comforts! However, there is no doubt that alcohol in excess does cause liver failure, probably affecting at least one in every 3000 people in Western countries. Certainly anyone with proven, persistent liver disease should try to abstain from alcohol, as should anyone during an episode of hepatitis. It is customary to suggest that after an attack of jaundice alcohol should be barred for 6 months, but the evidence to support this view is not absolute. My view is that if alcohol in moderation makes life tolerable for someone with severe haemophilia it should not be condemned.

The acquired immunodeficiency syndrome (AIDS)

AIDS seems to be a relatively new phenomenon, first coming to public notice in the United States in 1979. Its name suggests what happens in the body: the immune or defence system becomes compromised, opening the way for rather odd invaders that in health are kept at bay. This breakdown in defence is confined to cellular immunity, that part of the immune system in which T cells act (see page 12). Humoral immunity, dependent on B cells, is left intact so that, for instance, bacterial invaders are still resisted, whereas viruses and other organisms may gain access.

Immunodeficiency itself is not a new concept to doctors. Rarely, children are born without intact immune systems; these are the babies who used to live in bubble tents to protect them from infection. Nowadays this protection is given by injection of the necessary immune components. Far commoner are those patients in whom the immune system has been altered by drugs in an attempt either to control certain forms of cancer, or to help them accept a transplanted organ more readily.

What is odd about AIDS is that it is virtually confined to certain groups of people. The great majority (71%) of those with AIDS are male homosexuals.

Next are people who abuse intravenous drugs (13%) and people from, or who have visited, Haiti in the Caribbean (7%). At the time of writing (November 1983) haemophiliacs account for only about 1% of the total. Seventeen severely affected haemophiliacs have been notified as having AIDS in the United States (approximate total haemophilia population 20000) and two in the United Kingdom (approximate total haemophilia population 4500). Two of the American patients were thought to belong to other 'at risk' groups. Of these 19 people, 11 have died of an infection which causes a form of pneumonia.

No one with haemophilia has been found with the other manifestation of AIDS seen in the homosexual group. This is a rare cancer called Kaposi's sarcoma after the doctor who first described it in 1887. To date only one haemophilia B (factor IX-deficient) patient is listed as having AIDS.

Because haemophiliacs have developed immunodeficiency, and because affected homosexuals have donated their blood plasma, it has been assumed that whatever it is that causes AIDS is being spread by blood transfusion. This assumption has been developed into a theory that a virus with a very long incubation period is responsible. At this stage we do not know if these assumptions are justified. Immunodeficiency in a few haemophiliacs may be the result of repeated exposure to proteins and other antigens in blood products, and nothing whatsoever to do with what is happening in the homosexual community. However, as a precaution checks have been introduced to exclude people in the high risk groups from giving blood.

What should people with haemophilia do? The answer is straightforward: *they should continue to treat their bleeds as quickly and as effectively as possible.* Without treatment haemophilia cripples and kills. Hopefully, by the time this description of AIDS appears in print we will know some of the answers to the questions it poses to patients and their doctors. One of these is likely to be that, if there is an infectious agent in blood, its attack rate is very small and that only a few people will have trouble with it. The story of AIDS has many similarities to that of hepatitis B, and, as we have seen, hepatitis B can be controlled.

DEAMINO-D-ARGININE VASOPRESSIN (DDAVP)

Vasopressin is one of the hormones produced by the pituitary gland which lies at the base of the brain. Its main action is to help conserve water in the body through a switching effect on the kidneys, hence its other name anti-diuretic hormone (diuresis = promotion of secretion of urine). DDAVP is a synthetic derivative of the natural hormone, developed originally to help people with disease or injury of the pituitary gland. It may be given by intravenous injection or in the form of snuff, when it is absorbed through the membrane lining the nose.

Coincidentally, DDAVP raises the level of factor VIII in the bloodstream, and it has been found that this rise is sometimes sufficient to stop bleeds and to allow even major surgery to be performed. DDAVP is *only* effective when the person receiving it is already capable of producing some factor VIII. Thus it