THE LANCET

## Safer Factor VIII and IX

THE risk of contracting non-A, non-B hepatitis from factor VIII and IX concentrates was first recognised ten years ago.[1-3] The requirement for large pools of plasma, of up to 7000 donations in the UK, as starting material in manufacture, and even larger pools with some commercial preparations, has produced attack rates approaching 100% in recipients after first exposure to unheated factor VIII.[4,5] The acute illness was often mild; fulminating hepatitis was confined to patients with pre-existing chronic liver disease, often of non-viral origin. Unfortunately, it is now clear that there is a substantial long-term risk of chronic sequelae, such as chronic active hepatitis and cirrhosis of the liver. Reports[6,7] of serial liver biopsies in patients regularly treated with factor VIII and IX suggest that the risk of serious chronic liver disease may be as high as 16%. Surveillance of hepatitis B in the UK also shows that there is still a risk of contracting the infection from factor VIII and IX, despite the screening of plasma donations by radioimmunoassay (UK Haemophilia Directors' Hepatitis Working Party, unpublished). The effect of screening is to delay the onset of hepatitis B in patients receiving regular treatment by one to four years from first receipt of these products.

Despite intensive research, the virus or viruses associated with non-A, non-B (NANB) hepatitis have not been isolated or characterised. Such information as exists on the physical and chemical nature of the agent(s) is based on chimpanzee experiments and epidemiological studies in man. There is evidence that at least two viruses are involved,[8] but this has been disputed.[9] A carrier state has been confirmed in chimpanzees[10] and in man.[11]

Five years ago the first cases of acquired immunodeficiency syndrome were reported in the USA, and it has since become clear that human immunodeficiency virus (HIV, formerly HTLV-III/LAV) infection may be transmitted by both factor VIII and IX concentrates. Other viruses, such as human parvovirus, are transmitted by factor VIII therapy, but no illness has been reported with this mode of infection.[12] Viruses which are more cell-associated in vivo—eg, HTLV-I, Epstein-Barr virus (EBV), and cytomegalovirus (CMV)—although transmitted by fresh blood, platelets, and leucocyte transfusion, are not transmitted by fresh-frozen plasma or factor VIII or IX concentrates.

Failure to characterise NANB hepatitis viruses, and the marginal effect of serum alanine aminotransferase testing of blood donors on the incidence of NANB hepatitis[13] prompted investigation of physical and chemical inactivation of viruses present in factor VIII and IX while the coagulant activity of the concentrate was preserved by use of stabilising substances, such as sucrose. This approach is limited, however, by the lability of clotting factors to the methods of inactivation.

Use of dry heat—temperatures around 60°C for various lengths of time—in an attempt to pasteurise freeze-dried ampoules of factor VIII failed to inactivate NANB hepatitis virus(es);[14] wet heat was only partly successful.[15] Heating at a higher

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temperature with increased purity of factor VIII in the concentrate is also under investigation, but results of trials are not yet available. Use of ultraviolet light and β-propiolactone for factor IX concentrate, although apparently successful, has not been pursued owing to fears about the oncogenic potential of β-propiolactone[9] and reduced yields of the clotting factor.

An interesting approach by Prince and his colleagues[9] made use of a recognised method of factor VIII purification which itself inactivated lipid-containing enveloped viruses. They showed that HIV, one strain of NANB hepatitis virus, and hepatitis B virus were all inactivated by at least ten thousand infective doses per ml respectively. Since the method depends on the sensitivity of contaminating viruses to inactivation by TNBP/sodium cholate, serum parvovirus and enteroviruses are not inactivated. From the data presented by Bradley et al[8] it is possible that the second serotype of NANB hepatitis is due to an enterovirus; despite evidence presented by Prince and co-workers to the contrary, it remains to be seen whether a second type of NANB hepatitis is transmitted by the TNBP/cholate-treated product.

Initial results of prospective studies suggested that heat-treated factor VIII did not transmit HIV infection.[16] However, two recent reports[17,18] show that heat-treated products are occasionally implicated. The information in one case indicates a possible transmission of infection; AIDS has subsequently developed in one of the donors contributing to the batch of factor VIII. Presumably the plasma donations were not tested for anti-HIV; if so, then in future heat-treated factor VIII must be manufactured from suitably screened plasma.

The experience of transfusion-associated HIV infection shows that prevention depends on three precautions which are necessary to compensate for the increased risk of infection produced by use of large pools of plasma as source-material for factor VIII and IX concentrates:

(a) Efficient methods of screening through the use of educational methods so that persons at high risk for HIV infection are either dissuaded from attending the donor session or exclude themselves at the centre.

(b) Use of a sensitive and specific immunoassay for viral markers that will identify as many as possible of the donors who might transmit infection.

(c) Use of a method of inactivating viruses that increases the safety factor without significantly destroying the coagulation factors present in the concentrate.

Introduction of the above measures has raised the hope that factor VIII and IX concentrates free from the risk of HIV infection are a real possibility. It is also possible that the risk of NANB hepatitis might be substantially reduced. Partial inactivation of HIV in an infected batch of concentrate may leave only a small proportion of bottles in a contaminated batch capable of transmitting infection; for this reason large-scale surveillance of these products should be mounted to detect any transmission of viral infection.

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## Alcohol and Haemorrhagic Stroke

AS the British Medical Association struggles publicly[1] with its conscience over alcohol advertising and some of its members' activities, notably its wine club, the Royal College of Physicians, a quarter of a millenium after its first submission to Parliament on "so great and growing an evil", engages in the preparation of another report on the immoderate use of alcohol. It will be kept company by the Royal Colleges of Psychiatrists and General Practitioners. Meanwhile, the British nation spends more on alcohol than it does on its clothing or its cars.[2]

Popularly, alcohol intake has been associated, in terms of disease, with cirrhosis of the liver, and this has been regarded as an illness of heavy drinkers. In Europe, there is strong correlation between cirrhosis deaths and per caput consumption of pure alcohol.[3] In clinical practice, damaging consequences of alcoholic excess have also been recognised commonly to affect central and peripheral nervous systems,[4] skeletal muscle,[5] oesophagus,[6] gastrointestinal tract,[7] and pancreas,[8] nutritional state,[9] and the heart[10]—to say nothing of accidental injuries and mortality associated with alcohol misuse.

A relation between high alcohol intake and raised blood pressure has been appreciated more recently,[11,12] with estimates that alcohol accounts for up to 30% of all cases of hypertension.[13] Since hypertension is the dominant risk factor for stroke,[14] an association between alcohol abuse and stroke would be expected, irrespective of the association of alcohol with heart disease, diabetes, and cigarette smoking,

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