EDITORIAL / VAN DIE REDAKSIE

Blood transfusion and viruses with delayed expression

Most common viruses likely to be transmitted by the transfusion of blood or its products are either dealt with promptly by the recipient's immune system or expressed fairly quickly. More insidious and dangerous, however, are those whose clinical presence is not recognisable early, i.e. the retroviruses and those hepatitis viruses which can either give rise to acute and fulminating disease, or lead on to chronic liver conditions.

At least three, and possibly more, specifically hepatotropic viruses are of major significance.[1] The first of these to be recognised was hepatitis A. Its spread through the transfusion of blood or its products is rare, thanks largely to donor self-exclusion. The incubation period and viraemia are of relatively short duration, there is no carrier state, and because of silent childhood infections, the level of adult immunity is high in most populations.

Until it became possible to screen blood for the presence of viruses, hepatitis B was probably the infection most commonly associated with clinical disease following blood transfusion. During the Second World War it was responsible for the 'homologous serum jaundice' which often followed the administration of pooled human plasma,[2] but it was not until some time after the identification of the so-called 'Australia antigen' that this was recognised. Like the retroviruses and human parvovirus, it can remain infective even in blood products containing high titres of antibody against it. It is often present in apparently healthy chronic carriers, and may be present as a mild and unsuspected viraemia in potential patients well before any clinical signs develop. Hepatitis B virus that persists in the cells of the liver is frequently associated with primary hepatic carcinoma.[3]

The infectivity of the virus is sometimes judged from the presence or absence of the E antigen or its antibody. Persons who have recently become carriers often have this antigen in their plasma and are highly infective, while longer-term carriers possess the antibody and are less likely to transmit the virus.[3] In the context of blood transfusion the most reliable way of preventing transmission is by screening for the hepatitis B surface antigen (HBsAg) of the viral coat. This is done routinely in most developed countries, but where most inhabitants have been exposed to the virus at an early age, and have either acquired effective immunity or become chronic carriers, it may not be economically justifiable.[4] Even then, however, blood prescribed for unexposed foreigners or for administration to the very young should be free of the virus.[5]

At one time it was feared that its dangers would be multiplied by spread of the delta agent, a hepatotropic virus dependent on the presence of the hepatitis B virus for replication. It can be transmitted by transfusion,[6] and though innocuous itself may cause a more severe disease by potentiating and sometimes reactivating hepatitis B. The agent has turned out, however, to be neither as universally menacing nor as fast-spreading as was feared. Much more worrying have been the increasing number of dangers detected with regard to the non-A, non-B (NANB) hepatitides; the identification and characterisation of one of the viruses causing these, now named hepatitis C,[7] has not proved reasssuring. Although considerable uncertainty remains about its modes of spread, blood transfusion is indisputably one of them, and the virus may be associated with severe acute or chronic hepatitis.[8]

When it first appeared hepatitis B was greeted with a terror similar to that which nowadays attends HIV. There are some epidemiological, though few virological, similarities between them. HIV is a retrovirus which invades the actual genome, and though it may be contracted in much the same way as hepatitis B, is significantly less infectious but far more likely to have a fatal outcome. Transfusion of blood or blood products that contain the virus is certain to result in infection. The latent period before antibodies can be detected adds considerably to the risk. Even though the screening for antibody of every unit of blood donated is now mandatory in South Africa, and indeed has been for some time here and in most of the rest of the world, the existence of this 'window period' is of great concern. Efforts have been made to overcome its dangers as far as possible by introducing new screening tests, mostly expensive and not all effective, to detect the antibody earlier.

Another favoured strategy is the identification of donors considered to be at risk, and their exclusion as donors. More successful have been the efforts made by some blood transfusion services here and abroad to encourage donors who know themselves to be at risk to abstain voluntarily. This requires intensive donor indoctrination, facilitated by acceptance of the essentially social nature of blood donation, but it avoids the stigma of arbitrary elitism of which some services are sometimes accused. It also has the civic advantage of helping donors to be more careful about avoiding infection.

Another recently recognised retrovirus is also prospectively alarming, although not as much as HIV. The human T-cell lymphotropic virus type I (HTLV-I) has been found to be associated with both spastic paraparesis and adult T-cell lymphoma/leukaemia.[9] Blood transfusion transmission has been documented only for whole blood and cellular components,[10] and as causing only tropical spastic paraplegia. The incubation period is so long that the probability that transfusion-associated disease will result during the lifetime of the recipient is small,[11] and the association of this retrovirus with disease shows so much geographical variation that it is probable that current techniques of detection may by turning up a high proportion of false positives.[12] Consequently routine screening of blood donations is not recommended.

These viruses of delayed clinical effect are of great concern at present, but the fact that a vaccine effective against hepatitis B has been developed gives hope that similar methods may lead eventually to control of the rest. The structure and behaviour of the retroviruses have turned out to be so disconcertingly different that some authorities have expressed doubts whether this will be possible. The same, however, was claimed originally about hepatitis B, and it is far too early to lose faith in the ingenuity of all the workers at present active in this field.

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Hereditary haemochromatosis — a South African perspective

Haemochromatosis is the term applied when organ structure and function are impaired by the presence of excessive quantities of iron in parenchymal cells. By the time clinical manifestations appear, more than 15 g iron is present in the body, with the highest concentrations being in the liver, pancreas, heart, endocrine organs, skin and joints. Presenting clinical features include cirrhosis, diabetes, cardiomyopathy, hypogonadism, skin pigmentation and arthritis.

There are several ways in which too much iron can accumulate in the body.[1] Firstly, there are conditions in which mucosal behaviour is abnormal and amounts of iron are absorbed which are inappropriate to body needs. This occurs in hereditary haemochromatosis, a genetic disorder which is associated with the slow accumulation of iron in the body over several decades so that clinical manifestations usually occur in middle age. Iron absorption is also inappropriately increased in thalassaemia major and other refractory anaemias in which erythropoiesis is markedly increased but ineffective. The degree of overload is often further increased by iron derived from repeated blood transfusions. The rate of iron accumulation is much faster than in hereditary haemochromatosis and clinical sequelae of the iron deposits occur in the teens. The final cause of iron overload is prolonged exposure to a diet containing large quantities of bio-available iron.[2] This unique form of environmental overload, which may also include an uncharacterised genetic predisposition,[3] is extremely rare outside sub-Saharan Africa, where it occurs in adult blacks. It results from the brewing of traditional alcoholic beverages in iron containers.[2] Over the last 20 years its prevalence in urban areas has dropped dramatically due to the increasing consumption of Western-type liquors and the commercial brewing of traditional beers in stainless steel drums.[4] It still, however, remains a problem in rural communities in southern Africa.[5,6]

Hereditary haemochromatosis has until recently been regarded as a rare disease.[1] Because of its slow development and protean manifestations, there is an average delay between the development of symptoms and diagnosis of 5 - 10 years. The classic 'bronzed diabetes' triad of slatey-grey skin pigmentation, diabetes and cirrhosis is infrequently present and the diagnosis will be missed unless haemochromatosis is always thought of as a possible cause of skin pigmentation, diabetes, cirrhosis, cardiopathy, arthritis, impotence or sterility, asymptomatic hepatomegaly or unexplained elevation of liver enzyme levels, alone or in combination.[7] In this context, physicians who specialise in hepatology, cardiology, diabetes, endocrinology and rheumatology should be especially alert. Confirmation of the suspected diagnosis is not difficult. The transferrin saturation is usually over 90% and almost invariably over 70%, while the serum ferritin concentration is over 1 000 µg/l.[1] Final proof depends on the finding of hepatocytes loaded with iron on liver biopsy and high concentrations of the metal on biochemical testing. Removal of the excess body iron is achieved by a vigorous phlebotomy programme (i.e. at least 500 ml weekly until the excess iron has been removed). Such treatment can arrest or even reverse some of the complications of the disorder.[1] Cirrhosis is arrested, cardiomyopathy is reversed and the control of diabetes sometimes improves. Endocrinopathy and arthropathy are not, however, affected by treatment. Prolonged survival in a disease where the average survival was previously 4 - 5 years offers the most impressive evidence of the beneficial effects of phlebotomy. In a recent large German study 76% of patients were still alive at 10 years.[8]

Subjects with hereditary haemochromatosis are homozygous for an autosomal recessive gene, located close to the HLA locus on the short arm of chromosome 6, which is associated with the absorption of more iron than is required.[9] The fact that the gene is so close to the HLA locus makes it possible for HLA markers to be used in family studies to identify affected homozygotes in the immediate relatives, and particularly siblings, of patients with the clinical disease. This approach has considerably widened the clinical spectrum of the disease, since it has made it possible to identify many asymptomatic homozygotes prior to the development of severe iron overload and impaired organ function.[1] When a sibling is HLA-identical with the proband, the transferrin saturation and serum ferritin concentration should be measured and, if raised, a liver biopsy carried out. The finding of raised iron stores indicates the need for a bleeding programme. Homozygotes with normal stores are usually young and should be monitored over the years. Heterozygous family members can be reassured. While minor derangements of iron metabolism may occur, such subjects do not accumulate significant amounts of iron.

While the full-blown clinical and pathological presentation of hereditary haemochromatosis is encountered infrequently, family and epidemiological studies suggest that the HLA-linked iron-loading gene is one of the most common abnormal genes identified in Caucasians to date. Figures from several countries indicated that about 10% are heterozygotes and 0,3% homozygotes.[10] Indeed, an epidemiological study carried out in the western Cape, in which the combination of a persistently raised transferrin saturation and serum ferritin concentration was used as the marker, suggests an even higher frequency in subjects of Afrikaner descent.[10] The fact that only a proportion of individuals identified in this and other epidemiological studies exhibited significant iron overload indicates that full phenotypic expression does not occur in all homozygotes.[1] In this context, the tenfold greater prevalence of clinical manifestations in male homozygotes as compared with female homozygotes can be ascribed to losses of iron incurred by females through menstruation and pregnancy.[1]

What are the practical implications of all these findings? Few doctors know much about hereditary haemochromatosis and, as a result, the diagnosis is often missed for long periods. Treatment, when initiated, is often inadequate and affected relatives are not identified. The sense of grievance felt by many patients and their families, coupled with a desire to help fellow patients and their families and to promote research, has led to the establishment of haemochromatosis societies in the USA and Canada. These have successfully increased awareness of the disease through fund-raising, newsletters, medical meetings and lobbying. In so far as

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local patients are concerned, there are three pieces of good news. Firstly, the South African Haemochromatosis Society has been established to promote the interests of patients (Haemochromatosis Society of Southern Africa, PO Box 2163, Southdale, 2091). Secondly, the Genetics Service Division of the Department of National Health and Population Development has become actively involved. It has produced a brochure on the disorder, *Haemochromatosis and You*, which gives details of available counselling services. It also gives the names and addresses of specialists and referral centres where advice on the disease can be obtained by practitioners and patients. The third positive development is an undertaking by the various blood transfusion services to carry out the necessary venesection programmes on patients referred to them. All in all, it looks as if a new and hopeful era is dawning for homozygous carriers of the HLA-linked iron-loading gene in South Africa.

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Cancer outlook — any light at the end of the tunnel?

In Western populations a newborn boy can now expect to live for 72 years, and his sister 78 years, a far cry from 1900 when life expectancy in the UK was just under 50 years. Even among urban dwellers in some developing populations, respective figures are now about 60 and 65 years or more. Therefore, most people can nowadays expect to reach a good old age. However, they may not wish to live longer, but rather to enjoy as many *disease-free years* as possible, by delaying the development of the 'killer diseases' (chiefly coronary heart disease (CHD), cancer, and stroke) until later years. Recently, major falls have occurred in mortality rates from CHD and stroke, but only in respect of one cancer, gastric cancer.[1]

The burden of suffering from cancer is fearful, the anguish to the family devastating, and the outlook formidable. In the USA, cancer is the second leading cause of death.[2] By 2000 it will become the leading cause, when about one person in every three will die from it. It also carries a heavy economic burden, over 80 billion dollars a year. In Western populations, the mortality rate from cancer, while decreasing slightly in the young, is rising in the elderly.[3] With regard to developing populations, 'Cancer will "overwhelm" the Third World in the near future . . .. Among cancer patients 90% are incurable by the time diagnosis is made.'[4] While cancers of the oesophagus and liver will tend to fall, the incidence of diet-related cancers, breast, colon and prostate cancer, is rising.

In combating the disease, an insufficiently appreciated adverse factor is poverty. In the USA the following question has been asked: 'Does war on cancer equal war on poverty?'[5] Some new data suggest the answer to be 'yes'. Blacks are more susceptible to cancer, not because they are black, but because they are poor. When adjustment is made for income and education, blacks have a lower cancer incidence. In Melbourne, Australia, studies revealed that incidences of cancer of the stomach, lung and cervix demonstrated negative socio-economic state (SES) gradients.[6] In Western populations the dichotomy between rich and poor is increasing. In Third-World countries, e.g. in Africa, impoverishment is rising. Aid previously obtained from Western agencies is diminishing, and budgets are devoting less money to health maintenance, disease prevention and treatment.

Of environmental factors, tobacco use is reckoned to be responsible for 30% of all deaths from cancer, and dietary factors for about 35%. Reproduction practices, alcohol consumption and exposure to environmental carcinogens have each been held responsible for about 5% of cancers.[7]

Smoking contributes to 1 death in 5 in the USA. While the practice is associated primarily with lung cancer, it also contributes to cancers of the oral cavity and pharynx, oesophagus, pancreas, kidney and bladder. In the USA, while smoking practice has declined considerably, it remains high among students, 40% in males and 32% in females.[8] Interestingly, the proportion of doctors in the USA and UK who smoke is very low (10 - 12%), although for French doctors the figure is 57%.[9] Regrettably, the downward trend is levelling off. In all Third-World populations smoking practice is increasing, especially among males.

Alcohol promotes a number of cancers, principally of the oesophagus, larynx and liver.[10] Consumption in Western populations, while variable, is generally high. Doctors are among the highest consumers. In all Third-World populations, alcohol consumption is rising.

Reproduction practices can be both protective and promotive. With regard to breast cancer, the protective concatenation is late menarche, irregular cycles, early first child, high parity, and long lactations with associated amenorrhoea.[11] In contrast, early intercourse with multiple partners is a risk factor for cervical cancer.

With regard to diet, recommendations for cancer avoidance are now well known: reduce intakes of energy and fat, especially saturated fat, and increase intakes of fibre-containing foods — cereals, legumes, vegetables, fruit.[12] Our Western ancestors ate such a diet, as do Third-World populations with traditional lifestyles. Despite two decades of urging, the energy intakes of

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Western populations are steady or falling only slightly. In many countries, e.g. the USA and Australia, obesity is increasing. The percentage of energy derived from fat has fallen slightly, from 40% to 35% in the USA, replaced in part by polyunsaturated fats which may not be wholly innocuous.[13] Bread consumption is at an all-time low, 110 - 120 g per head daily, far removed from the 500 - 700 g daily of only a century or two ago. Regrettably, consumptions of vegetables and fruit are low;[14] in the USA, instead of the recommended five helpings, only half of the population have two helpings daily.[13] British nutritional reference values urge the doubling of consumptions of bread and vegetables, with that of fruit increased by half. Unfortunately, the advocated 'prudent' diet costs more than everyday diets.

Clearly, attempts to control cancer significantly will require herculean resolve, in the face of a slowing down in the trend toward reduced smoking, with alcohol consumption remaining high, with protective reproduction practices for breast cancer impossible to attain, and with a general reluctance to adopt dietary practices of sufficient impact to be ameliorative.

What can be done? First, ignorance must be remedied. Among poor Americans, half of the patients surveyed either denied or did not know that smoking was related to cancer development.[5] In Australia, an enquiry among medical students 'revealed worrying levels of incorrect knowledge'.[15] In Brazil the following question was asked: 'With free health services, why does the working class delay seeing the doctor?'[16]

With regard to screening, some studies have yielded disappointing results, but others are promising, as in Sweden where screening is reducing cervical cancer incidence by 4% annually. Overviews suggest a significant reduction in breast cancer to be possible. It has been commented that 'although successful screening for breast and cervical cancers are attractive goals, they are far less cost-effective than reducing the rate of smoking'.[17] Early detection usually enhances survival time significantly, especially in cases of melanoma, breast and colon cancers.

Some authorities are very sanguine about cancer control. According to a recent comprehensive review,[2] 'the astounding advances in our understanding of the molecular biology of cancer provide a unified concept of the nature of the cancer cell and also suggest new clinical approaches to cancer aetiology, prevention, and treatment . . .. It seems likely, therefore, that even before the year 2000 these powerful and unifying themes will accelerate advances in both cancer prevention and treatment, thus leading to major reductions in both the incidence and mortality of human cancer.' Others, however, remain unconvinced that advances in knowledge *per se* will ensure improvement.

Writers tend to differ as to what evidence they deem particularly encouraging. To the present authors, the best cause for hope in Western populations is the behaviour of a group of Mormon priests and their wives who, from their lifestyle habits, have less than half of the USA standard mortality ratios for cancer and CHD.[18] Among developing populations, there is the positive experience of people in the state of Kerala, India, where intensive community enterprise has reduced vital statistics (infant mortality rate, death rate) to half or less than those for the rest of India, and where intensity of efforts to educate, control, identify, and follow up cancer patients exceeds the endeavours of many Western populations.[19]

The depressing conclusion reached in a review by Muir and Sasco[9] is that the knowledge is there, but the will to change apparently not.

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