? to be raised as
an item for discussion on
5/10/82

3278 Vox Sanguinis (1981) 41[2], 110-122. Should donors with a history of jaundice still be rejected?

The contentious problem of whether blood donors with a history of jaundice should still be rejected is discussed by a panel of experts from North America and Europe only. Diverse opinions are given and these are too complex to abstract. Briefly, however, the outcome of transfusing blood from donors with a history of hepatitis (or jaundice) compared with donors without such a history has not been examined in a well-designed prospective study. Thus any decisions regarding this criterion are not sufficiently compelling (nor based on factual data). The most cogent arguments in favour of abandoning the history of jaundice as a criterion for donor exclusion are:

(1) Viral hepatitis is predominantly an anicteric relatively asymptomatic infection so that at least 75% of persons previously infected do not provide a history of jaundice.

(2) Individuals with anicteric (*i.e.* unrecognized) infections are as likely, or indeed even more likely, to become persistent carriers (of hepatitis B viral markers) than those with clinical jaundice, and numerically they represent the main source of transfusion-transmitted hepatitis [type B; hepatitis A is extremely rarely transmitted by the transfusion of blood. There are no specific laboratory tests for the virus(es) of non-A, non-B hepatitis].

(3) Among those with a history of jaundice and/or hepatitis, many donors are needlessly excluded because (a) their initial infection was hepatitis A, which does not result in a persistent carrier state; (b) the infection was hepatitis B (from which 90-95% fully recover if the infection is acquired after childhood) and sensitive screening laboratory tests are available for markers of hepatitis B virus. Routine screening tests for hepatitis B surface antigen are used [but other markers such as anti-HBc IgM are being considered by a few centres to reduce even further the risk of hepatitis B transmission by the rare donor in whose serum this marker is present alone]; and (c) the jaundice was unrelated to any type of viral hepatitis.

[The foregoing reasons were the principal ones why the British Department of Health and the World Health Organization recommended in 1975 that the exclusion of blood donors with a history of jaundice was not necessary provided hepatitis B surface antigen was not detected in the donor serum by a very sensitive test, and that the donor had not had hepatitis or jaundice during the 12 months before donation.]

Arguments in favour of retaining a policy of exclusion based on the history of jaundice or hepatitis include the following:

(1) The more recent identification of post-transfusion non-A, non-B hepatitis, which is a major remaining cause of transfusion-associated hepatitis in some countries, *e.g.* in the U.S.A.; in the absence of specific tests for non-A, non-B hepatitis, however, it is difficult to establish formally the prevalence of this infection, which is based on a diagnosis by exclusion.

(2) Screening for rises in aminotransferase activities may (at least in some countries), reduce the risk of transfusing potentially infectious blood donations. But this practice too is not widely accepted since biochemical tests of liver function are not specific.

(3) In areas with a traditionally low incidence of hepatitis a history of jaundice does not appear to lead to a significant loss of potential blood donors by retaining a policy of exclusion.

(4) However low the risk of transmitting hepatitis from donors with a past history of jaundice the risk cannot be justified until a test for non-A, non-B hepatitis becomes available.

[As mentioned above, the opinions expressed are diverse, and compelling data for justifying either policy are not available.] *A. J. Zuckerman*

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Hepatic granulomas

Granulomas are focal accumulations of modified macrophages. They are thought to form when macrophages ingest poorly soluble antigens. These can be viral, bacterial, fungal, parasitic, or unrelated to infection or infestation, so that when granulomas are found in the liver many different causes have to be considered.[1-6] Sarcoidosis and tuberculosis are high on the list in many series.

When liver biopsies are done in the course of investigation of systemic symptoms such as fever or loss of weight granulomas may be the principal or only histological abnormality. Clinician and pathologist must then set up series of further investigations until the cause is found. Alternatively, the pathologist may find one or more granulomas in a biopsy specimen showing changes of underlying liver disease. The granulomas may then help to establish the nature of this disease, as in primary biliary cirrhosis, in which granulomas are common in the early stages.[7] In other instances the granulomas, while not contributing to the diagnosis, are readily explained; for example, granulomas form in fatty livers when fat-laden liver cells rupture.[8] Sometimes granulomas seen in liver disease cannot be explained, and then it is prudent to try to exclude important causes such as tuberculosis, sarcoidosis, and brucellosis. Prolonged, exhaustive investigation is not, however, usually indicated.

To the pathologist hepatic granulomas fall into three groups. In the first the cause is seen under the microscope. Examples include granulomas forming around ova of *Schistosoma mansoni* and tuberculous lesions containing detectable tubercle bacilli. Unfortunately, few granulomas are so easily explained in Western countries, and even in proved tuberculosis bacilli are often not found histologically.[1 4 5] In the second group the cause is not seen, but histological features of the granulomas themselves or of the associated liver disease strongly suggest the diagnosis. Examples are extensive caseous necrosis in tuberculosis and granulomas near damaged bile ducts in a biopsy specimen showing other features of primary biliary cirrhosis. A recently recognised member of this group of granulomas with helpful diagnostic features is the lesion of Q fever: in some patients with this disease liver biopsy shows a distinctive pattern of epithelioid cells, segmented leucocytes, and fibrin surrounding fat vacuoles.[8 9] Histological characteristics are occasionally misleading, as in the rare instances of granulomas in sarcoidosis undergoing extensive necrosis. When histological features suggest but do not prove the diagnosis serological or microbiological confirmation is desirable.

In the third and last, unfortunately large, group the cause of the granulomas cannot be established with any degree of certainty, though there may be histological clues which help narrow the field and suggest a rational sequence of further investigation. An important cause of unexplained granulomas is drug hypersensitivity. McMaster and Hennigar[5] attributed 28 of 95 examples of hepatic granulomas to therapeutic drugs, several of them in common use such as sulphonamides and methyldopa. Most patients had fever and hepatomegaly, and some had peripheral eosinophilia. Histologically the lesions were both portal and intralobular, eosinophils were common, and in some biopsy specimens granulomas were located near damaged small bile ducts.

When all likely causes of granulomas have been excluded with reasonable certainty clinically and histologically a group of puzzling patients remains. In Klatskin's large series of 565 patients with hepatic granulomas,[4] no diagnosis could be established in 37. Nearly half of these had a prolonged feverish illness. Simon and Wolff[10] have described an idiopathic granulomatous hepatitis characterised by prolonged or recurrent fever, often with loss of weight, myalgia, arthralgia, or abdominal pain. Most patients failed to respond to a trial of antituberculous drugs but subsequently improved with corticosteroids. Though different and as yet undefined causes may contribute to this kind of illness, it is perhaps among the few for which the poorly defined term granulomatous hepatitis is appropriate. Possibly some such patients may have the polymyalgia rheumatica and giant-cell arteritis syndrome without clinical evidence of temporal arteritis.[11]

Granulomas in a liver biopsy specimen may have prognostic as well as diagnostic implications. In a series of 100 patients with primary biliary cirrhosis[7] granulomas were found less often in patients who subsequently died than in the survivors. Granulomas should therefore be taken into account in assessing the results of therapeutic trials in this disease. The relation between granuloma formation and clinical course needs confirmation and explanation, but it is in keeping with the known favourable prognostic implication of granulomas in other diseases such as Hodgkin's lymphoma and Crohn's disease.

PETER J SCHEUER

Professor of Clinical Histopathology,
Royal Free Hospital and School of Medicine,
London NW3 2QG

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Blood donors with a history of jaundice

Up till 1975 people with a history of jaundice were not acceptable as blood donors. The recommendation that this policy should be changed was made by an advisory group on testing for the presence of hepatitis B surface antigen (HBsAg; the "Australia" antigen) and its antibody.[1] The group's recommendation was that potential donors should no longer be excluded provided that their blood did not contain detectable HBsAg and that they "had not suffered from hepatitis or jaundice during the previous 12 months."

In 1979 the group was reconvened to consider any changes in policy that might be desirable in the light of advances in knowledge, and its report appeared in 1981.[2] Techniques for detecting HBsAg and its associated viral antigens and antibodies have improved rapidly, enzyme-linked immunoassay and radioimmunoassay taking the place of counterimmunoelectrophoresis and reverse passive haemagglutination. As a result, progressively fewer HBsAg-positive donations have been found, most positive donors being rejected early. Regional transfusion centres in Britain now find between one in 500 and one in 1000 new donors to be HBsAg positive with an overall incidence of about one in 4000 in the donor population as a whole. Yet despite the increased rate of detection not all carriers can be identified, and HBsAg-positive hepatitis (hepatitis B) still remains a hazard of blood transfusion.

The sensitivity of the method of testing is especially important for the use of some plasma products, rather than whole blood or packed cells. The products manufactured for treating the haemophilias, factor VIII and IX concentrates, are prepared from up to 5000 plasma donations, and the risk of contamination of these large pools is high. As a result the group has recommended that only the most sensitive techniques should be employed for all plasma donations sent for fractionation. The major difficulty in attempts to eliminate post-transfusion hepatitis, however, remains the absence of markers for the non-A, non-B viruses. So, though increased sensitivity of donor screening (together with the prospects[3] for immunisation of at-risk groups) will virtually, but not completely, remove the threat of HBsAg-positive disease, the diagnosis of non-A, non-B hepatitis remains non-specific, and its true incidence remains unknown. Experience with haemophiliacs suggests that the non-A, non-B infection is often subicteric, presenting as a short incubation influenza-like illness, and diagnosed correctly only by maintaining a high level of suspicion and finding disordered liver function values. Because of this the extent and severity of post-transfusion hepatitis due to non-A, non-B viral infection have yet to be determined, though it is thought to account for 90% of all such cases in the United States.[4] The diagnosis is important, because non-A, non-B infection may progress to chronic liver disease.

In Australia the only measures used to prevent post-transfusion hepatitis are the exclusion of donors jaundiced in the past two years and those whose donations are HBsAg positive on radioimmunoassay, and Cossart *et al*[5] have recently reported the development of hepatitis in 18 of 842 patients undergoing cardiac surgery. Three infections were caused by hepatitis B, one by cytomegalovirus, and 14 by probable non-A, non-B viruses. The authors found a correlation between the non-A, non-B infections and the presence of antibodies against hepatitis B core antigen (HBcAg) and HBsAg in the donor blood but concluded that only about half the non-A, non-B infections might be avoided if routine surveillance for these markers was introduced. Aach and Kahn[4] have suggested that screening of liver function, specifically by measuring alanine transaminase activity, would help eliminate some non-A, non-B infective donors.

Probably, then, the incidence of non-A, non-B infection might be reduced by routine testing for antibodies against HBcAg and HBsAg and measuring alanine transaminase activity, but on present evidence about half the infective donations would still pass scrutiny. From the donor viewpoint the additional tests would be both expensive and time consuming. In Britain the risk implied in accepting donors with a history of jaundice is minor. But what of the recipient? From his viewpoint the present risk of developing disordered liver function after transfusion of volunteer HBsAg-negative blood is about 10%,[6 7] and the risks rise with the number of donations he receives. Most of the experts at a recent international forum[8] thought that this risk was unacceptable. Their conclusion was that donors with a history of jaundice (some 0·5% of the donor population[6]) should continue to be excluded.

British policy differs from this view, but the advisory group has recommended that doctors should be encouraged to report all cases of post-transfusion jaundice. Where these might be due to non-A, non-B hepatitis, the facts should be reported to the appropriate advisers in blood transfusion at the DHSS or Scottish Home and Health Department.[2]

PETER M JONES

Consultant Paediatrician,
Newcastle Haemophilia Centre,
Royal Victoria Infirmary,
Newcastle upon Tyne NE1 4LP

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