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Alcohol and the blood

Though anaemia is common in alcoholic patients, in clinical practice it is often difficult to assess the relative contribution of inadequate nutrition, coexisting liver disease, and intercurrent illness. Furthermore, alcohol is itself a potential haemopoietic toxin.

Early papers[1–3] on the anaemia of alcoholism emphasised the importance of recurrent gastrointestinal haemorrhage and resulting iron deficiency in its pathogenesis. These conclusions were mostly based on patients with advanced cirrhosis, many of whom had presented with a major bleed. In a more recent series[4] of 65 consecutively admitted chronic alcoholics from the "skid row" area of Seattle, only five patients had an iron deficiency anaemia, and three of those had a history of recent blood loss from the intestinal tract. Marrow iron stores were absent in a further four non-anaemic patients. Occult blood loss seems, then, to be of little importance and in adequately nourished alcoholics typically the serum iron concentration is normal or raised.[5] The high iron content of most alcoholic drinks ensures an adequate intake for alcoholics.

Alcoholics often eat poorly, and folic acid deficiency is frequent. Nearly half of Eichner and Hillman's patients[4] showed megaloblastic changes due to folate deficiency. Of these, all except one had less than one regular meal a day. Two-thirds of a series of 30 patients reported by Cowan and Hines[6] were deficient in folate, as were no fewer than 65 of 70 patients described by Herbert *et al.*[7] Is dietary deficiency the only factor? Folate is found in some alcoholic beverages—beer and cider, for instance. Might alcohol suppress the haemopoietic response to folate or hinder its absorption? Sullivan and Herbert[8] showed that in doses consumed by heavy drinkers alcohol suppressed the reticulocyte response to physiological doses of folic acid (75 μg/day by injection). Giving larger doses (150 μg/day) overcame this inhibitory effect. Alcohol, given by mouth or intravenously, causes a fall in serum folate concentrations to subnormal values within hours of its administration despite a normal diet and satisfactory folate stores.[9] Folate metabolism in and release from the liver are both suppressed.[9 10] Alcohol also reduces folate absorption from the small bowel.[11 12] Serum concentrations of vitamin B_{12}, by contrast, are normal or sometimes raised.[5 13] Alcoholic drinks are uniformly deficient in B_{12}, but the large body stores and efficient enterohepatic circulation ensure that deficiency is rare.

Sideroblastic changes in chronic alcoholics were first described by Hines and Harris.[14] In a later report[15] 24 of 33 alcoholics were shown to have ring sideroblasts in marrow aspirates, and alcoholism is now regarded as the most common cause of sideroblastic anaemia in the United States.[16] Characteristically there is a subpopulation of microcytic hypochromic cells in the peripheral blood. The rapid resolution of sideroblastic features after withdrawal of alcohol suggests that this is a toxic effect. In two volunteers maintained on a high alcohol intake in whom sideroblastic anaemia was induced, conversion of pyridoxine (vitamin B_6) to pyridoxal phosphate was defective.[17] The sideroblastic changes did not remit after treatment with pyridoxine (or folic acid) but did resolve rapidly with pyridoxal phosphate. Serum concentrations of pyridoxal phosphate are usually reduced in these patients.[18] Dietary deficiency of pyridoxine is rare[19] but may be a contributory factor to the anaemia.

Alcoholic liver disease causes profound haematological changes:[3 20] extravascular red cell destruction occurs, chiefly localised to the spleen, but the haemolytic anaemia is rarely severe. The defect is both intracorpuscular and extracorpuscular:[21] the erythrocytes have a shorter survival time in recipient subjects and hypersplenism is therefore but one factor. Thrombocytopenia and, rarely, leucopenia may accompany the anaemia. A rarer form of haemolytic anaemia—spur cell anaemia—with erythrocytes resembling acanthocytes may herald the onset of liver failure.[22] Bone marrow depression and macrocytic and megaloblastic changes are well known in alcoholic cirrhosis, but these changes may well be due, at least in part, to direct toxic effects of alcohol. In general, the degree of anaemia does not parallel the degree of liver damage,[23] and patients may die in hepatic coma while their blood picture is improving. As liver failure progresses to its terminal phase coagulation abnormalities may, however, compound blood loss from gastric erosions or bleeding varices and result in the anaemia of acute haemorrhage. One variable that is easy to overlook is the plasma volume, which is often increased in cirrhotic patients.[3 24]

Haemolysis in the alcoholic is most commonly low grade, but an acute haemolytic anaemia—first described by Zieve[25] and now bearing his name—may occur after a binge. The erythrocyte membrane is altered in composition,[26] resulting in the development of spherocytes.[27] Vitamin E deficiency may further contribute to instability of the red cell membrane.[28]

The importance of alcohol as a direct haemopoietic toxin has been shown by Lindenbaum and Lieber,[29] who studied the effects of high doses of alcohol given to former alcoholic patients. Adequate nutrition and vitamin intake was ensured. At the onset of the study the volunteers had normal blood pictures and normal liver biopsy appearances. During the study seven of the nine patients developed vacuolation of the red cell precursors—a phenomenon first described by McCurdy *et al*[30] in acutely intoxicated alcoholics. There were similar, though less appreciable, changes in granulocyte precursors. Both these abnormalities were proportional to the amount of alcohol taken. Four patients developed thrombocytopenia, which was readily reversible when alcohol was stopped. Megakaryocytes appeared normal, and later work[31] has shown that platelet survival is reduced in these circumstances. Alcohol was continued for several weeks after the development of vacuolation but no morphological changes were found in the circulating red or white cells. Erythropoiesis remained normoblastic, and no ring sideroblasts were detected. The results of ferrokinetic studies were normal. So far no other quantitative abnormalities have been shown to occur in experimental alcohol loading, though reversible granulocytopenia and lymphopenia have been found in alcoholics.[32 33] Severe granulocytopenia often accompanies a septicaemic illness in these patients.

Whether abnormalities of red cell morphology—notably

macrocytosis—may be caused solely by direct alcohol toxicity remains in doubt, but on some occasions[34] alcohol may possibly induce macrocytic and even megaloblastic changes in patients with normal folate and B_{12} stores. Indeed, macrocytosis is so common in alcoholics that even if we understand its pathogenesis only incompletely its use as a screening test for alcoholism seems assured.

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Living with artificial valves

Nearly 20 years have passed since the first operations for the replacement of diseased heart valves.[1 2] Since then thousands of patients have benefited from valve surgery and their doctors have been spared the frustration of watching their decline from a simple mechanical fault. Any assessment of the results of all these operations and of the quality and prolongation of life[3] is a formidable task: the variables are so numerous. Even in cases with a single valve at fault the relevant factors include the patient's age and condition at operation; heart size, rhythm, pulmonary function, and the presence of cardiac failure; the type of valve used, whether tissue (human or animal) or prosthetic (and these are constantly subject to new methods of preparation and preservation or new design); and finally variations in management and in particular the use of anticoagulants or other antithrombotic drugs. Only a fraction of cardiothoracic centres publish their results, and these are usually the busiest, where greater experience would be expected to produce the best results; but even here follow-up data may be incomplete or inaccurate.

The debate continues on whether tissue or prosthetic valves serve better,[4–8] and opinions are inevitably modified with time. The operative mortality (variably defined as death within one to three months of surgery) is still by no means negligible, and may lie anywhere between 2%-3% and 15%; for example, Starr and colleagues[9] reported a 9% mortality rate at one month in 343 aortic valve replacements without coronary grafting.

Thromboembolism remains a constant danger to those with prosthetic valves. The early optimism[8 10 11] over the later designs of the Starr-Edwards valve (cloth-covered struts, composite seat) has not been borne out in practice[9 11 12] and permanent treatment with anticoagulants is now recommended.[9 12 13] Giving drugs that reduce platelet adhesiveness (dipyridamole[14] or aspirin[15]) will further reduce the incidence of embolism, so that many patients may find themselves permanently taking two drugs apart from any needed to control heart rhythm or cardiac failure. The cloth-covered valves, while less thrombogenic, are more prone to cause mechanical haemolysis, sometimes so severe as to force replacement of the valve. Some degree of haemolysis may, indeed, be detected in most patients with prosthetic valves.[16–18] Both ball-and-cage and tilting disc valves cause pressure gradients and are prone to mechanical faults, sometimes with sudden and catastrophic results.

Endocarditis remains a threat, both postoperatively and later, and is more likely to prove fatal than infection of a native valve. At the Mayo Clinic[19] the mortality rate in 45 patients with prosthetic endocarditis was 88% in early infections and 38% in later ones, the incidence of infection being about 1% in 4586 patients. Starr's group[20] reported an incidence of 4%, with an overall mortality rate of 60% in 48 infected patients. Opinion now favours early operation to replace infected prosthetic valves,[21 22] without awaiting the results of antibiotic treatment, particularly when there is a fungal infection.[23 24]

The patient with a tissue valve will be much less prone to thromboembolism and will usually be spared anticlotting drugs, unless these are given for other indications such as atrial fibrillation; his chance of acquiring endocarditis is also less. But the life of the valve is uncertain because of tissue degeneration, and the patient remains at risk from incompetence or stenosis with the prospect of a second operation.

A meaningful follow-up of patients with valve replacements requires periods of up to 10 years, with results preferably based on actuarial analysis.[25 26] One detailed review of reports of this duration showed that, whatever valve was used, no group could report more than half of the original patients alive and free from major complications.[8] The clinical implications are clear. The physician who finds a valve lesion must not forget that its anatomy may have changed little for many years—and may not do so appreciably for many more. In symptom-free patients, therefore, whatever their lesion, and in those mildly or even moderately limited, the clinician must carefully weigh the risks of leaving the patient with his own valve, imperfect though it is, against those of removing it. Valve replacement, though excellent treatment, remains a