Hepatocellular carcinoma and African iron overload

EDITOR,—Gangaidzo and Gordeuk (*Gut* 1995; **37**: 727–30) postulate that iron overload may be a risk factor for hepatocellular carcinoma (HCC) – a subject of obvious interest to workers in Africa. It is especially so to one of us (AW) who, originally, in 1953, propounded the iron overload hypothesis. This sought to explain the abnormal iron deposition (siderosis) present in many Africans, caused by a high adventitious intake of the element arising from food preparation in iron utensils.[1]

In comment, firstly, the above authors state that HCC is probably the commonest malignancy occurring in men worldwide. Actually it ranks eighth in numerical importance on a worldwide basis, accounting for 5·3% of new cancers in men and 2·6% in women.[2]

Next, it is insufficiently appreciated that its incidence in men in Africa is highly variable, ranging from 47·9 per 100 000 world population, in Mali,[3] to 7·5 in Uganda,[4] and 6·4 in South Africa.[5] In agreement with the latter, recently, in three rural widely separated hospitals, responsible for the needs of about 400 000 Africans, we found an average of five admissions of men for HCC per 100 000 annually. Interestingly, the latter rates are much the same as those of Afro-Americans, 5·0–6·6 per 100 000.[3] The citing of 100 cases per 100 000 in Mozambique is inapposite as no current study of the painstaking type made in Uganda,[4] has been pursued in Mozambique – a country at war for 20 years. We know of no present day excessively high rates for HCC in African countries south of the Equator.

Turning now to the noxiousness of iron overload, in the original hypothesis,[1] also in a subsequent local study based on 296 postmortem examinations at Baragwanath Hospital, Soweto, Johannesburg,[6] the pathogenicity of iron overload was doubted, for no constant correlation was found between the degrees of fibrosis and cirrhosis and the amount of iron pigment in the liver. However, later, at the same hospital, as recently detailed by Lynch,[7] associations were reported of siderosis with osteoporosis, diabetes, oesophageal cancer, and heart failure. The findings in these studies, however, made over 20 years ago, have not been currently confirmed. More to the point, over the decades, no attempt has been made at the village level to learn whether iron overload contributes significantly to morbidity and mortality; that is, is it disadvantageous to 1 per 100, or 1 per 1000?

In an investigation made in 1985 by Gordeuk *et al*[8] in Zimbabwe, it was estimated that there were about 80 000 cases of severe iron overload. In the same year, it was stated that in that country there were 14 587 cases of malaria, 2956 of tuberculosis, and 144 of cholera. Surely, were iron overload as pathognomonic as is conjectured, there should be a plethora of evidence incriminating it. This does not seem to be the case.

Gangaidzo and Gordeuk regret that in Africa, only about half of the cases of HCC are explicable on the basis of HBV infection. It must be recognised that apart from the cause and effect of classic deficiency diseases, the above proportion or less is common with multifactorial diseases – dental caries, coronary heart disease, and certain cancers. In brief, the balance of knowledge and ignorance regarding the causation of HCC is the usual.

We entirely support the authors in their urge that prospective studies should be undertaken to examine the possible role of African overload in the pathogenesis of HCC. However, at the village level, in the requisite studies, major difficulties will be encountered regarding participation, especially regarding blood taking and the fear of AIDS. A complicating factor for HCC, as Kew and associates[9] have shown, is that the infection rate of HBV, an important aetiological factor, varies not only from region to region, but from village to village. Additionally, there will be the usual difficulties in seeking to resolve whether iron overload, if implicated, is a causative or an associated factor. Not least of perplexities is the situation whereby a given parameter, for example, serum ferritin concentration, can have a differing significance according to the context. As a recent example of this phenomenon, at Belfast and Toulouse, there is the same average serum cholesterol value but a fourfold difference in mortality from coronary heart disease.[10]

Finally, should iron overload be meaningfully incriminated, the authors say 'it is eminently preventable through changing the practices of preparation and consumption of traditional beer, and it is treatable by phlebotomy therapy to remove iron from the body'. In our view, both of the suggested procedures, in the rural context, are non-starters.

To reiterate, while we are unconvinced of the clinical importance of iron overload, the issue must be resolved – that is, whether it is or is not of public health significance within the context of impoverished Africa.

A R P WALKER
Human Biochemistry Research Unit, Department of Tropical Diseases, School of Pathology of the University of the Witwatersrand, and the South African Institute for Medical Research, Johannesburg, South Africa

ISIDOR SEGAL
Gastroenterology Unit, Baragwanath Hospital and University of the Witwatersrand, Johannesburg, South Africa

1 Walker ARP, Arvidsson UB. Iron 'overload' in the South African Bantu. *Trans R Soc Trop Med Hyg* 1953; **47**: 536–48.
2 Tomatis L. *Cancer: causes, occurrence and control.* International Agency for Research on Cancer, IARC Scientific Publications No 100. Lyon: World Health Organization, 1990: 59.
3 Parkin BM, Muir CS, Whelan SL, *et al. Cancer incidence in five continents.* Vol 6. Lyon: IARC, 1992: 930.
4 Wabinga HR, Parkin DM, Wabwire-Mangen F, Mugerwa JW. Cancer in Kampala, Uganda, in 1989–91: changes in incidence in the era of AIDS. *Int J Cancer* 1993; **54**: 26–36.
5 Sitas F, Pacella R. *Cancer registry of South Africa, 1989.* Johannesburg: South African Institute for Medical Research, 1994: 33.
6 Higginson J, Gerritsen Th, Walker ARP. Siderosis in the Bantu of Southern Africa. *Am J Pathology* 1953; XXIX: 779–815.
7 Lynch SR. Iron overload: prevalence and impact on health. *Nutr Rev* 1995; **53**: 255–60.
8 Gordeuk VR, Boyd RD, Brittenham GM. Dietary iron overload persists in rural sub-Saharan Africa. *Lancet* 1986; i: 1310–3.
9 Kew MC. Chronic hepatitis B virus infection and hepatocellular carcinoma in Africa. *S Afr J Sci* 1992; **88**: 524–8.
10 Evans AE, Ruidavets J-B, McCrum EE, *et al.* Autres pays, autres coeurs? Dietary patterns, risk factors and ischaemic heart disease in Belfast and Toulouse. *Q J Med* 1995; **88**: 469–77.

Reply

EDITOR,—We thank Drs Walker and Segal for their perspectives on the prevalence of hepatocellular carcinoma (HCC) and the toxicity of iron overload in Africa.

High quality cancer epidemiological data are difficult to come by in Africa. With regard to the estimate of Drs Walker and Segal of five admissions for HCC per 100 000 population annually in rural South Africa, we note that hospital based studies may be unreliable estimates of countrywide incidence rates.[1] HCC is a common and important condition in Africa. At least one authority has observed, with regard to HCC, that 'some of the documented incidences are almost certainly underestimates, perhaps by as much as 50 percent in some countries'.[2] A contemporary textbook of gastroenterology in the tropics offers an adjusted rate for HCC of 113 per 100 000 per annum in Shangaan men inhabiting the border areas of Mozambique, Zimbabwe, and South Africa.[2] In Harare, Zimbabwe, HCC is the most common malignancy in men in the 1990s (Harare Cancer Registry, 1995). In the internal medicine wards of one of us (ITG) at Harare Central Hospital, HCC was the most common cancer diagnosis in men in 1993–1994 and accounted for 3·2% of admissions. Among those of us who regularly provide medical care to rural Africans (constituting more than 80% of the Zimbabwean population), there is general agreement that HCC represents a major health problem. We have seen 'few more depressing tasks than caring for a patient with this particular malignancy, . . . and there is no satisfactory treatment'.[3]

The question of whether iron overload in Africa is 'noxious', seems to recapitulate the discussion of 30 years ago about whether iron overload is damaging in people of European origin with hereditary haemochromatosis. As we learn more about states of excess iron, it is our opinion that the weight of evidence points to the conclusion that iron overload of whatever cause (HLA linked hemochromatosis, transfusions, ineffective erythropoiesis, or high dietary iron in Africa) is potentially toxic, and that medical practitioners are obligated to work to prevent and treat iron overload in their patients.[4] In a series of careful pathological studies 35 years ago, Professor T H Bothwell and colleagues at the University of the Witwatersrand provided convincing evidence that dietary iron overload directly causes cirrhosis.[5–7] Interestingly, in 1960 Bothwell reported that in Africans the hepatic iron threshold above which portal fibrosis and cirrhosis are likely to be present is a concentration of 360 μmol/g dry weight[5] (normal is less than 30 μmol/g dry weight). Twenty six years later Dr L Powell's group in Australia reported an almost identical threshold for hepatic damage among white subjects with hereditary hemochromatosis.[8] Support for the association between African iron overload and cirrhosis is provided by a study conducted in the late 1980s at a mission hospital in Swaziland: nine of 29 consecutive adults undergoing diagnostic liver biopsy had hepatic iron concentrations over 360 μg/g dry weight and seven of these subjects (78%) had either portal fibrosis or cirrhosis on histological examination.[9]

Two recent studies that we have conducted examine the noxiousness of dietary iron overload in data sets that span the historical spectrum of this disease. Firstly, we analysed data from the original study of iron overload in Africans, conducted by Dr A S Strachan between 1925 and 1928 at Johannesburg General Hospital, to determine if this form of iron loading may be associated with deaths from HCC or tuberculosis.[10] In the original