Review article

Iron overload in Sub-Saharan Africa: to what extent is it a public health problem?

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Excessive deposition of Fe in the organs and tissues of Sub-Saharan Africans was first described in South Africa in 1929. Fe overload, or siderosis, was initially attributed to infections and to metallic poisoning (Cu, Sn, Zn), and then to malnutrition. In 1953 it was hypothesized that it was due primarily to excessive Fe intake derived from foods and drinks prepared in Fe vessels. Recently, in 1992 it was advanced that a gene distinct from any HLA-linked locus may also play a role. As to sequelae, in early research on series of hospital patients, the condition was linked to scurvy, osteoporosis, diabetes, cirrhosis, and latterly, to hepatocellular cancer and tuberculosis. Accordingly, many have concluded that Fe overload is responsible for considerable morbidity and mortality, that adventitious Fe intake should be reduced, and that phlebotomy be recommended for those severely affected. However, there are numerous limitations in the evidence. There are also problems in interpretation, since levels of Fe in the serum are affected additionally by a variety of factors: infection, inflammation, certain cancers and alcohol intake. These considerations complicate attempts to assess to what extent the associations described denote causation, and whether Fe overload has significant ramifications for ill in the general African population. While the adverse sequelae of overload may be less of significance than many believe, the precise pathogenicity of the phenomenon will remain uncertain until further investigations, including prospective studies, are undertaken.

Iron overload: Africa: Cirrhosis: Hepatocellular carcinoma

'The first key to wisdom is assiduous and frequent questioning . . . For by doubting we come to inquiry, and by inquiry we arrive at truth.' Peter Abelard, 12th Century

Fe overload in Africans in South Africa was first described by Strachan (1929). It is now believed that it results primarily from excessive intake of dietary Fe in a highly bioavailable form (Walker & Arvidsson, 1953; Bothwell *et al.* 1964). Recently, it has been put forward that the overload in part may be genetically determined, and accordingly is the result of the combined effects of environmental and host factors (Gordeuk *et al.* 1992; Moyo *et al.* 1998). However, numerous questions remain unanswered.

In the present contribution, the aim is to seek to learn of the extent to which Fe overload in Africans presents a public health problem. It is proposed, first to describe the condition, then discuss its causation, its pathogenicity, complicating factors, and subsequently, the need for further research.

Iron overload in Sub-Saharan Africans

Early observations

As mentioned, Fe overload in Africans in South Africa was first described by Strachan (1929) in Johannesburg, in a thesis entitled 'Haemosiderosis and haemochromatosis in South African natives with a comment on the aetiology of haemochromatosis'. The dissertation was based on a necropsy study of 876 individuals from several parts of

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

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southern and central Africa, who died in Johannesburg between 1925 and 1928. Strachan concluded that 'haemochromatosis' is a not uncommon disease in regional groups of African natives. In his view, the chief incriminating factor appeared to be the diet. The development of the complete picture of bronzed diabetes depended on the degree of deposition of the pigment and of its rate of deposition. He noted that in mild cases pigmentation alone may occur (as seen in younger Africans), but in slightly more severe cases, cirrhosis may develop. Strachan considered Cu, Sn, or Zn, to be the probable aetiological factor.

Later, Gillman & Gillman (1947, 1951) also in South Africa, maintained that malnutrition and pellagra cause hepatic damage, with deposition of haemosiderin in the liver cells (cytosiderosis); later, this is followed by the excretion of Fe in the bile, with consequent reabsorption and widespread Fe deposition (siderosis). However, Higginson *et al.* (1953) from their post-mortem findings, noted Fe deposition to be widespread in the reticuloendothelial system from the beginning, and the need for division into two stages was doubted. It was considered unwise to isolate changes in the liver from those occurring in the rest of the body. It was argued that were Fe deposition a feature of pellagra, an approximately similar histologic picture would be expected in all cases of acute pellagra on admission to hospital, if the metabolic processes involved were similar in each. This was not reported by Gillman & Gillman (1951), nor was it the experience of Higginson *et al.* (1953). The latter noted that liver biopsies from patients suffering from many different diseases showed the same range of histological pattern of Fe deposition.

In the study just mentioned (Higginson *et al.* 1953), an examination was made of forty-four necropsies of Africans who represented cases of Fe overload of varying severity. Deposition of the element was found in the liver, spleen, heart, kidney and pancreas. Whereas normal Fe concentrations in liver and spleen averaged 0·7 and 1·4 g/kg respectively, they averaged 8 and 22 g/kg in the presence of moderate siderosis, and 30 and 43 g/kg with severe siderosis. Maximal concentrations of Fe in the liver and spleen were 55 and 105 g/kg DM respectively. Corresponding concentrations in haemochromatosis have been reported as 36 and 6 g/kg DM (Sheldon, 1935). From this small series of necropsies undertaken in Africans it was concluded that there was no constant correlation between the degree of fibrosis and the amount of Fe pigment in the liver. Cases of severe Fe deposition were seen without cirrhosis and vice versa. Later studies, however, undertaken in the 1960s, indicated a close-correlation between the degree of siderosis and the presence of significant portal fibrosis or cirrhosis (Seftel *et al.* 1966; Wapnick *et al.* 1971).

Additional sequelae were generalized osteoporosis with collapse of lumbar vertebrae reported in a number of African patients whose bone marrow revealed intense deposition of Fe (Grusin & Samuel, 1957). Two-thirds of such patients were scorbutic. In view of this association between osteoporosis and siderosis, previously known but unpublished, a series of thoracic vertebral bodies from consecutive necropsies of African adults, and from white adults as controls, were examined (Walker, 1955). Findings indicated that extremely high concentrations of Fe were common; thus 15 % of bodies had concentrations exceeding 10 g Fe/kg DM, i.e. about thirty times the proportion normally present. However, there appeared to be no clear-cut correlation between Fe concentration, and ash and Ca concentrations, reckoned on either percentage or volume basis. It was therefore concluded that severe siderosis in vertebral bodies is not necessarily associated with low mineral density.

In a study made on a random group of 100 African patients with diabetes, seven showed moderate siderosis together with portal fibrosis (Seftel *et al.* 1961).

Later clinical and pathological observations

Investigations have been made on series of patients and controls from a number of hospitals in Northern Province and Mpumulanga, South Africa (Friedman *et al.* 1990). Levels of serum ferritin indicated diverse degrees of Fe overload. In one group of patients, the majority of liver biopsies undertaken revealed heavy siderosis, associated with varying degrees of hepatic damage, namely fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Hepatitis B virus (HBV) infection rate was found to be high, approximately 70 % in both patients and controls in the same community. In terms of responsibility for HCC, the complexity of the situation is such that as many as 80 % of cases have been attributed to chronic HBV infection (Zhou *et al.* 1987; Kew, 1995). The possible interaction of HBV with hepatitis C virus (HCV) remains uncertain (Kew, 1994). According to this author, additional risk factors may include aflatoxin, alcohol consumption and smoking. For example, in 50 % of a large series of patients with HCC studied at Baragwanath Hospital, Soweto, Johannesburg, South Africa, a high consumption of alcohol was implicated (Paterson *et al.* 1985).

As regards Fe overload being a risk factor for HCC, a number of reports have provided potentially supportive data. At Baragwanath Hospital, in a study of tumour morphology conducted on ninety patients of rural and urban origins, Fe content was graded in liver tissue; the prevalence of severe hepatic Fe overload was 33·2 % (Paterson *et al.* 1985). This proportion was much higher than the proportion with Fe overload (liver Fe concentration $\geq$ 10 g/kg DM), namely, 24·6 %, found in a necropsy series of Africans dying from all causes at the same institution (MacPhail *et al.* 1979). In a recent rural-based study made in Eastern Province, South Africa, 203 biopsy specimens of liver tissue from 246 African patients with HCC were evaluated (Jaskiewicz *et al.* 1991). Cirrhotic livers were diagnosed in 45 %, and severe siderosis also in 45 % of patients; the presence of both cirrhosis and severe siderosis was found in 38 % of the specimens examined. Although the hypothesis that Fe overload is a risk factor for the development of HCC was not formally tested, the high proportion of 45 % of patients with severe siderosis, and of 38 % of patients with coexistent severe Fe overload and cirrhosis, was considered to be striking. As to the frequency of Fe overload, in the rural community in Gazankulu, South Africa (Friedman *et al.* 1990) evidence of severe Fe overload, on the basis of high ferritin values and transferrin

saturation percentages, was found in approximately 16 % of African men, all traditional beer drinkers. From the various observations described it was concluded that there is an urgent necessity to prevent further development of Fe overload in rural African communities. However, no elucidatory studies were undertaken regarding the state of health/ill-health of the segments of communities who were most severely marked by high ferritin levels.

Recently, a retrospective analysis was undertaken which enquired into some of the data given in the early thesis of Strachan (1929). Examinations concerned the necropsy findings in 714 adult Africans (Gordeuk *et al.* 1996). Of the men and women 19 % and 16 % respectively, had the highest grade of hepatic Fe concentration. The odds of death from HCC in patients with the highest grade of hepatic Fe concentration was 23·5-times the odds in patients with the three lowest grades (95 % CI 2·1, 225). The odds of death from tuberculosis with the highest grade of splenic Fe was 16·9-times the odds with the two lowest grades (95 % CI 4·8, 59·9). It was concluded that Fe overload in Africans may be a risk factor for death from HCC and from tuberculosis.

The iron overload hypothesis

This hypothesis maintains that Fe overload is primarily attributable to excessive Fe intake due to the uptake of adventitious Fe derived during the preparation of foods and drinks in Fe vessels (Walker & Arvidsson, 1953). The hypothesis arose orginally from observations made in 1944–5, when mineral-salt balance studies were carried out on a series of African male prisoners who were consuming their usual diet, which contained a high intake of maize-meal products (Walker *et al.* 1948). The amounts of Fe found in the food and in the faeces were almost invariably much higher than the intakes as determined from food analysis tables. As mentioned, subsequent research showed that Fe was being taken up during the preparation of foods and drinks in Fe vessels. These, in everyday life, included the traditional African three-legged Fe pots and also paraffin cans and drums, which were used ubiquitously in rural areas and in urban townships. In the cooking of cereal products and beans, the Fe content doubled. However, the uptake was found to be much higher in the case of a number of acid-fermented cereal foodstuffs, namely sour porridge (marewa) and traditional beer (sorghum beer). Both of these are of low pH value (pH 3·0–3·5) and large volumes were consumed, especially by men, sometimes daily. Extensive analyses of common foodstuffs after preparation for consumption indicated that the intake of Fe by Africans often was very high, in men reaching as much as 100 mg/d (Walker & Arvidsson, 1953). Accordingly, it was put forward that the deposition of Fe in African adults is due principally to their habitually high Fe intake with consequent high Fe retention.

It is important to note that the phenomenon of the uptake of the element from Fe vessels during food preparation had been reported previously (Fowler & Barer, 1937; McCance & Widdowson, 1937). However, in these instances it was considered that the uptake was not likely to be of much nutritional importance to populations.

It must be noted too that in a number of Western countries, short-term balance studies on white subjects revealed that a very high Fe intake can cause an excessive retention (Fowler & Barer, 1937; Widdowson & McCance, 1937). In the latter study, retention reached a level of 8·8 g in a 54 d period. From such observations it was concluded that no lesion of the digestive tract, nor of any other organ, need essentially be invoked to account for the siderosis observed in the African population. Later, extensive studies on African subjects confirmed the frequency of high Fe uptake from cooking vessels in the preparation of foods and drinks, and its ready biological availability (Bothwell *et al.* 1964).

In Johannesburg, within recent years it has become apparent that both the prevalence and severity of Fe overload in urban African men have fallen markedly. This has been attributed largely to a change in drinking habits, with Western liquors having partially replaced traditional beverages (MacPhail *et al.* 1979).

In experimental studies on small animals, the addition of Fe salts to the diet has been shown to cause excessive Fe deposition. The spleen is most affected, followed by the liver and the kidney, but with only traces in the pancreas. However, in the studies made on rats, the diets used had a much higher Fe concentration than that found in African diets (Finch *et al.* 1950; Theron *et al.* 1963). In the latter study it was fifty times higher. In this particular study, for reasons which were not clear, siderosis occurred more severely when the animals were fed on enriched maize-meal compared with enriched stock-diet. The pattern of distribution of Fe in the animals was found to be similar to that observed chemically and histopathologically in siderosis in Africans (Higginson *et al.* 1953).

The role of a genetic factor in iron overload

In any enquiry into the extent of the pathogenicity of African Fe overload it is necessary to take into account the possible role of other influencing factors, in particular of a genetic factor (Gordeuk *et al.* 1992; Moyo *et al.* 1998). In people of north European descent, haemochromatosis, an autosomal recessive disorder of Fe metabolism, is one of the most prevalent of genetic diseases: 1 in 300 individuals are afflicted and are homozygous for the condition, and 1 in 10 people carry the gene for the disease (Report of a Meeting of Physicians and Scientists at the Royal Free Hospital School of Medicine, 1997). In this disease there is continued absorption of Fe from the upper small intestine despite increasing body Fe overload. The excessive cellular Fe levels lead to tissue damage, in particular to the liver (cirrhosis, HCC), pancreas (diabetes mellitus), joints (arthralgia, arthritis), heart (cardiomyopathy) and pituary gland (hypogonadism). In late disease the skin may become pigmented because of the increased presence of melanin. The concentrations of Fe in the liver and pancreas may be 50- to 100-times higher than their normal values. When the presence of cirrhosis is marked, HCC develops in 25 to 30 % of cases. In haemochromatosis, the individuals affected with cirrhosis have a risk of developing HCC which is 200-fold greater than that in the general population (Gordeuk *et al.* 1996).

It is important to appreciate that the identity of the haemochromatosis gene has now been elucidated by positional cloning (Feder *et al*. 1996). According to these authors, 80 % or more of patients have the same genetic mutation. This finding of a single major haemochromatosis gene will have major implications for family and population screening where Fe indices are inconclusive. Its discovery has launched a new era of research into the regulation of Fe metabolism (Report of a Meeting of Physicians and Scientists at the Royal Free Hospital School of Medicine, 1997).

In African Fe overload, as mentioned, it has been proposed that a factor or factors other than high Fe intake may be involved (Gordeuk *et al*. 1992; Moyo *et al*. 1998). After carefully surveying the families of a series of African male beer-drinkers with Fe overload, it was concluded that the disorder was associated with a familial (and therefore probably genetic) factor which interacts with the beer drinking. Since HLA-typing studies of these families did not show any linkage to HLA phenotypes, the authors postulated the existence of a gene, distinct from the gene responsible for hereditary haemochromatosis, which could well be a contributing factor to the African Fe overload syndrome.

Iron values as affected by non-dietary factors

There are other factors which complicate attempts to learn more precisely the extent of the pathognomonic sequelae of elevated serum ferritin levels and of Fe load.

Ferritin levels are raised significantly in the case of a number of infections (Stoltzfus *et al*. 1997; Hulthen *et al*. 1998; Millman *et al*. 1998).

Parasites too have been stated to influence levels of serum ferritin and other components (Hercberg *et al*. 1986; Cooper *et al*. 1997). In Zanzibar, arising from studies made on the de-worming of series of African schoolchildren, it was concluded that where hookworm infections are prevalent and Fe intakes are poor, deworming programmes can marginally improve the Fe status of populations and may substantially reduce the incidence of moderate and severe anaemia (Stoltzfus *et al*. 1998).

Serum ferritin levels are also raised in the presence of inflammation. In populations in developing countries, the anaemia of inflammation reflects augmented ferritin synthesis as part of the host defence mechanism against invading pathogens and tumour cells (Konijn, 1994; Pettersson *et al*. 1994).

High levels of serum Fe have been associated with various cancers, especially HCC. In Nigeria, it has been suggested that serum ferritin could be used as a tumour marker for HCC in patients with chronic liver disease (Ola *et al*. 1995). In South Africa, in a study on twenty-four patients and forty-eight hospital controls, the risk of developing HCC in the Fe-loaded subjects was 10·6 (95 % CI 1·5, 76·8) relative to individuals with normal Fe status, after adjusting for alcohol consumption, chronic HBV and HCV infections and exposure to aflatoxin B1 (Mandishona *et al*. 1998). The population-attributable risk of Fe overload in the development of HCC was estimated to be 29 %. In a study of twenty cancer patients and seventy-five family members, the risk of developing HCC with Fe overload was 4·1 (95 % CI 0·5, 32·2). From these observations it was concluded that dietary Fe overload may contribute to the development of HCC in Africans. However, it must be noted that in a developing country, Korea, where the phenomenon of Fe overload has not been reported, it was revealed that in a series of patients with liver disease, those who had a serum ferritin level $\geqslant 300$ μg/l later developed HCC (Hann *et al*. 1989).

A further factor associated with hyperferritinaemia is alcohol consumption (Wiley *et al*. 1998). In South Africa, in Gazankulu, the mean serum ferritin level was 584 μg/l in African men with a high alcohol intake, but was far lower, 145 μg/l, in those not characterized in this respect (Friedman *et al*. 1990).

Discussion

Numerous problems are encountered in seeking to determine the bearing on health/ill-health of a given variable. An elevated variable can have different degrees of noxiousness as determined by the context. For example, regarding serum cholesterol concentration, while populations in Belfast and Toulouse have much the same mean serum cholesterol level, 6·16 *v.* 5·94 mmol/l, the CHD mortality rate is 3–4 times higher in the former compared with the latter city (Evans *et al*. 1995).

Problems in the interpretation of elevation of iron levels in serum

Early studies on the sera of young African males beginning work on the goldmines of the Witwatersrand, South Africa, and domiciled in Mozambique, Angola, Malawi and Tanzania, revealed elevated Fe values to be common (Gerritsen & Walker, 1953). Mean serum Fe values ranged from 18·0 to 64·8 μmol/l, and in total Fe binding capacity from 60·8 to 106·2 μmol/l; the transferrin saturation ranged from 29 to 60 %. In comparison, normal values in white men have been reported as 20·6 (SD 5·6) μmol/l, 57·0 (SD 6·5) μmol/l, and 16 to 55 % (Friedman *et al*. 1990).

In Table 1, mean serum ferritin levels and percentage transferrin saturation values are given for a number of groups of men and women. These two variables have been considered to be the best for assessing Fe overload (Expert Scientific Working Group, 1985). Mean values and SD, and where possible median values and ranges, are given for Africans studied in Zimbabwe (Gordeuk *et al*. 1986), in Gazankulu (rural) (Friedman *et al*. 1990), and in Cape Town (urban) (Nesamvuni *et al*. 1996; PJ Jooste, unpublished results). Corresponding values are given for a series of white men and women in the Second National Health and Nutrition Education Survey in the USA (NHANES II) (Expert Scientific Working Group, 1985; Gordeuk *et al*. 1986), and on series of vegetarian and omnivorous men and women studied in New Zealand (Alexander *et al*. 1994).

In African groups, particularly in the case of men, the mean values for the two variables are much higher than those of the groups of white persons cited. In the study made on Africans in Zimbabwe (Gordeuk *et al*. 1986), the criterion for Fe overload was a combination of a high serum ferritin level and a transferrin saturation greater

Table 1. Serum ferritin and percentage transferrin saturation in African and white men and women
(Mean values and standard deviations, ranges and medians)

	Serum ferritin (μg/l)				Transferrin saturation (%)			
	Mean	SD	Range	Median	Mean	SD	Range	Median
Africans*, Zimbabwe, rural patients > 40 years								
Men	698		213–2289		49	26		
Community men	476		163–1385		49	22		
women	55		12–251		30	11		
Africans†, Gazankulu, South Africa, rural								
Men (50 (SD 14) years)	448		103–1945		46	21		
Women (52 (SD 17) years)	176		23–1340		48	24		
Africans‡, Cape Town, South Africa, urban								
Men (45–54 years)	509·9	685·9	11–2228	285·0	29·2	20·7	4·4–107·2	25·7
Women (45–54 years)	149·0	247·0	1–1315	62·5	17·1	12·5	0·2–98·4	16·2
Whites*, NHANES II study								
Men (45–64 years)	136	117			28	10		
Women (45–64 years)	80	75			26	9		
Whites§								
Men, mean age 28 years, range 18–50 years								
Omnivores	105·4	78·7	9–287	101·4				
Vegetarians	36·6	36·0	8–122	22·5				
Women, mean age 26 years, range 18–55 years								
Onmivores	33·6	54·3	2–291	15·5				
Vegetarians	13·6	7·5	5–29	12·3				

NHANES II, Second National Health and Nutrition Education Survey (Expert Scientific Working Group, 1985).
* Gordeuk *et al.* (1986).
† Friedman *et al.* (1990).
‡ Nesamvuni *et al.* (1996); PJ Jooste, unpublished results.
§ Alexander *et al.* (1994).

than 70 %. A raised serum ferritin was taken as greater than 150 μg/l in females of 20–44 years of age, greater than 200 μg/l in males of 20–44 years and females of 45–64 years, and greater than 300 μg/l in males of 45–64 years and females of 65–74 years. Using these criteria, in the rural African community studied, Fe overload was present in 11·7 % of the men, but in none of the women. Unfortunately, the corresponding proportions of this variable in the studies made on Africans in Gazankulu and in Cape Town were not reported. In the NHANES II study, the proportion affected in this manner was 0·3 % for men and women combined (Expert Committee Working Group, 1985).

If, as indicated by Moyo *et al*. (1997), Fe overload in Africans is largely explained by a high level of intake of the element, then in a given community individuals with similar habits of traditional beer consumption would be expected to have similar Fe status, and increasing levels of beer consumption would be associated with increasing body Fe stores. Yet, as observed by these workers, there is a considerable variation in response, for half or more of the African men and women whom they studied and who had substantial beer consumption had normal serum ferritin levels. Others have noted limitations in respect of the relationship between ferritin levels and the extent of Fe stores (Sullivan & Sullivan, 1996). Clearly, the observations reported emphasize that the translation of serum ferritin concentration into amounts of stored Fe must be made with caution, and that in persons with high serum ferritin concentrations, causes other than increased Fe stores should be considered (Hallberg *et al*. 1997). Accordingly, there must be reticence, on the basis of present evidence, in maintaining that high Fe intake and consequent siderosis in Africans are responsible for significant morbidity and mortality. It will be appreciated that in all of the situations cited, the possible roles of genetic and other influencing factors require clarification.

The extent of ill-health burden in men in communities among whom body iron values are high

Apart from the nature of the various risk factors involved in the development of high Fe values and Fe overload lies the salient question of the pathogenicity of the condition, and the number likely to be adversely affected. In South Africa, an enquiry was made on the occurrence of HCC in rural areas, where Fe vessels are still used. It was found that in three widely separated hospitals, responsible for the health needs of about 400 000 Africans, the incidence rate of the malignancy in men was 8 per 100 000 ‘world’ population (Walker & Segal, 1996). This is in rough agreement with the incidence of 5·7 per 100 000 reported in the National Cancer Registry for African men in 1992 (Sitas *et al*. 1997). The rate in white men was 4·1 per 100 000. At this rate of occurrence, in a complex of African villages numbering, say 25 000 people, two males with HCC would be expected to suffer from the disease and to die from it annually. Even

were siderosis the primary cause of the disease, and even if the two patients who reached hospital are an underestimate of the prevalence of HCC (Kew, 1995), it will be apparent, epidemiologically, that the ill-health burden from siderosis, at least in its contributory role in respect of HCC, is very small, and hence tends to question the need to reduce Fe intake.

In Cape Town, as already mentioned, high serum ferritin levels are present in about a quarter of middle-aged African males (Nesamvuni *et al*. 1996; PJ Jooste, unpublished results). The median values for men and women were 285 μg/l and 62·5 μg/l respectively (Table 1). Yet in 1995–6, HCC was reported as the cause of death in 1·1 % of Africans (both sexes combined). This proportion is little different from 0·8 % reported for the white population and 0·9 % for the 'coloured' (Eur-African-Malay) population (Annual Report of the Medical Officer of Health, 1995/1996). Both the white and 'coloured' populations have little or no evidence of siderosis. Were the very high odds of death from HCC in patients with severe siderosis (Gordeuk *et al*. 1996) valid in the general population, a higher mortality from HCC would be anticipated in the African population.

In an investigation made in Zimbabwe (Gordeuk *et al*. 1986), it was estimated that there were about 80 000 cases of severe Fe overload. In Harare, Zimbabwe (population 1·4 million) the standardized incidence rates for HCC, in 1990–2, were 34·6 and 19·9 for African men and women, and 12·9 and 4·7 per 100 000 for white men and women respectively (Bassett *et al*. 1995*a*,*b*). In 1996, total deaths in that city included 12 598 Africans, 415 whites and thirty-two Asians. Total deaths from malignancies were 833. There were sixty-six deaths from HCC. Data for each sex were not given. At a maximum, this cancer, with a measure of responsibility from siderosis, could have accounted for 0·5 % of deaths of Africans (Annual Report of the City Health Department, 1996). Instead of being much higher, as would be expected since HCC is reported to be the commonest of cancers in patients admitted to hospital (Gangaidzo & Gordeuk, 1996), this percentage is of the same order as that reported for Africans in Cape Town.

As indicated, the crucial question in Sub-Saharan Africans, in terms of evidence based medicine, and in regard of the need to lessen the occurrence of the associated diseases mentioned, concerns the extent to which high Fe intake, with siderosis, is the primary causative factor. Succinctly, it could be asked: were high Fe intake lessened and the prevalence of siderosis, or at least of marked siderosis, reduced, would falls be detectable in the occurrence of liver diseases, and in decreases in morbidity and mortality? Unfortunately, the requisite cross-sectional and prospective studies in village and town communities have not been undertaken.

Future research

Numerous tasks require attention. In the first place, in respect of African Fe overload, further information is needed on (1) the extent of the present use of Fe vessels, and the current Fe content of prepared foods and drinks; (2) levels of habitual Fe intake; (3) the measure of association between habitual Fe intake and Fe status; and (4) the level of health/ill-health in groups of persons in communities among whom elevated Fe values in the serum are common.

In regard of the last question raised, in Cape Town in a series of African men aged 45–64 years, whose median serum ferritin level was 285 μg/l, it would be very informative to carry out a case–control study to learn of the degree of involvement of the various risk factors discussed. As further examples of questions unanswered (Baer, 1996): can a person who is genetically predisposed to African Fe overload accumulate toxic levels of Fe while ingesting less than the 50–100 mg Fe consumed daily by African beer drinkers? Can the existence of a genetic component in African Fe overload be reconciled with the observation that white volunteers have been shown to absorb as much Fe from traditional African beer as have African volunteers? (Bothwell *et al*. 1964).

There are a number of epidemiological situations where it would be particularly illuminating to learn of the serum ferritin levels in the general population, for example, in Mali, an African country with an extremely high incidence rate of HCC in men, namely, 47·9 per 100 000 'world' population (Parkin *et al*. 1992). This value is almost ten times higher than that reported in African men in South Africa, namely 5·7 per 100 000 'world' population (Sitas *et al*. 1997).

Conclusion

In discussions of the present nature, and in seeking to assess the extent of the pathogenicity of Fe overload in Africans, it is imperative to appreciate, first, that even in the most researched of chronic diseases, CHD, known risk factors explain only half of the variance in its occurrence (Leeder & Gliksman, 1990). The same lack of knowledge prevails with many cancers. Second, it is essential to appreciate that major differences of opinion may be reached by individuals and by authoritative bodies from precisely the same body of evidence. As a current example, diametrically opposite views are held on the role of NaCl intake in hypertension (Alderman *et al*. 1997; Stamler, 1997). It is therefore understandable that there are different points of view on the significance of Fe overload to health in Africans. On one hand, the conclusion has been reached that siderosis is an important public health problem, that steps should be taken to reduce the intake of adventitious Fe, and, furthermore, that those who are severely affected by Fe overload should be treated with phlebotomy (Gangaidzo & Gordeuk, 1996). Yet on the other hand, as noted, there is evidence that many factors additional to Fe intake have a bearing on the development of hyperferritinaemia and siderosis: a genetic factor, infections, inflammation, cancer and alcohol intake. As regards Fe stores and cancer, it has been stated that the relationship remains controversial, and that further investigation is needed to determine whether Fe does indeed play a pathogenic role (Lynch, 1995). These considerations, and the limited evidence of the extent of the health disadvantage of high serum ferritin levels in men in the everyday life of village and township communities, render it difficult to assess whether it is a significant public health problem, and hence the need to reduce its prevalence. Further

research should include longitudinal observations, to establish whether the sequelae of Fe overload are of concern to few or to many.

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