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Review Article

Iron Overload

By

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Definition of Iron Overload

Recent investigations have suggested that the average amount of usable storage iron in a normal male is about 1g, values above 1,5g being unusual, and above 2,2g constitute iron overload. (Weinfeld, 1970). In males about 0,4g of storage iron is present in liver.

Storage iron exists in tissues in two forms, viz., as ferritin which is soluble in water and does not stain with Prussian blue, and as haemosiderin which is insoluble and does stain with this reagent. At concentrations of less than approximately 0,25mg/g wet weight of tissue the iron is in the form of ferritin and so cannot be demonstrated histologically; above this concentration granules of haemosiderin are formed and these can be seen histologically. In both of these compounds iron is in the form of a colloidal complex.

It has been widely accepted until recently that the presence of stainable iron in liver indicates overload and most surveys in Southern Africa have used this as a criterion in estimating the prevalence of siderosis (iron overload) in the population (Buchanan, 1967). One study, however, has shown that 78 per cent. of healthy white males had slight to moderate amounts of stainable iron in liver parenchymal cells. (Weinfeld, Lundin and Lundvall, 1968). It is concluded that

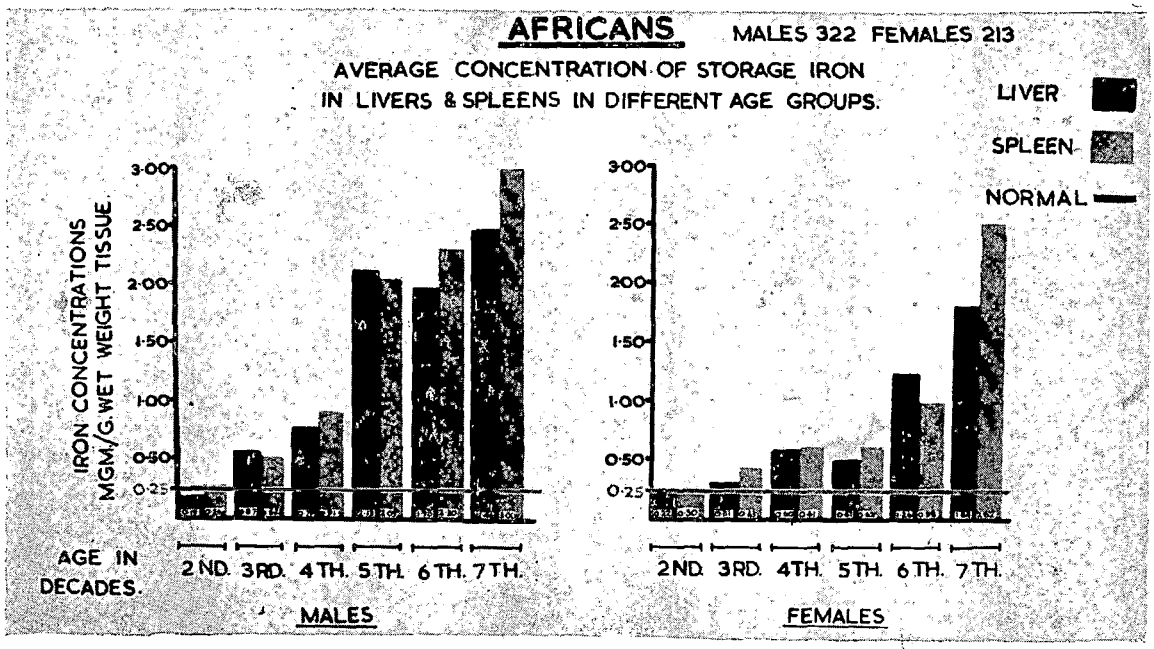


Fig. 1.

this is a normal finding. This means that the incidence of siderosis tends to be overestimated amongst Africans as a proportion of cases (albeit not large) have been included which would not now be accepted as having genuine overload.

INCIDENCE OF SIDEROSIS IN MASHONALAND. AFRICANS

I carried out a survey on autopsy material from 535 Africans over 10 years of age. I found stainable iron in the livers of 68,9 per cent. males and 52,7 per cent. females. Though there does not appear to be a dramatic difference in prevalence of siderosis between the sexes the proportion of females who have small amounts of haemosiderin and who would now not genuinely qualify as having overload is much higher than in males. Figure 1 shows that the average storage iron concentration in liver and spleen is considerably higher in males than females and that it is really only in females over the age of 50 that siderosis is fairly common or severe. Iron overload in some cases can be of an extreme degree. In my experience the highest African liver concentration was 28,12 mg/g giving a total liver iron of 32,9g. The highest spleen iron concentration was 36,64 mg/g and the total iron in this spleen was 12,9g. The average liver iron concentration in African males from the fifth decade onwards was approximately eight times that found in European males.

The average storage iron concentration found at autopsy in livers and spleens of Europeans in Rhodesia is shown in Fig. 2 and is similar to that found in normal subjects elsewhere in the world.

SOURCE OF IRON

A small survey of iron content of a typical African diet, cooked ready for eating, showed a daily iron intake of between 16 mg and 105 mg. Absorption of iron from food varies widely, but findings elsewhere (Callender, 1970) suggest that in the diet examined would probably be of the order of five per cent. for the smaller amounts of iron but less for the greater amounts. The actual amount of iron absorbed would, therefore, vary from less than 1 mg to about 5 mg. The former, though just adequate for a healthy male, would be insufficient for a female during reproductive life, while the latter would result in a progressive build-up of iron stores and siderosis in both sexes. The iron containers in which the food is prepared probably are the principal source of iron in prepared food because analyses of the same food before cooking proved that it was not particularly rich in iron.

In our African population there is another important source of ingested iron, viz., home-brewed beer. I believe this is the most important cause of iron overload. In this case the iron is derived from the drums used to brew the beer

and is facilitated by the acidity of the beer (mean pH 3,9). The mean iron concentration found in 130 samples of home-brewed beer was slightly in excess of 10 mg/100 ml. A sample survey of 185 male African outpatients revealed that the average consumption of home-brewed beer in subjects over 25 years of age was about 1 litre/day (Buchanan, 1967). The range of consumption was of course enormous. A litre of beer then of average iron content would provide 100 mg of iron which at two per cent. absorption (Bothwell, Seftel, Jacobs, Torrance and Baumslag, 1964) would mean 2 mg/day added to body stores.

African women (except the elderly) drink less than men. The average daily consumption of home-brewed beer worked out at about 130 ml providing 13 mg of iron which at four per cent. absorption 0,5 mg could be expected to be absorbed (Bothwell, *et. al,* 1964; Buchanan, 1967).

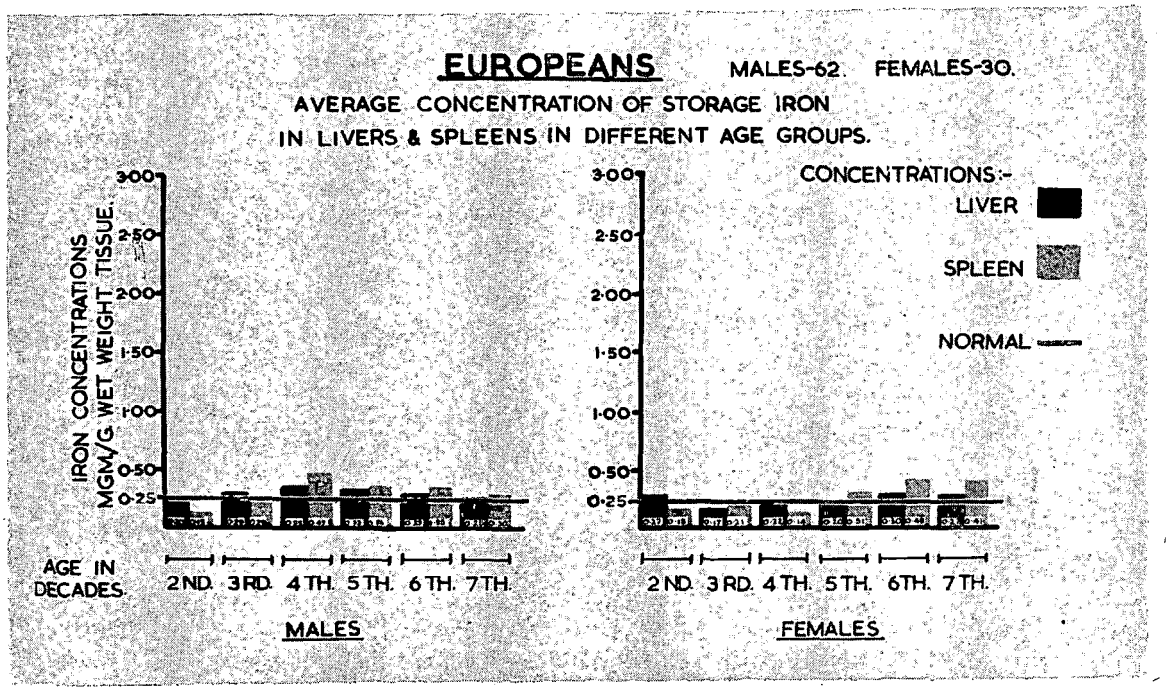
In short, if we add iron absorbed from food and beer together it becomes apparent that most adult Africans absorb more iron than they require and in some the excess absorbed is considerable. Calculating from the figures given above, the iron in food and beer could completely account for the degrees of iron overload found in our black population.

This survey also shows that there must be a number of women, albeit small, who absorb only just enough for body requirements and even a few who do not get enough and suffer from iron deficiency. One would expect the prevalence of iron deficiency anaemia to be small in this population and I have in fact found this to be so. I found some degree of iron deficiency anaemia in 8,3 per cent. women almost all of whom were in the child bearing age group (Buchanan, 1968). Some surveys in Britain have shown an iron deficiency anaemia in women of up to 21 per cent. (Kilpatrick, 1970) and in Germany of almost 14 per cent. (Siebold, 1970). The incidence of this type of anaemia in African males is low, viz., 2,7 per cent.

Before leaving the subject of iron absorption I would like to mention shortly some recent work I have done which suggests that protein malnutrition plays a significant role in excess iron accumulation in the body.

When guinea pigs are fed iron in amounts comparable to those ingested by our African population a moderate degree of siderosis results. (Buchanan, 1970). This is never severe in animals on a good protein diet. If on the other hand these animals are fed the same amount of iron but given a diet poor in protein the siderosis pro-

Fig. 2.



duced is much more severe. My experiments appear to indicate that in the animals on a good protein diet a level of iron storage is reached at which no more iron is absorbed despite continued ingestion of iron. On the other hand animals on a poor protein diet continue to absorb iron without regard to iron stores accumulated.

This brings us back to Granick's concept (Granick, 1946) that there is a "mucosal block" to further iron absorption when stores are adequate. It has long been known that this block is not complete and can be overcome if gross amounts of iron are ingested. Protein malnutrition would also seem to destroy the block. Why this should be I do not know. I would like, however, to make one or two suggestions.

Firstly, protein malnutrition may act by interfering with synthesis of gastroferrin. This last substance, which is missing from the gastric secretions of subjects with idiopathic haemochromatosis, is said to limit to some extent iron absorption. (Davis, Luke and Deller, 1966; Luke, Davis and Deller, 1967).

Alternatively, there may be a decreased synthesis of apoferritin in the bowel mucosal cells. In normal individuals apoferritin appears to be involved in the control of iron absorption by trapping some of the iron from the lumen of the bowel in the mucosal cells. (Millar, Goldberg and Cumming, 1970). The iron is therefore not absorbed but excreted as ferritin when these mucosal cells are sloughed off. This explanation is, however, not completely satisfactory as haemosiderin, which is synthesised from ferritin, is readily seen in mucosal cells in Bantu siderosis. Furthermore, when ferritin is decreased in mucosal cells as in iron deficiency anaemia (Millar, *et al.*, 1970) the percentage of iron absorption is increased while in Bantu siderosis this is decreased (Bothwell, *et al.*, 1964).

Lastly, protein malnutrition may facilitate continued iron absorption by interfering with the secretions of the exocrine pancreas. Various workers have shown that pancreatic secretions decreaseiron absorption (Taylor, Stiven and Reid, 1931; Davis and Badenoch, 1962).

BANTU SIDEROSIS COMPARED WITH IDOPATHIC HAEMOCHROMATOSIS

The total amount of body storage iron in idiopathic haemochromatosis is said to vary between 25 and 50 g (Sheldon, 1935). Total storage iron in severe cases of Bantu siderosis certainly come well within this range. One of my cases had 46 g in liver and spleen alone. If storage iron in other organs were added the total amount would be well in excess of 50 g. Thus in respect of mass of total body iron stores, Bantu siderosis and idiopathic haemochromatosis are comparable.

There are, however, a number of differences between the two conditions. The iron overload in Bantu siderosis can be attributed to the large amounts of this element ingested in the diet. There is no indication that percentage absorption of iron is increased; in fact, there is some evidence that it is depressed in Africans (Bothwell, *et al.*, 1964).

In idiopathic haemochromatosis it is generally accepted that dietary iron content is normal, but that absorption is enhanced. I must add that one well known worker in this field disagrees with this view (MacDonald, 1963).

The distribution of iron deposits in the body differs in the two conditions. In most cases of Bantu siderosis iron is confined to liver, reticulo-endothelial system, bone marrow and small bowel mucosa. By contrast, in idiopathic haemochromatosis iron is found in many epithelial tissues as well as the liver and to a very much lesser extent in small bowel mucosa and R.E. system.

In idiopathic haemochromatosis there is almost always nearly complete saturation of transferrin. In Bantu siderosis that is so in only a small proportion of cases. Diabetes is commonly associated with idiopathic haemochromatosis, but is relatively uncommon in Bantu siderosis.

All that said, a small number of subjects with Bantu siderosis are seen with most of the features of idiopathic haemochromatosis, viz., high percentage transferrin saturation, widespread epithelial iron deposits and diabetes. But though these cases resemble idiopathic haemochromatosis closely they differ in one major respect, viz., the R.E. cell iron deposits are much heavier in Bantu siderosis than idiopathic haemochromatosis.

Until recently I thought the heavy R.E. iron deposits in Bantu siderosis resulted from the prevalence of infection amongst Africans [Infection enhances iron uptake by R.E. cells from serum (MacDonald, MacSween and Pechet, 1969).] This may be partly the case, but infection cannot be the only factor as heavy R.E. deposits are produced in healthy guinea pigs on African beer (Buchanan, 1970a). Also, evidence has been presented suggesting that ascorbic acid deficiency may be an important cause of iron accumulation in R.E. tissues (Lipschitz, Bothwell, Seftel, Wapnick and Charlton, 1971). Overt scurvy is not common in Salisbury, but perhaps subclinical scurvy is more common than we suspect. The role of ascorbic acid in determining excess iron distribution stores requires further investigation.

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PATHOGENIC EFFECTS OF EXCESS IRON

It has long been thought that the liver cirrhosis found in most patients with idiopathic haemochromatosis was caused by the massive iron deposits in the organ. The incidence of liver fibrosis in Bantu siderosis is directly related to the level of iron concentration (Isaacson, Seftel, Keeley, and Bothwell, 1961; Buchanan, 1967). On the face of it this suggests that haemosiderin might be fibrogenic, but other explanations are possible, e.g., many haemochromatatics are alcoholics and almost all Africans with severe siderosis are heavy drinkers. Thus it may be the alcohol which causes the necrosis and fibrosis rather than the iron.

Repeated animal experiments have failed to produce cirrhosis even when massive amounts of haemosiderin are present in the liver. (Macdonald, 1964). Also it is not rare to find among Africans livers with massive iron deposits and no evidence of fibrosis. Gross excess of iron in thyroid, salivary glands, pituitary, adrenals, etc., does not appear to be accompanied by fibrosis. It is true that pancreatic fibrosis is fairly common in idiopathic haemochromatosis, but here again alcohol may be of more aetiological importance than iron. Pancreatic fibrosis is not common in Bantu siderosis, but when it does occur the patient usually gives a history of heavy drinking. While I am very doubtful about the role of haemosiderin in producing cirrhosis I do not believe the grossly excessive iron stores are completely inocuous. Bacteriologists have shown that when iron is added to serum in growth media certain bacteria, in particular some gram -ve bacteria, grow more rapidly. (Bullens and Rogers, 1969). It has also been shown that iron in the media lessens the efficacy of some anti-tuberculous drugs. (Martin, Jandl and Finland, 1963). Observations both in South Africa and Rhodesia suggest that the prevalence of tuberculosis in advanced siderotics is high and that the disease takes on a severe and rapidly progressive form in these cases. Though this is at present unconfirmed, in vitro evidence suggests that the iron in siderotics may make antituberculous drugs less effective in treating patients.

My colleagues and I in Harare Hospital have seen, at autopsy, a number of cases of peritonitis occurring in severe siderotics. In these cases no primary focus of infection could be found. Terminal shock with and without peritonitis has been seen in severe siderotics here. (Buchanan, 1970b, 1971). In some of these cases Klebsiella species and Esch.-coli have been cultured from blood and peritoneal fluid suggesting that the shock could be septic in nature. Similar cases of shock have been reported in idiopathic haemochromatosis (Jones, 1962).

I interpret these findings as meaning that people with severe siderosis and high percentage transferrin saturation are specially liable to infection and septic shock. Also there is the suggestion already mentioned that antibacterial drugs may be less effective in these cases.

In a survey of autopsy material I found primary carcinoma of liver in 3,4 per cent. males and 1,4 per cent. females (Buchanan, 1967). Few of these cases had heavy deposits of iron in the liver and rather more than half had no stainable iron at all. I concluded that iron played no part in the aetiology of primary liver cell carcinoma.

In South Africa there appears to be a substantial incidence of scurvy and osteoporosis amongst Africans with marked siderosis. The osteoporosis affects particularly the lumbar spine leading to vertebral collapse and paraplegia. This condition has not yet been reported from Rhodesia, but one case was seen in Zambia (Lowenthal, Siddorn, Patel and Fine, 1967).

SUMMARY

1. Iron overload is common in Rhodesian Africans.

2. It is more common and severe in men than women.

3. Its prevalence and degree in both sexes increases with age.

4. Its prevalence and degree are similar to those found in the South African Bantu.

5. The principal source of the iron is home-brewed African beer.

6. Iron absorption is enhanced by protein malnutrition.

7. It plays no part in the aetiology of carcinoma of liver and probably does not produce cirrhosis.

8. It promotes bacterial growth and is responsible for primary peritonitis and endotoxic shock in subjects with severe siderosis.

9. The iron overload seen in the black peoples of Southern Africa is distinct from idiopathic haemochromatosis.

10. When severe siderosis and scurvy occur together osteoporosis especially of the lumbar vertebrae results.

* * *

This paper is based on a talk given to post graduates at Mpilo Hospital, Bulawayo, on 16th September, 1971.

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