ORAL IRON OVERLOAD*

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There are 3 - 4 G of iron in the body of a healthy adult male.[1] Three-quarters is *functional* and is found in haemoglobin, myoglobin, a number of tissue enzymes, and attached to transferrin in the plasma. The remainder, amounting to about 1,000 mg., is *storage* iron and is distributed in various tissues in the form of ferritin and haemosiderin. The infant is born with a total of 300 mg. donated by his mother and, provided the diet is adequate, during childhood and adolescence a small positive daily balance results in a slow accumulation until the adult amount is reached. Thereafter the iron status of the normal individual remains stable. The amounts of iron absorbed and excreted each day are small, and once iron has been introduced into the body it is used again and again. The daily loss from exfoliated cells and secretions is from 0·5 - 1·0 mg. in adult males. In females excretion is approximately twice as great, since menstruation and childbearing represent an added drain. These obligatory iron losses are normally replaced by the absorption of iron from food, so that the total iron content of the body tends to remain fixed within relatively narrow limits. This delicate balance appears largely to depend on the behaviour of the absorbing cells of the upper gastro-intestinal tract, which are to a considerable extent able to adjust the amounts absorbed according to the needs of the individual. Thus the absorption rate tends to rise when the body is depleted of iron, and to fall when body stores are larger than normal. Iron excretion also varies, but within narrower limits (Fig. 1).

Iron balance may be disturbed in a variety of ways, but the end result is either iron deficiency or iron overload. Iron deficiency represents a major world-wide health problem; in contrast, an excess of iron in the body is relatively uncommon in most parts of the world. However, there are certain situations which lead to an increase in the body iron content, and when this occurs a number of interesting associations have been noted. Surplus iron may enter the body by either the parenteral or the oral route, and is quantitatively deposited in various tissues as ferritin and haemosiderin. With time, the total body iron content may be many-fold normal. Parenteral iron overload is usually the result of the repeated administration of blood transfusions to patients with refractory anaemias. While the consequences of such therapy have been extensively investigated, the topic falls outside the range of the present discussion and will therefore not be considered further. The classical form of oral iron overload is idiopathic haemochromatosis. In the past it has been customary to regard this condition as a rare hereditary disorder in which increased absorption of iron from a normal diet leads to excessive deposits in the tissues.[2] It is usually diagnosed in middle age, at a time when the iron content of the body is between 20 and 40 G. In this phase of the condition cirrhosis of the liver is invariably a feature, while diabetes, skin pigmentation, and cardiac failure are often present. Since the pathological manifestations of idiopathic haemochromatosis correlate well with the quantities of iron present in the affected organs, it has been generally believed that the iron plays an important role in the production of tissue damage. There are, however, certain disadvantages to considering idiopathic haemochromatosis as a prototype of the long-term effects of increased absorption of iron from the gut, since virtually nothing is known of the metabolic and pathological findings in that long latent period, possibly stretching over half a lifetime, during which iron is accumulating in the body. It is because of these deficiencies in current knowledge that it is probably more profitable to consider first the siderosis which occurs so commonly in the adult Bantu of Southern Africa, since it has been possible to study this condition at all stages of its development.

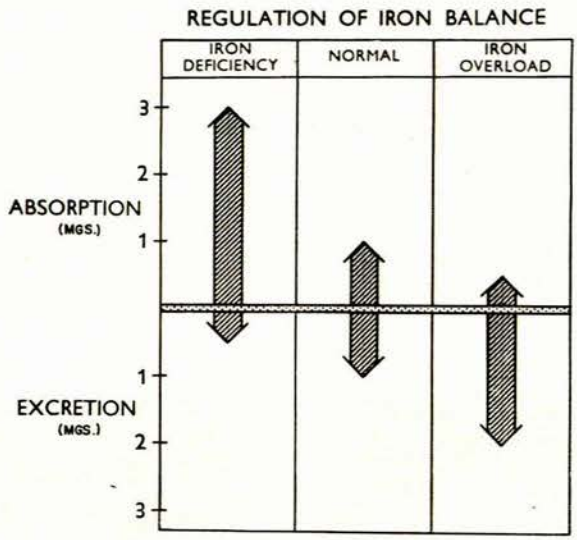

Fig. 1. Iron balance is regulated by the duodenal mucosa, which alters the absorption of available dietary iron according to body requirements. Obligatory iron loss also varies with the total body iron content, but to a lesser extent.

IRON OVERLOAD IN THE BANTU

Over 30 years have passed since it was first noticed that varying degrees of tissue siderosis are demonstrable in the majority of adult Bantu in South Africa.[3] These findings have been confirmed in a number of subsequent studies,[4-7] and iron overload has been shown to occur also in the Bantu of Rhodesia, Bechuanaland, Malawi, Mozambique,[5] Ghana,[8] and Tanzania.[9] In these various countries the condition is seen almost exclusively among the Bantu; it is not found in White subjects and is rare in Indians (Fig. 2)

*Based on the Annual Guest Lecture delivered in November 1964 by one of us (T.H.B.), to the American Association for the Study of Liver Diseases.

Although the incidence and severity of the siderosis is variable, the usual pattern is a remarkably constant one, with most of the excess iron confined to the liver and reticulo-endothelial system.[5]

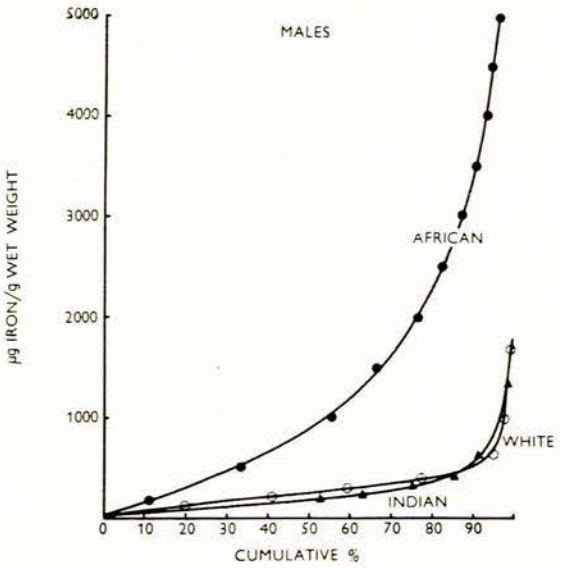

Fig. 2. Cumulative percentage incidence of various concentrations of storage iron in the livers of 109 White, 327 Bantu and 76 Indian males. (Data from Mayet and Bothwell.[58] Figure reproduced by courtesy of the Editor, *South African Journal of Medical Sciences.*)

The condition first becomes manifest in late adolescence, and the incidence and severity reach their greatest degree between the ages of 40 and 60 years.[6,10] Although commoner and more severe in males, a small proportion of Bantu females also accumulate large amounts of iron. In a recent study the extent of the problem in the Johannesburg area was defined by estimating the chemical concentrations of iron in the livers of several hundred Bantu males dying in hospital.[10] It was found that as many as 20% had hepatic iron concentrations in the range of those described in idiopathic haemochromatosis, i.e. more than 2% dry weight (Fig. 3).

Although it has always been accepted that the iron overload must be the result of increased absorption from the gut, there has been controversy in the past as to why this should occur. Originally it was postulated that there was an alteration in the behaviour of the bowel, induced by chronic malnutrition, which resulted in the absorption of higher percentages of the dietary iron.[4] More recently, it has been shown that the Bantu diet contains abnormally large amounts of iron.[11,12] The additional iron is derived from the utensils used in cooking and, more important, from the containers used in the preparation of home-brewed alcoholic drinks. In one study in which several hundred samples of various types of drink were analysed,[12] it was found that the mean iron concentrations were several mg./100 ml. in all except the distilled liquors (Table I). Since large volumes are consumed, calculations from these data reveal that the average Bantu male ingests between 50 and 100 mg. of iron daily in beer alone. The high daily intake has been established more directly by measuring the iron concentrations in faeces.[11,12] These have been found to be considerably higher than in a comparable White population. In one study the mean concentration of

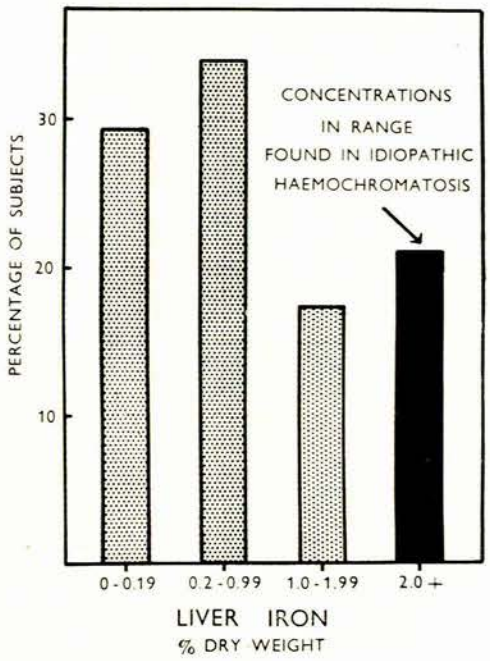

Fig. 3. Liver iron concentrations in 318 Bantu males dying in hospital in Johannesburg. In approximately 20% the iron concentration was more than 2% dry weight. (Data from Bothwell and Isaacson.[10])

iron in faeces collected from males on Monday mornings was found to be several times the figure on Thursday mornings[12] (Fig. 4). These variations probably reflect the weekend drinking habits of urban Bantu. Over 80% of the iron present in the drinks is in an ionized form. Isotopic studies carried out on radioactively tagged Bantu beer have

TABLE I. MEAN IRON CONCENTRATIONS IN SEVERAL HUNDRED SAMPLES OF VARIOUS TYPES OF BANTU ALCOHOLIC BEVERAGES*

	Ingredients	*Iron concentration (mg./100 ml.)*
Home-brewed beer ..	Malt, degermed maize meal	8·2
Barberton	Sugar, malt, bread	4·5
Hops	Yeast, sugar, malt, hops	5·1
Shimeyana	Sugar, malt, potato	7·5
Gin, tot-tot, etc. ..	Distillates made from other drinks	1·0
South African wines*		0·7

* Data from Bothwell *et al.*[12]

demonstrated that the iron is absorbed to the same degree as a simple ferric salt, and about one-third as well as the iron in a ferrous salt[12] (Fig. 5). In this investigation it was noted that the mean absorption rates in Bantu were lower than in Whites. This can be ascribed to the fact that the majority of the Bantu studied had varying degrees of iron overload, since it has been shown that an increase in the size of the iron stores tends to depress absorption.[13] It was

however demonstrated that Bantu ingesting 100 mg. iron daily in alcoholic beverages absorb at least 2 - 3 mg., which is quite sufficient to account for the degrees of siderosis found in middle age. At the same time, the fact that

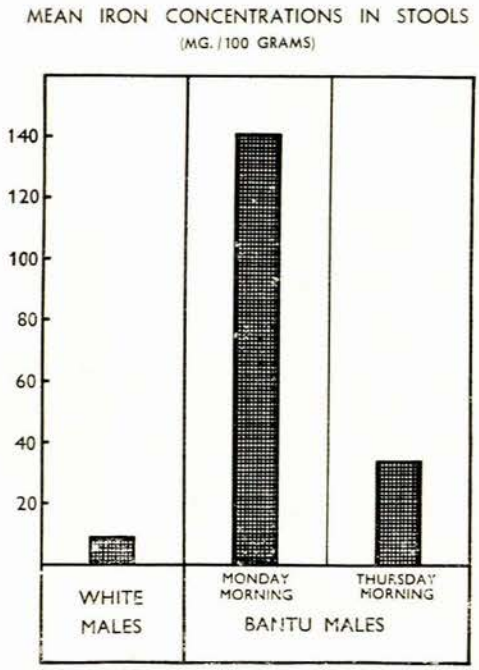

Fig. 4. Mean iron concentrations in specimens of stool from White and Bantu subjects. (Data from Bothwell *et al.*[12])

isotopic studies have not shown any evidence of abnormally *high* absorption rates in the Bantu can be taken as good evidence that the siderosis so commonly found in them is not the result of any intrinsic mucosal defect.

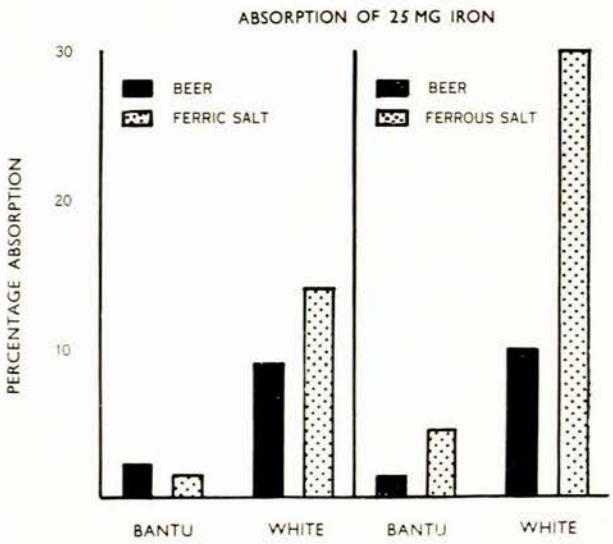

Fig. 5. The absorption of radioactively labelled iron in Bantu beer. (Data from Bothwell *et al.*[12])

The pathological findings in Bantu with siderosis are moderately constant.[7] In the earliest phases of iron overload haemosiderin granules can be detected in the parenchymal cells of the liver and in Kupffer cells. With concentrations of 5 - 10 times normal, increasing amounts of haemosiderin are present in these sites, and at this stage the portal tracts also show involvement. When the concentrations are 20 times normal, heavy deposits are present throughout the liver. Splenic deposits are also present from an early stage, and with increasing levels of iron, splenic concentrations are often higher than in the liver[5,7] (Fig. 6).

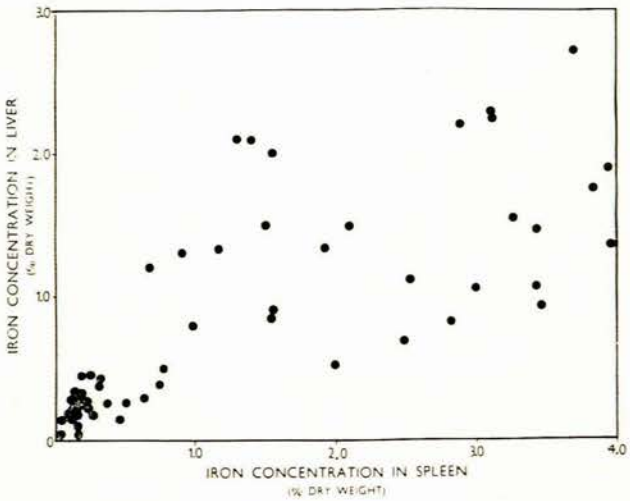

Fig. 6. A comparison between the iron concentrations in the livers and spleens of Bantu subjects. (Data include those reported by Bothwell and Bradlow[7] together with unpublished findings.)

Deposits in the reticulum cells of the bone marrow are also a feature, and the results of a recent *in vivo* isotopic study indicate that as much as 10 G of iron may be stored in this site.[14] In an extension of this investigation the concentration of iron in the marrows and livers of a large number of White and Bantu subjects were compared. There was a close correlation over a wide range (Fig. 7). Since the sizes of the marrow and of the liver are roughly comparable, these findings suggest that the reticulum cells of the bone marrow store as much iron in Bantu with iron overload as does the liver. Iron deposits elsewhere in the body are not a feature, and the majority of subjects thus show a characteristic pattern, with the major impact on the parenchymal cells of the liver and on the reticulo-endothelial system.[5,15] The parenchymal involvement of the liver is presumably due to the direct deposition of newly absorbed iron, transported via the portal system from the gut. To explain the reticulo-endothelial deposits is however more difficult, and two possibilities must be considered: In terms of the first, iron is delivered directly from plasma to reticulo-endothelial cells. However, there is experimental evidence to show that these cells have only a very limited capacity to remove iron from plasma.[16] The second possibility therefore seems the more likely one. With increased amounts of iron entering the plasma from

the gut and being taken up by red-cell precursors in the bone marrow, there is a slight decrease in the quantities of iron released each day by reticulo-endothelial cells.

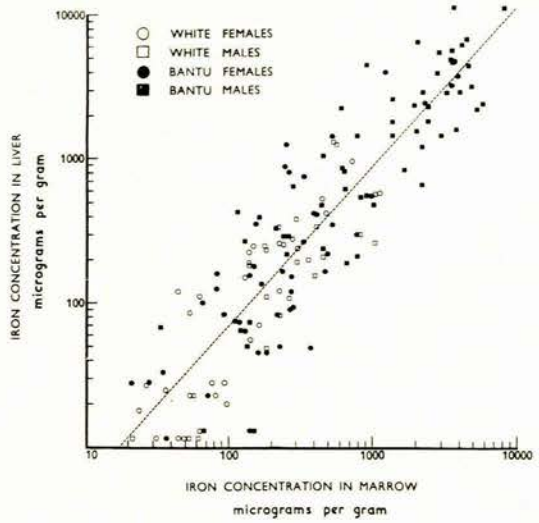

Fig. 7. Correlation between storage iron concentrations in the marrows and livers of 155 necropsy subjects. The regression line is indicated ($r = +0{\cdot}88$, $p < {\cdot}001$). (Data from Gale *et al.*[14] Figure reproduced by courtesy of the Editor, *Journal of Clinical Investigation.*)

This results in a steady build-up of iron derived from broken-down red cells in the reticulo-endothelial system (Fig. 8).

In assessing the relationship between iron overload in the Bantu and tissue damage, most attention has been directed to the hepatic findings, since this organ represents

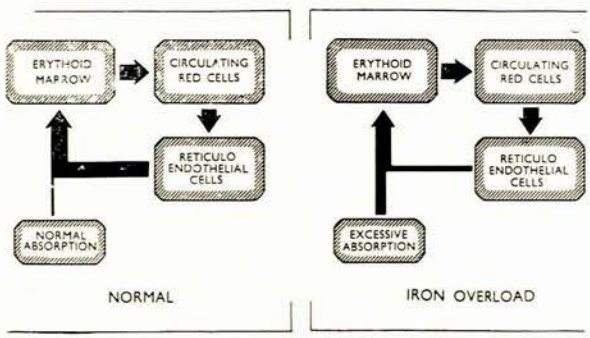

Fig. 8. Possible mechanism whereby excessive absorption of iron from the gut can lead to excessive deposition of iron in reticulo-endothelial tissues.

a major storage depot for iron. Several studies have shown a close relationship between the degree of overload and the presence of portal fibrosis or cirrhosis.[17,18] In one study a comparison was made between the histological findings and the chemical concentrations of iron present in the liver. It was found that moderately severe portal fibrosis or frank cirrhosis was present in the majority of livers in which the concentration of iron was more than 20 times normal (Fig. 9).[7,10] Although such changes were commoner in the older age groups, the cirrhosis could not be ascribed to this, since older male subjects without siderosis did not have more portal fibrosis than younger ones. The relationship between portal cirrhosis and siderosis was further clarified by another investigation, in which measurements were made of iron concentrations in the livers of a consecutive group of Bantu subjects showing

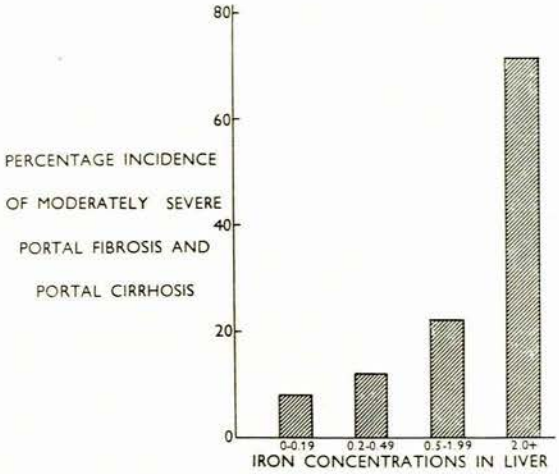

Fig. 9. Incidence of moderately severe portal fibrosis and portal cirrhosis in Bantu subjects with different concentrations of storage iron in the liver. (Data from Bothwell and Isaacson.[10])

macroscopic and microscopic evidence of portal cirrhosis at necropsy.[15] It was found that severe siderosis was almost invariably present. In contrast, there appeared to be no correlation between the presence of post-necrotic cirrhosis and the degree of iron overload. These various observations are therefore all compatible with the thesis that excessive deposits of iron can eventually lead to significant portal fibrosis or cirrhosis. This is however not the only point of interest that emerged in this and other similar studies. It was noted that in the presence of portal cirrhosis, significant deposits of iron were demonstrable in a number of parenchymal organs.[15,19] This was especially so in the pancreas, but significant quantities were also found in the thyroid, adrenals, pituitary and myocardium. This observation was confirmed by comparing the iron concentrations present in the various organs in subjects exhibiting severe siderosis and cirrhosis with a control group of Bantu with severe siderosis but no cirrhosis.[15] Although the concentrations of iron present in the livers and spleens of the two groups were comparable, the subjects with cirrhosis had in addition significant amounts in other organs (Fig. 10).

The reason for the different distribution of iron in subjects with iron overload and cirrhosis has not been established. It may however be related to the percentage saturation of the iron-binding protein of the plasma. In Bantu with siderosis, but no cirrhosis, the plasma-iron level is higher than normal, but there is, in addition, an increased amount of circulating transferrin, with the result that the percentage saturation is normal or only slightly raised.[20] In contrast, transferrin levels tend to be lower when cirrhosis is present, and the percentage satura-

tion is thus very high.[21] There is experimental evidence that iron is taken up more readily by tissues under such circumstances,[22] and it is therefore possible that this mechanism may play some part in the transfer of iron to

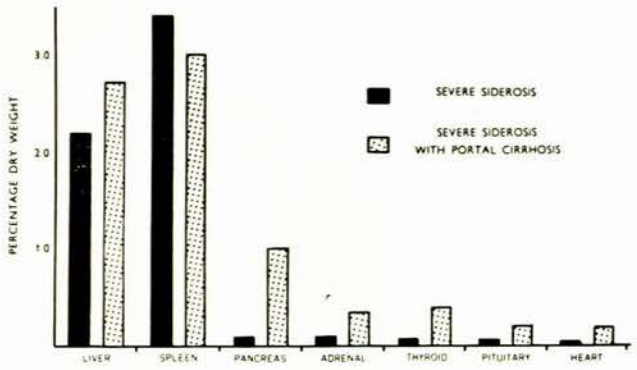

Fig. 10. A comparison of the concentrations of iron in various organs in 20 Bantu subjects with severe siderosis and 20 Bantu subjects with severe siderosis plus portal cirrhosis. (Data from Isaacson *et al.*[15])

epithelial cells in cirrhotic subjects.

Whatever the explanation for these findings, there is no doubt that a small proportion of adult Bantu exhibit pathological findings indistinguishable from those in idiopathic haemochromatosis. The similarity between the two conditions is further underlined by the clinical manifestations.[23] Analysis of clinical records has shown that more than 20% of Bantu with pathological evidence of haemochromatosis at necropsy were diabetic before death,[15] while in a recent survey of living diabetics attending an outpatient department, approximately 7% were found to be suffering from fully developed haemochromatosis.[21] The clinical picture in these patients is a fairly characteristic one. The condition is commoner in males (male to female ratio 2:1), and the majority of affected individuals are between the ages of 40 and 60 years. All give a history of excessive consumption of home-brewed alcoholic beverages. They are almost invariably underweight, a firm hepatomegaly is always present, and insulin is needed for control of the diabetes. These features serve to distinguish the condition from the common form of late onset diabetes found in the Bantu, since this usually occurs in middle-aged, obese females, and can often be controlled by diet or by oral hypoglycaemic agents.[21] The prognosis in Bantu subjects with haemochromatosis is poor, and death usually results from liver failure and/or portal hypertension.

Association between Severe Siderosis in the Bantu and Other Conditions

In recent years certain interesting associations have been noted between iron overload in the Bantu and other diseases. These include porphyria cutanea tarda, scurvy, and vertebral collapse. Although the incidence of porphyria cutanea tarda is higher in subjects with siderosis,[24] there is no evidence that its occurrence is directly related to the iron deposits as such, and it seems more reasonable to suppose that it is caused by liver damage resulting from the high intake of adulterated alcoholic drinks. Severe siderosis is almost invariably present in adult Bantu exhibiting clinical evidence of scurvy,[25] and the results of one recent study[26] suggest that it is extremely difficult to 'saturate' such subjects with ascorbic acid. Recently these observations have been confirmed and extended.[27] In these studies the working assumption has been made that when siderotic individuals subsist on a border-line diet, the available ascorbic acid is irreversibly oxidized by the large deposits of ferric iron. If this were so, then it might be anticipated that the administration of loading doses of ascorbic acid to siderotic individuals would be followed by the passage of only small amounts of ascorbic acid in the urine, but relatively large amounts of its oxidation products. The normal pathway of ascorbic acid oxidation involves the formation of dehydroascorbic acid followed by diketogulonic acid. The cleavage products of the diketogulonic acid are threonic and oxalic acids. Normal Bantu subjects and patients with severe iron overload were therefore given large doses of ascorbic acid, and the amounts of ascorbic acid and of oxalic acid subsequently appearing in the urine were measured. In normal individuals the level of ascorbic acid in the urine rose, but the level of oxalic acid did not change. In contrast, there was a marked increase in the excretion of oxalic acid, with little change in ascorbic acid levels in the siderotic subjects. These findings may well have relevance to another disease which has been noted to occur in association with iron overload in the Bantu. It has been recognized for several years that collapse of lumbar vertebrae occurs commonly in middle-aged Bantu.[28,29] Biochemical and histological studies indicate that the disease is osteoporosis, and thus far no evidence of any disturbance in calcium or phosphorus metabolism has been uncovered.[29] Recently it has been established that all subjects suffering from the condition give a history of excessive consumption of home-brewed alcoholic beverages, and are severely siderotic.[30] In addition, a large proportion have evidence of past or present scurvy.[29] It is known that ascorbic acid is necessary for the formation of bone matrix, and that guinea-pigs maintained on a diet low in ascorbic acid develop osteoporosis.[31] Current findings therefore raise the intriguing possibility that a proportion of malnourished siderotic Bantu develop osteoporosis as a result of irreversible oxidation of available ascorbic acid by the iron deposits.[26,27]

Idiopathic Haemochromatosis

When the various findings in Bantu subjects with severe iron overload are related to those in idiopathic haemochromatosis, there are obvious similarities. The most notable of these is the association of heavy parenchymal deposits of iron in the liver and pancreas with portal cirrhosis and diabetes respectively. The similarity between the two conditions has raised the question as to whether idiopathic haemochromatosis is, in fact, a specific metabolic disorder. Instead it has been suggested that it is no more than a variant of nutritional cirrhosis occurring in subjects exposed to a large intake of iron and alcohol.[32] There are several points in favour of this thesis. In the first place, it is known that a significant proportion of subjects with idiopathic haemochromatosis admit to an increased alcohol intake.[2,33] Secondly, there is the recent

observation by MacDonald[32] that a large number of American and European wines contain significant amounts of iron (Table II). On this basis it has been calculated that

TABLE II. IRON CONCENTRATIONS IN A NUMBER OF WINES OBTAINED FROM SEVERAL COUNTRIES*

Country	*Mean iron concentration (mg./litre)*
Italy	16·0
Portugal	13·4
Russia	12·1
France	8·8
Germany ..	5·8
USA (California) ..	4·9

*Data from MacDonald.[32]

many alcoholics have an iron intake several times normal. Further evidence suggests that the alcohol itself may directly influence iron absorption.[34] It was found that when whisky or brandy was given together with iron in different forms to normal fasting subjects, the absorption of ferric iron was markedly enhanced (Fig. 11). There was

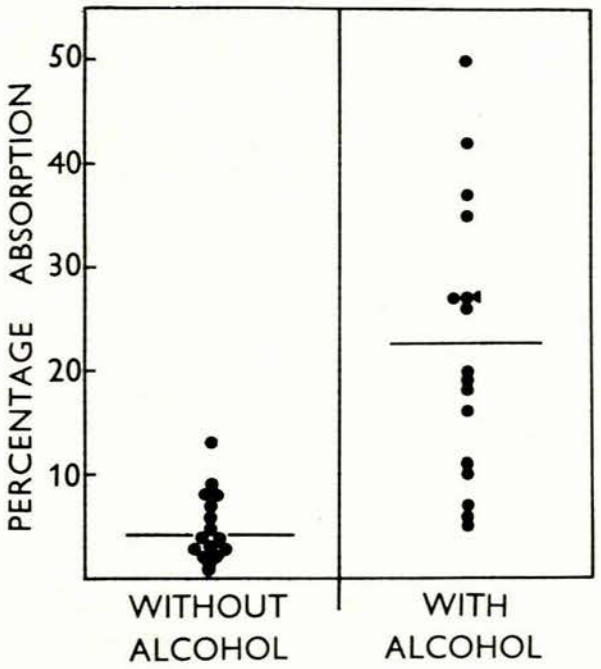

Fig. 11. The effect of alcohol given as whisky or brandy on the absorption of 5 mg. of ferric iron. (Data from Charlton *et al.*[34])

however no effect in the case of haemoglobin iron or ferrous iron. Even more support for an association between iron overload and an increased consumption of alcohol is provided by recent observations in subjects with chronic liver disease and chronic pancreatitis. Both of these conditions are common sequelae of alcoholism, and isotopic studies have demonstrated that a proportion of such subjects absorb iron excessively.[35,36]

Is there, in the light of these findings, a separate disease entity in which inappropriate absorption of iron from a normal diet results in the accumulation of massive tissue deposits? A number of observations suggest that there is. In the first place, clear-cut differences have been demonstrated between the distribution of iron in patients with idiopathic haemochromatosis and in Bantu haemochromatotics, who are exposed for long periods to a diet containing an excess of iron and alcohol.[37] These differences largely relate to the degree of reticulo-endothelial involvement in the two conditions. This is particularly striking in the spleen, where the iron concentrations in idiopathic haemochromatosis are usually much lower than in Bantu with iron overload.[5,37] Different patterns of iron distribution have also been found in the liver. In a recent study these differences were shown to be sufficiently clear-cut to allow a firm histological diagnosis to be made[37] (Fig. 12).

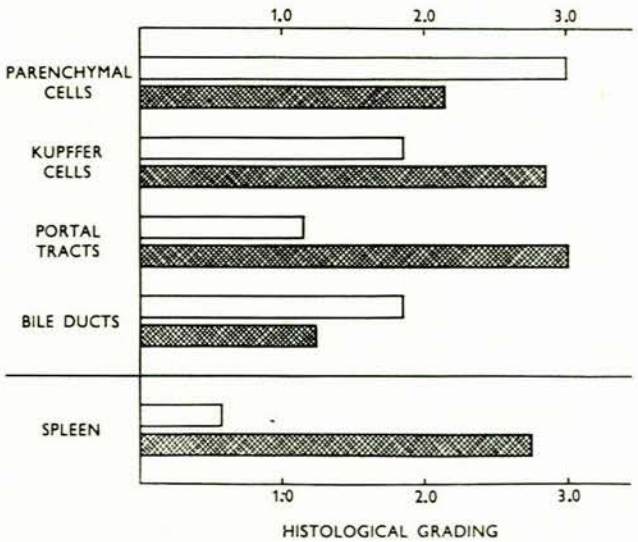

Fig. 12. A comparison between the mean histological gradings of iron deposits in different parts of the liver and in the spleen of subjects with idiopathic haemochromatosis (white columns) and Bantu haemochromatosis (hatched columns). (Data from Bothwell *et al.*[37] Figure reproduced by courtesy of the Editor, *A.M.A. Archives of Pathology.*)

Parenchymal involvement was more marked in idiopathic haemochromatosis, and reticulo-endothelial deposits were not as striking. In contrast, the reticulo-endothelial system was heavily involved in Bantu subjects. While it is possible that these findings merely reflect a more active form of liver disease in Bantu subjects, it seems more likely that they indicate some basic difference between the two conditions. It is noteworthy that the pattern of iron distribution in siderotic Bantu is very similar to that noted in animals fed large amounts of iron.[38] The different iron distribution in idiopathic haemochromatosis therefore suggests that it does not develop merely from exposure to a high iron diet.

Apart from the histological findings, there are other features which suggest that idiopathic haemochromatosis is a specific disorder. Firstly, it should be emphasized that a large number of reported patients with the disease have

not been alcoholic, and no other source of excessive dietary iron has been uncovered in these cases. Secondly, there are several family studies in which varying degrees of iron overload have been demonstrated in relatives of patients with haemochromatosis, thus supporting the concept of an inherited metabolic disorder[39,40] (Fig. 13). The

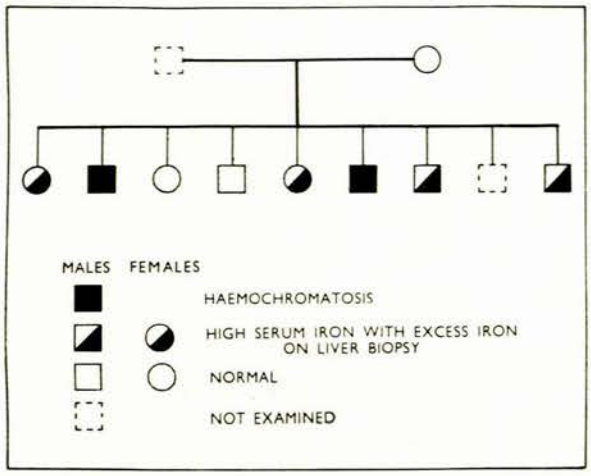

Fig. 13. A family tree illustrating the occurrence of varying degrees of iron overload in several siblings. (Data from Bothwell *et al.*[39])

fact that only a proportion of siblings living in the same household have shown increased stores can also be taken as evidence against the idea that some environmental factor, such as a high dietary intake, is essential in pathogenesis. In such studies it has been possible to follow the clinical courses of several young patients with the disease, and it is perhaps worth mentioning how characteristic the clinical picture is. Although skin pigmentation and firm hepatomegaly are always present, the most prominent features are hypogonadism, which is sometimes associated with clinical and biochemical evidence of pituitary hypofunction, and progressive cardiac decompensation.[1,41] Thirdly, it is noteworthy that abnormally high absorption of radio-iron has been demonstrated in some patients with the fully developed disease.[33] This is especially so in young subjects, and the failure to demonstrate increased absorption in some older patients may well be due to the inhibitory effect exerted by the enormous iron stores. Support for this contention has been provided by the finding of very high absorption rates in such individuals after reduction of stores by repeated phlebotomy.[42,43] This has been noted at a time when the haemoglobin level was normal and the serum iron normal or even raised. In addition, there is recent evidence to show that a proportion of asymptomatic relatives of patients with idiopathic haemochromatosis also absorb excessive amounts of iron.[44]

While there is therefore good reason to accept the existence of a specific metabolic disorder associated with increased absorption from the gut, the nature of the underlying defect is still unknown. Is there some change within the lumen of the bowel? The fact that chronic pancreatic disease leads to increased absorption[35] indicates that alterations in the intestinal secretions may have this effect. Of some interest, therefore, is the observation that the volume of pancreatic juice after secretin stimulation is abnormally increased in haemochromatosis.[45,46] While this observation may only be a consequence of impaired liver function,[45] it remains possible that it is of aetiological significance. In addition, there is suggestive evidence that the increased iron absorption in these patients can be reduced by the administration of pancreatic extract.[47]

A second possible site for the defect in idiopathic haemochromatosis is the mucosa of the upper gastro-intestinal tract. Recent experimental work from several laboratories has given some insight into the way in which absorption is regulated at the mucosal cell level.[48,49] There appear to be at least two phases in the absorptive process (Fig. 14).

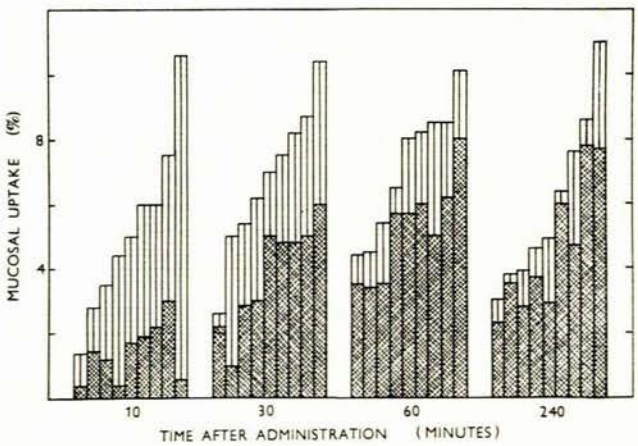

Fig. 14. Radioactively-labelled ferritin (hatched) and non-ferritin fractions in duodenal mucosae of rats at various times after feeding 10 μg. of iron as $Fe^{59}Cl_3$. (Data from Charlton *et al.*[49] Figure reproduced by courtesy of the Editor, *Journal of Clinical Investigation.*)

During the initial rapid absorption, most of the mucosal iron is present in an unidentified chemical form. With time the rate of absorption slows, and there is a progressive decline in the percentage of mucosal iron present in this form. This unidentified mucosal fraction, therefore, seems to be actively concerned in the transport mechanism. A second fraction of mucosal activity has been identified as ferritin, and this tends to increase over the first hour and then remain constant.[50] In animals made avid for iron by such manoeuvres as venesection, little or no labelled ferritin is formed, which suggests that it is not on the direct pathway of absorption. Further insight into the role of ferritin in the absorptive process is provided by the findings in iron-overloaded animals (Fig. 15). Two hours after administration of a dose of iron to such animals, a considerable amount of the iron which has entered the mucosal cells is present as ferritin, but little has been absorbed into the plasma. By 24 hours most of this mucosal iron is no longer present, but absorption in the animals has not increased significantly. The loss of mucosal iron has been shown to be due to the normal exfoliation of the iron-containing cells.[48] On the basis of such findings it is therefore possible to visualize a system

for the control of iron absorption in which deviation of iron entering the mucosal cells into ferritin protects the body from overload (Fig. 16). While it is not difficult to imagine how minor derangements in this mechanism could

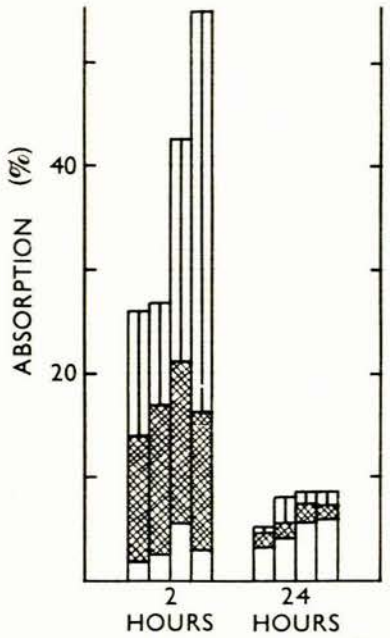

Fig. 15. The mucosal control of absorption illustrated in rats recently loaded with parenteral iron. Although by 2 hours after administration a considerable proportion of the 10 μg. dose of labelled iron has entered the mucosa (hatched = ferritin, vertical lines = non-ferritin fraction), only small amounts have crossed into the plasma (open columns). By 24 hours most of the mucosal activity has disappeared as a result of the physiological exfoliation of the epithelial cells, with little change in the amount absorbed. (Data from Charlton *et al.*[49])

lead to progressive overload, there is as yet no definite evidence to confirm this at the present time. However, it is of interest that small accumulations of ferritin are visible on electron-microscopy in the epithelial cells of the intestinal villae of normal humans, and it has been stated that these ferritin bodies are less frequently encountered in subjects with idiopathic haemochromatosis.[51] If this is, in fact, so, then it may be of fundamental importance in our understanding of the disease. It should be

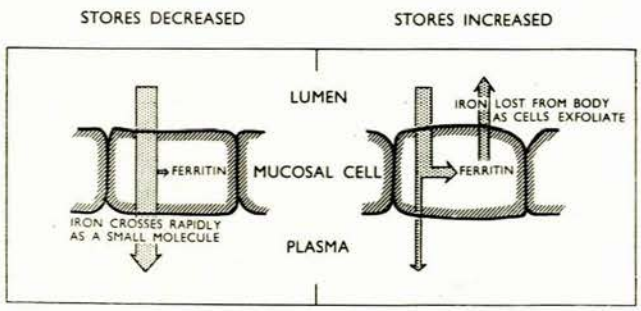

Fig. 16. A suggested scheme for the control of iron absorption in which deviation of iron into ferritin represents a mechanism for preventing excessive absorption.

stressed, however, that the ferritin mechanism only functions when physiological amounts of iron are administered.[49] It can readily be overwhelmed when the intake of iron is large, and prolonged exposure to a high intake, therefore, inevitably results in overload.

If the defect in idiopathic haemochromatosis does not reside in the lumen of the gut or in the mucosal cells, could it perhaps be due to an abnormal avidity of other tissues in the body for iron? Since iron in transport is carried on a protein, transferrin studies have been carried out to try to find out whether this protein is abnormal. Results of starch gel electrophoresis, salting out procedures, and immunoprecipitin studies have all yielded negative results.[52,53] However, other workers have recently reported that transferrin from subjects with idiopathic haemochromatosis takes up iron at a more rapid rate than does normal transferrin,[54] so that it is still possible that there is an abnormality of this protein in the condition.

Finally, the possibility exists that the liver, which is a major storage organ for iron, has an abnormal affinity for the metal in the disorder, and that the increased absorption from the gut is secondary to this. However, although minor derangements in hepatic iron kinetics have been noted in one study,[55] there is other evidence which shows that the liver has no abnormal propensity to take up iron in subjects with idiopathic haemochromatosis once their stores have been removed by repeated phlebotomies.[1]

Relationship between Oral Iron Overload and Tissue Damage

From the preceding discussion it is apparent that the pathogenesis of idiopathic haemochromatosis and siderosis in the Bantu are different. In addition, the pathological findings in the majority of siderotic Bantu are unlike those present in idiopathic haemochromatosis. At the same time it is evident that a small proportion of adult Bantu do exhibit clinical and pathological manifestations very similar to those in idiopathic haemochromatosis. The fact that these manifestations are related to the two organs containing the highest concentrations of iron (viz. the liver and pancreas) is compatible with the concept that excessive iron deposits are noxious to tissues. At the same time it must be admitted that there are still certain puzzling discrepancies. For example, in one reported study 30% of Bantu subjects with hepatic iron concentrations above 2·0% dry weight showed no significant portal fibrosis.[35] A finding such as this raises the possibility that iron is only a low-grade fibrogenic agent, and that other potentiating factors are often present. It is perhaps noteworthy that the major source of iron in the Bantu is an alcoholic drink which is adulterated in a number of ways. There is therefore the added damage of alcohol to the liver, together with the possible effects of unidentified adulterants and the associated malnutrition. In idiopathic haemochromatosis alcohol may well also be an aggravating factor in a proportion of cases.[33] The potentiating influence of such factors would certainly fit in well with a number of experimental observations, which indicate that the siderotic liver is particularly vulnerable to toxic, metabolic, and nutritional hazards.[56] It is however extreme-

ly unlikely that changes as specific as those present in haemochromatosis could be produced by such a variety of harmful stimuli acting alone, and it seems more reasonable to suppose that the iron deposits are of primary importance and that other factors only have a potentiating effect.

If it is accepted that excessive iron deposits localized in parenchymal tissues for long periods can eventually be harmful, then definitive therapy must include the removal of the large depots from the body. In idiopathic haemochromatosis this can be effectively achieved by repeated venesections (Fig. 17). After each phlebotomy iron is

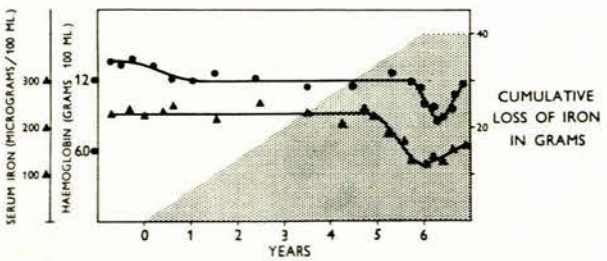

Fig. 17. Cumulative loss of iron in a subject with idiopathic haemochromatosis from whom approximately 180 pints of blood were removed over a period of 6 years.

mobilized from storage depots to satisfy the needs of the bone marrow, and the red-cell mass returns to normal. The net result of repeated venesections is therefore a depletion of body iron stores. An alternative form of therapy has recently been introduced in the form of the iron chelate, desferrioxamine.[57] Following an injection of this substance, available iron is bound and excreted in the urine. With such therapy about 20 - 30 mg. of iron is mobilized daily. Since this is only about half the amount withdrawn by an energetic programme of venesections, treatment with desferrioxamine is not indicated in uncomplicated cases of idiopathic haemochromatosis. However, desferrioxamine may still prove useful in certain situations where venesections are not possible. For example, iron overload occasionally occurs as a complication in subjects with refractory anaemias, such as thalassaemia major,[1] and under such circumstances desferrioxamine may be of theoretical benefit. To what extent the removal of excess iron alters the prognosis in subjects with haemochromatosis is still not known. While there is a growing body of evidence that phlebotomy regimes do ameliorate the course of idiopathic haemochromatosis,[1] there is as yet no reported study in which it has been unequivocally shown that the life span of affected individuals is increased. In this context it is worth stressing that South Africa offers an ideal area for assessing the long-term effects of venesection therapy, but to date no systematic effort has been made to initiate a venesection programme in Bantu with severe iron overload.

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