Effect of diet on the rate of iron accumulation in idiopathic haemochromatosis

W. R. BEZWODA, T. H. BOTHWELL, D. P. DERMAN, A. P. MACPHAIL, J. D. TORRANCE, R. W. CHARLTON

Summary
There is still controversy concerning the effects of increasing the dietary intake of iron on iron nutrition. This debate has not only centred on the question of efficacy but also on that of safety. At particular potential risk are those individuals with disorders such as idiopathic haemochromatosis, who absorb iron excessively from the diet. Data obtained in the present study and in several other investigations suggest that subjects homozygous for the mutant gene responsible for the disorder would develop clinical features of the disease at a younger age were the dietary iron intake to be increased. Iron stores in affected heterozygotes would increase but the size of the stores would probably equilibrate long before they had reached massive proportions. While these conclusions are drawn from a number of studies, there are enough unanswered questions to make it mandatory for any future fortification programmes, whether they be directed at the entire population or only at certain segments of it, to be carefully monitored. This can currently be achieved with serial plasma ferritin measurements, since the concentrations mirror the size of iron stores in the body.

A proposal to increase the level of iron fortification of flour in the USA from its current figure of 13.0 — 16.5 mg per pound to 40 mg per pound1 engendered a heated debate that extended over several years. Such a fortification programme would have been expected to have increased the average intake of iron in adult males from 17.9 to 21.5 mg per day. Eventually the proposal was rejected on the grounds of unproven efficacy and doubts about its safety. In terms of this second point it was felt that individuals suffering from several ‘iron loading’ states, such as idiopathic haemochromatosis, would be at particular risk. 2 In the first condition, there is an inborn error in metabolism, which is associated with the absorption of increased amounts of iron from a diet of normal iron content, while in thalassaemia major excess iron is derived from both increased absorption from the gut and from donor blood. 3 Although the number of subjects at risk is not accurately known, it has been estimated that there are about 20,000 individuals with idiopathic haemochromatosis and 5,000 with thalassaemia major in the USA. In a previous study we postulated, on the basis of available evidence, that the proposed increase in iron fortification in the USA would lead to the clinical presentation of haemochromatotic individuals at younger ages than is currently the case. This would lead to earlier detection and treatment. 4 At the same time we believed that it would be unlikely that the prevalence of the condition would increase significantly.

In the last several years much has been learnt concerning the inheritance of idiopathic haemochromatosis and there is now good evidence of a strong association between the disorder and certain HLA haplotypes (HLA-A3, HLA-B7 and HLA-B14), which suggests that the genetic defect is situated on chromosome 6 close to the A locus. 5 Adult siblings with two HLA haplotypes in common almost invariably have significant iron overload, while heterozygotes may have normal or slightly increased iron stores. 6 These findings indicate that idiopathic haemochromatosis is an inherited autosomal recessive disease and there are certain areas in which the gene frequency has been reported to be high (0.056 in Mormons in Utah6 and 0.044 in Scotland7). While such figures may have been inflated by biased ascertainment, they do suggest that carriers of the genetic disorder occur frequently enough for questions to be raised concerning the effects of increased iron fortification on their well-being.

The purpose of the present paper was to obtain more information on the rate of iron accumulation in subjects with idiopathic haemochromatosis, especially in so far as iron fortification is concerned. The information so obtained was then related to a model of iron balance in subjects with iron overload that was previously proposed by us. 4

Patients and methods

Patients

Absorption of iron at two different dosage levels was studied in 7 patients suffering from idiopathic haemochromatosis. The diagnosis of idiopathic haemochromatosis was based on the usual laboratory and clinical findings, including severe parenchymal iron overload on liver biopsy and a 24-hour urinary iron excretion of greater than 8 mg after the administration of desferri-oxamine. 8 All patients had been treated by repeated venesection therapy and at the time of the study more than 30 litres blood had been removed from each of them. The fact that their iron stores had been effectively depleted was confirmed by the fact that all serum ferritin concentrations were less than 33 µg/l (mean value for adult males ± 100 µg/l). Venesection therapy was discontinued for at least 4 weeks before the study and was not resumed until it was finished.
Administration of meals
Each subject ate two separate maize porridge meals on two successive mornings. One meal was fortified with 5 mg and the other with 10 mg iron. The maize porridge was prepared using 1 part of finely milled maize to 4 parts of water (w/v). The extra iron was added as ferric chloride in 0,01N HCl just prior to cooking. At the same time each morning the porridge was labelled with a different isotope of iron (2,5 μCi 59Fe or 5 μCi 55Fe in 0,01N HCl). Care was taken to ensure even mixing of the radio-isotopes with the unlabelled iron. The amount of cooked porridge given at each meal was weighed and was approximately 100 g. Each meal was given together with 100 ml pasteurized milk, 20 g sugar and a glass (200 ml) of fresh orange juice after an overnight fast. The total iron content of the meals (including the milk) were approximately 6,2 mg on day 1 and 11,3 mg on day 2 (Table I) and the ascorbic acid content of the orange juice was 60 mg per 200 ml portion. Blood was drawn for radioactive counting 14 days after the second meal, and following this, another absorption study was carried out, in which a readily available iron salt was given. In this second part of the test, 3 mg iron as ferrous sulphate, labelled with 2,5 μCi 59Fe, was made up in 3 ml 0,01N HCl, 30 mg freshly dissolved ascorbic acid was added and the total volume was made up to 50 ml.

Radiation exposure
It was calculated that if the entire dose of radio-iron was retained, the total radiation averaged over 13 weeks would be approximately 20% and 0,2% of the permissible whole body burden for continuous exposure to 59Fe and 55Fe respectively.

Ethical considerations
Prior to embarking on the study, approval was obtained from the Committee for Research on Human Subjects of the Faculty of Medicine, University of the Witwatersrand. Written consent was obtained from all subjects after the nature of the investigation had been explained to them and the study was carried out in accordance with the principles of the Declaration of Helsinki.8

Chemical and isotopic methods
Haemoglobin estimations were performed on blood drawn on the day of the absorption study using the cyanmethaemoglobin method. Plasma iron concentrations were measured by the ICSH technique4 and unsaturated iron-binding capacities by the method of Herbert et al.6 Plasma ferritin concentrations were measured by means of the radio-immunoassay described by Deppe et al.11 Iron absorption was calculated by measuring the radioactivity in red cells 14 days after administration of the second radio-isotope. Duplicate 10 ml blood samples were digested using the method of Katz et al.12 and the relative absorptions of the two isotopes was estimated after differential counting, assuming 100% incorporation of the isotope into red cells and a blood volume of 65 ml/kg body weight.13 Estimation of the iron content of the meals was performed on acid digests of aliquots of the meals by using a modification1 of the method of Lorber.14

Results
The haemoglobin concentrations varied from 12,9 to 15,3 g/dl (mean 13,9 g/dl) (Table I). The serum iron concentration ranged between 41 and 68 μg/dl (mean 54 μg/dl), the transferrin saturation between 12% and 25% (mean 17%) and the serum ferritin concentration between 18 and 32 μg/l (mean 25 μg/l). The percentage absorption of iron from meal 1 varied between 17% and 34% (mean 25%) and from meal 2 between 15% and 23% (mean 20%). Absorption of iron from the reference salt varied between 55% and 95% (mean 72%), thus indicating that all the subjects were iron-depleted and therefore avid for iron at the time of the study.

In order to find out whether the pattern of iron absorption at the two dosage levels was the same in the subjects with idiopathic haemochromatosis as in normal individuals, the results were compared with those previously reported by Layrisse et al.15 in normal subjects (Fig. 1). These workers added varying quantities of iron as ferric chloride to three types of meal and measured the total quantities absorbed. In each instance the amount of iron absorbed increased progressively as the iron content of the meal rose. While the absolute amount of non-haem iron that was absorbed was dependent on the nature of the diet, being greatest with meat and least with maize, the rate at which iron absorption increased with increasing dose was independent of the nature of the meal. The relationship between absorption and dose could be expressed as follows: Δ log iron absorption = 0,47 ⋅ Δ log dose of iron. When the results obtained in the present study were plotted in the same way as those of Layrisse et al.15 the relationship between the amounts fed and the quantities absorbed was as follows: Δ log iron absorption = 0,67 ⋅ Δ log dose of iron. This was not significantly different from that noted in normal subjects (F = 0,35; df = 1; df = 63). While the actual quantities absorbed were higher than those in the subjects studied by Layrisse et al.,15 the patients in the present study were more iron-deficient and, in addition, the meal they ate was not the same, especially in terms of its ascorbic acid content.

Discussion
In a previous paper we proposed a model of normal and

<table>
<thead>
<tr>
<th>TABLE I. HAEMATOLOGICAL AND IRON ABSORPTION DATA OF PATIENTS STUDIED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>F</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td>M</td>
</tr>
</tbody>
</table>

* 3 mg iron fed in the fasting state as ferrous ascorbate.
there is reasonably firm experimental evidence to back up the various presumptions on which our previous model of iron accumulation in idiopathic haemochromatosis was based, one aspect of it had not been substantiated at the time it was proposed. In our model, the data of Layrisse et al. 15 were used for predicting by how much various levels of iron fortification would raise the amounts absorbed from particular diets. However, these data were obtained in normal subjects and there was no assurance that they applied to subjects with a disordered absorption mechanism. The results obtained in the present study indicate that the slope of increased iron absorption with rising iron intake is very similar to that in normal subjects. On this basis it seems reasonable to believe that the rate of iron accumulation in subjects with the genetic predisposition to develop idiopathic haemochromatosis would be somewhat faster were staple foods to be fortified with iron and that clinical manifestations would, as a result, occur at a younger age. However, the relationships between iron absorption, iron excretion and the size of the iron stores would remain the same, so that the ultimate size of the body iron burden would not necessarily be much greater than previously. The major change would be that the equilibration point where iron absorption and excretion equalled each other might be expected to occur sooner.

While idiopathic haemochromatosis is a relatively rare disease, large numbers of people are heterozygous for the mutant gene. 5,6 Such individuals appear normal or show only minor derangements of iron metabolism. 8 The plasma ferritin concentration, which reflects the size of the iron stores, is usually within the normal range 15,16 and iron stores rise during life from an average of 0.2 to 1.3 g (normal value for adult males < 1 g). 3 These findings imply that initial absorption rates for iron are only slightly raised in heterozygotes and that the absorption and excretion rates usually equilibrate when stores are only modestly raised. Fortification of staple foods at the level proposed in the USA would therefore be expected to have only a limited impact. While the iron stores in heterozygous individuals would almost certainly increase, the increase would not be expected to be anywhere near the figures encountered in full-blown idiopathic haemochromatosis. If, in fact, the model previously suggested is a valid one, and the data presented in the present paper are certainly compatible with it, the initial absorption rate in heterozygotes of 2.0 mg per day would rise to 2.5 mg per day, if iron fortification at the level proposed in the USA were introduced. This might be expected to lead to an iron storage depot of at most 4.3 g by the age of 50 years, instead of one of 1.6 g. 1

While we realize that many of the points in the discussion are conjectural, they do underline the sort of information that is required if meaningful predictions on the effects of iron fortification are to be obtained. For example, it would be extremely valuable to know something about dietary iron absorption and stores in subjects with idiopathic haemochromatosis during a period of iron re-accumulation (i.e. after the completion of venesection therapy). Since there are a number of unanswered questions relating to the effects of dietary iron fortification on subjects with a tendency to absorb iron excessively, it is obvious that any projected fortification programme must be carefully monitored. In this connection, the
most important group to be followed-up would be heterozygous individuals carrying the mutant gene for idiopathic haemochromatosis. These subjects can, in fact, now be identified among the relatives of patients with the disease by HLA typing. Fortunately, it is now possible to monitor such individuals using a non-invasive technique, since repeated measurements of the serum ferritin concentration should provide an accurate index of enlarging iron stores.

In South Africa, the situation is different from that in most other countries, since large numbers of the population, namely adult Black males, have varying degrees of iron overload. Fortification of the diet with iron could therefore prove potentially deleterious to those many individuals who already have too much iron in their bodies. At the same time it must be realized that there are other members of the population, notably Indian females and underprivileged infants in whom iron deficiency occurs. Programmes to improve iron nutrition must therefore be specifically directed at the target groups. In infants this can be achieved at least in part by fortifying infant cereals with iron and ascorbic acid, while in the Indian population it may prove possible to fortify some key dietary constituent, such as curry powder, which is regularly consumed in large quantities by this group but not by others.

This work was supported by a grant from the Atomic Energy Board.

REFERENCES


Breast reconstruction following mastectomy

B. M. DE SAXE

Summary

Carcinoma of the breast is a formidable disease in which early detection is of paramount importance. Treatment is aimed at effecting cure and survival, but as the quality of life is also of great importance every effort should be made to rehabilitate the mastectomized patient. Breast reconstruction is discussed in some depth to include issues such as the proper selection of cases, the role that adequate discussion with the patient should play, the timing of the operation, the role played by the opposite breast and, in brief, the methods used to reconstruct an absent breast, the areola-nipple complex and the pectoralis major muscle.


Brenthurst Clinic, Parktown, Johannesburg

Date received: 3 July 1980.
Reprint requests to: Dr B. M. de Saxe, Suite 7, Brenthurst Clinic, 4 Park Lane, Parktown, 2193 RSA.

Modern society places considerable emphasis on breasts that are aesthetically proportioned. Plastic surgery has not only responded by providing techniques such as breast reduction, augmentation, equalization and elevation of ptotic breasts (mastopexy), but has also provided reconstructive procedures for the mastectomy patient whose problems and surgical rehabilitation form the subject of this article.

Carcinoma of the breast is a formidable affliction and by far the most common carcinoma occurring in females. Approximately 90000 new cases are diagnosed and treated yearly in the USA. Six per cent of all women will develop breast cancer, and 15% of these will be less than 40 years of age. With adequate treatment a substantial proportion of these will survive, especially where the primary tumour is less than 2 cm in diameter and where fewer than 2 axillary nodes are involved. Early detection is of paramount importance, and every effort must therefore be directed towards this goal. However, it is common knowledge that many patients are reluctant to report a swelling, either because of their anxiety about survival or because of their fear of a mutilating mastectomy. To combat this misplaced reasoning, women should be alerted to the facts, viz. that the earlier the detection, the better the chance of survival, the less likelihood of radical surgery, and the greater the likelihood of being a suitable candidate for a reconstructive procedure. They should also be made aware of the concept that reconstruc-