ABSORPTION OF MEDICAMENTAL IRON AND IRON FROM FOOD

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Abstract

Methods are reviewed for the measurement of iron absorption. The chemical balance method has been almost entirely supplanted by radioisotope methods, which include notably whole-body counting and measurement of incorporation of radioiron into red cells. A survey is also given of the various conditions that influence iron absorption, including chemical form of iron, amount of iron, accompanying diet. Absorption tests must be conducted under relevant conditions.

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1. INTRODUCTION

Iron deficiency is still among the most frequent deficiency conditions both in industrialized and in developing countries. Depending on the definition of iron deficiency, this condition is seen in 25 % to 45 % of women in the fertile age groups in industrialized countries[1-11]. In developing countries, iron deficiency is frequent in women, children and some groups of men[12,13] (Fig. 1). In South India, 96 % of pregnant women were reported to be iron deficient, and 80 % of non-pregnant women, 54 % of males and 75 % of school children were found to have iron deficiency anaemia[110]. The corresponding figures found in Egypt were 62 % of women and 36 % of children[111]. Even in industrialized countries, moderate laboratory signs of latent iron deficiency, or iron deficiency without anaemia, may be seen in 15 % of adolescent men[14].

Is all of this iron deficiency of clinical or social relevance? Manifest iron deficiency with severe anaemia would be expected to cause a decrease in the physical working capacity[15], which is correlated with the total amount of haemoglobin in the body[16]. It has been suggested[17] that for each 3.8 units by which the haematocrit is reduced, the physical working capacity is reduced by 15 %. Some authors find an increase in the physical working capacity after iron treatment[18]. If one accepts this suggestion, as not everybody does[19], and if one makes some additional assumptions, iron deficiency may be judged of major socio-economic importance even in industrialized countries. In Sweden it has been suggested[17] that the total annual cost of iron deficiency to society might be well over 10^9 Swedish crowns (e.g., Kr. 10×10^6 for medicaments, Kr. 18×10^6 for medical consultations, Kr. 1300×10^6 for lost production).

Unlike certain other deficiency diseases, iron deficiency cannot be attributed to a scarcity of the nutrient itself. In South India, the intake of dietary iron is 27 - 29 mg per day[110]. The crust of the earth would contain enough metallic iron for the world's population for 10^{16} years, even if every iron atom could be used only once. Although availability, accessibility and distribution may be of importance, it is obviously also relevant to examine iron absorption.

2. METHODS TO MEASURE ABSORPTION

2.1 Chemical balance

Theoretically, the chemical-balance method[20-25] for measuring iron absorption is simple. Iron is administered, the amounts of iron in the food and the faeces are determined by chemical analysis, and the balance is estimated. In practice, however, this method is laborious and unreliable, since it is difficult to collect the complete faeces and since the analysis of the food and the faeces is time-consuming. Only a limited number of subjects can be studied.

Isotopic methods likewise suggest that the results obtained by chemical-balance studies are rather unreliable. The chemical-balance method has largely been replaced by isotopic methods.

2.2 Therapeutic tests

Therapeutic tests can be used both to diagnose iron deficiency and to estimate the utilization or absorption of iron.

2.2.1 Diagnostic use

Garby and co-workers[10,27] showed, as did earlier workers[26], that in a group of women those probably suffering from iron deficiency responded to iron supplementation by increasing their haemoglobin and haematocrit values. The definition or diagnosis of iron deficiency anaemia could in theory be based upon the response of the individual haemoglobin concentrations to iron supplementation, on the assumption that such a response, if it occurs, brings the haemoglobin level of that subject to his optimal value.

2.2.2 Use in the study of iron absorption

Therapeutic tests can also be used to estimate the retention. They can be used as a sort of reversed balance study, where iron losses are determined exactly, and one can then estimate how much of the therapeutic iron has to be

absorbed to keep the patient in balance.

Ehn and co-workers[28] have made a long-term therapeutic study on apparently healthy volunteers. Initial sternal marrows were taken to estimate the amount of iron in the reticuloendothelial cells. The values of the haemoglobin, serum iron and total iron-binding capacity in peripheral blood were measured. The volunteers were then divided into different groups receiving different regimes of medication throughout the following year, during which they were phlebotomized, according to the Scandinavian blood donor routine, once every two months. In conjunction with the phlebotomy the total iron loss of these subjects could be determined rather accurately.

When the test period was over, the quantity of iron in the reticuloendothelial cells, the haemoglobin and the serum were measured again. The histochemical grading of bone-marrow iron permitted a rough estimate of the iron stores (Table 1). It is assumed that grades 1 - 2 correspond to 200 - 400 mg iron in stores, and grades 3 - 4 to 400 - 600 mg[47]. Where no change had occurred, the daily absorption could be assumed to equal the average daily loss.

Obviously, this test is time-consuming, but it requires little research equipment, and it does estimate the absorption of therapeutic doses under long-term clinical conditions.

2.3 Serum iron

In healthy persons, the serum-iron concentration rises following oral administration of 50 mg or more of ferrous iron, and this increase has been used to measure iron absorption[7,30,31,32]. Whereas it may be possible to use this method in health, many diseases affect the plasma clearance of iron sufficiently to invalidate the method. In inflammatory, infectious, and sometimes neoplastic disease, the plasma clearance of iron is sufficiently rapid to prevent any increase in the serum iron concentration after iron absorption. The rate of iron clearance from the plasma is also abnormal in the different anaemias and in iron deficiency itself. For this reason, the estimation of iron absorption on the basis of serum-iron concentration measurements has been largely replaced by other methods.

2.4 Faecal excretion

If a tracer dose of radioiron is given orally, and all radioactivity excreted in the faeces is collected for an appropriate length of time, the difference between the amount given and the amount excreted should equal the amount

absorbed and retained[33,34,35]. The method is relatively laborious and unpleasant. It suffers from the potential systematic error of incomplete collection, which results in estimates of mean absorption that are too high[36]. The method is improved if ^{131}Ba-sulphate or ^{140}La is given together with the ^{59}Fe[37-41]. Since these supplementary tracers are assumed not to be absorbed, the excretion of non-absorbed iron presumably ends when the barium or lanthanum excretion ends (Fig.2). Iron subsequently excreted is assumed to have been absorbed or taken up into intestinal mucosal cells before returning to the gut[39-41].

2.5 Double-tracer absorption studies with plasma measurements

Several methods for measuring iron absorption can be made more reliable by the simultaneous use of two radioisotopes of iron. The method based upon observation of the tracers in plasma will be dealt with first. The isotopes available are ^{55}Fe and ^{59}Fe. While ^{59}Fe is easily measured, ^{55}Fe presents greater analytical problems because of its low-energy (6 kev) electron-capture x-radiation[42]. Peacock et al.[43] were the first to measure ^{55}Fe and ^{59}Fe in a mixture of the two isotopes by using two Geiger-Müller tubes with different characteristics. This technique was then improved and utilized by Sailor and Finch[45] and Hallberg and Brise[44]. One of the isotopes, ^{59}Fe, is given orally, and simultaneously the other, ^{55}Fe, is injected intravenously and becomes bound to the patient's plasma protein. After a suitable interval the ratio of the isotopes in a serum sample gives a measure of absorption of the ^{59}Fe. If the intravenous dose is administered one hour before the oral dose, the turnover time of the plasma iron and the plasma volume can also be conveniently measured[46].

This method has the major advantage of giving results earlier than the other methods described here. It has two disadvantages. First, it is based upon the assumption that the absorbed iron and the parenterally administered iron are handled by the body in exactly the same way, not only in health, but also in iron deficiency, in iron overload, or in other diseases for whose study it is used. Second, the separate assay of ^{55}Fe requires careful preparation and concentration of samples.

2.6 Absorption measurements using erythrocyte incorporation

Of the methods requiring use of only one isotope, that most frequently applied is based on the assumption that normally 60% to 80% of absorbed iron, in iron deficiency even 100%, is incorporated into haemoglobin[46]. Ten to fourteen days after an oral dose has been given, the activity in an erythrocyte

sample is measured. If the blood volume is known, or if it can be calculated from the body weight, the total uptake of the administered radioiron into the haemoglobin can be calculated, and this sets a lower limit on the amount of iron absorbed. (The true value of absorption may be higher, due to the presence of additional absorbed iron elsewhere than in the erythrocytes.) If there is normal radioiron incorporation into erythrocytes, this lower limit of absorption obtained with the single isotope method is about 20 per cent lower than the actual absorption. It is closer to the actual value in iron deficiency. In patients with aregenerative or secondary anaemias, the method yields absorption figures that are again somewhat low. However, even in such conditions the absorption of two differently labelled iron compounds may be adequately compared, and if a second isotope is injected, the incompleteness of the incorporation of the radioiron into the erythrocytes can be corrected for. The correction is based on the plausible assumption that equal fractions of the oral and of the parenteral iron are incorporated.

2.7 Whole-body counting

Four different whole-body counting tests of iron absorption are available, here identified as single-dose administration, sequential-absorption test, double-isotope whole-body counting, and the prolonged-administration test.

2.7.1 Single-dose administration

After a tracer dose of iron is given orally, the whole-body radioactivity corresponding to 100 % of the administered dose can be determined by an immediate measurement in the whole-body counter, and the fraction remaining two weeks later can be determined by another measurement at that time. When the non-absorbed radioactivity is completely excreted, residual radioiron in the whole body is that which was absorbed (references reviewed in [48,49]). If these measurements are performed with a whole-body counter that is sufficiently geometry-independent to measure the initial isotope distribution with approximately the same efficiency as the final isotope distribution, then this procedure is probably the method of choice, both as regards simplicity and as regards reliability, to measure iron absorption. However, even when technically satisfactory absorption measurements are made with this (or any other) method, biological variability (e.g., mean coefficient of variation 18 per cent) in iron absorption from day to day and from individual to individual contributes a considerable ambiguity to the clinical interpretation.

2.7.2 Sequential-absorption test

When comparisons are intended between the absorption of different iron compounds, or between the respective influences of different food components on iron absorption, two methods are available. Either sequential measurements can be made using a single isotope, or two isotopes can be used simultaneously. In sequential measurements, the possible lingering presence of unabsorbed radioisotope in the intestine at the time of administration of the second tracer dose is a potential source of systematic error. Although average amounts of such residual unabsorbed radioactivity are small, the possibility that an individual subject may have a larger than average residuum in his intestine remains. Measurements on such subjects may lead to erroneous estimates of the absorption of both the first and the second doses.

2.7.3 Double-isotope whole-body counting

As an alternative to sequential administration of the isotope, a combination of the whole-body counting technique and the multiple-tracer technique may be employed. The two compounds to be compared may be labelled with ^{59}Fe and ^{55}Fe, respectively. They may be administered, under comparable conditions (e.g., on a fasting stomach), at an interval of a few hours. The ^{59}Fe absorption is measured in the whole-body counter just as after single-dose administration. The ^{55}Fe absorption is derived from the figure for ^{59}Fe absorption by multiplying the latter by the ratio:

$$\frac{(^{55}Fe/^{59}Fe \text{ in erythrocytes at 2 weeks})}{(^{55}Fe/^{59}Fe \text{ in administered doses})}.$$

In this way a reliable estimate of ^{55}Fe absorption can be obtained even when incorporation into erythrocytes is abnormal, since the same elevated or deficient incorporation may be assumed to apply to both ^{55}Fe and ^{59}Fe.

This method permits studies not only of healthy persons, but also of patients with a disturbed iron metabolism. It is not affected by kinetic differences between injected and absorbed radioactivity. It saves about 2 weeks of time, and reduces the day-to-day variation between the two compounds compared. However, it does substantially increase the radiation dose to the patients (Table 2) if an insensitive but simple liquid-scintillation measurement technique[42] is used for the ^{55}Fe. If the method of Eakins and Brown[107] is used,

giving greater sensitivity but consisting of 35 laboratory steps, the increment in radiation dose attributable to the ^{55}Fe tracer is comparatively small.

2.7.4 Prolonged-administration test

Attempts have been made to avoid the day-to-day variability in iron absorption and to perform the test under conditions resembling those used clinically, i.e. when prolonged therapy is given, by measuring the total iron retention after an extended period of radioiron administration, rather than after a single administration[112]. With this method, no simple, post-administration "100 per cent value" can be measured; instead, it must be indirectly deduced from supplementary measurements - for example on a phantom. Some values obtained with this method are given in Table 3. Under some experimental conditions this prolonged-administration absorption test is preferable to the single-administration test.

3. ABSORPTION OF FOOD IRON

3.1 Haemoglobin iron

There is satisfactory evidence that haemoglobin iron is absorbed into the intestinal mucosal cell as an intact porphyrin structure[50,51] which is degraded inside the cell[52,53]; ferric ions are then released to the portal blood[54,55], where they are bound to transferrin. Heinrich[56] has shown that ferri-haemoglobin (Fe 3+) is absorbed approximately like ferro-haemoglobin (Fe 2+) in controls, but a little better in iron-depleted subjects.

The part of the iron-absorption pathway preceding the release into the portal blood is thus different for iron administered in the form of haemo-compounds and iron administered in the form of ferrous and ferric complexes or salts. This may explain some of the differences between ferrous iron and haemoglobin iron with regard to the regulation of their absorption. It has for example been demonstrated[50] that ascorbic acid does not stimulate the absorption of haemoglobin iron, even though it does stimulate the absorption of ferrous iron. Similarly, some food components inhibit the absorption of ferrous iron, but not the absorption of haemoglobin iron (Table 4). There are also regulatory mechanisms that influence the absorption of ferrous iron but not that of haemoglobin iron, for example as revealed by the influence of prolonged treatment on iron absorption (Table 5). This influence is seen when ferrous iron is administered for prolonged periods of time; absorption of ferrous iron is inhibited[57], but not that of haemoglobin iron.

The elevated level of absorption found in iron deficiency when trace amounts of ferrous iron are administered is less pronounced when haemoglobin iron is given[50,58,59]. However, there is no significant difference in absorption between ferrous iron and haemoglobin iron when therapeutic doses are used (Table 6).

Haemoglobin iron constitutes approximately 70 % - 80 % of the iron in mammals. However, haemin iron constitutes less than 15 % of the iron intake in Sweden (Table 7), although there are several indications that this form of iron may be important from a nutritional point of view. First, its absorption is less vulnerable to suppression by food than is that of ferric or ferrous iron compounds (Table 4). Second, there are observations that populations a large part of whose iron intake is in the form of haemoglobin iron show iron deficiency less frequently than populations whose iron comes largely from vegetable sources[60]. Third, when a meal is given containing 80 % of the iron as ferrous and ferric compounds, and 20 % as haemin, about 80 % of the absorbed iron may be derived from the haemin iron[61]. Studies are therefore in progress with the goal of introducing more animal-source iron into human nutrition than is presently the case[80].

3.2 Iron complexes

It has been postulated that iron - with the exception of haem-iron - is absorbed in the ferrous form[56,62]. If ferric iron is administered, only the portion that is reduced to ferrous iron or that is solubilized by chelation is absorbed.

In nature, ionized iron occurs rarely in the intestine. Instead, iron is usually bound as a complex. Complex-binding may facilitate absorption but often inhibits it.

3.2.1 Iron complexes facilitating absorption

Dietary components that solubilize iron may enhance absorption[63,64], and those that cause precipitation or polymerization decrease absorption[65]. It has been shown that some constituents of the diet or of intestinal secretions may, by forming complexes of iron, maintain it in a soluble form at the alkaline pH of the small intestine[63,65]. Thus, some sugars, amino acids and amines occurring in the diet may interfere with the water bridges between iron molecules, form complexes, and keep the iron soluble. Ascorbic acid may even form ferric complexes in a similar way, and keep ferric iron as soluble as ferrous iron over a

wider range of pH[66]. It is not known if iron thus solubilized is absorbed as a complex, or if the various chelators derived from the diet or intestinal secretions merely serve to keep iron in a soluble state, rendering it suitable for absorption.

3.2.2 Iron complexes inhibiting absorption

Absorption of iron may also be influenced negatively by chelating substances.

Iron has a co-ordinating valence of six and tends to form complexes. In water solution, iron ions are more or less bound to each other by water bridges. When the water molecules thus surrounding ions are replaced by other molecules or ions, a metal complex is formed. At an alkaline pH, hydroxyl ions are available to form polymers or iron ions or iron-hydroxide precipitates.

The characteristics of the iron chelates formed vary widely, depending on the chemical nature of the chelator. It may either inactivate the iron by sequestering[62] all six co-ordinating bonds of the ion, forming a water-soluble stable iron chelate, or decrease absorption by precipitating or polymerizing the metal.

In the diet, iron-precipitating agents such as carbonates, oxalates, and phytates of acid phosphates occur rather frequently. They may precipitate iron by forming insoluble complexes that are poorly absorbed[67].

3.2.3 Effect of chelates on absorption

The complexes thus formed are more or less stable. They may be partly soluble, partly insoluble. It has been assumed that the effect of iron absorption attributed to the more soluble chelates depends more on polymerization than on precipitation of the metal ions[65]. For instance, iron-EDTA, a stable, water-soluble chelate, is poorly absorbed[67]. Nevertheless, it has been used for therapy and has been shown to have a haematinic effect almost comparable to that of ferrous sulphate in equivalent doses. The absorption of iron from this chelate was attributed to the portion of chelate split within the gastrointestinal tract, so as to release iron for absorption by the usual mechanism[68]. On the other hand, another potent and specific iron-chelating substance - desferrioxamine - was shown to decrease the absorption of ferrous iron significantly. It did not, of course, affect the absorption of haemoglobin iron[69]. Tetracyclines have also been shown markedly to reduce the absorption of ferrous iron by complex formation[70]. The long-term treatment of female acne patients with tetracyclines did not, however, produce signs of iron deficiency, indicating

that food iron may have been absorbed in an ordinary manner[71] despite tetracycline medication.

Iron has also been shown to have a haematinic effect when administered in a fat-soluble form, complex bound. Both the iron and the fat were absorbed. Whether the complex was absorbed as such, or the iron was split off in the intestine before absorption, has not been shown[72].

It may be said that binding of iron by various chelating substances occurs whenever iron is presented to organic materials. Chelating agents that enhance and those that decrease iron absorption have been demonstrated. It is probable that the transfer of iron into the mucosal cell and within the cell also depends on chelation mechanisms, the intimate nature of which is still obscure.

4. ABSORPTION OF MEDICAMENTAL IRON

In previous studies, differences in iron absorption values that are caused by variations in the experimental conditions have received inadequate attention. One should, however, distinguish the laboratory situation from the therapeutic or the nutritional situation (Table 8). In the laboratory situation, tracer amounts of a soluble iron salt are usually given on a fasting stomach, in the therapeutic situation, large multiple doses are always given, usually together with food, and previous doses may have an effect on the absorption of subsequent doses (the prolonged-treatment effect). In the nutritional situation, the intake of iron is also continuous but this iron is not in the form of soluble salts (Table 8). Together these differences suggest that, in order to be relevant for the therapeutic situation, iron absorption studies must be performed under clinical conditions. Results obtained under what are called laboratory conditions can only rarely be extrapolated to the therapeutic situation. Nevertheless, the absorption figures most often discussed are related to low dosages of iron under laboratory conditions. The addition of ascorbic acid is recommended by some groups[108], but is not practiced in all studies. The amounts of ascorbic acid vary at least between 30 mg[108] and 222 mg[106].

4.1 Laboratory conditions

4.1.1 Absorption from different doses in health

Table 9 shows the range of iron absorption values obtained by a number of authors who studied the absorption of iron from therapeutic doses. It is seen that even with ferrous salts absorption is relatively inefficient; the average

absorptions are 4% - 7%. The only exceptionally high results[75] are those obtained with the faecal excretion method, which may yield erroneously high absorption values[49]. When iron is given in therapeutic doses, food inhibits 30% to 60% of the absorption (Table 4), but when tracer doses are used, inhibition may be 90%[77]. The quality of the food is also important, as described in a separate section.

4.1.2 Absorption from different doses in iron deficiency

When tracer doses are used, very high absorptions have been found in iron deficiency by different authors[20,49,64,78,79,80], e.g. two to four times normal (Table 6). There is relatively little information regarding the situation when therapeutic doses are administered.

4.2 Clinical conditions

4.2.1 The effect of food on the absorption of medicamental iron

The absorption of medicamental iron can be influenced by food[31,81]. The effect can be either stimulatory or inhibitory. Cereals (e.g. dark bread, porridge, dried legumes, oil seeds and nuts) are rich in phytic acid. Iron absorption depends not only on the original quantity of phytic acid in the diet: the presence of phytase, which decreases the chelating capacity of phytic acid in the food or in the digestive tract, is also important. Several studies have shown that alcohol, proteins[82,83,84,85,109], some amino acids[109], ascorbic acid[86,87,109] and sugar[30,88] may promote absorption, whereas wheat bran[109], phytic acid[89,90,91,92] and egg white[79] have an inhibitory effect (Table 10). These findings may be explained by the formation of complexes between various dietary ingredients and iron[65], as discussed earlier. An iron-rich diet may saturate the intestinal mucosal cells and inhibit absorption. Moreover, non-haem iron in the food exchanges with medicamental iron[93], and competes with it for absorption.

4.2.2 Effect of continuous iron therapy on absorption

Despite a large consumption of medicamental iron, deficiency is still common and it may be asked if this phenomenon is explained by processes that regulate iron absorption in humans.

It has been shown clearly by several investigators that there is a strong relationship between iron absorption and iron stores in man, as represented by reticular bone marrow iron[14,100].

Hahn et al.[95] first put forward a theory about the blocking effect of the mucosal cells, and Granick[96] showed that iron orally administered blocks the absorption of a subsequent oral dose of iron. It was later shown by Brown et al.[97] that this block was not complete; by using large doses of inorganic iron it could easily be overcome. The administration of large amounts of inorganic iron causes passive diffusion of iron across mucosal cells.

Conrad and Crosby[98] have shown that in mice there is a relationship between the amount of iron absorbed and the content of iron in the duodenal mucosa. In man it has been more difficult to confirm this relationship. Allgood and Brown[99] studied the correlation between the iron concentration in human duodenal biopsies and iron absorption, but failed to find any. It is possible, however, that their mucosal material was too small to be representative.

Indirectly, it has been possible to show that the iron content of mucosa probably plays a major role in the regulation of iron absorption[57]. The absorption of a test dose of radioiron is thus inhibited by 4 weeks of treatment with oral iron (Table 5). This inhibitory effect is transitory; as early as 5 days after the end of treatment the iron absorption is high again, a fact that fits well with the known survival time of the intestinal mucosal cells. Thus, the oral iron treatment itself, by loading the mucosal cells with iron, seems to inhibit the capacity to absorb iron.

It has therefore been pointed out[76] that during oral treatment of iron deficiency the highest absorption values are found during the first 10 days, and it has been suggested that very high oral doses of iron be given during the first two weeks. However, the high incidence of side effects after extreme doses of ferrous iron limits the practicality of this advice.

In a clinical trial to prevent iron deficiency in blood donors, various doses of iron were orally administered daily and iron status of peripheral blood, stainable iron in bone marrow and iron absorption were studied at regular intervals (Table 1). It was shown that not even as high a dose as 100 mg of ferrous iron daily was able to prevent the development of signs of iron deficiency, such as diminished storage iron and increased absorption. It could be calculated that probably only 5 % of the administered dose was absorbed.

Years of clinical experience have shown that iron deficiency anaemia can almost always be efficiently treated with oral iron. However, iron stores are difficult to fill and so-called latent iron deficiency[49] remains frequent.

5. ABSORPTION OF FORTIFICATION IRON

Fortification of staple foods, especially cereal products, has been the traditional method to assure adequate iron intake. In Belgium, Canada, Switzerland and Sweden this fortification is voluntary, and in Denmark, Chile, Great Britain, Newfoundland and 27 of the states of the USA it is compulsory. In other countries, on the other hand, fortification is prohibited (France, Federal Republic of Germany, Italy, Luxembourg and the Netherlands)[101]. In Sweden, unenriched white flour contains about 1 mg iron/100 g, wholemeal flour contains 3 mg/100 g, and fortification amounts to 5.5 mg/100 g. The resulting concentration in bread is 4.5 mg/100 g. In other countries, fortification levels vary between 1.5 and 3.8 mg/100 g. Iron fortification is recommended by the World Health Organization. However, as has been pointed out in the literature, it has not been demonstrated that iron in the forms presently used for fortification is satisfactorily absorbed.

The absorption of the fortification iron from bread depends on the form of iron, on the kind of bread, and on the food eaten with the bread. In general, white bread alone does not inhibit iron absorption, whereas whole meal flour does (Table 11). One reason may be that white bread contains only about 29 mg phytic acid phosphorus per 100 g as compared to 71 mg in whole meal bread[64].

Metallic iron is a common form of fortification. Its absorption depends on its grain size and its age. Very coarse-grain iron is absorbed to about 1 %. Medium-grain iron is absorbed to about 3 % from white bread by blood donors, fine-grain iron to about 9 %; more may be absorbed of very fine-grain iron[103]. Similarly, powdered iron is less well absorbed than electrolytically precipitated reduced iron[104]. The older or the more oxidized the metallic iron, the lower its absorption. Reports on the final results of this form of iron fortification vary. In Norway, no significant increases in the serum iron and haemoglobin concentrations were found in women using bread fortified with metallic iron. More iron is absorbed when white bread is fortified with ferrous salts[101,102]. However, it has not been demonstrated that the absorption even of ferrous salts is satisfactory in the presence of absorption inhibitors, as for instance wholemeal bread or eggs[79,112].

It is possible that a search should be made for iron forms more suitable for fortification and less vulnerable to the absorption inhibitors found in bread and other foods. Alternatively, one may consider removing absorption inhibitors by purifying foodstuffs[108], or adding absorption promoters[109].

6. THERAPEUTIC AND PROPHYLACTIC RELEVANCE OF IRON ABSORPTION STUDIES

Only very rarely do clinical situations occur where the iron loss is larger over a prolonged period of time than the iron intake. Recommended dietary allowances of iron are up to 18 mg/day. If this were absorbed, it would correspond to a hypothetical average daily loss of 36 ml blood. Therapeutically, even a modest dose amounts to 60 mg of iron daily. If this were absorbed, it would make up for a blood loss of about 120 ml per day. It is obvious that iron absorption, rather than intake, is one of the bottle-necks, and absorption studies are thus clearly relevant.

Of medicamental iron about 4 mg are absorbed per 20 mg dose by iron-deficient patients in the laboratory situation (Table 12). In the therapeutic situation less than 2 mg are absorbed per 20 mg dose, or less than 6 mg per day. Therefore about 1 year would be needed to refill the iron stores if 60 mg of ordinary therapeutic iron tablets without ascorbic acid were administered per day with meals to a patient having iron deficiency anaemia with about 10 g of haemoglobin/100 ml blood, i.e. having a deficiency of about 2 g iron. In the case of persons donating blood every 2-3 months, Heinrich[105] was able to normalize in 127-144 days the haemoglobin values and iron stores (as reflected by iron absorption) by giving daily on a fasting stomach 100 mg of a quick-release iron preparation with 222 mg ascorbic acid.

A normal Swedish diet contains about 2 mg of haemoglobin iron per day, 0.4 mg of which is absorbed. The absorption is inhibited neither by other food constituents nor by previous iron medication (Table 13). The degree of absorption of the 10-15 mg non-haemin iron in the rest of the diet depends on the composition of the diet. It is not quite clear how much is absorbed on an average; probably only another 0.6 mg. The physiology of iron absorption thus explains why it is difficult to refill depleted iron stores in a limited period of time with orally administered iron, and emphasizes the importance of prophylaxis.

7. SUMMARY

Methods to measure iron absorption have been reviewed. The methods based upon measuring chemical balance, rise in serum iron, or faecal excretion of administered radioiron are not simple and reliable. A therapeutic test has been outlined, which may be advantageous in some situations. Double-tracer methods are often used, both with serum and with erythrocyte measurements of absorbed iron. Where whole-body counters are available, one must choose between single-dose

absorption measurements, sequential absorption studies, double-isotope whole-body counting or the prolonged administration test.

In studies of iron absorption it is recommended that the distinction be recognized between the nutritional, the laboratory, and the therapeutic situations; they differ in regard to the form of iron, the size of the dose and the time of administration.

Of the iron in the food, the haemoglobin iron is usually absorbed more efficiently than the non-haemin iron. Approximately 20 per cent of the haemoglobin iron is absorbed. The absorption of non-haemin iron is very variable; both absorption-promoting and absorption-inhibiting chelators occur in the food. The average absorption of non-haemin iron in food may be under 5 per cent.

Under laboratory conditions (fasting, single dose) typically 4 mg are absorbed from a 20 mg therapeutic dose of ferrous sulphate. Under clinical conditions (with meals, continuous therapy) absorption is less than 2 mg from a similar dose, so that a year is required to refill iron stores of a patient with iron deficiency anaemia and 10 g of haemoglobin per 100 ml blood who takes 60 mg iron as ferrous sulphate daily. If haemoglobin iron were used therapeutically in a similar dose, the time of treatment could perhaps be reduced to about 4 months.

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TABLE 1. MEAN AMOUNT OF STAINABLE BONE-MARROW IRON IN BLOOD DONORS, DONATING 420 ml OF BLOOD EACH SECOND MONTH WITH CONTINUOUS DAILY SUPPLY OF EITHER 20 OR 100 mg ORAL IRON (see text)

Number of cases	Daily iron medication (mg)	Mean amount of stainable bone-marrow iron, histochemical grades		
		Initially	After 4 donations	After 6 donations
7	20	3.8	1.6	1.6
10	100	3.4	2.4	2.4
12	0 (controls)	3.2	(3.4)[a]	(3.3)[a]

a) Controls donated no blood, but bone marrow was sampled at same time as that of donors.

TABLE 2. TYPICAL RADIATION DOSES (MILLIRAD) FROM A DOUBLE-TRACER TEST AFTER ORAL ADMINISTRATION OF 0.5 µCi ^{59}Fe and 70 µCi ^{55}Fe[a]

Isotope	Whole-body	G.I. tract	Critical organ	Ref.
^{55}Fe	21 - 42	52.5	280 - 350 (blood)	7, 117, 118
^{59}Fe	0.25 - 1.8	17	7 (spleen)	7, 29, 118
^{55}Fe and ^{59}Fe	21.25 - 43.8	69.5	300 - 370 (blood)	

a) Based on sensitivity of simplest liquid scintillation counting technique[42]. Use of more elaborate technique permits administration of as little as 3 - 5 µCi ^{55}Fe[107], with proportionate decrease in associated dose.

TABLE 3. PERCENTAGE OF TOTAL ADMINISTERED DOSE OF IRON ABSORBED IN PROLONGED ADMINISTRATION TEST AS COMPARED TO ISOLATED ADMINISTRATIONS. THE TABLE SHOWS THAT MORE IS ABSORBED WHEN 60 mg IS GIVEN AS 30 TABLETS OF 2 mg EACH THAN WHEN IT IS GIVEN AS 3 TABLETS of 20 mg EACH AT LONGER INTERVALS[73].

	3 tablets 20 mg Fe^{++} each, 1 tablet every 5th day (9 blood-donors)	30 tablets 2 mg Fe^{++} each, 1 tablet twice daily (10 blood donors)
Mean retention ± S.E.	7.8 ± 1.1	19.5 ± 3.7
Significance of difference between groups	$0.02 > p > 0.0$	

TABLE 4. ABSORPTION OF FERROUS SULFATE OR HAEMOGLOBIN IRON, UNACCOMPANIED OR ACCOMPANIED BY FOOD

Administered dose of iron (mg)	Ref.	No. of cases	Percentage absorption (mean ± S.E.)			
			$FeSO_4$	$FeSO_4$ plus food	Haemoglobin	Haemoglobin plus food
20	80	9	20.5 ± 3.3	11.0 ± 2.4	18.7 ± 4.4	17.0 ± 2.4
3.8 - 5	50	3	2.9 ± 0.6	0.9 ± 0.3	15.5 ± 2.7	15.8 ± 0.8
50	74	8	6.5 ± 1.1	1.8 ± 0.6	-	-
50[a)]	74	8	6.6 ± 1.6	2.9 ± 1.5	-	-
5	58	5	-	-	21.3 ± 3.5	23.1 ± 3.8
2	41	6-9	-	-	17.5 ± 1.2	17.1 ± 1.9
0.25	77	6	18.3 ± 1.9	1.7 ± 0.2	-	-

a) Sustained release

TABLE 5. EFFECT OF PROLONGED TREATMENT ON IRON ABSORPTION: ABSORPTION OF HAEMOGLOBIN IRON AND $FeSO_4$ AFTER TREATMENT FOR FOUR WEEKS WITH Fe-FUMARATE (30 mg Fe/day)

Administered iron	Ref.	Number of subjects	Absorbed iron (mean ± S.E.)	
			Before treatment (mg)	After treatment (mg)
3.45 mg as Hb	80	7	0.62 ± 0.15	0.48 ± 0.08
0.25 mg as $FeSO_4$	57	15	0.17 ± 0.01	0.07 ± 0.02

TABLE 6. EFFECT OF IRON DEFICIENCY ON THE ABSORPTION OF FERROUS AND HAEMOGLOBIN IRON

Type of iron	Ref.	Administered Fe (mg)	Percent absorption (mean ± S.E.)	
			Iron deficient	Non-iron-deficient
$FeSO_4$	59	0.56	81.1 ± 3.9	23.3 ± 1.4
$FeSO_4$	80	20	20.5 ± 3.3	
Haemoglobin	59	0.56	30.2 ± 3.0	20.1 ± 1.5
Haemoglobin	80	20	18.7 ± 4.4	
Muscle Iron	59	0.56	23.5 ± 2.8	12.3 ± 1.4
Liver Iron	59	0.56	25.7 ± 1.8	13.2 ± 1.3
Haemoglobin	58	5	15.9 ± 2.9	4.3 ± 0.4

TABLE 7. SOURCES OF IRON INTAKE IN SWEDEN (approximate figures in mg iron)

Total iron-intake	15
Vegetables	5
Meat and fish	
haemin-iron	2
non-haemin-iron	2
Fortification iron[a]	4.5
Medicamental-iron	1.5

a) Assuming an average bread-consumption of 100 g per person each day

TABLE 8. CONDITIONS OF IRON ABSORPTION

Situation	Form of iron	Dose, order of magnitude (mg)	Administration	State of stomach
Therapeutic	Fe^{++}	100	Continuous	Full
Laboratory	Fe^{++}	1	Single	Empty
Nutritional	Complex	1	Continuous	Full

TABLE 9. RANGE OF IRON ABSORPTION FROM THERAPEUTIC AND TRACER DOSES BY HEALTHY MALE VOLUNTEERS WITHOUT IRON DEFICIENCY

Conditions of administration	Administered iron (mg)	Absorbed iron (mg)	Ref.
Single dose fasting	0.3 - 50	0.1 - 4.2	58,64, 74,80,94
	120	16[a]	75
Single dose with food	0.6 - 50	0.1 - 1.5	34,74,76

a) Faecal excretion method

TABLE 10. EFFECT OF FOOD COMPONENTS (PORRIDGE, PHYTIC ACID, ASCORBIC ACID) ON IRON ABSORPTION

Author	Dose	Number of subjects	Fe absorption fasting (%)	Food component	Fe absorption with food component (%)	Effect of food component
Hallberg and Sölvell[58]	5 mg $FeSO_4$	5 blood donors	54.6	phytic acid	18.3	67% decrease
Hallberg and Sölvell[58]	5 mg $FeSO_4$	5 controls	4.0	200 mg ascorbic acid	4.9	22% increase
Ehn et al.[80]	20 mg $FeSO_4$	9 blood donors	20.5	porridge	11.0	47% decrease
Höglund and Reizenstein[64]	10 mg FeFum.	9 young women	9.8	200 mg ascorbic acid	28.3	190% increase

TABLE 11. ABSORPTION OF FORTIFICATION IRON IN BREAD

Author	Form of iron	Amount of iron in bread or test meal (mg)	Absorption (%)	Material eaten
Elwood et al.[101]	coarse grain reduced iron	0.3	1	bread[a]
Höglund and Reizenstein[64]	medium grain reduced iron	approx. 1.0	1.6	outmeal
Höglund and Reizenstein[102]	coarse grain reduced iron	approx. 1.0	3	bread[a]
Callender and Warner[116]	reduced iron grain size not stated	approx. 1.0	5.5[c]	white bread[b]
Höglund and Reizenstein[102]	$FeSO_4$	1.0	20	bread[a]
Callender and Warner[115]	$FeSO_4$	approx. 1.0[d]	approx. 9	brown bread[e]
Callender and Warner[116]	Ferric ammonium citrate	approx. 1.0	6[c]	white bread
Höglund and Reizenstein[102]	fine grain reduced iron	1.0	9	bread[a]
Ehn et al.[80]	haemoglobin	20.0	19	oatmeal

a) white bread from sifted flour

b) with butter, jam and tea

c) mean calculated by present authors based on investigators' partially iron-deficient subjects with normal gastric secretion

d) loaf with 8 mg iron eaten over 3 - 5 days, corresponding presumably to approx. 1 mg per meal

e) 20% bran and 80% white flour, presumably with food

TABLE 12. IRON ABSORPTION FROM FERROUS IRON IN MALE PATIENTS WITH IRON DEFICIENCY AND IN WOMEN

Conditions of administration	Administered iron (mg)	Absorbed iron (mg)	Ref.
Single dose fasting	0.3 - 20	0.2 - 4	79,80
	50[a]	8	94
Multiple and single dose fasting	50	6[b]	113
Single dose with food	20	2	80
	23	3.2[c]	20
	8[d]	3.7	78

a) with ascorbic acid

b) values in accordance with earlier data from same author[114]

c) faecal excretion method

d) tracer dose of $^{59}FeCl_3$ given with a meal containing 8 mg Fe

TABLE 13. IRON ABSORPTION FROM HAEMOGLOBIN AND HAEMIN IRON IN MALE VOLUNTEER BLOOD DONORS

Conditions of administration	Administered iron (mg)	Absorbed iron (mg)	Ref.
Single dose fasting[a]	3.5 - 20	0.6 - 4	58,80
Single dose with food[a]	5 - 20	1.1 - 3.4	58.80
Single dose fasting[b]	20	0.2	80

a) haemoglobin

b) haemin

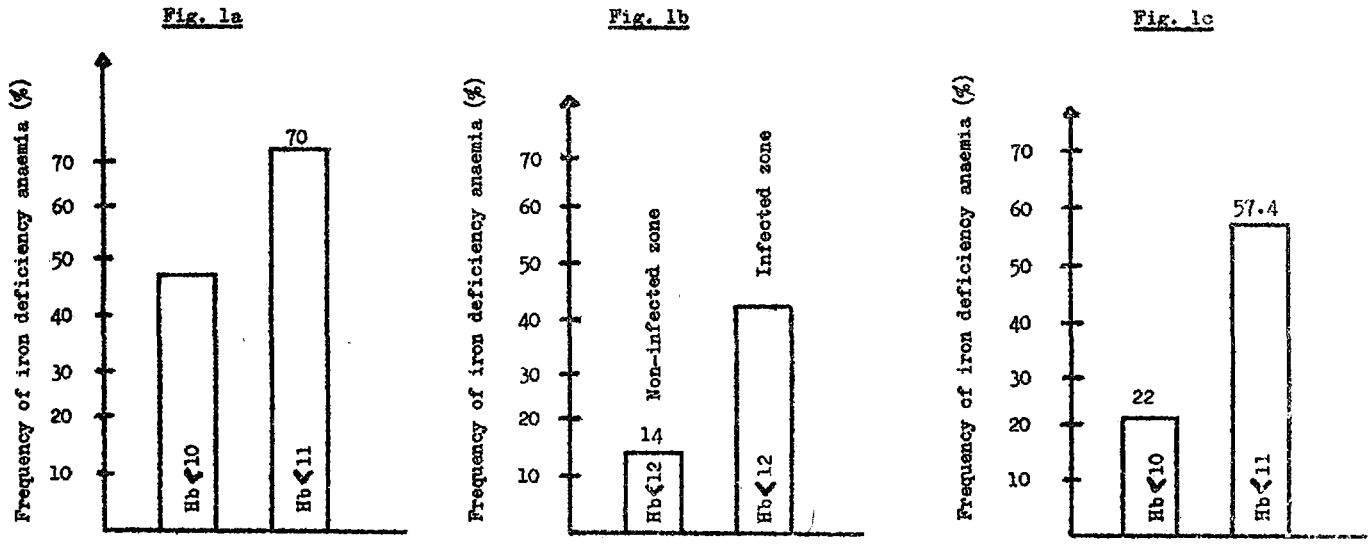

Fig. 1 Legend: Frequency of iron deficiency anaemia (as quoted in ref. 13)

Fig. 1a in pregnant women of rural population, Israel, as judged by two different criteria (haemoglobin g/100 ml blood);
Fig. 1b in general population in Venezuela in areas not infected and infected with hookworm;
Fig. 1c in pregnant women of urban population, India, as judged by two different criteria (haemoglobin g/100 ml blood).

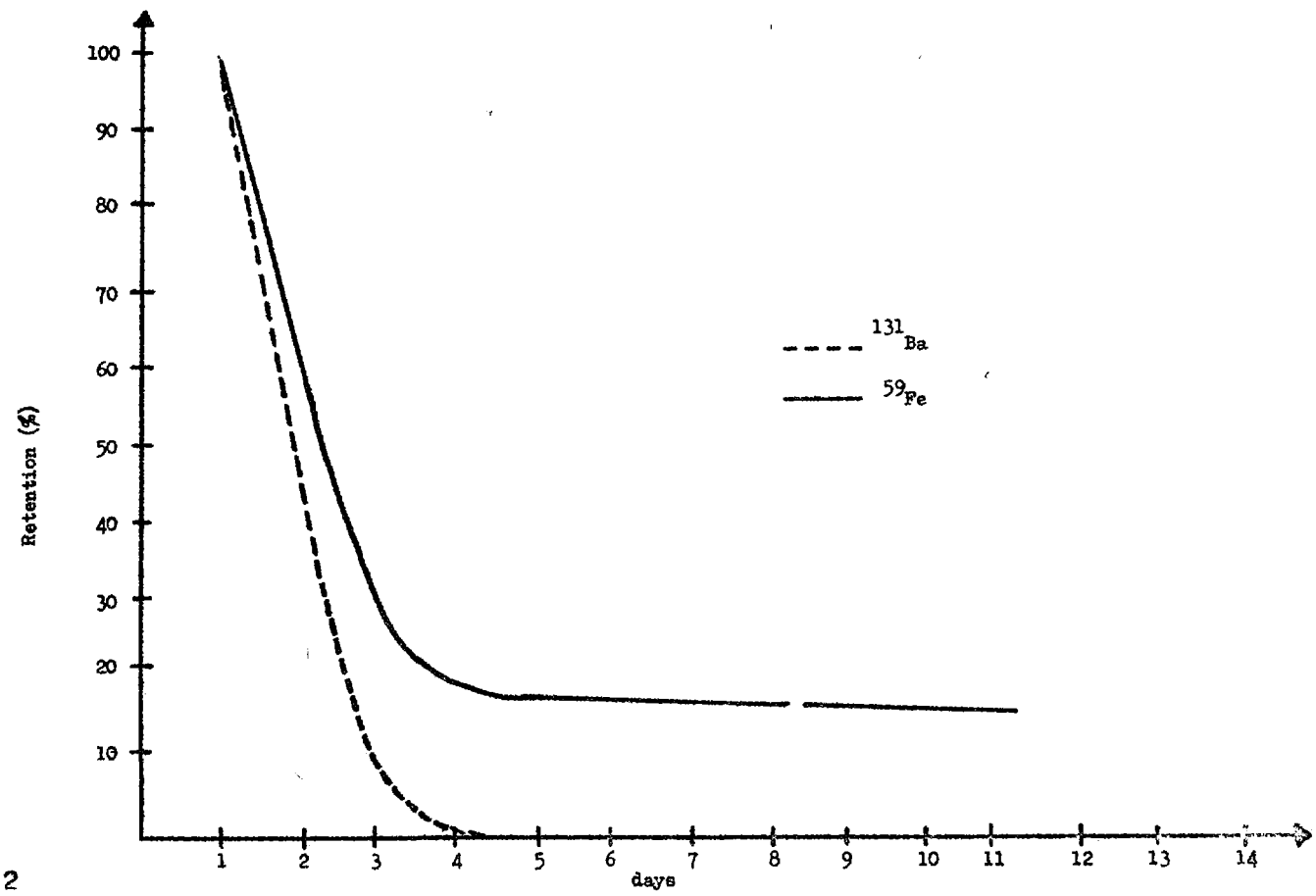

Fig. 2

Legend: Percentage of oral dose of ^{131}Ba and ^{59}Fe retained in body vs. time after administration