IAEA/WHO Programme on Iron Nutrition

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At an international symposium on iron deficiency in 1969, one of the foremost investigators in this field, the late Dr. Carl V. Moore, was called upon for a concluding statement. He summarized what the audience had been told in the words of the little rhyme:

Something old, something new,
Something borrowed, something blue.

He ended with "something blue": "It is depressing to realize that even though we can recognize and effectively treat iron deficiency, we really do not know how to prevent it on a country-wide or world-wide basis. It is a public health problem of great magnitude, yet to do what needs to be done, in an effective programme of prevention, to improve diets and to control factors like intestinal parasitism which increase blood loss, seems almost hopeless. Government or other research-supporting agencies seem much more interested in programmes with more dramatic and shorter-term objectives, and are reluctant to provide the financial help needed..... Any acceptable solution will surely need to be provided by a large co-operative effort, less exciting intellectually than is a study of the remaining problems in unravelling the intricate details of iron metabolism, but an effort which demands at least an equal portion of our total energies."[1]

For many years, both the World Health Organization and the International Atomic Energy Agency have sponsored research related to the subject of iron deficiency in humans. About four years ago their collective efforts were brought into focus in a co-ordinated research programme on iron nutrition. This may not yet be the "large co-operative effort" which Dr. Moore envisioned, but it has the same objectives. Through modest financial assistance, the central supply of certain essential materials, and the effective exchange of information among collaborating scientists, the programme attempts to understand the state of iron nutrition in several societies and to identify means by which it can be improved. For two reasons, the emphasis of this co-ordinated programme is on iron nutrition in the developing countries. First, nutrition in general and iron nutrition in particular are more often marginal in these countries than in the developed countries, and second, the developing countries have fewer resources of their own to devote to this problem.

The typical adult male contains in his body a total of about 4 grammes of iron. About 3 grammes are in the blood haemoglobin, while most of the remainder is either dispersed throughout the cells of the body as a component of various enzymes or is stored in reserve in the liver and bone marrow. Iron has many functions in the body, most of them related to supplying the body's energy needs. The immediate energy requirements of most living cells are met by the oxidation of organic substances by molecular oxygen, and this oxygen is transported from the lungs to the cells by the haemoglobin of the red blood cells. Beyond this, iron-containing enzymes in the cells catalyze the oxidation reactions. Numerous other iron-containing compounds participate in the transport and storage of iron in the body.

The body must absorb iron from the diet sufficient to meet its losses and to provide for growth. In health the losses are strikingly small. For example, a normal adult male may typically lose only about 0.8 milligrammes of iron (about 1/5000 of the total in his body) per day, mostly in cells shed from the lining of his intestines. Most additional losses occur through bleeding, either normal as in menstruating women or abnormal as for example in hookworm infestation. In a pregnant woman the transfer of iron to the foetus is a particularly important route of iron loss from her body, and to compensate she must absorb about four times as much iron from her diet as does an adult male. Children may have as high a demand for iron as an adult male to provide for growth.

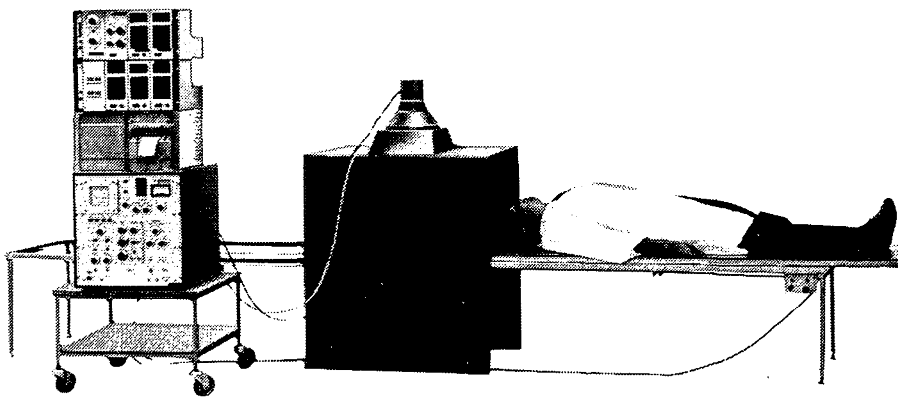
When the body's absorption of iron from the diet becomes inadequate, the stored reserves, if any, are first utilized and then the haemoglobin concentration of the blood begins to fall. The subject becomes anaemic. Many symptoms accompany severe anaemia, such as damage in numerous tissues, complications in pregnancy, and muscular weakness or fatigue. There is considerable uncertainty as to the consequences of milder anaemia. Without doubt, however, it reduces the body's capacity to cope with abnormal stress, such as bleeding, pregnancy, or even exertion.

Estimates have been made that as much as 10 - 30% of the world's population is iron deficient. Although many of these may be only marginally so, it is generally accepted that iron deficiency is a major public health problem.

Whether iron deficiency is caused primarily by inadequate amounts of absorbable iron in the diet, as is considered to be most frequently the case, or whether demand is elevated through, for example, parasitic infestation, improved iron nutrition should help to alleviate the condition. Where a limited and defined group is at risk, as with pregnant women, this may be effectively achieved in some societies by medication. However, where large segments of the population are involved, public health authorities are pessimistic about the feasibility of medication, and hope to find means to achieve the same end by improving the diet. In theory, at least, the diet could be modified to include more foodstuffs rich in iron, or to include iron supplements, or to exclude substances that restrict iron absorption, or to include substances that promote iron absorption. It may be expected that the effectiveness of these alternative procedures will vary according to the diet and social customs of the population in question. It is therefore necessary to study these individual issues in representative populations, and to take remedial action only when the circumstances are understood.

It is already possible to estimate with reasonable accuracy from tables of nutritional data the amount of iron in diets of specified composition. However, until recently very little has been known about the absorbability of that iron. Therefore **a primary theme of the IAEA/WHO co-ordinated research programme has been the study of iron absorption, either from native diets, or from diets supplemented with iron salts or with substances believed to promote absorption of the iron in the diet.**

Prior to the availability of isotopic tracers, iron absorption could be studied only with great difficulty and poor accuracy by chemical balance measurements. That is, the difference between iron consumed in the diet and iron excreted, both chemically assayed, would reflect, under suitable experimental conditions, the iron absorbed. Today, absorption studies are made almost exclusively with isotopic tracers because of the much greater convenience and accuracy which they afford. Both stable and radioactive tracers



Simple whole-body counter
provided in IAEA research contracts for measurement
of ^{59}Fe absorption.

are available; however, to date the latter have been by far the more extensively used because the associated techniques are simpler and more widely available than those required for stable tracers.

Two radioisotopes of iron are well suited to investigations of intestinal absorption, namely ^{55}Fe and ^{59}Fe. ^{55}Fe has a half life of 2.6 years, and emits only low-energy X-rays. ^{59}Fe, on the other hand, has a half life of 45 days, and emits both β-rays and energetic γ-rays. After a sample, for example a few ml of blood, has been processed by appropriate chemical techniques and introduced into a suitable detector, today usually a liquid scintillation counter, both radioisotopes can be individually assayed with high sensitivity even in the presence of each other. In addition, ^{59}Fe can be assayed with good accuracy by γ-ray counting even when the "sample" is as large and inconvenient as the living human body.

In a typical investigation of absorption, the radioactive test substance is administered orally, and after a period of about 2 weeks, which allows time for the absorbed tracer to be incorporated into blood cells and the unabsorbed tracer to be excreted from the body, the determination of percentage absorption can be made. One method is to assay the activity in a blood sample, and to calculate from an estimate of total blood volume the approximate activity in the entire body. A second method, suitable in the case of ^{59}Fe, is to measure the radioactivity of the whole body in a "whole-body counter". Many techniques have been explored for whole-body counting, and today measurements on ^{59}Fe in the body can be made accurate to within a few % with good sensitivity using comparatively simple equipment. In its research contract programme the Agency has supplied whole-body counters as illustrated to several participating laboratories.

Even when reliable methods for assaying iron radioisotopes have been established, there remain important problems in the meaningful use of these radioisotopes as tracers for iron in the diet. The radioisotope must appear in the diet in appropriate form, ideally as a label of the native iron in the foodstuff of interest. Otherwise, there may be doubt that the tracer and the food iron are treated by the body in the same way because their chemical form upon ingestion may be quite different. As a central contribution to this co-ordinated programme the Agency has contracted for the production of several vegetable foodstuffs, including soy beans, maize, wheat, rice, and certain other grains, whose native iron is thus labelled with ^{55}Fe. This production has been accomplished at an American university where these plants have been grown in nutrient solutions to which ^{55}Fe has been added at an appropriate stage of growth. By this means labelled vegetable foodstuffs have been made available to many laboratories around the world in sufficient quantity for a total of many hundreds of absorption studies.

Animal foodstuffs (meat, eggs) with labelled native iron have also been required in the programme, but these can be fairly easily prepared in individual laboratories by intravenous administration of the radioisotope at a suitable time prior to collection of the products.

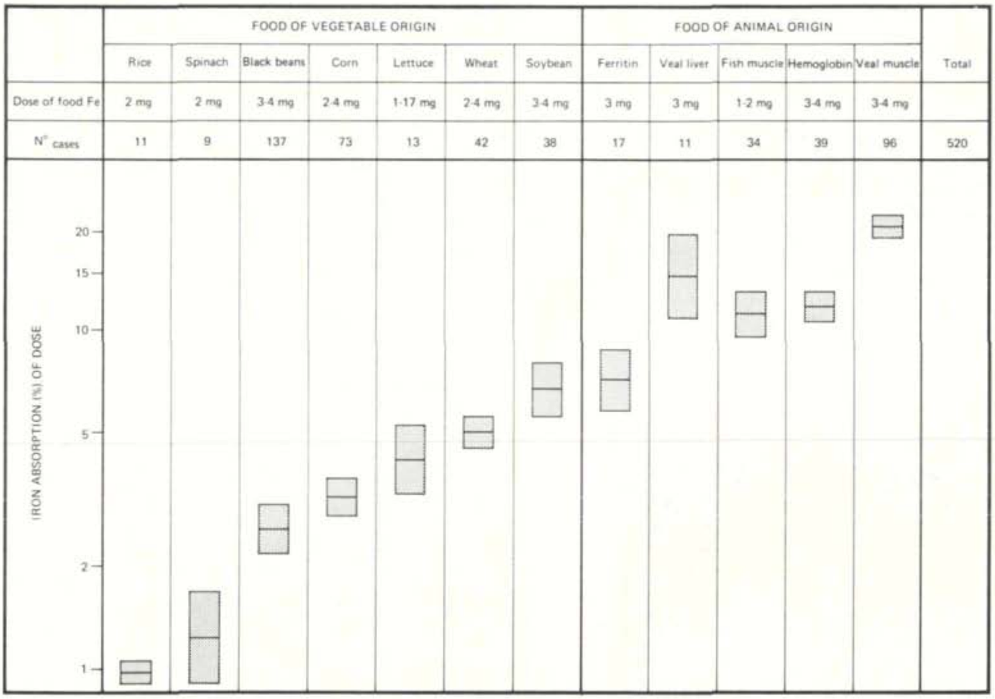
Additional difficulties confront the investigator, notably those associated with the wide variability observed in iron absorption from person to person or even from day to day in the same person. Good experimental design allows for the comparison of two different substances, ideally administered simultaneously using ^{55}Fe as the label for one item and ^{59}Fe as the label for the other. In addition, extensive replication of investigations is desirable. This whole methodology has been extensively discussed at meetings of investigators in this programme in the hope of achieving comparable and reliable results in all of the various laboratories.

Some or all of these methods have been introduced, under the sponsorship of the co-ordinated programme, in laboratories in the following countries: Bangladesh, India, Jamaica, Lebanon, Mexico, South Africa, Sweden, Thailand, the United States of America, and Venezuela. The co-ordinated programme has no sharp periphery, so that a two-way stimulation of ideas among laboratories both formally within and outside the co-ordinated programme takes place.

One of the most important results so far achieved deals with tracer methodology. This concerns the problem of determining iron absorption from a mixed diet, which is after all the most commonly consumed. It is not possible to label each foodstuff in a mixed diet with a different radioisotope of iron, since the components of a meal are too numerous. Also, it is extremely tedious to administer the same meal many times in sequence with a different single component labelled each time. However, a short-cut may be taken within an accuracy acceptable to a screening programme. It has been shown that all the iron in the components of a meal can be considered, to a reasonable approximation, to fall within one or the other of two pools,

Hydroponic growth of maize plants in nutrient solutions containing iron radioisotopes yield edible maize whose native iron is labelled with a tracer, for absorption studies. ▶

namely the pool of inorganic iron and the pool of haem iron. The haem of haemoglobin is the most prominent example of the latter pool. The iron of all the components within a single pool is absorbed approximately in the same percentage. Within this approximation, it is therefore necessary to introduce only two tracers into the meal, namely one radioisotope of iron in inorganic form and the other radioisotope in a haem compound. Indeed, these tracers need not be native to the foodstuff, but may be added extrinsically just before the meal is prepared and consumed. For the first time now a method of reasonable accuracy is available to allow iron absorption from entire meals to be studied, thereby permitting extensive investigation of the influence of many components of the diet upon the availability of dietary iron for human absorption.



Iron absorption from individual foodstuffs of vegetable and animal origin. The horizontal thick line shows the geometrical mean, and the cross-hatched area shows the limits of one standard error.[2]

Many individual foodstuffs have now been studied with respect to the availability of their iron for absorption. An example of the available data is shown (above). Here it is apparent that, when administered individually, foodstuffs show a wide range in the availability of their iron for absorption. Furthermore, it is clear that food of animal origin contains iron (namely that in the haem pool) which is typically much more readily absorbed than that of vegetable foods.

Further data show, in conformity with the two-pool concept, that when two or more individual foodstuffs are consumed together in a meal the availability of the total iron is intermediate between that of the individual components when administered separately. Also, it has been shown that certain amino acids found in meat enhance the absorption of inorganic iron contained in vegetable foodstuffs.

Now that a picture of iron availability in various meals is beginning to emerge, it is reasonable to consider what may be done to improve iron nutrition. Indeed, corrective action was initiated in several countries many years ago, but it is now known that at least some of these programmes were futile due to inadequate understanding of iron absorption. It must be recognized at the outset that remedial action must be inexpensive. For that large fraction of the world's population whose per capita income is less than US $ 1 per day, it is unreasonable that iron nutrition should claim as much as 1 cent per capita per day.

One obvious means of improving iron nutrition is by altering the diet. However, this is an impractical suggestion in the case of many societies. Until now public health measures have focussed entirely upon the addition of iron supplements to the diet. In several developed countries the favoured vehicle for supplementation has been flour, and numerous investigations are under way to determine the effectiveness of this measure in improving iron nutrition. However, in most developing countries the suitability of flour or similar products as a vehicle is very doubtful, as they are prepared in too many mills (indeed in individual homes) to permit central control of the supplementation programme. In one investigation associated with the co-ordinated programme, evidence shows that in Thailand a practical and effective means of introducing iron into the diet may be to add the iron supplement to a fish sauce that is widely used in rather standard quantities as a condiment. Common salt is a favourite target of those who wish to supplement diets, as it is often produced in a comparatively small number of establishments. Tests have already been made in India under the co-ordinated programme on the addition of various iron compounds to salt, but as yet a favourable procedure has not been found.

A different approach is to supplement the diet not only with iron, but also with some substance which increases the absorbability of dietary iron. It is known, for example, that vitamin C has such properties, and investigation of its possible effectiveness is under way in South Africa and other countries.

Much work remains for the future. It may be necessary in each culture to determine by laboratory tests what means are technically feasible for increasing iron absorption in the population, and, by further studies, which of these are acceptable on economic and social grounds. Finally, there is the large question of safety. Any public health authority organizing remedial measures in iron nutrition must assure itself in advance that no segment of the society is endangered by the programme, a possibility that would exist if a supplement were consumed in unexpectedly large quantities by certain individuals. It is hoped that the IAEA/WHO co-ordinated research programme on iron nutrition will continue to contribute usefully to the solution of these problems.

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