Absorption and Storage of Iron

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The myriad of facts about metabolism acquired by a variety of techniques still leave unexplained such tantalizing problems as those of iron absorption and iron storage. The present discussion is confined to a survey of some work of the last 10 years. Fortunately a critical survey by McCance & Widdowson (1937) of the studies of iron metabolism in the 19th Century and early 20th Century proposed that the intestine
exercised a control over absorption. These authors considered that ‘absorption of iron is conditioned mainly by the relative concentrations of ionized iron in the intestine and its epithelial cells’. A low plasma iron concentration, maintained by the storage of iron in tissues, was deemed to be sufficient to prevent any reverse diffusion from cells into the intestinal lumen. This view has greatly influenced many present investigations. It raised two interrelated problems: the mechanism whereby the intestine controls absorption of iron and the means whereby it senses the state of iron metabolism within an organism.

Whatever theory is proposed for iron absorption, it needs to meet certain facts acceptable with certainty. Normally, and unless exposed to abnormal amounts of dietary iron, an organism conserves, almost completely, its few grams of iron in a fairly steady amount (Dubach et al., 1946). Like other transitional elements, iron is not excreted by the kidney, except in unusual circumstances. The bulk of faecal iron comes mostly from foodstuffs and is roughly proportional to iron intake. So tenaciously does the human body retain iron that little except 1–2mg/day is lost by the skin, sweating and mucosal debris (Moore, 1959–60). Such minute losses may mistakenly be written off as physiologically insignificant. They are close to the daily requirement of man of 0.5–2.5mg, and in some circumstances may easily tilt a positive balance to a negative one. Many measurements indicate that about 10% of dietary iron is daily absorbed by man and the few animals so far studied. In contrast, in uncomplicated clinical or experimental iron deficiency, 25% or more of dietary iron may be absorbed. The intestine then adjusts its absorption of iron to satisfy body need, although in abnormal conditions, as in haemochromatosis, its control may be overwhelmed.

From the conflicting evidence it is not obvious that the concentration of plasma iron or of blood haemoglobin affects iron absorption. Storage of iron in the bone marrow, liver and spleen and the rate of erythropoiesis may be more influential. The latter may be the more important. The daily turnover of 8–10g of haemoglobin/day corresponds to one of 20–30mg of iron/day, i.e. several times the absorption of iron by the intestine. Somehow the intestine senses the state of iron metabolism in an organism, but by what system or agent is unexplained. However, there are features of iron deficiency needing closer examination, for example changes in enzyme activity of tissues (Beutler et al., 1960; McCall et al., 1962).

In 1943 Hahn and Whipple and their colleagues proposed the theory of mucosal block to explain intestinal control of iron absorption (Hahn et al., 1943). They fed rather high doses of iron salts, tagged with radio-iron, to dogs made iron-deficient by dietary means or by bleeding, and confirmed that compared with control animals anaemic dogs absorbed a higher percentage of the administered dose. Some of their observations have been forgotten. Feeding of large doses of iron diminished the absorption of radio-iron in test doses. In acute anaemia the absorption of radio-iron was less than in chronic anaemia, since, as was explained, hours were necessary for depletion of iron in the epithelial cells. These findings have influenced many investigations. From them Hahn et al. (1943) postulated the existence in the mucosal cells of an acceptor that could take up iron to a limited extent and pass it into the organism when iron concentrations fell. This acceptor governed the acceptance and refusal of iron by the intestine. It was identified with ferritin by Granick (1946), who elaborated the mucosal block theory.

The mucosal block theory does not cover a number of facts. For instance, it is well established that with increase in the test dose the total amount of iron absorbed increases whereas the percentage of retention falls. In haemochromatosis absorption continues even when mucosal iron content is high. Confusion surrounds the function of ferritin. There is no doubt that, as assayed by an immunological technique, apoferritin or ferritin is found in the mucosa exposed to iron salts (Charlton et al., 1965; Britton & Raval, 1970; Sheehen & Frenkel, 1972; G. E. Newman, J. R. P. O'Brien & G. Patrick, unpublished work). Certainly, in the normal animal, as much as 90% of the absorbed iron appears rapidly as ferritin accompanied by a small amount of non-ferritin iron; in iron-deficient animals the reverse occurs. The presence of ferritin does not stop absorption, nor does that of apoferritin. A surprising feature of experiments on ferritin synthesis in mucosa, often of short duration, is the rapidity of the synthesis compared with that in
the liver (Lotfield & Eigner, 1958). Dubiety about the role of ferritin as a blocking agent has prompted suggestions of the existence of a transport system for iron located in the mucosal membrane, and that this may be subject to the cytoplasmic iron content (Bannerman et al., 1962; Sheehen & Frenkel, 1972).

A feature of the intestinal mucosa that has been emphasized (Bannerman et al., 1962; Crosby, 1963), but often ignored in short-term experiments, is the rapid turnover of its cells. This may be about 3–5 days in animals (Leblond, 1956); some 50–80g of mucosal cells may be daily exfoliated from the intestine tract (Leblond & Stevens, 1948). From the results of an extensive series of experiments Crosby (1963) has proposed an obligatory excretion of iron as ferritin as a consequence of the continuous desquamation of epithelial cells associated with their turnover. In his view ferritin is not a stage in the absorption of iron, but is a means of stopping its absorption. This may be so in normal animals, but his suggestion that in iron-deficient animals this blocking system fails is not in keeping with the finding by Britton & Raval (1970) that apoferritin synthesis in the mucosa of such animals may be elicited by iron salts. Nevertheless it would seem advisable to note in studies on iron absorption that the intestine presents a changing surface of cells, old and new, of possibly differing absorptive capacities. Further, rats in which an uncomplicated iron deficiency was produced by dietary means show a marked hypertrophy of the duodenum and jejunum, which might affect the regeneration of the epithelial cells and their absorption characteristics (J. R. P. O'Brien & G. Patrick, unpublished work).

Naturally enough, iron absorption has been studied by a multitude of techniques in vitro, perfusion of lengths of intestine, blind loops of gut, everted sacs etc. So varied are the techniques, the species and the metabolic state of the experimental animals that the conflicting results are not easily described. As illustrative, some investigations may be mentioned. The existence of an active transport system for iron can be shown by the transport of iron against its electrochemical gradient and in the case of intestinal preparations in vitro by transport across the wall. Several workers (e.g. Brown & Justus, 1958; Rummel et al., 1968) have found that everted sacs of rat intestine did not transport iron against a concentration gradient into the serosal fluid. In many of such experiments the normal potential gradient obtained was mucosal side negative, and therefore transfer of cations into the serosal fluid would be against the potential gradient. The observed kinetics of the transfer of iron pointed to diffusion, and in different ways anaerobiosis or metabolic inhibitors decreased or, even, increased transport. Yet, others with similar experimental techniques (Dowdle et al., 1960; Manis & Schacter, 1962), claim to have shown iron transport by everted sacs of rats intestine against a concentration gradient. The abolition of this process by anaerobiosis or metabolic inhibitors suggests its dependence on oxidative metabolism. There is also the possibility that iron may be transported as a chelate of amino acids or ascorbate (Jacobi et al., 1956). It is difficult to reconcile these contrasting results, which may be a consequence of the retention of iron in the submucosal spaces. We have carried out experiments on the absorption of \(^{59}\)Fe by everted sacs of intestine prepared from rats on an iron-free diet or the same diet supplemented with iron (J. R. P. O'Brien & G. Patrick, unpublished work; Patrick, 1968). Our tentative conclusions are as follows. Iron passes by simple diffusion across the mucosal membrane into the epithelial cells from the intestinal lumen, there being a two-way movement of iron across the luminal membrane. Iron enters a labile pool in the epithelial cells from which some passes into the plasma. Transfer to the plasma may be by diffusion in the iron-replete animal and may be bi-directional; in iron deficiency it may be increased by active transport. Iron not transferred to the plasma is stored temporarily in the epithelial cells and lost to the lumen by cell turnover. None of these conclusions may apply to conditions in vivo, for conditions in an everted sac are far removed from the dynamic changes within the living intestine. They may, however, suggest that intestinal control over iron absorption is a delicate interplay of mucosal and serosal transfer of iron, iron deposition in the mucosal cells and the turnover of these cells. Perhaps studies on the uptake of iron by simpler systems, such as micro-organisms, may provide guiding ideas (C. Ratledge & B. J. Marshall, personal communication).
In man roughly 0.5–1.5g of iron is stored in the cells of the liver, spleen and bone marrow. Most of this iron is as ferritin in one form or another. Knowledge of the exchanges of these stores among themselves and with the plasma iron is meagre. Iron can act as a stimulant to apoferritin and ferritin synthesis, particularly in the liver. More obscure is the way in which iron is lost from the stores into the plasma. Possibly iron of the liver ferritin is released as ferrous iron by the action of xanthine oxidase (Mazur et al., 1958). In any case, the rate of release of iron from its stores is low compared with the rate of erythropoiesis. But, when needs be, iron as ferritin or haemosiderin can be mobilized for haemoglobin synthesis.

Moore, C. V. (1959–60) Harvey Lect. 55, 67–101