How little we know about the absorption of iron\textsuperscript{1–3}

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Unlike most metals, iron is not excreted from the body. Hence, regulation of iron content depends on modification of the rate of absorption from the intestinal tract. In the current issue of this journal, Hallberg et al.\textsuperscript{(1)} present the results of their meticulous double-isotope studies, documenting the relation between serum ferritin concentration and absorption of inorganic iron on the one hand and heme iron on the other. As in earlier studies, it is apparent from their elegant investigations that iron deficiency results in more efficient iron absorption from the gastrointestinal tract and that as body iron stores increase, the amount of iron absorbed tends to decrease to match iron losses from desquamation of cells and blood loss.

It is important for iron uptake to be regulated tightly. Too little iron results in anemia and deficiency of iron enzymes (2); too much iron causes tissue damage—cirrhosis of the liver, cardiomyopathy, diabetes, and arthropathy, presumably through the generation of free radicals by excess, unbound iron (3). The question of how the body manages to achieve proper balance through regulation of iron absorption has been under investigation for more than half a century, but we do not yet understand how iron is absorbed from the gastrointestinal tract and almost nothing has been learned about the regulatory mechanism.

More than 60 y ago in one of the earliest studies using radioiron to measure iron absorption, it was suggested that there was a "mucosal block" that prevented absorption when the intestine had recently been exposed to iron (4). The concept of a mucosal block remained at center stage in the field for many years, and is cited even in very current studies (5). The lack of an experimental basis for this concept is not generally appreciated. Three dogs were given iron. It was observed that when a large dose of iron was followed within 1.3–6 h by a dose of radioiron, less radioactivity appeared in the erythrocytes than the expected absorption in four of five cases. However, it is difficult to know what would have been "expected" because there were no controls. Moreover, one experiment gave the reverse result, but this was rationalized by assuming that there had been uneven contact of the iron with the so-called "blocking" solution because the dog had developed diarrhea. It was only later that it was found that no "block" to intestinal absorption existed. In both humans and mice the administration of progressively larger doses of iron results inevitably in absorption of a larger absolute amount of iron, although the percentage of iron absorbed decreases progressively. What is clear, however, is that at any given dose more iron is absorbed in iron deficiency and less in iron overload than in the normal state. Thus, although there is no mucosal block, mucosal intelligence may be said to exist. Iron absorption is, indeed, regulated to meet the needs of the body. But how does this regulation come about?

It is difficult to believe that we will understand how the absorption of iron is regulated in the intestinal tract before we understand the mechanism by which it is absorbed, and there is a great void in our knowledge of this process. In recent years, Conrad et al.\textsuperscript{(6, 7)} successfully isolated what may be parts of the absorptive pathway, i.e., intestinal mucus, a 56-kD protein designated mobilferrin, an integrin, and a ferrireductase. However, the mechanism of iron absorption will probably not prove to be a single process moving along one pathway. As Hallberg et al point out, there are differences in the absorption of inorganic iron and heme iron. It is entirely possible that the pathways of absorption of these two dietary forms of iron are quite different. As their study shows, both are regulated but the mechanism of regulation may be different. Another major advance in the regulation of iron metabolism has been the recognition of iron-responsive elements in the messenger RNA (mRNA) of proteins such as ferritin and transferrin receptor, proteins that are regulated by the abundance or deficiency of iron. The binding of aconitase, an iron-sulfur protein, to such structures increases protein synthesis by stimulating translation of some messages and in others decreases it by destabilizing the mRNA. Thus, although some knowledge has been gained, today we are still far from understanding the sequence of events that leads to the absorption of iron, and know nothing of how it is regulated.

Insights into complex biological processes are often gained when one of the steps of the process is missing or abnormal, and Nature has provided us with a means of understanding many such processes through mutations that occur in patients. For example, the existence of most of the factors in the coagulation cascade became known through the study of patients with hereditary bleeding disorders. For iron absorption it is possible that we will be able to gain the necessary understand-

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ing through the study of the disorder in which regulation of absorption is aske, ie, hereditary hemochromatosis. It is for this reason that several groups of investigators have attempted to identify the gene responsible for this disorder, known to be linked to the HLA-A locus on chromosome 6 (8). In 1996 Feder et al (9) succeeded in the positional cloning of the gene that causes most cases of hereditary hemochromatosis. To the surprise of most, the deduced product of this gene, designated HLA-H, has the structure of a class I HLA protein. It is by no means obvious how a mutation that appears to affect \( \beta-2 \)-microglobulin binding by HLA-H results in increased iron absorption. Is HLA-H a transport molecule that binds iron and passes it on to another protein? Is it a regulator that measures the iron content of the cell or of its environment and then initiates a cascade of events that affect iron absorption? Is the binding groove that all HLA class I molecules contain functional? If so, does it bind a peptide or some other substance, perhaps one that contains iron such as heme?

No doubt, finding the answers to these questions will take years, but with the finding of the gene that causes hemochromatosis we have, for the first time, a robust, biochemical starting point for studies of iron absorption. We hope that the discovery of HLA-H will lead to identification of members of the iron-transport chain, for such a chain must surely exist. Only then will we be able to understand the control of iron absorption and the mechanisms underlying the phenomena described by Hallberg et al in this issue.

**REFERENCES**