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The ironies of iron[1,2]

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The many unusual aspects of iron metabolism have fascinated scientists for decades. First, iron is abundant, yet insufficient. Although iron is one of the most plentiful minerals in the earth's crust, iron deficiency is one of the most common nutritional problems in both the developing and the developed worlds. Second, iron is cheap, yet costly. It is an inexpensive metal but is a critical component of one of the world's most costly liquids—blood (1). Third, need tends to be the inverse of intake. The physiologic demand for iron is markedly lower in men than in growing children and in women during their reproductive years, yet iron intake is considerably higher in men than in children or premenopausal women. Fourth, the amount of iron consumed is many times greater than the amount absorbed. Although the diet usually contains ≈25–29 μg Fe/kJ (6–7 μg/kcal), only a small portion of dietary iron is absorbed. Fifth, excess iron is deleterious, yet excretion is severely limited. Iron is not readily excreted through the body's usual excretory routes of urine, bile, and sweat; rather, the primary way in which iron is lost is through shedding of cells from the skin or gastrointestinal tract or through blood loss, as in menstrual blood loss or chronic or acute hemorrhage.

Absorption and excretion of iron are regulated tightly by the body. Absorption appears to be the prime factor controlling the amount of iron in the body. The question then is, How is iron absorption controlled? Hunt and Roughead (2) address this query in their interesting report on iron absorption, fecal ferritin excretion, and blood indexes of iron status. Their work provides further support for the hypothesis that iron absorption is regulated by the mucosal cells in the upper small intestine (3). Intestinal cells are programmed to contain ferritin in larger amounts when iron stores are high and in lower amounts when stores are low. The cells are formed in the crypts of the villi and move to the villi tip, where they are sloughed off. This trip takes 2–3 d and ends with the loss of the iron in the ferritin contained in the discarded cell. The amount of fecal ferritin is directly associated with both mucosal and serum ferritin (4). Absorption of both heme and nonheme iron are inversely associated with fecal ferritin (5). When iron stores are being loaded, as with oral or intravenous iron administration, fecal ferritin increases (4). At a minimum, fecal ferritin appears to be a passive indicator of the degree of iron absorption; whether it has a more prominent role as a controlling factor has yet to be determined.

Hunt and Roughead (2) closely observed 21 premenopausal women who consumed 2 different diets for 8 wk each. The 2 diets are described as being nonvegetarian and lactoovovegetarian. The iron contributors in these diets were *1*) meat (beef and chicken), enriched refined white bread, fruit, and vegetables and *2*) legumes, whole grains, fruit, and vegetables, respectively. Other differences between the diets include a higher content of fruit and vegetables, ascorbic acid, phytic acid, and fiber in the lactoovovegetarian diet than in the nonvegetarian diet.

An issue not addressed by Hunt and Roughead is the influence of menstrual cycling. Although most subjects completed 4 menstrual cycles during the two 8-wk diet periods, some completed only 3 and others 5. Evaluations of iron absorption and other assessments of iron status were performed on arbitrary days dependent on the day of the experiment, not on the day of the individual subject's cycle, ie, regardless of whether the subject was in the follicular, ovulatory, or luteal phase of her cycle. Thus, there may have been unaccounted for hormonal influences on the data.

Additional hormonal effects could have been caused by hormonal oral contraceptive agents (OCAs). The authors noted that 9 of 21 subjects took OCAs. These agents eliminate variation in the menstrual cycle and are associated with lower losses of menstrual blood. Thus, the higher serum ferritin values noted for those takings OCAs could be expected physiologically, as could the higher fecal ferritin concentration and lower rate of iron absorption (6, 7).

Overall, however, the study, which was conducted at the US Department of Agriculture research laboratories at Fargo, ND, was well controlled. Experimental control, which is particularly keen for resident (ie, chaperoned) subjects at this US Department of Agriculture laboratory, extends to a high degree to nonresident (ie, nonchaperoned) subjects as well. Furthermore, the crossover design of the study allowed each subject to serve as her own control.

Hunt and Roughead's data on serum ferritin support the results of our 1988 report of free-living, nonpregnant, premenopausal women consuming self-selected diets but not iron supplements: serum ferritin concentrations were highest in women who habitually consumed meat, lower in lactoovovegetarian women, and lowest in women who habitually consumed fish (8). Note, however, that the fecal ferritin concentrations reported by Hunt and Roughead are at the lower end of values reported by others and

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were particularly low in the lactoovovegetarian premenopausal women. Serum ferritin concentrations were similarly low. Hunt and Roughead make convincing arguments for both biological control and adaptive control in the regulation of iron absorption.

The recent discovery of a divalent metal transporter in rats is important to this discussion (9). The transporter is a protein of 561 amino acids that can transport Fe^{2+}, Zn^{2+}, Mn^{2+}, Co^{2+}, Cd^{2+}, Cu^{2+}, Ni^{2+}, and Pb^{2+}. It was recently suggested that the transporter, which was originally named natural resistance associated macrophage protein (Nramp-2) and subsequently divalent cation transporter 1, be renamed divalent metal transporter 1 (DMT-1) (10). DMT-1 is expressed predominantly in the proximal portion of the duodenum. Dietary iron deficiency up-regulates DMT-1, leading to the supposition that DMT-1 is a key mediator in intestinal iron absorption in rats. A similar transporter in humans has yet to be identified.

The ultimate irony of iron may be apparent only when we finally understand this abundant yet not abundantly absorbed and less abundantly excreted metal that is essential for life. Too much is lethal; too little is incompatible with life. This delicate balance is achieved by close control of iron absorption and, at the same time, exquisite regulation of iron excretion.

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