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Conrad M E, Jr. & Crosby W H. Intestinal mucosal mechanisms controlling iron absorption. *Blood* 22:406-15, 1963.

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The findings published in this paper provided a model for the regulations of iron absorption within the small intestinal mucosa. It showed that iron was deposited into intestinal epithelial cells proportional to body stores and postulated that this iron might saturate iron receptors so that increased quantities of dietary iron would enter these cells in iron-deficient animals and little uptake would occur in iron overload. [The *SCI*® indicates that this paper has been cited in over 170 publications.]

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The development and testing of nuclear weapons throughout the world led to considerable fallout of radioisotopes in many geographic areas. In order to study body burdens of various radioisotopes in soldiers who had been stationed in various portions of the world, the US Army built several 4-pi liquid scintillation detectors large enough to contain an adult human.[1] These counters were devised before shadow shielding became popular and were huge devices constructed from the armor plate of dismantled battleships, which had been built with pre-atomic-age steel. These machines were exquisitely sensitive and permitted measurements of fractions of a microcurie of most gamma emitters. Their availability stimulated other lines of investigation.

Prior to the development of whole-body counters, iron absorption was quantified by either cumbersome balance studies or by indirect radioisotopic methods. During the late 1950s, we began using whole-body counters to measure iron absorption directly. As anticipated, iron-deficient subjects absorbed more iron than normal humans. Unexpectedly, daily observations of body retention of the oral test doses of radioiron showed that the absorption was completed in iron-deficient subjects almost a week before that observed in normal humans. This could not be explained by differences in intestinal motility in normal and iron-deficient subjects.

Studies in other laboratories using tritiated thymidine had recently demonstrated that intestinal mucosal cells of the small intestine were born in the crypt of Lieberkühn and traveled along the intestinal villus to be sloughed from the tip at the end of a two- to three-day lifespan.[2] Using oral-dose Fe^{59} and autoradiography, radioiron was found throughout the villus absorptive cells of normal animals immediately following the test dose, but only in distal cells near the tip one or two days later. Little radioiron was observed in the epithelial cells of iron-deficient animals and iron-loaded animals, suggesting rapid transit into the body in iron deficiency and diminished uptake in iron overload. When radioiron was administered intravenously, incorporation of radioisotope was shown predominantly in the crypts with migration toward the tip of the villus in subsequent days.

The hypothesis that the quantity of iron within absorptive cells was related to the state of iron repletion and important in the regulation of iron absorption was confirmed by biochemical studies of intestinal mucosa.[3,4] Later, this was challenged by studies measuring iron in isolated mucosal cells.[5] However, more recent studies using electron microscopy and methods of staining iron within cells have confirmed the initial hypothesis that there is little iron within the absorptive cells of iron-deficient animals and a plethora in iron-loaded animals.[6] This is consistent with the hypothesis that iron absorption is regulated by iron acceptors within the intestinal mucosa and that the uptake of dietary iron is diminished when these metal-binding receptors are bound with iron derived from either the diet or body stores. The article has been highly cited because of the lack of alternative hypotheses and the importance of iron deficiency as a worldwide nutritional problem.

1. **van Hoek R & Conrad M E, Jr.** Iron absorption. Measurement of ingested $iron^{59}$ by a human whole-body liquid scintillation counter. *J. Clin. Invest.* 40:1153-9, 1961. (Cited 55 times.)
2. **Hughes W L, Bond U P, Brecker G, Cronkite E P, Painter R B, Taashker H & Sherman F G.** Cellular proliferation in the mouse as revealed by radioautography with tritictil thymide. *Proc. Nat. Acad. Sci. US* 44:476-9, 1958. (Cited 365 times.)
3. **Conrad M E, Weintraub L R & Crosby W H.** The role of the intestine in iron kinetics. *J. Clin. Invest.* 43:963-73, 1964. (Cited 125 times.)
4. **Chitashi L & Izak G.** The effect of acute hemorrhage and acute haemolysis in the intestinal iron absorption in the rat. *Brit. J. Haematol.* 12:611-22, 1966.
5. **Bakerzak S P & Greenberger N J.** Iron content of isolated intestinal epithelial cells in relation to iron absorption. *Nature* 220:270-1, 1978.
6. **Parmley R T, Barton J C, Conrad M E & Austin R L.** Ultrastructural cytochemistry of iron absorption. *Amer. J. Pathol.* 93:707-18, 1978.

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