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Commentary: Hepcidin mimetics from microorganisms? A possible explanation for the effect of *Helicobacter Pylori* on iron homeostasis.

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In their paper "The Hematologist's View of Unexplained Iron Deficiency Anemia in Males: Impact of *Helicobacter pylori* Eradication" Hershko and his colleagues add to our existing fund of knowledge further evidence for the involvement of *H. pylori* in the etiology of iron deficiency anemia. Eradication of the organism seems very beneficial to some patients with iron deficiency anemia, and there are even those, as documented in their paper, whose iron deficiency anemia is cured merely by treating the bacterial infection: iron therapy does not seem to be required.

There are some aspects of the relationship between infection with this particular organism and iron deficiency anemia that are easy to explain. It is not difficult to construct a scenario that explains the development of iron deficiency in these patients. Absorption of food iron is less efficient in patients with gastric achlorhydria, and gastritis may cause bleeding from time-to-time, even if examination of random stools for blood is negative. But there are other aspects of the relationship between *H.Pylori* infection and iron deficiency that are puzzling. Why do these patients not respond to oral iron therapy? This phenomenon has been documented previously as well as in the current study: some patients with *Helicobacter* infection do not respond to oral iron until the infection is eradicated. The proposal has been made that this failure to respond to iron is due to sequestration of iron by the microorganism itself(1). This seems unlikely, if only on quantitative grounds.

We now recognize that the anemia of chronic inflammation is mediated, in part, by the stimulation of hepcidin by cytokines(2,3). The absorption of iron from the human gastrointestinal tract and its partition between different cell types is largely regulated by the hepcidin/ferroportin system. It has been suggested that this is the reason for the failure of patients with *H.Pylori* infection to respond to iron (4), but this explanation is less than satisfying, since the failure to respond to iron seems to be singularly severe with infection with this specific organism; yet the usually manifestations of a cytokine response, such as fever and malaise, are absent.

There is another explanation that seems worth considering. *Helicobacter pylori*, like many other organisms, is exquisitely dependent upon iron for its survival. It might be possible for microorganisms to subvert the human iron regulatory mechanism in a manner that is beneficial to them but deleterious to the host. Whatever the mechanism that the microorganism might employ, its result might be the same as upregulating hepcidin or downregulating ferroportin. Such perversion of iron homeostasis could be achieved by the production of hepcidin mimicks that prevent response to iron, even as upregulation of hepcidin appears to do in patients with acute inflammation.

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As yet, the technology for investigating this hypothesis is immature. We have added *H. pylori* organisms to cultures of cells expressing on its surface the ferroportin-green fluorescent protein fusion protein (obtained through the courtesy of Dr. Jerry Kaplan). This did not result in internalization of ferroportin. The system could, however, be complex with interaction between microorganism and tissue in a way that is difficult to simulate *in vitro*. Moreover, it may be only certain strains that have the capacity of subverting the human iron homeostatic mechanism. After all, nearly 50% of the population is infected with *H. pylori* and only a few become iron deficient. Rigorous examination of the interaction of microbial products with the hepcidin/ferroportin system will have to await the development of quantitative bioassays for hepcidin. None exist today.

It is well known that microorganisms are highly adaptable to their environment, and it would not be surprising if *H. pylori* or other organisms have learned to manipulate host iron homeostasis in a manner that ensures their survival.

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