Editorials

Pumping Iron

VIRTUALLY EVERY practicing physician who reads this editorial will have now or will have had in the past patients with genetic hemochromatosis in his or her practice. But few will be aware of it.

Embedded in the short arm of chromosome 6, in close physical proximity to the DNA region coding for the HLA histocompatibility complex, lies a gene of unknown function. When both copies of this gene are abnormal, however, dietary iron is absorbed with increased avidity throughout the lifetime of the host—that is, hemochromatosis. It is rare, indeed, that a recessive genetic disorder leads to an increase of a physiologic mechanism, in this case a continued inappropriate absorption of iron in the face of its pathologic accumulation. Until this aberrant gene is finally identified, perhaps by positional cloning, it is unlikely that we shall know how it normally acts to monitor the adequacy of iron stores and thereafter, acting on that information, how it controls the efficiency of iron transport across the intestinal epithelium.

But, then, the normal homeostatic mechanisms for iron metabolism are strange indeed. The level in the body of no other key inorganic substance depends exclusively on the control of absorption. Iron cannot be excreted; it is lost only in small amounts (perhaps 1.0 mg per day) through sloughing of cells or seepage of blood. In the absence of increased bleeding or pregnancy, any daily absorption of more than approximately 1.0 mg will inexorably lead to its accumulation.[1,2]

How does the intestine normally sense the level of iron stores or the rate of erythropoiesis (the other seemingly independent variable in iron absorption)? This remains unknown at present. Does hemochromatosis represent an enhancement of this putative feedback signal? Alternatively, does it represent an intrinsic abnormality in the gut mucosa itself that overrides a normally functioning feedback signaling mechanism? The application of molecular genetics should allow these questions to be answered in the not-too-distant future.

Hemochromatosis represents an overall failure of this gating mechanism in the intestine, such that approximately 2 to 4 mg of iron is absorbed daily. In the absence of bleeding, this is sufficient to increase iron stores by 0.5 to 1.0 gram per year. Over several decades a cumulative pool size characteristic of clinical hemochromatosis (15 to 35 grams) results. Actually, hemochromatosis will undoubtedly prove to be a spectrum of derangements of its miscreant gene when its structure can be specifically analyzed. More than 100 mutations of hemoglobin have been identified. Similarly, we can anticipate that a number of different lesions of the hemochromatotic gene may interfere with its normal function, whatever that might be, and in the process produce wide variations in the resulting peculiar avidity for absorbing dietary iron. Other variables include the level of iron in the diet (normally about 12 to 20 mg per day) and its bioavailability (heme iron is more readily absorbed than free iron). As a result, in a homozygotic patient, sufficient iron to produce the organ damage characteristic of clinical hemochromatosis may accumulate in less than two decades, or never. Most characteristically, this accumulation occurs—or, rather, it is recognized—in the fifth to seventh decades of life. The genetic disease itself is present at birth; its phenotypic expression is long delayed.

How does excessive iron damage the host? Like so many aspects of this common disorder, the answer to that question is still unclear. Evidence suggests that excess iron leads to a peroxidation of key cellular lipids.[3] As an example, cytoplasmic lysosomes contain and sequester powerful hydrolytic enzymes within their lipid membranes. If these membranes are disrupted by peroxidation, however, they may release these enzymes injuriously into the cells' cytoplasm. This is thought to be a major pathogenesis of acute gouty arthritis—that is, the injury of leukocytic lysosomes, in this case by the ingested crystals of monosodium urate. If lysosomal injury is a key, is hemochromatosis a sort of "iron pseudogout" of certain parenchymal organs? The analogy is amusing but not revelatory. Iron overload also diminishes hepatic levels of cytochrome P450 and impairs mitochondrial oxidative metabolism. Some think that excess iron also increases hepatic collagen synthesis in the absence of an overt necrosis of hepatocytes.

Hemochromatosis is one of the most common genetic diseases of whites, exceeding cystic fibrosis in prevalence, for example.[4] Compelling evidence, mostly from the past two decades, strongly supports that conclusion. Approximately 10% of whites carry one abnormal hemochromatotic gene; perhaps 1 person out of every 300 to 400 in the white population is homozygotic for this gene—that is, has genetic hemochromatosis. How has this been established? The data come largely from surveys for biomedical evidence of iron overload in adults (in the absence of other known causes such as transfusions or persistently increased erythropoiesis). Further cases can then be identified in a given family by determining haplotype and allele sharing. Close linkage has been established most frequently with *HLA-A3*, but also with *HLA-B7, -B14*, and *-A11*. It is probable that this linkage, representing physical proximity of the genes on chromosome 6, is entirely fortuitous. Nevertheless, before the hemochromatotic gene itself is identified, this guilt by association allows the diagnosis of both heterozygotes and homozygotes to be established in the families of a given index case, even in the absence of iron overload.

Why has hemochromatosis persisted as such a common disorder? Selection pressures might be expected to have diminished its prevalence. On the other hand, clin-

ical manifestations of the disease usually occur after the period of reproduction, although not in the atypical case described elsewhere in this issue of the journal.[5] It has also been postulated that a modest increase in the efficiency of iron absorption in heterozygotes might represent a countervailing positive feature, analogous to the protective effect of heterozygous sickle-cell trait against falciparum malaria.

The clinical manifestations of hemochromatosis vary widely and may be subtle.[1,2] Clearly, physicians must not wait for the appearance of bronzed diabetes with cirrhosis before the diagnosis is considered. If 1 of every 300 to 400 white patients seen in a hospital, clinic, or office has hemochromatosis, the diagnosis is more frequently missed than made. It is true that the full disease does not develop in carriers of the disorder and that women, who are genetically hemochromatotic as frequently as are men, much more rarely accumulate sufficient iron for clinical manifestations to develop (in one study only about 15% of women with genetic hemochromatosis were clinically affected). Menstrual periods and pregnancies allow for substantial iron loss and serve to protect against iron overload. In fact, when clinical hemochromatosis does appear in women, it is usually after menopause. As a result, its manifestations tend to occur later in women than in men.

Weakness, lethargy, abdominal pain, seronegative arthritis, impotence, and glucose intolerance are some of the nonspecific early manifestations of hemochromatosis. How can the diagnosis be made then? The disease must be suspected much more frequently than has been customary in the past. In the absence of a means to detect the abnormal gene itself, we are currently confined to studying the time-delayed phenotypic expression of the disease, that of iron overload. For practical purposes, iron overload (especially greater than 4 grams) in the absence of excessive transfusions, or more rarely, prolonged enhanced erythropoiesis, is almost always due to hemochromatosis. When the diagnosis is made in a patient, it can then be traced in his (more rarely, her) family by HLA linkage analysis. At present, the transferrin saturation test has proved to be the most useful test for detecting iron overload.[6] Other tests are described elsewhere.

Therapy is simple and effective if the diagnosis is made before severe liver disease or the destruction of pancreatic islet beta cells occurs. A hemochromatotic gut slowly but inappropriately pumps iron into the body; a phlebotomist can rapidly pump it out. Removing 500 ml of whole blood removes 200 to 250 mg of iron. Heme itself is the ideal chelator. A weekly phlebotomy can therefore remove 10 to 12 grams of iron per year, which may represent the accumulation of two decades. The genetic defect remains, but its adverse effect can be easily obviated if an early diagnosis is made. Even when the diagnosis is delayed, heart failure and abnormal liver function may be reversed, and even glucose tolerance may improve.

Hemochromatosis is both prevalent and insidious. We must consider this diagnosis much more frequently because genetic "pumping iron" leads to organ destruction, not to body building.

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REFERENCES

1. Smith LH Jr: Overview of hemochromatosis. West J Med 1990; 153:296-308
2. Rouault TA: Hereditary hemochromatosis (Clinical Conference). JAMA 1993; 269:3152-3154
3. Mak IT, Weglicki WB: Characterization of iron-mediated peroxidative injury in isolated hepatic lysosomes. J Clin Invest 1985; 75:58-64
4. Edwards CQ, Griffen LM, Goldgar D, Drummond C, Skolnick MH, Kushner JP: Prevalence of hemochromatosis among 11,065 presumably healthy blood donors. N Engl J Med 1988; 318:1355-1362
5. Niihara Y, Brouwer DW, Cantos KA: Multiple organ dysfunction in a 33-year-old woman due to hereditary hemochromatosis. West J Med 1995; 162:362-364
6. Edwards CQ, Kushner JP: Screening for hemochromatosis. N Engl J Med 1993; 328:1616-1620

Advances in Diagnosing and Managing Pituitary Adenomas

IN THE PAST DECADE we have seen a tremendous increase in knowledge regarding the pathogenesis, diagnosis, and management of pituitary tumors, as summarized by Aron and colleagues in this issue of the journal.[1] Their review reflects the experience of a major academic center for pituitary tumor research. What salient points can be gleaned from this experience and from other recent advances?

First, pituitary lesions are not rare. Magnetic resonance (MR) imaging reveals focal pituitary hypointensities in as many as 40% of healthy persons.[2] Most of these are small microadenomas or other benign lesions, but macroadenomas are occasionally found when patients undergo computed tomographic or MR scanning for unrelated indications. How should cases of pituitary mass lesions be evaluated?

To answer this question, it is helpful to review the clinical effects of pituitary adenomas. Pituitary tumors usually present with some combination of three syndromes: symptoms due to the mass itself, symptoms due to a disruption of normal pituitary function, and symptoms due to the oversecretion of pituitary hormones. The first two syndromes depend on the size of the tumor, and the third can occur with small lesions. Therefore, patients with large lesions require formal visual field examination and assessment of normal pituitary function, whereas all patients require assessment of excess hormone secretion.

What is the appropriate biochemical assessment of pituitary function in patients with pituitary mass lesions? There is no single answer to this question, but recent discoveries provide some guidelines:

• *Prolactin oversecretion*: Prolactinomas are the most common pituitary tumor and, in general, are the only ade-