

## Fatigue of Anemia

Fatigue has a hundred faces. Depressed patients feel fatigued on arising to face the day. Patients recovering from infectious mononucleosis or viral hepatitis feel strong in the morning but tire later in the day and need a nap. Patients who have chronic fatigue syndrome are tired all day long or become exhausted from minimal exercise. Writers facing a blank page feel the fatigue of inertia—a weariness that wanes only when they set to work and so tap the energy that was there all along.

The fatigue of anemia has its own face. Patients with mild or moderate anemia generally feel normal at rest and note fatigue only with exertion. In fact, exercise can help differentiate common causes of fatigue. Strenuous exercise may be the only thing to unmask mild anemia, as in three college athletes—all diagnostic problems initially—who lost stamina because of iron deficiency anemia.<sup>1</sup> This abstract focuses on iron deficiency anemia, the most common anemia in America.

### Iron and Physical Energy

Getting extra iron has long been thought of positively. "Iron-poor tired blood" is legendary. The government mandates adding iron to flour. The supplement industry touts iron, not only in tonics, but also in top-selling multivitamin/mineral capsules. Popeye got heroic strength from the iron in spinach, even though the original researchers had their decimal point wrong and overestimated its iron content tenfold.<sup>2</sup> Most athletes think they need extra iron. All told, the lure of supplementing with iron is strong. Despite the enduring popularity of supplementing, however, most people—even most women—do not need more iron than they get in their regular diet.

Sufficient iron is key for normal energy. Iron is necessary for forming hemoglobin and myoglobin, the oxygen carriers in red blood cells and muscles, respectively. Iron is also part of several mitochondrial electron transport proteins required for the oxidative phosphorylation of ADP to ATP. Iron may also influence energy in four other ways. It is a cofactor for an enzyme in the tricarboxylic acid cycle. It is a cofactor in the synthesis of carnitine, which carries fatty acids across the mitochondrial membrane. It powers

an enzyme rate-limiting step for gluconeogenesis. And it plays a role in the function of certain neurotransmitter amines.<sup>3</sup>

In short, because it delivers oxygen to cells, facilitates the use of oxygen by cells, and spurs other metabolic pathways, iron is essential for energy. Iron is as vital as oxygen in converting chemical energy from food into metabolic energy for life.<sup>4</sup>

### Prevalence of Anemia

A recent report on the prevalence of iron deficiency in the United States—a sampling of nearly 25,000 persons in the third National Health and Nutrition Examination Survey—finds approximately 10% of young women are iron deficient and 3–5% are anemic. Similar figures were seen in toddlers. The authors conclude iron deficiency and anemia are still relatively common among women of child-bearing age (and in toddlers), especially those who are black, Mexican American, poor, and have less education and many children.<sup>5</sup>

### Problem Defining Anemia

The above study defined anemia in women as a hemoglobin concentration less than 120 g/L. Although this cutoff is conventional, it misses the point that anemia is relative—a point rediscovered often in sports medicine research. Consider two recent studies by Cornell researchers.<sup>6,7</sup>

The researchers read one study as showing iron therapy improves endurance in women who are iron deficient but not anemic.<sup>6</sup> They recruited young women who were active but untrained. All were defined as iron depleted but not anemic because serum ferritin was less than 16 mcg/L but hemoglobin was greater than 120 g/L. The trial was randomized, double blind, and placebo controlled. After 2 weeks of iron or placebo therapy, all subjects completed 4 weeks of aerobic training. Endurance capacity was tested at the start and end by 15-km cycling time trials.

Ferritin rose in those on iron versus placebo. Hemoglobin tended to rise on iron versus placebo, but not significantly. Multiple regression analysis, however, showed that a rise in hemoglobin improved "energetic efficiency." Gains in hemoglobin led to decreased energy expenditure, increased work rate, and increased efficiency during the

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time trial. As a result, improvement in the time trial was twice as great in the iron group as in the placebo group (3.4 versus 1.6 minutes faster than baseline).

In other words, women on iron grew fitter and cycled faster than those on placebo, even though none were "anemic" at the outset. The researchers rightly concluded that women with hemoglobin greater than 120 g/L might still be "functionally anemic."

In a cross-sectional study, these researchers measured  $VO_2$  max in two groups of women defined as "nonanemic" because all had hemoglobin levels greater than 120 g/L. One group was iron depleted (ferritin < 12 mcg/L); the other was not. The former group had a lower  $VO_2$  max than the latter. This should have been expected, because mean hemoglobin was lower in those who were iron depleted versus those who were iron replete (136 g/L versus 145 g/L). So even though all the iron-depleted women had hemoglobin levels greater than 120 g/L, they were *anemic* compared with the iron-replete women.<sup>7</sup>

### Anemia is Relative

The point is that anemia is relative. In the Cornell studies, slight differences in hemoglobin, all greater than 120 g/L, affected athletic performance. Anemia is best defined as a subnormal hemoglobin level for the *individual*. For example, a female athlete whose hemoglobin is 130 g/L is anemic if her normal hemoglobin is 140 g/L. No magic "cut-off value" defines anemia.

A corollary is that anemia is more prevalent than general surveys suggest.<sup>5</sup> The more an athlete asks of her body, the more she notes exertion fatigue from mild anemia. Team physicians would be wise to screen female athletes for hemoglobin and ferritin. The University of Oklahoma screens annually and finds 10–20% or more of female athletes to be iron depleted. Many of these women are anemic, some with hemoglobin levels less than 120 g/L, some greater than 120 g/L.

Some researchers argue that athleticism predisposes to iron deficiency anemia. They point to increased loss of iron in sweat,<sup>8</sup> to gastrointestinal bleeding,<sup>9</sup> and to meatless diets in female athletes.<sup>10</sup> They argue that endurance athletes are especially prone to anemia and call for supplementing all athletes who have low ferritin levels.<sup>11</sup> This view holds some merit. But by and large, athleticism seems more to *unmask* anemia rather than cause it.

### Iron and Mental Energy

Whether iron deficiency can impair mental energy is unclear. In animal models at least, brain iron influences myelination and neurotransmitter function.<sup>3,12</sup> The human link, however, is tenuous. Seven studies tie iron deficiency anemia to lower scores on tests of mental and motor development in infancy.<sup>12</sup> Other studies show such children—after anemia is cured—still test lower in mental and

motor functioning years later.<sup>13</sup> A recent study found infants with iron deficiency anemia did not improve mental test scores after 6 months of iron therapy and cure of anemia, and were disadvantaged as to family background and feeding practices.<sup>14</sup> Iron deficiency anemia may therefore be a mere marker for diverse nutritional and family disadvantages that impair infant development.

The same caveat applies to the notion that iron therapy improves verbal learning and memory in iron-deficient but nonanemic adolescent girls.<sup>15</sup> This study got banner headlines, probably because it is nice to think a few iron pills can get your daughter into Harvard. But this study is confounded in that some girls *were* anemic (mean hemoglobin rose significantly in the iron versus placebo group) and improvement was seen in only one part of one of four tests of cognitive functioning. In short, this study was overblown. No cogent reason yet exists to believe iron deficiency per se saps mental energy.

### Concluding Tips

Iron deficiency will result from any condition in which dietary iron intake or absorption fails to meet physiologic needs.<sup>16</sup> Consequently, rapidly growing children and women of childbearing age are at highest risk, as are vegetarians. No physiologic pathway exists for iron excretion, so men seldom get iron deficiency anemia in the absence of abnormal blood loss.

Dietary iron supply can be increased by the following: eating more lean red meat; not consuming tea or coffee with meals; drinking orange juice with breakfast; cooking in cast-iron cookware; and frequently eating mixed meals, so the protein factor in meat, fish, or poultry will enhance iron absorption from grain, beans, and legumes.<sup>4</sup> Not widely known is that excessive zinc supplementation can cause copper deficiency and in turn an anemia related to abnormal iron handling in mitochondria of red blood cell precursors.<sup>17</sup>

Finally, the habit of some health-conscious or athletic men to supplement with iron is a potential hazard. In the United States, up to one person in 200 is genetically programmed to develop hereditary hemochromatosis by absorbing daily two to three times more dietary iron than normal. As a group, men are less likely to develop iron deficiency than iron overload. Iron supplements will accelerate iron overload, so as a group, men would be wise to shun iron supplements. In general, if many women need more iron than they get, many men get more iron than they need.

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