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Iron Deficiency

One of the most common health problems worldwide and potentially one of the most treatable, iron deficiency can have devastating effects. It can jeopardize a child's mental and physical development

by Nevin S. Scrimshaw

Iron deficiency is the most prevalent nutritional problem in the world today. Two thirds of children and women of childbearing age in most developing nations are estimated to suffer from iron deficiency; one third of them have the more severe form of the disorder, anemia. Furthermore, unlike classical nutritional diseases—such as vitamin A deficiency, which can lead to blindness, and iodine deficiency, which can cause retardation and deafness—iron deficiency is found in all societies, developing and industrial alike. In the U.S., Japan and Europe, for instance, between 10 and 20 percent of women of childbearing age are anemic.

Iron deficiency commonly remains unrecognized. Because of subtle symptoms such as pallor, listlessness and fatigue, the disorder is not regarded as life-threatening. Yet iron deficiency can have a multitude of effects—and can even result in death.

In the past several years researchers have found that iron deficiency is associated with the often irreversible impairment of a child's learning ability and other behavioral abnormalities. Although the neurochemical roles of iron are not fully understood, it is clear that low levels of the nutrient can have a significant adverse impact on brain function. In addition, diminished levels of iron in adults can affect work capacity and productivity and, by impairing the immune system, increase the chances of acquiring and dying from infection.

Despite the possibilities for low-cost intervention, many countries lack an effective system for diagnosing, treating and preventing iron deficiency. Consequently, progress in combating iron deficiency has been slight. Whereas the administration of effective treatments for deficiency in vitamin A and in iodine can be made uniform in nearly all countries, therapies for iron deficiency must be tailored to suit individual cultures and countries.

The situation could soon improve. This year a United Nations subcommittee on nutrition established a working group to promote the control of iron deficiency. The group is collaborating with the World Health Organization (WHO) in developing a 10-year plan to eliminate this public health scourge. Understanding the multiple functional consequences of iron deficiency is crucial to that effort.

Iron has diverse biological functions, and it is this diversity that accounts for the wide-ranging impact of its deficiency. The metal is best known for its role in the transport of oxygen in blood. As a component of hemoglobin, iron helps the molecule pick up oxygen in the lungs and shuttle and release it throughout the body. Approximately 73 percent of the body's iron is found in hemoglobin, where it is constantly recycled as more red blood cells are created.

Of the balance of the body's iron, 12 to 17 percent is stored in two molecules—ferritin and hemosiderin—both of which can bind large numbers of iron atoms. (Each molecule of ferritin alone binds 4,500 iron atoms.) Myoglobin accounts for another 15 percent of the iron, acting as a reservoir of oxygen for muscle cells. A small but extremely important amount (0.2 percent) of body iron is bound to transferrin, a compound that shuttles iron from sites of release to sites of need. Lactoferrin—a compound found in breast milk, mucosal tissues and white blood cells, or leukocytes—also binds a percentage of the body's iron so that it is not available for bacterial growth, thereby stemming infection.

The minute amount of iron not accounted for by these compounds is found in myriad enzymes crucial to metabolism. These enzymes include oxidases, catalases, reductases, peroxidases and dehydrogenases. Each enzyme

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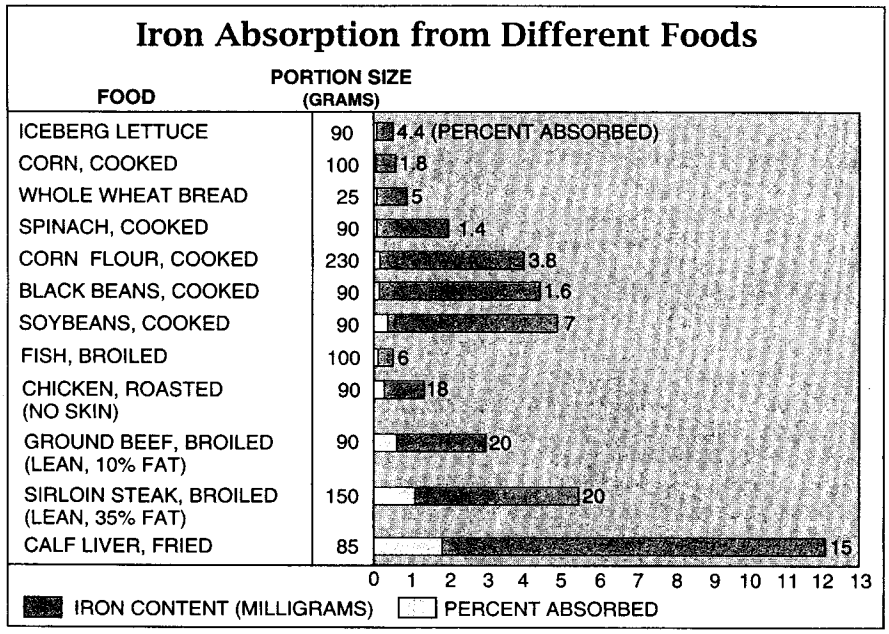
GUATEMALAN WOMAN and boy sell fruit in a marketplace in the highlands. Iron deficiency is often caused by the predominantly vegetarian diets common to most developing nations.



plays an important role as a reversible donor or acceptor of electrons during cellular metabolism.

All the iron needed to execute these diverse tasks comes from diet. Although vegetables, particularly spinach, are regarded as impressive sources of iron, plant (nonheme) iron is relatively poorly absorbed. For instance, only 1.4 percent of the iron from spinach can be taken in by the body; other vegetables yield slightly more: 1.6 percent from black beans, 4.4 percent from lettuce and 7 percent from soybeans.

In contrast, 20 percent of iron from red meat, in the form of heme iron, can be absorbed. Iron from poultry, fish and breast milk is equally well assimilated, but the concentrations are lower. The composition of a meal can influence the amount of iron that is retained. For example, if a meal contains both heme and nonheme iron, the former will improve the absorption of the latter. Vitamin C enhances the utilization of nonheme iron, but substances like tannin from tea as well as fiber and phytates from plants inhibit it. Absorption also changes in accordance with the amount of iron in the body: it decreases if individuals are iron replete and increases if they are iron deficient.

Poor absorption from the predominantly vegetarian diets of most people in developing countries is a primary cause of iron deficiency. For the poor, meat is expensive and consumed in small quantities or not at all. Iron deficiency and anemia affect the majority of individuals in such populations.

Iron deficiency is not caused by dietary imbalances alone—it can occur even when the diet has adequate iron. Other culprits are chronic blood loss caused by hookworm and schistosomiasis and the excessive storage of iron as hemosiderin, a result of malaria. Abnormal uterine bleeding is another cause.

Hookworm eggs from human feces hatch on moist soil to produce tiny larvae that painlessly enter the skin of the feet. The bloodstream and lymph vessels then carry these larvae to the lungs. From there they find their way into the trachea, or windpipe, to the pharynx and, ultimately, to the small intestine after they are swallowed. They bind to the intestinal lining and secrete an anticoagulant that causes bleeding proportional to the number of worms. As many as three million worms may be recovered after severe cases are treated.

Hookworm rarely kills its victims, but it can leave them weak and listless. Children with hookworm disease are not only pale and anemic but slow and dull. Indeed, the parasite was largely responsible for the image of laziness of poor Southern whites in the U.S. Because poor whites formed the bulk of the Confederate Army during the Civil War, some scholars have suggested that hookworm disease was a significant factor in the army's defeat by the North.

Although hookworm has been largely eradicated in the U.S. and other industrialized nations, it continues to plague over 900 million people—more than one fifth of the world's population. Schistosomiasis afflicts more than 200 million people, and malaria causes 200 to 300 million deaths every year.

Shortages of iron, whether caused by disease or diet, or both, are described in three overlapping stages, beginning as deficiency and culminating as anemia. (There are many additional causes for anemia, including genetic defects and other nutritional disorders.) Although anemia is the more severe condition, the impairment of many bodily functions, such as harmful changes in biochemistry and in the effectiveness of important iron-containing enzymes, occurs long before anemia sets in.

In the first stage, stored iron is depleted, a process reflected in declining levels of ferritin. Next, levels of serum iron plummet, and as a result the iron transport protein, transferrin, is no longer fully saturated. At this second stage, cellular compounds requiring iron begin to be affected. As the deficiency persists, the synthesis of hemoglobin is inhibited, and anemia develops. This last stage is characterized by reduced numbers of now small, pale blood cells.

One of the more devastating consequences of iron deficiency and anemia has been elucidated over the past 15 years, although it is far from clearly understood. Anemic children and adults have often been described as backward or apathetic, but these behavioral aspects were historically attributed to the lack of oxygen transported in the blood. Recently remarkable advances in probing the relation between iron status and cognition have illuminated these symptoms.

Although there were a number of early studies in animals, it was not until 1973 that Frank A. Oski of Johns Hopkins University School of Medicine and his colleagues at Syracuse University reported that anemic infants improved their performance on certain behavioral tests after a single large injection of iron. The tests, called the Bayley Scales of Infant Development, measure a broad range of activities, including motor skills, affective responses and attention span, as well as general cognitive function. Five years later Oski and Alice S. Honig, also at Syracuse, found similar improvements after such treatment in anemic infants when compared with normal infants who received the same treatment.

In 1982 Ernesto Pollitt of the University of California at Davis provided the first demonstration of the adverse effects of subclinical iron deficiency as opposed to anemia. Pollitt, then at the Massachusetts Institute of Technology, found that three- to six-year-olds in Cambridge, Mass., who were mildly iron deficient had poorer scores on a battery of behavioral tests than did preschoolers whose iron status was nor-

mal. He then showed that the scores significantly improved after 11 to 12 weeks of iron therapy.

Pollitt repeated these studies with both iron-deficient and anemic preschool children in Egypt, Guatemala and Indonesia. This time he found only limited improvement in the Guatemalan and Egyptian children, even when their blood levels of iron returned to normal. Only the Indonesian children, who were from a town near Bandung, did significantly better on the test after iron supplementation, presumably because their deficiency was less severe. Other researchers have found the same irreversibility during double-blind studies in Costa Rica, Chile and various parts of Guatemala.

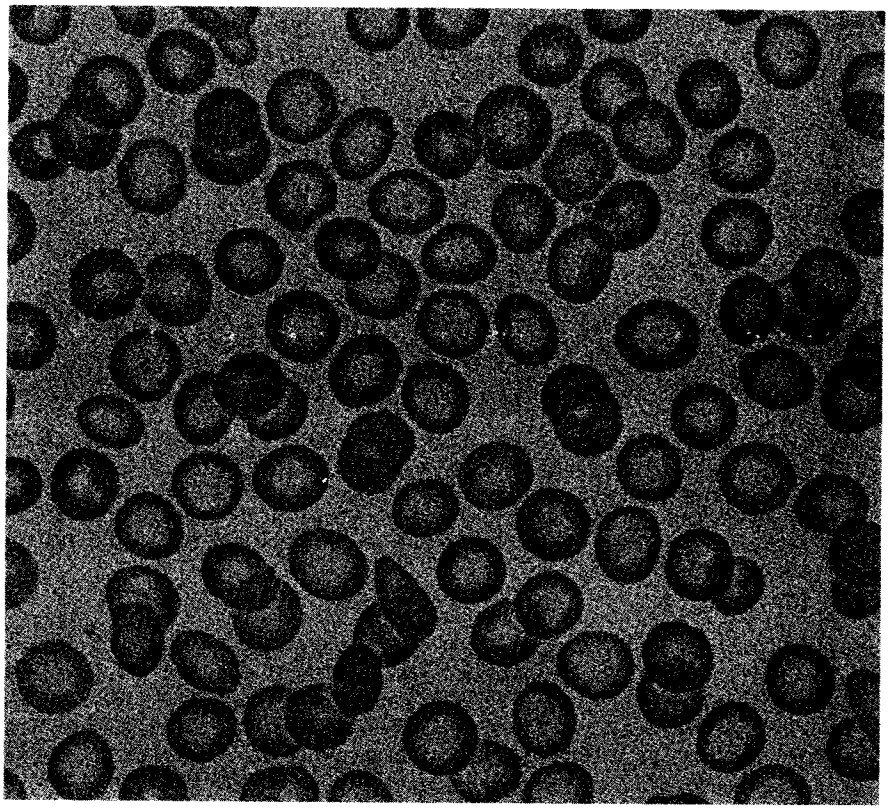
The adverse effects of iron deficiency on cognitive performance also proved irreversible in a study of 2,000 children in Thailand. There, Pollitt and his collaborators found a significant correlation between iron levels, IQ and a Thai language achievement test: the higher the iron levels, the better the scores. Studies in other parts of the world, including India, Papua New Guinea and Semerang in Indonesia, have consistently found a similar association.

Apparently iron deficiency is educationally deleterious regardless of ethnicity or physical or social environment. The lack of recovery in many children after iron supplementation underscores the importance of preventing iron deficiency.

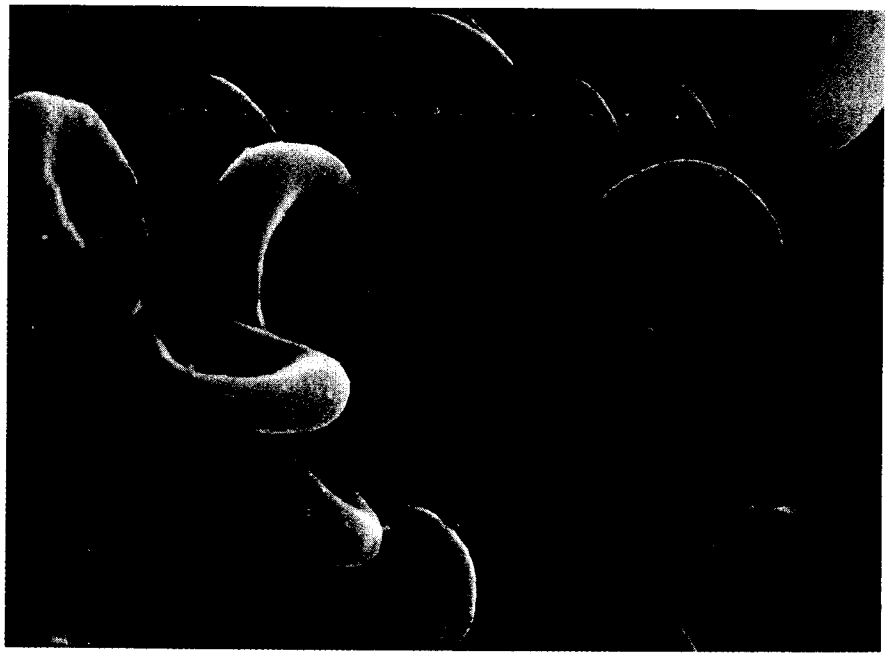
A possible neurochemical basis for these problems has recently been suggested. Moussa B. H. Youdim of the Technion Medical School in Haifa and Shlomo Yehuda at Bar-Ilan University in Ramat-Gan, Israel, found that rats with low levels of iron had fewer D_2 receptors—one of several families of dopamine receptors—in certain regions of the brain. These findings suggest that iron is important to the normal development and functioning of dopaminergic neurons and that early changes could lead to permanent damage.

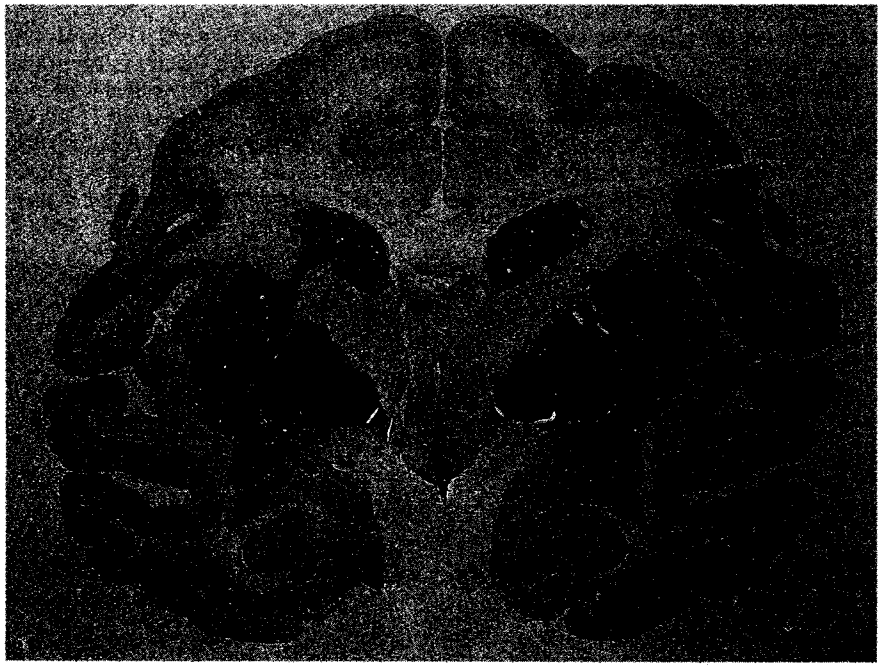
The precise role of iron in the brain, however, has not been determined. The nutrient is distributed quite unevenly but appears to reflect the location of certain neurons that release the neurotransmitter gamma-aminobutyric acid, or GABA [*see illustration on next page*]. The release of GABA inhibits neuronal transmission. It is also noteworthy that iron is found in monoamine oxidase, an enzyme vital to the production of a host of neurotransmitters, including serotonin, norepinephrine and epinephrine as well as dopamine. Thus, there are tantalizing indications of how iron deficiency might affect the central nervous system.

Behavioral changes caused by iron deficiency are not found solely in infants and young children. Physicians visiting developing countries have repeatedly demonstrated a connection between iron levels and work capacity and productivity in adults. In 1970 I found that certain laborers on Guatemalan sugar and coffee plantations performed poorly on the Harvard Step Test (HST), which requires that they step up on and then down off a bench every two seconds for a maximum of five minutes, if pos-



ANEMIC RED BLOOD CELLS are paler and smaller (*above*) than robust erythrocytes (*below*). By limiting the production of hemoglobin, the shortage of iron impairs the ability of these cells to transport oxygen.





RHESUS MONKEY BRAIN shows the presence of iron in the darkly stained areas. The location of the nutrient reflects the termination sites of a class of neurons that produce gamma-aminobutyric acid (GABA). Researchers believe low levels of iron may interfere with degradation of GABA or may impair the performance of dopamine-producing neurons. Photograph courtesy of Joanna M. Hill of the National Institutes of Health.

sible. All these workers, considered lethargic and stupid by the plantation owner, proved to be anemic.

My observation was confirmed by Fernando E. Viteri of the University of California at Berkeley. Earlier studies in animals had shown an association between poor performance on a treadmill and low hemoglobin levels. Viteri, then at the Institute of Nutrition of Central America and Panama, saw the same correlation in Guatemalan laborers. After treatment with iron, the subjects' HST results improved remarkably. Coincidentally, Samir S. Basta, who was then my graduate student at M.I.T., made similar discoveries among road construction workers and rubber tappers in Indonesia.

A question remained: Did these differences in physical capacity have any effect on the laborers' productivity? Basta, who is now director of UNICEF in Europe, established a strong correlation between hemoglobin levels, HST results and the amount of rubber the Indonesian tappers collected. He determined that anemic tappers who were given iron supplements for 60 days augmented their take-home pay by 30 percent. Iron supplementation also increased the productivity of tea pickers in Indonesia and Sri Lanka and of laborers in Kenya and Colombia.

One of Basta's observations suggested the mechanism by which iron depletion hindered performance. He discovered that both the road construction workers and the tappers were better able to work after only 30 days of iron supplementation—before there was any significant increase in hemoglobin. It became clear that iron depletion did not solely affect oxygen transport in the blood but also interfered with oxygen exchange in muscles. Indeed, blood transfusions that restored hemoglobin levels to normal in anemic tea pickers in Sri Lanka failed to improve their treadmill performance: further evidence that the oxygen-carrying capacity of blood is not the single culprit.

Studies in animals further clarified some of the biochemical mechanisms at work in muscles. For example, iron-deficient rats were found to have lower levels of such important proteins as myoglobin, cytochromes and mitochondrial and other oxidative enzymes. Human studies are still lacking, in part because it is inconvenient to take biopsies of muscles.

In addition to reducing the ability of premenopausal women to perform work, iron deficiency curtails their ability to successfully produce and raise healthy children. In many underprivileged populations the limited availability of iron in the diet and the pathological losses associated with parasites increase the likelihood that a woman will experience iron deficiency. Already struggling with poverty and the demands of procuring and preparing food, maintaining a home and caring for a family, many such women are jeopardizing their own health and that of their fetuses.

Although the shortage of iron affects both sexes, women are particularly at risk. Normally men lose only one milligram of iron every day through urine, skin and feces, an amount easily replenished. Such losses are proportionally less in women because of their smaller body size: only about 0.7 to 0.8 milligram a day.

Over the course of a month, however, women lose far greater amounts than men. Menstrual bleeding causes an additional average daily loss of 0.4 to 0.5 milligram, and 10 percent of women lose three times that amount. Intrauterine devices can lead to even more bleeding. Although menstruation ceases during pregnancy, women lose iron to the placenta and to the fetus—roughly five milligrams a day during the second and third trimesters, or a total of 370 milligrams by delivery. This loss is compounded by blood lost during and after delivery.

Iron deficiency during pregnancy can prove dangerous. Maternal mortality, prenatal and perinatal infant death and prematurity are significantly increased. If the mother is iron deficient while she is pregnant, the child is born with poor iron reserves and is at greater risk of morbidity, mortality and learning disorders. Low-birth-weight babies exhaust their iron stores at an earlier age than do normal infants, and they soon require more iron than breast milk can supply.

Treatment works—if it reaches the child in time. In studies in Indonesia, children receiving iron grew more than did those receiving placebo. (Studies of this kind receive ethical approval if they are designed to determine the need for iron supplementation and if, after it is determined that such therapy is effective, the placebo group is also given iron until hemoglobin levels become normal.) The results suggest that iron either has a direct metabolic effect on the child or exerts an indirect effect by increasing appetite, a known boon of iron therapy in people of all ages.

Iron supplementation may also help children by reducing the severity or incidence of infection. Malnutrition in any form is likely to decrease resistance to infection, and nutritional deficiencies are ubiquitous among underprivileged populations. Still, iron deficiency remains the most common, and it is clear-

ly associated with increased illness resulting from infection.

As early as 1928, British physicians reported that bronchitis and gastroenteritis were more likely to develop in poorly nourished infants than in well babies. When malnourished infants received iron supplementation, the incidence of these diseases decreased.

Almost 40 years later the first controlled study of iron and morbidity was published. Morten B. Andelman and Bernard R. Sered of the Chicago Board of Health studied more than 1,000 infants from poor Illinois families. One group received a formula containing vitamins but no iron; the other group received formula with vitamins and iron. The results were striking: the second group had half as many respiratory infections as the first.

Similar findings were reported in Alaska by the wife-and-husband team of Carolyn and Robert Brown of the U.S. Public Health Service. They found a direct correlation between low hemoglobin levels and the prevalence of diarrheal and respiratory diseases in native Alaskan children. Another researcher, Robert Fortuine, also with the U.S. Public Health Service in Alaska, found that meningitis in anemic children often proved deadly, whereas the disease did not prove fatal in any of the nonanemic children he studied.

Although knowledge of the mechanisms by which iron deficiency results in increased morbidity is far from complete, both animal and human studies offer clues. Raymond B. Baggs, a graduate student at M.I.T., fed rats progressively less iron and simultaneously infected the animals with salmonella, a bacterium that causes diarrhea. He found that as the amount of iron in the animals' diet declined, the incidence of morbidity and mortality from the infection rose.

To kill bacteria, white blood cells sharply increase oxygen consumption, a process called respiratory burst. Respiratory burst, in turn, produces an oxygen radical, peroxide. Baggs searched for the cause of the findings and discovered that although white blood cells in the gastrointestinal tract of iron-deficient animals could engulf bacteria, the cells had low levels of the iron-dependent enzyme myeloperoxidase. Without this enzyme, a cell cannot create the free oxygen radicals needed to kill the ingested bacteria.

In studies in Indian children, Ranjit K. Chandra, now at the Memorial University of Newfoundland, showed that respiratory burst diminishes as levels of transferrin fall. At the same time, there is an increase in the number of surviving bacteria in lymphocytes infected in vitro and a fall in the production of new lymphocytes, also in vitro.

Other researchers in India have shown that as the amount of serum transferrin falls, the capacity of tuberculosis patients to respond to a skin test gradually disappears. This failure could result either from the protein deficiency responsible for the decrease in transferrin or from the associated decline in serum iron. This type of response, referred to as delayed cutaneous hypersensitivity, is an important indicator of the health of the cell-mediated immune system.

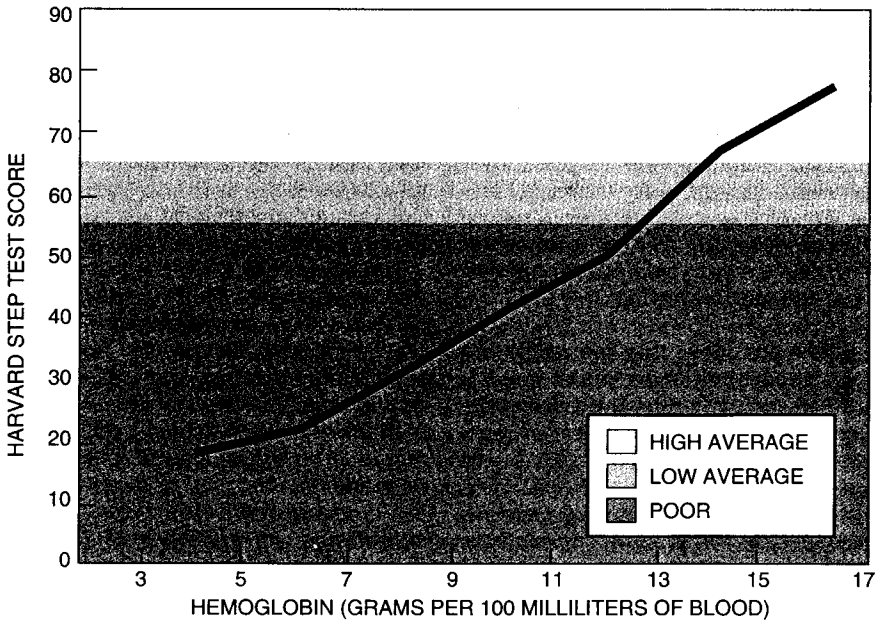
Another little-known consequence of iron deficiency was discovered by chance during a study of behavioral changes in iron-deficient children. Oski noticed that the blood levels and the urinary excretion of epinephrine were much higher in his subjects than in normal children. In 1975 he speculated that his finding was related to the behavioral changes he had observed. It is common for animal studies to point to the need for confirmatory investigations in human subjects, but in this case the opposite occurred.

Three years later Erick Dillman of the Institute of Nutrition in the Hospital for Nutritional Diseases in Mexico City and a group of collaborators at the University of Washington decided to explore Oski's findings, this time using rats. They discovered that iron-deficient rats were unable to maintain a normal body temperature when exposed to cold. In these rats, oxygen consumption was also reduced, indicating a lower metabolic rate and therefore less heat production. In addition to epinephrine, the hormone thyroxine, which is secreted by the thyroid gland and which regulates metabolic rates, was abnormally high in the rats' urine.

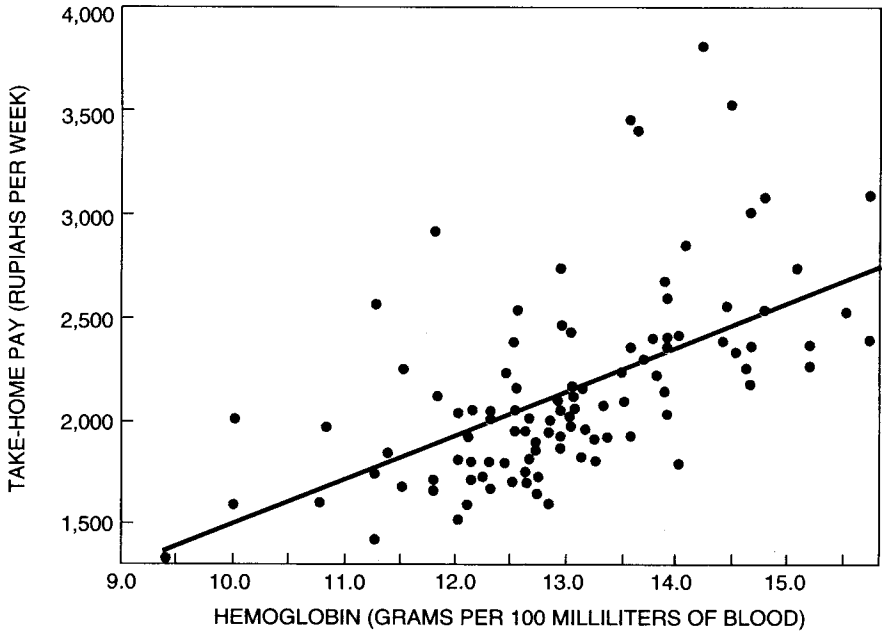
Miguel Layrisse of the Institute of Scientific Investigations in Caracas, Venezuela, learned of these results and decided to investigate further. He placed anemic and nonanemic men in a water tank under conditions in which blood pressure, body temperature and oxygen consumption could be monitored and periodic blood samples obtained. The water in the tank was held at body temperature (37 degrees Celsius) for one hour and then lowered to 28 degrees C.

Layrisse's findings paralleled Dillman's. Five subjects with severe iron deficiency proved unable to maintain their body temperature. Moreover, oxygen consumption decreased and epinephrine levels in urine increased in individuals with mild as well as severe iron deficiency. When they were given 60 milligrams of iron three times a day for seven days, oxygen consumption returned to normal, even though there was not time enough for the hemoglobin levels to change significantly. The observation that iron deficiency lowers resistance to cold exposure and that this phenomenon is reversible may be particularly significant for those anemic elderly who are already more susceptible to cold because of less subcutaneous fat or poor circulation.

Despite the clear advantage of iron



WORK PERFORMANCE has been linked to the level of iron in the blood. Anemic Guatemalan laborers performed poorly on a physical test (the Harvard Step Test), whereas those with higher hemoglobin levels performed well.



PRODUCTIVITY of Indonesian rubber tappers varies with hemoglobin levels. The diagonal line marks the association between income and hemoglobin.

supplementation in restoring temperature regulation or counteracting reduced work capacity, treating iron deficiency is not as straightforward as treating some other nutritional disorders. For example, in iodine deficiency, iodine is easily supplied by iodized salt and, unlike iron, is not harmful in large amounts. The same is true for vitamin A deficiency: a dosage of 300,000 international units every four to six months is safe and effective.

Iron supplementation at a level not exceeding 100 milligrams of ferrous sulfate daily is beneficial for normal individuals who are deficient because of poor absorption of dietary iron and the effects of parasites and other infections. Most populations can also benefit from a staple food fortified with somewhat less iron—for example, cereals, bread, sugar, salt and even monosodium glutamate. Yet the fortification of multiple dietary sources for a population should be avoided.

The old adage that too much of a good thing is no longer good is particularly relevant to iron supplementation. One of the first insights into the dangers of iron excess was provided by South African Bantu men, who have a high incidence of a serious liver disease called hemochromatosis. In this disease the liver is characterized by the excessive accumulation of iron, the development of fibrous tissue and often the occurrence of fatal cancer.

Investigation revealed that the individuals affected were, and still are, accustomed to consuming large quantities of beer fermented locally in iron pots. Because the acid of fermentation leaches iron into the beer and because the quantities consumed daily are very large, toxic iron overloads develop. Obviously these circumstances are unusual, but they have also been reported in a number of other African countries. (Hemochromatosis can also develop in individuals who have a relatively rare genetic defect that destroys the person's ability to modulate the absorption of iron in response to need.)

In 1970 Hylton McFarlane of Manchester University in England reported from South Africa that intramuscular injections of iron given to severely malnourished children to correct their anemia were associated with fatal infections. Reports from Nigeria, New Guinea and Somalia have also indicated that iron injections exacerbate malaria.

The reason for such a result is that iron is valuable not only to the individual but also to the organism infecting that individual. Usually the body has several mechanisms for withholding iron as part of its resistance to such infections. When white blood cells disintegrate after ingesting and killing bacteria and viruses, they release interleukin-1, whose many functions include stimulating the synthesis of ferritin, the efficient iron storage protein. Ferritin production ensures that the iron released from decaying red blood cells will not be available to invading organisms. Disintegrating leukocytes will also discharge lactoferrin at sites of inflammation. Lactoferrin binds iron more strongly than can infecting organisms.

There is little doubt that the body's methods of withholding the iron needed by microorganisms for their multiplication constitute an important way of reducing the virulence of bacterial and protozoan infections. (These mechanisms have been extensively reviewed by Eugene D. Weinberg of Indiana University.) In the presence of too much iron, however, these protective mechanisms are overwhelmed and ineffective.

This complication does not mean that iron deficiency is ever a desirable state. It does mean, however, that giving malnourished individuals large doses of iron is potentially dangerous. Particular care must be taken so that individuals whose cell-mediated immunity has been compromised by iron deficiency do not become overwhelmed by infection before recovery of immunity can occur. Modest daily amounts of iron contribute to a healthy immune system without weakening the protective mechanisms that withhold iron from microorganisms.

The serious consequences of iron deficiency for human health, behavior and performance and the wide prevalence of this disorder are urgent reasons for the strong national and international efforts to curb this illness. Both UNICEF and WHO will need to coordinate strategies for fortifying appropriate foods with iron and providing iron supplements to vulnerable groups. At the same time, infections must be prevented, particularly those causing blood loss, such as hookworm, schistosomiasis and malaria. With concerted international effort, iron deficiency, and the unacceptable suffering it causes so many people around the world, could become another of the major public health problems eliminated in this century.

FURTHER READING

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