

Erythropoiesis and Iron

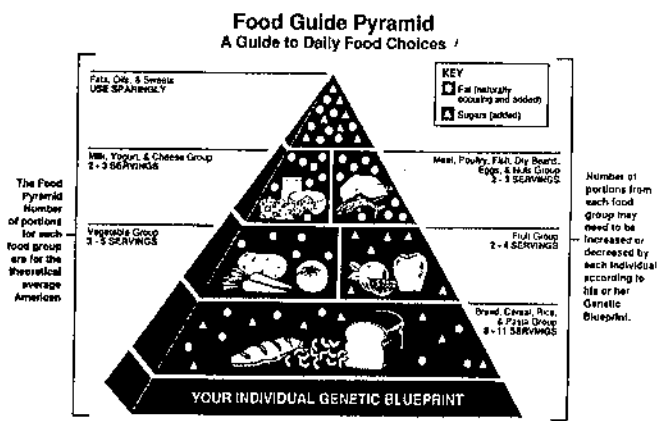
V. Herbert, New York

Genetic nutrition

Most chronic disorders, including the chronic disorders that afflict many pregnant women, have a genetic predisposition component. Some women are predisposed to iron deficiency due to a genetic predisposition to heavy menses determined by a genetic blueprint for a particular array of release of hormones during the month, as well as prior to and during the menses. Environmental factors determine whether the genetic predisposition is expressed or suppressed.

The US food guide pyramid

Five basic food groups are taught by the US Government as the basis of sound nutrition and a healthy diet for all the diverse ethnic groups in the US.



Genetic Nutrition Food Guide Pyramid [© Herbert 1992] updating the 1992 USDA Food Guide Pyramid by adding a base consisting of "your genetic blueprint" and sidebars noting that the food pyramid number of portions are for the nonexistent theoretical average American and therefore may need to be increased or decreased by each individual according to his or her unique genetic blueprint.

Figure 1: Food guide pyramid with genetic base

This diet is graphically represented by the food guide pyramid (Figure 1). As the base of the pyramid we added (©1993 Victor Herbert) "Your Individual Genetic Blueprint". This genetic base underlies the US Government's diet base, which is the grain group (bread, cereals, pastas), of which we recommend five portions a day for the average American. In the next two groups (the fruit and vegetable groups), we recommend three to five servings of vegetables and two to four servings of fruit a day. From the milk group (which includes yoghurt, cheese, and even ice cream), we recommend two to three servings a day. The "meat" group (more properly called the "high protein group" because it includes fish, poultry, eggs, nuts and legumes as well as meat) should comprise about two servings a day, which works out to about two eggs a week, which is the current American Heart Association recommendation. It is not food cholesterol which is problematic, but rather serum cholesterol, 85% of which we make in our own livers from the saturated fat we absorb, not from the cholesterol we eat. One major caveat: the values expressed in the food guide pyramid represent the number of portions from each food group for the theoretical average American - who does not exist. Everyone is born with at least three genetic defects which affect how much we absorb from each nutrient and anti-nutrient we eat, how we transport it in our circulation, how we deliver it to cells and how we do or don't metabolize it and/or excrete it. For example, about 12% of Caucasians and about 30% of Blacks are born with a genetic defect in the ability to limit iron absorption called the hemochromatosis gene, inherited from either parent, which causes them to absorb about 50% more iron daily than the rest of us from their food. One in about 200 Caucasians and one in about 100 Blacks is born with two such genes, one from each parent. Those with this homozygous hemochromatosis, causing absorption daily of about 3 times as much iron as the rest of us, will die of the complications of iron overload unless they are vigorously phlebotomized every month of their lives. We recommend that heterozygotes be phlebotomized (i.e., donated at the blood bank) about three to four times a year.

Heterozygotes for hemochromatosis should be vegetarians because vegetable iron averages only 3% absorbability, whereas animal iron is 15% absorbable. The average Western diet is omnivorous, containing both animal and vegetable components, resulting in an average absorption of about 10% of the iron in the diet. One gene for

iron overload means absorption of about 50% more, and 50% more than the 3% absorbed from a vegetarian diet is only 4.5%, which is not a problem. However, 50% of 10% absorbed from an omnivorous diet means 15% iron absorption, and that is a modest problem. The problem is severe in homozygotic hemochromatosis, where about 30% of the dietary iron is absorbed.

Absorbed iron requirement

The absorbed iron requirement (i.e., the amount which must be absorbed from food) per day for normal men and non-menstruating women is 0.5 mg to 1.0 mg, which requires eating 5 mg to 10 mg, since only 10% of the iron in the omnivorous Western is absorbed. The average fertile female needs 0.7 mg to 2.0 mg because about a unit (500 ml) of blood is lost monthly.

The cost in iron of pregnancy is severe. The fetus will take all the iron it needs to be born normal. In studies we carried out under the auspices of the World Health Organization (WHO) Nutritional Anemias Group in the mid-1960s in Argentina, it was found that pregnant women with hookworm had hemoglobins as low as 2.8 mg. They could still bring a normal fetus to term because the fetus was able to pull all the iron it needed through the placenta, bringing the mother's iron stores down to nothing. Adolescents need 1 mg to 2 mg a day of absorbed iron; children 0.4 mg to 1.0 mg, and infants 0.5 mg to 1.5 mg.

The red cells of the adult contain about 2,500 mg of iron (Figure 2). About 3 mg of iron is in the blood plasma, and storage iron in the male adult averages about 1,000 mg. The healthy adult Western female in the child-bearing years averages only about 300 mg of storage iron because of her monthly blood loss.

Iron distribution (Figure 2)

Of the adult male's 4.0 g of total body iron or the adult female's 2.8 g, about 2.5 g is contained in hemoglobin when there is no anemia. Of that 2.5 g of iron, much will move from the red cell pool to the storage pool if the individual is suffering from a significant degree of non-iron deficiency anemia, such as folic acid deficiency anemia or vitamin B12 deficiency anemia.

When the bone marrow of a pregnant woman with severe folic acid deficiency anemia and no iron deficiency is examined under the microscope, one observes iron overload because all the iron from the missing red cells is now in the marrow. Serum ferritin

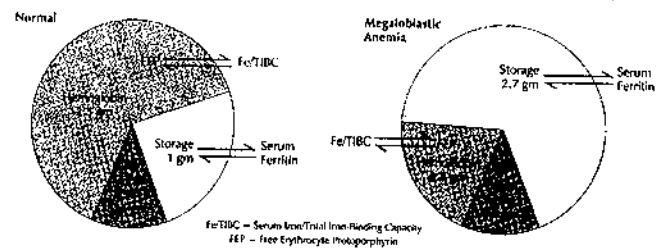


Figure 2. Chart illustrates the distribution of body iron (total, 4 gm) in normal subjects and in patients with megaloblastic anemia, which, when uncomplicated by iron deficiency, produces a laboratory profile that gives a false suggestion of iron overload. Note that serum ferritin is in equilibrium with storage iron. In patients with iron deficiency anemia, storage iron is low, so serum ferritin is low. In patients with megaloblastic anemia, iron from missing

cells is added to storage iron, so serum ferritin is high. Therefore, when iron deficiency coexists with vitamin B₁₂ or folate deficiency, serum ferritin may be normal (deficiencies balance each other), high (vitamin-folate deficiency dominates), or low (iron deficiency dominates). Serum iron and total iron-binding capacity are in equilibrium with free erythrocyte protoporphyrin in normal subjects and in patients with megaloblastic anemia.

Figure 2: Distribution of body iron

iron is in equilibrium only with storage iron, because there are surface receptors for ferritin protein only on reticuloendothelial (storage) cells. Measuring ferritin iron measures the amount of iron stored in the patient's body. The iron-binding protein, transferrin, is the delivery protein to all cells that need it. Cell surface receptors for transferrin are on every cell that needs iron (bone marrow cells, brain cells, etc.).

In iron deficiency, while ferritin protein and ferritin iron fall, the number of transferrin receptors on red cells increases dramatically. Some detach and circulate. Circulating transferrin receptors, elevated in iron deficiency, can be measured as a parameter of iron deficiency, bearing in mind that, in aplastic and hypoplastic anemias, red cell surface receptors for transferrin also increase dramatically. Sequential stages of iron status are shown in Figure 3. The test results in an iron-normal individual are shown below under the heading "Normal". For every nutrient, and iron is no exception, there are four stages of negative balance:

Stage 1 of negative balance is inadequate absorption. Iron initially falls in the peripheral blood; consequently, there is less iron on transferrin, which rises to pull more iron in across the gut wall. Less iron is delivered to cells, and less iron means less ferritin protein, since free iron is the trigger for ferritin protein production. Serum iron is the iron on transferrin protein which contains the iron on its surface. Serum iron does not include the iron in ferritin, which is not only inside the ferritin protein shell, but also in the normally well over 200,000 circulating transferrin molecules per circulating ferritin molecule.

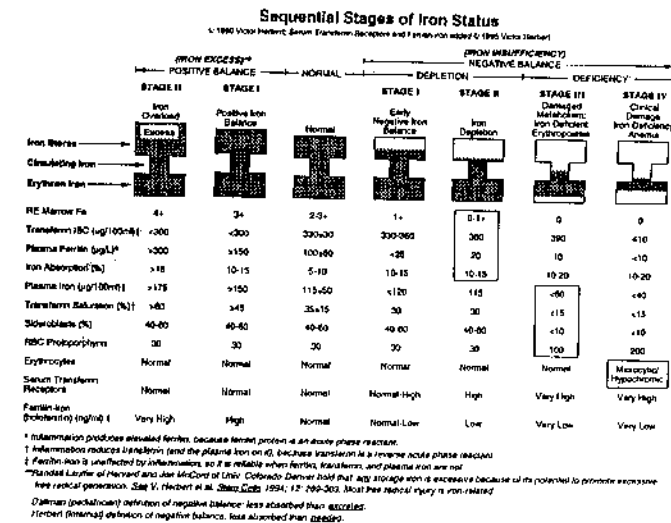


Figure 3: Sequential stages of iron status

Stage 2 of negative iron balance is storage depletion measured by at least four abnormal tests. Only after stores are depleted is there enough iron for normal iron biochemistry, including normal hemoglobin synthesis. This is **Stage 3** negative iron balance, the first stage of deficiency, which is biochemical deficiency. **Stage 4** is deficiency so severe that it is clinically manifest anemia. The biochemical deficiency in hemoglobin production has so reduced hemoglobin production that the red cells have become microcytic and then hypochromic (under-colored). Ferritin protein is an acute phase reactant. High ferritin protein (ferritin > 150 µg/l) always means either inflammation or iron overload. Hallberg and his group recently reported that, in Swedish college women who had flu during an epidemic, serum ferritin went up from normal (~30 to 100 in females) to 300 to 600, and stayed up above 300 for six weeks, even though the active flu was over in a week (Hallberg et al., personal communication). Ferritin protein elevations from the chronic inflammation of rheumatoid arthritis, hepatitis, nephritis, cancer, or any other chronic inflammatory process stay elevated as long as the inflammatory process continues, but ferritin protein iron content is low. Each ferritin protein molecule is capable of binding up to 4,500 atoms of iron.

Serum total ferritin

With increasing body iron stores, such as in iron overload disorders, not only does ferritin protein go up, but the number of atoms in each ferritin molecule goes up sharply.

Ferritin composition

As body iron stores increase, the percentage of the total weight of each ferritin protein molecule, which is the weight of the iron in it, progressively rises. The Salt Lake City group did a long-term study of patients with both heterozygous and homozygous hemochromatosis, and found that, although the high serum ferritin gradually went higher, because the study subjects daily absorbed more iron than they needed and got increasingly higher iron stores, neither the serum iron initially above normal nor the percent saturation of the iron binding capacity (i.e., of transferrin protein) went up.

Ferritin iron is high not only in heterozygous and homozygous hemochromatosis (where ferritin iron is often $>1,000 \mu\text{g/l}$), but also in situations of iron overload due to frequent blood transfusions, such as in hemolytic anemia like thalassemia and sickle cell disease.

Iron status

In iron deficiency, ferritin iron is below 10 (Figure 3). In iron depletion (Figure 3), ferritin iron can range from 5 to 15; in normal individuals, ferritin iron ranges from 20 to 50 $\mu\text{g/l}$, and in heterozygous hemochromatosis and early iron overload, well above that. With chronic long-term inflammation, serum ferritin iron does go up moderately, because chronic long-term inflammation means chronic release of noxious ferrous iron, some of which is sucked up by circulating ferritin.

Iron is the source of more than half of all the free radicals released in the human body (Figure 4). Free radicals in moderate amounts are necessary for life: for intact cell membranes and for intracellular metabolism. Free radicals are the price we pay for breathing. Oxygen is breathed in; water is urinated out. In the process of going from inhaling oxygen to urinating water, there are major free radical-generating biochemical reactions. While in small amounts, free radicals are necessary for life, in large amounts, they can mutate DNA and cause many other harms.

Vitamin C over-supplementation is a fad prevalent in the United States, with over 40%

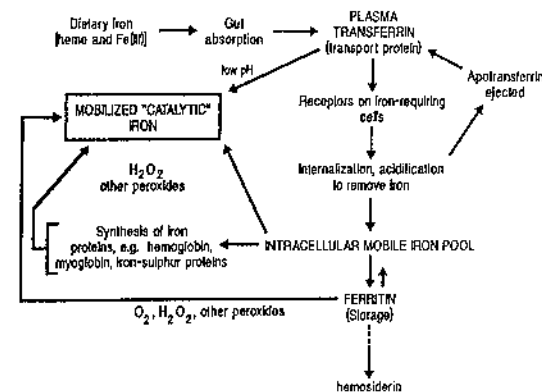


Figure 4: Pathways to catalytic Fe

of Americans participating. The claims that vitamin C pills are pure anti-oxidants is contrary to the fact that they are redox agents, anti-oxidant in some circumstances and pro-oxidant in other circumstances. The first demonstration of the pro-oxidant action of 1 g per day vitamin C was in our paper in the New England Journal of Medicine in 1963. We studied a patient with folic acid deficiency megaloblastic anemia, who also had scurvy because his only food was donuts, coffee, and restaurant thin hamburgers steamed long enough to destroy both the vitamin C and folic acid in them.

The patient was put on a folic acid-free diet to determine if vitamin C would correct the megaloblastic anemia. He was given 1 g vitamin C daily, and his reticulocytes, which had increased 5% to almost 10% before he was given vitamin C, plummeted to nothing after five days of vitamin C supplementation, proving our belief that vitamin C deficiency could produce megaloblastic anemia was wrong. However, on vitamin C, in 5 days, his serum iron went from 60 to 346, saturating his iron binding capacity. Vitamin C mobilizes harmless ferric iron from stores, converting it to the free ferrous form, which then leaks out of the 6 pores of the ferritin protein shell as catalytic

ferrous iron (Figure 5).

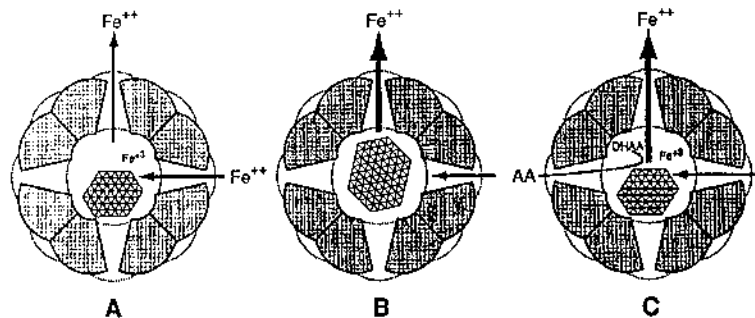


Figure 5: How ascorbic acid (AA) releases catalytic ferrous iron from harmless ferric iron stored in the ferritin protein shell

In patients with iron overload, genetic or acquired, 1 g vitamin C daily has the potential to pull so much iron out of their high iron stores that it can supersaturate every iron-binding protein in the body, with the excess free ferrous iron producing arrhythmias causing instant death.

References (selected readings)

Simopoulos A, Herbert V, Jacobson B.

Genetic Nutrition: Designing A Diet Based on Your Family Medical History. Macmillan Publishing Co., New York, and Maxwell Macmillan International, New York, Toronto, Oxford, Singapore, Sydney. 1993, 335 pages.

Herbert V, Subak-Sharpe GJ (Editors).

Total Nutrition: The Only Guide You'll Ever Need: From the Mount Sinai School of Medicine. St. Martin's Press, 175 Fifth Avenue, New York, NY, 1995. 811 pages. ISBN 0-312-11386-92.

Herbert V.

Iron supplementation study causes confusion. J Am Diet Assoc 1992;92(6):675- 676.

Herbert V.

Introduction. American Institute of Nutrition (AIN) Symposium on "Prooxidant Effects of Antioxidant Vitamins." J Nutr 1996;126(Suppl 4):1197S-1200S and Herbert V, Shaw S, Jayatilleke E. Vitamin C-driven free radical generation from iron. J Nutr 1996;126(Suppl. 4):1213S-1220S.

WHO Scientific Group on Nutritional Anemias.

World Health Organization Technical Report Series (Herbert V, redactor). 1968;405:1-37.

Herbert V, Shaw S, Jayatilleke E, Stopler-Kusdan T.

Most free-radical injury is iron-related: It is promoted by iron, hemin, holoferitin, and vitamin C, and inhibited by desferrioxamine and apoferritin. Stem Cells 1994;12:289-303.

Discussion

I. Cavill: It only goes to show that Victor Herbert is just as challenging in a sitting position as ever he is when he is standing up, or more particularly parachuting in onto your head! If any of you have any illusions which have not yet been shattered, any pre-conceptions that have not been challenged, and any other mantras that should be broken, let's have some questions.

C. Breymann: What is the main reason for malabsorption of iron?

V. Herbert: Good question; let me see if I can come up with a good or bad answer! See, he is a very bright guy, Dr. Breymann; I always take only bright people as fellows, because then they do very well and people say 'Gee, Victor Herbert is a brilliant mentor.' It is not that, it is just that I know how to pick students. It is like Harvard in the United States; it is considered by far the greatest medical school because its graduates are so good. I was on Harvard's medical school's admissions committee during the five years I was there and the reason our graduates were so good is because we only took the best students. All the best students apply to Harvard, so we take them; we could be lousy teachers but they would still come out great students! [Laughter]

So - I don't know, Dr. Breymann, what the major cause of malabsorption of iron is, but I know that malabsorption of iron occurs dietarily, for many reasons - for example, phytates bind iron and prevent it from being absorbed, so if you are eating a diet high in phytates (that is a high grain diet) you will have less iron absorption. That is one of the reasons vegetarians have less iron absorption. If you drink lots of tea, you will have less iron absorption because tannin in tea converts the iron you eat to iron tannate, which is totally unabsorbable. Tom Bothwell in South Africa and several others did a beautiful study showing that in the various ethnic groups in South Africa the worst iron deficiency was among the Indian women who drank lots of tea, so all their iron became iron tannate and was totally unabsorbable.

C. Breymann: What about heterozygous disease of malabsorption syndrome? Celiac disease?

V. Herbert: That also will reduce iron absorption. Any generalized malabsorption syndrome will reduce iron absorption. Talking about celiac disease, it is very important to bring that up because only one case in about 30 is diagnosed. With most

physicians, when a patient comes to them and they take a history, all the physician asks is 'Do you have diarrhea?' and the patient says: 'No'. This is not the case with the people I train at Mount Sinai. All of our medical students when taking a medical history are trained to say 'How many bowel movements do you have a day?', and not 'Do you have diarrhea?' or 'Do you have constipation?' This is because early on, I saw a patient in the clinic and the intern had done the preliminary examination; the patient was emaciated and the notes said 'No diarrhea'. I said 'How can this guy have no diarrhea? He is emaciated; he looks as though he just came out of a concentration camp'. The intern said 'Well, I asked him', so I said to the patient 'Do you have diarrhea?' and he said 'No'. I said 'How many bowel movements do you have a day?' and he said '12'. I said 'That is normal for you?' and he said 'Yes'. We looked at him and he had celiac disease, so never ask a patient: 'Do you have constipation, or diarrhea?'. Ask him how many bowel movements he has a day, and whether they flow.

J. Faes: Are there other clinical symptoms of iron deficiency? If the answer is yes, where would you put the cut-off?

V. Herbert: I assume you have asked that as a general question rather than just for pregnant women? The clinical symptoms are those of inadequate delivery of iron to iron-containing enzymes, which precedes the development of anemia. When you get inadequate delivery of iron for synthesizing hemoglobin early on, you do not yet have anemia; that does not start for another three or four months. Early on when you have inadequate delivery of iron to hemoglobin, you simultaneously have inadequate delivery of iron to all the new cytochromes being made. Those are the iron respiratory enzymes, so you get tired tissues before you get anemia.

This was first described by Ernie Beutler in 1963 to great laughter, but he turned out to be right. You get tired tissues first from inadequate iron in the respiratory enzymes, and that inadequate iron makes you feel tired and run down. People with early iron deficiency feel tired and run down, and if the physician carries out a hemoglobin test, it is normal; but it is still iron deficiency. However, there is a caveat, which is that weakness, tiredness and feeling run down are early symptoms not only of iron deficiency but also of iron overload. Remember, 10% of all Caucasians, male and female, have iron overload. That excess iron crushes bone marrow cells and produces

weakness, tiredness and a feeling of being run down. Never make a diagnosis of iron deficiency from the symptoms; always get a blood measure of iron status.

J. Faes: Thank you; does hair also need iron? Young women who lose hair?

V. Herbert: That is never due to iron deficiency. If a young woman loses hair it is due to something else. The most frequent cause of loss of hair in young women is the same as for young men - a genetic baldness. That is unless you are taking selenium pills; of course selenium pills in large doses produce baldness, and also your fingernails fall out.

I. Cavill: Could I just tell two little stories to bolster the point that Victor was making about the inhibitory effects of dietary substances on iron absorption? There is a case report coming out in the journal which I edit, where even oral ferosulphate absorption was inhibited and shown to be irreversibly inhibited by excess tea drinking. Do not treat these dietary stories as just anecdotes. They are real, and the diet has a powerful inhibitory effect in limiting the amount of iron that is available for absorption on the duodenal surface. It does not matter how much iron is in the diet, if it is not water soluble by the time it hits the duodenal mucosa it will never be available for absorption. Popeye - remember Popeye? - and the spinach and the iron?

V. Herbert: Sure, but of course Popeye lied!

I. Cavill: I'll tell the story! Iron in spinach is almost totally unabsorbable. If Popeye got any iron from that spinach he got it from contamination from the tin, not from the spinach itself!

V. Herbert: Exactly correct, and that is because spinach contains oxalate and iron oxalate is unabsorbable.