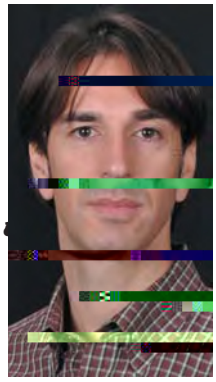
HEREDITARY HEMOCHROMATOSIS



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Hereditary hemochromatosis (HH) is the most common single-gene disorder in Caucasians, especially those of northern European descent. However, it is also underdiagnosed in the general population and often untreated. It is an autosomal recessive disorder associated with mutations in the HFE gene, one of the genes thought to regulate iron absorption, which is located on the short arm of chromosome 6. The diagnosis is based on a combination of clinical, laboratory and pathologic findings. The estimated mortality is 1.7 cases per 10,000 deaths, but life expectancy is close to normal if the disorder is detected early and treated properly before the onset of diabetes, liver cirrhosis or heart disease.

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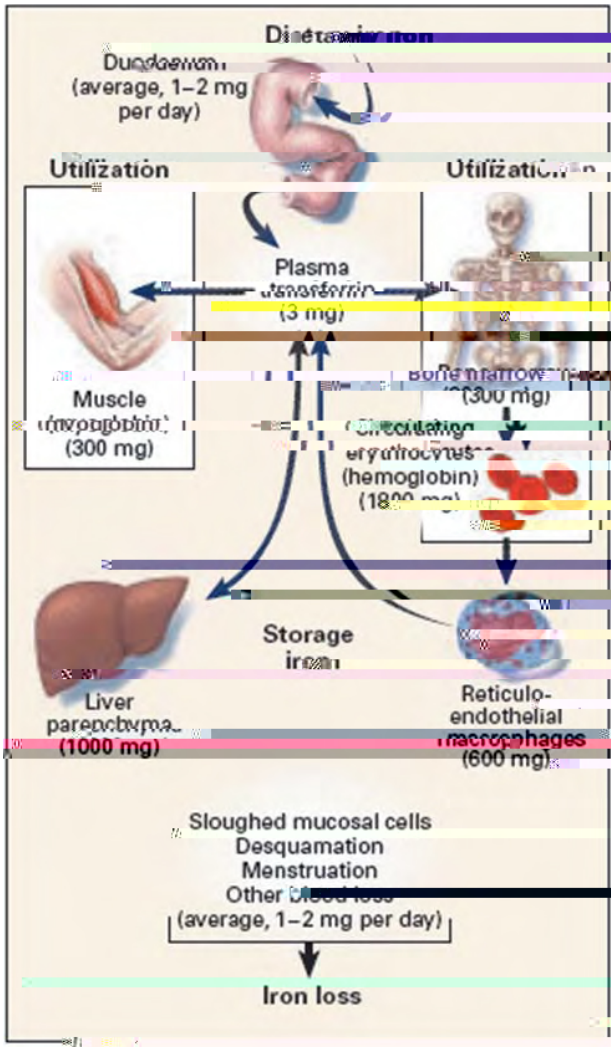
Iron is essential to life. Its ability to be both an electron donor and an electron acceptor makes it ideal for transporting oxygen, but it is also potentially toxic if excessive amounts are deposited in vital organs. Normal iron metabolism is critical for maintaining health and for producing erythrocytes (red blood cells). Iron is obtained by either intestinal absorption of dietary iron, or by recycling iron from senescent (aging) red blood cells via the reticuloendothelial system (RES). Both of these processes are tightly regulated depending on the body's metabolic needs.

Figure 1 (next page) shows the distribution of iron in adults. Healthy human adults have approximately 3,000-4,000 mg of iron in their bodies, most (around 2,500 mg) of which is found in hemoglobin within erythrocytes. Approximately 1,000 mg are stored in the liver and only 3-4 mg circulate in the plasma pool.

An adult male loses approximately 1 mg of iron per day via intestinal excretion, sweat and skin cell exfoliation, and urine. An adult female loses an average of about 2 mg daily during childbearing years, and an additional 500 mg with each pregnancy. These losses are offset by the absorption of 1-2 mg of dietary iron, most of which takes place in the duodenum (and to a lesser extent in the upper jejunum). Here, iron is absorbed by the villi of the enterocytes when it binds with the protein apoferritin, and is then either stored as the iron compound ferritin or transferred to the plasma via apotransferrin (a transport protein). The transfer to plasma of iron from the enterocytes takes place through specific iron channels (ferroportins), and is assisted by the protein hephaestin, which converts iron from the ferrous to the ferric form.

Another protein, divalent metal transporter 1 (DMT1), facilitates the transfer of iron (as well as other trace metals) across the intestinal epithelial walls. When apotransferrin binds to iron, it forms transferrin, which is the primary means of transfer for iron



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throughout the body. Transferrin helps maintain iron in the human body in a non-toxic state. It has two binding sites and is about 30% saturated under normal conditions, allowing additional room to transport excess iron if required.

Cells have transferrin receptors on their plasma membranes, which enable iron to be imported into cells in response to intracellular iron concentrations. Some iron ions are transported to the bone marrow, while others are transported to the liver, where they are stored in the hepatocytes. Erythrocyte precursors obtain iron for hemoglobin synthesis from plasma transferrin or from recycled senescent red cells by macrophages in the bone marrow, spleen and liver. Excess iron not required for hemoglobin production is stored in macrophages.

Iron is stored in the human body as either ferritin or hemosiderin, an insoluble protein that is a product of hemolysis.

Iron stores can be released from macrophages when needed for erythropoeisis (the production of red blood cells). Ferritin levels are, therefore, a good indicator of iron stores, and transferrin saturation a good indicator of recycled iron. Erythrocytes transport oxygen from the lungs to cells throughout the body, but in order to carry out this function they require ferritin, which is stored in hemoglobin, where it helps in binding oxygen molecules.

[See Figure 2, next page]

Although the amount of iron absorbed by the enterocytes is small, efficient regulation of iron absorption is vital for maintaining the body's homeostasis. Hepcidin, a protein synthesized in the liver, plays a key role in iron regulation. It inhibits ferroportin release and signals enterocytes to retain any absorbed iron (to be eliminated in a few days), thereby reducing the flow of iron into plasma. A decrease in hepcidin results in increased iron absorption.

Most individuals with hereditary hemochromatosis have mutations in the HFE gene which result in hepcidin deficiency. Iron toxicity occurs when there is free (or unbound) iron in cells, which generally occurs when iron levels exceed the capacity of transferrin to bind the iron. Iron overload is harmful, as it promotes the formation of free radicals such as the hydroxyl radical and the superoxide radical. These result in oxidative stress and can ultimately lead to cell injury and fibrosis.

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Hereditary hemochromatosis (also referred to as primary hemochromatosis) is a primary iron-overload condition which affects approximately 1 in 300 people. HH affects men more than women (1.8:1), and iron overload develops less frequently in women, likely due to blood loss through menstruation and therefore slower accumulation of iron. Over 70% of individuals with hereditary hemochromatosis are

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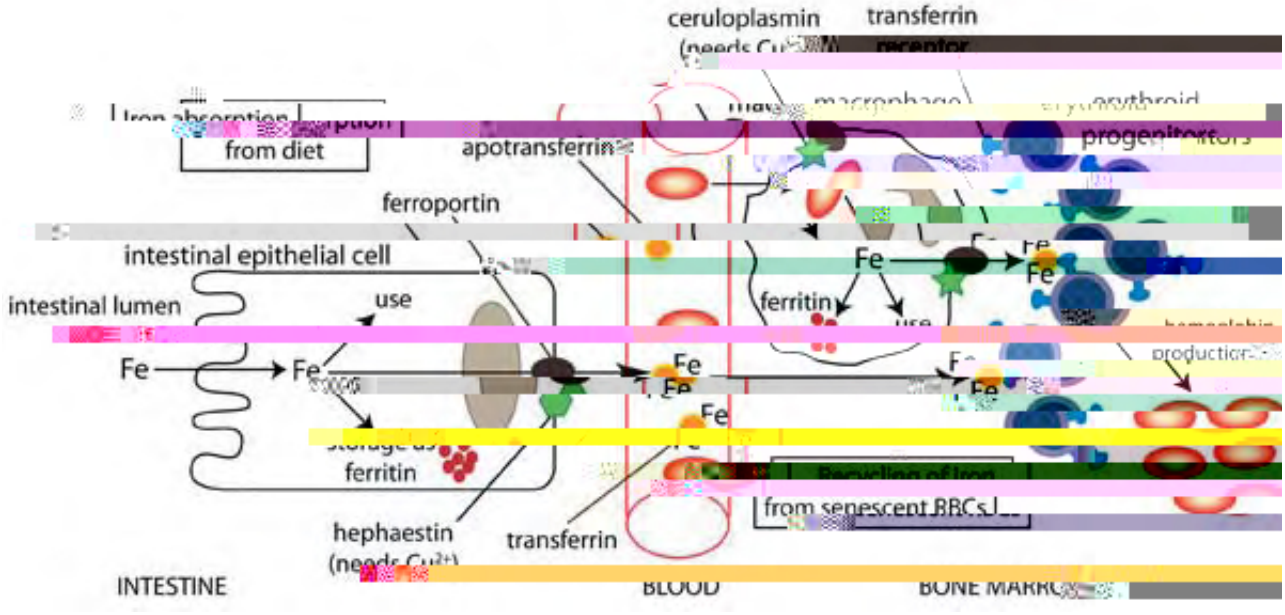

homozygous for the missense mutation C282Y, the substitution of tyrosine for cysteine at amino acid position 282 of the HFE gene. The highest prevalence seen for C282Y homozygosity is 1 in 83 people in Ireland, which is why hemochromatosis has also been called "the Celtic curse." Another missense mutation, H63D, is also associated with hereditary hemochromatosis, but its clinical effects appear to be much milder.

Individuals who are heterozygous for the C282Y mutation are not considered to have hereditary hemochromatosis. Those with compound heterozygosity for C282Y/H63D, however, seem to be more at risk for iron overload. An additional mutation associated with iron overload is in the gene encoding transferrin receptor 2 (TfR2), but few cases have been reported. Another form of hemochromatosis is juvenile hemochromatosis, in which iron accumulation begins much earlier (generally between the ages of 15 and 30). This form, however, is not associated with mutations in the HFE gene, but with the HJV gene and in some cases with the HAMP gene. The HFE, TfR2 and HJV genes all encode for proteins that affect hepcidin.

As people with hereditary hemochromatosis absorb only a few milligrams of excessive iron per day, clinical manifestations are usually not apparent until after many years, once the iron stores are 15 mg-50 mg. Disease expression usually occurs after age 40 in men and after age 50 in women, but it may occur much earlier.

The following are clinical manifestations of HH:

- Arthropathy
- Hypogonadism or impotence in males
- Skin pigmentation
- Liver disease
- Diabetes mellitus
- Cardiac enlargement

Some individuals never have any clinical manifestations, and many (between 50% and 70% of patients) are asymptomatic. In the past, hemochromatosis was diagnosed at older ages, with cardiac disease frequently a presenting manifestation (in up to 15% of cases). Today, a diagnosis most often occurs after routine lab testing shows elevated serum iron levels in asymptomatic people. Other patients might be diagnosed after being tested due to a family history of hemochromatosis.

Many cases are not suspected due to the patients' vague symptoms. Figure 3 (next page) shows the symptoms and manifestations of hemochromatosis over time. Today, due to genetic testing and early detection, full clinical expression of hemochromatosis is observed in only a minority of cases.

The most common early symptoms are fatigue and arthralgia. Males may also have hypogonadism (causing decreased libido and impotence) as a result of iron accumulation in the pituitary gland. Later in the course of the disease, patients may present with skin bronzing (hemochromatosis is sometimes referred to as bronze diabetes) or skin hyperpigmentation

disease. Serum ferritin, which indicates the amount of iron stored in the body, is highly sensitive for iron overload, but can also be elevated in the setting of infections and other inflammatory conditions even in the absence of iron overload.

The normal range of serum ferritin concentration in adult men is 20-300 mcg/L, and the normal range for adult women is 20-200 mcg/L. A ferritin level above 1,000 mcg is highly suggestive of liver fibrosis or cirrhosis. Patients with hemochromatosis commonly have high transferrin saturation levels, a high serum iron level and a low total iron binding capacity (TIBC).

In addition to genetic testing, important laboratory test results in diagnosing and following hemochromatosis are:

- Transferrin saturation
- Serum iron
- Ferritin
- Total iron binding capacity (TIBC)

Other laboratory tests to consider are those that pertain to the target organs.

In the past, liver biopsy and histologic evaluation with iron staining were recommended in order to diagnose hemochromatosis, but it is no longer essential for diagnosis in many cases, particularly with the availability of testing for the C282Y mutation. However, a liver biopsy is still considered the gold standard for determining the degree of fibrosis, and may be indicated either for individuals with ferritin levels in excess of 1,000 mcg/L or for those with hereditary hemochromatosis and elevated liver enzymes. Iron accumulation in the hepatocytes and biliary epithelial cells (staining shows a brownish pigment in the hepatocytes and Perl's Prussian blue staining confirms iron), and relative sparing of Kupffer cells are common findings in those with hemochromatosis. However, iron tends to accumulate in Kupffer cells of individuals with transfusional iron overload or from parenteral iron. Hemosiderotic liver damage does not typically result in significant inflammation; liver enzymes may be mildly elevated or normal even when there is significant fibrosis.

Genetic testing for the HFE mutation is indicated in first-degree relatives r iE il p tran emU p
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another common finding. Dilated cardiomyopathy can also result from hereditary hemochromatosis. These cases are characterized by a dilated left ventricle (or both ventricles) and impaired contraction, with a low ejection fraction. Patients may have significant arrhythmias such as sick sinus syndrome. Iron deposition in the bundle of His and in Purkinje fibers can result in conduction defects. Sudden death can also occur. Cardiac MRIs can also be useful for the diagnosis of cardiac involvement. In any event, HH with cardiac involvement carries a poor prognosis.

- – This is the major site of iron storage, and progressive iron deposition can result in tissue damage. Hepatomegaly develops early in the course of the disease, followed by fibrosis and then can progress to cirrhosis, which is one of the most common manifestations of HH. This can then progress to hepatocellular carcinoma, which is one of the main causes of death in hemochromatosis. Liver function abnormalities occur in a high percentage of individuals with hemochromatosis. Those with hereditary hemochromatosis and cirrhosis have a significant risk of developing hepatocellular carcinoma (over 200-fold). One study, which followed 95 patients with HH and cirrhosis, showed that 20% of the patients developed hepatocellular carcinoma. The cumulative survival for all patients was 88% at 1 year, 69% at 5 years and 56% at 20 years.

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Treatment is usually initiated for those with presumed iron overload, suggested by elevated serum ferritin concentration. Phlebotomy is the treatment of choice as it is simple, effective and inexpensive. The goal of this treatment is to remove iron from the body so as to avoid iron overload before it causes ferrit ú l ʈ

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