Conferences and Reviews

Overview of Hemochromatosis

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Hemochromatosis is a unique genetic disorder, or possibly a group of disorders, whose phenotypic expression is that of continued excessive absorption of dietary iron.[1-4] As a result, the body's iron stores typically increase markedly (Figure 1). The clinical manifestations of the disease result from damage to those organ systems in which iron has been pathologically deposited, most commonly the liver (cirrhosis), pancreas (diabetes mellitus), anterior pituitary (gonadotropin deficiency), heart (cardiomyopathy), and joints (arthritis). Hemochromatosis is one of the most common genetic disorders of whites. The diagnosis is frequently missed, however, because the early clinical manifestations of hemochromatosis are often subtle and atypical. Furthermore, many patients, especially women, do not develop any disability despite being homozygous for this condition. An effective, simple treatment is available, that of iron removal by phlebotomy; it is therefore particularly important that physicians become much more knowledgeable about this common disease.

Historical Background

Hemochromatosis received its name from von Recklinghausen exactly 100 years ago.[5] As is so frequently true, however, earlier descriptions can be traced to others, such as Trousseau and Troisier. Sheldon first suggested that hemochromatosis was an inborn error of metabolism and elaborated upon this theme and the clinical and pathologic description of hemochromatosis in his monumental monograph in 1935.[6] Twenty years later Finch and Finch further clarified the definition of the disease and the usefulness of iron depletion therapy by phlebotomy.[7] Over the succeeding years many investigators have contributed to our understanding of normal iron metabolism and the abnormalities characteristic of iron storage disorders. The genetic transmission of hemochromatosis remained unclear, however, until the seminal discovery by Simon and his colleagues of the close linkage of the phenotypic expression of hemochromatosis with HLA-A.[8] This has allowed the definitive demonstration that hemochromatosis is transmitted as an autosomal recessive disease. The last decade has witnessed new insights into the prevalence of hemochromatosis and the intricacies of iron metabolism at both the cellular and molecular levels. The basic abnormality of hemochromatosis still awaits elucidation, however.

Key Questions

As an "inborn error of metabolism," to use Garrod's venerable term, or as an autosomal recessive genetic disease, as it is now known to be, hemochromatosis produces a characteristic metabolic derangement. Most metabolic diseases are diseases of "too much" or of "too little." Hemochromatosis, a disease of "too much," is thought to be simply an inappropriate avidity for the absorption of dietary iron with resulting tissue damage from its pathologic deposition. Despite the advances of recent years, however, a number of questions remain:

1. What is the gene product, encoded on chromosome 6, the absence or defective nature of which leads to excessive absorption of iron?
2. What is the normal function of this presumed protein in controlling iron absorption? For example, is it expressed and does it function in the intestinal mucosal cell? Or is it a signal protein (i.e., a hormone) that informs the mucosal cell about the body's need for iron (the level of body stores or the rate of erythropoiesis)?
3. Is the pathophysiologic abnormality solely in the absorptive mechanism for dietary iron or are there additional abnormalities elsewhere in the internal economy of iron metabolism?[9]
4. Why has this genetic disorder persisted at such a high prevalence in whites?
5. How does excessive iron injure cells and thereby lead to the manifestations of the disease?
6. How can the diagnosis best be made? Should we screen routinely for this relatively common disorder?
7. Why does hemochromatotic liver disease so frequently lead to hepatoma?

These are but some of the questions that remain despite the rapid advances of the past decade.

Normal Iron Metabolism

An understanding of the abnormal metabolism of iron that is the hallmark of hemochromatosis requires a brief description of its normal metabolism.

STATE OF IRON IN THE BODY (Figure 2, Table 1). The average adult has approximately 3 to 4 grams of body iron.[10] Of this approximately two thirds is functional, largely in the heme groups of hemoglobin and myoglobin but also in the cytochromes, peroxidases, catalase, and other enzymes. There is no evidence of abnormalities in the synthesis of these iron-containing constitutents in hemochromatosis except as a nonspecific secondary effect of tissue damage, such as in cirrhosis. Storage iron ($\sim$1.0 g) is predominantly found in two forms—in ferritin and in hemosiderin.

Ferritin is a large (480,000 dalton), complex protein consisting of 24 subunits that combine to produce a shell around a core that is specialized to receive and bind iron as ferric hydroxyphosphate.[1] As many as 4,500 atoms of iron can be stored within a single ferritin molecule, to be released as needed for functional purposes. In fact, a number of ferritins exist in different organs, consisting of different mixes of H and L subunits, but no clearcut functional differ-

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ences of these various forms of ferritin have been demonstrated. Ferritin is also found in plasma, where its concentration tends to correlate with overall iron stores, despite the fact that most circulating ferritin is in the glycosylated form with low iron content. Normally about two thirds of storage iron is in ferritin, the synthesis of which is enhanced by an increase in iron stores.[11]

Hemosiderin, the poorly soluble aggregated form of tissue "stainable iron," probably represents the product of lysosomal degradation of tissue ferritin. It normally represents about one third of storage iron but is that form in which iron most markedly increases in iron overload syndromes. Hemosiderin iron can also be mobilized, through mechanisms that are unclear, for reutilization.

Transferrin, a specialized transport protein for iron, is largely synthesized in the liver and circulates in plasma with a half-life of about 8 days. This 77,000 dalton protein, which has two distinct binding domains for ferric molecules, is normally present in a concentration that can bind at saturation approximately 300 to 350 μg of iron per deciliter of plasma. It is normally about one third saturated with iron (ranges, 20% to 50% saturated). Transferrin is increased in concentration in the plasma and extracellular fluids during iron deficiency and decreased during iron overload. Normally only 4 to 5 mg of iron is found bound to transferrin.

Transferrin receptor.[12] Diferric transferrin molecules interact with specific cell surface receptors and are then internalized into the cell by receptor-mediated endocytosis (Figure 2). After the iron is released in the endocytic vesicle, both the receptor and the apotransferrin are recycled to the cell surface and become available for further use. The synthesis of the transferrin receptor is normally suppressed during iron loading and increased during iron deficiency, as might be anticipated teleologically.

Ferrokinetics (Figure 3). The body's iron does not exist in a homogeneous pool; it is found in various storage and functional forms. Nevertheless, all of it is ultimately available for mobilization and use. The shuttle movement of iron among cells and tissues, largely involving transferrin, is estimated at 25 to 35 mg per day in the average-sized adult. Ferritin and possibly other proteins may also serve to transport iron, in addition to the role played by transferrin.[13] This comparatively large internal circulation of iron is to be compared with a net input and loss of about 1.0 mg per day.

Absorption of Dietary Iron (Figure 4)

This brief review of hemochromatosis does not allow for an extensive discussion of the absorption of iron from the diet.[10] In general, two factors are paramount in controlling the amount of iron that is absorbed: (1) the amount and the bioavailability of iron in the diet and (2) the transport "set" of the intestinal mucosa.

TABLE 1.—*Iron-Containing Compounds in Humans**

	mg in a 75 kg male (approximate)	*mg/kg (approximate)*
Functional compounds		
Hemoglobin	2,300	31
Myoglobin	320	4
Heme enzymes	80	1
Nonheme enzymes	100	1
	2,800	
Storage complexes		
Ferritin	700	9
Hemosiderin	300	4
	1,000	13
Total	3,800	50

*From Bothwell TH, Charlton RW, Motulsky A: Hemochromatosis. *In* Scriver CR, et al (Eds): The Metabolic Basis of Inherited Disease. 6th ed. New York, McGraw-Hill, 1989, p 1433.

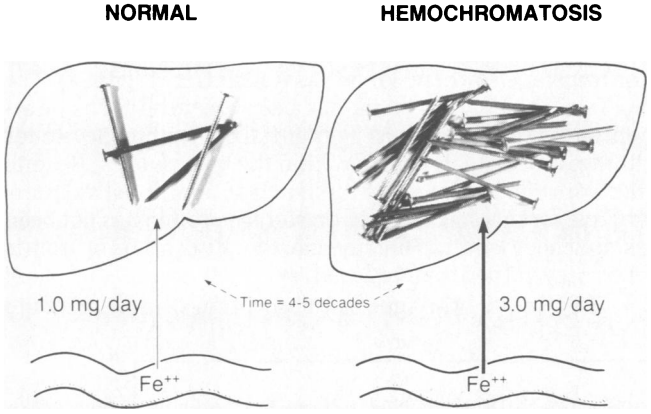

Figure 1.—Schematic illustration of the excessive absorption and storage of iron in hemochromatosis.

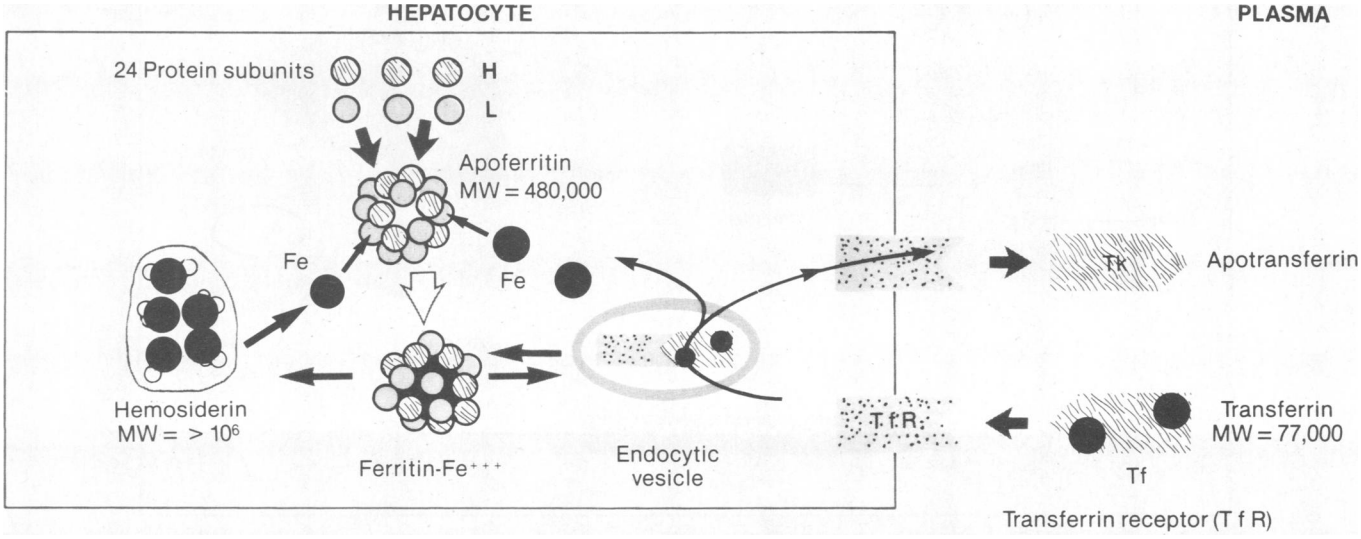

Figure 2.—The transport, storage, and use of iron in the body as illustrated by the hepatocyte. MW, molecular weight.

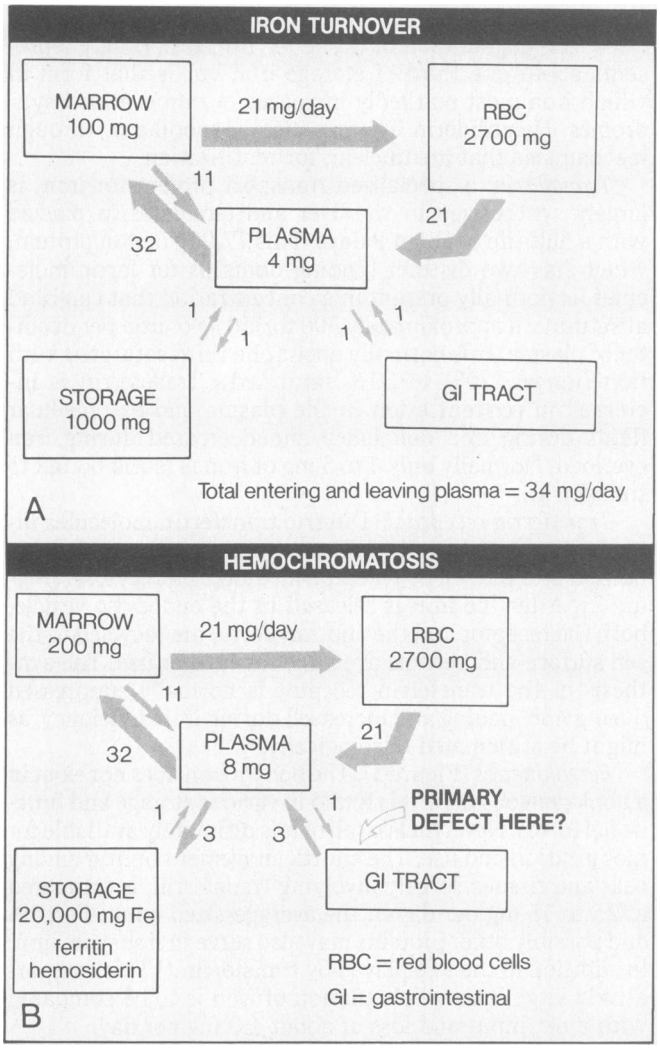

Figure 3.—A, Iron pools and turnover in normal humans; **B,** Iron pools and turnover in hemochromatosis.

Dietary Iron. The average American diet contains about 6 mg of iron per 1,000 kcal, or about 12 to 20 mg of iron per day. Of this approximately 90% is "free" iron and 10% is bound in heme. Heme iron is much more readily absorbed (~25%) as the intact molecule with subsequent intracellular release of iron by heme oxygenase. Nonheme iron is more poorly absorbed (~3%), presumably because of inhibition by certain ligands and other factors. Ascorbic acid greatly improves the absorption of nonheme iron both by reducing it to its more readily absorbed ferrous form and also by binding to it directly. Intraluminal factors seem not to play a primary role in the pathophysiology of hemochromatosis, so they will not be discussed further here.

Mucosal Transport. Normally there is a loss of only about 1.0 mg of iron from the body a day, largely through desquamation of cells and the loss of a small amount of blood.[1,10] This loss may be doubled in women through the blood loss of menstruation and the iron loss of pregnancy (approximately 500 mg). *There is no effective physiologic mechanism for the body to control iron balance through alteration of excretion if absorption is deranged.* This is unique for iron among the body's inorganic components, cations or anions. Homeostasis therefore requires a tightly controlled mechanism for the active absorption, or exclusion, of iron by the intestinal mucosa.

The components of the mucosal cell's mechanism for selective absorption of iron are unclear.[14,15] Included must be mechanisms for uptake of both heme and nonheme iron from the lumen, transport within the cell, possibly storage and sequestration within the cell, and release into the body for transfer elsewhere, largely as transferrin (Figure 4). The apoferritin/ferritin system has been a central focus of attention for many years as a potential controlling device for storage or transport of iron within the mucosal cell. Despite the work of many investigators, such an additional monitoring role for this specialized iron storage protein has not been established. In atransferrinemia the absorption of iron is enhanced rather than reduced.[13]

The "set" of the mucosal absorption of iron seems to

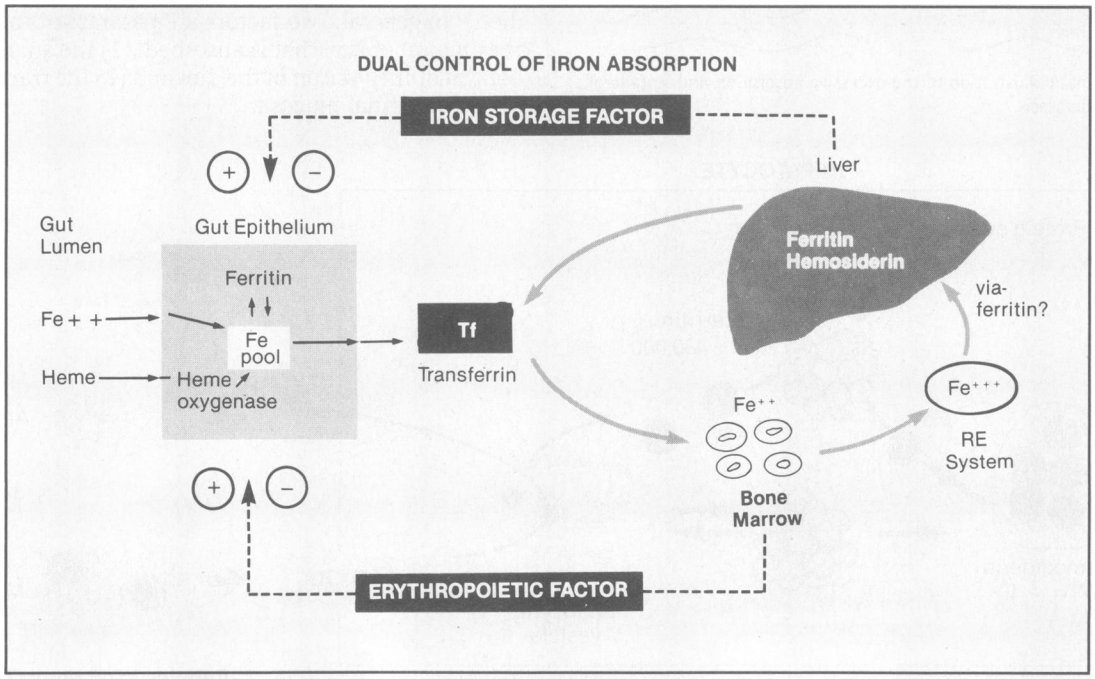

Figure 4.—A simplified illustration of the two physiologic variables that control iron absorption. The molecular details of the mechanism of iron transport control by the intestinal epithelium and the nature of the feedback signals remain to be elucidated.

depend on at least two independent variables[1,10] (Figure 4):

1. The state of iron stores. There is a very close adaptation of the absorption of iron to the amount of storage iron. Iron deficiency enhances absorption; iron excess depresses absorption. How the mucosal cell senses the state of the iron stores is unclear. Is it a local adaptation based on iron stores within the cell itself or does it receive a hormonal signal or some other type of signal from elsewhere?
2. The rate of erythropoiesis. An abnormally high rate of erythropoiesis will enhance iron absorption even in the presence of iron stores. This has been particularly noted in syndromes with ineffective erythropoiesis, such as that found in the thalassemic syndromes or in some of the sideroblastic anemias. This stimulus to iron absorption, presumably originating in the bone marrow, obviously requires a distal signal to the intestinal mucosa, but what that signal might be has not been established.

In brief, the control of the absorption of iron by the mucosal cell is the principal mechanism for maintaining a normal balance of iron. Two seemingly independent variables control the "set" of the mucosal cell: the state of iron stores and the rate of erythropoiesis. The cell biology of how absorption is appropriately adjusted by the intestinal mucosa and the nature of the signal or signals that it receives have not yet been clarified.

Pathophysiology of Hemochromatosis

Hemochromatosis is characterized by a loss of rate control resulting in a continued inappropriate absorption of dietary iron in the face of a pathologically enlarged store of iron. Both heme and nonheme iron seem to be absorbed excessively.[15] The rate of iron absorption may be reduced to normal as storage iron expands, but it remains inappropriately high for the level of storage iron attained. The excessive absorption is usually in the range of 1 to 3 mg of iron per day, leading to a total pool of 15 to 35 grams of iron over 35 to 60 years (see Figure 1).

The derangement leading to this abnormal avidity for iron remains obscure. Ferrokinetics are normal in hemochromatosis, except for the higher level of circulating iron (see Figure 3). No consistent abnormality of transferrin or its receptor has been found, and the genes for both are on chromosome 3 rather than chromosome 6, where the gene for hemochromatosis is found. Similarly, no abnormality of any of the isomeric forms of ferritin has been consistently found. The ratio of H to L subunits of intestinal ferritin was found to be normal, although the total level of ferritin was lower than would be predicted from the levels of plasma ferritin.[15] As already noted, the ferritins are not attractive candidates for the abnormal gene product of hemochromatosis because their coding genes are not on chromosome 6. The reticuloendothelial system seems to be relatively spared in hemochromatosis, with the major deposition of iron appearing in parenchymal cells, in contrast to what is typical in other iron overload syndromes.[9] Although this may be simply the result of the very slow accretion of iron over decades, attempts have been made to document abnormalities in iron metabolism in cells other than mucosal cells. An increase in the release of ferritin by monocytes from hemochromatotic patients has been recently described,[16] but this awaits confirmation.

In brief, although the general pathophysiology of hemochromatosis is clear, the specific abnormal gene product is not yet known. It is possible that elucidation of the abnormality may become apparent first through "reverse genetics," i.e., through isolating the abnormal gene prior to identifying its product, as was the case for Duchenne muscular dystrophy.[17]

Genetics of Hemochromatosis

The demonstration in 1975, since widely confirmed, that hemochromatosis is closely linked to HLA-A3 has led to major progress in understanding the disease[8,18] and may ultimately lead to isolation of the gene at fault (Table 2). In brief review, the gene for hemochromatosis is believed to be in close physical proximity to the HLA complex on the short arm of chromosome 6, probably found between the HLA-A and HLA-B loci and within 1,100 to 1,600 kb of HLA-A. This tight linkage to HLA leads to a recombination rate of only about 0.01. In addition to the linkage disequilibrium with HLA-A3, associations have also been noted with HLA-B7, HLA-B14, and HLA-A11. The reason for this tight linkage with HLA-A is unclear; it is probably due to the fortuitous location of a wholly unrelated gene. It has been postulated that the linkage of hemochromatosis to certain haplotypes of HLA-A and HLA-B could be caused by an initial rate mutation, presumably in an A3, B7 founder, followed by various chromosomal recombinations, one of the earliest of which led to A3, B14. The sequence of other chromosomal recombinations together with population migrations might have then led to the dispersal of the gene for hemochromatosis and its linkage that we find today.[18]

Some of the practical aspects of the discovery of the HLA linkage of hemochromatosis are as follows:

1. This has allowed the clear demonstration of the genetic nature of the disease and its autosomal recessive transmission (Figure 5).
2. Within families it has allowed the definitive diagnosis of homozygotes and heterozygotes and therefore the opportunity for early therapeutic intervention (Figure 5).
3. It has clarified "pseudodominant transmission" of the disease as being the result of the mating of a homozygous and a heterozygous parent.

TABLE 2.—*Linkage Disequilibrium Between Hemochromatosis and HLA**

HLA	Hemochromatosis	Controls
A3	73%	20-30%
B7	46%	20-25%
B14	20%	6-9%

*Data from Simon M et al: The genetics of human chromatosis. Prog Med Genetics 1980; 4:135

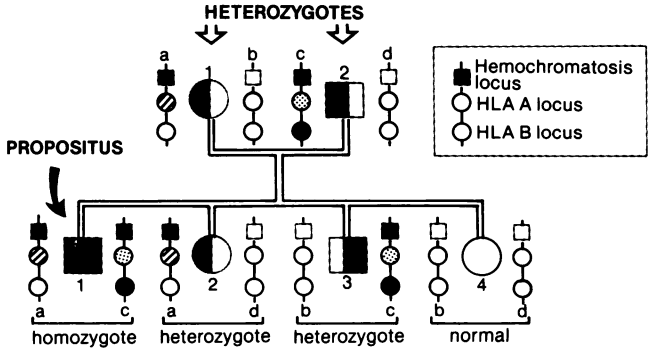

Figure 5.—Linkage of hemochromatosis alleles with HLA haplotypes in a family with a precise mendelian distribution. The relationships between the gene and the A and B loci are shown as topographic approximations. (Reprinted by permission of Beaumont CM, Simon M, Fauchet R, et al: Serum ferritin as a possible marker of the hemochromatosis allele. N Engl J Med 1979; 301:169.)

4. It may well allow for isolation of the abnormal gene and the determination of the true phenotypic nature of hemochromatosis rather than its indirect study as reflected in aberrant iron metabolism.

HLA typing is of no practical use in surveying for hemochromatosis in the population at large. Neither is it of use in the diagnosis of an individual patient if the particular linkage of HLA and hemochromatosis has not been established in at least one member of that family by the independent means of demonstrating iron overload.

Prevalence of Hemochromatosis

In the absence of a direct marker for the disease, the prevalence of hemochromatosis can be approximated only by large surveys for the detection of iron overload. Iron overload is presumed to represent hemochromatosis in the absence of other known causes, such as excessive ingestion of iron, transfusions, increased erythropoiesis, and other possible diagnoses to be discussed later. When an index case is identified, other cases of hemochromatosis can be identified by family studies based on haplotype and allele sharing.

A large number of such studies, carried out in many parts of the world, have demonstrated reasonably consistent findings for individuals of European origin.[19,20] First, the gene frequency for hemochromatosis is approximately 0.05; i.e., approximately 10% of whites carry one gene for hemochromatosis and are therefore heterozygotes. Second, approximately 1 in every 300 to 400 individuals is homozygous for hemochromatosis. (Recent Swedish studies suggest that the figure may be closer to one in every 1,000 persons.[20]) This means that possibly 500,000 to 700,000 persons in the US have hemochromatosis, allowing for presumed ethnic differences in population. Hemochromatosis may therefore be the most prevalent genetic disease of whites, roughly comparable to the prevalence of sickle cell disease in blacks. The prevalence of hemochromatosis in nonwhites seems to be much less, but this finding has not yet been well studied. These surprising conclusions have raised the following questions:

1. Why would a recessive disorder such as hemochromatosis continue at such a high prevalence? Is there some countervailing advantage to being a carrier of hemochromatosis, comparable to the protective effect of sickle cell trait against falciparum malaria? Is it possible that the increased ability to absorb iron exhibited by the heterozygote may have had some selective advantage? Is it alternatively possible that the HLA-A3 haplotype has carried some selective advantage and that the hemochromatosis gene has been the passive beneficiary through chance propinquity? Hemochromatosis carries very little reproductive disadvantage, since its major manifestations usually occur after the time of most active reproductive function.
2. Why is hemochromatosis so rarely diagnosed if 1 out of every 300 to 400 patients who enter our hospitals and clinics has this disease? This conundrum will be discussed subsequently.

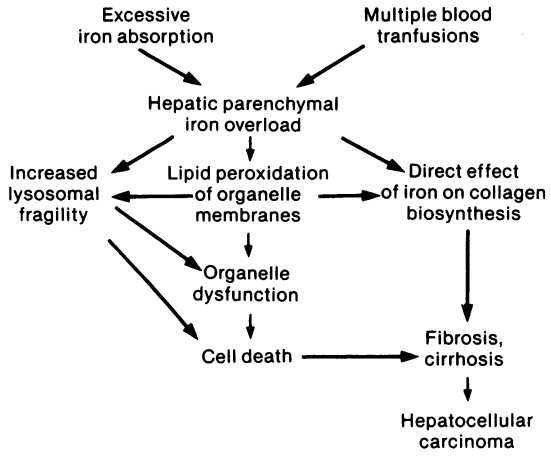

Figure 6.—Proposed pathophysiologic mechanisms of liver injury in chronic iron overload. (From Bacon BR, Brittenham GM, Park CH, et al: Lipid peroxidation in experimental hemochromatosis. Ann NY Acad Sci 1988; 526:155.)

Mechanisms of Tissue Damage in Iron Overload

The exact mechanisms by which chronic iron overload leads to tissue injury and fibrosis are not established. The current leading theories are reflected in Figure 6. Iron overload results in peroxidation of cellular lipids both in vitro and in vivo, either through the formation of oxygen-free radicals or through the formation of ferrous-dioxygen-ferric chelate complexes.[21] Peroxidation of lipids injures lysosomal membranes with the intracellular release of hydrolytic enzymes and impairs hepatic mitochondrial oxidative metabolism.[22] Hepatic microsomal function is also impaired in experimental iron overload, as reflected in a decrease in cytochrome P-450 concentration and aminopyrine demethylase activity. Excess hepatic iron may also directly increase the synthesis of collagen in the liver independently of producing necrosis of hepatocytes. Excess iron increases the catabolism of ascorbic acid and may lead to scurvy when dietary sources of that vitamin are marginal.

Clinical Manifestations of Hemochromatosis

Variables in the Clinical Expression of Hemochromatosis

As a genetic disorder, hemochromatosis is present from birth. Insofar as is known, however, the only adverse effect of the abnormal (or missing) gene product is that of continued excessive absorption of iron and its excessive storage in parenchymal cells. No definitive abnormality in the body's internal economy of iron usage and exchange has been found other than its excessive storage. Typically, hemochromatosis becomes clinically manifest in later life, in men more frequently than women (9–10:1), and in the presence of expansion of the body's storage iron by 20- to 30-fold. At least five variables influence the age of onset and the severity of the manifestations of the disease.

1. *Time.* As previously noted, the extra absorption of iron in hemochromatosis is usually in the range of 1 to 3 mg per day. Because of this slow accretion, the 15 to 35 grams of storage iron characteristic of the disease usually accumulate over decades, with the clinical manifestations of the disease most commonly appearing in the 5th and 6th decades.[6,7]

2. *Dietary availability of iron.* The rate of iron absorption in hemochromatosis is influenced by the amount of dietary iron and by other variables that normally affect iron absorption, such as ingestion of ascorbic acid, action of intraluminal ligands, mix of heme and nonheme iron, and other factors.[10]

3. *Loss of iron.* For practical purposes, this means the loss of blood. Hemochromatosis is an autosomal disorder, occurring equally in men and women. The clinical manifestations of the disease are found much more rarely in women, however, who represent only about 10% of reported cases. This has been attributed to the extra loss of iron in women through menstruation and pregnancies; however, other factors may be at play, including lower levels of dietary iron.

4. *Genetic heterogeneity.* Hemochromatosis may present with severe iron overload during childhood or, conversely, may produce no clinical abnormalities throughout the life of the patient. As is the case for other genetic disorders, it can be assumed that a number of different mutations at the hemochromatotic locus may impair the function of the gene product to varying degrees and in this manner contribute to the variable phenotypic severity of the disease.

5. *Specific organ involement.* The pattern of organ damage in hemochromatosis does not follow a predictable sequence. The causes of these variations are unknown.

Frequency of Clinical Manifestations of Hemochromatosis in Homozygotes and Heterozygotes

As noted, the use of HLA linkage studies within families permits the diagnosis of homozygous and heterozygous hemochromatosis independent of studies of iron metabolism. This has allowed for estimations of the frequency with which abnormalities of iron metabolism and clinical manifestations of iron overload occur in the presence of the abnormal gene or genes.[23,24] In these studies adult heterozygotes were found not to develop the clinical manifestions of hemochromatosis, but approximately one third of them exhibited evidence of minor iron overload (somewhat increased transferrin saturation, increase of hepatic iron by stain and analysis). All adult male homozygotes exhibited major iron overload, and some clinical manifestations attributable to hemochromatosis were present in 11 of the 13 studied (85%). All female homozygotes also exhibited some iron overload but less than that of their male counterparts (average body iron of about 8 grams as opposed to 20 grams for men). Only one of the seven women studied had clinical manifestations of hemochromatosis.

This small series is consistent with previous observations of the increased frequency of the clinical manifestations of hemochromatosis in men and the greater iron overload in men as an explanation of that fact.

Symptoms and Signs of Hemochromatosis (Figure 7)

Patients may exhibit a wide variety of symptoms and signs at the time of initial presentation.[1-3] Many of these are nonspecific or may suggest other disorders. The classical manifestations of hemochromatosis (the triad of cirrhosis, diabetes mellitus, and pigmentation) are late complications and occur together in a minority of patients. In view of its high prevalence, hemochromatosis must be considered more frequently in the presence of presentations such as atypical arthritis, impotence, cardiomyopathy, and upper abdominal pain. The clinical abnormalities of hemochromatosis will be discussed for convenience under the various organ systems involved. As noted, however, the mix of organ dysfunction may vary widely among individual patients for reasons that are unclear.

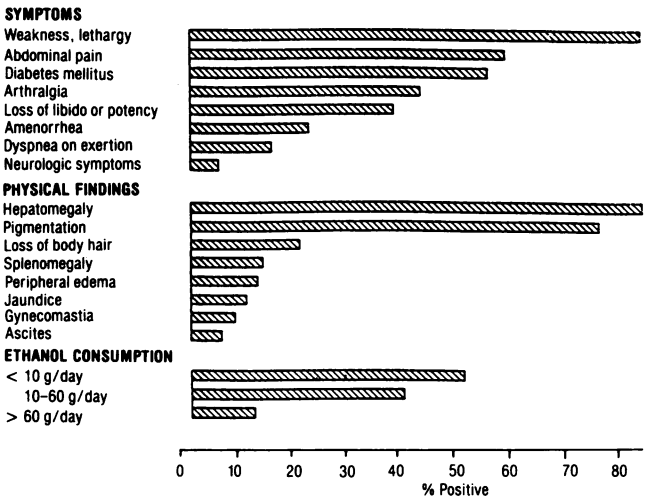

Figure 7.—Frequency of clinical symptoms and signs at the time of diagnosis in 163 patients with hemochromatosis. (From Bothwell TH, Charlton RW, Motulsky A: Hemochromatosis. *In* Scriver CR, et al (Eds): The Metabolic Basis of Inherited Disease. 6th ed. New York, McGraw-Hill, 1989, p 1433.)

LIVER. The liver is normally a major site of iron storage. It is not surprising, therefore, that it is often pathologically and clinically involved in hemochromatosis.[7,10] In fact, measurement of the concentration of iron in the liver is the most definitive test for the diagnosis of an index case of hemochromatosis. Levels may exceed the normal level of 40 to 120 μg of iron per 100 mg dry weight by 50- to 100-fold. Typically, hemosiderin granules are seen as stainable iron, particularly in hepatocytes and in bile duct epithelium. Iron is rarely seen in the Kupffer cells until the later states of the disease, in contrast to the iron overload seen in secondary hemochromatosis, such as that occurring after multiple transfusions.[9] Accompanying the iron deposition, degeneration of hepatocytes and varying degrees of fibrosis are seen. In advanced hemochromatotic liver disease there is hepatomegaly with macronodular cirrhosis. The classification of the initial histologic findings in a series of 71 cases is shown in Figure 8.[25]

The clinical manifestations of liver disease in hemochromatosis tend to be subtle and insidious in onset. Synthetic function is usually well maintained (albumin, prothrombin) and esophageal varices and ascites are less frequently present than in Laennec's cirrhosis. Three aspects of hemochromatotic liver disease are worthy of note:

1. The frequent association of clinical hemochromatosis and alcohol abuse has long been noted. Advanced cirrhosis may occur in hemochromatosis in the absence of alcohol ingestion, however. Patients with hemochromatosis who drink alcohol actually tend to have lower rather than higher levels of hepatic iron,[26] presumably due to a poorer diet, bleeding from gastritis, and other factors. It seems likely, therefore, that alcohol is an inde-

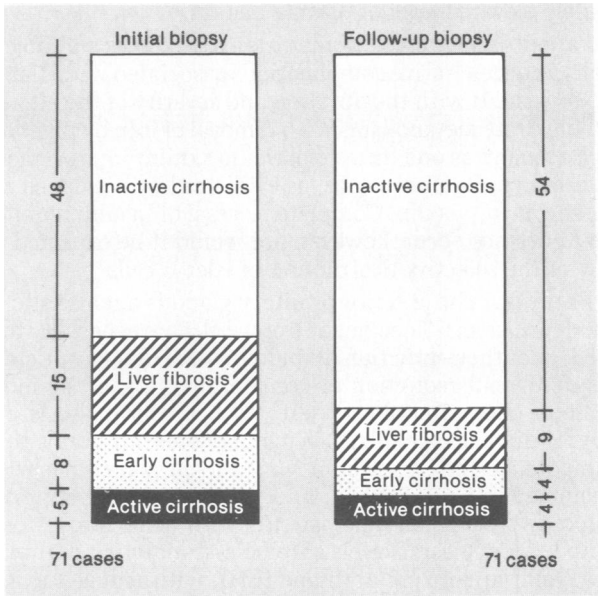

Figure 8.—Classification of initial histologic findings and follow-up findings in liver biopsies from a 71-case series. (From Tiniakos G, Williams R: Cirrhotic process, liver cell carcinoma and extrahepatic tumors in idiopathic hemochromatosis. Appl Pathol 1988; 6:128.)

pendent hepatotoxin in hemochromatosis, although it may add to the injury attributable to iron storage disease.

2. Hepatic function often improves markedly following the removal of excess iron by repeated phlebotomy. Actual reversal of fibrosis has been described, but this may be due to biopsy sampling errors. In a careful follow-up study of 71 patients during an average of 7 years of therapy, the histologic changes were classified as follows: unchanged, 62%; worse, 32%; improved, 5%.[25]
3. Hepatoma is a frequent complication of hemochromatosis, occurring in as many as 15% to 20% of those patients who have developed cirrhosis.[27] The increased risk of hepatoma in hemochromatosis is estimated to be 200-fold. Unfortunately, the successful removal of the excess hepatic iron by phlebotomy does not seem to reduce the risk of subsequent hepatoma.

As will be noted below, the development of hepatic cirrhosis adversely affects the long-term prognosis of patients with hemochromatosis.

PANCREAS. The association of hemochromatosis with diabetes mellitus was noted early.[28] It remains, however, as a complex relationship. The reported prevalence of diabetes mellitus in hemochromatosis has varied widely depending on the stage of the disease at which the diagnosis was made. A figure of 40% to 60% of overt diabetes mellitus in hemochromatosis is most frequently reported.[2,7] Most pancreatic iron in hemochromatosis is deposited in acinar cells, but no exocrine deficiency of the pancreas has been described. In the islets iron is selectively deposited in the B cells, with no abnormalities of the islet cells A, D, and PP cells.[29] The islets are similar in iron overload of either genetic or secondary origin and differ markedly in structure from those found in either type I or type II diabetes mellitus. In hemochromatotic diabetes the insulin response to a glucose load is significantly impaired, but the secretion of glucagon is normal. An additional factor appears to be a degree of insulin resistance. Even in the presence of a normal glucose tolerance test, patients with hemochromatosis demonstrate a tendency toward insulin resistance as reflected in an inappropriately elevated level of plasma insulin.[30]

Patients with hemochromatosis and diabetes are subject to all the degenerative complications associated with diabetes, consistent with the duration and severity of the altered carbohydrate metabolism. With removal of iron by phlebotomy, as many as one third of patients exhibit improvement in carbohydrate intolerance, as evidenced by a reduced requirement for insulin. Complete reversal of insulin requirement does not occur, however, nor would it be expected in view of the selective destruction of islet B cells.

PITUITARY. The anterior pituitary gland is a major site of iron deposition.[31] The gonadotropic cells are especially targeted and their function impaired. It is not surprising, therefore, that reduction of gonadal function is the most common endocrine abnormality in hemochromatosis except for diabetes mellitus. The clinical presentation is that of impotence and loss of libido in the male, sometimes with accompanying testicular atrophy. In some studies approximately two thirds of male patients with hemochromatosis exhibited low plasma levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), with reduced to absent response to stimulation by clomiphene or by luteinizing hormone-releasing factor (LHRH).[30] This is a pattern diagnostic of gonadal failure secondary to pituitary insufficiency. When the diagnosis for homozygosity for hemochromatosis was made earlier by HLA linkage studies, only 5 of 41 men were found to have hypogonadism.[32]

Although the majority of patients have hypogonadotropic hypogonadism, a few have been described with evidence of primary testicular (Leydig cell) failure as manifested by low levels of plasma testosterone and elevated levels of gonadotropic hormones (LH and FSH) together with failure to respond to exogenous gonadotropic stimulation.[33] Other hormones of the anterior pituitary gland are usually secreted normally, or else abnormalities in their secretion are demonstrable only by sophisticated endocrinologic studies.

Patients with hemochromatotic cirrhosis and hypogonadism differ from those who have alcoholic cirrhosis and hypogonadism not only in the relative specificity of the pituitary lesion but also in their lack of the associated signs of hyperestrinism, such as gynecomastia and spider angiomata.[30] The gonadal deficiency of hemochromatosis is usually irreversible and may require androgen replacement therapy in the male. A few patients have had a return of normal endocrine function following phlebotomy.[32]

Hypogonadism is rarely seen in women with hemochromatosis, presumably because of their lower iron overloads and the usual presentation of the disease in women after the time of menopause. In one study of 23 women with hemochromatosis, none had any laboratory evidence of gonadotropin deficiency and none had had a premature menopause or loss of libido.[32] A few younger women with hemochromatosis have been reported to have amenorrhea, with response to the removal of iron.

In summary, the gonadotrope of the adenohypophysis shares with the B cell of the pancreatic islet a special susceptibility to iron injury. As a result, impotence and loss of libido in men may be subtle early manifestations of hemochromatosis. Although other isolated endocrine abnormalities have been sporadically reported in hemochromatosis, their association with this common metabolic disorder may be fortuitous. In contrast to some of the other manifestations of hemochromatosis, endocrine deficiency is usually irreversible.

SKIN. Increased pigmentation of the skin was noted early as a manifestation of hemochromatosis as "bronze diabetes." In one series of 100 cases, hyperpigmentation was noted in 98%,[34] but with more sensitive recent methods for earlier diagnosis this sign of hemochromatosis is much less frequently found. The increased pigmentation, classically described as slate-gray or metallic gray but often shading into brown, is usually diffuse but tends to be exacerbated in exposed areas, in the external genitalia, in the nipple areola, and in flexion folds. Approximately 20% of patients have associated hyperpigmentation of the buccal mucosa and conjunctivae. Pathologically, both melanin and dermal iron are increased, the latter occurring most typically as siderosis around eccrine sweat glands. The shade of pigmentation and the relative degrees of melanosis and siderosis correlate poorly. With phlebotomy the skin pigmentation tends to lighten with the loss of siderosis, but some excess of melanin remains. The pathogenesis of melanosis in iron overload states is unclear.

Other dermal manifestations of hemochromatosis include (1) atrophy, often with scleroderma-like changes, most prominently in a pretibial location; (2) ichthyosis, varying from simple xerosis to generalized ichthyosis vulgaris; (3) koilonychia, together with longitudinal striations and brittleness of the nails; and (4) loss of body hair, including pubertal hair.[34] The latter may be related to gonadal failure.

HEART. The heart is frequently involved both pathologi-

cally and clinically in patients with hemochromatosis. Approximately one third of patients with untreated hemochromatosis die of cardiac failure. For reasons that are obscure, this is particularly common with severe hemochromatosis that presents clinically in early life. In the heart, iron deposits in the sarcoplasm of the myocytes with little or none being deposited in the interstitium.[35] The ventricles are more involved than the atria. Degeneration and necrosis of muscle fibers may result, but there is comparatively little inflammation or fibrosis. These findings are readily demonstrable by endomyocardial biopsy.[36] The most frequent resulting abnormality is that of dilated cardiomyopathy (dilated ventricles, reduced ejection fraction) with congestive heart failure. Much less commonly there is restrictive cardiomyopathy that may resemble the clinical picture of constrictive pericarditis. The ventricular wall is usually normal in thickness.[37] Atrial tachyarrhythmias are often observed. The electrocardiographic findings are nonspecific, most commonly showing ST and T wave changes with or without low voltage.

The cardiomyopathy of hemochromatosis is potentially reversible with the removal of iron, but this may be a prolonged process. With severe cardiac involvement, many patients die during the months necessary for effective removal of the iron overload.

BONE AND JOINTS. In a recent study osteopenia was found in 10 of 22 men with hemochromatosis,[38] confirming and extending previous observations. By means of spinal radiography, spinal and forearm bone mineral density estimations, dynamic skeletal histomorphometry, and biochemical measurements the osteopenia was determined to be that of osteoporosis. No evidence of osteomalacia or osteitis fibrosa (hyperparathyroidism) was found. The osteoporosis was found to be associated with evidence of both inadequate bone formation and excessive bone resorption. The radiographic changes seen in bone adjacent to joints involved in hemochromatotic arthritis are described below.

Arthritis is now the most common clinical manifestation of hemochromatosis[39] and not infrequently is the first evidence for the presence of the disease. Approximately 50% of patients develop arthritis, although the percentage tends to be higher in women than in men. How iron overload leads to arthritis has not been established. In hemochromatosis iron can frequently be demonstrated in chondrocytes and in synovial lining cells, particularly in those that are synthetic rather than phagocytic,[40] but there is poor correlation between the histologic findings and the clinical or radiographic abnormalities. When effusions are present, they tend to be noninflammatory except when there is microcrystalline synovitis of pseudogout associated with calcium pyrophosphate dihydrate (CPPD) or hydroxyapatite crystals. Ferric ions inhibit the action of pyrophosphatase and in that manner may increase the local concentration of pyrophosphate and its tendency to crystallize. The potential role of iron to produce oxidant injury has been described already. The relative frequency with which joints are involved in hemochromatosis is shown in Table 3.

Many of the features of arthritis in hemochromatosis resemble those of degenerative joint disease, and this misdiagnosis is frequently made. Notable is the frequency of associated chondrocalcinosis, occasionally complicated by pseudogout. More typical is a form of chronic arthritis in-

TABLE 3.—*Joints Involved in the Arthropathy of Hemochromatosis (Percentage of 159 Patients)**

Metacarpophalangeal	48%	Hips	30%
Proximal interphalangeal	47%	Wrists	28%
Knees	45%	Shoulders	27%
Back and neck	36%	Distal interphalangeal	21%
Feet	32%	Ankles	10%

*From Schumacher HR, Straka PC, Krikker MA, et al: The arthropathy of hematochromatosis: Recent studies. Ann NY Acad Sci 1988; 526:224.

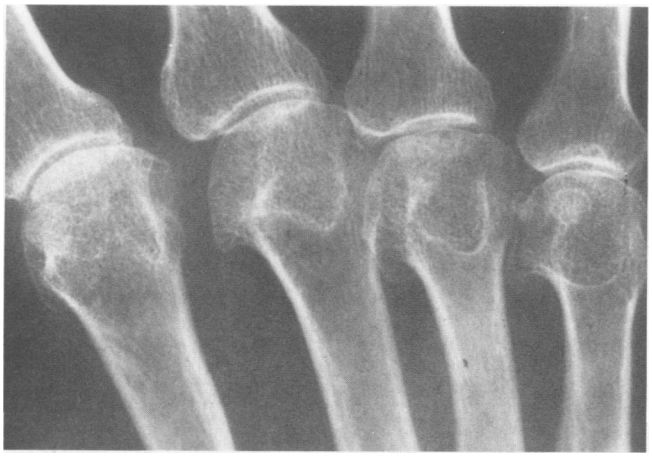

Figure 9.—An oblique radiograph of the metacarpophalangeal joints demonstrates typical changes consisting of narrowing of joint spaces, subchondral sclerosis, collapse of subarticular bone producing a "squared-off" configuration, and prominent "teardrop" osteophytes. (Courtesy of Harry K. Genant, MD.)

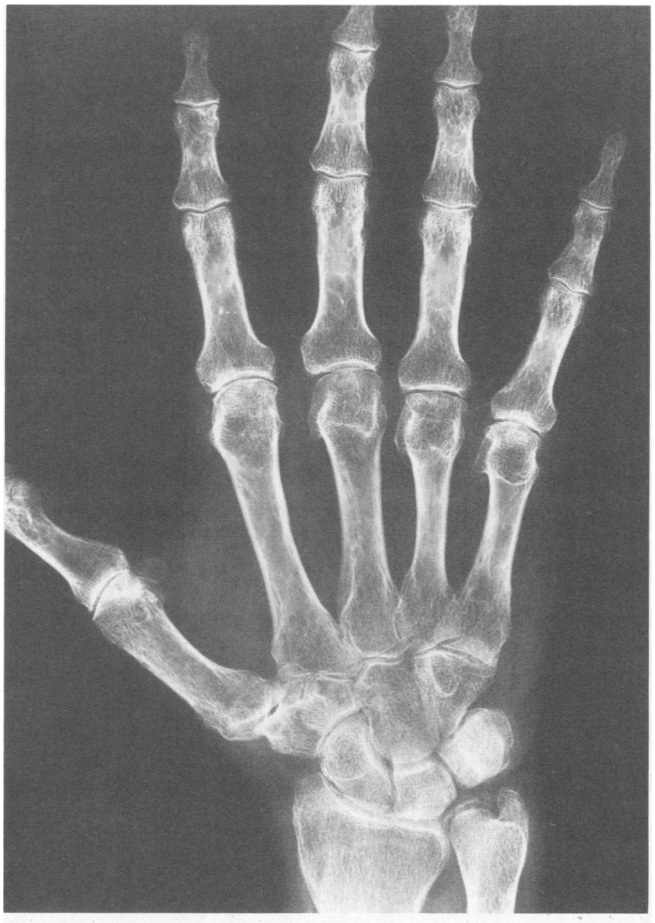

Figure 10.—PA radiograph of the hand demonstrates generalized osteopenia of the osseous structures, chondrocalcinosis of the triangular cartilage at the wrist, and degenerative changes at the metacarpophalangeal joints, all characteristic of the osteoarticular changes of hemochromatosis. (Courtesy of Harry K. Genant, MD.)

volving the metacarpophalangeal and proximal interphalangeal joints of the second and third digits.[40] This characteristic presentation is often mistaken for seronegative rheumatoid arthritis or for degenerative joint diseases. Certain radiographic findings in the hands strongly suggest the presence of hemochromatosis (Figures 9 and 10):

1. The joint spaces of the affected joints are narrowed with loss of cartilage and delicate cyst formation and with osteopenia in the metacarpal heads.
2. The metacarpal heads tend to be squared off with a type of bone overgrowth that leads to "teardrops" or hooked osteophytes.
3. Chondrocalcinosis may be present in as many as 50% of patients.

These particular radiographic findings, associated with chronic arthritis most prominent in the metacarpophalangeal joints, strongly suggest the diagnosis of hemochromatosis, even in the presence of normal levels of circulating iron.

In general the arthritis of hemochromatosis does not usually improve significantly following the removal of iron by phlebotomy. In one large series (129 patients), only 20% reported that they were better in joint symptoms during or after treatment.[40]

Abdominal Pain. Patients with hemochromatosis not infrequently complain of persistent epigastric or right upper quadrant aching pain.[2,27] Most frequently this pain is associated with cirrhosis, occasionally marking the appearance of a complicating hepatoma; however, often no cause for the pain can be assigned. It tends to improve greatly or to disappear with successful removal of iron by phlebotomy.[41]

Infections. Patients usually manifest hemochromatosis in later life and not infrequently have debility associated with diabetes mellitus, cirrhosis, and/or heart disease. It is not surprising, therefore, that they may develop infectious complications as well. The availability of iron is a limiting factor in the growth of some microorganisms, and the withholding of iron from these microorganisms by the body's binding proteins is considered to be a form of host defense.[42] It follows that patients with hemochromatosis (in whom iron is much more readily available) may be at increased risk for infections caused by such organisms as *Yersinia enterocolitica*,[43] *Pasteurella pseudotuberculosis*, and *Vibrio vulnificus*.[44] Beyond being a limiting nutrient for the invading microorganism, iron overload may possibly impair phagocytosis and may also have a variable number of adverse effects on lymphocytes and macrophages.[45] Despite these effects, an increased susceptibility to infection is not usually a prominent feature of hemochromatosis.

Neoplasms. The marked association of hepatoma with hemochromatotic cirrhosis has been described earlier. An increased incidence of other malignant tumors in patients with excess body iron has been reported[46] and its existence denied.[41] Iron may be carcinogenic when injected into experimental animals, but usually with the production of sarcomas. Iron overloading suppresses the tumoricidal activity of macrophages.[47] It remains to be shown, however, that malignant tumors other than hepatoma occur more frequently in patients with hemochromatosis than in age-matched controls. The nonhepatoma neoplasms that have been noted have not demonstrated any characteristic pattern.

Central Nervous System. In one notable study changes in mental status were found in approximately one third of patients with hemochromatosis.[2] Most frequently observed were lethargy, psychomotor retardation, and inability to think clearly, although progression to disorientation and decreased responsiveness to external stimuli sometimes occurred. These symptoms tended to improve with the removal of iron by phlebotomy. Episodic confusion and dementia have been described in other patients with hemochromatosis.[48] No correlation with central nervous system pathology has been described. The specificity of these manifestations in an older population with chronic debility, cirrhosis, diabetes mellitus, and/or heart disease is difficult to ascertain, but these observations are provocative and warrant careful appraisal of central nervous system function in all patients with hemochromatosis. Peripheral neuropathy has been noted in patients with diabetes or with concomitant alcoholism.

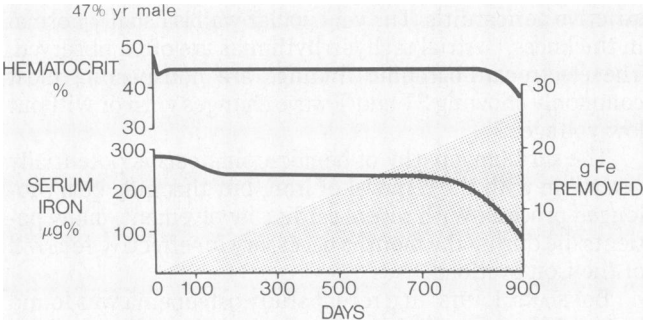

Figure 11.—Response to weekly phlebotomy therapy in hemochromatosis. Patient was a 47-year-old man.

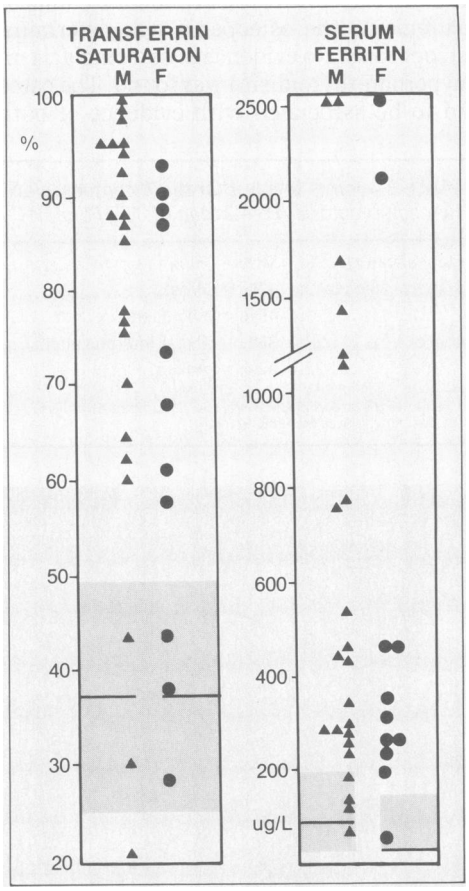

Figure 12.—Transferrin saturation and serum ferritin values in 34 young hemochromatosis subjects. Males=triangles; females=circles. Shaded areas are reference ranges and solid horizontal lines are the normal means. (Redrawn from Bassett ML, Halliday JW, Ferris RA, et al: Diagnosis of hemochromatosis in young subjects: Predictive accuracy of biochemical screening tests. Gastroenterology 1984; 87:628.)

Diagnosis of Hemochromatosis

The diagnosis of hemochromatosis is frequently missed. Certainly the diagnosis is not being established in one out of every 300 to 400 white patients who enter our hospitals and clinics, although virtually all surveys agree that this is the true prevalence of the disease. The first barrier to early diagnosis is that of considering the disease in patients who do not have the triad of cirrhosis, hyperpigmentation, and diabetes but who exhibit other more subtle manifestations of the disease.

In the absence of knowing the gene product that is abnormal or missing in hemochromatosis, the diagnosis depends upon documentation of the secondary phenotypic expression of that abnormality, namely the excessive accumulation of iron. The differential diagnosis is that of other causes of iron overload, as noted already. Within a given family, when an index case of hemochromatosis has been diagnosed by the aforementioned method, other family members can be identified as homozygous or heterozygous by HLA typing, as already described (see Figure 5).

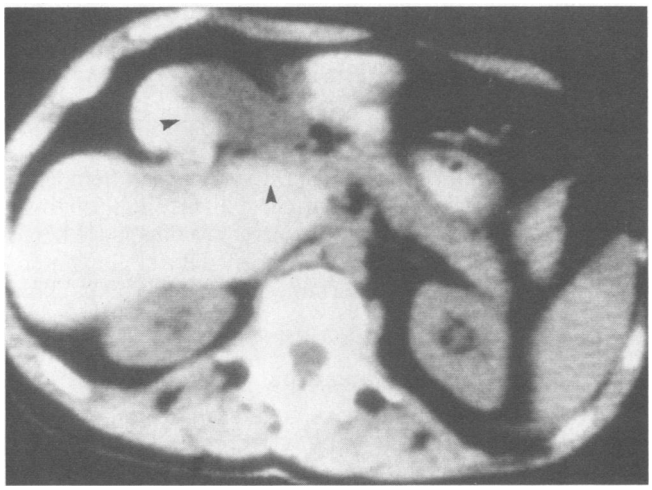

Figure 13.—Computed tomography (CT) showing increased density of the liver in hemochromatosis. The less dense area, indicated by arrows, represents a complicating hepatoma. (Courtesy of Henry I. Goldberg, MD.)

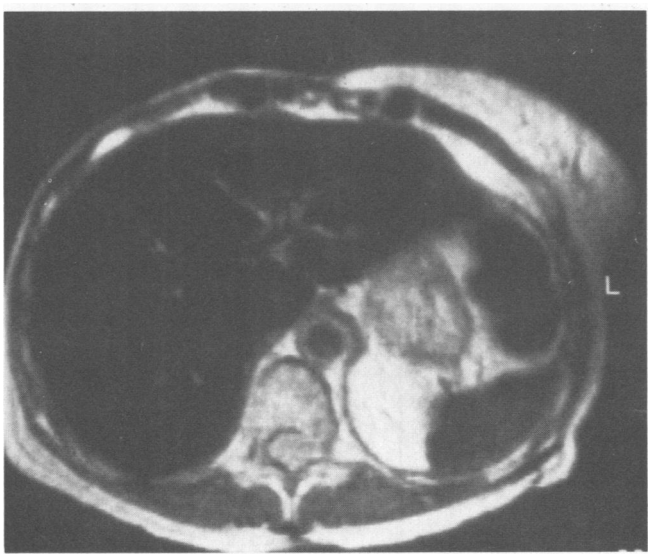

Figure 14.—In this patient with transfusional hemochromatosis the MR image intensity of the liver is markedly reduced compared with that normally seen with this spin echo technique (TR=1.0 sec, TE=28 msec). (From Stark DD, Moseley ME, Bacon BR, et al: Magnetic resonance imaging and spectroscope of hepatic iron overload. Radiology 1985; 154:137.)

The ultimate standard for determining iron overload at this time is that of quantifying its content in hepatic tissue obtained by biopsy, together with a more qualitative analysis of the amount of stainable iron and its distribution. A biopsy also allows an assessment of hepatic damage and fibrosis. The total iron stores can also be approximated retroactively by weekly phlebotomies that are continued until the time of impaired erythropoiesis as a reflection of depletion of these stores. Depending upon the state of circulating erythrocytes, the removal of each unit of 500 ml of blood removes about 200 mg to 250 mg of iron, requiring that the body shift a corresponding amount from tissue stores to heme. Normal stores (~ 1 gram) are depleted by four to five phlebotomies or less; in iron overload, depletion of iron stores from removal of about 1 gram per month (four to five phlebotomies) may require several years (Figure 11).[7] Usually, however, two indirect indices of iron stores are used to survey for the possible presence of hemochromatosis (Figure 12):

1. *Saturation of transferrin.* Plasma transferrin is normally about one third saturated (100 to 120 μg iron per deciliter; 300 to 330 μg iron-binding capacity). In hemochromatosis the saturation of transferrin tends to rise with increasing iron stores. For survey purposes cut-off points of >55% saturation[19] and >62% saturation[49] have been used to define populations at high risk for hemochromatosis. Because of diurnal and also seemingly sporadic variations in plasma iron, borderline findings should be repeated on morning fasting specimens. A transferrin saturation of >70% to 75% is virtually diagnostic of iron overload in an otherwise normal individual. A few younger patients with hemochromatosis, expecially women, will have values <55% saturation.
2. *Serum ferritin concentration.* The level of serum ferritin tends to correlate closely with mobilizable body iron.[9,49] In hemochromatosis, levels are therefore usually above normal (>200 μg per liter in men or >150 μg per liter in women). Serum ferritin levels are sometimes elevated in conditions other than in excessive iron storage, e.g., in the presence of other forms of liver disease, inflammatory reactions, certain tumors, and rheumatoid arthritis. A few patients with hemochromatosis and iron overload have had normal levels of serum ferritin. Nevertheless, taken with transferrin saturation, the measurement of serum ferritin has been a useful survey test.

Other screening tests have been used, such as the total serum iron or the urinary excretion of iron following the injection of a standard amount (10 mg per kilogram) of the chelator protein desferrioxamine, but these tests seem to have less utility.

Newer approaches to noninvasive measuring of body iron are being developed but by and large have not yet reached the stage of validation and availability.[50] These include computed tomography (CT), magnetic resonance imaging (MRI), and magnetic susceptibility measurement (MSM). In CT (Figure 13), most success has come from using a dual energy technique to measure the difference in CT number. In MRI (Figure 14), there is a particularly marked attenuation of the T_2 signal with a resulting "black hole" in the image.[31,51]

Magnetic susceptibility measurement requires a superconducting quantum interference device susceptometer to measure changes in the magnetic susceptibility of the liver secondary to the paramagnetic properties of ferritin and hemosiderin.[50] MSM is a promising new technique that is not yet widely available.

It seems highly probable that future developments in these or analogous physical techniques will allow accurate and convenient assessment of the body's iron stores without the requirement for liver biopsy or the depletion of iron stores by phlebotomy.

When the diagnosis of hemochromatosis is established in a patient, HLA typing should be carried out to allow for diagnosing other cases within the family and for early therapeutic intervention before the onset of organ damage.

Differential Diagnosis of Hemochromatosis (Table 4)

The differential diagnosis is usually not a difficult one, once the possibility of hemochromatosis is considered and the presence of iron overload is established. Iron overload from transfusions is apparent from the history, and the iron burden can be estimated from the number of transfusions received. Iron overload from excessive ingestion in the absence of genetic hemochromatosis is extremely rare except in South African blacks, in whom it has been attributed to iron solubilization from pots used in fermentation in the preparation of beer. Ineffective erythropoiesis, as noted previously, may stimulate excessive absorption of iron. This is seen most frequently in the thalassemias and in some cases of sideroblastic anemia, much more rarely in hemolytic anemia. These hematologic disorders, usually resulting in anemia, should not be difficult to detect, if thought is given to them in the presence of demonstrated iron overload. Sporadic porphyria cutanea tarda (PCT), caused by reduced levels of hepatic uroporphyrinogen decarboxylase, is usually associated with modest (2 to 4 gram) iron overload and usually responds clinically to the removal of this iron by phlebotomy. There is now gathering evidence, however, that these persons are heterozygous (occasionally homozygous) for hemochromatosis.[52] It is presumed that excess hepatic iron is somehow necessary for the phenotypic expression of PCT and that concurrent heterozygosity for hemochromatosis is the most common pathogenesis for creating that excess. The extremely rare genetic condition of atransferrinemia is associated with excessive absorption of iron and siderosis in humans and in a murine model.[13] The most troublesome differential diagnosis is that between hemochromatosis and alcoholic cirrhosis with hepatic siderosis, in which both transferrin saturation and plasma ferritin levels may be increased as well. In alcoholic cirrhosis, however, the Kupffer cells tend also to contain stainable iron, in contrast to hemochromatosis, but more importantly the levels of hepatic iron never reach those seen in hemochromatosis. The total excess hepatic iron in alcoholic cirrhosis rarely exceeds 1 to 3 grams. The presence of genetic hemochromatosis can be further strengthened if a sibling heterozygote or homozygote, determined by HLA typing, shows evidence of iron overload.

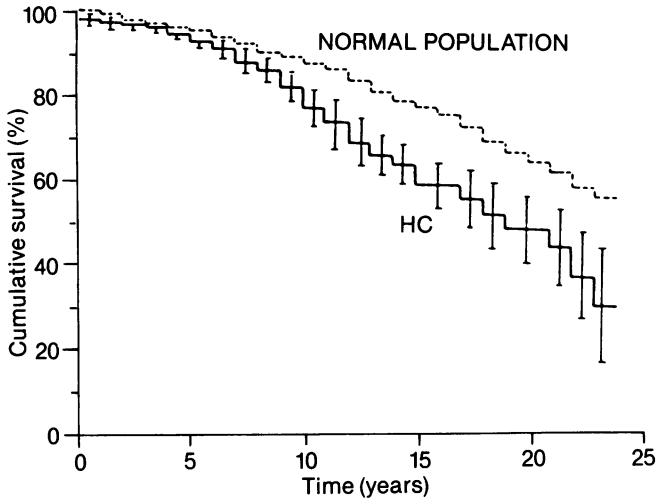

Figure 15.—Cumulative survival in 163 patients with hemochromatosis. The vertical bars represent the calculated 95% confidence interval. (Reprinted with permission from Niederau C, Fischer R, Sonnenberg A, et al: Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. N Engl J Med 1985; 313:1256.)

Treatment of Hemochromatosis

As an autosomal recessive genetic disease, hemochromatosis cannot currently be cured by replacing the presumably absent or defective gene product. Since all of the known adverse effects of hemochromatosis seem to be caused by the pathologic burden of iron, the primary treatment of the disease is to remove the excess iron as rapidly as is feasible. This is accomplished most effectively by re-

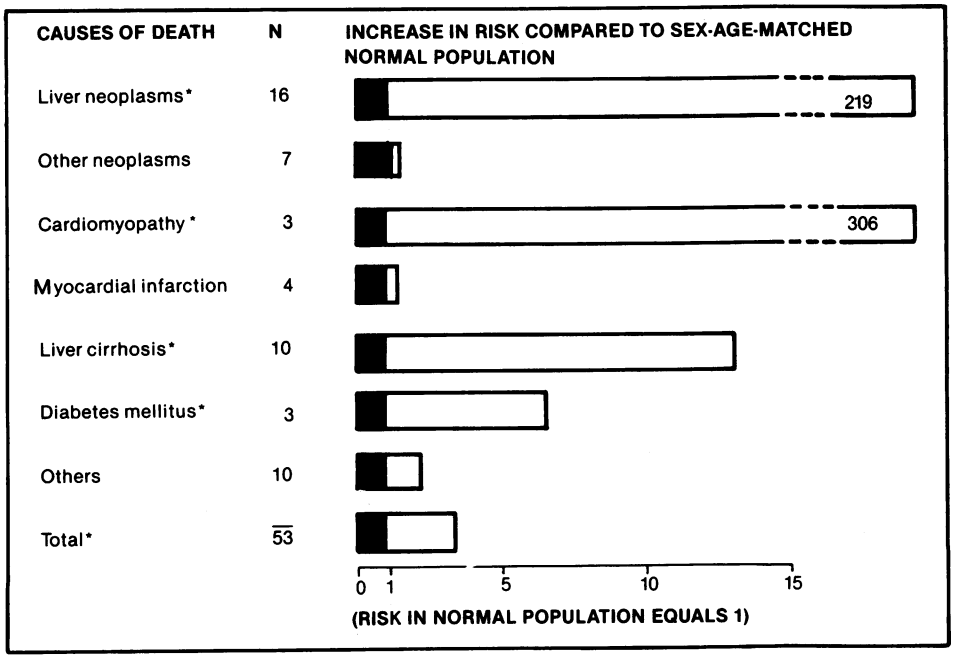

Figure 16.—Causes of death in 53 patients with hemochromatosis. Also shown is the relative risk of dying from each specific cause as compared with a matched control population. The values marked by asterisks are considered statistically significant (fall outside the 95% confidence limit). (From Strohmeyer G, Niederau C, Stremmel W: Survival and causes of death in hemochromatosis. Ann NY Acad Sci 1988; 526:245.)

TABLE 4.—*Differential Diagnosis of Iron Overload*

Hemochromatosis
Repeated transfusions
Hereditary anemias (ineffective erythropoiesis)
Alcoholic cirrhosis
Excessive ingestion of iron (rare)
Porphyria cutanea tarda
Atransferrinemia

peated phlebotomy. In the process of replacing the erythrocytes, the bone marrow then mobilizes iron from storage ferritin and hemosiderin. With a weekly phlebotomy, about 10 to 13 grams of iron can be removed annually. To deplete the iron stores in hemochromatosis may therefore require two or even three years of therapy. The hematocrit and the level of plasma ferritin are usually followed as guides to therapy (see Figure 11). After the removal of the excess iron, maintenance therapy by phlebotomy is required, usually four to six times annually, to counteract the continued excessive absorption of iron that characterizes the disease. This simple program suffices for the treatment of most patients. Rarely, in the presence of severe hemochromatotic heart disease it is important to supplement the phlebotomy program with the continuous infusion of desferrioxamine to accelerate the removal of iron and to protect the patient from further deterioration of cardiac function during therapy. In the face of iron overload, ascorbic acid should be given with great caution since there is evidence that it may mobilize intracellular iron and participate in the peroxidation of lipids to exacerbate iron injury.[21,53]

The treatment of the complications of hemochromatosis will not be discussed here. They include in individual patients the treatment of diabetes mellitus, liver failure, chronic arthritis, deficiency of sex hormones, and congestive heart failure. The importance of surveying family members for the presence of hemochromatosis has been previously emphasized.

Prognosis

Many patients with hemochromatosis have few symptoms that can be clearly attributed to the disease and relatively little disability, and they survive normally to die of other causes. This is the lesson that has been learned from the extensive population surveys that have been carried out, supplemented by HLA haplotype identification of other members within families. This presumably is the major explanation for the marked disparity that exists between the now-accepted prevalence of homozygous hemochromatosis of 3 to 4 cases per 1,000 people of European origin and the comparative rarity with which the disease is diagnosed, even at autopsy.

The cumulative survival of a large series of patients with hemochromatosis compared with that in an age- and sex-matched control group is shown in Figure 15.[41] It is important to note that these patients were all treated by phlebotomy, although some did not survive to allow completion of the removal of iron, and that they tended to represent relatively advanced symptomatic cases. (Only 10% had no cirrhosis or hepatic fibrosis.) In patients without cirrhosis overall survival time did not differ from that in the control population. Not unexpectedly, survival in hemochromatotic patients with diabetes was less favorable than in those without this complication.

The causes of death in 53 patients with symptomatic hemochromatosis are shown in Figure 16, together with a calculation of the relative risk of death from that cause in hemochromatosis as compared with an age- and sex-matched control group.[41] Liver neoplasms (13 hepatomas and 3 bile duct carcinomas) were the most frequent cause of death, with an increased risk of 200-fold. As noted previously, hepatoma occurs only in the presence of cirrhosis, but the risk continues even after successful removal of iron.

Summary

Hemochromatosis is an autosomal recessive genetic disorder that occurs with high prevalence in populations of European origin. The gene that is abnormal in hemochromatosis is found on the short arm of chromosome 6 in close proximity (~1 centimorgan) to HLA-A, but the product coded for by that gene is unknown. The pathogenetic mechanism in hemochromatosis is that of continued, excessive absorption of dietary iron with loss of normal control mechanisms, leading to a gradual but vast expansion of storage iron as ferritin and especially as hemosiderin. Through mechanisms that probably include peroxidation of lipid membranes, the excess iron injures hepatocytes, islet B cells, gonadotropes in the anterior pituitary, myocardium, synovial cells, and chondrocytes, and probably other cells and tissues as well. Most patients with hemochromatosis remain undiagnosed throughout life. Removal of the excess iron by phlebotomy will prevent all of the complications of hemochromatosis when begun early and will significantly improve survival in virtually all patients. It is important, therefore, that the diagnosis of hemochromatosis be considered much more frequently in clinical medicine in order that this effective therapy be utilized.

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