

## Hemochromatosis: A Common, Rarely Diagnosed Disease

***Hemochromatosis is a common, preventable disease that is rarely diagnosed. About 30,000 homozygous cases exist nationwide within the entire KP Program, but probably fewer than 1000 are diagnosed: one case—diagnosed or not—is seen by each KP clinician every two weeks. Typically, the end organ damage caused by hemochromatosis is readily ascribed to other, even more common disease processes. When hemochromatosis becomes symptomatic, major therapeutic advantage is lost. Ideally, everyone should be screened once per lifetime by having serum iron levels and total-iron-binding capacity (TIBC) measured. Treatment has two goals: normalization of body iron load (through lifetime phlebotomy) and identification and treatment of the patient's affected relatives.***

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The first study of published cases of hemochromatosis was organized by Sheldon<sup>3</sup> in an extraordinary monograph which analyzed 311 of 345 cases collected from the world medical literature and concluded that hemochromatosis was not a complication of diabetes, cirrhosis, or copper excess, but a familial disorder in which “... the fundamental nature of the disease consists in a disorder of metabolism ... [where] ... the tissues have an abnormal avidity for iron.” In 1950, Davis and Arrowsmith (cited by Edwards and Kushner)<sup>4</sup> ingeniously proposed phlebotomy as a treatment for hemochromatosis. The next major advance came when autopsy studies showed a much higher prevalence of the disease than was being diagnosed clinically and led to population studies showing a homozygous prevalence of 3-10 cases per thousand, far greater than ever expected. Nonetheless, multiple supporting studies published in leading journals<sup>2,4,6</sup> led to no change in clinical practice: hemochromatosis continues to be dismissed as a rare disease. By the end of the 1980s, however, researchers had shown that early treatment blocked phenotypic expression of the disease and thus that hemochromatosis should be diagnosed through screening.<sup>7</sup> Saturation of TIBC became recognized as the best test; liver biopsy and ferritin measurements were shown to have major limitations. The next major advance came in 1996, when the gene for hereditary hemochromatosis was identified.<sup>8</sup> A genetic probe was created almost immediately, and the population prevalence of homozygous hemochromatosis (1:250) was confirmed in multiple cities as well as specifically among KFHP members within the Kaiser Permanente Local Market Area in San Diego (KPSD), where the first permanent, ongoing, population-based hemochromatosis screening program in the nation was established.

### Introduction

Hemochromatosis is the most common, life-threatening genetic disorder in North America, yet most physicians have never personally diagnosed a case: all see an unrecognized case in their offices every two weeks. Hemochromatosis is important because of its prevalence, its serious nature, and even more so because it is totally preventable. Until recently, the disease was thought to be rare.

The recent advent of genetic analysis has confirmed that homozygous hemochromatosis has a documented prevalence of 1:250 in the U.S. population. Thus, the average practicing physician sees a case every 10 working days. Most of those cases are presymptomatic when seen, but many are misdiagnosed as some other, more familiar condition which has the same initial appearance. Moreover, the gamut of clinical presentations is far more extensive than would be suggested by, for example, the classic triad of darkened skin, diabetes, and cirrhosis—which we all learned about and then never saw. Put differently, Kaiser Foundation Health Plan (KFHP) nationwide has identified hundreds among probably more than 30,000 members with homozygous hemochromatosis. It is now technologically possible to correct this disparity simply and inexpensively, to everyone's benefit.

### Historical Background

Hemochromatosis was first described by Trousseau in 1865<sup>1</sup> and was given its current name in 1889 by von Recklinghausen,<sup>2</sup> who established that iron caused the pigmentary changes seen in the disease.

### Terminology Issues

Our expanding knowledge of hemochromatosis taxes conventional terminology and includes several concepts. *Hemosiderosis* is a histologic term that refers to tissue deposition of iron, regardless of mechanism or presence of clinical disease. *Iron overload disease* refers to any disorder involving iron overload, regardless of mechanism; moreover, iron overload disease may be focal (eg, Hallervorden-Spatz Disease, primary pulmonary hemosiderosis) or diffuse (eg, hemochromatosis). *Hemochromatosis* has been used to refer to the tissue damage produced by any systemic iron overload disease, including the transfusion iron overload seen in thalassemia, which obviously does not involve the HFE



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gene. Because of this potential for confusion, the term *hereditary hemochromatosis* should be used to specify the systemic, genetically determined iron overload disease caused in humans by excessive intestinal iron absorption.

As is generally agreed, most patients homozygous for hemochromatosis become symptomatic, given sufficient time for excess iron to accumulate. Nonetheless, now that we can identify the HFE gene, a further distinction between the genotypic and phenotypic stages of hereditary hemochromatosis is important to prevent life insurance companies from automatically construing a diagnosis of "hemochromatosis" to necessarily imply serious organ damage. With early diagnosis and treatment, genotypic hereditary hemochromatosis need never progress to phenotypic expression. Early treatment is now well documented to prevent development of organ damage and allow normal life expectancy.<sup>7</sup>

Understanding all this, we must remember that the pathology of all iron overload diseases is the direct result of iron overload and is not related to the mechanism by which iron enters the body.

### Epidemiology

Hemochromatosis is an autosomal-recessive disease which has a population prevalence of about 4 cases per thousand in Europe, and hence in our hemisphere. Therefore, one of every eight Americans is a heterozygous carrier.<sup>b</sup> Fortunately, the heterozygous state is only infrequently symptomatic (exceptions are discussed later). Hemochromatosis is less common in black people of any ethnic origin and is rare in mainland Asian persons; the prevalence in people of Filipino origin approximates that of white people. Essentially nothing is known of the prevalence in other Pacific Islanders. Hispanic persons have the same prevalence as white persons not of Hispanic origin, but among Irish persons, the prevalence of the homozygous state is thought to be approximately 1:80, leading many researchers to hypothesize that the original mutation occurred in Ireland during ancient times and then spread to mainland Europe. In our Hemochromatosis Registry, the prevalence of Irish names is striking. The exact prevalence of some manifestations of hemochromatosis is still unsettled but is ethically unlikely to be investigated in humans by traditional statistical methods (ie, by comparing treated persons with an untreated homozygous control group).

In July 1997, a permanent Hemochromatosis Screening Program was established in the Health Appraisal Clinic of KPSD Preventive Medicine Department to serve the 500,000 KFHP members who reside in KPSD. Each year, approximately 50,000 adult

members receive once-in-a-lifetime screening for iron overload disease as they pass through this clinic. As a result of this screening, more than 200 patients are currently enrolled in our phlebotomy program. However, given that KPSD probably has about 1900 members with hemochromatosis, this number is only a beginning. The number of Irish names in our Hemochromatosis Registry is notable, but even more remarkable is the diversity of origins reflected by names in the Registry. As expected in screening, many of the hemochromatosis patients identified are presymptomatic, an ideal situation when dealing with a disease whose phenotypic expression can be blocked by early treatment.

### Biochemical Pathophysiology

Only in recent decades has hemochromatosis been understood to be a hereditary disorder in which excess iron is absorbed from food. We now know that the basic pathophysiology of hemochromatosis lies in a defective gene controlling the intestine's mucosal barrier to iron absorption. Although essential to enzymatic and metabolic processes, iron is highly toxic and irritative when an excessive amount is absorbed. The human body can not excrete excess iron; the amount which enters the body remains there permanently unless lost through skin desquamation, childbirth, menstruation, or other blood loss such as by donation or hemorrhage. Normally, iron absorption is tightly regulated by the intestinal mucosa to approximately 1.5 mg/day. In persons with hemochromatosis, this is approximately doubled. Ascorbic acid, citric acid, and low dietary phosphate further increase iron absorption. Conversely, iron absorption is inhibited by achlorhydria and by oxalates, tannates, phytates, and phosphates, all of which form insoluble iron complexes in the intestine. The practical implication of this is that the bioavailability of ingested iron varies greatly. Popeye's spinach contains abundant iron but is only a metaphor for an iron source, because oxalates in spinach inhibit absorption of its iron. Overall, vegetable-derived iron has low bioavailability; the iron obtained from red meat has high bioavailability; white meat and seafood have less available iron than is absorbable from red meat. Given the high prevalence of vitamin C supplementation in the general population, we may suppose that the large minority of our population that is heterozygous for hemochromatosis runs some risk of seriously accelerated iron absorption. Indeed, vitamin C supplementation by heterozygotes is a confounding issue in screening.

At birth, no person with hemochromatosis has iron overload—only the genetic capacity for that process to begin after foods containing iron are ingested.

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(However, this genetic capacity does not characterize neonatal hemochromatosis, which is nonetheless an iron overload disease). Iron absorption is approximated by measuring the amount of iron moving between the intestine and other parts of the body. This amount is increased in hemochromatosis, producing a higher than normal saturation of the TIBC of blood. Eventually, loading of the iron stores is indicated by rising ferritin levels. Then, after iron stores are filled, iron overload occurs, causing tissue damage. Ultimately, organs fail. Regardless of the diagnostic approach taken, understanding this straightforward pathophysiologic sequence is essential for interpreting the disease at its various stages. Hemochromatosis is a totally preventable disease but only when diagnosed in its presymptomatic stage; symptoms indicate that the disease has reached a late stage where some therapeutic opportunity has already been lost. The stages of pathophysiologic progression and their relation to available tests are approximated in Table 1.

The pathology of hemochromatosis is totally a function of iron overload. Exceeding the body's normal capacity for binding or storing iron allows iron to exist in an unbound state where it is reactive and hence toxic. Fortunately, the serum iron (SI) level in normal people is sufficiently low that no more than a third of the sites available in the TIBC are bound, providing a large safety margin. The most reliable measure of the key process underlying hemochromatosis is the increased saturation of the TIBC and is expressed by the equation  $(SI \div TIBC)$ . This measure is loosely referred to as “transferrin saturation” even though transferrin comprises only about 85% of the TIBC. Each transferrin molecule binds one or two atoms of iron, permitting the iron to be moved without reactivity in serum.

As iron loading progresses, iron is stored mainly in the liver within the complex protein, ferritin; each molecule of ferritin can bind as many as 4500 atoms of iron. Only a tiny fraction of the body's ferritin circulates in plasma, but circulating ferritin levels have an approximate relation to total iron stores. The adult human body contains about 4 g of iron, of which 3 g are bound in hemoglobin, myoglobin, and enzyme systems; for example, each 500 mL of blood contains about 200 mg of iron. The additional 1 g of iron is stored in reserve. (Occasionally, over many decades, a patient may accumulate a total body iron load as high as 30 g—equivalent to an ounce of metallic iron—and thus set off airport metal detectors!) When excess amounts of iron are absorbed (as in hemochromatosis) or infused (as in repeated transfusion therapy for chronic hemolytic disorders), the excess iron ultimately is deposited in various organs, where the iron induces an inflammatory reaction that induces fibrotic damage to the organ. The basis for selective variability in organ deposition is unknown; however, a hereditary mechanism is possible, given that identical twins have identical patterns of iron deposition in organs.<sup>9</sup> Only infrequently does the classic triad of darkened skin, cirrhosis, and diabetes develop; and the lungs, kidneys, and eyes are never damaged by the disease.

### Genetic Pathophysiology

In 1996, investigators at Mercator Genetics Corporation (Menlo Park, California) identified the gene for hereditary hemochromatosis.<sup>8</sup> This gene, HFE, lies on chromosome 6. Identifying HFE was difficult because its location permitted few crossovers, with their analytic advantages for genetic localization. HFE controls formation of an HLA-like glycoprotein that contains a  $\beta_2$ -microglobulin-binding site. The importance

**Table 1. Pathophysiologic progression and impact of hemochromatosis on related tests**

Age	Genetic test	Physiological measures		Tissue overload/organ damage
		Iron saturation	Ferritin	
Birth	positive <sup>c</sup>	normal	low	none
6 months	positive	elevating	low	none
10 years	positive	elevated	low-normal	none
30 years	positive	elevated	normal-elevating	none-starting
50 years	positive	elevated	high	starting-clearcut
70 years	positive	elevated	high	clearcut



of  $\beta_2$ -microglobulin in iron metabolism is suggested by the iron accumulation that occurs in a mouse (the " $\beta_2$ -microglobulin knockout mouse") in which the HFE gene site is functionally deleted.<sup>10</sup>

Techniques suitable for clinical genetic analysis were soon developed, and two clinically significant mutations were found in the HFE gene: one at the 845 nucleotide locus, causing substitution of tyrosine for cysteine in codon 282; and one at the 187 nucleotide locus, causing substitution of aspartic acid for histidine in codon 63. The mutations are therefore sometimes designated C282Y and H63D, respectively, although the nucleotide-based notation which assigns the names 845A and 187G to these mutations is more appropriate terminology.<sup>11</sup> The HFE mutations producing hemochromatosis evidently act by causing deficiency of the HFE protein, not by changing its characteristics.<sup>12</sup> However, the mechanism by which HFE protein regulates iron absorption is not yet understood.

The location of a mutation within the HFE gene determines its clinical significance. For instance, homozygous mutation at the 845 locus has high penetrance when untreated—given there is sufficient time for iron to be absorbed. Indeed, most cases of clinical hemochromatosis show homozygosity at the 845 locus. Conversely, abundant iron overload is unlikely in the 845 heterozygous state but is certainly possible in special circumstances (eg, high intake of ascorbic acid or alcohol or concurrent thalassemia minor). Iron overload is also unlikely, but possible, in the 187 homozygous mutation. The 187 heterozygous state has no clinical significance and should be considered normal. A double (compound) heterozygous state exists where one 845 and one 187 allele are mutated; clinical iron overload occurs in a small percentage of these cases of polymorphic mutation. The determinants of variable penetrance in humans are poorly understood but may include unrecognized polymorphism, increased absorption of other trace elements,<sup>12</sup> and dietary factors.<sup>13</sup>

These sophisticated technologies should not mislead us into thinking that genetic analysis supersedes traditional chemical forms of laboratory diagnosis in individual cases. Although genetic abnormalities can be prognostically helpful, the gene currently identified leads to confirmation of hereditary hemochromatosis in only about 85% of proven cases. Although not yet found in preliminary investigations, additional mutations can also be expected to cause hemochromatosis. Moreover, the variable penetrance of polymorphous mutations within the HFE gene indicates a degree of clinical complexity not yet appreciated. Genetic analysis can predict the statistical likelihood of iron overload disease developing over time and

### Case Example: One Physician's Own Medical History

*The diagnosis of clinically active hemochromatosis is easily overlooked, as illustrated by Dr. Graydon Funke, a disability-retired pediatrician from Southern California Permanente Medical Group (SCPMG) in Harbor City, California. Hoping to stimulate other physicians to be screened for this disease, Dr. Funke describes his own case:*

I am now 68 years old. I had no major medical problems for the first 35 years of my life. I then developed some pain and swelling of the metacarpophalangeal joints of the index and middle fingers of both hands. I was diagnosed with gout and had uric acid levels between 6 and 11 mg/dL, and several joint taps were said to show the presence of uric acid crystals. Wrists, fingers, and toes were affected, but never a large joint. Allopurinol has prevented all acute attacks in the last 10 of the 15 years I've taken it. I was quite physically active for most of my life. By age 45, however, arthritic symptoms developed in my ankles, hands, back, and neck. I gradually became easily fatigued. I consulted with several internists and orthopedists, none of whom suggested a specific diagnosis. A brief trial of cortisone during a bike trip gave me much relief.

Once at age 59, while I was skiing, severe hip pain developed suddenly; the next year, I had a total left hip replacement. No one was certain whether I had arthritis alone or also had aseptic necrosis. Chronic atrial fibrillation developed a week after surgery, and attempts at cardioversion were never successful.

I became depressed, and my joint symptoms progressed to where I had to accept disability retirement at age 60. We moved to San Luis Obispo, and last year, at age 67, I came under the care of a local rheumatologist, Dr. Barry Eibschutz, who saw my rheumatic knuckles and said at the first visit, "I think you have hemochromatosis." My serum ferritin level was 2250 ng/mL. I had seen six internists, five rheumatologists, three orthopedists, two physiatrists, and one psychiatrist, but no practitioner—including myself—ever considered hemochromatosis.

MRI scan of my liver showed the increased density typical of iron overload. Results of my liver function tests were normal, and I chose not to have liver biopsy. I have now had 40 weekly phlebotomies of 500 mL that have reduced my serum ferritin level to 20 ng/mL. Diabetes had been developing, but my blood sugar levels are now becoming normal, perhaps owing to removal of the excess iron. My depression and fatigue have greatly improved with phlebotomy, although the arthritis has not.

In retrospect, my family history is interesting. My mother's skin darkened in her later years, and she had arthritis in her wrists. She died of congestive heart failure at age 83. My father died at age 69 of a blood dyscrasia and liver problem and had a terminal pulmonary embolism. I have no siblings.

I urge all of you reading this to get a simple blood test to rule out this common condition. It could save you a lot of pain and grief—and possibly your life. I also want to see our Medical Group start testing children for this condition. Such testing would certainly be cost-effective, given my experience.

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can help to explain clinical situations that previously were confusing. Thus, genetic analysis—an extraordinary scientific accomplishment—contributes to clinical understanding but does not supersede it. Finding cases—not genetic analysis—is the goal and is still best accomplished by testing for saturation of TIBC.

### Clinical Features

Its broad clinical spectrum is part of the reason why hemochromatosis is so infrequently diagnosed: Each of its manifestations has other, more common explanations. Indeed, to cardiologists, hemochromatosis is unexplained cardiomegaly; to orthopedists, it is a need for hip replacement; to gynecologists, it is infertility; to urologists, impotence; and to family practitioners, the disease is identified as fatigue with depression. The situation is reminiscent of a fable: three blind men each try to identify an elephant by feeling a different part of the creature, thereby missing its essence. Dr. Funke's case illustrates this point. Notwithstanding the need to understand hemochromatosis in its totality, for purposes of discussion the diverse clinical features of this disease are conveniently grouped by organ system affected.

### Musculoskeletal

Unlike the description of the "classic triad," arthralgia is the most common symptom of hemochromatosis. However, nothing is distinctive about this symptom. Arthritis is common and often misdiagnosed as seronegative rheumatoid arthritis. A pattern of arthritis involving the metacarpophalangeal and proximal interphalangeal joints of the second and third fingers suggests hemochromatosis.<sup>14</sup> However, its appearance can be indistinguishable from osteoarthritis, gout, or pseudogout. In addition, because iron overload disease underlies many cases of chondrocalcinosis, a radiographic finding of chondrocalcinosis should prompt evaluation for hemochromatosis.<sup>15</sup> Occasionally, joint cartilage is rust-colored, but this finding is not specifically diagnostic. Many persons having joint replacement, particularly at younger ages, have hemochromatosis that remains unrecognized. The KPSD orthopedics department is currently collaborating with our clinic in an effort to determine the prevalence of hemochromatosis appearing initially as arthritis requiring joint replacement.

Typically, phlebotomy does not improve the arthritic symptoms of hemochromatosis; they sometimes worsen despite phlebotomy, illustrating the importance of diagnosing and treating hemochromatosis in its presymptomatic stage. However, Cutler<sup>16</sup> has described great improvement of arthritic symptoms from use of deferoxamine. Many agree that arthritic

symptoms can be reliably prevented if phlebotomy is done before their onset. However, much remains to be learned about the arthritis of hemochromatosis: Crosby<sup>17</sup> pointed out that arthritis was not described as a complication of this disease before 1962. Moreover, the detailed monograph by Sheldon<sup>3</sup> reported no cases of arthritis among 311 untreated, advanced cases of hemochromatosis, although joints were examined grossly and microscopically. The implications of this are unclear but suggest that some other factor, possibly dietary, may help to explain the current prevalence of arthritis in hemochromatosis. The videotape, "*Hemochromatosis in Orthopedics and Rheumatology*," illustrates the experience of four KPSD members who have hemochromatosis with extensive skeletal involvement.<sup>18</sup>

### Gastrointestinal

Although hemochromatosis is typically conceived as a hepatic disorder, the classic triad of cirrhosis with darkened skin and diabetes actually defines an uncommon combination found only in advanced disease; the diagnosis of hemochromatosis is thus usually overlooked. Hepatomegaly is common in hemochromatosis, but transaminase values are frequently normal in uncomplicated disease, particularly if the patient's medical history does not include alcoholism or hepatitis B or C. Indeed, as Dr. Funke's case illustrates, normal liver enzyme levels do not preclude the need to consider hemochromatosis as a possible diagnosis.

In hereditary hemochromatosis, iron accumulates distinctively in periportal hepatocytes. By contrast, in secondary hemochromatosis (eg, resulting from transfusional iron overload or thalassemia), macrophages process out large numbers of red blood cells, and iron is deposited in the reticuloendothelial macrophages (which, in the liver, are termed Kupffer cells). Those cases of alcoholic cirrhosis in which minor deposits of iron are found in the hepatocytes could be due to the confounding influence of a coincident heterozygous state for hemochromatosis. When other processes like alcoholism or chronic hepatitis are present with hemochromatosis, the threshold for cirrhosis is lowered.

Once viewed as the standard procedure for diagnosing hemochromatosis, liver biopsy is increasingly being seen as unsuitable for this purpose because its results are frequently normal at early stages of the disease. Heavily iron-laden liver specimens taken at biopsy certainly provide meaningful information for diagnosing iron overload disease; however, as the pathophysiology of hemochromatosis shows, the earlier a biopsy is done in the disease, the more likely are the results to be normal or equivocal. For instance,



half of liver biopsies done in presymptomatic cases have shown normal results. Even in symptomatic cases, about 8% of liver biopsies do not produce diagnostic results (ie, grade 3 or 4 when Perls' stain is used).<sup>19</sup> Thus, liver biopsy results and their derivative measures (eg, the Hepatic Iron Index) are often misleadingly normal at precisely the stages of hemochromatosis where therapeutic opportunity is greatest.

The same logic applies to use of magnetic resonance imaging (MRI) and magnetic susceptometry (SQUID) to evaluate liver iron stores because these techniques also show normal stores of iron in the liver early in the disease. No matter how sophisticated the approach, any diagnostic technique focused on liver iron stores is limited to diagnosis of advanced cases only; worse yet, early cases will predictably be missed. On the other hand, because hepatoma is a potential outcome of untreated hemochromatosis, those who favor liver biopsy argue that it has a role in demonstrating cirrhosis with its implications for development of hepatocellular carcinoma. Others see little purpose in attempting this prediction.

Splenomegaly occurs in hemochromatosis and should suggest that disease as a possible diagnosis. Abdominal pain is common in hemochromatosis: the pain is often located low in the abdomen, suggesting mechanisms other than simple stretching of Glisson's capsule. Chronic diarrhea also occurs commonly in hemochromatosis and has an episodic quality that is easily confused with irritable bowel syndrome.

### Endocrine

The endocrine manifestations of iron overload are all disorders of hypofunction. Excess iron deposited selectively in the pituitary gland causes gonadal failure (hypogonadotrophic hypogonadism): impotence and bilateral testicular atrophy occur in men, whereas menstrual irregularity, infertility, and premature menopause occur in women. Both sexes commonly manifest loss of axillary, pubic, and limb hair. Secondary osteoporosis can also be expected. Hypothyroidism is more common in iron overload disease than in the general population and results from end organ fibrosis and thyroid autoantibodies.<sup>20</sup> By contrast, hyperthyroidism has sometimes provided false evidence of hemochromatosis by causing elevated iron saturation and serum ferritin levels.<sup>21</sup> Iron overload disease has rarely been reported to cause hypoparathyroidism<sup>22</sup> and adrenal failure.<sup>23</sup>

If deposited in the pancreas, excess iron induces diabetes mellitus. Conflicting reports on the prevalence of iron overload disease in diabetes probably reflect the stage at which hemochromatosis was diagnosed: late (ie, because suggested by clinical ap-

pearance) or early (eg, through screening). Neither Type 1 nor Type 2 diabetes characterizes the diabetes mellitus seen in hemochromatosis; multiple causative mechanisms seem possible, perhaps depending on the stage of the disease.<sup>24</sup> Early treatment of hemochromatosis has been shown to reverse some cases of diabetes.<sup>25</sup> In addition, treatment with deferoxamine greatly improved glycemic control in some cases of hyperferritinemic diabetes.<sup>26</sup> Hemochromatosis should be treated early to prevent diabetes, and all diabetic patients should be screened once for underlying iron overload disease.

### Cardiac

Both the conduction and the pumping systems of the heart can be damaged by iron overload. Cardiomegaly, bradycardia, arrhythmia, and congestive heart failure result. Cardiomyopathy of hemochromatosis may be either dilated or restrictive and is usually alleviated greatly by phlebotomy. Iron overload is therefore an important diagnosis to consider for all patients who have cardiomyopathy, congestive heart failure,<sup>27</sup> atrial fibrillation, or nonathletic bradycardia. When hemochromatosis manifests in adolescence, as it occasionally does, the heart is the organ most affected—and cardiac death from arrhythmia or congestive heart failure is the typical outcome. Such an adolescent case with cardiac death is illustrated in our videotape, *"Hemochromatosis at Autopsy: A Mother's Story."*<sup>28</sup> What portion of cases of "idiopathic cardiomyopathy" actually represent undiagnosed hemochromatosis is yet to be determined. Cardiomyopathy and arrhythmia are well-documented outcomes of iron overload,<sup>27</sup> but a currently contested hypothesis proposes that elevated iron stores are related to coronary artery disease in heterozygotes.<sup>29-31</sup>

### Hematologic

Contrary to popular expectation, anemia can result from iron overload. This point is important to remember lest a patient's anemia lead the physician to avoid diagnostic consideration of hemochromatosis. Indeed, many cases of iron overload disease are worsened by repeated prescription of ferrous sulfate for nonresponsive forms of anemia caused by unrecognized hemochromatosis. In this anemia, which typically resolves as iron is removed from the patient, excess iron causes toxic suppression of marrow function. We recently treated a middle-aged KPSD member whose hematocrit level rose from 32 to 43 as 40 units of blood were removed! Marrow iron stores correlate poorly with total body iron and may be low in presence of major iron overload; marrow examination is therefore not diagnostically helpful.

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### Dermatologic

Skin changes (classically described as bronzing) are most readily recognized as axillary tanning, which occurs at a relatively late stage in the disease. Two mechanisms are involved: 1) iron stimulates melanin, producing a tan color, and 2) direct iron deposition adds a greyish hue. Loss of body hair (already described here as an endocrine process) is another dermatologic effect. An uncommon blistering lesion of areas exposed to sunlight, porphyria cutanea tarda, is associated with underlying iron overload as well as with chronic hepatitis C. Porphyria cutanea tarda responds well to treatment of the underlying iron overload.<sup>32</sup> All patients with porphyria cutanea tarda should be tested for hemochromatosis, and all patients with hemochromatosis should be examined for presence of photosensitive, vesiculating dermatitis.

### Neuropsychiatric

The biomedical literature contains little discussion of nervous system effects caused by systemic iron overload disease. However, clinical depression that is out of character for the individual occasionally occurs and is reversed by phlebotomy.<sup>33</sup> Mild dementia not confounded by coincident alcoholism or liver failure may develop rapidly and is reversed by phlebotomy.<sup>34</sup> Profound fatigue, too, may develop suddenly and is reversed by phlebotomy.<sup>34</sup> The brain in hemochromatosis contains a large amount of iron, and a prominent neuropeptide-like distribution pattern of transferrin receptors in the brain suggests that transferrin may have a neuromodulating function.<sup>35</sup> Deafness is well known to be associated with hemochromatosis.<sup>3</sup> Less clear is whether peripheral neuropathy, in the absence of diabetes, and tinnitus are also associated with hemochromatosis.

### Infection and Malignancy

Hemochromatosis lowers the threshold for development of chronic active viral hepatitis, whose coincidence with iron overload disease is distinctly higher than expected. Any patient with this condition should therefore be screened for hemochromatosis. In addition, reduction of iron levels in chronic hepatitis C might improve the effectiveness of interferon treatment. Patients with *Vibrio vulnificus*, *Listeria monocytogenes*, and *Yersinia* infections should also be screened for hemochromatosis because iron overload predisposes patients to infection by these organisms.<sup>36-38</sup> Hepatoma, too, is well known to have higher prevalence in hemochromatosis.<sup>39</sup>

### Comparison of Diagnostic Methods Saturation of TIBC

Currently, hemochromatosis is most reliably diagnosed by "transferrin saturation" testing, which costs

only about \$2 per test and is required only once per lifetime. The test, which indicates whether excess iron is being absorbed, gives reliable results for patients aged  $\geq 1$  year but not for neonates.<sup>39</sup> For both sexes, excess iron absorption is suggested by  $>50\%$  saturation in randomly drawn specimens. Some researchers have recommended a threshold of 55% saturation for men, but 8% of our homozygous male patients with hemochromatosis would have received misdiagnoses if the higher value had been selected as the diagnostic. To assure a reliable conclusion free of confounding influences, any initial test showing elevated iron levels should be repeated after the patient has fasted overnight and consumed no vitamin or mineral supplements for at least 24 hours; vitamin C (ascorbic acid) supplementation is particularly responsible for raising serum iron levels (especially in heterozygotes) because it increases intestinal absorption and releases iron from ferritin. Moreover, diurnal transferrin saturation levels vary: fasting morning specimens have higher saturation. Our experience with tens of thousands of randomly drawn specimens shows that 2.5% of KPSD members have saturation  $\geq 50\%$  at initial random testing, whereas the rate of abnormal results drops to 0.4% for patients who are retested after they have fasted overnight and ingested no dietary supplements for at least 24 hours. Fasting saturation values persistently  $>62\%$  are highly likely to indicate hemochromatosis.

Illness, infection, and other factors can alter serum iron levels or TIBC, but these alterations balance each other, causing transferrin saturation to remain relatively unaffected.

### Serum Ferritin Level

Measurement of serum ferritin level gives useful—though imperfect—estimates of total body load but is not as useful as serum iron saturation for screening hemochromatosis. For instance, serum ferritin levels remain normal in all patients at the early stages of hemochromatosis, whereas serum ferritin levels are commonly elevated in alcoholism and in unrecognized chronic hepatitis—conditions which routine testing has shown to be more common than we may think. Infrequently, serum ferritin level is normal in symptomatic iron overload disease, possibly indicating increased density of iron packing in the ferritin latticework.<sup>40</sup>

### Liver Biopsy and Other Tests

In addition to being expensive, not without risk, and likely to cause some patients to reject diagnostic testing (and thus to evade treatment), liver biopsy is clearly problematic as a diagnostic tool in hemochromatosis: it can detect iron overload and

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organ damage only to the extent that an affected patient has had sufficient time to absorb excess iron; liver biopsy can thus diagnose only advanced cases. This limitation of liver biopsy—a limitation that makes negative results nondiagnostic—is shared by computed tomography (CT) scanning, MRI, and magnetic susceptometry. For the same reason, too, biopsy (or autopsy) of organs other than liver—skin, atrophic testis, gastric mucosa, and even myocardium—may be nondiagnostic for hemochromatosis that has not yet progressed to phenotypic expression in that organ.

Clinical diagnosis of hemochromatosis must be distinguished from population diagnosis because they are not equally efficient or cost-effective. Clinical diagnosis of hemochromatosis requires each practitioner to be constantly vigilant as well as familiar with a range of possible presentations, yet is certain at best to identify only patients whose disease is already beyond full preventive treatment. In contrast, population diagnosis can identify many presymptomatic cases and requires only a simple, inexpensive, one-time test given to large numbers of persons, most of whom will prove normal. Overall, the contrast between the approaches is similar to the difference between diagnosing a case of tetanus and immunizing patients with tetanus toxoid.

### Confirming the Diagnosis

The diagnosis of hemochromatosis can be confirmed by any of several methods, but some are more reliable and practical than others:

- Quantitative demonstration of body iron overload by phlebotomy or chelation,
- Biopsy or autopsy demonstration of tissue iron overload,
- HLA typing identical to a proven case in a close relative,
- Genetic analysis demonstrating homozygous presence of the HFE gene.

Testing the patient's response to quantitative phlebotomy is simple, inexpensive, safe, and highly effective. Given the fact that an adult body has about 1 g of storage iron and that a pint (500 mL) of blood contains 200-250 mg of iron, weekly phlebotomy of 500 mL will normally induce iron depletion anemia within four to five weeks. In an iron-overloaded individual, anemia will not occur for many months, the exact time depending on the total body load of accumulated iron. An additional advantage of this approach is that it also affects treatment.

A different quantitative test sometimes used to confirm the diagnosis is measurement of the urinary iron removed after a single subcutaneous injection of 0.5 g of the chelating agent, deferoxamine.<sup>41</sup> However, this

approach should not be considered reliable in teenagers or children who have high serum iron saturation but low serum ferritin levels, because major iron overload has not yet occurred in these patients. The only tool for confirming the diagnosis in these patients is genetic analysis, understanding its limited (85%) sensitivity.

### Family HLA Typing

HLA testing of close relatives was formerly used in family screening because all family members with hemochromatosis have the same tissue type (the hemochromatosis gene is tightly linked to the locus of HLA genes). However, HLA testing is expensive, now unnecessary for diagnosis, and has been replaced by genetic analysis.

### Genetic Analysis

In families where the proband is genetically abnormal for the currently recognized gene, genetic analysis can identify individuals who are homozygous for the HFE gene. Genetic analysis is desirable as an adjunct but not absolutely necessary for diagnosis or treatment. It does have significant practical value in convincing doubtful physicians that their patients have hemochromatosis. It is currently not an appropriate screening test, although it is being so used by some who do not understand its limitations.

### Treatment

Because the essence of hemochromatosis is iron overload, the goal of treatment is to normalize the total body load of iron—usually by weekly phlebotomy in 500 mL amounts until iron levels are normalized. More extensive phlebotomy—removal of two units of blood per week—may be needed by patients who are urgently symptomatic when diagnosed, and this treatment is well tolerated by most such patients. However, phlebotomy is optimally started in advance of symptoms because phlebotomy can block phenotypic expression only in the early, presymptomatic stages of hemochromatosis. (This limitation clearly indicates the need for early diagnosis through screening.) It is as wrong to delay treatment until symptoms occur as it would be to delay treatment of hypertension until stroke or cardiomegally supervened. To normalize total body iron loads, symptomatic hemochromatosis patients often need removal of 20-80 pints of blood, depending on how far the disease has progressed when diagnosed. Treatment outcome is monitored by periodic serum ferritin measurement. At KPSD, we use a computerized Hemochromatosis Registry (the computer program is available with manual for the cost of copying) to track the progress of all treated cases.<sup>42</sup> At KPSD, all

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phlebotomy is done at the blood donor center, which was developed and is operated by the pathology department; this arrangement is more efficient than adding these cases to the already busy nurses clinics. Unfortunately, this blood is not used for transfusion in the United States; it has safely been transfused in Sweden for three decades.

Whether the total body iron load should be reduced to upper or lower levels of normal and whether iron saturation should also be managed are not known. Our practice at KPSD has been to use the lower limits (ie, serum ferritin level of 20 ng/mL; iron saturation of 20%) as approximate goals. After total body iron load has been reduced to normal levels, phlebotomy is done every two to four months for the remainder of that patient's life to prevent reaccumulation of excess iron. Excessive phlebotomy (which can create serious iron deficiency) is easily avoided by determining a hematocrit level below which blood will not be drawn.

For all patients with hemochromatosis, we immunize against hepatitis A and B because these pose a threat to the liver, which is probably already damaged; affected patients should also greatly limit alcohol consumption for similar reasons: we also advise these patients against eating raw shellfish because of the increased risk from *Vibrio vulnificus* in this setting. We advise patients against taking iron supplements and vitamin C because they increase the iron load that must then be removed. Special diets are generally not needed (because the essence of the disease is excessive absorption of iron from ordinary food sources) but have not been carefully studied. Substitution of tea for coffee with meals has the logical advantage of forming insoluble iron tannates in the intestine. Particularly in view of animal studies,<sup>13</sup> we may anticipate an important role for dietary intervention in pediatric cases, especially as increasing numbers of presymptomatic homozygous children are diagnosed through screening.

Deferoxamine may be given daily by intravenous or subcutaneous infusion to treat iron overload from transfusion when intractable anemia does not respond to erythropoietin therapy (ie, where phlebotomy is not appropriate) but is cumbersome, relatively inefficient, and expensive. Under uncommon circumstances, however, it may be the best available approach.<sup>43</sup> Daily intramuscular or subcutaneous injection is also possible, although still less efficient.

Liver transplantation is of course the treatment of last resort for hemochromatosis. Surprisingly, transplanted hemochromatosis cases are not routinely deironed before or afterwards. In a similar vein, most

explanted livers are never iron stained. Livers containing hepatomas have not been routinely iron stained,<sup>39,44</sup> including in our organization.

But, whereas liver transplantation is currently the final treatment for hemochromatosis, the discovery of the HFE gene makes it realistic that someday gene therapy may be the first treatment. This would make diagnosis at a pre-symptomatic stage, preferably in childhood, all the more appropriate. The fact that the genetic defect manifests itself at intestinal level expectedly will make in vivo gene delivery at easier task.

### Education

Education of each patient is particularly important, given the present unfamiliarity of most physicians with hemochromatosis, and the consequent dismissive attitude sometimes taken toward its possible diagnosis. We therefore provide informational materials to newly diagnosed patients for their own protection. Included is a gift videotape in which patients describe the range of their presentations.<sup>45</sup> We also sell each patient a book<sup>46</sup> about iron overload diseases. Useful information is also available on the Internet, both for physicians<sup>47</sup> and for patients.<sup>48,49</sup>

### Family Screening

Diagnosis of hereditary hemochromatosis has two beneficiaries: the patient and the patient's not-yet-diagnosed relatives. Family screening is therefore important, especially given the hemochromatosis gene frequency, which predicts a 1:8 chance that a homozygote will pair with a heterozygote: half the children of this pair will be homozygotes. The concept of the Index Case has an important application: at KPSD, affected patients' children and other primary relatives are screened through transferrin saturation testing. We give authorization letters to affected patients for their relatives to take to local clinical laboratories to have appropriate tests done. This important step is conceptually simple but is too often avoided by relatives who are reluctant to contemplate the possibility of a hereditary disorder.

### Discussion

#### Theory vs. Practice

Having discussed the theoretical aspects of disease development, diagnosis, and treatment, we might wonder: what actually happens to people who have hemochromatosis? Most cases are never diagnosed, and some patients with unrecognized disease die prematurely. The few diagnosed cases are often of patients who start treatment but who almost never continue it for their entire lifetime. Virtually none of these patients have their entire fami-

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lies screened. Centralized diagnosis, centralized treatment, and institution of a Hemochromatosis Registry have been valuable, easy steps for our organization and provide our KPSD members a service that is infrequently approached elsewhere in the country in quality, usefulness, and cost-effectiveness. In the next few years, as clinicians see more cases of hemochromatosis, its diagnosis will be considered more frequently and more of our estimated 29,000 unidentified cases will be found and given phlebotomy by their own physicians. Screening programs such as the one initiated at KPSD ultimately will identify most cases among our members. We can expect about 40 cases of hemochromatosis in our partner physicians nationwide; Dr. Funke is only the first affected partner identified. Might you be the next? If so, will you be symptomatic or presymptomatic when diagnosed?

#### Clinical and Economic Benefits of Screening

In 1995, the costs related to hemochromatosis at KPSD were informally studied by a Centers for Disease Control and Prevention (CDC) medical economist who concluded that it costs us \$1,100 to diagnose a case. The analysis supposed that neither liver biopsy nor genetic analysis was used as a diagnostic method. Lifetime treatment cost was calculated at \$6,400 per patient. In contrast, taking the probability of various outcomes into account, the mean lifetime cost of caring for an undiagnosed case of hemochromatosis was estimated at \$46,000.

Even though treating a presymptomatic case of homozygous hemochromatosis prevents all manifestations of iron overload disease (ie, blocks phenotypic expression of the genotype)<sup>7</sup> and presymptomatic cases can be diagnosed only through screening, change will be difficult—especially because most physicians were taught that hemochromatosis is dismissably rare, and multiple recent articles to the contrary have not yet altered this widespread belief.<sup>2,4-6</sup> Accordingly, a current argument concerns whether population screening should take place. In 1996, the College of American Pathologists issued a detailed analysis supporting their formal recommendation for universal screening in the U.S. population aged  $\geq 20$  years.<sup>5</sup> Adams et al<sup>50</sup> came to a similar conclusion in their detailed cost analysis of screening for hemochromatosis. After a divided meeting, which a news article erroneously reported as supporting screening,<sup>51</sup> the CDC decided to delay decision until “more factual information” was available. This scenario recalls Benjamin Franklin’s comment about how long a useful truth may be known to exist before it is generally known and practiced.

Given the documented prevalence of 1:250 for the homozygous state in European and North American populations, each Permanente physician’s panel probably includes approximately 10 cases. In the ever-increasing KPSD cohort of cases who are homozygous for hemochromatosis at the 845-nucleotide locus, one third are aged  $>65$  years and hence have had sufficient time for iron overload to become symptomatic. Of these patients, only 10% have no signs or symptoms attributable to iron overload disease. Thus, most of our members with homozygous hemochromatosis have become symptomatic over time. This conclusion is consonant with the long-term study by Powell et al<sup>52</sup> of 50 homozygotes, of whom 47 accumulated excess iron to the point of overload over sufficient time.

A powerful argument can therefore be made for universal, once-in-a-lifetime screening: Only screening can lead to treatment that prevents phenotypic expression of the genotype. Still uncertain, however, is the age at which screening should be done. If neonatal screening were instituted, genetic analysis would be the only possible tool, and 15% of cases would thereby be missed; if screening were carried out in middle age, the few rapidly fatal adolescent cases would be missed. A reasonable compromise might be to screen patients at age 18 years and designate transferrin saturation of  $>50\%$  as highly suspect. Were our organization to do this, we would improve the lives of our patients, benefit ourselves economically, and help the nation by setting a trend that urgently needs to be set. ♦

<sup>a</sup> Joseph H. Sheldon, MD, FRCP (1893-1972), was Hunterian Professor at the Royal College of Surgeons of England.

<sup>b</sup> If one in eight persons is a carrier, then each carrier has a 1:8 chance of marrying another carrier. Thus, one in 64 marriages will be between heterozygotes. In such a mating, one in four children will be homozygous for hemochromatosis. Ultimately,  $1:64 \times 1:4 =$  approximately 1:250 homozygotes in the general population.

<sup>c</sup> Of proven cases of hereditary hemochromatosis, 15% are missed by the current gene test.

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## Screening for Hemochromatosis: An Important Opportunity

*Commentary by David Baer, MD, FACP Kaiser Permanente, Oakland*

There is abundant justification for the current explosion of interest in hereditary hemochromatosis.<sup>1</sup> Population surveys have confirmed repeatedly that roughly one in 250 individuals of Northern European descent has evidence of an increased propensity to absorb dietary iron (commonly termed hereditary hemochromatosis) and deposit it in vulnerable organs such as the liver, pancreas, heart, and pituitary gland.<sup>2-5</sup> Furthermore, retrospective reviews<sup>6-8</sup> strongly suggest that the initiation of phlebotomy therapy before the onset of organ injury can largely prevent adverse outcomes for patients with this condition. An exciting recent development has been the demonstration that a single point mutation (termed C282Y) of the newly cloned HFE gene<sup>9</sup> is responsible for 85% to 90% of cases of hereditary hemochromatosis.<sup>10</sup> The cloning of the HFE gene offers the potential for more accurate diagnostic evaluations and new insights into pathophysiology.

Doctor Felitti has provided a timely and thoughtful overview of hereditary hemochromatosis. His account of the history, pathophysiology and clinical consequences of hemochromatosis is beautifully organized and delightfully easy to read. Most importantly, though, he has presented a cogent and persuasive argument to incorporate a once-per-lifetime screen for hemochromatosis into the routine preventive health care we offer our health plan members. The powerful testimonial of Dr. Funke, a Permanente physician whose life has been devastated by the effects of iron overload, bears witness to the unnecessary personal ruin that can come from overlooking this important diagnosis. Though many of the effects of iron-related organ injury will reverse with phlebotomy therapy, advanced cirrhosis and the common crippling arthritis will not.

To fully understand the issues surrounding screening, however, it is important to understand why an expert panel, recently convened by the Center for Disease Control and Prevention (CDC), fell short of endorsing universal screening and concluded:

*"Despite the promise of prevention of hemochromatosis, this review indicates that we lack evidence to recommend hemochromatosis screening for all adults ..."*<sup>11</sup>

The panel went on to state:

*"Gaps in the evidence include the clinical penetrance and burden of disease associated with hemochromatosis."*

The uncertainty surrounding the penetrance of this genetic condition is illustrated by examining our own experience at the Oakland Kaiser Permanente Medical Center.<sup>12</sup> In 1989, we screened 4000 consecutive men for hemochromatosis using the transferrin saturation test. The study population consisted of consecutive men over age 30 who took a routine multiphasic health examination. We concluded, on the basis of liver biopsy results, that 8 of the 4000 had hemochromatosis. Since 7 of the 8 came from among the 2000 white patients in our study sample, we confirmed the prevalence of the disease that had been described by others. However, of the 8 patients we identified, 1 had arthritis but the other 7 were entirely asymptomatic.

All 8 were referred for phlebotomy therapy. Thus, our experience did not address the question: how many of these would have ever developed symptomatic disease had they gone undiscovered and continued to absorb iron for the rest of their lives? A normal individual will shut off the absorption of dietary iron after the accumulation of one or two grams of storage iron so that iron deficiency will develop after only 5 or 10 phlebotomies. (Each unit of phlebotomized blood contains about 200 mg of iron.) Our patient with arthritis was 39 years old and required over 80 phlebotomies to deplete his iron stores, implying that his total body iron load was over 16 grams. However, a 66-year-old man and a 48-year-old man, both asymptomatic, each had  $\leq 4$  grams of total body iron and a 63-year-old man had 6.5 grams. What would have happened to these patients had they not been discovered and referred for phlebotomy? Felitti reports that 90% of patients with hemochromatosis over the age of 65, diagnosed in the KPSD screening program, had signs or symptoms of iron overload. This is an important and original observation, but it remains to be confirmed by others.

In contrast are the observations of Willis et al<sup>13</sup> who studied the medical records of the Norfolk and Norwich Hospital in Norwich, England, an area with a population of 500,000. They concluded that less than 10% of affected individuals with hemochromatosis will ever manifest symptomatic disease.<sup>13</sup> Is the penetrance only 10% or is it as great as 90%? Does it matter? One could argue that a once-in-a-lifetime hemochromatosis screen could be justified even if only 10% of individuals with this common, inherited condition were to have potentially preventable tragic outcomes like Dr. Funke.

Another issue is the possibility of genetic discrimination. Might patients labeled with a genetic condition be refused health or life insurance or even employment opportunities? This concern over discrimi-

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*"An exciting recent development has been the demonstration that a single point mutation (termed C282Y) of the newly cloned HFE gene<sup>9</sup> is responsible for 85 to 90% of cases of hereditary hemochromatosis."<sup>10</sup>*

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*"In 1989, we screened 4,000 consecutive men for hemochromatosis using the transferrin saturation ... of the eight patients we identified, one had arthritis but the other seven were entirely asymptomatic ... our experience did not address the question: how many of these would have ever developed symptomatic disease had they gone undiscovered and continued to absorb iron for the rest of their lives?"*

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nation based on genetic diagnoses has taken a prominent place in our national debate. With this potential "adverse effect" in mind, ought we to seek specific consent before testing a patient for hemochromatosis, or should such a test be regarded as similar to a fasting glucose or serum cholesterol test?

If a consensus could be achieved over the need to introduce universal screening for hemochromatosis, important decisions would still have to be made regarding the optimal method of screening. Should HFE mutational analysis, in either a confirmatory role or even perhaps as a primary screen, be part of the screening approach? Do we know enough about iron overload in African Americans,<sup>14-16</sup> Hispanics,<sup>17</sup> or other non-Northern European groups to justify designing a screening program that will look at these persons? Do we know how to screen for iron overload in these patients even if we wanted to? What is the optimal way to handle patients incidentally found to have possible iron deficiency during a screen for iron overload? There is much to learn about all of these important questions.

What about the costs associated with a screening program? Dr. Fellitti's estimates are based on several very favorable assumptions that need to be confirmed in other settings over time. Will others be able to operate with the same efficiencies that his centralized, preventive health program in San Diego has been able to achieve? If his estimates of penetrance are too high, perhaps his calculation of cost savings may be too optimistic.

The expenses of any screening program would be greatly reduced and the overall social benefit would be increased if patients with hemochromatosis could donate their blood for therapeutic use. Unfortunately, most blood banks, at least in California, will not accept blood from "medical phlebotomies" on the grounds that a "medical" donor is not truly a voluntary donor and may be less likely to provide a truthful history regarding "high-risk" behaviors.

Is it premature, as suggested by the CDC panel, to recommend universal screening, or rather is it time to make screening for hemochromatosis a routine preventive health test as proposed by Dr. Felitti? Kaiser Permanente is uniquely suited to take the lead in this important area. Our tradition of leadership in the area of preventive medicine, our programs for large-scale patient and physician education, our experience with genetic counseling, and our growing information technology capability all provide us with

a unique opportunity to create screening programs that can effectively and efficiently address this important need. ♦

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*"The expenses of any screening program would be greatly reduced and the overall social benefit would be increased if patients with hemochromatosis could donate their blood for therapeutic use."*