

# Hemochromatosis: Diagnosis and Management

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Hereditary hemochromatosis (HH) is a common inherited disorder of iron metabolism that affects between 1 in 200 and 1 in 400 persons of northern European descent and is characterized by increased gastrointestinal iron absorption with subsequent tissue iron deposition.<sup>1-3</sup> Although the autosomal recessive inheritance pattern of HH has been recognized for more than 25 years,<sup>4</sup> identification of the responsible gene proved elusive until recently. Identified in 1996, the gene (called *HFE*) was found to encode a previously unidentified major histocompatibility complex (MHC) class 1–like molecule<sup>5</sup> that may modulate cellular iron transport by binding with the transferrin receptor. The identification of *HFE* has established the foundation for a better understanding of the molecular and cellular biology of iron homeostasis and its altered regulation in HH. Additionally, the ability to accurately diagnose iron overload disorders has been strengthened, family screening has been improved, and evaluation of patients with other forms of liver disease complicated by moderate-to-severe iron overload is now possible. Finally, the role of *HFE* testing in generalized population screening for HH is still in the process of being determined.

## Classification of Iron Overload Syndromes

The term *hereditary hemochromatosis* is generally reserved to describe an inherited disorder of iron metabolism leading to progressive iron loading of parenchymal cells of the liver, pancreas, and heart. When it is fully developed, organ structure and function are impaired. The most common form of this disease is caused by homozygosity for the C282Y mutation in the *HFE* gene. However, other hereditary forms of iron overload not caused by *HFE* mutations have recently been recognized.<sup>6,7</sup> Patients have also been identified as being homozygous for the C282Y mutation who have no evidence of iron overload; they carry the genetic mutation responsible for HH but do not have phenotypic expression. Thus, 4 stages of the disorder have been described: (1) genetic predisposition with no other abnormality; (2) iron overload (approximately 2–5 g) but without symptoms; (3) iron overload with early symptoms (e.g., leth-

argy, arthralgias); and (4) iron overload with organ damage, particularly cirrhosis.<sup>8</sup> A classification of the various iron overload syndromes/disorders is given in Table 1.<sup>8</sup>

## Genetics of Hemochromatosis

The HH gene has been known to be linked to the HLA region on the short arm of chromosome 6 since the mid-1970s.<sup>3</sup> Twenty years later, in 1996, a positional cloning approach was used to detect a candidate gene for HH,<sup>5</sup> now known as *HFE*. *HFE* codes for a novel MHC class 1–like molecule that requires interaction with  $\beta_2$ -microglobulin for normal presentation on the cell surface.<sup>5</sup> Structural homology with other MHC class 1 proteins and x-ray crystallographic studies indicate that *HFE* protein has a large extracellular domain, a single transmembrane region, and a short cytoplasmic tail<sup>5,9,10</sup> (Figure 1). *HFE* protein lacks a functional peptide-binding groove needed for antigen presentation.<sup>9</sup> Two missense mutations were initially identified in *HFE*; one results in a change of cysteine at position 282 to tyrosine (Cys282→Tyr, C282Y); the second results in a change of histidine at position 63 to aspartate (His63→Asp, H63D).<sup>5</sup> Other mutations have recently been identified,<sup>11,12</sup> but their frequency seems low, and thus their clinical impact may be limited. In the original study by Feder et al.,<sup>5</sup> 83% of typical phenotypic HH patients (148 of 178) were homozygous for the C282Y mutation; an additional 8 patients (4%) were compound heterozygotes, with one allele containing the C282Y mutation and the other allele containing the H63D mutation. Numerous additional studies have now confirmed the original observations of Feder et al.<sup>5</sup> and have shown homozygosity for the C282Y mutation in 64%–100% of patients with typical phenotypic HH from the United States, France, Italy, Canada, and Australia.<sup>2</sup> In these studies from around the world, approximately 10%–

*Abbreviations used in this paper:* DMT-1, divalent metal ion transporter 1; HH, hereditary hemochromatosis; HIC, hepatic iron concentration; HII, hepatic iron index; NASH, nonalcoholic steatohepatitis; PCT, porphyria cutanea tarda; TS, transferrin saturation.

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0016-5085/01/\$35.00

doi:10.1053/gast.2001.21913

**Table 1.** Classification of Iron Overload Syndromes

HH
<i>HFE</i> -related
C282Y/C282Y
C282Y/H63D
Other mutations
Non- <i>HFE</i> -related
Acquired iron overload
Anemia caused by ineffective erythropoiesis
$\beta$ -Thalassemia
Sideroblastic anemia
Aplastic anemia
Pyruvate kinase deficiency
Pyridoxine-responsive anemia
Liver disease
Alcoholic liver disease
Chronic viral hepatitis B and C
Porphyria cutanea tarda
Postportocaval shunting
Transfusional and parenteral iron overload
Red blood cell transfusions
Iron dextran injections
Associated with long-term hemodialysis
Dietary iron overload
Miscellaneous
Iron overload in sub-Saharan Africa
Neonatal iron overload
Aceruloplasminemia
Congenital atransferrinemia

15% of patients still have a clinical syndrome that is phenotypically similar to HH but do not have the C282Y mutation. Recently, a 3-generation pedigree from Italy was identified with typical phenotypic HH but no mutations in *HFE*, identifying a new inherited abnormality of iron overload in this Italian family.<sup>6</sup> Mutations in the gene for transferrin receptor 2 can also result in iron overload.<sup>7</sup> It may be that other familial syndromes of iron loading in C282Y-negative individuals will be described identifying other, less common genes regulating iron metabolism.

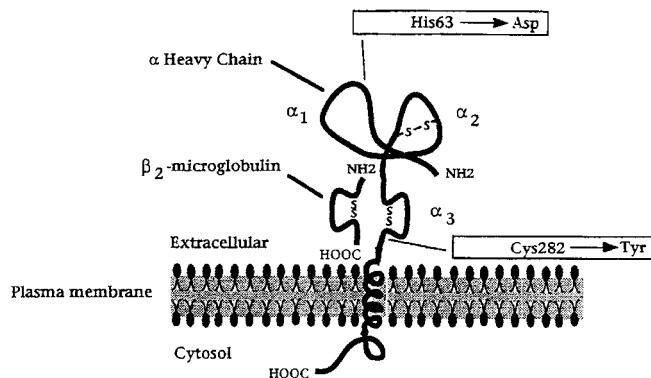
### Pathophysiology of *HFE*

Since the discovery of *HFE*, numerous studies have been performed that have begun to elucidate the pathophysiologic mechanisms operative in normal iron absorption and in the dysregulated iron absorption found in HH. The creation of *HFE*-knockout mice and C282Y homozygous mice that have a phenotype similar to that found in humans with HH (increased transferrin saturation, increased hepatic iron concentration, and parenchymal iron distribution) confirms that *HFE* is the gene responsible for HH.<sup>13–15</sup> *HFE* protein is found in the crypt cells of the duodenum associated with  $\beta_2$ -microglobulin and transferrin receptor.<sup>16,17</sup> It has been hypothesized that *HFE* protein may facilitate transferrin receptor-dependent iron uptake into crypt cells and that

mutant *HFE* protein may lose this ability, leading to a “relative” iron deficiency in duodenal crypt cells.<sup>16–18</sup> In turn, this may result in an increase in the expression of a recently identified iron transport protein called divalent metal ion transporter 1 (DMT-1, also called DCT-1 or Nramp2) that is responsible for dietary iron absorption in the villus cells of the small intestine.<sup>19</sup> Up-regulation of DMT-1 expression has been confirmed in the *HFE*-knockout mouse<sup>20</sup> and in humans with HH,<sup>21</sup> providing supportive evidence for this pathophysiologic mechanism of increased iron absorption in HH.

### Clinical Features of HH

Several symptoms (e.g., fatigue, malaise, abdominal pain, arthralgias, and impotence) and clinical findings (e.g., hepatomegaly, abnormal liver enzymes, skin pigmentation, diabetes, and cardiomegaly) have been identified in patients with fully established HH, and all physicians should be aware of these symptoms and findings (Table 2).<sup>1–3,8</sup> Table 3 summarizes typical laboratory findings in symptomatic and asymptomatic patients with HH. However, recent series of patients with HH have shown that many patients are newly identified as a result of (1) serum iron studies obtained as a part of screening chemistry panels, (2) screening of family members of an affected proband, or (3) population screening studies.<sup>22</sup> When the diagnosis of HH is established in these ways, most patients (>75%) are asymptomatic and have a low frequency (<25%) of cirrhosis, diabetes, or skin pigmentation. Two recent large population surveys from Australia and San Diego have shown that an even higher percentage of patients are asymptomatic when identified by screening.<sup>23,24</sup> Thus, in the face of abnormal iron study results, clinicians should not wait for typical symptoms or findings of HH before considering the diagnosis.



**Figure 1.** Model of *HFE* protein. The large extracellular domain consists of 3  $\alpha$  domains, and  $\alpha_3$  binds to  $\beta_2$ -microglobulin. *HFE* protein also has a transmembrane region and a short cytoplasmic tail. The C282Y mutation substitutes a tyrosine for a critical cysteine involved in disulfide bond formation in the  $\alpha_3$  domain.<sup>5</sup>

**Table 2.** Symptoms and Physical Findings in Patients With HH

Symptoms
Asymptomatic
Abnormal serum iron study results on routine screening chemistry panel
Evaluation of abnormal liver test results
Identified by family screening
Identified by population screening
Nonspecific, systemic symptoms
Weakness
Fatigue
Lethargy
Apathy
Weight loss
Specific, organ-related symptoms
Abdominal pain (hepatomegaly)
Arthralgias (arthritis)
Diabetes (pancreas)
Amenorrhea (cirrhosis)
Loss of libido, impotence (pituitary, cirrhosis)
Congestive heart failure (heart)
Arrhythmias (heart)
Physical findings
Asymptomatic
No physical findings
Hepatomegaly
Symptomatic
Liver
Hepatomegaly
Cutaneous stigmata of chronic liver disease
Splenomegaly
Liver failure: ascites, encephalopathy, etc.
Joints
Arthritis
Joint swelling
Heart
Dilated cardiomyopathy
Congestive heart failure
Skin
Increased pigmentation
Endocrine
Testicular atrophy
Hypogonadism
Hypothyroidism

## Diagnosis of HH

Once the diagnosis of HH is considered, either by evaluation of abnormal screening iron study results, in the context of family studies, in population surveys, or in the evaluation of a patient with any of the above-mentioned symptoms or findings, a definitive diagnosis is relatively straightforward. Fasting transferrin saturation (TS; serum iron  $\div$  transferrin or total iron-binding capacity  $\times$  100%) and ferritin levels should be obtained. Both of these values are elevated in symptomatic patients, but TS is the earliest phenotypic marker of HH and may be elevated with a normal ferritin level in young individuals. Thus, the sensitivity and specificity of these tests become problematic when young individuals are

being evaluated or when patients have abnormal iron study results in the context of other illnesses, most notably liver disease. A large population study from San Diego shows that approximately 36% of C282Y homozygotes have TS  $\leq$  45%, and it is not known whether these individuals will ever go on to have significant or symptomatic iron overload.<sup>24</sup> In addition, serum ferritin levels can be abnormal in approximately 50% of patients with alcoholic liver disease, nonalcoholic steatohepatitis (NASH), or chronic hepatitis C virus (HCV) in the absence of HH.<sup>25–27</sup> Other inflammatory disorders (e.g., rheumatoid arthritis) and various neoplastic diseases (e.g., lymphoma) can cause elevated ferritin levels. Thus, serum iron studies may have many false-positive and false-negative results; therefore, reliance on these studies alone for the diagnosis of HH is fraught with error. The development of a widely available genetic test has contributed to better characterization of patients with underlying liver disease and abnormal serum iron study results. How this test should be used in population studies is still being characterized.

In the past, if either a fasting TS or ferritin level was elevated, a liver biopsy would be performed to establish a diagnosis by using histochemical iron stains (Perls' Prussian blue stain) and biochemical determination of hepatic iron concentration (HIC) with calculation of the hepatic iron index (HII). Currently, in this setting, genetic testing is performed, and if individuals are C282Y homozygotes or compound heterozygotes under the age of 40 years with normal liver enzyme levels, no further work-up is necessary.<sup>28</sup> Thus, as genetic testing has become more available and understood, liver biopsy has assumed less importance. Nonetheless, when liver biopsy is performed, iron deposition is found preferentially in periportal (acinar zone 1) regions of the hepatic lobule, with a decrease in grading in acinar zones 2 and 3.<sup>29</sup> With significant iron loading, Kupffer cell aggregates (siderotic nodules), bile duct epithelium, and fibrous tissue in portal tracts or septa will also show iron deposition by Perls' Prussian blue staining. Other processes that result in histologically detectable iron in the liver may show similar features when iron deposition is heavy, but in the initial stages of acquired iron overload, iron accumulates preferentially in sinusoidal lining cells (Kupffer cells) in a more diffuse distribution within the acinus. Histologic evaluation of iron staining provides complementary information to traditional biochemical tests for iron overload and the recently identified genetic testing. A recent study has shown that a non-HH pattern of iron distribution reliably predicts the absence of homozygosity for C282Y or the compound heterozygous

**Table 3.** Laboratory Findings in Patients With HH

Measurements	Normal subjects	Patients with HH	
		Asymptomatic	Symptomatic
Blood (fasting)			
Serum iron level ( $\mu\text{g}/\text{dL}$ )	60–180	150–280	180–300
Serum transferrin level ( $\text{mg}/\text{dL}$ )	220–410	200–280	200–300
Transferrin saturation (%)	20–45	45–100	80–100
Serum ferritin level ( $\text{ng}/\text{mL}$ )			
Men	20–200	150–1000	500–6000
Women	15–150	120–1000	500–6000
Genetic ( <i>HFE</i> mutation analysis)			
C282Y/C282Y	wt/wt	C282Y/C282Y	C282Y/C282Y
C282Y/H63D <sup>a</sup>	wt/wt	C282Y/H63D	C282Y/H63D
Liver			
Hepatic iron concentration			
$\mu\text{g}/\text{g dry wt}$	300–1500	2000–10,000	8000–30,000
$\mu\text{mol}/\text{g dry wt}$	5–27	36–179	140–550
Hepatic iron index <sup>b</sup>	<1.0	1.0 to >1.9	>1.9
Liver histology			
Perls' Prussian blue stain	0, 1+	2+ to 4+	3+, 4+

<sup>a</sup>Compound heterozygote.

<sup>b</sup>HII is calculated by dividing the HIC (in  $\mu\text{mol}/\text{g dry wt}$ ) by the age of the patient (in years). With increased knowledge of genetic testing results in patients with iron overload, the specificity of HII has diminished.

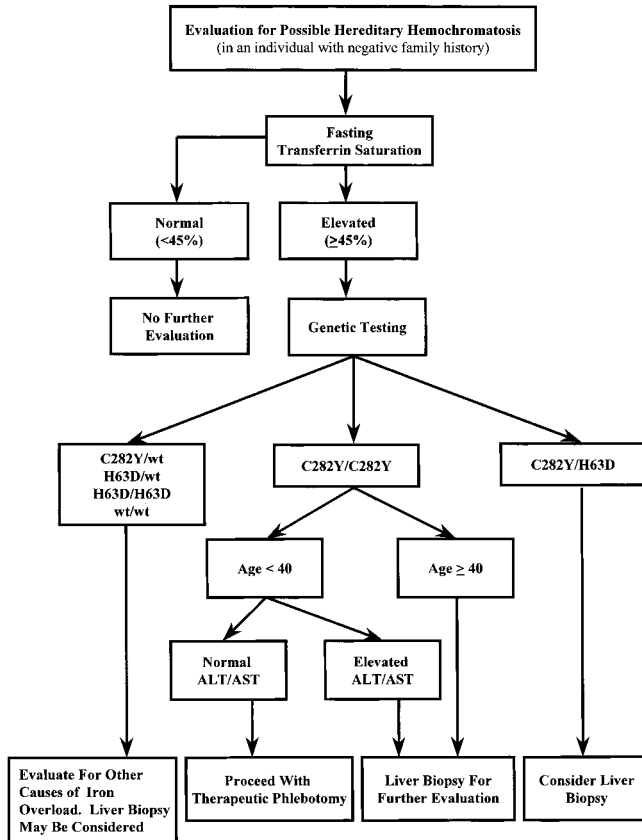
state (C282Y/H63D).<sup>29</sup> Conversely, the HH pattern of iron deposition can be seen in other forms of liver disease in the absence of C282Y homozygosity.<sup>29</sup>

The role of the HII is much less important in the diagnosis of HH than it was previously. In the past, the HII was one of the most important means of establishing a diagnosis of HH and differentiating heterozygotes or patients with alcoholic liver disease and secondary iron overload from homozygotes. The HII is based on the concept that patients with HH have a progressive increase in HIC with age, whereas heterozygotes for HH or patients with various forms of secondary iron overload do not have a progressive increase with age.<sup>30</sup> The HII is calculated by taking the HIC (in millimoles per gram dry weight) and dividing by the patient's age (in years). Numerous previous studies showed that an HII of >1.9 was consistent with homozygous HH. However, recent studies have shown that as many as 15% of patients with HH (identified as C282Y homozygosity) will have an HII of <1.9. Conversely, determining the specificity of the HII (i.e., those patients with an HII of >1.9 without HH) probably is not important. The HII only determines the relative degree of iron overload. Thus, by definition, all patients with an HII of >1.9 will be iron loaded, and differentiation between HH and other iron overload syndromes (e.g., transfusional iron overload) will depend on hepatic cellular and lobular iron distribution, history, and other laboratory tests and can be further clarified by *HFE* mutation analysis. Thus, with the availability of genetic testing, determination of HII

has reduced value. Recent studies have shown that the combination of age <40 years, serum ferritin level <1000 ng/mL, absence of hepatomegaly, and absence of abnormal liver enzyme levels represents a combination of findings that is associated with no increase in hepatic fibrosis in C282Y homozygous patients with HH.<sup>28,31,32</sup> Thus, when these criteria are met by a patient with abnormal serum iron study results who is a C282Y homozygote, liver biopsy is not necessary, and treatment with phlebotomy can be initiated with confidence. The algorithm outlined in Figure 2 illustrates these points.

### Treatment of HH

Despite advances in the molecular understanding of HH and the impact of *HFE* mutation analysis on diagnosis, the treatment of HH remains simple, inexpensive, safe, and "low tech." Patients should be encouraged to have weekly therapeutic phlebotomy of 500 mL of whole blood (equivalent to approximately 200–250 mg of iron, depending on the hemoglobin level). Some patients can tolerate twice-weekly phlebotomy, but this regimen is considered tedious and may be inconvenient. Therapeutic phlebotomy should be performed until iron-limited erythropoiesis develops, identified by failure of the hemoglobin level and hematocrit to recover before the next phlebotomy. Although not absolutely necessary, it is reasonable to monitor TS and ferritin levels periodically (every 3 months) to predict the return to normal iron stores and to provide a means of encouragement to



**Figure 2.** Proposed algorithm for evaluation of possible HH in a person with a negative family history.<sup>28</sup>

patients who are undergoing phlebotomy. Therapeutic phlebotomy should be continued until the TS is <50% and serum ferritin level is <50 ng/mL; some clinicians favor bringing the ferritin level down to 20 ng/mL. It is not necessary for patients to become anemic or iron deficient, just depleted of their excess iron stores. Once the initial therapeutic phlebotomy has been completed, most patients will require maintenance phlebotomy in which 1 unit of blood is removed every 2–3 months. Occasionally, in a few patients in whom HH is accurately diagnosed, iron does not reaccumulate for reasons that are unclear.

### Family Screening for HH

Once a proband with HH has been identified, family screening is necessary, and it is recommended for all first-degree relatives. In the past, *HLA* typing was recommended as a surrogate genetic test, but with the advent of *HFE* mutation analysis, *HLA* typing is no longer indicated. Both the C282Y and H63D mutations should be analyzed. In young probands with children, it is useful to perform *HFE* mutation analysis in the spouse to accurately predict the genotype in the children.<sup>33</sup> If

the spouse has either mutation, then the children will also need to undergo *HFE* mutation analysis, although the value of genetic testing in children is still being debated. Because C282Y and H63D are such common mutations, occurring in approximately 35% of individuals singly or in combination, there is approximately a 1 in 3 chance that the spouse will have a mutation in *HFE*. If C282Y homozygosity or compound heterozygosity (C282Y/H63D) is found in adult relatives of the proband, serum iron studies should be requested. If TS and/or ferritin levels are increased, therapeutic phlebotomy should be considered. In this situation, as long as liver test results (alanine aminotransferase, aspartate aminotransferase) are normal and ferritin level is <1000 ng/mL, liver biopsy probably is not necessary.<sup>28,31,32</sup>

### Population Screening

The role of population screening for HH is controversial. HH has a number of features that fulfill criteria established by the World Health Organization for population screening. These criteria include (1) a recognized latent or early asymptomatic stage; (2) adequately understood natural history of the condition, including its development from latent to declared disease; (3) availability of a reliable screening test; (4) acceptability of the test to the population; (5) an accepted policy on whom to treat; and (6) demonstration that screening is cost-effective.<sup>8</sup> Unfortunately, problems with case definition, phenotypic and genotypic definition, and which screening methods and protocols should be used must be clarified and further refined.<sup>8</sup> Another concern relates to the fact that when a genetic disease has been identified, there may be a risk that the patient will lose health insurance or employment or be stigmatized as a result of being labeled with a disease. With the recent completion of the human genome project, genetic diagnoses will become increasingly common, and it is hoped that legislators will create appropriate legislation to prevent this type of genetic discrimination. Another important question relating to population screening is which members of the population should be tested and at what age. HH is a disorder of northern European origin with the highest prevalence in Ireland, Germany, Portugal, and France. Despite genetic admixture in individuals of African or Asian descent, it is rare to find a non-white patient with a C282Y mutation. Thus, based on the available data, it is reasonable to limit screening for *HFE* mutations to white populations. When screening for iron overload (as opposed to screening for *HFE*-linked HH), extension to other racial groups should be considered. Because it is rare for HH to cause any morbidity before

age 20 years, screening should be limited to adults. Rather than every member of the population being evaluated, a more likely scenario is to increase patient and physician awareness and to screen all adults at one time when they visit a primary care physician. The National Institutes of Health is currently supporting a large screening effort in which approximately 100,000 individuals in 6 sites across North America will be screened. It is hoped that this will provide valuable insight into how screening programs should be developed from the standpoint of a national public health policy.

### ***HFE* Mutation Analysis in Patients With Liver Disease**

Abnormalities in serum iron study results are common in patients with a variety of liver diseases. These abnormal iron study results are generally observed in patients with hepatocellular liver diseases rather than in those with cholestatic liver diseases. Approximately 50% of patients with alcoholic liver disease, NASH, and chronic viral hepatitis have serum abnormalities of iron metabolism.<sup>25-27</sup> These abnormalities usually involve an increased ferritin level, but occasionally patients can have an elevated TS as well. HIC is typically normal or increased slightly, but not to the level seen in HH. Genetic screening for the mutations found in *HFE* has now been applied to groups of patients with alcoholic liver disease, NASH, chronic HCV, and porphyria cutanea tarda (PCT).<sup>34,35</sup> When *HFE* mutations have been examined in patients with alcoholic liver disease, there was no increase in the prevalence of C282Y or H63D in alcoholic patients compared with a control population.<sup>36</sup> More importantly, there was no relationship between *HFE* mutations and hepatic iron levels in patients with alcoholic liver disease.<sup>36</sup> Thus, although many patients with alcoholic liver disease have abnormalities in serum iron study results and some have an elevated HIC, it appears that mechanisms other than mutations in *HFE* are responsible.

In patients with chronic HCV, the relationship between HIC and response to treatment with interferon has been known for several years.<sup>37,38</sup> Numerous studies have shown that patients whose disease does not respond to interferon monotherapy have a higher mean HIC than those who have a response.<sup>37-40</sup> This has led to the use of therapeutic phlebotomy to deplete iron stores before treatment or retreatment with interferon. Iron depletion treatment has typically led to a reduction in serum alanine aminotransferase levels without any significant difference in sustained virologic response (undetectable HCV RNA levels) after interferon treatment.<sup>41-43</sup> Evi-

dence suggests that an increased HIC is associated with increased hepatic fibrosis in patients with chronic HCV.<sup>44-47</sup> Recent studies in which *HFE* mutation analysis has been performed in patients with chronic HCV have shown no difference in the prevalence of C282Y or H63D mutations in patients with chronic HCV and a control population.<sup>42,45,46,48-50</sup> Some studies have reported that the presence of *HFE* mutations (especially C282Y) in patients with HCV is associated with increased fibrosis and cirrhosis,<sup>45,46</sup> but other studies have not found this association.<sup>47,49,50</sup> Further investigation is needed to examine the role of *HFE* mutations and iron in HCV-induced liver injury and to evaluate whether long-term iron removal by phlebotomy decreases the progression of hepatic fibrosis in patients with chronic HCV.

In patients with NASH, 2 recent studies have shown a higher prevalence of the C282Y mutation (either heterozygotes or homozygotes).<sup>51,52</sup> Not all patients with NASH with elevated iron stores have the C282Y mutation, indicating that other factors are involved.<sup>51</sup> Both studies observed an increase in fibrosis in patients with NASH who had the C282Y mutation. However, another study failed to find an increase in disease severity caused by coexistent iron in patients with NASH followed up for up to 20 years.<sup>53</sup> It is still unclear whether the increased frequency of abnormalities of iron metabolism in these 2 series of NASH patients<sup>51,52</sup> represents ascertainment bias or if there truly is an association between the presence of C282Y and NASH. If this observation holds true, a role for phlebotomy therapy and iron reduction may be apparent as at least one form of treatment for patients with NASH. Because therapeutic phlebotomy is simple, inexpensive, and safe, this form of therapy should be analyzed prospectively in a large group of NASH patients.

In PCT, the relationship between abnormalities of iron metabolism and disease progression and symptoms has been known for many years.<sup>54</sup> Strong associations with chronic HCV and alcohol consumption have also been identified in patients with PCT.<sup>54</sup> Compared with *HFE* mutations in PCT, several studies from the United States, the United Kingdom, and Australia have shown that approximately 40% of PCT patients are either homozygous or heterozygous for the C282Y mutation.<sup>55-58</sup> The situation is different for Italian PCT patients, who do not have an increased prevalence of the C282Y mutation, but rather have a higher prevalence of the H63D mutation that is not related to iron status.<sup>59</sup> Other predisposing conditions such as chronic HCV and alcohol consumption may be more important than the C282Y mutation in Italian patients with PCT. Iron

reduction by therapeutic phlebotomy has been a mainstay of treatment of PCT for many years.<sup>54</sup> Thus, the role of genetic screening for mutations in *HFE* seems quite valuable in patients with PCT, NASH, or chronic HCV, but it is less likely to be important in patients with alcoholic liver disease.

## Summary

HH should be distinguished from the other syndromes of iron overload. Many patients with HH have abnormal serum iron values before the development of any significant symptoms or clinical findings, and liver biopsy is less important in these patients. *HFE* mutation analysis has strengthened our ability to diagnose HH accurately and is useful in family studies. *HFE* mutations may play a contributory role in some patients with PCT, NASH, or chronic HCV. Generalized population screening for HH may someday become a reality and lead to the identification and treatment of more patients before they have tissue damage or increased morbidity. With the identification of the *HFE* gene, we are beginning to unravel many of the mysteries of both normal iron absorption and the disorder of iron metabolism found in patients with HH.

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Received September 29, 2000. Accepted November 23, 2000.

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