Hemochromatosis: Ancient to the Future*

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The original description of hemochromatosis has usually been attributed to a case report by Trousseau in 1865.1 In that report, a patient was described with diabetes, pigmented cirrhosis, and bronze-colored skin, later leading to the term “bronze diabetes” by Victor Hanot. Phlebotomy treatment for medical disease has a much longer history and was commonly used by Chinese healers and physicians in the Middle Ages (Fig. 1). The Perls’ Prussian blue stain for iron in tissues was developed in 1867, but it was used in autopsies until percutaneous liver biopsies were developed in the 1920s. It was called “Prussian blue” because it had been used to dye Prussian army uniforms. In 1889, Von Recklinghausen determined that the increased pigment in the liver was iron, and because internal bleeding was considered to be the source of this liver coloration, he called the disease “hemochromatosis.” The field advanced significantly with the 1935 publication of a book entitled Haemochromatosis (Fig. 2) by Joseph Harold Sheldon, an émigré from King’s College Hospital in London (United Kingdom not Ontario) to Wolverhampton.
in the Black Country of the West Midlands, whose nickname derives from Industrial Revolution pollution caused by the coal mines, iron foundries, brickworks, and the like, which discolored the city. In his retrospective review of 311 patients, Sheldon stated presciently that it was likely that haemochromatosis was a congenital metabolic disorder. In his series of 295 men and 16 women, life expectancy was only 18 months. Sheldon concluded that haemochromatosis was the key to understanding how cells normally process metals, which at the time was shrouded in mystery.

Progress in diagnosis followed the discovery of blood tests for serum iron and transferrin in the 1950s and serum ferritin in the 1970s. Serum ferritin and transferrin saturation (serum iron/total iron binding capacity [Fe/TIBC %]) were the mainstay of diagnostic tests for many years, although it became apparent that these tests had many false-positive results, and they were more specific for iron deficiency than iron overload. The debate continued whether hemochromatosis was a variation of alcoholic liver disease, as popularized by Boston pathologist Richard A. MacDonald, based on his studies with local alcoholics that included estimating their cumulative intake of the iron found in cheap wine. In the mid-1970s, Marcel Simon in Rennes, France, pursued a genetic etiology for hemochromatosis and used human leukocyte antigen (HLA) typing of peripheral blood, a technique used in renal transplant matching, within families of patients with hemochromatosis. The high association with HLA-A3 and the concordance of this antigen with iron overload within families strongly suggested that the hemochromatosis gene was near the HLA complex on the short arm of chromosome 6.

In 1977, I started my personal journey into hemochromatosis by taking a summer job as a medical student under theegis of Prof. Leslie Valberg in London, Ontario (not United Kingdom), who had a well-established career in hemochromatosis research. He suggested that I visit known families with hemochromatosis throughout Ontario and Quebec, and obtain blood samples from as many family members as possible. This turned out to be an extraordinary adventure as I drove countless miles across rural Canadian highways in the pursuit of finding the hemochromatosis gene. I visited weddings and funerals, and even had a large industrial mill shut down so that all employees could provide a blood sample for the good of medical research. And, by the way, everyone in the mill (n = 500) was related!

**FIG 1** Physicians from the Middle Ages commonly used phlebotomy to treat a wide range of medical conditions. (Engraving by F. Baretta after P. Mainoto. Credit: Wellcome Collection. CC BY)
This was a golden era of hemochromatosis research as genomics was evolving as a new science, and large research groups developed in many countries in which the population was affected by hemochromatosis. Gene discovery was not the exclusive domain of university-based research, however, as the \textit{HFE} gene mutation for hereditary hemochromatosis was discovered in 1996 by a team led by John Feder at Mercator Genetics using identity by descent cloning.\(^6\) The discovery of the \textit{HFE} gene and a simple genetic blood test for the C282Y mutation of this gene that is associated with iron overload due to unconstrained intestinal iron absorption ushered in a new confirmatory test for the diagnosis of hemochromatosis. Consequently, the sensitivity and specificity of diagnostic iron tests could be judged by a new gold standard.\(^7\) Thus, the case definition of hemochromatosis had to be reassessed so that currently most investigators use a combination of iron abnormalities and a positive genetic test.\(^8\)

A new era of evidence-based medicine had been introduced by clinical trial designers, epidemiologists, and statisticians, and hemochromatosis researchers were encouraged to move toward population-based studies. A landmark paper described the screening of a healthy cohort of outpatients in San Diego using the new genetic test and comparing signs and symptoms with a control population with normal genetic testing.\(^7\) When you screen healthy people you find healthy people, whereas only liver disease demonstrated a small but significant increase in prevalence of C282Y homozygotes.\(^7\) The National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) launched the Hemochromatosis and Iron Overload Study (HEIRS) in 2000, in which 101,168 participants in the United States and Canada were screened for \textit{HFE} mutations and elevations in serum transferrin saturation and ferritin.\(^8\) For myself, this was a career-building move into NIH funding at the time of the Human Genome Project. The use of the genetic test as the initial and diagnostic investigation was of concern to genetic counselors, because we could not predict who would experience development of clinical disease. Neonatal genetic screening in France\(^9\) had discovered a significant number of cases and family members but raised concerns among ethicists.\(^10\) Thereafter, many thought that population screening was over and done with, but in 2019, the UK Biobank project published on 451,243 participants in Northern England, among whom there was increased liver morbidity in their C282Y homozygotes (1 in 156 cases)\(^{11}\) (Fig. 3). As part of a larger project on health and the genome, it likely will pave the way toward patients having total genomic sequencing available in their medical record to assess all medical problems.

Another major discovery in 2001 was hepcidin, a small molecule synthesized in the liver that regulates iron balance (Fig. 5).\(^{12}\) Several iron-related diseases including C282Y-linked hemochromatosis were found to be associated with low serum hepcidin levels that would logically lead to increased intestinal iron absorption (Table 1). It has become apparent that the HFE protein interacts with transferrin receptors 1 and 2 at the cell membrane. A homozygous C282Y mutation triggers a cascade of events with many other proteins, including hemouvelin, bone morphogenetic protein 6 (BMP6), and SMAD proteins, which eventually lead to a decrease in hepcidin, which leads to an increase
in intestinal iron absorption. The effects on heme iron absorption have not been well defined. Because there are so many steps in the cascade, it had been considered that mutations in these other proteins may explain the wide clinical expression of hemochromatosis. Although C282Y homozygotes have been found with other genetic mutations, this is rare and does not explain the heterogeneity of the clinical presentation. In the HEIRS study, non-HFE iron overload was evaluated in many patients with an elevated ferritin, and no cases of iron overload were discovered. It should be emphasized that iron overload is vanishingly rare due to non-HFE mutations, but these deserve mention because they nicely illustrate the complex interactions in bodily iron homeostasis (Figs. 3, 4, and 5).

The origins of hemochromatosis now date back to the bog men of Ireland more than 4000 years ago (Fig. 6), in whom the cysteine-to-tyrosine substitution at amino acid 282 (C282Y) is often referred to as the “celtic” mutation, perhaps a donation from the Viking invaders. It is very unlikely that patients with hemochromatosis will ever be extinct, whereas there is a risk that hemochromatosis investigators could become so, especially as many of the founding fathers of that halcyon iron age have passed away. Young investigators of iron metabolism, who are less abundant than previously, actively need to be supported and mentored to preserve our patients’ futures. Although there is direct evidence that mutations in HFE are responsible for hereditary hemochromatosis, in this context it is tantalizingly ironic* that the precise mechanism by which the mutated HFE gene product causes excessive iron absorption and overload has yet to be agreed on.

*The author of this essay cannot be blamed for any lame puns therein, which are solely the amusement of the series editor.
### TABLE 1. IRON OVERLOAD STATES

| Disease                                      | Gene          | Mode of inheritance | Age of Onset | Clinical Disease Manifestation/Affected Organs | TfS | Mechanism                                      |
|----------------------------------------------|---------------|---------------------|--------------|-----------------------------------------------|-----|-----------------------------------------------|
| Genetic hemochromatosis                      | HFE 1-associated hemochromatosis | Autosomal recessive | Adult        | Liver fibrosis and cirrhosis                  | ↑   | Relative hepcidin deficiency                 |
|                                              | HFE           |                      |              | Diabetes                                      |     |                                               |
|                                              |               |                      |              | Arthropathy with chondrocalcinosis and pseudogout |     |                                               |
|                                              |               |                      |              | Rarely heart failure                           |     |                                               |
|                                              |               |                      |              | Liver cirrhosis                               | ↑   |                                               |
|                                              |               |                      |              | Heart failure                                  |     |                                               |
| Non-HFE hemochromatosis                     | TFR2          | Autosomal recessive | Young adult  | Heart failure                                  |     | Absolute hepcidin deficiency                 |
|                                              |               |                      |              | Hypogonadism                                   |     |                                               |
| Juvenile hemochromatosis                    | HAMP          | Autosomal recessive | Juvenile     | Liver cirrhosis                               |     |                                               |
|                                              |               |                      |              | Heart failure                                  |     |                                               |
|                                              |               |                      |              | Hypogonadism                                   |     |                                               |
| Hepatic iron overload (including African iron overload "Bantu Siderosis") | BMP6          | Autosomal recessive | Adult        | Mild hepatic siderosis                         |     | Relative deficiency                           |
|                                              | SLC40A1       |                      | Adult        | Heart failure                                  |     | Hepcidin resistance or loss of ferroportin function |
| Acruloplasminemia                            | CP            | AR                  | Adult        | Hepatic siderosis but no fibrosis              |     | Hepcidin resistance or loss of ferroportin function |
| Iron-loading anemias (without transfusion)   | TF            | AR                  | Children     | Anemia                                         |     | Hyperabsorption of iron from the diet due to anemia-triggered bone marrow signals (FAM123B mediate?) |
|                                              | CDAN 1A       | AR                  | Children/Young adults | Hepatic siderosis and fibrosis | ↑   |                                               |
|                                              | CDAN 2        |                     |              | Heart failure                                  |     | Hepcidin resistance or loss of ferroportin function |
|                                              | SLC11A3 (DMT1) | AR                | Young adults | Hypopituitarism and hypogonadism               |     |                                               |
| Hypochromic microcytic anemia with iron overload | SIDBA1 | AR | Children | Heart failure                             | ↑   |                                               |
| Sideroblastic anemia                         | SIDBA1        | AR                  | Children     | Hypopituitarism and hypogonadism               |     |                                               |
| Intermediate thalasemia                      | Variable-multiple | AR                | Children     | Hypopituitarism and hypogonadism               |     |                                               |
| Hemolytic anemias                            | G6PDH, PK, Spectrin, etc. | AR | Children | Hypopituitarism and hypogonadism               |     |                                               |
| Exogenous (iatrogenic) hepatic iron overload | Thalassemia major | Multiple | Children/Young adults | Anemia                                      |     | Transfusional iron overload                   |
| Parenteral iron therapy (diagnosis patients) | n/a           | n/a                | Any age      | Hepatic siderosis and fibrosis                 |     | Parenteral iron overload                      |
| Parenteral iron therapy (diagnosis patients) | Polygenic     | Complex            | Adult        | Hepatic siderosis and fibrosis                 |     | Reduced (inappropriate) hepcidin production due to hepatocellular impairment |
| Parenteral iron therapy (diagnosis patients) | n/a           | n/a                | Any age      | Heart failure                                  |     | Parenteral iron overload                      |
| Parenteral iron therapy (diagnosis patients) | Polygenic     | Complex            | Adult        | Signs of liver disease with positive diagnost-ic test results for specific liver disease | n-t | Parenteral iron overload                      |

Adapted with permission from Dooley JS, Lok ASF, Garcia-Tsao G, Pinzani M. Sherlock’s Diseases of the Liver and Biliary System, 13th ed. Hoboken: John Wiley & Sons Ltd.; 2018.
In this estimable discourse on the history of hereditary hemochromatosis, devoted jazz percussionist (as evidenced by his choice of subtitle for his essay; https://www.youtube.com/watch?v=CCRlAryhXXA&feature=youtube [video link was provided with the author’s permission]) and ferrophile hepatologist, Paul C. Adams has highlighted the quest for the hereditary basis of the common and rare forms of
the disease, which can now be identified precisely genetically. Diagnosis is easily achieved nowadays by combining commercially available \textit{HFE} mutation testing with serological measurements that reflect bodily iron stores, that is, iron overload. Although establishing a diagnosis is relatively easy, as is treatment by the time-honored medieval practice of blood-letting. Remarkably, however, there is still uncertainty concerning the precise mechanism by which the unequivocal genetic defect actually causes the disease it identifies. In this regard, Dr. Adams reasons that the plausible dogma that \textit{HFE} mutation operates through reduced hepcidin activity may not turn out to be the only truth to which a provocative case report bears witness (see Adams et al.\textsuperscript{16}).

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