Handbook of Iron Overload Disorders

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Foreword

When Jim Barton and Corwin Edwards edited their multi-authored text *Hemochromatosis: Genetics, Pathophysiology, Diagnosis, and Treatment* published in 2000 by Cambridge University Press, it filled a void in learning resources for iron overload disorders, in particular those related to the then-recently discovered *HFE* gene and its common deleterious mutations. I commented in my Foreword to that text that "phenotypic expression … was virtually invariable in individuals possessing the abnormal allele on both chromosomes 6." That statement has proved to be incorrect in the light of subsequent research demonstrating that phenotypic expression of *HFE* C282Y homozygous mutation is both unpredictable and variable in its manifestations. This reversal of previous dogma in genetic hemochromatosis and other important new data illustrate the need for an update on iron overload disorders in general.

In the 10 years since the publication of that text, much information has been discovered that provides new insights into the regulation of iron metabolism, and the causation and cosmopolitan distribution of diverse iron overload disorders. These discoveries have come about through the combined research efforts of many investigators, including biochemists, molecular biologists, experimental and clinical pathologists, geneticists, epidemiologists, clinical and research hematologists, and hepatologists. New iron-regulatory proteins and their genes have been discovered that provide an emerging awareness of the complexity of the integration and interactions of all genes, proteins, and tissues that participate in iron homeostasis in humans and other vertebrates.

It is not surprising that this awareness has brought confusion to the practicing clinician, who is often faced with the interpretation of an array of clinical data, laboratory tests, mutation analyses, and histopathological, epidemiological, and public health observations. Add to this confusion, patient questions regarding genetic guidance and one can understand the need for a succinct *Handbook of Iron Overload Disorders*.

Therefore, the decision to change from a multi-authored, highly detailed, large textbook to a smaller, more succinct, practical handbook may well have been prompted by these perceived needs of practicing clinicians. It is a tribute to the earlier editors and to Cambridge University Press that this has been achieved by condensing the author/editor team to just five experts, all recognized, authoritative "ferrophiles" (or "ferrophobes" – depending on their particular vantage points in the spectrum of iron-related disorders). They are, respectively, two hematologists, an internist/epidemiologist, a research experimental pathologist, and a clinical investigator/hepatologist. It is admirable that this combined endeavor has avoided compartmentation of their efforts by assuring that, while each of the five has taken primary responsibility for individual chapters, they have come together as a team to produce a cohesive product. Because each of them has contributed to every topic, one finds no identification of individual authorship for each chapter. In this way, the reader is offered the combined wisdom of some very wise, highly experienced experts.

The overall product of these efforts is unique in my experience, namely, a comprehensible handbook of practical information written with the authoritative imprimatur of recognized experts, while retaining a most accessible, succinct style worthy of the best monographs so respected by those of us who grew up in the era of the revered, professorial authority. In the relatively short space of 368 pages, readers will find valuable information and guidance on a myriad of iron overload disorders relevant to their respective practices. In addition to those disorders primarily related to dysregulation of iron absorption and metabolism, the reader will find new information about conditions, both genetic and acquired, in which iron is emerging as a significant contributor to

progression or complications. Newer diagnostic tests are described and practical information is offered for the availability and interpretation of molecular genetic tests. Finally, innovative pharmacologic approaches to iron removal are described that offer renewed hope among those afflicted with iron overload disorders that are not amenable to phlebotomy management.

It remains a privilege for me to be able to write a Foreword to this most worthy handbook, with the knowledge that all who access the information and guidance contained within it will come away enthused by the topic of iron metabolism and iron overload disorders, and be far better equipped to handle the challenges of iron overload disorders in their daily practice.

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Preface

Hemochromatosis and iron overload comprise a group of common disorders. Their ascent from curiosities at necropsy in the nineteenth century to clinically important conditions in the twenty-first century has been a long and difficult one. Eighty years passed from Trousseau's description of hemochromatosis in 1855 to Sheldon's suggestion in 1935 that this disorder was possibly heritable. Thirty-nine years later, Saddi and Feingold reported that the common type of hemochromatosis was inherited as an autosomal recessive trait. In 1975, Simon and colleagues demonstrated linkage of hemochromatosis to the human leukocyte antigen (HLA) complex on the short arm of chromosome 6, especially HLA-A*03. In 1988, Edwards and colleagues reported their observations of 11 065 Utah blood donors and their families who were evaluated with iron phenotyping, liver biopsies, and HLA typing. This landmark study demonstrated that hemochromatosis in western European whites is common, heritable, and often undetected. In 1996, Feder and colleagues discovered a HLA-linked hemochromatosis gene, now known as *HFE*. Subsequent important discoveries include those of non-*HFE* types of hemochromatosis, and the central role of hepcidin in controlling iron absorption.

The discovery of *HFE* stimulated a renaissance of learning about iron biology and disease. Using diverse plant and animal models and in vitro systems, basic scientists have explored the genetics, molecular biology, and toxicology of iron absorption and metabolism. Clinician scientists have sought unusual cases in their clinical rosters, study of which has permitted greater understanding of the genetics and pathophysiology of iron overload. Cooperative investigator groups have performed large screening studies to identify population and individual characteristics associated with hemochromatosis, iron overload, and deleterious iron-related mutations, and their respective implications for personal and public health. Biochemists have designed new drugs to diminish morbidity and mortality among persons with heritable and acquired iron overload disorders. After almost 150 years, hemochromatosis and iron overload are recognized as common, treatable, and cosmopolitan disorders. The present authors contributed to a Cambridge University Press monograph entitled "*Hemochromatosis: Genetics, Pathophysiology, Diagnosis and Treatment*" published in 2000. Today, its applicability to diagnosis and treatment is limited, consistent with advances of the last decade.

Many patients with hemochromatosis or iron overload remain undiagnosed or untreated. Until now, there were few practical yet comprehensive learning resources for clinicians and other experts about these disorders. The Cambridge University Press *Handbook of Iron Overload Disorders* fulfills a need for a handy and affordable text on this topic. This up-to-date volume describes the signs and symptoms, laboratory and pathology testing, imaging procedures, genetics, differential diagnosis, and management of iron overload disorders in a convenient format supplemented with informative tables and figures. This handbook was designed to be used by primary care and internal medicine physicians, gastroenterologists, hepatologists, hematologists, endocrinologists, oncologists, cardiologists, rheumatologists, geneticists, genetic counselors, translational research investigators, and public health scientists. The ascent of hemochromatosis and iron overload to importance in daily office and hospital practice in 2010 inspired us to write the present handbook, and we hope that you will enjoy it.

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