IRON DEFICIENCY AND OVERLOAD
IRON DEFICIENCY AND OVERLOAD

From Basic Biology to Clinical Medicine

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The Nutrition and Health series of books have, as an overriding mission, to provide health professionals with texts that are considered essential because each includes (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted inter-chapter referrals, (8) suggestions of areas for future research, and (9) balanced data-driven answers to patient /health professionals' questions that are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research- and practice-oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Iron Deficiency and Overload: From Basic Biology to Clinical Medicine, edited by Shlomo Yehuda and David I. Mostofsky, fully exemplifies the Nutrition and Health Series' goals. Iron, an essential micronutrient for humans, is critical for the synthesis of DNA and proteins and serves as a co-factor for numerous enzymes involved in energy metabolism and brain biochemical functions, as well as being required for the transfer of oxygen to all cells in the body. Iron is also the most abundant transition metal in the human body. Yet, many nutritionists are more aware of the adverse effects of iron overload than its critical role in brain development. This volume is very timely as there is currently no up-to-date volume for professionals concerning the role of iron in nutrition and clinical medicine. Moreover, the fastest growing population in the United States as well as globally is those over 60 years of age and especially the oldest-old, those over 80 years of age; and iron status, both deficiencies as well as iron overload, becomes more of a medical issue as we age. This important text provides a timely review of the latest science concerning iron metabolism as well as practical, data-driven options to manage at-risk populations with the best accepted therapeutic nutritional interventions. The overarching goal of the editors is to provide fully referenced information to health professionals so they may enhance the nutritional welfare and overall health of clients and patients who are at risk for less than optimal iron status. This excellent, up-to-date volume will add great value to the practicing health professional as well
as those professionals and students who have an interest in the latest information on the science behind iron requirements during the lifespan, and the potential for iron to modulate the effects of chronic diseases and conditions that are widely seen in the majority of patient populations.

Drs. Yehuda and Mostofsky, who have edited two other volumes in the Nutrition and Health Series, *Fatty Acids* and *Nutrients, Stress and Medical Disorders*, are internationally recognized leaders in the field of bioactive nutrients that affect the brain and nervous system. Both editors are excellent communicators and they have worked tirelessly to develop a book on iron that will be the benchmark in the field because of its extensive, in-depth chapters covering the most important aspects of the complex interactions between cellular functions, diet and iron requirements, and their impact on the chronic diseases as well as the acute conditions that can adversely affect the quality of life and health of both men and women. The introductory chapters provide readers with the newly recognized basics of the complexities involved in assuring that iron is absorbed and moves from the absorptive surface to the intestinal cell, then to the blood, and then to target organs and organelles without oxidizing the vital molecules that are nearby. The chapters in the first part of the volume concerned with iron biochemistry and metabolism provide the reader with a clear understanding of the state of the science and where gaps in knowledge still remain so that the clinically related chapters can be more easily understood. Chapters include clear explanations of the importance of serum ferritin as the best measure of body iron stores. The value of other, less sensitive measures of body iron stores, including serum iron, total iron-binding capacity, and transferrin saturation, are explained. Of importance to patient care, normal values for the more common iron status measures that are not directly related to body iron stores, including hemoglobin, hematocrit, and erythrocyte protoporphyrin, are provided in informative tables.

There is an important update on the genetics of iron metabolism and the role of mutations in the discoveries of critical ligands responsible for import and export of iron from cells. Moreover, the authors have provided excellent diagrams that help the reader to visualize the movement of iron within the cellular compartments, especially the mitochondria. The final chapter in this part reviews the administration of iron and provides practical information about the myriad of compounds that can be given to reduce iron deficiency, including oral as well as parenteral choices. Detailed information about dosing and potential drug/iron interactions is tabulated. Additionally, therapy for iron overload from either primary or secondary hemochromatoses is described in detail. Thus, in the first part of the volume, the reader is provided with valuable information about the basics of iron metabolism as well as its use to prevent deficiencies, and also the treatment of iron overload.

The second part of the volume contains seven chapters that examine the effects of iron overload and deficiency in depth. Specific emphasis is placed on the importance of iron in brain function. Iron is required for the optimal functioning of the enzymes responsible for the synthesis and degradation of the major brain neuropeptides, including dopamine, serotonin, and noradrenaline. Iron is found in specific sites within the brain, and the activity of neurotransmitters that require iron and the site of iron within the brain have been correlated with behavioral effects seen with iron deficiency, especially in the youngest children that are affected. Iron is also required for the synthesis of myelin, and the consequences of low iron status in the neonatal brain may be the result of lower than normal formation of the protective myelin sheath covering critical brain neurons. Important new studies that examine the interaction between zinc and iron in the brain are described and provide further evidence of the complexity of nutrient–nutrient interactions. In addition to the adverse effects of low iron status in children, excess iron within the brain has been associated with a number of neurodegenerative diseases, some of which are also associated with aging. These include Parkinson’s disease, Alzheimer’s disease, Friedreich’s ataxia, Wilson’s
disease, and others. Additionally, as we age, there is an accumulation of iron in the brain that may participate in oxidative damage to neural tissues. Enhanced synthesis of enzymes that result in increased iron in mitochondria and concomitant increased oxidative damage have been seen in the brain tissues from animal models of human neurodegenerative diseases as well as in the tissues from affected human brains. Separate chapters examine the importance of iron to the synthesis of brain neuromodulators including dopamine. Dopamine is required for the processing of environmental information involved in forming perceptions and also for movement. Iron is required for the synthesis of dopamine, and the recent data on the effects of dietary deficiency on brain dopamine secretion and function are well described. Impairment of the dopamine system in the brain is associated with psychotic and psychoaffective disorders including illicit drug use. Attention-deficit hyperactivity disorder (ADHD) may also be related to low iron in the brain although further research is needed to determine if the association is linked to cause and effect. The depth of information in this volume is clearly exemplified by the chapter that looks at the distribution of iron in the neurons and oligodendrocytes that are responsible for synthesizing myelin during iron deficiency, normal iron intake, as well as iron overload. Under normal conditions, cellular iron concentrations in the brain are tightly controlled. When iron is lacking, brain neurons alter their metabolism and less myelin is formed. Dietary iron deficiency is associated with a decrease in IQ and depression in mood; there is a concomitant decrease in dopamine levels. As in animal models, duration and magnitude of iron deficiency determines the extent of cognitive deficits. Neonatal iron deficiency can adversely affect hearing, the endocrine system, and the immune system.

When iron levels are abnormally high, the brain reduces the level of iron taken into the brain and is resistant to the adverse effects of iron overload initially, but peripheral changes may result in secondary damage to the brain that results in oxidative damage. Aging is also associated with progressive increases in brain iron levels. Neurodegenerative diseases seen in aging can be characterized by their impaired iron homeostasis; however, it is not clear if this is a cause-and-effect relationship or that the iron excess occurs after some initiating event.

The essentiality of iron for hemoglobin production and the consequences of iron deficiency as well as iron deficiency anemia are described in detail in Chapter 10 concerning the peripheral effects of iron deficiency. In addition to the adverse effects of iron deficiency on oxygen-carrying capacity of the blood, there are many non-hematological clinical manifestations of iron deficiency. Often, the skin color will be reduced and this may be due to vasoconstriction in the skin; there may be increased cardiac output and breathing may be labored; muscle fatigue and cramping are often seen. Endurance is lessened and may be the consequence of reduction in iron-requiring enzymes. Detailed descriptions of the peripheral effects of human iron deficiency are tabulated for the reader. The final chapter in the second part reviews the newest research on the interactions between the brain and the immune system and how iron status affects these interactions, mainly through the effects of cytokines on cerebral neurons.

Part III includes chapters that examine the newest diagnostic tools that can be used to detect iron in the brain and also chapters that describe the clinical aspects of iron-associated central nervous system disorders. High-field magnetic resonance imaging scanners can identify iron deposits in distinct parts of the brain. MRIs can distinguish between iron in the form of hemoglobin, iron released in a hemorrhagic stroke or small hemorrhages, and endogenous iron within brain cells. Because MRIs are non-invasive, these have become a critically important tool in diagnosing the genetic defects associated with increased brain iron; the disorders are tabulated in the chapter. The next clinically focused chapter provides extensive information concerning the association of iron levels in specific areas in the brain with the development of Alzheimer’s disease and, in the next chapter, the potential role of iron metabolism in brain mitochondria and the
physical manifestations of the most common genetically inherited disorders of the central nervous system. A number of genetic defects result in abnormal accumulation of iron in certain cerebral areas whereas iron accumulation appears to be secondary in other inherited disorders. The adverse consequences of reactive iron on brain tissue and cells, and even the subcellular compartments, are described in detail. Valuable explanations for differential diagnoses and treatment of defects in iron handling in the genetic disorders discussed, including Friedreich’s ataxia and hemochromatosis, are included.

The final part of the volume addresses the public health issues of iron status (both overload and deficiency) in populations around the globe. The first chapter in this part reviews the survey data that examine the association of iron overload with cardiovascular disease risk and finds no clear, consistent association between these two factors in studies that have looked in populations across the world. This chapter includes unique tables containing heretofore unpublished analyses from the Center for Disease Control that compare serum transferrin to ferritin levels and these biomarkers in different age groups and sexes. With regard to iron deficiency, low iron status is a critical risk factor for optimal development of the growing fetus and young child and the health of women especially during pregnancy. Globally, it has been recognized for nearly 50 years that iron deficiency and the more severe iron deficiency anemia are the most common nutritionally related deficiencies seen throughout the world. The chapter on the global consequences of iron deficiency includes a comprehensive review of the history, World Health Organization (WHO) activities, and biological effects of this deficiency, especially in women of childbearing potential and young children in developing as well as in the developed nations. Because of the clinical importance of iron status in young children and women of childbearing potential, each of these population groups is examined in depth in subsequent separate chapters. We are reminded in the chapter on children that there remains no “gold standard” test for iron deficiency anemia and thus the criteria used by nations differ. Yet, it is agreed that iron deficiency alone can result in reduced cognitive function and other mental deficits that may not be reversible. Low birth weight and premature birth are the risk factors for neonatal iron deficiency as there was insufficient time for iron storage. Other physiological factors as well as nutritional factors that increase risk are outlined along with suggestions for reducing the risk of iron deficiency in childhood. The following chapter outlines the factors that increase the risk of iron deficiency in women of childbearing potential as well as the consequences of iron deficiency, the alterations in iron measures during pregnancy and lactation and their relevance to actual iron status, the association of low iron status and infertility, and the effects of low iron status on overall women’s health.

The editors of this comprehensive volume have chosen 29 of the most well-recognized and respected authors who are internationally distinguished researchers, clinicians, and epidemiologists who provide a broad foundation for understanding the role of iron in the molecular, genetic, cellular, and clinical aspects of nutritional and therapeutic management of iron status. Hallmarks of all of the 19 chapters include complete explanations of terms with the abbreviations fully defined for the reader and consistent use of terminology between chapters. Key features of the volume include informative bulleted summary points and key words that are at the beginning of each chapter, and appendices that include a detailed list of food sources of iron as well as an up-to-date compilation of the normal values for blood levels for iron constituents Recommendations and practice guidelines are included at the end of relevant chapters. The volume contains more than 65 detailed tables and informative figures, an extensive, detailed index, and more than 2000 up-to-date references that provide the reader with excellent sources of worthwhile information about nutrition options to help maintain optimal iron status.
In conclusion, *Iron Deficiency and Overload: From Basic Biology to Clinical Medicine*, edited by Shlomo Yehuda and David I. Mostofsky, provides health professionals in many areas of research and practice with the most up-to-date, well-referenced volume on the importance of iron status in determining the potential for optimal human development, especially in the central nervous system. This volume will serve the reader as the benchmark in this complex area of interrelationships between the essentiality of iron; its functions throughout the body including the biochemistry of iron-containing enzymes and other active molecules involved in iron absorption, transport, metabolism, and excretion; the importance of optimal iron status on immune function, the function of the heart, blood, lungs, kidney, muscle, bone, and the brain. Moreover, the interactions between genetic and environmental factors and the numerous co-morbidities seen with both iron deficiency and iron overload in the most at-risk populations are clearly delineated so that students as well as practitioners can better understand the complexities of these interactions. Drs. Yehuda and Mostofsky are applauded for their efforts to develop the most authoritative resource in the field to date, and this excellent text is a very welcome addition to the Nutrition and Health Series.

*Adrianne Bendich, PhD, FACN*
Preface

In Shakespeare’s *The Twelfth Night*, the story is told of a young woman who became severely depressed because she was in love with somebody and could not tell anyone about it, not even the beloved himself. She is described as suffering from a “green and yellow melancholy,” a green sickness resulting from the teenager having fallen in love. It is a fact that iron deficiency commonly occurs after a few menstrual periods and imparts a green color to the complexion, while the yellow is no doubt due to jaundice and liver disease that will often cause a person to become depressed.

Iron deficiency is ever-present among all populations throughout the world, irrespective of race, culture, or ethnic background. Even with the latest advances in medicine, improved nutrition, and the ready availability of cheap oral iron, there is still no satisfactory explanation for the widespread occurrence of iron deficiency or for the absence of effective treatment. Several thousand years ago, human societies changed with the advent of the agrarian revolution, when humans turned to agriculture and to eat more fruits and vegetables than meat. The diet became iron-deficient and new epidemic infections emerged due to the stressors of crowding and lifestyle changes. This change of diet increased the frequency of iron deficiency. Some historians go so far as to claim that nutritional deficiency and iron deficiency, in particular, were the major factors responsible for the disappearance of the Maya culture.

The old notion that iron deficiency effects are mediated by the hemoglobin system and its corresponding decrease in oxygen supply to the tissues has been replaced by the findings that, in addition to the impact on the oxygen system, iron plays a major role in brain neurochemistry (e.g., neurotransmitters) and brain structure (e.g., myelin). Recent studies indicate that overload of iron might be linked to severe CNS age-related disorders, not least because iron is a substrate for free radicals. The story is unfolding, and clearly multidisciplinary approaches are needed to study the integrated effects of iron and brain and behavior and health disorders.

*Iron Deficiency and Overload: From Biology to Clinical Medicine* represents our attempt to present a sampling of the major issues in iron research, from the most basic research level to human applications. We have assembled chapters whose topics reflect the excitement in current theoretical development and laboratory activity in this area. The distinguished authors who contributed to this volume address their presentations to professionals and graduate students from diverse areas, disciplines, who need to be better informed about the concepts, methodologies, and current status of the field. Such information is all too often to be found only in the specialized scientific literature of some neighboring discipline and not likely to be routinely consulted by all. We leave the reader to forge the individual integration of the information provided in this volume.
We are most appreciative of the support provided by Humana Press in bringing this book to publication. We are especially grateful to Paul Dolgert, Editorial Director, and to Dr. Adrianne Bendich, Series Editor, for their constant guidance and help. We hope that this book will encourage more scientists and researchers to focus on issues in the topic of iron deficiency and iron overload, in order to gain a better understanding of the problems and to devise better methods to overcome those problems.

Shlomo Yehuda
David I. Mostofsky
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