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PREFACE

In prefaces to previous volumes of the *Annual Review of Nutrition*, the attempt has been made to point out that the topics range from updated findings at the basic science end of our discipline to those extensions that may be considered applied. Given the unwarranted trepidation of some to use such terms as "basic" and "applied," I can offer the two sides of this argument by quoting well-known earlier scientists: Louis Pasteur wrote in 1871 that "... there does not exist a category of science to which one can give the name applied science. There are science and the applications of science ..." (translated by I. B. Cohen from *Revue Scientifique*). Somewhat later Albert Einstein wrote in 1931 that "... you should understand about applied science in order that your work may increase man's blessings." (Address at the California Institute of Technology.)

As seen in previous volumes and in numerous discourses on what is a nutritionist, it is satisfying to most of us that we can fit our expertise and interest somewhere in the broad span from the molecular-oriented sciences of life to the preventive and corrective measures that carry into public health and clinical practice. Again the topics of chapters in the present volume offer some of this diverse menu. Much of what has been discovered at the basic level, as in the past, will surely lead to useful applied outcome. With regard to the mix of basic and applied topics of nutrition to be found in this volume, one can read updates of a basic, molecular nature that are found in the chapter on catabolism of folate by J. Suh, A. K. Herbig, & P. Stover or on mammalian selenium-containing proteins by D. Behne and A. Kyriakopoulos. Subjects that bridge from basic to applied are represented by such a chapter as by M. Hambidge and N. Krebs that deals with key variables of human zinc homeostasis as relate to dietary requirements or by C. Stephensen on vitamin A and its impact on immune function. Clearly there are other extrapolations that a careful reader may draw from chapters dealing with findings from basic science, just as all of us should be pleased by those applications that guide us toward better health. At the applied and clinical level is a chapter by M. Serdula et al that reviews dietary assessment of preschool children, and the problems with present nutritional management of maintenance dialysis patients are considered by R. Mehrotra and J. Kopple in their chapter. L. Hallberg has provided us in the prefatory chapter with his scholarly perspectives on nutritional iron deficiency. Though our species of major consideration is the human, there are some interesting findings of a comparative nature with chapters by P. Trotter on genetics of fatty acid metabolism in yeast and by M. Wells and his colleagues on fat metabolism in insects.

My thanks as always to our Associate Editors (Drs. Bier and Cousins), the Editorial Committee and guests (listed in the front), and to Lisa Dean, the production editor, Roberta Parmer, the copyeditor, and Dr. Sam Gubins as president of Annual Reviews.

Donald B. McCormick
Editor

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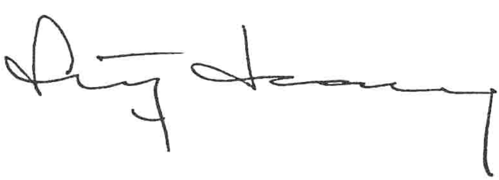

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ERRATA

An online log of corrections *The Annual Review of Nutrition* chapters (if any have yet been occasioned, 1997 to the present) may be found at http://nutr.AnnualReviews.org/

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PERSPECTIVES ON NUTRITIONAL IRON DEFICIENCY

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Key Words iron absorption, iron requirements, bioavailability, iron absorption regulation, liabilities of iron deficiency

■ **Abstract** Nutritional iron deficiency (ID) is caused by an intake of dietary iron insufficient to cover physiological iron requirements. Studies on iron absorption from whole diets have examined relationships between dietary iron bioavailability/absorption, iron losses, and amounts of stored iron. New insights have been obtained into regulation of iron absorption and expected rates of changes of iron stores or hemoglobin iron deficits when bioavailability or iron content of the diet has been modified and when losses of iron occur. Negative effects of ID are probably related to age, up to about 20 years, explaining some of earlier controversies. Difficulties in establishing the prevalence of mild ID are outlined. The degree of underestimation of the prevalence of mild ID when using multiple diagnostic criteria is discussed. It is suggested that current low-energy lifestyles are a common denominator for the current high prevalence not only of ID but also of obesity, diabetes, and osteoporosis.

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INTRODUCTION

Iron deficiency (ID), the most common deficiency disorder in the world, affects millions of people (26). ID develops when absorption of dietary iron cannot cover the physiological losses and requirements of iron. This review deals with nutritional ID and focuses on new information, new approaches, and new interpretations of available information.

PATHOGENESIS OF NUTRITIONAL IRON DEFICIENCY

Iron metabolism is unique in several aspects. The body is economical in its handling of iron in the body. When a red cell dies, its iron is reutilized. Iron absorption is in some ways controlled by the requirements of the body. Extra iron can be stored by a specially designed protein (ferritin), which is utilized at times of increased iron requirements. The highly reactive properties of iron are balanced by unique control and transport systems. In spite of these ingenious mechanisms, ID is the most common deficiency disorder in the world and the main remaining deficiency in the industrialized, developed world. To understand this paradox, and to find effective ways to combat the deficiency, it is necessary to examine incomes (absorption) and expenditures (requirements) of iron, as well as current knowledge of the various control systems in the body responsible for maintenance of iron balance. An important observation was made by McCance & Widdowson in 1937 (70). In their studies, they found that iron was not excreted from the body, which implies that iron balance was maintained by a regulation of iron absorption.

PHYSIOLOGICAL IRON REQUIREMENTS

Basal iron losses from the exterior and internal surfaces of the body, menstrual iron losses, and iron needed for growth, including pregnancy, determine physiological iron requirements.

Basal Iron Losses

Iron lost from exterior and interior surfaces of the body constitute basal iron losses. A collaborative study showed that basal iron losses in men were of a magnitude of 14 μg/kg of body weight/day (38). The study was based on the rate of decrease of the specific activity of the long-lived radioisotope ^{55}Fe administered intravenously. The dilution of the tracer by the absorption of iron to cover these losses was followed for several years. This ingenious principle was developed in 1959 by Finch (30). Further studies indicated that about half of these losses represented "physiological" blood losses (12).

Loss of iron from sweating was once considered marked, especially in the tropics (33). However, indirect studies comparing total iron losses in those living in hot and humid environments with those living in nontropical environments showed no differences (38). Direct studies of the iron content of sweat under controlled conditions showed that sweat iron losses are negligible (15).

Menstrual Iron Losses

An early study showed that menstrual iron losses varied between 6 and 179 milliliters in 100 healthy women (8). The intraindividual variation was examined in 13 women and was considered marked. This finding was in contrast to later observations that for each individual, iron losses were almost constant (54). A probable reason for the different results was the great care taken in the latter studies to ensure a complete sampling of the menstrual blood. These unexpected observations had important consequences for understanding iron balance in menstruating women. By studying a random sample of women at a time before the introduction of contraceptive pills and intrauterine devices, the basal variation in iron requirements in women could be established (47). Later studies in a random sample of Swedish women confirmed the distribution of iron requirements, and the effect of contraceptive pills could be examined (55). Studies in nonidentical and identical twins (83) indicated that menstrual blood losses were genetically controlled and that this control was mediated by the contents of plasminogen activators in the uterine mucosa (82). Several studies in geographically widely separated countries strongly suggest that menstrual iron losses are the same worldwide and, thus, that iron requirements have been the same for very long time, probably many thousands of years. It could thus be concluded that differences in prevalence of ID is mainly related to differences in absorption of dietary iron, disregarding differences in iron losses related to parity and birth spacing and degree of infestation with, mainly, hookworm.

Growth Requirements

The Newborn, Full-Term Infant Iron requirements during the first 4–6 months of life are negligible, especially if late clamping of the umbilical cord has occurred. This unique situation for iron is explained by the excess of circulating hemoglobin (Hb) the infant is born with. This is due to the high affinity of fetal Hb for oxygen. The fetus thus "wins" over the mother in the struggle for oxygen at the placental interface. However, as a direct consequence, the delivery of oxygen from fetal Hb to tissues is lowered. The fetus thus needs more Hb to deliver a certain amount of oxygen to its tissues (regulated by erythropoietin). At delivery, the production of fetal Hb is exchanged for the production of normal Hb A, and oxygen is more readily available from the lungs. Successively, much iron is thus released to build up iron stores of the infant. This extra iron covers iron needs for the infant during the first 4–6 months of life. After about 6 months, when iron stores are exhausted, the iron requirements are very high, especially during the following 18 months, the weaning period. Iron requirements may amount to about 100 μg/kg/day, which is about four times more than for an average adult menstruating woman. After about the age of 2 years, iron requirements per unit of body weight are reduced.

Adolescence The growth spurt during adolescence is another period of high iron requirements. For boys, puberty is associated with both considerable growth and a marked increase in Hb concentration and mass. Iron requirements for boys are about 20% higher than average iron requirements for menstruating women. For girls, growth is not completed at menarche and thus total iron requirements are high. For 14-year-old girls, for example, median iron requirements can be about 30% higher than for their mothers (79).

Pregnancy

Iron requirements in pregnancy are very high, as discussed in previous reviews (41, 42). A main problem is the uneven distribution of the requirements over the duration of pregnancy. Because of the absence of menstrual iron losses and the negligible needs of the fetus, iron requirements in the first trimester are very low. They get successively higher as the pregnancy continues, reaching a maximum in the third trimester. The ability to absorb dietary iron increases as the iron requirement increases. Despite the increased propensity to absorb iron, however, even with a highly bioavailable diet, iron needs during pregnancy cannot be met by diet alone, especially during the second half of pregnancy. In addition, during the second half of pregnancy, when requirements are high, the actual absorption of iron from the diet is far below the need. This is true also for a highly bioavailable Western-type diet. Thus, to a great extent, iron balance during pregnancy is dependent on the amount of stored iron. It may be the main physiological role of iron stores. The problem is the low iron stores in present-day women in both developed and developing countries. It can be estimated that in our early ancestors, who consumed high-meat diets, iron stores may have amounted to about 500 mg, which is approximately the amount of stored iron needed to cover iron requirements during pregnancy. This is the reason for the paradoxical, unphysiological necessity of supplying pregnant women with iron supplements during the later half of pregnancy. The very high iron requirement of pregnancy is a special problem in teenage pregnancies because girls in their teens may not have reached their full growth. The anemia that is seen in early pregnancy (the physiological anemia of pregnancy) (41) is due primarily not to ID but to an increased plasma volume combined with the increased capacity of red blood cells to deliver oxygen to the placenta, which is probably mainly due to an increased concentration in red blood cells of 2,3-diglycerophosphate (41). This is a mechanism similar to that seen in "sports anemia," where the change is less well adapted to its purpose. (53).

DIETARY IRON ABSORPTION

The first studies to estimate the absorption of dietary iron were chemical balance studies. Some of these early, meticulous studies gave good information about the magnitude of iron absorption from the diet. No information was obtained, however,