Enteric pathogens are thought to alter the permeability of the intestinal mucosa, permitting entry of normally excluded, immunogenic macromolecules, although conclusive evidence is lacking. Uptake of intact egg protein (ovalbumin) in humans and animals with gastroenteritis has been demonstrated (Keljo et al. 1987; Walker 1981; Gruskay and Cooke 1955). If operative, the effect of such uptake may result in induction of allergy, autoimmunity (particularly immune complex-mediated disease), and other disorders (Walker 1981).

Nonimmunologic Mechanisms

The causes of nonimmunologic adverse reactions to foods include food toxicities, food poisonings, and pharmacologic or metabolic reactions. Such intolerances occur more frequently than true food allergies and are related to dose as well as to the concurrent presence of medications, other diseases, or genetic errors of metabolism.

One example is sulfite-induced asthmas. Sulfur dioxide and sulfiting agents are widely used to retard deterioration of perishable produce, to condition dough, to prevent microbial growth, and to provide antioxidant action. The average intakes of sulfite and sulfite derivatives are estimated to be 6 mg per capita per day but are higher for wine and beer drinkers and for individuals consuming larger amounts of sulfite-treated foods. These amounts may exceed current estimates of safe levels of intake (IFT 1986). Approximately 1 to 8 percent of people with asthma are sensitive to ingestion of sulfite, and those using steroid control agents are affected more frequently. Adverse reactions vary with the individual's sensitivity threshold, the type of sulfiting agent, and the type of food in which it is consumed (Bush, Taylor, and Busse 1986). The FDA has proposed that sulfite be declared on labels when levels exceed 10 ppm as total sulfite dioxide and that its "Generally Recognized As Safe" (GRAS) status be rescinded, but no final rules have been issued.

Other examples include asthma induced by tartrazine, a yellow dye used to color medicines, soft drinks, and foods; a syndrome caused by monosodium glutamate (see chapter on neurologic disorders); and symptoms caused by preservatives such as benzoic acid and sulfiting agents (Butkus and Mahan 1986). Nonimmunologic reactions also include lactose intolerance (an intestinal deficiency of the digestive enzyme lactase) and celiac sprue, the inability to metabolize gluten (see chapter on gastrointestinal diseases). In addition, toxic contaminants such as bacteria, insect parts,

and molds; vasoactive amines (e.g., histamine) found in tomatoes, avocados, cheeses, pineapples, and wines; and caffeine may cause symptoms in sensitive individuals. Other gastrointestinal diseases, such as reflux peptic esophagitis, peptic ulcers, gallbladder disease, and mesenteric vascular insufficiency are associated with acute symptoms after eating. Persons suffering adverse reactions may mistakenly attribute the cause to a food allergy rather than to their underlying illness (AAAI 1984). Finally, psychologic mechanisms can provoke physical and mental symptoms of food sensitivity that do not appear to be mediated by the immune system. In individuals with psychologically induced allergic symptoms, no physiologic or biochemical nonimmunologic mechanisms can be identified (May 1984) and true immunologic mechanisms are rarely found (Johansson 1984).

Prevention and Treatment

Individuals with food intolerances should exclude the offending foods from their diet either completely or partially. Those with potentially life-threatening sensitivities should carry an epinephrine-containing syringe (Atkins 1983) and wear a bracelet identifying the problem. Desensitization shots, oral desensitization, and use of bee pollen are not effective treatments for food allergies (Butkus and Mahan 1986).

The likelihood of an infant developing an IgE-mediated reaction is estimated at 58 percent when both parents are affected, 38 percent when one parent is affected, and 12.5 percent when neither parent is affected (Butkus and Mahan 1986). Special precautions should be taken in feeding infants at high risk, especially during the first year (Glaser 1966). Some research suggests that the incidence of food allergies is decreased if breastfeeding is continued for 3 to 6 months (Hamburger et al. 1983; Saarinen and Kajosaari 1980; Chandra 1979). Other research, however, disputes this suggestion (Kovar et al. 1984). Because some food antigens are transferred through the breast milk to the infant, mothers should avoid foods to which the infant is sensitive. Likewise, formula-fed infants sensitive to cow milk or to soybean-based formulas should be given formulas prepared from casein hydrolysate (Butkus and Mahan 1986). Delaying the introduction of solid foods, especially those most likely to induce allergies, may prevent or minimize the development of food allergies (Chandra 1979; Hamburger et al. 1983). As a general rule, new foods should be introduced into the infant diet one at a time to permit observations of allergic reactions (see chapter on maternal and child nutrition).

Food-borne Microbial Diseases

Ingestion of water or foods that are contaminated with chemicals, pathogenic micro-organisms, or the toxins they elaborate can lead to illness. Food-borne pathogens commonly cause diarrhea, vomiting, abdominal cramps, or other gastrointestinal symptoms. Less commonly, they affect the liver or nervous system. Symptoms range from minor discomfort to severe disease and even death. Their causes are listed in Table 11-1. In 1982, the factors most common to food-borne disease outbreaks, in order of frequency, were (1) improper food handling, (2) food from an unsafe source, (3) inadequate cooking, (4) poor personal hygiene, and (5) contaminated equipment (CDC 1985). Appropriate public health procedures related to food handling and storage can usually prevent these problems.

The preferred treatment for most forms of food-borne illnesses is fluid and electrolyte replacement for dehydration caused by diarrhea (Rohde et al. 1983). Antimicrobial drugs may be useful in some instances; in rare cases, such as botulism poisoning, an antitoxin should be administered. However, because most food-borne illnesses are self-limiting and antibiotics may disturb normal bacterial flora and prolong the illness, antibiotic therapy is not routinely used (Altman 1985). Food-borne infections that trigger an acute-phase response will be accompanied by nutritional losses comparable to those seen in other infections.

The major microbial causes of food-borne illness are bacteria, viruses, and parasites. Chemical contamination of foods occasionally causes illness. Bacterial food poisoning, the most common type, is caused by ingestion of water or food that contains living organisms or toxins they produce or enterotoxins produced in the intestine after their ingestion. These diseases are most common in the developing world where the water supply is inadequately treated and food easily becomes contaminated.

As mentioned earlier, food-borne illnesses affect large numbers of people in the United States. For example, more than 40,000 cases of salmonellosis (excluding typhoid fever) were reported to CDC in 1982 (CDC 1983), although only about 2,000 of them were confirmed. Among these cases, eight deaths were reported (CDC 1985). More than 18,000 cases of shigellosis were reported in the United States in 1982; although the true incidence is thought to be considerably higher (CDC 1983), only 116 of the reported cases were confirmed (CDC 1985). At least one outbreak of gastrointestinal disease has been traced to *Campylobacter fetus* contami-

nation of raw milk (Klein et al. 1986), but some investigators believe that the incidence of campylobacter-induced illness is greater than the total combined cases of salmonellosis and shigellosis (Blaser 1983; Skirrow 1977; Archer and Kvenberg 1985). *Clostridium perfringens* was confirmed as the etiologic agent in nearly 2,000 cases of food-borne illness in 1982 (CDC 1985). *Clostridium botulinum* causes an average of 15 outbreaks of food-borne botulism annually in the United States, with 21 outbreaks involving 30 people and 8 deaths reported for 1982 (CDC 1985). An estimated 20,000 cases of *Yersinia* infection occur annually in the United States, causing acute abdominal symptoms (Kvenberg and Archer 1987). Although more than 23,000 cases of hepatitis A were reported to the CDC in 1982 (CDC 1983), only 325 cases were confirmed (CDC 1985). Hepatitis A is transmitted almost exclusively by the fecal-oral route through food and water contaminated by food handlers. In 1982, approximately 5,000 cases of food-borne Norwalk gastroenteritis were reported to the CDC (CDC 1985). These derived from two large outbreaks, one related to eating bakery items with contaminated icing and the other associated with eating contaminated coleslaw. Other outbreaks have involved shellfish and drinking water.

Implications for Public Health Policy

Dietary Guidance

General Public

Adequate nutrient and energy intake is critical to the maintenance of optimal immune function. However, evidence related to the role of specific dietary factors such as fatty acids, vitamin C, or zinc is insufficient to recommend changes in dietary guidance policy for the general public. Evidence related to the role of microbial and chemical contamination of food and water in human health suggests that the general public should receive information on appropriate food handling and storage methods to prevent outbreaks of food-borne disease.

Although the overall public health significance of breastfeeding in the United States is uncertain, studies in developing countries have shown the importance of breastfeeding in preventing diarrheal diseases and in reducing their severity. The immune protection conferred by breastfeeding also helps reduce the severity of certain infectious diseases among infants. Breastfeeding should continue to be recommended to pregnant women and to new mothers as the optimal method of infant feeding.

Although the relationship between malnutrition and changes in immune function observed with aging is not well understood, it is clear that adequate intake of nutrients is basic to the adequate immune protection in older Americans.

Special Populations

Infections produce well-documented adverse effects on nutritional status, and nutritional rehabilitation restores immune function and reduces the severity of infectious disease complications. Thus, the nutritional status of persons with infectious illnesses should be assessed regularly, and appropriate nutritional support measures should be instituted whenever necessary. Qualified health professionals should advise persons with food allergies and intolerances on the diagnosis of these conditions and on diets that exclude foods and food substances that induce symptoms.

Nutrition Programs and Services

Food Labels

Evidence related to diet-immune function interactions reinforces the need for food manufacturers to include explicit and complete ingredient statements to protect individuals who may have severe adverse reactions to foods.

Food Services

Current evidence about the role of dietary factors in the maintenance of optimal immune function has no special implications for change in policy related to food service programs. Evidence related to the spread of infections suggests that food service personnel should receive adequate training in sanitary food handling and storage procedures.

Food Products

Evidence related to diet-immune function interactions suggests that food product manufacturers should take special precautions to use good manufacturing practices to avoid contamination with ingredients that may produce severe reactions and to reduce microbial and chemical contamination during production and storage. Manufacturers should continue to develop new products that are free of substances likely to induce allergic symptoms in susceptible individuals.

Special Populations

Patients with infectious diseases should be treated as rapidly and effectively as possible to minimize the depletion of body nutrients. Convalescing patients should be counseled and assisted in the development of diets that provide adequate intake of nutrients to regain an appropriate nutritional status. Patients with food intolerances should be counseled and assisted in the development of diets that omit foods and food factors that induce symptoms.

Research and Surveillance

Research and surveillance issues of special priority related to interactions between diet, infection, and immunity should include investigations into:

- The mechanisms by which generalized malnutrition depresses the function of specific components of the immune system.
- The effects of deficient or excess intake of single nutrients such as vitamin A, zinc, iron, or dietary fat on specific elements of the immune system and on immune function.
- The mechanisms by which deficient or excess intake of single nutrients might depress or improve immune system function.
- The factors in breast milk that protect infants from infectious disease.
- The role of breast milk in transmitting allergens, infectious agents, or toxicants such as drugs.
- The role of nutrition in maintaining adequate immune function in older persons.
- The mechanisms by which infectious diseases alter nutrient metabolism and impair nutritional status.
- The most effective means of restoring nutritional status to malnourished individuals recovering from infectious illnesses.
- The identification of natural food products and chemical additives that induce adverse physiologic responses and the mechanisms by which they do so.
- The basic biochemistry of food antigens and biologically active components.
- The effects of processing and digestion of food substances with conversion to or inactivation of allergenic fractions.
- The value of therapeutic procedures designed to induce tolerance to food antigens.

- The prevalence of food-borne infections and intolerances and immunologic reactions to food in the population.
- The identification of behavioral determinants of unsanitary food handling and storage procedures and the development of effective educational methods to prevent transmission of food-borne illnesses.
- The effect of nutritional status on susceptibility to infectious diseases, including HIV infection, and on the complications of AIDS.

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Chapter 12

Anemia

She was very anaemic. Her thin lips were pale, and her skin was delicate, of a faint green colour, without a touch of red even in the cheeks.
W. Somerset Maugham
Of Human Bondage, 1915

Introduction

Anemia occurs when the concentration of the pigment hemoglobin in red blood cells falls below normal. Hemoglobin is essential for delivering oxygen from the lungs to the body's tissues, and anemia impairs the capacity of the blood to supply the tissues with oxygen for the production of cellular energy in the form of adenosine triphosphate. Severe deficits in the delivery and use of oxygen increase fatigability, decrease work capacity, impair brain function, and lessen ability to maintain body temperature (Bothwell et al. 1979; Dallman, Siimes, and Stekel 1980; Finch 1982; Dallman 1986).

Historical Perspective

Chlorosis, the green sickness or "virgin's disease," was a condition associated with anemia that afflicted young women in Europe and North America from about 1500 to 1900 (see quotation). Chlorotic women appeared pale and suffered weakness, lassitude, breathlessness, and menstrual disorders. This condition was attributed to lovesickness, ovarian insufficiency, or the pressure from a tight corset on the spleen. Treatment consisted of bloodletting and the administration of iron tonics and pills, especially in the 19th century after it was established that the disease involved iron deficiency (Loudon 1980). Today, with improved nutrition and better health care, chlorosis is no longer observed. However, iron deficiency is still prevalent (Crosby 1987).

The credit for introducing iron into therapeutic use is usually given to the 18th-century English physician Sydenham, who observed improvements

in his anemic patients when he prescribed a "steel tonic" prepared by steeping iron filings in Rhine wine (McCollum 1957).

Iron was one of the first substances identified as essential in the human diet. The physiologic function of iron in hemoglobin and its role in anemia was determined over a 200-year period, from the 1680's, when Boyle first analyzed the chemical composition of blood, to the 1860's, when iron was first recognized as an essential nutrient for animals.

Although chlorosis disappeared during the first part of the 20th century, a relatively rare but more deadly nutritional anemia continued to puzzle clinicians and scientists until the 1920's. In 1849, Addison first described pernicious anemia, so called because no cure could be discovered. Not until 1926 was it learned that extracts of liver—now known to contain vitamin B_{12}—could cure the disease (Herbert 1984). A few years later, Wills discovered that an impure extract of liver could reverse a macrocytic anemia found in Hindu women in Bombay, particularly in those who were pregnant. Scientists now know that this extract contained folic acid and that requirements for this vitamin increase during pregnancy.

The first public health efforts in the United States to prevent iron deficiency occurred during World War II when the Food and Drug Administration developed regulations for the fortification of cereal and grain products, including flour (Food and Nutrition Board 1974; Yetley and Glinsmann 1983). Infant cereals were first fortified with iron after about 1950, and infant formulas began to be fortified with iron in the late 1950's (Marsh, Long, and Stierwolt 1959). As a result of this and other public health measures reviewed in this chapter, rates of iron deficiency have declined rapidly.

Significance for Public Health

Anemia has genetic, environmental, and nutritional causes. For example, the most frequent causes of anemia among older persons are infection and chronic disease. Iron deficiency, however, is the most common cause of anemia among young women and children and is the major focus of this discussion. When used precisely, the terms anemia, iron deficiency, and iron deficiency anemia all have distinct meanings. Anemia signifies a blood hemoglobin concentration that is two standard deviations below the mean for normal individuals of the same age and sex. Although iron deficiency is generally the most common cause of anemia, there are many other nutritional, genetic, and environmental causes as well. In this chapter, iron deficiency refers to a lack of iron that not only results in loss of iron stores,

but that also would be expected to impair iron-dependent physiologic functions. The term "impaired iron status" has a similar connotation (LSRO 1984b) and is applied to individuals in whom two or more laboratory tests of iron metabolism are abnormal. Iron deficiency anemia refers to anemia that results from iron deficiency or impaired iron status. Iron-dependent physiologic functions can become impaired before anemia develops. These issues are discussed in greater detail below.

Iron deficiency has received much attention over the years in the United States, although its overall prevalence is low. The best recent estimates of impaired iron status are derived from the second National Health and Nutrition Examination Survey (NHANES II), conducted by the National Center for Health Statistics between 1976 and 1980 (LSRO 1984b; Dallman, Yip, and Johnson 1984).

Iron-dependent physiologic functions can be impaired before anemia becomes apparent (see below). To estimate the prevalence of impaired iron status, with or without concurrent anemia, survey results were analyzed by averaging the results of three methods that detect iron deficiency at varying stages of development of anemia. The prevalence of impaired iron status revealed by these methods is given by age and gender in Table 12-1. These methods found the highest prevalences of iron deficiency among children ages 1 to 2 (9.3 percent), women ages 15 to 19 (7.2 percent), and women ages 20 to 44 (6.3 percent). The lowest prevalence, less than 1 percent, was in men between the ages of 15 and 64.

Because iron deficiency anemia represents a late stage of impaired iron status, rates of clinical anemia would be expected to be even lower than these figures. Both anemia and iron deficiency were less common in NHANES II than was anticipated from the limited data of earlier surveys (Dallman, Yip, and Johnson 1984). Furthermore, the anemia surveillance data collected primarily on low-income children by the Centers for Disease Control show a gradual decline in overall prevalence of anemia (as assessed by stringent laboratory criteria), from 7.8 percent in 1975 to 2.9 percent in 1985 (Anonymous 1986; Stockman 1987; Yip, Binkin, et al. 1987). Prevalences among middle-income children were even lower (Yip, Walsh, et al. 1987). The paucity of moderate or severe anemia in recent analyses may indicate that iron deficiency is becoming less common in the United States.

Among infants and younger children in the United States, increased breastfeeding, greater use of iron-fortified infant formula and cereals, and decreased consumption of cow milk during infancy have also improved iron

Table 12-1
Estimates for Percent Prevalence of Impaired Iron Status: Average of Estimates Using Three Methods[a]: NHANES II, 1976–80

Age (years)	Males and Females	Males	Females
	Average percent prevalence (range)		
1–2	9.3 (9.2–9.4)		
3–4	4.3 (3.6–5.5)		
5–10	3.9 (3.2–4.5)		
11–14		4.1 (3.5–12.1)	2.8 (2.7–6.1)
15–19		0.6 (0.1–0.9)	7.2 (2.5–14.2)
20–44		0.7 (0.6–0.8)	6.3 (4.0–9.6)
45–64		2.0 (1.9–2.0)	4.4 (3.8–4.8)
65–74		2.8 (1.8–3.6)	3.2 (2.7–3.7)

[a]Three methods:
1. Prevalence of two or three abnormal laboratory values using serum ferritin, transferrin saturation, and erythrocyte protoporphyrin.
2. Prevalence of two or three abnormal laboratory values using mean red cell volume, transferrin saturation, and erythrocyte protoporphyrin.
3. Relative prevalence of anemia derived from the rise in median hemoglobin after exclusion of persons with abnormal laboratory values.

Source: Life Sciences Research Office. 1984. *Assessment of the iron nutritional status of the U.S. population based on the data collected in the second National Health and Nutrition Examination Survey, 1976–1980,* ed. S.M. Pilch and F.R. Senti, p. 65, Bethesda, MD: Federation of American Societies for Experimental Biology.

status. Some of these changes may have resulted from public health programs aimed at prevention of iron deficiency.

Although iron deficiency anemia can occur in all socioeconomic groups, it has historically been most common among the poor (LSRO 1984b; DHHS/USDA 1986) and is still the case today (Yip, Binkin, et al. 1987; Yip, Walsh, et al. 1987). This observation provides a basis for the particular attention to iron nutrition in Federal programs such as the School Lunch Program and the Special Supplemental Food Program for Women, Infants, and Children (WIC). The WIC program provides iron-fortified formulas and cereals and periodic health screenings and has been associated with improved iron status in its participants independent of socioeconomic status (Yip, Binkin, et al. 1987).

Studies in Sweden have shown a decline in anemia rates among women, from 30 percent in 1965 to 7 percent only 10 years later (Hallberg et al. 1979). This decline was attributed to a relatively high level of fortification

of food with iron, and the increased use of iron tablets, increased consumption of ascorbic acid, and the effects of oral contraceptive use. Extrapolation of these results to women in the United States, however, must be made with caution because both the severity of anemia and levels of fortification differ in the two countries.

Variations in diagnostic criteria according to age and sex present an additional difficulty in interpreting data on prevalence rates of anemia. Screening programs often use hemoglobin status as an initial criterion for diagnosis. Hemoglobin levels, however, differ with age and gender and must be compared with appropriate standards. They may also differ with race. Data from NHANES indicate that hemoglobin levels are somewhat lower among black than among white Americans (LSRO 1984b), and some studies have suggested that such differences remain even after diet, gender, and socioeconomic factors are taken into account. However, other studies found that the small differences of mean hemoglobin values between blacks and whites may be attributable to a subset of blacks who have mild hereditary anemia such as thalassemia traits (Yip, Schwartz, and Deinard 1984; Castro et al. 1985). Whether these observations mean that the hemoglobin levels of blacks and whites should be compared with different standards is as yet uncertain.

Scientific Background

Causes of Anemia

There are three main causes of anemia: (1) reduced production of red blood cells and hemoglobin; (2) hemolysis, or increased destruction of red blood cells; and (3) loss of blood from the circulation, as in internal or external bleeding. Because the synthesis of blood cells requires many cellular and metabolic steps, a deficiency of any nutrient essential to hemoglobin production produces adverse effects on these processes. Good nutrition is fundamental to adequate red cell production. Nutritional anemia may be due to a dietary deficiency of iron, folate, vitamin B_{12}, protein, vitamin E, vitamin A, vitamin B_6, riboflavin, vitamin C, zinc, or copper. Because the most common nutritional cause of anemia in the United States and in other developed countries is iron deficiency (LSRO 1984b; Dallman, Yip, and Johnson 1984), it is the principal focus of this discussion. Deficiencies of folate (LSRO 1984a), vitamin B_{12}, and other nutrients are far less significant causes. Other causes of anemia include the inherited or acquired inability to use nutrients required for hemoglobin production, chronic inflammatory or infectious diseases, and lead poisoning. Normal levels of hemoglobin also vary according to genetic factors such as race. Thus,

diagnosis of anemia must distinguish nutritional from other potential causes and must relate hemoglobin levels to appropriate standards.

Nutritional anemia should be distinguished from deficiencies *per se* of iron, folate, or vitamin B_{12}, because an individual may have manifest any one of these deficiencies without being anemic. Iron deficiency, for example, in its early stages is typically present without anemia. The term "iron deficiency anemia" signifies that the iron deficiency has become severe enough to depress the hemoglobin concentration below the normal range. Although this chapter focuses on nutritional anemia, there are many additional health consequences of nutritional deficiencies that occur concomitantly with anemia but are not caused by the anemia itself. For example, iron is not only required for hemoglobin biosynthesis but is also an essential component of many enzymes required for the production of energy in cells throughout the body. In iron deficiency, the impairment of these and other iron-dependent processes may account for disorders in immune function and behavior that are not directly attributable to the anemia. Similarly, the impaired nerve function of vitamin B_{12} deficiency occurs independently of anemia. Thus, anemia is just one possible consequence of these nutritional deficiencies.

Role of Iron in the Body

The total amount of iron in the body is slightly less than the weight of a 5-cent coin, about 4 g for adult males (Bothwell et al. 1979). Most of this iron is used to transport and use oxygen in the production of cellular energy. The distribution of iron in the bodies of men, women, and infants is given in Table 12-2. An average of about 58 percent of the body's iron for men and 73 percent for women is contained in hemoglobin, and 11 percent for men and 14 percent for women is present in myoglobin (which stores oxygen and makes it available to the muscle when it is needed during contraction). A smaller but critically important amount of iron, about 3 percent, is present in iron-containing enzymes such as the cytochromes, which are required for the production of cell energy.

In addition to these essential iron compounds that fulfill physiologic functions, two proteins, ferritin and hemosiderin, serve as a storage reserve. These storage compounds account for an average of 25 percent of body iron in men and 10 percent in women and are located primarily in the liver, spleen, and bone marrow. There, they serve as alternate sources of iron to produce essential compounds when dietary supplies are insufficient. The vulnerability of an individual to iron deficiency depends on the abundance of these iron reserves. In some individuals, however, these reserves can accumulate to toxic levels, most often as a result of a genetically deter-

Table 12-2
Total Body Iron and Storage Iron

	Men	Women	Infants (age 1 year)
Total iron, g	4.0	2.7	0.45
Hemoglobin iron, %	58	73	78
Myoglobin iron, %	11	14	6
Enzyme iron, %	3	3	5
Storage iron, %	25	10	11

Source: Bothwell et al. 1979.

mined failure to reduce iron absorption when stores are adequate. This and other causes of iron overload suggest a need for prevention of excessive iron intake in certain individuals.

Almost all compounds containing iron in the body are continuously broken down and resynthesized (Bothwell et al. 1979). The iron released by the degradation of hemoglobin and other iron-containing proteins is efficiently conserved and reused to replace these compounds. An important consequence of this metabolism is that very little iron is lost from the body on a daily basis, except when bleeding occurs. In adult men, normal iron losses in the feces, sweat, and sloughed cells amount to about 0.9 mg/day, equivalent to less than one-tenth of 1 percent of iron stores. This amount is readily absorbed from the diet. Women in their childbearing years require an average of 1.3 mg/day to make up for the additional iron that is lost in menstrual blood (Bothwell et al. 1979). In children, a proportionately more generous amount of iron is required for growth (Dallman, Siimes, and Stekel 1980). Consequently, premenopausal women and children are more likely to develop iron deficiency than are men.

Iron Absorption

The bioavailability of iron—that is, the amount absorbed from food—is determined both by the nature of the diet and by regulatory mechanisms in the intestinal mucosa that reflect the body's physiologic need for iron. Two types of iron are present in food: heme iron, which is found principally in animal products, and nonheme iron, found mainly in plant products.

Nonheme Iron. Most of the iron in the diet, usually more than 80 percent, is present as nonheme iron and consists primarily of iron salts. The composition of a meal determines nonheme iron solubility in the upper part of the small intestine, which, in turn, determines the absorption of the iron

(Hallberg 1981; Charlton and Bothwell 1983). Consequently, the amount of iron finally absorbed is influenced by other constituents of the diet that either enhance absorption by increasing iron solubility or inhibit absorption by decreasing solubility in the intestine. For example, nonheme iron absorption from a representative meal containing enhancers such as meat, fish, or chicken is about four times greater than when foods containing inhibitors (e.g., milk, cheese, or eggs) are substituted (Cook and Monsen 1976).

Iron absorption tends to be poor from meals in which whole grain cereals and legumes predominate, but the addition of even relatively small amounts of meat or foods containing vitamin C (ascorbic acid) substantially increases the absorption of iron from the entire meal. Compared with water, orange juice or foods containing vitamin C increase absorption of nonheme iron from a meal. Tea and coffee, on the other hand, decrease absorption of nonheme iron when compared with water (Hallberg 1981; Rossander, Hallberg, and Bjorn-Rasmussen 1979).

Breast milk is relatively low in iron, but its iron is relatively well absorbed (Saarinen, Siimes, and Dallman 1977) in comparison with iron in cow milk or unfortified cow milk formula. This increased iron absorption may explain why breastfed infants are less vulnerable to iron deficiency than infants fed unfortified cow milk formula.

The absorption of iron from infant foods varies with the form of iron, its concentration, the total iron content and composition of the meal, and, presumably, the iron status of the child. For example, one study found that only about 4 percent of the iron was absorbed from a cow milk formula that was fortified with about 12 mg of iron per liter in the form of ferrous sulfate and with ascorbic acid (Rios et al. 1975; Saarinen and Siimes 1977). Even at this low percentage of absorption, the amount of iron in fortified formula meets the Recommended Dietary Allowances for this age group. Other investigators have reported higher rates of absorption, especially from formulas supplemented with both iron and ascorbic acid (Stekel et al. 1986).

Heme Iron. Heme iron comes from the hemoglobin and myoglobin in meat, poultry, and fish. Although heme iron accounts for a smaller proportion of iron in the diet than nonheme iron, its role is important; the body absorbs a much greater percentage of heme iron, and its absorption is less affected by other dietary constituents than absorption of nonheme iron (Hallberg 1981).

When both forms of iron in the diet are considered, men absorb an average of about 6 percent of total dietary iron and women absorb 13 percent in their childbearing years (Charlton and Bothwell 1983). The higher absorption in women is related to their lower iron stores and helps to compensate for iron losses of menstruation.

Intestinal Regulation. The regulation of iron entry into the body takes place in the mucosal cell of the small intestine (Charlton and Bothwell 1983), and transferrin may act as an iron carrier (Huebers and Finch 1987). If iron stores are low, as is true for most women and children, transferrin in the intestinal mucosa readily takes up iron and increases the proportion absorbed from the diet. The saturation of transferrin is decreased in iron deficiency. Conversely, the high iron stores typical of men and older women reduce the percentage of iron absorbed, thereby offering some protection against iron overload (which is discussed later in this chapter).

Key Scientific Issues

- Role of Iron in Anemia
- Role of Folate and Vitamin B_{12} in Anemia

Role of Iron in Anemia

Because iron is one of the earth's most abundant elements, it may seem surprising that iron deficiency should ever become a nutritional problem. One explanation is that the most common forms of iron in food are relatively insoluble and cannot be absorbed from the intestine. Other factors predisposing to iron deficiency are related to evolving changes in the diet, not only during past millennia, but also within the last century (Eaton and Konner 1985). As noted above, iron is best absorbed from diets that are rich in meat, poultry, fish, and ascorbic acid and is poorly absorbed from diets consisting primarily of whole grain cereals and legumes (Hallberg 1981; Charlton and Bothwell 1983). Even though whole grain foods contain substantial amounts of iron, the form of iron cannot be as readily dissolved and absorbed. Thus, in some cases, the iron content of whole grain cereals and legumes may not wholly compensate for their decreased absorption. This problem may be one reason that iron deficiency anemia remains much more common in developing countries than in the United States where cereal grain products are commonly fortified with iron (Florentino and Guirriec 1984).

Stages of Iron Depletion

Iron depletion occurs in three stages (Cook and Finch 1979). The first involves a decrease in iron stores (as measured by a decrease in serum ferritin) without loss of essential function. This stage is not associated with adverse physiologic consequences, but it does represent a condition of vulnerability. In the United States, women of childbearing age, for example, may characteristically have very low iron stores, but in only a very small number is there a progression to anemia (LSRO 1984b). The risk of developing anemia is minimized by the body's ability to increase iron absorption as iron stores diminish.

The second stage is characterized by biochemical changes that reflect the lack of sufficient iron for normal production of hemoglobin and other essential iron compounds, as indicated by a fall in transferrin saturation levels and an increase in erythrocyte protoporphyrin. Because the hemoglobin concentration has not yet fallen below levels considered anemic, this stage is regarded as iron deficiency without anemia.

The third stage is frank iron deficiency anemia, which occurs when hemoglobin production has been sufficiently depressed to result in a hemoglobin concentration (and mean corpuscular volume) below the normal reference range for individuals of the same age and sex. In this chapter, the term iron deficiency refers to the second and third stages.

Causes of Iron Deficiency

The major causes of iron deficiency are insufficient assimilation of iron from the diet, dilution of body iron by rapid growth, and blood loss (Bothwell et al. 1979; Dallman, Siimes, and Stekel 1980). Because the manifestations of iron deficiency are rarely obvious, most cases are detected by laboratory tests done at a routine examination. The groups at highest risk for iron deficiency are infants, children, adolescents, and women, especially pregnant women, between the ages of menarche and menopause (LSRO 1984b).

Age-Related Factors in Susceptibility

Infants. The prevalence of iron deficiency among infants is highest between about 4 months, when neonatal iron stores accumulated during fetal life are first likely to become depleted, and 3 years of age (Dallman, Siimes, and Stekel 1980). During this period, total iron in the body should more than double to accommodate a rapid rate of growth and an increase in red cell mass. Excessive consumption of cow milk, which is a poor source of iron and commonly associated with occult intestinal blood loss in early infancy,

is a frequent cause of iron deficiency in young infants (Fomon et al. 1981). In premature infants and in twins, iron deficiency anemia may develop as early as 3 months after birth because their neonatal iron stores are smaller and weight gain is proportionately greater than in full-term or single infants. In older children, iron deficiency results from inadequate dietary intake and is associated with poverty (DHHS/USDA 1986).

Adolescents. Iron deficiency is common during adolescence (LSRO 1984b; Dallman, Yip, and Johnson 1984). Boys gain an average of 10 kg, or 22 lb, during the peak year of their growth spurt, usually between 12 and 15 years of age. At about the same age as the growth spurt, and in relation to sexual maturation, the concentration of hemoglobin increases between 0.5 and 1.0 g/dl/year towards values that are characteristic of adult men. The double burden of increased red cell mass and increased hemoglobin concentration requires an increase of about 25 percent in total body iron during the year of peak growth. Adolescent girls also need more iron. Their average weight gain during the peak years of the growth spurt—9 kg, or 20 lb, usually between 10 and 12 years of age—is almost as great as in boys. Although the concentration of hemoglobin changes very little during this period, the onset of menstruation imposes additional iron needs.

Women of Childbearing Ages. The major factors that predispose to iron deficiency anemia in this group are menorrhagia (excessive loss of blood during menstruation) and pregnancy (Bothwell et al. 1979). Heavy blood loss occurs in about 20 percent of women (Hallberg et al. 1966). The use of intrauterine devices increases the prevalence of menorrhagia to about 30 to 50 percent of women, depending on the type used (Israel, Shaw, and Martin 1974). Oral contraceptives, on the other hand, decrease menstrual blood loss by about half and are rarely associated with menorrhagia (Hefnawi, Askalani, and Zaki 1974).

Many women with menorrhagia are usually unaware that they have greater-than-normal menstrual blood loss (Hallberg et al. 1966). For this reason, blood tests at routine health examinations can sometimes detect anemia in women, even when the history of menstrual blood loss is unimpressive.

Iron deficiency anemia may develop during pregnancy (Svanberg et al. 1975) because of the increased requirements for iron to supply the expanding blood volume of the mother as well as the rapidly growing fetus and placenta. True anemia, however, must be distinguished from low hemoglobin values that normally occur as a result of blood volume expansion and must be diagnosed with the use of appropriate standards. Healthy women who are not pregnant have about 2.6 g of total body iron, but only about 0.3