g of this amount is storage iron. The total iron requirement during the entire course of pregnancy averages 1 g and, therefore, exceeds the amount of storage iron in most women. However, an increase in efficiency of dietary iron absorption compensates in part for the limited iron stores. Most of the additional iron is needed for growth of the fetus and placenta during the last half of pregnancy (Bothwell et al. 1979).

Even with the normal adaptive increase in iron absorption that takes place during pregnancy, iron stores may become depleted. For this reason, clinicians commonly recommend an iron supplement that provides the equivalent of about 30 mg of elemental iron or more per day during the last half of pregnancy. After delivery, the iron requirement of the mother is temporarily reduced below normal as the expanded mass of red cells decreases to baseline levels.

Mild iron deficiency in the pregnant woman generally has no detectable effect on hemoglobin concentration in the newborn. However, the severe iron deficiency anemia seen in pregnant women in some developing countries can cause decreased placental weight and birth weight as well as anemia in the newborn (Singla et al. 1978).

Men and Postmenopausal Women. Normally, iron stores increase throughout adult life in men and after menopause in women (Cook, Finch, and Smith 1976), so overt nutritional iron deficiency rarely develops in these groups. Among older persons, anemia is more commonly associated with chronic diseases, inflammation, and infections than with iron deficiency. However, factors that can predispose these groups to iron deficiency anemia include frequent blood donations (three or more times a year) and blood losses due to chronic aspirin ingestion, bleeding ulcers, and colorectal cancers.

Frequent aspirin consumption impairs blood coagulation and leads to blood loss from the intestine, usually in minute amounts that can be detected only by sensitive tests. For example, one study found that 300 mg of aspirin taken three times a day for a week increased intestinal blood loss to 5 ml/day (which averages several times normal menstrual losses) from a normal average of 0.5 ml/day (Pierson et al. 1961).

When there is no known basis for iron deficiency anemia, lesions such as a peptic ulcer or carcinoma may cause chronic and inapparent blood loss from the intestine. Parasitic infestation, particularly with hookworm, commonly causes inapparent intestinal blood loss in some developing countries, but is relatively rare in the United States.

Consequences of Iron Deficiency

The manifestations of iron deficiency can be subtle and depend on the relative severity of functional impairment caused by reduced levels of the "essential" iron compounds (Dallman 1982). These manifestations are related to the effects of iron deficiency on other tissues, to the resultant anemia, or to a combination of the two (Dallman 1986). One difficulty in interpreting studies in this area is that the effects of impaired iron status may differ among iron-deficient individuals who are—or are not—anemic.

Work Performance. Studies in humans as well as in rats show that iron deficiency causes a substantial reduction in work capacity, particularly when the concentration of hemoglobin falls below 10 g/dl, which is 2 to 4 g/dl below the lower limit of normal for adults. Some studies in humans indicate that even mild anemia can decrease performance in brief, hard exercise (Viteri and Torun 1974). To determine the practical significance of these findings for productivity, manual laborers in developing countries who were suffering from iron deficiency anemia were studied. For example, among men on a rubber plantation in Indonesia (Basta et al. 1979) and women on a tea plantation in Sri Lanka (Edgerton et al. 1979), the productivity of iron-deficient individuals was significantly less than that of workers with a normal hemoglobin concentration. After iron supplementation, the performance of the iron-deficient subjects improved, with the greatest improvement occurring in those who had the lowest initial hemoglobin concentrations.

In these studies, it has not been possible to distinguish the extent to which this impaired work performance is due to anemia *per se* or to the tissue abnormalities accompanying iron deficiency. Experiments with rats have shown that dietary iron deficiency also results in a marked impairment in the oxidative production of cellular energy in skeletal muscle (Finch et al. 1976; McLane et al. 1981; Davies et al. 1984). The major consequence of this muscle impairment is a lessened capacity for prolonged exercise or physical endurance, whereas anemia primarily restricts the performance of brief, strenuous exercise (McLane et al. 1981; Davies et al. 1984).

Body Temperature Regulation. An impaired capacity to maintain body temperature in a cold environment is another characteristic of iron deficiency anemia. This abnormality is related to decreased secretion of thyroid-stimulating hormone and thyroid hormone (Beard et al. 1984) and to the anemia itself; studies of the iron-deficient rat show that a transfusion of red blood cells corrects the abnormality. Furthermore, normally fed rats

develop impaired heat production when they are made anemic by an exchange transfusion that replaces red blood cells with plasma that lacks hemoglobin.

Behavior and Intellectual Performance. Increasing evidence suggests that changes in behavior and impaired development and intellectual performance may result from iron deficiency (Lozoff and Brittenham 1986; Pollitt 1985). Most studies have evaluated infants between 6 months and 2 years of age using the Bayley Scale of Infant Development, a test to evaluate sensory development, fine and gross motor skills, and language development in this group. By this standard, infants who are even mildly iron deficient have a statistically significant decrease in responsiveness, activity, and attentiveness and have increased body tension, fearfulness, and tendency to fatigue (Lozoff et al. 1982b). The long-term significance of these observations has not been determined. Of particular interest is the observation that these deficits are most profound in the oldest infants (19 to 24 months), in whom iron deficiency may have been present for the longest period (Lozoff et al. 1982a). Another important finding is that even infants with very mild iron deficiency anemia, or simply with early evidence of impaired hemoglobin production, do not score as well as infants with no laboratory evidence of iron deficiency or evidence merely of depleted iron stores (Lozoff et al. 1982b; Oski et al. 1983; Walter, Kovalskys, and Stekel 1983). Although the results of these studies are not as conclusive, the behavioral abnormalities are significant because the brain's rapid rate of growth and differentiation during infancy might make it particularly vulnerable to nutrient deficiencies. Because the same adverse environmental factors that lead to iron deficiency could also be responsible for behavioral deficits, these studies are difficult to interpret. This complexity may help to explain why some children display a rapid improvement in the Bayley score after iron treatment (Oski et al. 1983), whereas others do not (Lozoff et al. 1982a, 1982b).

Resistance to Infections. Decreased resistance to infection is characteristic of iron deficiency in both humans and experimental animals (Beisel 1982; Vyas and Chandra 1984; Dallman 1986). Iron-deficient children have abnormalities in lymphocytes and neutrophils, two types of white blood cells that help defend against infections (see chapter on infections and immunity). Although infections are associated with decreases in measures of iron status, these decreases may not be related to deficient iron intake.

Despite numerous studies that show an impaired resistance to infection under laboratory conditions, no conclusive evidence demonstrates that iron deficiency itself causes an increased rate of infections in free-living

individuals. Iron deficiency anemia and infections are both common among poor populations, but a cause-and-effect relationship, although plausible, has not been established (Strauss 1978). These issues are discussed further in the chapter on infections and immunity.

Lead Poisoning. Iron deficiency substantially increases the risk of lead poisoning, particularly in young children. Iron-deficient individuals absorb increased amounts of lead (Watson et al. 1986), and elevated blood lead concentrations have been observed among some children with laboratory evidence of iron deficiency (Yip and Dallman 1984).

Prevention of Iron Deficiency

Iron deficiency can be prevented by increasing dietary iron intake, improving the bioavailability of iron in the diet, or decreasing body losses of iron. Dietary iron intakes can be improved by increasing the consumption of iron-rich foods, administering iron supplements to specific target populations, and fortifying certain food products with iron. Parental awareness of appropriate diet is especially important for infants, whose diet is relatively simple. Typically, an infant's diet is discussed during routine health maintenance visits.

Fortification of cereal and grain products is a relatively inexpensive and effective means of increasing iron intake (International Nutritional Anemia Consultative Group 1982; Clydesdale and Wiemer 1985). These foods usually reach the population as a whole in adequate amounts to make a difference without the need for individual counseling. Nevertheless, several aspects of fortification are controversial. Because some iron compounds are poorly absorbed (Cook and Reusser 1983; Yetley and Glinsmann 1983; Hurrell 1984), it is difficult to document that eating fortified foods helps prevent iron deficiency, especially because baseline data are unavailable. Readily absorbed forms of iron react with foods and sometimes decrease shelf life. One compound that may strike a reasonable compromise between shelf life and bioavailability is finely powdered metallic iron, although some studies find that this form, too, is poorly absorbed (Elwood et al. 1968; Hallberg, Brune, and Rossander 1986).

Continuation of breastfeeding for 6 months or more confers substantial protection against development of iron deficiency in full-term infants (AAP Committee on Nutrition 1985). Iron-fortified infant formula, which was introduced about two decades ago in the United States, has gradually supplanted most unfortified formulas and fresh cow milk as infant food during the first year of life (Martinez and Nalezienski 1979). In a large

survey conducted in 1984, 77 percent of 5- to 6-month-old infants in the United States who were receiving cow milk formula were consuming the iron-fortified form (Martinez 1985). Today, iron deficiency in otherwise healthy infants is almost entirely restricted to those on a diet of fresh cow milk (Sadowitz and Oski 1983) or unfortified cow milk formula (Saarinen 1978).

Vitamin C (Ascorbic Acid) Fortification. The absorption of iron from fortified cereals can be increased twofold to threefold if the cereals are also fortified with about 5 mg of vitamin C per mg of iron (International Nutritional Anemia Consultative Group 1982; Cook and Bothwell 1984). Some of the effectiveness of iron-fortified infant formulas in preventing iron deficiency has been attributed to their fortification with this vitamin (Stekel 1984).

Iron Supplements. Supplementation has the disadvantage of requiring extra effort and expense compared with fortified foods. People do not always remember to take medications consistently and regularly. Supplements are less available to the poor and other groups most likely to be iron deficient. Supplementation is, however, a reasonable approach to prevention of iron deficiency in breastfed premature infants, in pregnant women, and in targeted high-risk population groups. In these situations, a large amount of dietary iron is provided over a short period of time. Its usefulness for a given individual requires evaluation by a qualified health professional. Iron supplement use and recommendations to increase dietary iron intake are usually not necessary for the general population. Among Americans as a whole, poor iron status is relatively rare (LSRO 1984b) and iron supplements are not associated with improved iron status (Looker et al. 1987). An additional concern is that increased iron intake can harm individuals who are susceptible to iron overload (LSRO 1984b).

Federal Food Programs. Because iron deficiency is more common among the poor than among persons above the poverty line (DHHS/USDA 1986), iron status should improve as a result of Federal food programs that serve socioeconomically disadvantaged groups. In one study, infants and children who had not received aid from the WIC program in 1973–74 were far more frequently anemic than a similar population in 1977 who were enrolled in the WIC program since birth (Miller, Swaney, and Deinard 1985). Although differences unrelated to iron intake probably existed between the two groups, which might account for differences in iron status, the foods provided by the WIC program included several sources of iron or enhan-

cers of iron absorption: formula fortified with 12 mg of iron per liter for infants up to 12 months of age, and iron-fortified infant cereal and ascorbic acid-fortified fruit juice for infants between 6 and 12 months of age.

Potentially Adverse Consequences. Under ordinary circumstances, a modest excess of dietary iron (over requirements) does not have adverse consequences. On the other hand, increased iron intake might be harmful for some individuals. A much discussed example is the hereditary condition hemochromatosis, in which abnormal amounts of tissue iron accumulate over the years as a result of a genetic defect in absorption, eventually damaging the liver, heart, pancreas, and adrenal glands (Bothwell et al. 1979). A subset of homozygous individuals with hemochromatosis usually develops symptoms by middle age. Heterozygous carriers of the hemochromatosis gene may be at slightly increased risk for iron overload (Brown 1981), but the clinical significance of this risk is uncertain. Although there is no direct evidence that current levels of iron fortification are harmful, concerns have been raised that any increased level of iron in the food supply may harm individuals susceptible to iron overload. Individuals who require repeated blood transfusions for relatively rare conditions, such as thalassemia, may also accumulate excess iron, which is then deposited in soft tissues. Fortification iron adds an undesirable, but relatively small, load compared with that administered by transfusion.

Excessive iron intake may affect the absorption of other trace elements. Although a high dose of iron medication impairs the absorption of zinc or copper administered at the same time (Solomons and Jacobs 1981), this interaction probably does not occur at the much smaller fortification levels. Of greater concern is the possibility of compromised zinc or copper absorption in groups who take larger amounts of iron as supplements, such as infants and pregnant women (Breskin et al. 1983; Hambidge et al. 1987).

Excessive iron administration may increase the risk of infection (Pearson and Robinson 1976; Beisel 1982). The basis for this concern is that a high degree of unsaturation in the iron-binding protein transferrin suppresses the growth of many bacteria. Conditions of iron overload are associated with very low levels of unsaturation. Although this issue may be important in clinically diagnosed iron overload, recent U.S. survey data have found a low prevalence of abnormally high transferrin saturation values in the general population (LSRO 1984b).

Role of Folate and Vitamin B_{12} in Anemia

Although deficiencies of folate or vitamin B_{12} are relatively rare among the general U.S. population, certain groups are particularly at risk for developing these nutrient deficiencies. Folate deficiency is of special concern. Its extent in the general population is virtually unknown. Low socioeconomic groups at vulnerable stages of the life cycle are at greatest risk—pregnant women (especially adolescents), infants (especially those who are small or premature), young children, and older persons (Shojania 1984). Surveys of the folate status of these groups have been too limited in sample size and methodology to permit adequate evaluation (LSRO 1986).

Folate requirements for pregnant women are greatest in the last trimester of pregnancy; however, most women's diets meet these requirements. Oral folate supplementation during this period is often recommended for high-risk groups. Premature infants, particularly those of very low birth weight, may need more folate to support their growth than is provided by infant formula or breast milk. Under a physician's guidance, this folate can be supplied as an oral supplement. Infants fed primarily unfortified goat milk are also at risk for folate deficiency because of the unusually low folate content of this food.

Other risk factors for folate deficiency include chronic disease and use of alcohol and drugs. Chronic and severe diarrhea, as in tropical sprue or celiac disease, for example, can cause folate deficiency. Folate deficiency also occurs among alcoholics (see chapter on alcohol). As discussed in the chapter on drug-nutrient interactions, individuals who use oral contraceptives and other medications may be at increased risk for folate deficiency, but the extent and public health significance of these interactions is uncertain (LSRO 1984a).

A dietary vitamin B_{12} deficiency can occur in strict vegetarians who avoid all foods derived from animals, including eggs and dairy products. Nursing infants of women consuming such diets or of women who are vitamin B_{12}-deficient are also at risk because the vitamin B_{12} content of the breast milk decreases as the mother's vitamin B_{12} stores decline (Shojania 1984). Any strict vegetarian who becomes pregnant should be advised to supplement her diet with vitamin B_{12}.

Implications for Public Health Policy

Dietary Guidance

General Public

Prevention of nutrition-related anemia depends on adequate dietary intake of iron, vitamin B_{12}, and folate as well as the full complement of other essential nutrients. Except for younger children and women of reproductive age, who are at greater risk for iron deficiency, it appears that current iron consumption levels are sufficient for most of the population.

Special Populations

Routine health care for infants and pregnant women, the groups at highest risk for anemia, should include laboratory evaluation for anemia and nutritional advice on methods to ensure adequate iron intake. Nonpregnant women in their childbearing years and adolescents are also at greater risk for iron deficiency anemia; these individuals should be monitored and should receive special counsel on preventing iron deficiency. Frequent blood donors, another high-risk group, should be advised by blood bank personnel about dietary methods to enhance iron intake and absorption. Groups who may need iron supplements, such as premature infants, pregnant women, women with excessive menstrual bleeding, frequent blood donors, strict vegetarians, and regular aspirin users, should also receive advice from health professionals on enhancing iron bioavailability from the diet. Specific education efforts directed toward these special groups, even though difficult, are needed.

Folate deficiency anemia usually occurs among women late in the course of pregnancy, among small and premature infants, and among alcoholics. These groups, especially from low-income families, should receive advice about dietary and supplemental sources of this vitamin.

Strict vegetarians who consume no foods of animal origin, especially women who are pregnant or nursing, should be advised to consume supplemental sources of vitamin B_{12}.

Nutrition Programs and Services

Food Programs

Because groups that benefit from food programs are those at highest risk for anemia, such programs should continue to be made available to high-

risk groups and should encourage consumption of foods rich in iron and folate. Evidence suggests that current levels of iron fortification are safe and adequate, and no changes should be recommended at this time.

Food Labels

Evidence related to the role of iron and folate in anemia suggests that food labels should indicate the content of these nutrients.

Special Populations

Patients with anemia should receive counseling and assistance to develop diets that have adequate amounts of bioavailable iron, folate, or vitamin B_{12} from dietary or supplemental sources.

Research and Surveillance

Research and surveillance issues of special priority related to the role of diet in anemia should include investigations into:

- Screening for earlier stages of iron deficiency using tests that identify iron depletion (e.g., erythrocyte protoporphyrin).
- Elucidation of the health consequences of conditions of iron depletion prior to development of anemia.
- Validation of methodologies for identification of the extent of deficiencies of iron, folate, and vitamin B_{12} in the general population and in high-risk groups.
- Interactions between iron, folate, vitamin B_{12}, and other nutrients consumed in the diet.
- Improved methods for analysis of the folate content of food.
- Determination of iron requirements at various stages of the life cycle and under various physiologic conditions.
- Identification of appropriate levels and types of iron in the food supply for individuals with hereditary conditions of excess iron absorption.
- Identification of the level of iron intake that confers maximum protection against major infections.
- Determination of trends in iron fortification in the U.S. food supply.
- Development of effective methods to educate the general public and high-risk groups about consuming diets adequate in iron and folate.

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Chapter 13

Neurologic Disorders

The man is, above all else, the mind of the man, and not only the mind as an organ of conscious thought but the mind as an organ of bodily nutrition. . . .
James J. Putnam
Boston Medical and Surgical Journal (1899)

Introduction

Historical Perspective

Since biblical times, brain function and certain nutritional factors have been thought to be related, but knowledge of the interaction between nutrition and neurology is still sparse. Scientific interest in the link between nutrition and brain function began in the early 19th century when Magendie proposed that the central nervous system controlled appetite (Anand 1961; Widdowson 1982). Due to the predominance of theories that hunger was purely a peripheral sensation (Cannon and Washburn 1912), it was not until the 1930's that control of feeding began to be attributed to specific regions of the brain.

Classically, nutritional deficiencies have also been related to brain function. Starvation was shown to produce a variety of overt behavioral changes as well as mental deterioration (Blanton 1919), and severe malnutrition in animals is now associated with impaired brain development and learning (Winick 1976). The absence of specific vitamins or minerals from the diet has been known for many years to produce behavioral or neurologic symptoms in animals (Funk 1911). In the early 20th century, disorders of the human nervous system were observed as consequences of deficiencies of certain vitamins, copper, and magnesium in the diet (Widdowson 1972). In most industrialized societies, however, only a few nutritional deficiency diseases, such as those associated with alcoholism (see chapter on alcohol), occur with sufficient frequency to be of substantial concern to policymakers and the public.

Because the brain appears to be protected by the blood-brain barrier from fluctuations in plasma nutrient levels caused by eating, it has been difficult to demonstrate effects of specific foods or dietary components on brain function. Furthermore, the nutrient transport and cellular uptake mechanisms as well as the factors affecting the nutrient content of the brain are not fully understood (Pardridge 1986). In laboratory animals, brain levels of certain essential constituents have been reported to vary markedly as a function of the nature and timing of food consumption (Pardridge 1977; Wurtman, Hefti, and Melamed 1981; Blusztajn and Wurtman 1983), but whether human neurotransmitter systems are affected by the intake of dietary precursors (Wurtman, Wurtman, and Growdon 1981b; Blusztajn and Wurtman 1983) is as yet uncertain.

This chapter reviews these and other nutritional aspects of neurologic phenomena, and because cerebrovascular diseases account for such a large proportion of neurologic cases and hospital admissions, it also reviews the relationship between diet and stroke.

Significance for Public Health

Stroke is the most common life-threatening neurologic disease in the United States: It ranks third after heart disease and cancer as a cause of death and is also a major cause of long-term disability (NCHS 1986). Although stroke mortality rates have declined dramatically in recent years (see chapter on high blood pressure), in part as a result of improved high blood pressure management, about 500,000 new cases still occur annually. About 2 million Americans are estimated to suffer from stroke-related disabilities at an annual cost of more than $11 billion (NINCDS 1986). The mortality rate among black Americans is almost twice that of whites. Because a significant portion of the important risk factors for stroke are under behavioral control, efforts to reduce these risks seem to be especially worthwhile.

Other neurologic conditions are also prevalent in the U.S. population. Approximately 2 million Americans suffer from epilepsy, at an estimated health care cost of $3 billion. Chronic headaches afflict 40 million people in the United States and are responsible for 8 million annual visits to a physician and 64 million days of work lost due to pain. Alzheimer's disease affects 2 to 3 million Americans, at an estimated annual health care cost of up to $50 billion (NINCDS 1986). Whether any appreciable fraction of these conditions can be prevented or ameliorated by dietary means is unknown but seems unlikely given current evidence.

Scientific Background

Nutritional Needs of the Nervous System

The brain and nervous system probably require the full complement of essential nutrients and energy to develop and to maintain their neurons and supporting cells. Although it seems reasonable to expect that a deficiency of any one of the essential nutrients or of energy would impair the development and subsequent maintenance of these structurally and functionally complex tissues, evidence to support this hypothesis has been difficult to obtain (Shoemaker and Bloom 1977; Nowak and Munro 1977).

The human brain normally metabolizes 100 to 150 g of glucose per day as fuel, but the mature nervous system is relatively insensitive to restrictions of energy and protein. During starvation, it adapts and uses ketones, derived from breakdown of body fat stores, for energy and thus spares blood glucose and conserves body protein. The documented behavioral changes that occur in starving individuals—depression, apathy, irritability, and loss of libido—do not necessarily reflect damage to the nervous system (Kerndt et al. 1982).

Most direct research on the neurologic effects of nutritional deprivation has been performed on experimental animals. In part because of species variability in the time course of neurologic development, the results of this research may not be applicable to humans.

Additional information on the effects of dietary deficiencies on human brain development and nervous system function derives from "natural experiments" of human starvation or inadequate dietary intake. With a few notable exceptions, it has been difficult to separate the effects of nutritional deficits in these situations from those of other environmental, social, and medical problems that often accompany poor nutritional status (Pollitt and Thomson 1977).

Nonetheless, severe deficiencies of vitamins, especially the B-complex group, impair nervous system function (Dreyfus 1988; Lipton, Mailman, and Nemeroff 1979). Thiamin deficiency causes beriberi neuropathy as well as a peripheral neuropathy and polyneuritis that leads to Wernicke-Korsakoff's syndrome (paralysis of the eye muscles, loss of muscular coordination, and memory loss) in long-term alcoholics (Dreyfus 1988; see chapter on alcohol). Inadequate niacin intake causes pellagra, with symptoms that include intellectual impairment and dementia, in individuals of all ages. Deficiency caused by vitamin B_{12} malabsorption in untreated pernicious

anemia or as a result of a long-term vitamin B_{12} deficient vegetarian diet can result in subacute degeneration of the spinal cord, optic nerves, cerebral white matter, and peripheral nerves (Dreyfus 1988). Severely deficient intakes of other vitamins of the B-complex group also affect neurologic function. In the early stages, these symptoms are readily overcome by increased dietary intake of the appropriate vitamin, but nerve damage in later stages appears to be irreversible (Lipton, Mailman, and Nemeroff 1979). Whether subclinical deficiencies of these vitamins affect nervous system function is as yet uncertain (Goodwin, Goodwin, and Gary 1983).

Deficiencies of other nutrients may relate to defects in nervous system function. For example, iodine deficiency during brain development causes mental retardation and neuromotor abnormalities. Chronic iron deficiency is associated with deficits in cognitive abilities (Lozoff et al. 1987). A few cases of vitamin E deficiency-induced spinal cord, cerebellar, and peripheral nerve degeneration with muscle wasting have been reported among patients with severe cholestatic liver disease or malabsorption syndromes (Muller, Lloyd, and Wolff 1983; Laplante et al. 1984; Weder et al. 1984). Levels of vitamin E are greatly reduced in the peripheral nerves of such patients (Traber et al. 1987). In most cases, neurologic damage resolves with administration of vitamin E (Sokol et al. 1985), suggesting that vitamin E deficiency may be responsible.

The effects of nutritional deficiencies on the developing nervous system are difficult to interpret. Studies in rats have almost always restricted total dietary intake rather than that of specific nutrients. These studies have indicated that nutritional deprivation at various stages of fetal and postnatal development produces its own constellation of defects. Early maternal malnutrition reduces fetal brain weight and brain protein and DNA content. Postnatal malnutrition also induces deficits in brain weight and, in addition, reduces myelination and dendrite formation and retards development of mature enzyme patterns (Shoemaker and Bloom 1977). These changes persist even after adequate nutrition is restored (Nowak and Munro 1977; Winick 1976). In experimental studies of pregnant animals, diets deficient in zinc and folate result in high rates of malformations such as neural tube defects and spina bifida in the offspring (Hurley and Shrader 1972; see chapter on maternal and child nutrition). Supplementation of these animals resulted in a significant reduction in the incidence of these congenital nervous system defects.

Studies in animals have shown that the neuropathology resulting from intrauterine starvation or postnatal malnutrition does not produce recognizable focal lesions but instead produces diffuse anatomical effects that

appear to be spread throughout the brain. Different effects occur in different brain regions depending on the rate of cell division within each region. Because changes of this type provide little information about functional connections, the significance of these changes for cognitive and behavioral function is uncertain (Nowak and Munro 1977).

The relevance of animal studies for human brain development and cognitive functioning is also uncertain. Reduced cellularity and myelination have been shown to occur in the brains of severely nutritionally deprived human infants. Malnutrition during and after pregnancy produces human infants with lower birth weights, smaller stature, and, therefore, smaller head circumferences and lower brain weights. None of these changes, however, has been demonstrated to affect higher mental processes (Dobbing 1984).

Dietary Precursors of Brain Neurotransmitters

Nervous system function is mediated through the work of various neurotransmitters such as serotonin, the catecholamines (dopamine and norepinephrine), and acetylcholine. These neurotransmitters are manufactured by the action of enzymes in the brain on the precursor amino acids tryptophan, tyrosine, and choline, respectively. Because the brain cannot make adequate quantities of the various precursors, it must rely on uptake from the bloodstream. Studies in animals have suggested that meal composition can affect plasma levels of the precursors and, therefore, synthesis of these neurotransmitters (Wurtman, Hefti, and Melamed 1981; Pardridge 1977).

Whether the various high dose dietary contributions to precursors of brain neurotransmitters affect neurologic function in animals other than the rat is uncertain (Trulson 1985). The effects of dietary precursors of neurotransmitters on animal function and behavior are also uncertain (see chapter on behavior). Also unknown is whether dietary precursors of neurotransmitters can alter normal human behavior (Spring 1986; Young 1986) or correct abnormal behavior (Growdon 1979a; Van Praag and Lemus 1986).

Clinical investigators have tested the utility of neurotransmitter precursors as treatments for diseases associated with neurotransmitter deficiencies such as Alzheimer's and Parkinson's diseases, depression, and sleep disorders (Growdon 1981; Growdon and Wurtman 1982; Growdon and Gibson 1982; Young 1986; Van Praag and Lemus 1986). There is no evidence that such conditions result from nutritional deficiencies. Thus, tryptophan, tyrosine, and choline (as such or as phosphatidylcholine) were given in

these studies in purified form independent of other food constituents. In the case of choline, doses were greater than would ordinarily be consumed in the normal diet.

Pharmacologic amounts of L-tryptophan, for example, have been administered to human subjects to induce sleep (Hartmann 1982), treat insomnia in older persons (Jenicke 1985), relieve anxiety and suppress food consumption in obese persons (Wurtman, Hefti, and Melamed 1981), suppress posthypoxic myoclonus (Growdon 1979b), and treat certain pain syndromes (Hosobuchi, Lamb, and Bascom 1980; Lieberman et al. 1982; King 1980). However, the effectiveness of tryptophan for these purposes has not been established, and its use remains controversial (DeFeudis 1987). Similarly, tyrosine, the dietary precursor of the neurotransmitters dopamine and norephinephrine, has been used to accelerate dopamine turnover in patients with Parkinson's disease (Growdon and Melamed 1982) and to treat patients with mild Parkinson's disease (Growdon 1981) or endogenous depression (Van Praag and Lemus 1986); however, these applications are also preliminary and require further confirmation.

Large doses of choline and purified phosphatidylcholine, precursors for the neurotransmitter acetylcholine, have been reported to improve the symptoms of patients with tardive dyskinesia (Growdon and Wurtman 1982) and mania (Cohen et al. 1980). These observations remain to be confirmed. Similar treatment of patients with Huntington's disease, Gilles de la Tourette's syndrome, familial ataxias, and epilepsy has produced negative or inconclusive results (Wood and Allison 1982).

Despite a single report that suggests that the administration of phosphatidylcholine for at least 6 months might retard the progression of Alzheimer's disease in a subset of older patients with this disorder (Little et al. 1985), more than a dozen additional studies have found choline to be ineffective in the treatment of this condition (Bartus et al. 1982). Evidence is also lacking for the hypothesis that Alzheimer's disease is a consequence of the breakdown of phosphatidylcholine in neuronal membranes to produce choline for acetylcholine biosynthesis (Blusztajn and Wurtman 1983).

Key Scientific Issues

- Role of Diet in Cerebrovascular Disease (Stroke)
- Role of Diet in Other Neurologic Disorders
- Role of Noncaloric Dietary Components in Neurologic Disorders

Role of Diet in Cerebrovascular Disease (Stroke)

Stroke is the sudden loss of brain function caused by one of four vascular events: thrombosis, or blood clot, in a cerebral artery; embolism, or blockage, of a cerebral artery by a circulating clot; stenosis, or narrowing, of a cerebral artery by atherosclerosis; or hemorrhage from rupture of a cerebral artery. These events deprive the brain of blood and oxygen and cause tissue death and irreversible damage to nervous tissue. The effects of the damage depend on the location and size of the tissue loss. Symptoms range from those too trivial for the victim to notice to major sensory deficits, blindness, paralysis, speech loss, coma, and death. Although some return of function is possible in tissues damaged but not destroyed, losses persisting beyond weeks are likely to be permanent.

Persons at greatest risk for stroke are those with hypertension and diabetes and those who smoke cigarettes and display impaired cardiac function due to coronary heart disease, congestive heart failure, or hypertensive heart disease. These major risk factors for stroke are in part related to nutritional, dietary, and lifestyle factors. Current evidence suggests that certain dietary substances that promote high blood pressure or diabetes may increase the likelihood of stroke. Thus, excessive dietary consumption of calories (if it results in obesity), sodium, and alcohol may increase the risk for stroke. The evidence that links dietary factors to high blood pressure and diabetes is reviewed in detail in the chapters devoted to those topics. Although there is a wealth of evidence supporting the relationship between diet, blood cholesterol levels, and atherosclerotic coronary disease (see chapter on coronary heart disease), the link to cerebrovascular disease is less clear.

Persons with hypertension are at greatly increased risk for stroke. This risk increases with elevations in blood pressure regardless of age and sex; it decreases when blood pressure is reduced. How hypertension predisposes to stroke is not fully understood, but it appears to injure cerebral artery walls. Diabetes and high blood cholesterol may also act, alone or in concert, to injure the inner wall of a cerebral artery. Through consequent platelet interaction, the injury becomes the site of plaque formation and subsequent atherosclerosis. Thus, hypertension seems to be the precursor of the hemorrhagic, the stenotic, and the embolic types of stroke.

Moderate sodium restriction (Koolen and Van Brummelen 1984; Kawasaki et al. 1978), high potassium intake (Treasure and Ploth 1983; Langford 1983; Kaplan et al. 1985), vegetarian diets (Ophir et al. 1983), calcium (Blaustein

and Hamlyn 1983; McCarron et al. 1984), weight reduction, and alcohol restriction all have been suggested as factors associated with blood pressure lowering. Of these, weight reduction and restriction of sodium have the most evidence to substantiate this association, but excessive consumption of alcohol is associated with increased rates of hypertension (Klatsky et al. 1977; MacMahon and Norton 1986; Potter and Beevers 1984). Epidemiologic evidence associates excessive drinking with increased frequency of subarachnoid hemorrhage and cerebral infarction (Hillbom and Kaste 1978, 1982), and heavy alcohol intake has been identified as an independent risk factor for stroke in humans (Gill et al. 1986).

The effect of dietary potassium on stroke has also been investigated recently. In a prospective study, individuals consuming somewhat higher levels of potassium from food sources had a reduced risk for stroke-associated mortality (Khaw and Barrett-Connor 1987). The effects of specific dietary factors on causation of stroke warrant further investigation.

Role of Diet in Other Neurologic Disorders

Headache

Headache, one of the most common complaints evaluated by neurologists, is estimated to affect 40 million Americans. Clinical investigations of the role of foods in precipitating vascular or migraine headaches remain controversial (Dreyfus 1988). The foods most frequently implicated often contain tyramines (e.g., cheese, red wines) or more rarely phenylethylamine (e.g., chocolates) (Dreyfus 1988; Egger et al. 1983). The "Chinese Restaurant Syndrome" is associated with numbness around the mouth, tingling, flushing of the face, dizziness, and headache (Kenny 1980). Use of the artificial sweetener aspartame has been found not to be associated with increased susceptibility to headache (Schiffman et al. 1987).

Current evidence suggests that dietary factors are unlikely to be responsible for most cases of headache, although toxicity of vitamin A, caused by excess intake of supplements, has been reported to cause headaches. Until conclusive evidence has established the link between certain foods and the occurrence of headaches, especially migraine, it may be prudent for such individuals to abstain whenever possible from those foods thought to provoke an attack (Dreyfus 1988).

Epilepsy

Low levels of magnesium can cause seizures, and the magnesium-deficient rat is used as a model of experimental epilepsy (Buck, Mahoney, and

Hendricks 1978). Magnesium deficiency in humans most often results from kidney disease and is not a significant cause of epilepsy in people. A wide variety of neurobehavioral symptoms common in the general population, including epilepsy, have been reported to occur in people consuming the artificial sweetener aspartame (Wurtman 1985). No well-controlled clinical studies have indicated that a causal relationship exists. Ketogenic diets (low in carbohydrate) have been used for decades to treat certain forms of intractable epilepsy. The mechanism of action of this diet is not understood (Withrow 1980), and it is tolerated poorly by some patients (Trauner 1985). Furthermore, it is nutritionally inadequate, unpalatable, and inappropriate for use in young children. Other specific nutrients such as vitamin D_3 have been suggested to have beneficial effects on seizure thresholds in rats (Siegel et al. 1984), but more information is needed before conclusions can be drawn about the role of diet in epilepsy.

Role of Noncaloric Dietary Components in Neurologic Disorders

Excessive Vitamin Intake

Vitamin A intoxication can result from the chronic use of relatively low levels (14,000 IU/day in infants and 25,000 to 50,000 IU/day in adults) of the vitamin (Farris and Erdman 1982), and toxic symptoms may appear suddenly with the onset of liver dysfunction due to other causes (Hatoff et al. 1982). Excessive intake of vitamin A causes reversible intracranial hypertension, which when not so identified has led to needless surgery; it can also occasionally result in headache, blurred vision, seizures, and encephalopathy. High doses of pyridoxine (vitamin B_6) have been used to treat conditions such as carpal tunnel syndrome; however, excessive pyridoxine in gram quantities has recently been associated with peripheral nerve deterioration, and more recent studies indicate that lesser amounts may produce toxic symptoms (Ditmars and Houin 1986; Dreyfus 1988; Schaumberg et al. 1983).

Endogenous and Exogenous Toxins

Naturally occurring food-borne toxins either consumed in the diet or produced by the body as a result of rare metabolic diseases also affect the mature nervous system; brain damage resulting from lung, liver, or kidney failure is a common example. Moreover, rare metabolic diseases or inborn errors of metabolism can cause naturally occurring food constituents to become toxic (e.g., copper in Wilson's disease, phenylalanine in phenylketonuria) (Dreyfus 1988). The seeds of certain cycad plants contain neurotoxic substances that, when ingested by experimental animals, cause symptoms similar to those of amyotrophic lateral sclerosis (ALS), parkin-

sonism, or Alzheimer's disease (Spencer et al. 1987). However, in man, the role of cycad plants and other dietary factors in ALS is still controversial (Garruto and Yase 1986). Other neurotoxins have caused acute poisonings on those rare occasions when they have contaminated foods in large quantities. These include ingestion of lead-contaminated paint, soil, or food and water (Mahaffey 1981); industrial contamination of shellfish with methyl mercury; and paralytic poisons produced by certain shellfish (Hatten et al. 1983).

Specific dietary constituents, such as heavy and trace metals, may have especially adverse effects on the nervous systems of older adults. For example, increased amounts of aluminum and calcium have been reported in brains of patients with Alzheimer's disease, and concentrations are especially high in the damaged neurons of the cortex (Linton et al. 1987), particularly in association with the senile plaques and tangles. Whether aluminum causes the cellular damage or accumulates simply because the cells are dying has not been established (see chapter on aging).

Food Additives

Numerous compounds added to foods can affect the nervous system. Some investigators have reported that very high levels of the dipeptide sweetener aspartame raise brain levels of tyrosine in rats and, as a consequence, impair synthesis of catecholamine neurotransmitters (Yokogoshi et al. 1984; Pardridge 1977), but others have not been able to identify such effects (Potts, Bloss, and Nutting 1980; Torii et al. 1986). The rat, unlike humans, rapidly converts phenylalanine (a component of aspartame) to tyrosine. Until aspartame has been tested in well-controlled human clinical studies, its effects on the nervous system remain speculative.

Drug-Nutrient Interactions

Some of the drugs used to treat neurologic diseases can lead to vitamin deficiencies by changing the metabolism of the vitamins, causing a secondary impairment of brain function (see chapter on drug-nutrient interactions). Dilantin, used to treat epilepsy, can increase folate requirements and cause vitamin K deficiency in the infants of mothers treated with this drug. In addition to the hypertensive medication effects on mineral metabolism described in the chapter on drug-nutrient interactions, hydralazine is a vitamin B_6 antagonist that can cause peripheral neuropathy. Tranquilizers such as chlorpromazine and other phenothiazines may cause hyperphagia and weight gain. Monoamine oxidase inhibitors can cause acute hypertensive crises, including excruciating headaches or fatal intracranial hemor-