

## Nutritional Neuropathies

Neeraj Kumar, MD<sup>a,b,\*</sup>

<sup>a</sup>*Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA*

<sup>b</sup>*Mayo Clinic College of Medicine, Rochester, MN 55905, USA*

Optimal functioning of the central and peripheral nervous system is dependent on a constant supply of appropriate nutrients. Estimates provided by the United Nations Food and Agricultural Organization suggest that in 2004 approximately 852 million people in the world were malnourished [1]. Neurologic signs occur late in malnutrition. Neurologic consequences of nutritional deficiencies are not restricted to underdeveloped countries. Individuals at risk in developed countries include the poor and homeless; the elderly; patients on prolonged inadequate parenteral nutrition; those who have food fads or eating disorders, such as anorexia nervosa and bulimia; those suffering from malnutrition secondary to chronic alcoholism; and patients who have malabsorption syndromes, such as sprue, celiac disease, inflammatory bowel disease, and pernicious anemia (PA). Not infrequently, multiple nutritional deficiencies coexist. Of particular concern in the developed world is the epidemic of obesity. The rising rates of bariatric surgery are accompanied by neurologic complications related to nutrient deficiencies. The preventable and potentially treatable nature of these disorders makes this an important subject. Prognosis depends on prompt recognition and institution of appropriate therapy.

Particularly important for optimal functioning of the nervous system are the B-group vitamins (vitamin B<sub>12</sub> [B<sub>12</sub>], thiamine, niacin, and pyridoxine), vitamin E, copper, and possibly folic acid. Most of this review is limited to the discussion of peripheral nervous system manifestations related to the deficiency of these key nutrients. The second sections deals with the neurologic complications associated with bariatric surgery. In the final section, conditions discussed include those that have a geographic predilection or historical significance and those patients in whom either a precise nutrient

---

\* 200 First Street, SW, Rochester, MN 55905.

E-mail address: [kumar.neeraj@mayo.edu](mailto:kumar.neeraj@mayo.edu)

deficiency has not been identified definitively or disorders attributed to multiple coexisting deficiencies.

## Nutrient deficiencies

### *Vitamin B<sub>12</sub>*

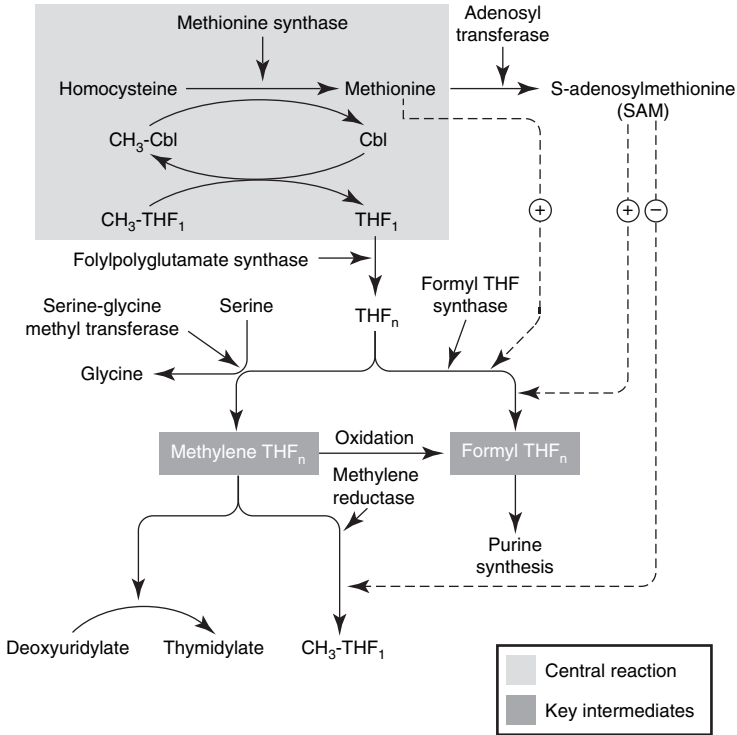
Even though B<sub>12</sub> refers specifically to cyanocobalamin (cyanoCbl), for this review the terms cobalamin (Cbl) and B<sub>12</sub> are used interchangeably. CyanoCbl is a stable synthetic pharmaceutical that has to be converted to other cobalamins to become metabolically active.

### *Function*

The two active forms of Cbl are methylCbl and adenosylCbl (Fig. 1) [2]. MethylCbl is a cofactor for a cytosolic enzyme, methionine synthase, in a methyl transfer reaction that converts homocysteine (Hcy) to methionine. Methionine is adenosylated to S-adenosylmethionine (SAM), a methyl group donor required for biologic methylation reactions involving proteins, neurotransmitters, and phospholipids. Decreased SAM production leads to reduced myelin basic protein methylation and white matter vacuolization in Cbl deficiency [3]. Methionine also facilitates the formation of formyltetrahydrofolate (formylTHF), which is involved in purine synthesis. During the process of methionine formation, methylTHF donates the methyl group and is converted into THF, a precursor for purine and pyrimidine synthesis. Impaired DNA synthesis could interfere with oligodendrocyte growth and myelin production. AdenosylCbl is a cofactor for L-methylmalonyl-coenzyme A (CoA) mutase, which catalyzes the conversion of L-methylmalonyl-CoA to succinyl-CoA in an isomerization reaction. Accumulation of methylmalonate and propionate may provide abnormal substrates for fatty acid synthesis. The branched-chain and abnormal odd-number carbon fatty acids may be incorporated into the myelin sheath [4]. Definite evidence supporting this hypothesis is lacking. Data from animal models of the Cbl neuropathy suggest impairment of the methylCbl-dependent methionine synthetase reaction is the more important defect [5]. In the Cbl-deficient fruit bat with neurologic manifestations, no defect in the methylation of myelin lipid or basic protein has been shown. It is suggested that overproduction of the myelinolytic tumor necrosis factor- $\alpha$  and the reduced synthesis of epidermal growth factor and interleukin-6 may play a role in the pathogenesis of the neurologic manifestations of Cbl deficiency [6].

### *Requirements and sources*

The recommended dietary allowance (RDA) of Cbl for adults is 2.4  $\mu\text{g}$  per day and the median intake from food in the United States is 3.5  $\mu\text{g}$  per day for women and 5  $\mu\text{g}$  per day for men (Table 1) [7]. No adverse effects are associated with excess Cbl intake. Foods of animal origin, such as meats,



Cobalamin (Cbl);  $\text{CH}_3$  = methyl group;  $\text{THF}_1$  and  $\text{THF}_n$  = monoglutamated and polyglutamated forms of tetrahydrofolate

Fig. 1. Biochemistry of Cbl and folate deficiency. See text for details.  $\text{CH}_3$ , methyl group;  $\text{THF}_1$  and  $\text{THF}_n$ , monoglutamated and polyglutamated forms of tetrahydrofolate. (Adapted from Tefferi A, Pruthi RK. The biochemical basis of cobalamin deficiency. Mayo Clin Proc 1994;69:181-6; with permission.)

eggs, and milk, are the major dietary sources. The richest sources of Cbl include shellfish; organ meats, such as liver; some game meat; and certain fish. In the United States, milk and Cbl-fortified cereals are particularly efficient sources. Even though vegetables lack Cbl, strict vegetarians generally do not develop overt clinical deficiency, because an adequate amount is present in legumes.

*Physiology*

In the stomach, Cbl bound to food is dissociated from proteins in the presence of acid and pepsin [7,8]. The released Cbl binds to R proteins secreted by salivary glands and gastric mucosa. In the small intestine, pancreatic proteases partially degrade the R proteins-Cbl complex at neutral pH and release Cbl, which then binds with intrinsic factor (IF). IF is a Cbl-binding protein secreted by gastric parietal cells. The IF-Cbl complex binds to specific receptors in the ileal mucosa and is internalized. In addition to the IF-mediated

Table 1  
Summary of sources, causes of deficiency, neurologic significance, laboratory tests, and treatment for deficiency states related to cobalamin, folate, copper, and vitamin E

Nutrient	Sources	Major causes of deficiency	Neurologic significance associated with deficiency	Laboratory tests	Treatment
Cobalamin	Meats, egg, milk, fortified cereals	PA, food-Cbl malabsorption (elderly), gastric surgery, acid reduction therapy, gastrointestinal disease, N <sub>2</sub> O toxicity	Myelopathy or myeloneuropathy, peripheral neuropathy, neuropsychiatric manifestations, optic neuropathy	Serum Cbl, serum MMA, plasma total Hcy, anemia, macrocytosis, neutrophil hypersegmentation, Schilling test, serum gastrin, IF, and parietal cell antibodies	Intramuscular B <sub>12</sub> 1000 µg twice weekly for 2 weeks, followed by weekly for 2 months and monthly thereafter
Folate	In virtually all foods	Alcoholism, gastrointestinal disease, folate antagonists	Neurological manifestations are rare and indistinguishable from those due to Cbl deficiency	Serum folate, RBC folate, plasma total Hcy	Oral folate 1 mg 3 times/d followed by a maintenance dosage of 1 mg/d
Copper	Organ meats, seafood, nuts, whole grain products	Gastric surgery, zinc toxicity, gastrointestinal disease	Myelopathy or myeloneuropathy	Serum copper and ceruloplasmin	Oral elemental copper: 6 mg/d for a week followed by 4 mg/d for a week and 2 mg/d thereafter

Vitamin E	Vegetable oils, leafy vegetables, fruits, meats, nuts	Chronic cholestasis, pancreatic insufficiency, AVED, homozygous hypobetalipoproteinemia, abetalipoproteinemia, chylomicron retention disease	Spinocerebellar syndrome with peripheral neuropathy, ophthalmoplegia, pigmentary retinopathy	Serum vitamin E Ratio of serum $\alpha$ -tocopherol to sum of serum cholesterol and triglycerides	Variable dose and route (see text)
Thiamine	Enriched, fortified, or whole grain products	Recurrent vomiting, gastric surgery, alcoholism, dieting, increased demand with marginal nutritional status	Beriberi (dry, wet, infantile), WE, KS	Urinary thiamine, serum thiamine, erythrocyte transketolase activation assay, RBC TDP	50 to 100 mg (intravenous, intramuscular, oral)
Niacin	Meat, fish, poultry, enriched bread, fortified cereals	Corn as primary carbohydrate source, alcoholism, malabsorption, carcinoid and Hartnup syndrome	Encephalopathy (peripheral neuropathy)	Urinary excretion of methylated niacin metabolites	25 to 50 mg of nicotinic acid (intramuscular, oral)
Pyridoxine	Meat, fish, eggs, soybeans, nuts, dairy products	B <sub>6</sub> antagonists, alcoholism, gastrointestinal disease	Infantile seizures, peripheral neuropathy (pure sensory neuropathy with toxicity)	Plasma PLP	50 to 100 mg of pyridoxine daily (oral)

*Abbreviations:* AVED, ataxia with vitamin e deficiency; Cbl, cobalamin; Hcy, homocysteine; IF, intrinsic factor; KS, Korsakoff's syndrome; MMA, methylmalonic acid; N<sub>2</sub>O, nitrous oxide; PA, pernicious anemia; PLP, pyridoxal phosphate; RBC, red blood cells; TDP, thiamine diphosphate; WE, Wernicke's encephalopathy.

absorption of ingested Cbl, there is a nonspecific absorption of Cbl that occurs by passive diffusion at all mucosal sites. This is a relatively inefficient process by which 1% to 2% of the ingested amount is absorbed [9]. Cbl is transferred across the intestinal mucosa into portal blood where it binds to transCbl II (TC II). The liver takes up approximately 50% of the Cbl and the rest is transported to other tissues. TC II is the form that delivers Cbl to the tissues through receptors for TC II [10]. TC II-bound Cbl is taken up by cells through receptor-mediated endocytosis. Intracellular lysosomal degradation releases Cbl for conversion to methylCbl or adenosylCbl. Most of the Cbl secreted in the bile is reabsorbed. If circulating Cbl exceeds the Cbl binding capacity of blood, the excess is excreted in the urine. The estimated daily loss of Cbl is 1  $\mu\text{g}$ . This is minute compared with body stores of 2500  $\mu\text{g}$ . Hence, even in the presence of severe malabsorption, 2 to 5 years may pass before Cbl deficiency develops [11]. Similarly, a clinical relapse in PA after interrupting Cbl therapy takes approximately 5 years before it is recognized.

#### *Causes of deficiency*

The majority of patients who have Cbl deficiency have PA [8,12]. Cbl deficiency is particularly common in the elderly [13]. In a study, the prevalence of metabolic Cbl deficiency in the 65- to 99-year-old age group was 14.5% [14]. This most likely is the result of the high incidence of atrophic gastritis and achlorhydria-induced food-Cbl malabsorption rather than reduced intake [13,15]. Cbl deficiency commonly is seen after gastric surgery [16]. Acid reduction therapy, as with  $\text{H}_2$ -blockers, also can cause Cbl deficiency [17]. Other causes of Cbl deficiency include conditions associated with malabsorption, such as ileal disease or resection, bacterial overgrowth, and tropical sprue. Competition for Cbl secondary to parasitic infestation by the fish tapeworm, *Diphyllobothrium latum*, may cause Cbl deficiency. Certain hereditary enzymatic defects also can manifest as disorders of Cbl metabolism [18]. Increased prevalence of  $\text{B}_{12}$  deficiency is recognized in HIV-infected patients who have neurologic symptoms but the precise significance of this is unclear [19,20]. In AIDS-associated myelopathy, the Cbl- and folate-dependent transmethylation pathway is depressed and CSF and serum levels of SAM are reduced [21].

Nitrous oxide ( $\text{N}_2\text{O}$ ) is a commonly used inhalational anesthetic that is abused because of its euphoriant properties.  $\text{N}_2\text{O}$  irreversibly oxidizes the cobalt core of Cbl and renders methylCbl inactive [22]. Clinical manifestations of Cbl deficiency appear relatively rapidly with  $\text{N}_2\text{O}$  toxicity because the metabolism is blocked at the cellular level. They may, however, be delayed up to 8 weeks [23]. Postoperative neurologic dysfunction can be seen with  $\text{N}_2\text{O}$  exposure during routine anesthesia if subclinical Cbl deficiency is present [23,24]. The other setting associated with  $\text{N}_2\text{O}$  (laughing gas) toxicity is inhalant abuse [25]. Earlier reports were among dentists and other medical personnel. More recently it is reported among university

students [26]. Rarely, it may be seen in medical personnel working in poorly ventilated surgeries [25]. A generalized toxic polyneuropathy is reported after excessive intentional inhalation of compressed N<sub>2</sub>O delivery from cartridges through a whipped-cream dispenser [27].

B<sub>12</sub> deficiency only rarely is the consequence of diminished dietary intake. Strict vegetarians may develop Cbl deficiency after years. The consequences often are mild and often only subclinical. Clinical consequences are more likely when poor intake begins in childhood wherein limited stores and growth requirements act as additional confounders. Not infrequently the cause of Cbl deficiency is unknown.

### *Clinical significance*

Neurologic manifestations may be the earliest and often the only manifestation of Cbl deficiency [12,28,29]. The severity of the hematologic and neurologic manifestations may be inversely related in a particular patient [29,30]. Relapses generally are associated with the same neurologic phenotype [31]. The recognized neurologic manifestations may include a myelopathy with or without an associated neuropathy, cognitive impairment, optic neuropathy, and paresthesias without abnormal signs [29].

The best characterized neurologic manifestation of Cbl deficiency is a myelopathy commonly referred to as subacute combined degeneration [32,33]. This term refers to the pathologic process seen in B<sub>12</sub> deficiency myelopathy. The most severely involved regions are the cervical and upper thoracic posterior columns. Changes also are seen in the lateral columns. Involvement of the anterior columns is rare. Spongiform changes and foci of myelin and axon destruction are seen in the spinal cord white matter. There is myelin loss followed by axonal degeneration and gliosis [33]. The neurologic features typically include a spastic paraparesis, extensor plantar response, and impaired perception of position and vibration. Symptoms start in the feet and are symmetric. Neuropsychiatric manifestations include decreased memory, personality change, psychosis, and, rarely, delirium [12,29]. MRI abnormalities include a signal change in the subcortical white matter and posterior and lateral columns [34,35]. Contrast enhancement involving the dorsal or lateral columns may be present [36]. The dorsal column may show a decreased signal on T1-weighted images [36]. Other reported findings include cord atrophy and anterior column involvement [37,38]. Treatment may be accompanied by reversal of cord swelling, contrast enhancement, and signal change [34–36,38]. Similar MRI findings are seen with N<sub>2</sub>O toxicity [26].

Clinical, electrophysiologic, and pathologic involvement of the peripheral nervous system is described. Earlier studies failed to provide pathologic evidence of peripheral neuropathy [33]. More recently, detailed pathologic studies of distal sensory or motor nerves and electrophysiologic studies demonstrate axonal degeneration with or without associated demyelination [39–41]. In a recent study, Cbl deficiency was detected in 27 of 324 patients

who had a polyneuropathy [42]. Clues to possible B<sub>12</sub> deficiency in a patient who had polyneuropathy included a relatively sudden onset of symptoms, findings suggestive of an associated myelopathy, onset of symptoms in the hands, macrocytic red blood cells (RBCs), and the presence of a risk factor for Cbl deficiency. Autonomic dysfunction with orthostatic hypotension is described [40,43,44]. Electrophysiologic abnormalities include nerve conduction studies suggestive of a sensorimotor axonopathy and abnormalities on somatosensory evoked potentials, visual evoked potentials, and motor evoked potentials [35,45].

Cbl can be normal in some patients who have Cbl deficiency and serum methylmalonic acid (MMA) and total Hcy levels are useful in diagnosing patients who have Cbl deficiency [11,46–49]. The sensitivity of the available metabolic tests has facilitated the development of the concept of subclinical Cbl deficiency [50]. This refers to biochemical evidence of Cbl deficiency in the absence of hematologic or neurologic manifestations. These biochemical findings should respond to Cbl therapy. The frequency of subclinical Cbl deficiency is estimated to be at least 10 times that of clinical Cbl deficiency [50]. Subclinical Cbl deficiency increases with age [51,52]. These individuals may have subtle neurologic and neurophysiologic abnormalities of uncertain significance that respond to Cbl therapy [53]. It is equally important to recognize that the presence of a low Cbl in the association with neurologic manifestations does not imply cause and effect or indicate the presence of metabolic Cbl deficiency. The incidence of cryptogenic polyneuropathy and Cbl deficiency increases with age and the latter may be a chance occurrence rather than a cause of the neuropathy [54]. The clinical impact of subclinical Cbl deficiency and its appropriate management are uncertain. If it is unclear whether or not elevated MMA or Hcy is the result of Cbl deficiency, the response to empiric parenteral B<sub>12</sub> replacement can be seen. A trend to normalize with replacement favors Cbl deficiency as the likely cause [55].

### *Investigations*

Serum Cbl determination is the mainstay for evaluating Cbl status [11,56]. The older microbiologic and radioisotopic assays have been replaced by immunologically based chemiluminescence assays. Although a widely used screening test, serum Cbl measurement has technical and interpretive problems and lacks sensitivity and specificity for the diagnosis of Cbl deficiency [47,48,55]. A low Cbl level may be seen in pregnancy, with oral contraceptive or anticonvulsant use, with transCbl I (TC I) deficiency, with folate deficiency, in association with HIV infection, and in multiple myeloma [50]. The Cbl radioassay may give falsely low readings if performed soon after radionuclide isotope studies, such as bone scans [57]. Patients who have mild TC I deficiency may be responsible for 15% of all unexplained low Cbl levels and many of these patients may be heterozygotes for hereditary TC I deficiency [58]. Falsely elevated Cbl levels may be seen with renal failure, liver disease, and myeloproliferative disorders [59].



Levels of serum MMA and plasma total Hcy are useful as ancillary diagnostic tests in the diagnosis of Cbl deficiency [48,55]. MMA is a byproduct of methylmalonyl-CoA and it accumulates in Cbl deficiency. Its specificity is superior to that of plasma Hcy [60]. Elevated MMA levels may be seen with renal insufficiency, in infancy, with methylmalonyl-CoA mutase deficiency, and possibly with volume contraction [50,56]. Urinary MMA levels may be useful to exclude falsely elevated serum levels resulting from renal insufficiency. Although plasma total Hcy is a sensitive indicator of Cbl deficiency, its major limitation is its poor specificity [47,48,51]. Causes of an elevated Hcy level include renal insufficiency, folate deficiency, alcohol abuse, hypothyroidism, increased age, hypovolemia, psoriasis, inherited metabolic disorders, and certain inborn errors of Hcy metabolism [50,56]. Elevated Hcy levels also are noted in associated with isoniazid (INH) use, renal transplantation, leukemia, and enzyme polymorphisms (eg, methylenetetrahydrofolate reductase [MTHFR]) [50].

A rise in mean corpuscular volume may precede development of anemia [61]. The presence of neutrophil hypersegmentation may be a sensitive marker for Cbl deficiency and may be seen in the absence of anemia or macrocytosis. The Cbl-TC II complex is believed to be the metabolically active fraction of circulating Cbl [62]. It is suggested that measuring the Cbl attached to TC II might lead to greater sensitivity and specificity [63]. The clinical usefulness seems limited [64].

In order to determine the cause of Cbl deficiency, tests directed at determining the cause of suspected malabsorption are undertaken. Concerns regarding cost, accuracy, and radiation exposure have led to a significant decrease in the availability of the Schilling test. An elevated serum gastrin and decreased pepsinogen I is seen in 80% to 90% of patients who have PA, but the specificity of these tests is limited [65]. Elevated gastrin levels are a marker for hypochlorhydria or achlorhydria, which invariably are seen with PA. Elevated gastrin levels may be seen in up to 30% of the elderly [15]. Elevated serum gastrin levels are approximately 70% specific and sensitive for PA [66]. Anti-IF factor antibodies are specific but lack sensitivity and are found in approximately 50% to 70% of patients who have PA [67–69]. Recent studies suggest that antiparietal cell antibodies may not be seen as commonly as believed earlier and, therefore, have limited usefulness [69]. Further, false-positive results for the gastric parietal cell antibody are common. They may be seen in 10% of people over age 70 and also are present in other autoimmune endocrinopathies.

### *Management*

The goals of treatment are to reverse the signs and symptoms of deficiency, replete body stores, ascertain the cause of deficiency, and monitor response to therapy. With normal Cbl absorption, oral administration (3 to 5  $\mu\text{g}$ ) may suffice. In patients who have food-bound Cbl malabsorption resulting from achlorhydria, cyanocbl (50 to 100  $\mu\text{g}$ ) given orally often is

adequate [70]. Patients who have Cbl deficiency resulting from achlorhydria-induced food-bound Cbl malabsorption show normal absorption of crystalline B<sub>12</sub> but are unable to digest and absorb Cbl in food because of achlorhydria. The more common situation is one of impaired absorption where parenteral therapy is required. A short course of daily or weekly therapy often is followed by monthly maintenance therapy. A common regimen is intramuscular injection, 100 µg daily for 2 weeks or 1000 µg twice weekly for 2 weeks followed by weekly injections of 1000 µg for 2 months. Lifelong therapy with monthly intramuscular injection (1000 µg) often is required. If the oral dose is large enough, even patients who have an absorption defect may respond to oral Cbl [71].

Patients who have B<sub>12</sub> deficiency are prone to develop neurologic deterioration after N<sub>2</sub>O anesthesia. It is preventable by prophylactic B<sub>12</sub> given weeks before surgery in individuals who have a borderline B<sub>12</sub> level who are expected to receive N<sub>2</sub>O anesthesia. Intramuscular B<sub>12</sub> should be given to patients who have acute N<sub>2</sub>O poisoning. Methionine supplementation also is proposed as a first-line therapy [72]. With chronic exposure, immediate cessation of exposure should be ensured. In AIDS-associated myelopathy, possible benefit of administration of the SAM precursor, L-methionine, is suggested by a pilot study [73] but not confirmed in a subsequent double-blind study [74].

Response to treatment may relate to extent of involvement and delay in starting treatment [29]. Remission correlates inversely with the time lapsed between symptom onset and therapy initiation. Most of the symptomatic improvement occurs during the first 6 months [75]. Response of the hematologic derangements is prompt and complete. Reticulocyte count begins to rise within 3 days and peaks at approximately 7 days. RBC count begins to rise by 7 days and is followed by a decline in mean corpuscular volume with normalization by 8 weeks. MMA and Hcy levels normalize by 10 days. Cbl levels rise after injection regardless of the benefit. Hence, MMA and Hcy are more reliable ways to monitor response to therapy. In patients who have severe B<sub>12</sub> deficiency, replacement therapy may be accompanied by hypokalemia resulting from proliferation of bone marrow cells that use potassium. Response of the neurologic manifestations is more variable and may be incomplete.

HydroxoCbl has superior retention and may permit injections every 2 to 3 months [76]. Compared with hydroxoCbl, cyanoCbl binds to serum proteins less well and is excreted more rapidly [77]. Intranasal administration of hydroxoCbl is associated with fast absorption and normalization of Cbl levels [78]. Advantages of delivering Cbl by the nasal or sublingual route are unproven. Oral preparations of IF are available but not reliable. Antibodies to IF may nullify its effectiveness in the intestinal lumen.

Neurologically affected patients may have high folate levels [79]. Folate therapy may delay recognition of the Cbl deficiency and cause neurologic deterioration. Anemia resulting from Cbl deficiency often responds to folate

therapy but the response is incomplete and transient. It is unclear if routine folate supplementation may compromise the early diagnosis of the hematologic manifestations or worsen the neurologic consequences. Not infrequently, iron deficiency also is seen in patients who have PA [80].

### *Folic acid*

#### *Function*

Folate functions as a coenzyme or cosubstrate by modifying, accepting, or transferring one-carbon moieties in single-carbon reactions involved in the metabolism of nucleic and amino acids [81,82]. The biologically active folates are in the THF form. MethylTHF is the predominant folate and is required for the Cbl-dependent remethylation of Hcy to methionine. Methylation of deoxyuridylate to thymidylate is mediated by methyleneTHF (see Fig. 1). Impairment of this reaction results in accumulation of uracil, which replaces the decreased thymine in nucleoprotein synthesis and initiates the process that leads to megaloblastic anemia.

#### *Requirements and sources*

The RDA for men and women is 400  $\mu\text{g}$  per day of dietary folate equivalents [81]. Dietary folate equivalents adjust for the lower bioavailability of food folate compared with that of folic acid. The tolerable upper intake level (UL) for adults is set at 1000  $\mu\text{g}$  per day of folate from fortified food or as a supplement, exclusive of food folate. Folate is found in virtually all foods (see Table 1). Spinach, yeast, peanuts, liver, beans (such as kidney beans and lima beans), and broccoli are particularly rich sources. Folate in food usually is reduced, often is methylated, may be protein bound, and is in the polyglutamate form. Folate in foods may have a bioavailability of less than 50%. Folic acid supplements are in the monoglutamate form and have a bioavailability approaching 100%. Fortification of cereals and grain products with folic acid (140  $\mu\text{g}/100\text{ g}$ ) has been mandated in the United States since 1998 to prevent neural tube defects. There is a concern that excess fortification may be associated with an adverse outcome in individuals who have Cbl deficiency. The reduced folates in food are labile and readily lost under certain cooking conditions, such as boiling.

#### *Physiology*

Folate is absorbed by saturable and unsaturable mechanisms [82]. The saturable process is specific and occurs in the proximal small intestines. The specific absorption is mediated by the reduced folate carrier, which has a high affinity for reduced folates and is located in the cellular brush border membranes [83]. In the enterocyte, folate is converted into methylTHF and a carrier-mediated mechanism exports it into the bloodstream. Nonspecific, unsaturable absorption predominates in the ileum. The absorbed folate is cleared from the bloodstream and enters various

compartments. The reduced folate carrier also is involved in cellular uptake of reduced folates in tissues. Cellular folate uptake also occurs nonspecifically via passive diffusion. Once internalized, folate undergoes polyglutamation that permits its attachment to enzymes. Polyglutamated folates have greater metabolic activity and are retained better by cells compared with monoglutamated folates [84]. Daily folate losses may approximate 1% to 2% of body stores. The ratio of body stores to daily requirement is 100:1 [82]. Therefore, a few months of poor nutrition can result in folate deficiency. Clinically significant depletion of normal folate stores may be seen within 3 months, more rapidly with low stores or coexisting alcoholism. Serum folate falls within 3 weeks of decrease in folate intake or absorption; RBC folate declines weeks to months later [85].

#### *Causes of deficiency*

Folate deficiency rarely exists in the pure state [82]. It often is associated with conditions that affect other nutrients. Hence, attribution of neurologic manifestations resulting from folate deficiency requires exclusion of other potential causes.

Marginal intake in association with conditions that compromise folate status, such as alcoholism, result in folate deficiency, particularly when hard liquor is consumed. Beer contains folate. Alcohol abuse affects enterohepatic recycling of Cbl, affects folate metabolism, forms aldehyde adducts with folates, and accelerates folate breakdown [86]. Other populations at increased risk of folate deficiency include premature infants and adolescents. Increased folate requirements also are seen in pregnancy, lactation, and chronic hemolytic anemia. Folate deficiency also may result from restricted diets, such as those used to manage phenylketonuria. Folate deficiency is seen with small bowel disorders associated with malabsorption, such as tropical sprue, celiac disease, and inflammatory bowel disease. Folate absorption may be decreased in conditions associated with reduced gastric secretions, such as gastric surgery (partial gastrectomy), atrophic gastritis, acid-suppressive therapy, and acid neutralization by treatment of pancreatic insufficiency [87–89].

Several drugs, such as aminopterin, methotrexate (amethopterin), pyrimethamine, trimethoprim, and triamterene, act as folate antagonists and produce folate deficiency by inhibiting dihydrofolate reductase [90]. The mechanism by which anticonvulsants, antituberculosis drugs, and oral contraceptives result in folate deficiency is uncertain.

#### *Clinical significance*

In adults who have acquired folate deficiency, neurologic manifestations are rare and mild. The reason for this is not clear, because methionine synthase requires folate as cosubstrate. The megaloblastic anemia resulting from folate deficiency is indistinguishable from that seen in Cbl deficiency.

The occurrence and frequency of neurologic manifestations of folate deficiency is a matter of debate [91]. It likely is less common compared with the myeloneuropathy and cognitive symptoms associated with Cbl deficiency. The myeloneuropathy or neuropathy seen in association with folate deficiency is indistinguishable from Cbl deficiency [92–96]. Folate deficiency is associated with affective disorders [97]. A low folate level may be seen in elderly asymptomatic individuals and more commonly with psychiatric disease and Alzheimer's dementia [98]. In recent years, there has been evidence that suggests that chronic folate deficiency may increase stroke risk and cause cognitive impairment [99]. The precise significance of these observations awaits further studies.

Congenital errors of folate metabolism can be related either to defective transport of folate through various cells or to defective intracellular use of folate resulting from some enzyme deficiencies. These often are associated with severe central neurologic dysfunction [100].

Metabolic folate deficiency, suggested by elevated plasma total Hcy levels that improve with folate therapy, can be seen in asymptomatic individuals [91]. The increased Hcy seen with folate deficiency is associated with an increased risk of cardiovascular and cerebrovascular disease [91]. In a recent study, moderate reduction of Hcy levels with folate, Cbl, and vitamin B<sub>6</sub> (B<sub>6</sub>) had no effect on vascular outcomes in patients who had stroke at 2 years follow-up [101].

### *Investigations*

Microbiologic assays for folate measurement largely have been replaced by radioisotopic assays. More recently, automated immunologic methods using chemiluminescence or other nonisotopic detection are used. Folate results are dependent on the method used and laboratory where they were performed [102]. Generally, serum folate, 2.5 µg/L, is taken as the cut-off for folate deficiency. Plasma Hcy levels are slightly elevated and respond to folate supplementation in persons who have folate levels as high as 5 µg/L [103]. This has led to the suggestion that serum folate levels between 2.5 and 5 µg/L may be indicative of a mildly compromised folate status. Serum folate fluctuates daily and does not correlate with tissue stores [104]. Erythrocyte folate is more reliable than plasma folate because its levels are less affected by short-term fluctuations in intake [105]. RBC folate assay, however, is subject to greater variation depending on the method and laboratory [102]. Reticulocytes have a higher folate content than mature RBCs. Their presence can affect RBC folate levels as can blood transfusions. Plasma Hcy levels are shown to be elevated in 86% of patients who have clinically significant folate deficiency [48].

### *Management*

In women of childbearing age who have epilepsy, a daily folate supplement, 0.4 mg, is recommended for prophylaxis against neural tube defects.

With documented folate deficiency, an oral dosage, 1 mg 3 times a day, may be followed by a maintenance dosage, 1 mg a day. Acutely ill patients may need parenteral administration, 1 to 5 mg. Despite malabsorption, patients respond to oral folic acid because it is absorbed readily by nonspecific mechanisms. Even in high doses, toxicity resulting from folic acid is rare [106]. Doses higher than 1 mg need a prescription because of concerns regarding masking Cbl deficiency. Coexisting Cbl deficiency, therefore, should be ruled out before instituting folate therapy. Reduced folates, such as folinic acid (N5-formylTHF), is required only when folate metabolism is impaired by drugs, such as methotrexate, or by an inborn error of metabolism. In a patient therapy with subacute combined degeneration resulting from folate deficiency, methyl folate use was associated with a significant response [95]. Therapy with folic or folinic acid could be considered in patients who have folate deficiency who have neuropsychiatric symptoms, neuropathy or myelopathy, and normal B<sub>12</sub> levels [90]. Plasma Hcy likely is the best biochemical tool for monitoring response to therapy; it decreases within a few days of instituting folate therapy but does not respond to inappropriate Cbl therapy [107]. Because folate deficiency generally is seen in association with a broader dietary inadequacy, the associated comorbidities need to be addressed.

### *Copper*

Copper deficiency-associated myelopathy is described in various animal species [108]. Often seen in ruminants, it is referred to as swayback or enzootic ataxia. Menkes' disease is the copper deficiency-related disease in humans and is the result of congenital copper deficiency. Comparative pathologic studies show similarity between Menkes' disease and swayback [108]. Only in recent years have the neurologic manifestations of acquired copper deficiency in humans been recognized. The most common manifestation is that of a myelopathy or myeloneuropathy that resembles the subacute combined degeneration seen with Cbl deficiency [109,110].

### *Functions*

Copper functions as a prosthetic group in several metalloenzymes, which act as oxidases [111,112]. Many of these have a critical role in maintaining the structure and function of the nervous system. Some of these include copper/zinc superoxide dismutase (antioxidant defense), cytochrome *c. oxidase* (ATP synthesis), dopamine  $\beta$ -monooxygenase (norepinephrine biosynthesis), tyrosinase (dopamine and melanin synthesis), peptidylglycine  $\alpha$ -amidating monooxygenase (neuropeptide processing), ferroxidase I (ie, ceruloplasmin) and ferroxidase II (iron metabolism), hephaestatin (ferroxidase activity), and lysyl oxidase (cross-linkages of elastin and collagen for development of connective tissues).

### *Requirements and sources*

The RDA of copper for adult men and women is 900 µg per day; the median intake of from food in the United States is 1.0 to 1.6 mg per day; and the UL is 10,000 µg per day [111]. Copper is distributed widely in foods. Foods rich in copper include organ meats, seafood, nuts, seeds, wheat bran cereals, whole grain products, and cocoa products (see Table 1). Foods with a low copper content include tea, potatoes, milk, and chicken.

### *Physiology*

Copper absorption occurs primarily in the small intestine [112]. Some absorption may occur in the stomach where the acidic environment facilitates solubilization of copper by dissociating it from copper-containing dietary macromolecules. As dietary copper increases, the fraction absorbed declines and the amount absorbed increases. Absorption occurs by a saturable active transport process at lower levels of dietary copper and by passive diffusion at high levels of dietary copper. The Menkes P-type ATPase (ATP7A) is responsible for copper trafficking to the secretory pathway for efflux from enterocytes and other cells [113]. Absorbed copper is bound to albumin and transported via the portal vein to the liver for uptake by liver parenchymal cells. Copper then is released into the plasma. Ninety-five percent of the copper is bound to ceruloplasmin. The Wilson P-type ATPase (ATP7B) is responsible for copper trafficking to the secretory pathway for ceruloplasmin biosynthesis and for endosome formation before biliary secretion [113]. Biliary copper is adjusted to maintain balance. Urinary excretion normally is low, less than 0.1 mg per day. Excretion of copper into the gastrointestinal tract is the major pathway that regulates copper homeostasis and prevents deficiency or toxicity.

### *Causes of deficiency*

Although rare, acquired copper deficiency is well documented in humans [112,114,115]. Because of copper's ubiquitous distribution and low daily requirement, acquired dietary copper deficiency is rare. Dietary factors may affect copper bioavailability. These include antacids, iron deficiency, ascorbic acid, and amount of copper, molybdenum, or zinc in the diet. Excessive zinc ingestion is a well-recognized cause of copper deficiency [116,117]. The zinc-induced inhibition of copper absorption could be the result of competition for a common transporter or a consequence of induction of metallothionein in enterocytes. Metallothionein has a higher binding affinity for copper than for zinc [118]. Copper is retained within the enterocytes and lost as the intestinal cells are sloughed off. It may occur in malnourished infants [119], nephrotic syndrome [120], and enteropathies associated with malabsorption [121]. Copper deficiency may be a complication of prolonged total parenteral nutrition [122], particularly when copper supplementation in total parenteral nutrition is withheld because of cholestasis [123]. Enteral feeding with inadequate copper also is known to result in copper deficiency [124]. Copper

deficiency after gastric surgery (for peptic ulcer disease or bariatric surgery) increasingly is recognized [125–127]. Not infrequently, the cause of copper deficiency is unknown. Emerging knowledge about copper transport may help clarify the etiology of idiopathic hypocupremia [128].

### *Clinical significance*

The most common neurologic manifestation is that of a myelopathy presenting with a spastic gait and prominent sensory ataxia resulting from dorsal column dysfunction [109,110,117,121,126,127,129,134]. The onset may be subacute. Also reported are central nervous system demyelination [135,136] and optic neuritis [137]. Hyperzincemia may be present even in the absence of exogenous zinc ingestion [109,110,130,131,136]. The precise significance of this is unclear. Copper and Cbl deficiency may coexist [109]. Continued neurologic deterioration in patients who have a history of Cbl deficiency–related myelopathy who have a normal B<sub>12</sub> level on B<sub>12</sub> replacement should be evaluated for copper deficiency. Clinical or electrophysiologic evidence of an associated peripheral neuropathy is common. Neurophysiologic studies show varying degrees of axonal peripheral neuropathy [138]. Abnormalities in somatosensory evoked potential studies indicating central conduction delay is a common finding [138]. Other reported electrophysiologic abnormalities noted in patients who have copper deficiency and neurologic manifestations include prolonged visual evoked potentials [135] and impaired central conduction on transcranial magnetic stimulation [129]. Spinal cord MRI in patients who have copper deficiency myelopathy may show increased signal on T2-weighted images, most commonly in the paramedian cervical cord (Fig. 2A, B) [133]. Follow-up imaging may show resolution of the dorsal column signal change with improvement in serum copper [133].

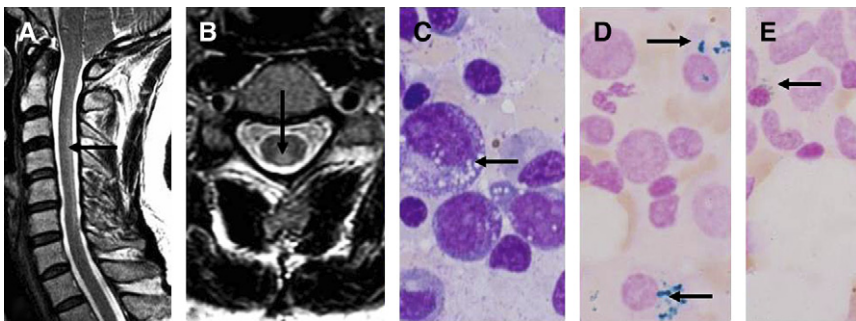


Fig. 2. Sagittal (A) and axial (B) T2-weighted MRI in a patient who had copper deficiency showing increased signal in the paramedian aspect of the dorsal cervical cord. (From Kumar N, Ahlskog JE, Klein CJ, et al. Imaging features of copper deficiency myelopathy: a study of 25 cases. *Neuroradiology* 2006;48:78–83; with permission [panels A–B]). Bone marrow study (C–E) in a patient who had copper deficiency myelopathy showing vacuolated myeloid precursors (C). Also shown is iron staining (D and E) showing iron-containing plasma cells (D) and ringed sideroblasts (E). (Reprinted from Kumar N. Copper deficiency myelopathy (human sway-back). *Mayo Clin Proc* 2006;81(10):1371–84; with permission [panels C–D].)



The hematologic manifestations of acquired copper deficiency include anemia, neutropenia, and a left shift in granulocytic and erythroid maturation with vacuolated precursors, iron-containing plasma cells, and ringed sideroblasts in the bone marrow (see Fig. 2C–E) [116]. Patients may be given a diagnosis of sideroblastic anemia or myelodysplastic syndrome [116,132,137]. Thrombocytopenia and resulting pancytopenia are relatively rare [139]. The neurologic syndrome resulting from acquired copper deficiency may be present without the hematologic manifestations [109,117,140].

### *Investigations*

Laboratory indicators of copper deficiency include serum copper or ceruloplasmin and urinary copper excretion but these parameters are not sensitive to marginal copper status. Changes in serum copper usually parallel the ceruloplasmin concentration. Ceruloplasmin is an acute-phase reactant and the rise in ceruloplasmin probably is responsible for the increase in serum copper seen in a variety of conditions, such as pregnancy, oral contraceptive use, liver disease, malignancy, hematologic disease, myocardial infections, smoking, diabetes, uremia, and various inflammatory and infectious diseases [141]. Copper deficiency could be masked under these conditions. Urinary copper declines only when dietary copper is low [112]. It is suggested that serum copper may be inadequate for assessing total body copper stores and activity of copper enzymes, such as erythrocyte superoxide dismutase and platelet or leukocyte cytochrome c oxidase, may be a better indicator of metabolically active copper stores [142,143]. Red cell superoxide dismutase does not increase with other conditions that increase serum copper.

### *Treatment*

With severe copper deficiency, serum copper and ceruloplasmin fall, often to low levels, and respond promptly to copper supplementation [115]. In patients who have zinc-induced copper deficiency, discontinuing the zinc may suffice and no additional copper supplementation may be required [144]. Despite a suspected absorption defect, oral copper supplementation generally is the preferred route of supplementation. Studies in yeast show that the copper transport pathways are high-affinity pathways, active in conditions of low copper concentration, and increasing the concentration of copper may result in the pathways being bypassed [128]. This may explain why in a majority of patients, normal serum copper levels can be achieved by increasing the amount of copper ingested. In most patients, oral administration, 2 mg of elemental copper a day, seems to suffice. A comparable dose of elemental copper may be given intravenously. At times, prolonged oral therapy may not result in improvement and parenteral therapy may be required. Some have used initial parenteral administration followed by oral therapy [134]. Commonly used copper salts include copper gluconate and copper chloride. A commonly used regimen is administration of elemental

copper, 6 mg a day orally for a week, 4 mg a day for the second week, and 2 mg a day thereafter [110]. Alternatively, elemental copper, 2 mg, may be administered intravenously for 5 days and periodically thereafter. Periodic assessment of serum copper is essential to determine adequacy of replacement and to decide on the appropriate long-term maintenance.

Response of the hematologic parameters (including bone marrow findings) is prompt and often complete [109,110,116,124,131,132,137]. Hematologic recovery may be accompanied by reticulocytosis. Recovery of neurologic signs and symptoms seen in association with copper deficiency is variable. Improvement in neurologic symptoms generally is absent, although progression typically is halted [109,110,131,136]. Improvement when present is slight, often subjective, and preferentially involves sensory symptoms. Early recognition and prompt treatment may prevent significant neurologic morbidity.

### *Vitamin E*

In humans,  $\alpha$ -tocopherol is the active form of vitamin E. The terms, vitamin E and  $\alpha$ -tocopherol, are used interchangeably. Vitamin E is the collective name for molecules with the antioxidant activity of  $\alpha$ -tocopherol. The chemically synthesized  $\alpha$ -tocopherol is not identical to the naturally occurring form. Vitamin E supplements contain esters of  $\alpha$ -tocopherol, such as  $\alpha$ -tocopheryl acetate, succinate, or nicotinate. The esters prevent vitamin E oxidation and prolong its shelf life. These esters are hydrolyzed readily in the gut and absorbed in the unesterified form [145]. The exception to this is in patients who have malabsorption.

### *Function*

Vitamin E serves as an antioxidant and free radical scavenger. It prevents the formation of toxic free radical products, seems to protect cellular membranes from oxidative stress, and inhibits the peroxidation of polyunsaturated fatty acids of membrane phospholipids.

### *Requirements and sources*

The RDA for men and women is 15 mg (35  $\mu$ mol) per day of  $\alpha$ -tocopherol [146]. The UL for adults is set at 1000 mg (2325  $\mu$ mol) per day. Rich sources of vitamin E include vegetable oils, leafy vegetables, fruits, meats, nuts, and unprocessed cereal grains (see Table 1). The bioavailability of vitamin E is dependent on the fat content of food [147]. Vitamin E bioavailability from fortified breakfast cereal is greater than that from encapsulated supplements [148].

### *Physiology*

The overall efficiency of vitamin E absorption is less than 50%. Vitamin E is absorbed from the gastrointestinal tract by a nonenergy-requiring

diffusion mechanism. Vitamin E absorption requires bile acids, fatty acids, and monoglycerides for micelle formation. After uptake by enterocytes, all forms of dietary vitamin E are incorporated into chylomicrons. During chylomicron catabolism in plasma, vitamin E is transferred to circulating lipoproteins, which deliver it to tissues. The chylomicron remnants are taken up by the liver, which selects the  $\alpha$ -tocopherol form for secretion in very low-density lipoproteins (VLDLs). In the liver, the  $\alpha$ -tocopherol transfer protein (TTP) incorporates  $\alpha$ -tocopherol into VLDLs, which are secreted into plasma. Lipolysis of VLDL results in enrichment of circulating lipoproteins with RRR- $\alpha$ -tocopherol, which is delivered to peripheral tissue. Most ingested vitamin E is eliminated by the fecal route. The majority of vitamin E in the human body is localized in the adipose tissue. Analysis of adipose tissue  $\alpha$ -tocopherol content provides a useful estimate of long-term vitamin E intake. More than 2 years is required for adipose tissue  $\alpha$ -/ $\gamma$ -tocopherol ratios to reach new steady-state levels in response to changes in dietary intake [149].

#### *Causes of deficiency*

Because of the ubiquitous distribution of tocopherols in foods, vitamin E deficiency virtually is never the consequence of a dietary inadequacy [150]. Vitamin E absorption requires biliary and pancreatic secretions. Hence, vitamin E deficiency is seen with chronic cholestasis and pancreatic insufficiency. Vitamin E deficiency also is seen with other conditions associated with malabsorption, such as celiac disease, Crohn's disease, cystic fibrosis, blind loop syndrome, and extensive small bowel resection. It is suggested that the vitamin E supplementation in total parenteral nutrition may be inadequate to maintain vitamin E stores [151].

Vitamin E deficiency may be seen resulting from genetic defects in  $\alpha$ -TTP (ataxia with vitamin E deficiency [AVED]), in apolipoprotein B (homozygous hypobetalipoproteinemia), or in the microsomal triglyceride transfer protein (abetalipoproteinemia). An additional cause is defect in chylomicron synthesis and secretion (chylomicron retention disease). AVED is an autosomal recessive disorder in which isolated vitamin E deficiency occurs without generalized fat malabsorption or gastrointestinal disease. Mutations in the  $\alpha$ -TTP gene on chromosome 8q13 are responsible [152,153]. The defect lies in impaired incorporation of vitamin E into hepatic lipoproteins for tissue delivery [154]. Patients who have hypobetalipoproteinemia or abetalipoproteinemia have an inability to secrete chylomicrons or other apolipoprotein B-containing lipoproteins, specifically VLDLs and low-density lipoproteins (LDLs) [150]. Homozygous hypobetalipoproteinemia patients have a defect in the apoB gene. ApoB-containing lipoproteins secreted into the circulation turn over rapidly. Abetalipoproteinemia patients have a genetic defect in microsomal triglyceride transfer protein, which prevents normal lipidation of apoB, and the secretion of apoB-containing lipoproteins is nonexistent. In

chylomicron retention disease, there is impaired assembly and secretion of chylomicrons and chylomicron retention in the intestinal mucosa is present [155].

### *Clinical significance*

The neurologic manifestations of vitamin E deficiency include a spinocerebellar syndrome with variable peripheral nerve involvement [156–158]. The phenotype is similar to that of Friedreich's ataxia. The clinical features include ataxia, hyporeflexia, and proprioceptive and vibratory loss. Cutaneous sensations may be affected to a lesser degree. Findings suggestive of cerebellar involvement include dysarthria, tremor, and nystagmus. Ophthalmoplegia, ptosis, and pigmentary retinopathy are reported. An associated myopathy may be present [159,160]. It is rare for vitamin E deficiency to present as an isolated neuropathy [161]. Somatosensory evoked potential studies may show evidence of central delay and nerve conduction studies may show evidence of an axonal neuropathy [162,163]. Spinal MRI in patients who have vitamin E deficiency-related myeloneuropathy may show increased signal in the cervical cord dorsal column [164]. In children who have cholestatic liver disease, neurologic abnormalities appear as early as the second year of life. In AVED, hypolipoproteinemia, and abetalipoproteinemia, neurologic manifestations start by the first or second decade. Development of neurologic symptoms in adults who have acquired fat malabsorption syndromes takes decades.

The neuropathy associated with vitamin E deficiency preferentially involves centrally directed fibers of large myelinated neurons. Loss of myelinated nerve fibers may be seen on sural nerve biopsy before onset of neurologic signs and symptoms [165]. Reduction of peripheral nerve tocopherol may precede the axonal degeneration [166]. Swollen dystrophic axons (spheroids) are seen in the gracile and cuneate nuclei of the brainstem. Lipofuscin may accumulate in the dorsal sensory neurons and peripheral Schwann's cell cytoplasm. The peripheral nerves, posterior columns, and sensory roots show degeneration of large myelinated fibers.

### *Investigations*

Serum vitamin E levels are dependent on the concentrations of serum lipids, cholesterol, and VLDL. Hyperlipidemia or hypolipidemia independently can increase or decrease serum vitamin E without reflecting similar alterations in tissue levels of the vitamin [167]. Effective serum  $\alpha$ -tocopherol concentrations are calculated by dividing the serum  $\alpha$ -tocopherol by the sum of serum cholesterol and triglycerides [168,169]. Serum  $\alpha$ -tocopherol concentrations may be in the normal range in patients who have  $\alpha$ -tocopherol deficiency resulting from cholestatic liver disease, a disorder that also is associated with high lipid levels [170]. In patients who have neurologic manifestations resulting from vitamin E deficiency, the serum vitamin E levels frequently are undetectable. Additional markers of fat malabsorption,

such as increased stool fat and decreased serum carotene levels, may be present.

### *Management*

In patients who have vitamin E deficiency resulting from cholestasis and malabsorption, large oral dosages (up to 200 IU/kg per day) [54] or intramuscular administration of dl- $\alpha$ -tocopherol (0.8 to 2.0 IU/kg per day) are used [171]. In patients who have cystic fibrosis and who are receiving oral pancreatic enzyme therapy, dosages of 5 to 10 IU/kg per day are sufficient [54]. With cholestatic liver disease, treatment with fat-soluble vitamin E may be ineffective because of fat malabsorption. A water-miscible product, d- $\alpha$ -tocopherol glycol 1000 succinate, is shown to raise plasma and tissue levels of  $\alpha$ -tocopherol to normal [172]. The target should be a normal ratio of  $\alpha$ -tocopherol to total lipids. Because of limited absorption, patients who have abetalipoproteinemia may need high doses [173]. Plasma  $\alpha$ -tocopherol levels are not affected significantly but measurement of adipose tissue levels show the increased concentration [174]. In AVED, supplementation with vitamin E (600 IU twice daily) raises plasma concentration to normal and is accompanied by beneficial effects on neurologic function. An empiric approach is to start with a lower dose, increase it gradually, and, based on the clinical and laboratory responses, consider a higher dose or parenteral formulation. Supplements of bile salts may be of value in some patients.

### *Thiamine*

Beriberi has the distinction of being the first-identified human nutritional deficiency disorder. During the industrial revolution of the nineteenth century, introduction of milled rice was accompanied by epidemics of beriberi [54]. A connection between the consumption of polished rice and beriberi was shown in the latter part of the nineteenth century. In the 1950s, universal enrichment of rice, grains, and flour products with thiamine was successful in achieving significant worldwide control. The terms vitamin B<sub>1</sub> (B<sub>1</sub>) and thiamine are used interchangeably.

### *Function*

Thiamine functions as a coenzyme in the metabolism of carbohydrates and branched-chain amino acids [175]. After cellular uptake, thiamine is phosphorylated into thiamine diphosphate (TDP), the metabolically active form that is involved in several enzyme systems. TDP is a cofactor for the pyruvate dehydrogenase complex,  $\alpha$ -ketoglutarate dehydrogenase ( $\alpha$ -KGDH), and transketolase (TK). Pyruvate dehydrogenase and  $\alpha$ -KGDH are involved in the oxidative decarboxylation of  $\alpha$ -ketoacids, such as pyruvate and  $\alpha$ -ketoglutarate, to acetyl-CoA and succinate, respectively. TK transfers activated aldehydes in the hexose monophosphate shunt in the generation of nicotinamide adenine dinucleotide phosphate for reductive

biosynthesis. Thiamine deficiency results in reduced synthesis of high-energy phosphates and lactate accumulation. It is suggested that decreased  $\alpha$ -KGDH, rather than decreased pyruvate dehydrogenase complex, constitutes the “biochemical lesion” in thiamine deficiency encephalopathy [176].  $\alpha$ -KGDH is the rate-limiting enzyme in the tricarboxylic acid cycle. Decreased activity of  $\alpha$ -KGDH results in decreased synthesis of amino acid neurotransmitters, such as glutamate and  $\gamma$ -aminobutyric acid [177]. TDP may be phosphorylated further to thiamine triphosphate, which may activate high-conductance chloride channels and have a role in regulating cholinergic neurotransmission because of its regulatory properties on proteins involved in the clustering of acetylcholine receptors [178].

#### *Requirements and sources*

The RDA for adults is 1.2 mg per day for men and 1.1 mg per day for women [175,179]. The median intake of thiamine from food in the United States is approximately 2 mg per day. The highest concentrations of thiamine are found in yeast and in the pericarp of grain. Most cereals and breads are fortified with thiamine. Organ meats are a good source of thiamine. Dairy products, seafood, and fruits are poor sources. Thiamine does not occur in fats and oils. Prolonged cooking of food, baking of bread, and pasteurization of milk all are potential causes of thiamine loss.

#### *Physiology*

At low concentrations, thiamine is absorbed in jejunum and ileum by active transport [175]. At higher concentration absorption takes place by passive diffusion. After gastrointestinal uptake, thiamine is transported by portal blood to the liver. The areas most vulnerable to thiamine deficiency are those with the highest turnover rates, such as the caudal brain and cerebellum [180]. The half-life of thiamine is only 10 to 14 days [54]. Because of the rapid turnover rates and absence of significant storage amounts, a continuous dietary supply of thiamine is necessary. A thiamine-deficient diet may result in manifestations of thiamine deficiency in just 18 days [181].

#### *Causes of deficiency*

Causes of thiamine deficiency include decreased intake, decreased absorption, defective transport, increased losses, and enhanced requirements [162,175,179,182]. Thiamine deficiency may be seen with persistent vomiting, anorexia nervosa, dieting, malnutrition, severe gastrointestinal or liver disease, gastrointestinal surgery (including bariatric surgery), and AIDS. Thiamine deficiency in alcoholism results from inadequate dietary intake, reduced gastrointestinal absorption, and reduced liver thiamine stores. Additionally, alcohol inhibits transport of thiamine in the gastrointestinal system and blocks phosphorylation of thiamine to TDP [183]. Thiamine requirement is dependent on the body's metabolic rate with the requirement being the greatest during periods of high metabolic demand or high glucose

intake. Symptoms of thiamine deficiency may be seen in high-risk patients during periods of vigorous exercise and high carbohydrate intake as with intravenous glucose administration and refeeding. In patients who have a marginal nutritional status, increased metabolic demand, as is seen in hyperthyroidism, malignancy, and systemic infections, may precipitate symptoms. Pregnant and lactating women have increased thiamine requirements and infant beriberi may be seen in infants who are breastfed by thiamine-deficient asymptomatic mothers. Maternal thiamine deficiency may result from eating a staple diet of polished rice with foods containing thiaminase or antithiamine compounds.

### *Clinical significance*

The best-characterized human neurologic disorders related to thiamine deficiency are beriberi, Wernicke encephalopathy (WE), and Korsakoff's syndrome (KS). The three forms of beriberi are dry beriberi, wet beriberi, and infantile beriberi [175]. Dry beriberi is characterized by a sensorimotor, distal, axonal peripheral neuropathy often associated with calf cramps, muscle tenderness, and burning feet [184,185]. Autonomic neuropathy may be present. A rapid progression of the neuropathy may mimic Guillain-Barré syndrome (GBS) [185]. Classic descriptions report hoarseness and tongue and facial weakness [54]. Pathologic studies of beriberi in nonalcoholics are limited [163,184,186]. Axonal degeneration is noted in distal nerves. Chromatolysis of dorsal root ganglion (DRG) neurons and anterior horn cell (AHC) neurons may be seen resulting from axonal degeneration. Segmental demyelination is rare and likely secondary to axonal degeneration. Severe cases may have involvement of the vagus and phrenic nerves. Degeneration of the posterior columns may be present. Pedal edema may be seen resulting from coexisting wet beriberi. Wet beriberi is associated with a high-output congestive heart failure with peripheral neuropathy. This distinction is of limited significance, because the wet form may be converted to the dry form after diuresis. Shoshin beriberi is the name given to a fulminant form that presents with tachycardia and circulatory collapse. Acute quadriplegia resulting from central-pontine myelinolysis is reported in Shoshin beriberi [187]. Although called infantile beriberi, it bears little resemblance to the adult form. Infantile beriberi is seen between 2 and 6 months of age and may present with the cardiac, aphonic, or pseudomeningitic forms [175].

The clinical features of WE include a subacute onset of ocular palsies, nystagmus, gait ataxia, and confusion [162,188]. Involvement of the hypothalamic and brainstem autonomic pathways may be associated with hypothermia and orthostatic hypotension. Skin changes, tongue redness, features of liver disease, and truncal ataxia may be present. More than 80% of patients may have an associated peripheral neuropathy. Reliance on the described triad of ophthalmoplegia, ataxia, and confusion and not recognizing thiamine deficiency in nonalcoholics may result in missing the diagnosis [182]. Typical MRI findings include increased T2 or proton

density or diffusion-weighted imaging signal around the third ventricle, periaqueductal midbrain, dorsomedial thalami, and mammillary bodies [189]. Rarely, symmetric cortical involvement with contrast enhancement may occur [190]. The signal abnormalities resolve with treatment but shrunken mammillary bodies may persist as sequelae. The frequency of WE in various autopsy studies ranges from 0.8% to 2.8%, far in excess from what is expected from clinical studies [182,191,192]. In one series, only 20% of the cases were diagnosed during life [192]. Sudden death may occur and is related to hemorrhagic brainstem lesions [193]. In some autopsy-confirmed cases of WE, the only clinical manifestation was that of psychomotor retardation [194]. KS is an amnesic-confabulatory syndrome that follows WE and emerges as ocular manifestations and encephalopathy subside. Rarely, KS may be present without WE or may be present at the time of diagnosis of WE. Neuropathologic findings in WE include symmetric lesions of the periventricular regions of the thalamus and hypothalamus, nuclei at the level of the third and fourth ventricle, and superior cerebellar vermis [195,196]. Involvement of the mammillary bodies is characteristic. Histology shows necrosis, neuronal loss, edema, prominent capillaries with endothelial proliferation, and hemorrhagic foci. In the late stages, there is cell loss with astrocytic and microglial proliferation. Patients who have KS also have involvement of the dorsal median nucleus of the thalamus.

### *Investigations*

Urinary thiamine excretion and serum thiamine levels may be decreased but do not reflect tissue concentrations accurately and are not reliable indicators of thiamine status. The preferred tests are the erythrocyte transketolase activation assay or measurement of TDP in RBC hemolysates using high-performance liquid chromatography [197,198]. The erythrocyte transketolase activation assay is an assay of functional status and is based on measurement of transketolase activity in hemolysates of RBCs in the absence of (and in the presence of) added excess cofactor (TDP). Because these laboratory abnormalities normalize quickly, a blood sample should be drawn before initiation of treatment.

### *Management*

Intravenous glucose infusion in patients who have thiamine deficiency may consume the available thiamine and precipitate an acute WE. At-risk patients should receive parenteral thiamine before administration of glucose or parenteral nutrition. Patients suspected of having beriberi or WE should receive parenteral thiamine promptly. The recommended dose of thiamine in beriberi is 100 mg intravenously followed by 100 mg intramuscularly daily for 5 days and permanent oral maintenance [196]. At times, high-dosage thiamine (100 mg intravenously every 8 hours) may be required [190]. The parenteral form is used when there is doubt about adequate gastrointestinal absorption. Oral maintenance, 50- to 100-mg thiamine, is used. A lipophilic



form of thiamine (benfotiamine) is used in chronic alcoholism-related neuropathy, 320 mg per day for 4 weeks followed by 120 mg per day for an additional 3 weeks [199].

In wet beriberi, a rapid improvement is seen with clearing of symptoms within 24 hours to 1 week [184]. Improvement in motor and sensory symptoms takes weeks or months [184,185]. Response in WE is variable. Apathy and lethargy improve over days or weeks. Even with thiamine treatment, the mortality is 10% to 20%. As the global confusional state recedes, some patients are left with KS: a disorder of impaired memory and learning. Ophthalmoplegia improves rapidly (ie, ocular signs improve in a few hours) [200]. A fine horizontal nystagmus may persist in 60% of patients. Improvement in gait ataxia and memory is variable and often delayed [201].

### *Niacin*

#### *Function*

Niacin in humans is an end product of tryptophan metabolism. It is converted into nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate. Both are coenzymes important in carbohydrate metabolism.

#### *Requirements and sources*

Dietary requirements of niacin consider the tryptophan and niacin content [202]. The RDA for adults is 16 mg per day of niacin equivalent for men and 14 mg per day of niacin equivalent for women. One mg of niacin equivalent equals 51 mg of niacin or 60 mg of tryptophan. The median intake of preformed niacin is approximately 28 mg for men and 18 mg for women. The UL for niacin in adults is 35 mg per day and is based on flushing as the critical side effect. In most developed countries, niacin commonly is added as an enrichment to bread. Most niacin intake comes from meat, fish, poultry, enriched and whole grain bread and bread products, and fortified ready-to-eat cereals (see Table 1).

#### *Physiology*

Niacin and its amide are absorbed through the intestinal mucosa by simple diffusion [203]. Fifteen percent to 30% of niacin is protein bound. Complexed and free niacin are taken up by tissue. Niacin is retained by metabolic trapping to nicotinamide adenine dinucleotide. Niacin and nicotinamide are metabolized by separate pathways. The major metabolite of niacin is nicotinic acid and the major metabolite of nicotinamide is N<sup>1</sup>-methylnicotinamide and its oxidized products, 2- and 4-pyridones.

#### *Causes of deficiency*

Pellagra is rare in developed countries [203]. Niacin deficiency is seen predominantly in populations dependent on corn as the primary carbohydrate

source. Corn lacks niacin and tryptophan. Nonendemic pellagra rarely is seen with alcoholism and malabsorption. Pellagra may be seen in the carcinoma syndrome, because tryptophan is converted to serotonin instead of being used in niacin synthesis. Biotransformation of tryptophan to nicotinic acid requires several vitamins and minerals, such as B<sub>2</sub>, B<sub>6</sub>, iron, and copper. Because tryptophan is necessary for niacin synthesis, B<sub>6</sub> deficiency can result in secondary niacin deficiency. Diets deficient in these nutrients can predispose to pellagra. INH depletes B<sub>6</sub> and can trigger pellagra. Excess of neutral amino acids in the diet, such as leucine, can compete with tryptophan for uptake and predispose to niacin deficiency by impairing its synthesis from tryptophan. Hartnup syndrome is an autosomal recessive disorder characterized by impaired synthesis of niacin from tryptophan and results in pellagra-like symptoms.

### *Clinical significance*

Pellagra affects the gastrointestinal tract, skin, and nervous system [202,203]. The classical hallmarks of pellagra are alluded to by mnemonic dermatitis, diarrhea, and dementia. Skin changes include a reddish-brown hyperkeratotic rash, which has a predilection for the face, chest, and dorsum of the hands and feet. Gastrointestinal manifestations include anorexia, abdominal pain, diarrhea, and stomatitis. The neurologic syndrome resulting from niacin deficiency is not well characterized. Reported cases are confounded by the presence of coexisting nutrient deficiencies, as is common in alcoholics. Reported manifestations include a confusional state which may progress to coma, spasticity, and myoclonus. Unexplained progressive encephalopathy in alcoholics that is not responsive to thiamine should raise the possibility of pellagra. The peripheral neuropathy seen in pellagra is indistinguishable from the peripheral neuropathy seen with thiamine deficiency and may be the result of deficiencies of other vitamins, likely B-group, because it does not respond to niacin supplementation alone [54,202,204,205].

### *Investigations*

The most reliable and sensitive measures of niacin status are urinary excretion of the methylated metabolites, N<sup>1</sup>-methylnicotinamide and its 2-pyridone derivative (N<sup>1</sup>-methyl-2-pyridone-5-carboxamide) [202]. There are no sensitive and specific blood measures of niacin status. It is suggested that measures of erythrocyte nicotinamide adenine dinucleotide and plasma metabolites may serve as markers of niacin status.

### *Management*

Oral nicotinic acid (50 mg 3 times a day) or parenteral doses (25 mg 3 times a day) are used for treatment of symptomatic patients [162]. Nicotinamide has comparable therapeutic efficacy in pellagra. Advanced stages of pellagra can be cured with intramuscular nicotinamide (50 to 100 mg 3 times a day for 3 to 4 days followed by similar quantities orally) [203].

## *Vitamin B<sub>6</sub>*

The term pyridoxine generally is used interchangeably with B<sub>6</sub>. Pyridoxal and pyridoxamine are two other naturally occurring compounds that have comparable biologic activity. All three compounds are converted readily to pyridoxal phosphate (PLP).

### *Function*

B<sub>6</sub> is essential for cellular functions and growth because of its involvement in important metabolic reactions [206]. PLP serves as a coenzyme in many reactions involved in the metabolism of amino acids, lipids, nucleic acid, and one-carbon units, in the pathways of gluconeogenesis, and in neurotransmitter and heme biosynthesis. The interconversion and metabolism of B<sub>6</sub> is dependent on riboflavin, niacin, and zinc. Niacin, carnitine, and folate require B<sub>6</sub> for their metabolism.

### *Requirements and sources*

The RDA for young adults is 1.3 mg; the median intake of B<sub>6</sub> from food in the United States is approximately 2 mg per day for men and 1.4 mg per day for women; and the UL for adults is 100 mg per day [207]. Meat, fish, eggs, soybeans, nuts, and dairy products are rich in B<sub>6</sub>. Starchy vegetables, noncitrus foods, and whole grain cereal products are additional sources. Milling of grain, cooking, and thermal processing can result in significant losses (see Table 1).

### *Physiology*

Humans and other mammals cannot synthesize B<sub>6</sub> and, thus, must obtain this micronutrient from exogenous sources via intestinal absorption [206]. B<sub>6</sub> uptake by intestinal epithelial cells occurs by a carrier-mediated, pH-dependent mechanism that has saturable and nonsaturable components [208]. B<sub>6</sub> (mostly in the form of pyridoxal) enters the portal circulation and is transported bound to albumin in plasma and hemoglobin in RBCs. Absorbed dietary pyridoxine, pyridoxal, and pyridoxamine are phosphorylated for metabolic trapping. Tissue uptake of B<sub>6</sub> from circulation requires dephosphorylation. PLP and pyridoxal are the main circulating forms of B<sub>6</sub>.

### *Causes of deficiency*

Most diets are adequate in B<sub>6</sub> [206]. Its deficiency is seen with B<sub>6</sub> antagonists, such as INH, cycloserine, hydralazine, and penicillamine [209]. Alcohol intake antagonizes B<sub>6</sub> status through production of acetaldehyde, which competes with PLP for binding sites of PLP-dependent enzymes [210]. Individuals at risk of developing B<sub>6</sub> deficiency include pregnant and lactating women and elderly individuals. Plasma PLP levels are reduced in celiac disease, inflammatory bowel disease, and renal disease.

### *Clinical significance*

Dietary deficiency of pyridoxine or congenital dependency on pyridoxine may manifest as infantile seizures. Adults are more tolerant of pyridoxine deficiency. Even with low levels, symptoms are rare. Chronic B<sub>6</sub> deficiency results in a microcytic hypochromic anemia. A form of sideroblastic anemia can be treated with pyridoxine supplementation [211]. Neuropathic symptoms in association with pellagra-like dermatitis are described in association with use of the B<sub>6</sub> antagonist desoxypyridoxine [212]. INH use is associated with painful distal paresthesias that can progress rapidly to limb weakness and sensory ataxia [213]. INH-associated neuropathy is dose related. Up to 50% of slow activators may develop a peripheral neuropathy when treated with INH [162]. Axonal degeneration and regeneration affect myelinated and unmyelinated fibers [214]. Excess consumption of B<sub>6</sub> is associated with a pure sensory peripheral neuropathy or ganglionopathy [215,216]. It is characterized by sensory ataxia, areflexia, impaired cutaneous and deep sensations, and positive Romberg's sign. The site of lesion most likely is the dorsal root ganglia. The presence of Lhermitte's sign in some patients suggests involvement of the spinal cord also [54]. The risk of developing this decreases at dosages less than 100 mg per day [207].

### *Investigations*

Microbiologic assays measure total B<sub>6</sub> [207]. High-performance liquid chromatography methods allow estimation of the various forms of B<sub>6</sub>. B<sub>6</sub> status can be assessed by measuring its levels in the blood or urine. The most commonly used measure is plasma PLP. A plasma PLP concentration of over 30 nmol/L is considered to indicate adequate status [217]. A concentration greater than 20 nmol/L is considered a more conservative cut-off value [207]. Functional indicators of B<sub>6</sub> status are based on PLP-dependent reactions. The methionine load test is used as a functional indicator of B<sub>6</sub> status. B<sub>6</sub> deficiency results in a higher postmethionine-load Hcy concentration resulting from impairment of the transsulfuration pathway. B<sub>6</sub> deficiency has little effect on fasting plasma Hcy concentration.

### *Management*

INH-induced neuropathy is reversible by drug discontinuation or B<sub>6</sub> supplementation [216]. B<sub>6</sub> may be supplemented, 50 to 100 mg per day, to prevent development of the neuropathy. In an isolated report, peripheral neuropathy symptoms associated with hemodialysis were ameliorated with supplemental pyridoxine (250 mg per day) [218]. The neuropathy resulting from B<sub>6</sub> toxicity may reverse once the supplementation is withdrawn. Patients who have congenital dependency on pyridoxine develop symptoms despite a normal dietary supplementation of pyridoxine. High doses of B<sub>6</sub> are required and even after years and seizures reappear within days of B<sub>6</sub> withdrawal.

## **Bariatric surgery**

### *Types of surgeries*

The epidemic of obesity and limited efficacy of medical treatments have led to increasing use of bariatric surgical procedures for the treatment of medically complicated obesity. Several different surgical procedures are used [219–222]. The earliest surgical treatments for obesity were malabsorptive procedures, such as the jejunoileal shunt and jejunoileal bypass. These operations were abandoned because of severe metabolic derangements and associated malnutrition, which required revision surgeries in many patients. Gastric restriction procedures used have included gastric partitioning, gastropasty, and vertical banded gastropasty. These procedures separate the stomach into a small pouch that empties into the greater stomach through a narrow channel, thus restricting the quantity and rate of food ingested without affecting digestion or absorption. The weight loss after these procedures, however, has not been found to be sustained either because the surgical technique was not durable or because patients developed maladaptive eating behaviors that circumvented the restriction. Gastric bypass procedures result in weight loss by a more physiologic mechanism. They restrict the volume ingested, cause partial malabsorption of fat, and induce a dumping syndrome with a high-carbohydrate meal, thus leading to sustained weight loss. The Roux-en-Y gastric bypass often is the procedure of choice and often is done laparoscopically. Recently, a laparoscopically placed adjustable gastric band has gained popularity. This procedure differs from previously performed restrictive procedures in that there is adjustment of the band in response to rate of weight loss and absence of an enterotomy or permanent change to the anatomy. Additional procedures that result in greater degrees of maldigestion and malabsorption combined with partial gastric resection are advocated for the treatment of patients who have “super” obesity (body mass index over 50 kg/m<sup>2</sup>). These include distal gastric bypass, biliopancreatic diversion with duodenal switch modification, partial biliopancreatic bypass, and very, very long limb Roux-en-Y gastric bypass.

### *Vitamin deficiencies*

B<sub>12</sub> deficiency is the most common nutritional deficiency noted after bariatric surgery [16,223–228]. A low B<sub>12</sub> level has been noted in 70% of patients undergoing gastric bypass surgery and B<sub>12</sub> deficiency in nearly 40% [227]. It may result from inadequate intake, impaired hydrolysis of B<sub>12</sub> from dietary protein, or abnormal IF and B<sub>12</sub> interaction [16,224–226]. B<sub>1</sub> deficiency frequently is seen [223,229]. B<sub>1</sub> deficiency after bariatric surgery is the result of intractable vomiting, rapid weight loss, and inadequate vitamin repletion and associated neurologic complications due to B<sub>1</sub> deficiency, such as WE, and peripheral neuropathy may be seen as early as 6 weeks after gastric

surgery [230,231]. Also recognized are deficiencies in other vitamins, such as folate [16,223,227] and vitamin D [232–234].

### *Mineral deficiencies*

The most commonly identified mineral that is deficient after bariatric surgery is iron, seen in nearly half of patients [16,225,227]. Aches and pains occurring after 1 year of bypass surgery has been called “bypass bone disease” and is believed the result of bone demineralization from impaired calcium absorption, often with concurrent vitamin D deficiency [225]. Other identified minerals that are deficient include copper [125–127] and potassium [16].

### *Abnormal fat and carbohydrate metabolism*

Reports of neurologic disorders after bariatric surgery resulting from rapid fat metabolism are of uncertain significance [235,236]. Recurrent spells of encephalopathy with lactic acidosis after high-carbohydrate diets are reported after jejunioileostomy [237]. The elevated D-lactate is believed to result from fermentation of carbohydrates in the colon or bypasses segment of the small bowel.

### *Types and frequency of neurologic complications*

Neurologic complications after gastrectomy for ulcer disease or bariatric surgery are well recognized but frequently the cause is not determined [229,235,236,238–242]. Neurologic complications may be noted in 5% to 16% of patients undergoing surgery for obesity [229,240]. Specific vitamin and mineral deficiencies are identified after bariatric surgery. Central and peripheral neurologic complications often are multifactorial in etiology.

A recent review of reported cases of neurologic complications of bariatric surgery identified 96 patients [243]. A peripheral neuropathy was identified in 60 and encephalopathy in 30. Among the patients who had peripheral neuropathy, 40 had a polyneuropathy and 18 had a mononeuropathy. Lumbar plexopathy or radiculopathy were rare and each seen in one case only. Forty of the polyneuropathy cases were attributed to thiamine deficiency. Wernicke-Korsakoff syndrome or WE was identified in 27 cases, optic nerve involvement was identified in eight, a myelopathy in two, and primary muscle disease in seven.

In a controlled retrospective study of peripheral neuropathy after bariatric surgery, peripheral neuropathy developed in 71 of 435 patients: sensory-predominant polyneuropathy in 27, mononeuropathy in 39, and radiculoplexopathy in five [240]. A rapid progression of the peripheral neuropathy may mimic GBS [244]. The neuropathy after bariatric surgery may mimic a sensory ganglionopathy [235].

### *Risk factors for neurologic complications after bariatric surgery*

Risk factors for neurologic complications include rate and absolute amount of weight loss, prolonged gastrointestinal symptoms, not attending a nutritional clinic after bariatric surgery, less vitamin and mineral supplementation, reduced serum albumin and transferrin, postoperative surgical complications requiring hospitalization, and having jejunioileal bypass [240]. In a series of 23 patients who had neurologic complications associated with bariatric surgery, protracted vomiting was noted in all affected patients [229].

### *Management*

Prevention, diagnosis, and treatment of these disorders are necessary parts of lifelong care after bariatric surgery [245]. Long-term follow-up with dietary counseling is important. All bariatric surgery patients should have 6-month follow-up laboratory studies that include complete blood count, serum iron, iron-binding capacity, B<sub>12</sub>, calcium, and alkaline phosphatase [225,246]. It is unclear which patients may develop copper deficiency after gastric surgery and if routine screening and supplementation should be considered. Oral supplementation containing the RDA for micronutrients can prevent abnormal blood indicators of most vitamins and minerals but are insufficient to maintain normal plasma B<sub>12</sub> levels in approximately 30% of gastric bypass patients [228]. Multivitamins with mineral supplements may not prevent development of iron deficiency or subsequent anemia [247]. Indefinite use of the following daily supplements is suggested [225]: a multivitamin-mineral combination containing B<sub>12</sub>, folic acid, vitamin D, and iron; an additional iron tablet, preferably with vitamin C; an additional B<sub>12</sub> tablet of 50 to 100 µg; and a calcium supplement equivalent to 1 g of elemental calcium.

### **Other considerations**

#### *Alcoholic neuropathy*

The direct role of alcohol in the pathogenesis of neuropathy related to chronic alcoholism has been a matter of debate [248]. The peripheral neuropathy associated with alcoholism generally is considered nutritional in origin [249]. Even though a specific nutrient often is not implicated, deficiencies in B-group vitamins, in particular thiamine, are believed the main cause. Alcohol displaces food in the diet, increases the demand for B-group vitamins, causes decreased absorption of lipid soluble vitamins resulting from pancreatic dysfunction, and possibly has a role as a secondary neurotoxin [196]. A slowly progressive, distally predominant, painful, symmetric, sensorimotor, axonal neuropathy is the typical finding [250,251]. Midline cerebellar degeneration may be an additional cause of gait ataxia.

Some patients may have a subacute presentation that mimics GBS [252]. Trophic skin changes and a distal neuropathic arthropathy may be present. It is likely that in at least a subgroup of patients the direct toxic effects of alcohol are responsible [250,251,253,254]. These patients may have a painful sensory neuropathy with autonomic involvement [251,253]. The presence of a vagal neuropathy may be associated with a higher mortality [255].

### *Tropical neuropathies and myeloneuropathies*

There are many descriptions of neuropathies and myeloneuropathies from the tropics for which a nutritional cause has been postulated [196]. “Burning feet” were described first in 1826 by a British medical officer in the Indian army. Conditions described in the late nineteenth century included Strachan’s Jamaican neuropathy, Cuban retrobulbar optic neuropathy, and the Cuban “amblyopia of the blockade.” Similar disorders were reported among prisoners of war in tropical and subtropical regions during World War II and in victims of the Spanish Civil War. The term “happy feet” was used to describe similar symptoms in prisoners of war in camps in the tropics in World War II. Restoration of a normal diet and vitamin supplementation improved symptoms but often some deficits remained. Lack of multiple dietary components, in particular B-group vitamins, likely was the cause.

More recently, from 1991 to 1994, an epidemic in Cuba affected more than 50,000 persons and caused optic neuropathy, sensorineural deafness, dorsolateral myelopathy, and axonal sensory neuropathy [256,257]. Identified risk factors included irregular diet, weight loss, smoking, alcohol, and excessive sugar consumption [257]. Patients responded to B-group vitamins and folic acid. Overt malnutrition was not present.

The term, tropical myeloneuropathies, had been used to describe two major groups of conditions: patients who have prominent sensory ataxia (tropical ataxic neuropathy) and those who have prominent spastic paraparesis (tropical spastic paraparesis [TSP]). Human T-lymphotropic virus (HTLV)-I myelitis had been called TSP in many equatorial regions and HTLV-I-associated myelopathy (HAM) in Japan. HAM and TSP now are believed to be identical syndromes [258]. HTLV-II also is recognized to cause a chronic myelopathy that resembles TSP [259] or tropical ataxic neuropathy [260].

### *Organophosphate toxicity*

Triorthocresyl phosphate is an organophosphate compound that has been used as an adulterant. In 1930, thousands of Americans developed neurologic deficits after consuming a popular illicit alcoholic beverage (Jamaica ginger extract or “jake”) that had been adulterated with triorthocresyl phosphate [261]. Jamaican ginger paralysis was associated with peripheral neuropathy and spastic paraparesis.



An outbreak of acute polyneuropathy occurred in a tea plantation in Sri Lanka during 1977 to 1978 affecting adolescent girls [262]. The cause was attributed to tricresyl phosphate, which was present as a contaminant in a type of cooking oil that, because of its presumed nutritive value, was given in large amounts to pubertal girls in the postmenarche period. Contamination likely occurred when the oil was transported in containers previously used to store mineral oils. Sensory abnormalities were minimal. A distal axonopathy and pyramidal tract dysfunction were present. Significant improvement was noted over a 3-year period [263].

Organophosphate-induced delayed neurotoxicity (OPIDN) is a well-recognized complication of organophosphorus compounds [264]. OPIDN occurs 1 to 3 weeks after acute exposure and after a more uncertain duration after chronic exposure. The symptoms include distal paresthesias, progressive leg weakness, and cramping muscle pain. Distal weakness and wasting is seen. There may be evidence of upper limb involvement and central nervous system dysfunction. Sensory loss when present is mild. The RBC cholinesterase activity is depressed less rapidly than the serum cholinesterase activity and is a measure of chronic exposure to organophosphates [265]. Most modern organophosphate pesticides do not cause the delayed neurotoxic syndrome. OPIDN is the result of phosphorylation and subsequent aging of a protein neurotoxic esterase in the nervous system [266]. The signs and symptoms of acute organophosphate toxicity are the result of acetylcholinesterase inhibition and resulting muscarinic and nicotinic dysfunction. In some patients, after resolution of the cholinergic crisis, an intermediate syndrome develops [267]. This is characterized by weakness of neck flexors and proximal limb and respiratory muscles. This weakness may relate to depolarization blockade at the neuromuscular junction.

Prevention of organophosphate insecticide toxicity requires good occupational practices, including use of gloves and protective clothing. Pralidoxime is a reactivator of inhibited acetylcholinesterase and is the specific antidote for organophosphate poisoning. It is used in conjunction with atropine in the acute stages.

### *Lathyrism*

*Lathyrus sativus* (grass pea or chickling pea) is an environmentally tolerant legume that resists drought conditions. Lathyrism is a self-limiting neurotoxic disorder that presents as a spastic paraparesis and afflicts individuals who consume *L sativus* as a staple. It is endemic in parts of Bangladesh, India, and Ethiopia. The spastic paraparesis is associated with greatly increased tone in thigh extensors, thigh adductors, and gastrocnemius, leading to a lurching scissoring gait characterized by patients walking on the balls of their feet [268]. Sensory symptoms may be reported at onset in the legs. In individuals who are affected severely, pyramidal signs also may be present in the upper limbs. The onset may be abrupt, subacute, or

insidious. An early improvement in limb strength is seen and may be substantial. In the early stages, there may be diffuse and transitory central nervous system excitation of somatic motor and autonomic function, including the presence of bladder symptoms [268]. The degree of neurologic deficit has been classified as the “no-stick stage,” “one-stick stage,” “two-stick stage,” and “crawler stage.” Some patients stabilize in a subclinical, asymptomatic stage with minimal deficits. Electrophysiologic studies suggest subclinical anterior horn cell involvement [269]. Neuropathologic studies show loss of axons and myelin in the pyramidal tract in the lumbar cord and mild degeneration of the anterior horn cells at the same level [270]. Studies suggest that beta-N-oxalyl-amino-L-alanine, an excitotoxic amino acid in *L sativus*, is the responsible toxin [271]. It is a potent agonist of the excitatory neurotransmitter, glutamate. It is suggested that neurolathyrism may be prevented by mixing grass pea preparations with cereals [272] or detoxification of grass peas through aqueous leaching [273].

### *Cyanide toxicity*

Weeks of high dietary cyanide exposure resulting from consumption of insufficiently processed cassava in parts of Africa, such as Zaire and Tanzania, results in konzo, a distinct tropical myelopathy characterized by the abrupt onset of symmetric, nonprogressive, spastic paraparesis [274,275]. Upper limb involvement and central visual field defects may be present. There is absence of sensory or autonomic disturbance. Improvement after onset is seen. Permanent deficits remain. Brain and spinal cord MRI are normal. Motor evoked potentials on magnetic brain stimulation may be absent [276]. Decreased sulfur intake with impaired conversion of cyanide to thiocyanate may be responsible [275]. Drought increases the natural occurrence of cyanogenic glucosides in the cassava roots [274]. Because of food shortages, the processing procedure normally used to remove cyanide before consumption is shortened. Minor improvement in food processing may be preventive [275]. The distribution of konzo is similar to that of HAM/TSP. The abrupt onset and nonprogressive course differentiates konzo from HAM/TSP. Lathyrism bears clinical similarities to konzo but has a different geographic distribution, is the result of a different diet, may have autonomic dysfunction, and does not have visual involvement. In parts of Africa, such as Nigeria, a syndrome characterized by slowly progressive ataxia, peripheral neuropathy, and optic atrophy is described [277]. Years of low dietary cyanide exposure resulting from cassava consumption likely is the cause.

### *Subacute myelo-optic neuropathy*

Subacute myelo-optic neuropathy (SMON) is a myeloneuropathy with optic nerve involvement that affected approximately 10,000 individuals in Japan between 1955 and 1970 [278]. A similar syndrome also has been

reported rarely outside Japan [279]. Epidemiologic studies suggest that SMON was the result of toxicity from the antiparasitic drug, clioquinol. SMON was characterized by subacute onset of lower limb paresthesias and spastic paraparesis with optic atrophy [280]. Tendon hyperreflexia and extensor plantar responses were seen, although at times the ankle jerk was absent. Electrophysiologic studies show delayed central conduction and normal conduction in peripheral sensory axons [281]. Autopsy studies show symmetric axonal degeneration in the corticospinal tracts in the lumbar spine, gracile columns at the cervicomedullary junction, and optic tracts [282]. Morphometric studies show only slight reduction of large myelinated fibers in the sural nerve [283].

### *Protein-calorie malnutrition*

Protein and calorie deficiency in infants and children in underdeveloped countries results in two related disorders: marasmus and kwashiorkor [162]. Marasmus is the result of caloric insufficiency and results in growth failure and emaciation in early infancy. Kwashiorkor presents with edema, ascites, and hepatomegaly and is the result of protein deficiency. Generalized muscle wasting and weakness with hypotonia and hyporeflexia are seen. Cognitive deficits may be permanent. Autopsy studies show cerebral atrophy and immature neuronal development. During the initial stages of dietary treatment, an encephalopathy may be seen.

## References

- [1] Food and Agricultural Organization. The state of food insecurity in the world 2004. Rome: Food and Agriculture Organization of the United Nations; 2004. Available at: [www.fao.org](http://www.fao.org).
- [2] Tefferi A, Pruthi RK. The biochemical basis of cobalamin deficiency. *Mayo Clin Proc* 1994; 69:181–6.
- [3] Scott JM, Dinn JJ, Wilson P, et al. Pathogenesis of subacute combined degeneration: a result of methyl group deficiency. *Lancet* 1981;2:334–7.
- [4] Cardinale GJ, Carty TJ, Abeles RH. Effect of methylmalonyl coenzyme A, a metabolite which accumulates in vitamin B 12 deficiency, on fatty acid synthesis. *J Biol Chem* 1970; 245:3771–5.
- [5] Metz J. Cobalamin deficiency and the pathogenesis of nervous system disease. *Annu Rev Nutr* 1992;12:59–79.
- [6] Scalabrino G. Cobalamin (vitamin B(12)) in subacute combined degeneration and beyond: traditional interpretations and novel theories [erratum appears in *Exp Neurol* 2005; 194:561]. *Exp Neurol* 2005;192:463–79.
- [7] Institute of Medicine. Vitamin B12. In: Food and Nutrition Board, editor. Dietary reference intakes: thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998. p. 306–56.
- [8] Carmel R. Cobalamin (vitamin B12). In: Shils ME, Shike M, Ross AC, et al, editors. *Modern nutrition in health and disease*. 10th ed. Baltimore: Lippincott Williams and Wilkins; 2006. p. 482–97.
- [9] Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. *Acta Med Scand* 1968;184:247–58.

- [10] Seetharam B, Alpers DH. Absorption and transport of cobalamin (vitamin B12). *Annu Rev Nutr* 1982;2:343–69.
- [11] Green R, Kinsella LJ. Current concepts in the diagnosis of cobalamin deficiency. *Neurology* 1995;45:1435–40.
- [12] Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med* 1988;318:1720–8.
- [13] Carmel R. Cobalamin, the stomach, and aging. *Am J Clin Nutr* 1997;66:750–9.
- [14] Pennypacker LC, Allen RH, Kelly JP, et al. High prevalence of cobalamin deficiency in elderly outpatients. *J Am Geriatr Soc* 1992;40:1197–204.
- [15] Hurwitz A, Brady DA, Schaal SE, et al. Gastric acidity in older adults. *JAMA* 1997;278:659–62.
- [16] Halverson JD. Micronutrient deficiencies after gastric bypass for morbid obesity. *Am Surg* 1986;52:594–8.
- [17] Marcuard SP, Albernaz L, Khazanie PG. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B12). *Ann Intern Med* 1994;120:211–5.
- [18] Rosenblatt DS, Cooper BA. Inherited disorders of vitamin B12 utilization. *Bioessays* 1990;12:331–4.
- [19] Kiebertz KD, Giang DW, Schiffer RB, et al. Abnormal vitamin B12 metabolism in human immunodeficiency virus infection. Association with neurological dysfunction. *Arch Neurol* 1991;48:312–4.
- [20] Robertson KR, Stern RA, Hall CD, et al. Vitamin B12 deficiency and nervous system disease in HIV infection. *Arch Neurol* 1993;50:807–11.
- [21] Di Rocco A, Bottiglieri T, Werner P, et al. Abnormal cobalamin-dependent transmethylation in AIDS-associated myelopathy. *Neurology* 2002;58:730–5.
- [22] Deacon R, Lumb M, Perry J, et al. Selective inactivation of vitamin B12 in rats by nitrous oxide. *Lancet* 1978;2:1023–4.
- [23] Schilling RF. Is nitrous oxide a dangerous anesthetic for vitamin B12-deficient subjects? *JAMA* 1986;255:1605–6.
- [24] Kinsella LJ, Green R. 'Anesthesia paresthetica': nitrous oxide-induced cobalamin deficiency. *Neurology* 1995;45:1608–10.
- [25] Layzer RB. Myeloneuropathy after prolonged exposure to nitrous oxide. *Lancet* 1978;2:1227–30.
- [26] Ng J, Frith R. Nanging. *Lancet* 2002;360:384.
- [27] Sahenk Z, Mendell JR, Couri D, et al. Polyneuropathy from inhalation of N2O cartridges through a whipped-cream dispenser. *Neurology* 1978;28:485–7.
- [28] Carmel R. Pernicious anemia. The expected findings of very low serum cobalamin levels, anemia, and macrocytosis are often lacking. *Arch Intern Med* 1988;148:1712–4.
- [29] Healton EB, Savage DG, Brust JC, et al. Neurologic aspects of cobalamin deficiency. *Medicine (Baltimore)* 1991;70:229–45.
- [30] Savage D, Gangaidzo I, Lindenbaum J, et al. Vitamin B12 deficiency is the primary cause of megaloblastic anaemia in Zimbabwe. *Br J Haematol* 1994;86:844–50.
- [31] Savage D, Lindenbaum J. Relapses after interruption of cyanocobalamin therapy in patients with pernicious anemia. *Am J Med* 1983;74:765–72.
- [32] Russell JSR, Batten FE, Collier J. Subacute combined degeneration of the spinal cord. *Brain* 1900;23:39–110.
- [33] Pant SS, Asbury AK, Richardson EP Jr. The myelopathy of pernicious anemia. A neuropathological reappraisal. *Acta Neurol Scand* 1968;44(Suppl 5):1–36.
- [34] Timms SR, Cure JK, Kurent JE. Subacute combined degeneration of the spinal cord: MR findings. *AJNR Am J Neuroradiol* 1993;14:1224–7.
- [35] Hemmer B, Glocker FX, Schumacher M, et al. Subacute combined degeneration: clinical, electrophysiological, and magnetic resonance imaging findings. *J Neurol Neurosurg Psychiatry* 1998;65:822–7.

- [36] Locatelli ER, Laurenro R, Ballard P, et al. MRI in vitamin B12 deficiency myelopathy. *Can J Neurol Sci* 1999;26:60–3.
- [37] Bassi SS, Bulundwe KK, Greeff GP, et al. MRI of the spinal cord in myelopathy complicating vitamin B12 deficiency: two additional cases and a review of the literature. *Neuroradiology* 1999;41:271–4.
- [38] Karantanas AH, Markonis A, Bisbiyiannis G. Subacute combined degeneration of the spinal cord with involvement of the anterior columns: a new MRI finding. *Neuroradiology* 2000;42:115–7.
- [39] Fine EJ, Hallett M. Neurophysiological study of subacute combined degeneration. *J Neurol Sci* 1980;45:331–6.
- [40] McCombe PA, McLeod JG. The peripheral neuropathy of vitamin B12 deficiency. *J Neurol Sci* 1984;66:117–26.
- [41] Heyer EJ, Simpson DM, Bodis-Wollner I, et al. Nitrous oxide: clinical and electrophysiologic investigation of neurologic complications. *Neurology* 1986;36:1618–22.
- [42] Saperstein DS, Wolfe GI, Gronseth GS, et al. Challenges in the identification of cobalamin-deficiency polyneuropathy. *Arch Neurol* 2003;60:1296–301.
- [43] White WB, Reik L Jr, Cutlip DE. Pernicious anemia seen initially as orthostatic hypotension. *Arch Intern Med* 1981;141:1543–4.
- [44] Eisenhofer G, Lambie DG, Johnson RH, et al. Deficient catecholamine release as the basis of orthostatic hypotension in pernicious anaemia. *J Neurol Neurosurg Psychiatry* 1982;45:1053–5.
- [45] Fine EJ, Soria E, Paroski MW, et al. The neurophysiological profile of vitamin B12 deficiency. *Muscle Nerve* 1990;13:158–64.
- [46] Allen RH, Stabler SP, Savage DG, et al. Diagnosis of cobalamin deficiency I: usefulness of serum methylmalonic acid and total homocysteine concentrations. *Am J Hematol* 1990;34:90–8.
- [47] Lindenbaum J, Savage DG, Stabler SP, et al. Diagnosis of cobalamin deficiency: II. Relative sensitivities of serum cobalamin, methylmalonic acid, and total homocysteine concentrations. *Am J Hematol* 1990;34:99–107.
- [48] Savage DG, Lindenbaum J, Stabler SP, et al. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. *Am J Med* 1994;96:239–46.
- [49] Stabler SP. Screening the older population for cobalamin (vitamin B12) deficiency. *J Am Geriatr Soc* 1995;43:1290–7.
- [50] Carmel R, Green R, Rosenblatt DS, et al. Update on cobalamin, folate, and homocysteine. *Hematology* 2003;1:62–81.
- [51] Lindenbaum J, Rosenberg IH, Wilson PW, et al. Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;60:2–11.
- [52] Metz J, Bell AH, Flicker L, et al. The significance of subnormal serum vitamin B12 concentration in older people: a case control study. *J Am Geriatr Soc* 1996;44:1355–61.
- [53] Karnaze DS, Carmel R. Neurologic and evoked potential abnormalities in subtle cobalamin deficiency states, including deficiency without anemia and with normal absorption of free cobalamin. *Arch Neurol* 1990;47:1008–12.
- [54] Saperstein DS, Bahron RJ. Neuropathy associated with nutritional and vitamin deficiencies. In: Dyck PJ, Thomas PK, editors. *Peripheral neuropathy*. 10th ed. Philadelphia: Elsevier Saunders; 2005. p. 470–81.
- [55] Stabler SP, Allen RH, Savage DG, et al. Clinical spectrum and diagnosis of cobalamin deficiency. *Blood* 1990;76:871–81.
- [56] Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. *Arch Intern Med* 1999;159:1289–98.
- [57] Kinsella LJ. Megaloblastic anemias—vitamin B12, Folate. In: Noseworthy JN, editor. *Neurological therapeutics principles and practice*. Abingdon, United Kingdom: Informa Healthcare; 2006. p. 1478–84.

- [58] Carmel R. Mild transcobalamin I (haptocorrin) deficiency and low serum cobalamin concentrations. *Clin Chem* 2003;49:1367–74.
- [59] Carmel R, Vasireddy H, Aurangzeb I, et al. High serum cobalamin levels in the clinical setting—clinical associations and holo-transcobalamin changes. *Clin Lab Haematol* 2001;23:365–71.
- [60] Bolann BJ, Solli JD, Schneede J, et al. Evaluation of indicators of cobalamin deficiency defined as cobalamin-induced reduction in increased serum methylmalonic acid. *Clin Chem* 2000;46:1744–50.
- [61] Carmel R. Macrocytosis, mild anemia, and delay in the diagnosis of pernicious anemia. *Arch Intern Med* 1979;139:47–50.
- [62] Seetharam B. Receptor-mediated endocytosis of cobalamin (vitamin B12). *Annu Rev Nutr* 1999;19:173–95.
- [63] Lindemans J, Schoester M, van Kapel J. Application of a simple immunoabsorption assay for the measurement of saturated and unsaturated transcobalamin II and R-binders. *Clin Chim Acta* 1983;132:53–61.
- [64] Carmel R. Measuring and interpreting holo-transcobalamin (holo-transcobalamin II). *Clin Chem* 2002;48:407–9.
- [65] Carmel R. Pepsinogens and other serum markers in pernicious anemia. *Am J Clin Pathol* 1988;90:442–5.
- [66] Miller A, Slingerland DW, Cardarelli J, et al. Further studies on the use of serum gastrin levels in assessing the significance of low serum B12 levels. *Am J Hematol* 1989;31:194–8.
- [67] Rothenberg SP, Kantha KR, Ficarra A. Autoantibodies to intrinsic factor: their determination and clinical usefulness. *J Lab Clin Med* 1971;77:476–84.
- [68] Fairbanks VF, Lennon VA, Kokmen E, et al. Tests for pernicious anemia: serum intrinsic factor blocking antibody. *Mayo Clin Proc* 1983;58:203–4.
- [69] Carmel R. Reassessment of the relative prevalences of antibodies to gastric parietal cell and to intrinsic factor in patients with pernicious anaemia: influence of patient age and race. *Clin Exp Immunol* 1992;89:74–7.
- [70] Verhaeverbeke I, Mets T, Mulken K, et al. Normalization of low vitamin B12 serum levels in older people by oral treatment. *J Am Geriatr Soc* 1997;45:124–5.
- [71] Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret? *JAMA* 1991;265:94–5.
- [72] Stacy CB, Di Rocco A, Gould RJ. Methionine in the treatment of nitrous-oxide-induced neuropathy and myeloneuropathy. *J Neurol* 1992;239:401–3.
- [73] Di Rocco A, Tagliati M, Danisi F, et al. A pilot study of L-methionine for the treatment of AIDS-associated myelopathy. *Neurology* 1998;51:266–8.
- [74] Di Rocco A, Werner P, Bottiglieri T, et al. Treatment of AIDS-associated myelopathy with L-methionine: a placebo-controlled study. *Neurology* 2004;63:1270–5.
- [75] Ungley CC. Subacute combined degeneration of the cord: I. Response to liver extracts. II. Trials with B12. *Brain* 1949;72:382–427.
- [76] Skouby AP. Hydroxocobalamin for initial and long-term therapy for vitamin B12 deficiency. *Acta Med Scand* 1987;221:399–402.
- [77] Tudhope GR, Swan HT, Spray GH. Patient variation in pernicious anaemia, as shown in a clinical trial of cyanocobalamin, hydroxocobalamin and cyanocobalamin–zinc tannate. *Br J Haematol* 1967;13:216–28.
- [78] Slot WB, Merkus FW, Van Deventer SJ, et al. Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients. *Gastroenterology* 1997;113:430–3.
- [79] Carmel R, Melnyk S, James SJ. Cobalamin deficiency with and without neurologic abnormalities: differences in homocysteine and methionine metabolism. *Blood* 2003;101:3302–8.
- [80] Carmel R, Weiner JM, Johnson CS. Iron deficiency occurs frequently in patients with pernicious anemia. *JAMA* 1987;257:1081–3.

- [81] Institute of Medicine. Folate. In: Food and Nutrition Board, editor. Dietary reference intakes: thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998. p. 196–305.
- [82] Carmel R. Folic acid. In: Shils ME, Shike M, Ross AC, et al, editors. Modern nutrition in health and disease. 10th ed. Baltimore: Lippincott Williams and Wilkins; 2006. p. 470–81.
- [83] Sirotnak FM, Tolner B. Carrier-mediated membrane transport of folates in mammalian cells. *Annu Rev Nutr* 1999;19:91–122.
- [84] Moran RG. Roles of folypoly-gamma-glutamate synthetase in therapeutics with tetrahydrofolate antimetabolites: an overview. *Semin Oncol* 1999;26(2, Suppl 6):24–32.
- [85] Eichner ER, Pierce HI, Hillman RS. Folate balance in dietary-induced megaloblastic anemia. *N Engl J Med* 1971;284:933–8.
- [86] Halsted CH. Folate deficiency in alcoholism. *Am J Clin Nutr* 1980;33:2736–40.
- [87] Elsborg L. Malabsorption of folic acid following partial gastrectomy. *Scand J Gastroenterol* 1974;9:271–4.
- [88] Russell RM, Krasinski SD, Samloff IM, et al. Folic acid malabsorption in atrophic gastritis. Possible compensation by bacterial folate synthesis. *Gastroenterology* 1986;91:1476–82.
- [89] Russell RM, Golner BB, Krasinski SD, et al. Effect of antacid and H2 receptor antagonists on the intestinal absorption of folic acid. *J Lab Clin Med* 1988;112:458–63.
- [90] Lambie DG, Johnson RH. Drugs and folate metabolism. *Drugs* 1985;30:145–55.
- [91] Green R, Miller JW. Folate deficiency beyond megaloblastic anemia: hyperhomocysteinemia and other manifestations of dysfunctional folate status. *Semin Hematol* 1999;36:47–64.
- [92] Grant HC, Hoffbrand AV, Wells DG. Folate deficiency and neurological disease. *Lancet* 1965;2:763–7.
- [93] Reynolds EH, Rothfeld P, Pincus JH. Neurological disease associated with folate deficiency. *BMJ* 1973;2:398–400.
- [94] Manzoor M, Runcie J. Folate-responsive neuropathy: report of 10 cases. *BMJ* 1976;1:1176–8.
- [95] Lever EG, Elwes RD, Williams A, et al. Subacute combined degeneration of the cord due to folate deficiency: response to methyl folate treatment. *J Neurol Neurosurg Psychiatry* 1986;49:1203–7.
- [96] Parry TE. Folate responsive neuropathy. *Presse Med* 1994;23:131–7.
- [97] Shorvon SD, Carney MW, Chanarin I, et al. The neuropsychiatry of megaloblastic anaemia. *BMJ* 1980;281:1036–8.
- [98] Reynolds EH. Benefits and risks of folic acid to the nervous system. *J Neurol Neurosurg Psychiatry* 2002;72:567–71.
- [99] Diaz-Arrastia R. Homocysteine and neurologic disease. *Arch Neurol* 2000;57:1422–7.
- [100] Zittoun J. Congenital errors of folate metabolism. *Baillieres Clin Haematol* 1995;8:603–16.
- [101] Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* 2004;291:565–75.
- [102] Gunter EW, Bowman BA, Caudill SP, et al. Results of an international round robin for serum and whole-blood folate. *Clin Chem* 1996;42:1689–94.
- [103] Brouwer DA, Welten HT, Reijngoud DJ, et al. Plasma folic acid cutoff value, derived from its relationship with homocysteine. *Clin Chem* 1998;44:1545–50.
- [104] Eichner ER, Hillman RS. Effect of alcohol on serum folate level. *J Clin Invest* 1973;52:584–91.
- [105] Lucock M, Yates Z. Measurement of red blood cell methylfolate. *Lancet* 2002;360:1021–2.
- [106] Butterworth CE Jr, Tamura T. Folic acid safety and toxicity: a brief review. *Am J Clin Nutr* 1989;50:353–8.

- [107] Stabler SP, Marcell PD, Podell ER, et al. Elevation of total homocysteine in the serum of patients with cobalamin or folate deficiency detected by capillary gas chromatography-mass spectrometry. *J Clin Invest* 1988;81:466–74.
- [108] Tan N, Ulrich H. Menkes' disease and swayback. A comparative study of two copper deficiency syndromes. *J Neurol Sci* 1983;62:95–113.
- [109] Kumar N, Gross JB Jr, Ahlskog JE. Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. *Neurology* 2004;63:33–9.
- [110] Kumar N. Copper deficiency myelopathy (human swayback). *Mayo Clin Proc* 2006;81(10):1371–84.
- [111] Institute of Medicine. Copper. In: Food and Nutrition Board, editor. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press; 2000. p. 224–57.
- [112] Turnlund JR. Copper. In: Shils ME, Shike M, Ross AC, et al, editors. Modern nutrition in health and disease. 10th ed. Baltimore: Lippincott Williams and Wilkins; 2006. p. 286–99.
- [113] Harris ZL, Gitlin JD. Genetic and molecular basis for copper toxicity. *Am J Clin Nutr* 1996; 63:836S–41S.
- [114] Williams DM. Copper deficiency in humans. *Semin Hematol* 1983;20:118–28.
- [115] Danks DM. Copper deficiency in humans. *Annu Rev Nutr* 1988;8:235–57.
- [116] Fiske DN, McCoy HE 3rd, Kitchens CS. Zinc-induced sideroblastic anemia: report of a case, review of the literature, and description of the hematologic syndrome. *Am J Hematol* 1994;46:147–50.
- [117] Kumar N, Gross JB Jr, Ahlskog JE. Myelopathy due to copper deficiency. *Neurology* 2003; 61:273–4.
- [118] Yuzbasiyan-Gurkan V, Grider A, Nostrant T, et al. Treatment of Wilson's disease with zinc: X. Intestinal metallothionein induction. *J Lab Clin Med* 1992;120:380–6.
- [119] Cordano A, Baertl JM, Graham GG. Copper deficiency in infancy. *Pediatrics* 1964;34: 324–36.
- [120] Cartwright GE, Gubler CJ, Wintrobe MM. Studies on copper metabolism. XI. Copper and iron metabolism in the nephrotic syndrome. *J Clin Invest* 1954;33:685–98.
- [121] Kumar N, Low PA. Myeloneuropathy and anemia due to copper malabsorption. *J Neurol* 2004;251:747–9.
- [122] Karpel JT, Peden VH. Copper deficiency in long-term parenteral nutrition. *J Pediatr* 1972; 80:32–6.
- [123] Spiegel JE, Willenbacher RF. Rapid development of severe copper deficiency in a patient with Crohn's disease receiving parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1999;23:169–72.
- [124] Tamura H, Hirose S, Watanabe O, et al. Anemia and neutropenia due to copper deficiency in enteral nutrition. *JPEN J Parenter Enteral Nutr* 1994;18:185–9.
- [125] Hayton BA, Broome HE, Lilenbaum RC. Copper deficiency-induced anemia and neutropenia secondary to intestinal malabsorption. *Am J Hematol* 1995;48:45–7.
- [126] Kumar N, McEvoy KM, Ahlskog JE. Myelopathy due to copper deficiency following gastrointestinal surgery. *Arch Neurol* 2003;60:1782–5.
- [127] Kumar N, Ahlskog JE, Gross JB Jr. Acquired hypocupremia after gastric surgery. *Clin Gastroenterol Hepatol* 2004;2:1074–9.
- [128] Valentine JS, Gralla EB. Delivering copper inside yeast and human cells. *Science* 1997;278: 817–8.
- [129] Schleper B, Stuerenburg HJ. Copper deficiency-associated myelopathy in a 46-year-old woman. *J Neurol* 2001;248:705–6.
- [130] Hedera P, Fink JK, Bockenstedt PL, et al. Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin: further support for existence of a new zinc overload syndrome. *Arch Neurol* 2003;60:1303–6.
- [131] Greenberg SA, Briemberg HR. A neurological and hematological syndrome associated with zinc excess and copper deficiency. *J Neurol* 2004;251:111–4.



- [132] Kumar N, Elliott MA, Hoyer JD, et al. "Myelodysplasia," myeloneuropathy, and copper deficiency. *Mayo Clin Proc* 2005;80:943–6.
- [133] Kumar N, Ahlskog JE, Klein CJ, et al. Imaging features of copper deficiency myelopathy: a study of 25 cases. *Neuroradiology* 2005;48:78–83.
- [134] Rowin J, Lewis SL. Copper deficiency myeloneuropathy and pancytopenia secondary to overuse of zinc supplementation. *J Neurol Neurosurg Psychiatry* 2005;76:750–1.
- [135] Prodan CI, Holland NR. CNS demyelination from zinc toxicity? *Neurology* 2000;54:1705–6.
- [136] Prodan CI, Holland NR, Wisdom PJ, et al. CNS demyelination associated with copper deficiency and hyperzincemia. *Neurology* 2002;59:1453–6.
- [137] Gregg XT, Reddy V, Prchal JT. Copper deficiency masquerading as myelodysplastic syndrome. *Blood* 2002;100:1493–5.
- [138] Crum BA, Kumar N. Electrophysiologic findings in copper deficiency myeloneuropathy. *Neurology* 2005;64(Suppl 1):A123.
- [139] Wasa M, Satani M, Tanano H, et al. Copper deficiency with pancytopenia during total parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1994;18:190–2.
- [140] Kumar N, Gross JB, Ahlskog JE. Myelopathy due to copper deficiency [letter]. *Neurology* 2004;62:1656.
- [141] Mason KE. A conspectus of research on copper metabolism and requirements of man. *J Nutr* 1979;109:1979–2066.
- [142] Uauy R, Castillo-Duran C, Fisberg M, et al. Red cell superoxide dismutase activity as an index of human copper nutrition. *J Nutr* 1985;115:1650–5.
- [143] Milne DB. Assessment of copper nutritional status. *Clin Chem* 1994;40:1479–84.
- [144] Gyorffy EJ, Chan H. Copper deficiency and microcytic anemia resulting from prolonged ingestion of over-the-counter zinc. *Am J Gastroenterol* 1992;87:1054–5.
- [145] Cheeseman KH, Holley AE, Kelly FJ, et al. Biokinetics in humans of RRR- $\alpha$ -tocopherol: the free phenol, acetate ester, and succinate ester forms of vitamin E. *Free Radic Biol Med* 1995;19:591–8.
- [146] Institute of Medicine. Vitamin E. In: Food and Nutrition Board, editor. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press; 2000. p. 186–283.
- [147] Hayes K, Pronczuk A, Perlman D. Vitamin E in fortified cow milk uniquely enriches human plasma lipoproteins. *Am J Clin Nutr* 2001;74:211–8.
- [148] Leonard SW, Good CK, Gugger ET, et al. Vitamin E bioavailability from fortified breakfast cereal is greater than that from encapsulated supplements. *Am J Clin Nutr* 2004;79:86–92.
- [149] Handelman GJ, Epstein WL, Peerson J, et al. Human adipose  $\alpha$ -tocopherol and  $\gamma$ -tocopherol kinetics during and after 1 y of  $\alpha$ -tocopherol supplementation. *Am J Clin Nutr* 1994;59:1025–32.
- [150] Traber MG. Vitamin E. In: Shils ME, Shike M, Ross AC, editors. *Modern nutrition in health and disease*. 10th ed. Baltimore: Lippincott Williams and Wilkins; 2006. p. 396–411.
- [151] Steeph AC, Traber MG, Ito Y, et al. Vitamin E status of patients receiving long-term parenteral nutrition: is vitamin E supplementation adequate? *JPEN J Parenter Enteral Nutr* 1991;15:647–52.
- [152] Ben Hamida C, Doerflinger N, Belal S, et al. Localization of Friedreich ataxia phenotype with selective vitamin E deficiency to chromosome 8q by homozygosity mapping. *Nat Genet* 1993;5:195–200.
- [153] Cavalier L, Ouahchi K, Kayden HJ, et al. Ataxia with isolated vitamin E deficiency: heterogeneity of mutations and phenotypic variability in a large number of families. *Am J Hum Genet* 1998;62:301–10.
- [154] Traber MG, Sokol RJ, Burton GW, et al. Impaired ability of patients with familial isolated vitamin E deficiency to incorporate  $\alpha$ -tocopherol into lipoproteins secreted by the liver. *J Clin Invest* 1990;85:397–407.

- [155] Aguglia U, Annesi G, Pasquinelli G, et al. Vitamin E deficiency due to chylomicron retention disease in Marinesco-Sjogren syndrome. *Ann Neurol* 2000;47:260–4.
- [156] Harding AE. Vitamin E and the nervous system. *Crit Rev Neurobiol* 1987;3:89–103.
- [157] Sokol RJ. Vitamin E deficiency and neurologic disease. *Annu Rev Nutr* 1988;8:351–73.
- [158] Ben Hamida M, Belal S, Sirugo G, et al. Friedreich's ataxia phenotype not linked to chromosome 9 and associated with selective autosomal recessive vitamin E deficiency in two inbred Tunisian families. *Neurology* 1993;43:2179–83.
- [159] Tomasi LG. Reversibility of human myopathy caused by vitamin E deficiency. *Neurology* 1979;29:1182–6.
- [160] Burck U, Goebel HH, Kuhlendahl HD, et al. Neuromyopathy and vitamin E deficiency in man. *Neuropediatrics* 1981;12:267–78.
- [161] Palmucci L, Doriguzzi C, Orsi L, et al. Neuropathy secondary to vitamin E deficiency in acquired intestinal malabsorption. *Ital J Neurol Sci* 1988;9:599–602.
- [162] So YT, Simon RP. Deficiency diseases of the nervous system. In: Bradley WG, Daroff RB, Fenichel GM, et al, editors. *Neurology in clinical practice*, vol. II. 4th ed. Philadelphia: Butterworth Heinemann; 2004. p. 1693–708.
- [163] Suarez GA. Peripheral neuropathy associated with alcoholism, malnutrition and vitamin deficiencies. In: Noseworthy JN, editor. *Neurological therapeutics principles and practice*, vol. 3. Abingdon, United Kingdom: Informa Healthcare; 2006. p. 2294–306.
- [164] Vorgerd M, Tegenthoff M, Kuhne D, et al. Spinal MRI in progressive myeloneuropathy associated with vitamin E deficiency. *Neuroradiology* 1996;38(Suppl 1):S111–3.
- [165] Sokol RJ, Bove KE, Heubi JE, et al. Vitamin E deficiency during chronic childhood cholestasis: presence of sural nerve lesion prior to 2 1/2 years of age. *J Pediatr* 1983;103:197–204.
- [166] Traber MG, Sokol RJ, Ringel SP, et al. Lack of tocopherol in peripheral nerves of vitamin E-deficient patients with peripheral neuropathy. *N Engl J Med* 1987;317:262–5.
- [167] Behrens WA, Thompson JN, Madere R. Distribution of alpha-tocopherol in human plasma lipoproteins. *Am J Clin Nutr* 1982;35:691–6.
- [168] Horwitt MK, Harvey CC, Dahm CH Jr, et al. Relationship between tocopherol and serum lipid levels for determination of nutritional adequacy. *Ann N Y Acad Sci* 1972;203:223–36.
- [169] Traber MG, Jialal I. Measurement of lipid-soluble vitamins—further adjustment needed? *Lancet* 2000;355:2013–4.
- [170] Sokol RJ, Heubi JE, Iannaccone ST, et al. Vitamin E deficiency with normal serum vitamin E concentrations in children with chronic cholestasis. *N Engl J Med* 1984;310:1209–12.
- [171] Sokol RJ, Guggenheim MA, Iannaccone ST, et al. Improved neurologic function after long-term correction of vitamin E deficiency in children with chronic cholestasis. *N Engl J Med* 1985;313:1580–6.
- [172] Sokol RJ, Butler-Simon N, Conner C, et al. Multicenter trial of d-alpha-tocopheryl polyethylene glycol 1000 succinate for treatment of vitamin E deficiency in children with chronic cholestasis. *Gastroenterology* 1993;104:1727–35.
- [173] Azizi E, Zaidman JL, Eshchar J, et al. Abetalipoproteinemia treated with parenteral and oral vitamins A and E, and with medium chain triglycerides. *Acta Paediatr Scand* 1978;67:796–801.
- [174] Kayden HJ, Hatam LJ, Traber MG. The measurement of nanograms of tocopherol from needle aspiration biopsies of adipose tissue: normal and abetalipoproteinemic subjects. *J Lipid Res* 1983;24:652–6.
- [175] Butterworth RF. Thiamin. In: Shils ME, Shike M, Ross AC, editors. *Modern nutrition in health and disease*. 10th ed. Baltimore: Lippincott Williams and Wilkins; 2006. p. 426–33.
- [176] Butterworth RF. Effects of thiamine deficiency on brain metabolism: implications for the pathogenesis of the Wernicke-Korsakoff syndrome. *Alcohol Alcohol* 1989;24:271–9.
- [177] Butterworth RF, Heroux M. Effect of pyridoxamine treatment and subsequent thiamine rehabilitation on regional cerebral amino acids and thiamine-dependent enzymes. *J Neurochem* 1989;52:1079–84.

- [178] Bettendorff L. Thiamine in excitable tissues: reflections on a non-cofactor role. *Metab Brain Dis* 1994;9:183–209.
- [179] Institute of Medicine. Vitamin B1. In: Food and Nutrition Board, editor. Dietary reference intakes: thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998. p. 58–86.
- [180] Rindi G, Patrini C, Comincioli V, et al. Thiamine content and turnover rates of some rat nervous regions, using labeled thiamine as a tracer. *Brain Res* 1980;181:369–80.
- [181] Singleton CK, Martin PR. Molecular mechanisms of thiamine utilization. *Curr Mol Med* 2001;1:197–207.
- [182] Reuler JB, Girard DE, Cooney TG. Current concepts. Wernicke's encephalopathy. *N Engl J Med* 1985;312:1035–9.
- [183] Rindi G, Imarisio L, Patrini C. Effects of acute and chronic ethanol administration on regional thiamin pyrophosphokinase activity of the rat brain. *Biochem Pharmacol* 1986;35:3903–8.
- [184] Ohnishi A, Tsuji S, Igisu H, et al. Beriberi neuropathy. Morphometric study of sural nerve. *J Neurol Sci* 1980;45:177–90.
- [185] Koike H, Misu K, Hattori N, et al. Postgastrectomy polyneuropathy with thiamine deficiency. *J Neurol Neurosurg Psychiatry* 2001;71:357–62.
- [186] Wright H. Changes in neuronal centers in beriberi neuritis. *BMJ* 1901;1:1610–6.
- [187] Aguiar AC, Costa VM, Ragazzo PC, et al. Mielinólise pontina e extra-pontina associada a Shoshin beriberi em paciente etilista. *Arq Neuropsiquiatr* 2004;62:733–6.
- [188] Caine D, Halliday GM, Kril JJ, et al. Operational criteria for the classification of chronic alcoholics: identification of Wernicke's encephalopathy. *J Neurol Neurosurg Psychiatry* 1997;62:51–60.
- [189] Doherty MJ, Watson NF, Uchino K, et al. Diffusion abnormalities in patients with Wernicke encephalopathy. *Neurology* 2002;58:655–7.
- [190] Foster D, Falah M, Kadom N, et al. Wernicke encephalopathy after bariatric surgery: losing more than just weight. *Neurology* 1987;2005:65.
- [191] Torvik A, Lindboe CF, Rogde S. Brain lesions in alcoholics. A neuropathological study with clinical correlations. *J Neurol Sci* 1982;56:233–48.
- [192] Harper C. The incidence of Wernicke's encephalopathy in Australia—a neuropathological study of 131 cases. *J Neurol Neurosurg Psychiatry* 1983;46:593–8.
- [193] Harper C. Wernicke's encephalopathy: a more common disease than realised. A neuropathological study of 51 cases. *J Neurol Neurosurg Psychiatry* 1979;42:226–31.
- [194] Butterworth RF, Gaudreau C, Vincelette J, et al. Thiamine deficiency and Wernicke's encephalopathy in AIDS. *Metab Brain Dis* 1991;6:207–12.
- [195] Kril JJ. Neuropathology of thiamine deficiency disorders. *Metab Brain Dis* 1996;11:9–17.
- [196] Roman GC. Nutritional disorders of the nervous system. In: Shils ME, Shike M, Ross AC, editors. *Modern nutrition in health and disease*. 10th ed. Baltimore: Lippincott Williams and Wilkins; 2006. p. 1362–80.
- [197] Dreyfus PM. Thiamine and the nervous system: an overview. *J Nutr Sci Vitaminol (Tokyo)* 1976;22(Suppl):13–6.
- [198] Talwar D, Davidson H, Cooney J, et al. Vitamin B(1) status assessed by direct measurement of thiamin pyrophosphate in erythrocytes or whole blood by HPLC: comparison with erythrocyte transketolase activation assay. *Clin Chem* 2000;46:704–10.
- [199] Woelk H, Lehl S, Bitsch R, et al. Benfotiamine in treatment of alcoholic polyneuropathy: an 8-week randomized controlled study (BAP I Study). *Alcohol and Alcoholism* 1998;33:631–8.
- [200] Cole M, Turner A, Frank O, et al. Extraocular palsy and thiamine therapy in Wernicke's encephalopathy. *Am J Clin Nutr* 1969;22:44–51.
- [201] Salas-Salvado J, Garcia-Lorda P, Cuatrecasas G, et al. Wernicke's syndrome after bariatric surgery. *Clin Nutr* 2000;19:371–3.

- [202] Institute of Medicine. Niacin. In: Food and Nutrition Board, editor. Dietary reference intakes: thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998. p. 123–49.
- [203] Bourgeois C, Cervantes-Laurean D, Moss J. Niacin. In: Shils ME, Shike M, Ross AC, editors. Modern nutrition in health and disease. 10th ed. Baltimore: Lippincott Williams and Wilkins; 2006. p. 442–51.
- [204] Spies TD, Aring CD. The effect of vitamin B1 on the peripheral neuritis of pellagra. *JAMA* 1938;110:1081–4.
- [205] Spies TD, Vilter RW, Ashe WF. Pellagra, beriberi and riboflavin deficiency in human beings: diagnosis and treatment. *JAMA* 1939;113:931–7.
- [206] Mackey AD, Davis SR, Gregory JFI. Vitamin B6. In: Shils ME, Shike M, Ross AC, et al, editors. Modern nutrition in health and disease. 10th ed. Baltimore: Lippincott Williams and Wilkins; 2006. p. 452–61.
- [207] Institute of Medicine. Vitamin B6. In: Food and Nutrition Board, editor. Dietary reference intakes: thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998. p. 150–95.
- [208] Said HM, Ortiz A, Ma TY. A carrier-mediated mechanism for pyridoxine uptake by human intestinal epithelial Caco-2 cells: regulation by a PKA-mediated pathway. *Am J Physiol Cell Physiol* 2003;285:C1219–25.
- [209] Bhagavan HN, Brin M. Drug—vitamin B6 interaction. *Curr Concepts Nutr* 1983;12:1–12.
- [210] Lumeng L. The role of acetaldehyde in mediating the deleterious effect of ethanol on pyridoxal 5'-phosphate metabolism. *J Clin Invest* 1978;62:286–93.
- [211] Mason DY, Emerson PM. Primary acquired sideroblastic anaemia: response to treatment with pyridoxal-5-phosphate. *BMJ* 1973;1:389–90.
- [212] Vilter RW, Mueller JF, Glazer HS, et al. The effect of vitamin B6 deficiency induced by desoxypyridoxine in human beings. *J Lab Clin Med* 1953;42:335–57.
- [213] Goldman AL, Braman SS. Isoniazid: a review with emphasis on adverse effects. *Chest* 1972; 62:71–7.
- [214] Victor M, Adams RD. The neuropathology of experimental vitamin B6 deficiency in monkeys. *Am J Clin Nutr* 1956;4:346–53.
- [215] Schaumburg H, Kaplan J, Windebank A, et al. Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome. *N Engl J Med* 1983;309:445–8.
- [216] Parry GJ, Bredesen DE. Sensory neuropathy with low-dose pyridoxine. *Neurology* 1985; 35:1466–8.
- [217] Leklem JE. Vitamin B-6: a status report. *J Nutr* 1990;120(Suppl 11):1503–7.
- [218] Okada H, Moriwaki K, Kanno Y, et al. Vitamin B6 supplementation can improve peripheral polyneuropathy in patients with chronic renal failure on high-flux haemodialysis and human recombinant erythropoietin. *Nephrol Dial Transplant* 2000;15:1410–3.
- [219] Brolin RE. Bariatric surgery and long-term control of morbid obesity. *JAMA* 2002;288: 2793–6.
- [220] Buchwald H, Buchwald JN. Evolution of operative procedures for the management of morbid obesity 1950–2000. *Obes Surg* 2002;12:705–17.
- [221] Deitel M, Shikora SA. The development of the surgical treatment of morbid obesity. *J Am Coll Nutr* 2002;21:365–71.
- [222] Livingston EH. Obesity and its surgical management. *Am J Surg* 2002;184:103–13.
- [223] MacLean LD, Rhode BM, Shizgal HM. Nutrition following gastric operations for morbid obesity. *Ann Surg* 1983;198:347–55.
- [224] Crowley LV, Olson RW. Megaloblastic anemia after gastric bypass for obesity. *Am J Gastroenterol* 1983;78:406–10.
- [225] Crowley LV, Seay J, Mullin G. Late effects of gastric bypass for obesity. *Am J Gastroenterol* 1984;79:850–60.
- [226] Schilling RF, Gohdes PN, Hardie GH. Vitamin B12 deficiency after gastric bypass surgery for obesity. *Ann Intern Med* 1984;101:501–2.

- [227] Amaral JF, Thompson WR, Caldwell MD, et al. Prospective hematologic evaluation of gastric exclusion surgery for morbid obesity. *Ann Surg* 1985;201:186–93.
- [228] Provenzale D, Reinhold RB, Golner B, et al. Evidence for diminished B12 absorption after gastric bypass: oral supplementation does not prevent low plasma B12 levels in bypass patients. *J Am Coll Nutr* 1992;11:29–35.
- [229] Abarbanel JM, Berginer VM, Osimani A, et al. Neurologic complications after gastric restriction surgery for morbid obesity. *Neurology* 1987;37:196–200.
- [230] Chaves LC, Faintuch J, Kahwage S, et al. A cluster of polyneuropathy and Wernicke-Korsakoff syndrome in a bariatric unit. *Obes Surg* 2002;12:328–34.
- [231] Sola E, Morillas C, Garzon S, et al. Rapid onset of Wernicke's encephalopathy following gastric restrictive surgery. *Obes Surg* 2003;13:661–2.
- [232] Banerji NK, Hurwitz LJ. Nervous system manifestations after gastric surgery. *Acta Neurol Scand* 1971;47:485–513.
- [233] Marinella MA. Ophthalmoplegia: an unusual manifestation of hypocalcemia. *Am J Emerg Med* 1999;17:105–6.
- [234] Alvarez-Leite JI. Nutrient deficiencies secondary to bariatric surgery. *Curr Opin Clin Nutr Metab Care* 2004;7:569–75.
- [235] Feit H, Glasberg M, Ireton C, et al. Peripheral neuropathy and starvation after gastric partitioning for morbid obesity. *Ann Intern Med* 1982;96:453–5.
- [236] Paulson GW, Martin EW, Mojzisek C, et al. Neurologic complications of gastric partitioning. *Arch Neurol* 1985;42:675–7.
- [237] Dahlquist NR, Perrault J, Callaway CW, et al. D-Lactic acidosis and encephalopathy after jejunoileostomy: response to overfeeding and to fasting in humans. *Mayo Clin Proc* 1984;59:141–5.
- [238] Banerji NK. Acute polyneuritis cranialis with total external ophthalmoplegia and areflexia. *Ulster Med J* 1971;40:14–6.
- [239] Hoffman PM, Brody JA. Neurological disorders in patients following surgery for peptic ulcer. *Neurology* 1972;22:450.
- [240] Thaisetthawatkul P, Collazo-Clavell ML, Sarr MG, et al. A controlled study of peripheral neuropathy after bariatric surgery. *Neurology* 2004;63:1462–70.
- [241] Chang CG, Adams-Huet B, Provost DA. Acute post-gastric reduction surgery (APGARS) neuropathy. *Obes Surg* 2004;14:182–9.
- [242] Berger JR. The neurological complications of bariatric surgery. *Arch Neurol* 2004;61:1185–9.
- [243] Koffman BM, Greenfield LJ, Ali II, et al. Neurologic complications after surgery for obesity. *Muscle Nerve* 2006;33:166–76.
- [244] Chang CG, Helling TS, Black WE, et al. Weakness after gastric bypass. *Obes Surg* 2002;12:592–7.
- [245] Mason ME, Jalagani H, Vinik AI. Metabolic complications of bariatric surgery: diagnosis and management issues. *Gastroenterol Clin North Am* 2005;34:25–33.
- [246] Brolin RE. Gastric bypass. *Surg Clin North Am* 2001;81:1077–95.
- [247] Brolin RE, Gorman RC, Milgrim LM, et al. Multivitamin prophylaxis in prevention of post-gastric bypass vitamin and mineral deficiencies. *Int J Obes* 1991;15:661–7.
- [248] D'Amour ML, Butterworth RF. Pathogenesis of alcoholic peripheral neuropathy: direct effect of ethanol or nutritional deficit? *Metab Brain Dis* 1994;9:133–42.
- [249] Victor M, Adams RD. On the etiology of alcoholic neurologic disease with special reference to the role of nutrition. *Am J Clin Nutr* 1961;9:379–97.
- [250] Behse F, Buchthal F. Alcoholic neuropathy: clinical, electrophysiological, and biopsy findings. *Ann Neurol* 1977;2:95–110.
- [251] Koike H, Mori K, Misu K, et al. Painful alcoholic polyneuropathy with predominant small-fiber loss and normal thiamine status. *Neurology* 2001;56:1727–32.
- [252] Tabaraud F, Vallat JM, Hugon J, et al. Acute or subacute alcoholic neuropathy mimicking Guillain-Barre syndrome. *J Neurol Sci* 1990;97:195–205.

- [253] Monforte R, Estruch R, Valls-Sole J, et al. Autonomic and peripheral neuropathies in patients with chronic alcoholism. A dose-related toxic effect of alcohol. *Arch Neurol* 1995;52:45–51.
- [254] Koike H, Iijima M, Sugiura M, et al. Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. *Ann Neurol* 2003;54:19–29.
- [255] Johnson RH, Robinson BJ. Mortality in alcoholics with autonomic neuropathy. *J Neurol Neurosurg Psychiatry* 1988;51:476–80.
- [256] Roman GC. An epidemic in Cuba of optic neuropathy, sensorineural deafness, peripheral sensory neuropathy and dorsolateral myeloneuropathy. *J Neurol Sci* 1994;127:11–28.
- [257] Cuban Neuropathy Field Investigation Team. Epidemic optic neuropathy in Cuba—Clinical characterization and risk factors. *N Engl J Med* 1995;333:1176–82.
- [258] Roman GC, Osame M. Identity of HTLV-I-associated tropical spastic paraparesis and HTLV-I-associated myelopathy. *Lancet* 1988;1:651.
- [259] Jacobson S, Lehky T, Nishimura M, et al. Isolation of HTLV-II from a patient with chronic, progressive neurological disease clinically indistinguishable from HTLV-I-associated myelopathy/tropical spastic paraparesis. *Ann Neurol* 1993;33:392–6.
- [260] Harrington WJ Jr, Sheremata W, Hjelle B, et al. Spastic ataxia associated with human T-cell lymphotropic virus type II infection. *Ann Neurol* 1993;33:411–4.
- [261] Morgan JP, Penovich P. Jamaica ginger paralysis. Forty-seven-year follow-up. *Arch Neurol* 1978;35:530–2.
- [262] Senanayake N, Jeyaratnam J. Toxic polyneuropathy due to gingili oil contaminated with tri-cresyl phosphate affecting adolescent girls in Sri Lanka. *Lancet* 1981;1:88–9.
- [263] Senanayake N. Tri-cresyl phosphate neuropathy in Sri Lanka: a clinical and neurophysiological study with a three year follow up. *J Neurol Neurosurg Psychiatry* 1981;44:775–80.
- [264] Weiner ML, Jortner BS. Organophosphate-induced delayed neurotoxicity of triarylphosphates. *Neurotoxicology* 1999;20:653–73.
- [265] Jaga K, Dharmani C. Sources of exposure to and public health implications of organophosphate pesticides. *Pan American J Public Health* 2003;14:171–85.
- [266] Lotti M, Becker CE, Aminoff MJ. Organophosphate polyneuropathy: pathogenesis and prevention. *Neurology* 1984;34:658–62.
- [267] Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. *N Engl J Med* 1987;316:761–3.
- [268] Ludolph AC, Hugon J, Dwivedi MP, et al. Studies on the aetiology and pathogenesis of motor neuron diseases. 1. Lathyrism: clinical findings in established cases. *Brain* 1987;110(Pt 1):149–65.
- [269] Drory VE, Rabey MJ, Cohn DF. Electrophysiologic features in patients with chronic neurolathyrism. *Acta Neurol Scand* 1992;85:401–3.
- [270] Striefler M, Cohn DF, Hirano A, et al. The central nervous system in a case of neurolathyrism. *Neurology* 1977;27:1176–8.
- [271] Spencer PS, Roy DN, Ludolph A, et al. Lathyrism: evidence for role of the neuroexcitatory aminoacid BOAA. *Lancet* 1986;2:1066–7.
- [272] Getahun H, Lambein F, Vanhoorne M, et al. Food-aid cereals to reduce neurolathyrism related to grass-pea preparations during famine. *Lancet* 2003;362:1808–10.
- [273] Spencer PS, Palmer VS. Lathyrism: aqueous leaching reduces grass-pea neurotoxicity. *Lancet* 2003;362:1775–6.
- [274] Howlett WP, Brubaker GR, et al. Konzo, an epidemic upper motor neuron disease studied in Tanzania. *Brain* 1990;113(Pt 1):223–35.
- [275] Tylleskar T, Banea M, Bikangi N, et al. Cassava cyanogens and konzo, an upper motoneuron disease found in Africa. *Lancet* 1992;339:208–11.
- [276] Tylleskar T, Howlett WP, Rwiza HT, et al. Konzo: a distinct disease entity with selective upper motor neuron damage. *J Neurol Neurosurg Psychiatry* 1993;56:638–43.
- [277] Osuntokun BO. Cassava diet, chronic cyanide intoxication and neuropathy in the Nigerian Africans. *World Rev Nutr Diet* 1981;36:141–73.

- [278] Konagaya M, Matsumoto A, Takase S, et al. Clinical analysis of longstanding subacute myelo-optico-neuropathy: sequelae of clioquinol at 32 years after its ban. *J Neurol Sci* 2004;218:85–90.
- [279] Baumgartner G, Gawel MJ, Kaeser HE, et al. Neurotoxicity of halogenated hydroxyquinolines: clinical analysis of cases reported outside Japan. *J Neurol Neurosurg Psychiatry* 1979; 42:1073–83.
- [280] Sobue G, Ueno-Natsukari I, Okamoto H, et al. Phenotypic heterogeneity of an adult form of adrenoleukodystrophy in monozygotic twins. *Ann Neurol* 1994;36:912–5.
- [281] Shibasaki H, Kakigi R, Ohnishi A, et al. Peripheral and central nerve conduction in subacute myelo-optico-neuropathy. *Neurology* 1982;32:1186–9.
- [282] Konno H, Takase S, Fukui T. Neuropathology of longstanding subacute myelo-optico-neuropathy (SMON): an autopsy case of SMON with duration of 28 years. *No To Shinkei* 2001;53:875–80.
- [283] Shiraki H. The neuropathology of subacute myelo-optico-neuropathy, “SMON”, in the humans:—with special reference to the quinoform intoxication. *Jpn J Med Sci Biol* 1975; 28(Suppl):101–64.