Nutritional Disorders

Nutritional deficiency can adversely affect the nervous system, both centrally and peripherally, leading to problems in thinking and other brain functions as well as in the brain's regulation of the body.

In developing countries such deficiency is usually the result of starvation or dietary restriction. In developed countries, the major causes of nutritional deficiency are alcoholism, diseases that cause malabsorption of particular nutrients, chronic illnesses that involve general physical wasting, psychiatric illnesses, food faddism, infantile malnutrition, and, rarely, genetic disorders.

The most clearly defined nutritional deficiencies producing neurological symptoms and signs involve vitamins—organic compounds required for normal metabolic functions but not synthesized in the body.

The signs and symptoms of vitamin deficiencies that may prompt a person to seek medical attention differ, depending on the particular vitamin.

Because vitamins are not produced in the body, they must either be provided in sufficient amounts in your daily diet or be taken as dietary supplements.

Vitamins are classified as water soluble or fat soluble.

Deficiency of fat-soluble vitamins is often a result of malabsorption associated with liver, pancreatic, or gastrointestinal disease. With the exception of vitamin B12 (cobalamin), deficiency of water-soluble vitamins is usually the result of inadequate intake.

Malnutrition (including that associated with alcoholism) seldom produces a deficiency of just one or two vitamins; the symptoms and signs are likely the result of multiple deficiencies.

A popular misconception is that if taking some vitamins are good, then taking more must be better. However, excessive intake of certain vitamins can be neurotoxic—the medical term for the effects of such an excess is hypervitaminosis.

Because water-soluble vitamins are rapidly excreted from the body, symptomatic hypervitaminosis usually involves fat-soluble vitamins.

Water-Soluble Vitamins

Thiamine (Vitamin B1)

Thiamine works together with a number of enzymes to metabolize glucose. Because body stores of thiamine are limited, symptoms of deficiency can appear after only a few weeks of inadequate intake.

In developing countries, thiamine deficiency is most likely to produce beriberi, with cardiac failure and peripheral neuropathy. In Europe and North America, thiamine deficiency, especially in alcoholics, is more often associated with symptoms indicating harm to the central nervous system—namely, Wernicke-Korsakoff disease, which is really two disorders arising from the same cause.

Wernicke's syndrome has three clear characteristics:

- *Altered mental function*
  Mental symptoms include drowsiness, inattentiveness, impaired memory, and slowed thinking, which, if untreated, can progress to coma and death over days.

- *Abnormal eye movements*

Abnormal eye movements include rhythmic jerking, usually from side to side (nystagmus), and restricted eye movements, which can progress to complete immobility (ophthalmoplegia).

- *Loss of balance (gait ataxia).*
  Gait ataxia can progress to an inability to walk or stand unaided.

Treatment of Wernicke's syndrome includes 50 to 100 milligrams of thiamine given intravenously or intramuscularly daily for several days (to saturate body stores,) along with multivitamins. Thereafter, doses of more than a few milligrams daily will simply be excreted. Symptoms usually improve over days, but treatment delay can result in permanent neurological impairment. Some mental symptoms may remain; these most often consist of a relatively selective memory loss (Korsakoff syndrome) in both learning new memories (anterograde) and retrieving old memories (retrograde), sometimes with confabulation (filling in amnesic gaps with false memories). Eye movements may return but nystagmus is often persistent, and gait may improve but with a continuing unsteadiness and a tendency to fall.

In diagnosing Wernicke-Korsakoff disease, a physician may order blood tests. These can show thiamine deficiency because it causes elevated levels of two blood chemicals, lactate and pyruvate, and, more specifically, decreased levels in red blood cells of an enzyme called transketolase. The diagnosis is usually based on symptoms and signs, however, and it is standard practice to give thiamine and multivitamins to any hospitalized alcoholic.

In autopsied brains of patients with Wernicke-Korsakoff disease, there are characteristic pathological abnormalities of neurons, glia, and blood vessels in deep regions of the cerebrum (thalamus and hypothalamus) and in the brain stem and cerebellum. In some

patients, cerebellar damage and gait ataxia occur without other features of Wernicke's syndrome; the relative contribution of thiamine and other vitamin deficiencies to this more restricted cerebellar disorder is unclear. Similarly uncertain is the role of specific vitamin deficiency in alcoholics with optic neuropathy (impaired vision caused by degeneration of the optic nerve) and peripheral neuropathy, which causes pain and sensory loss in the feet and hands and sometimes weakness of the arms or legs, and autonomic symptoms—for example, light-headedness on standing and palpitations.

Niacin

Also called nicotinic acid (and having no chemical relationship to tobacco), niacin is converted in the body to active forms that are involved in tissue respiration. Deficiency causes pellagra, a disease that affects the skin, the gastrointestinal tract, and the central and peripheral nervous systems. Pellagra is so dramatically debilitating that before it was understood to be a niacin deficiency; people suffering from this disorder were confined to institutions. A sunburn-like rash on light-exposed areas can progress to darkening and even scarring. The tongue becomes red and sore, and nausea, vomiting, and watery or bloody diarrhea result in weight loss.

Neurological manifestations include mental change (anxiety, irritability, insomnia, fatigue, depression, and impaired memory, progressing to dementia or psychosis with delusions and hallucinations, and then to delirium or coma), sensorimotor peripheral neuropathy (weakness and sensory loss in the arms or legs), spinal cord damage (weakness in both legs and loss of bladder and bowel control), optic nerve and retinal damage (impaired vision), and seizures.

Diagnosis can be confirmed by measuring niacin metabolites in the urine but is usually based on history and examination. Treatment is with 50 to 150 mg a day of niacin (or a precursor compound,

nicotinamide), given orally, plus other vitamins. Symptoms usually improve, but mental abnormalities may be permanent.

Niacin is used to treat hyperlipidemia (elevation in the serum of cholesterol and other fats), and high doses cause flushing, vomiting, diarrhea, liver dysfunction, delirium, and retinal damage.

In 1989 several thousand people taking tryptophan (a niacin precursor) obtained in health food stores developed muscle pain, weakness, impaired memory, peripheral neuropathy, and elevations of particular white blood cells in their blood. The disorder is believed to have been caused by a contaminant rather than by tryptophan (or niacin) itself.

Pyridoxine (Vitamin B6)

Vitamin B6 consists of three compounds—pyridoxine, pyridoxal, and pyridoxamine—each of which is converted in the body to a common metabolite that works with a number of enzymes. Pyridoxine deficiency causes seizures and sensorimotor peripheral neuropathy, but ascribing particular symptoms in a malnourished person to pyridoxine deficiency alone is difficult because an affected individual is nearly always deficient in other nutrients as well.

More specific are 'pyridoxine dependency' diseases. For example, the drugs isoniazid, used to treat tuberculosis, and hydralazine, which may be prescribed to treat hypertension, inactivate pyridoxine, requiring dietary supplements to prevent the development of sensory peripheral neuropathy. For reasons that are unclear, some newborns develop seizures that respond to pyridoxine only in doses several times the standard daily requirement.

Pyridoxine taken in mega-doses (2 to 6 grams daily for months) also causes severe sensory peripheral neuropathy, including loss of distal limb proprioception (the ability to sense the position of one's feet when walking), resulting in gait ataxia. Improvement following pyridoxine withdrawal may take months or years.

Cobalamin (Vitamin B_{12})

Cobalamin is obtained from meat, fish, liver, milk, and eggs. Strict vegetarians therefore require supplementation. In the body, active forms of cobalamin work with enzymes involved in carbohydrate and amino acid metabolism; in the process, folic acid is activated. When folic acid is not activated, the result is anemia.

Considerable cobalamin is stored in the body, mostly in the liver, so deficiency states can exist for years before symptoms appear.

Cobalamin deficiency has several causes. In pernicious anemia, loss of 'intrinsic factor,' a compound normally present in the stomach lining, results in malabsorption of cobalamin. Nitrous oxide, popular among recreational 'sniffers,' inactivates cobalamin (without lowering blood levels), so habitual sniffers develop symptoms of deficiency. Estimates of cobalamin deficiency in the elderly are as high as 20 percent, the result of changes in the gastrointestinal tract associated with aging.

Systemic symptoms of cobalamin deficiency include a red, sore tongue, anorexia, vomiting, diarrhea, weight loss, and, secondary to severe anemia, generalized weakness and fainting. Specific neurological damage involves the spinal cord and the peripheral nerves, causing numbness or tingling, most often in the legs; with progression, there is impaired proprioception and gait ataxia. Leg weakness is less common. Less often a person may have impaired memory, psychiatric symptoms, and decreased vision. Significantly, more than one fourth of patients with cobalamin deficiency and neurological symptoms do not have anemia.

The diagnosis of cobalamin deficiency is based on low blood levels of the vitamin. Borderline levels may be difficult for a physician to interpret, however, and confirmation of true deficiency can be made by the finding of elevated blood levels of metabolites—homocysteine and methylmalonic acid—dependent on cobalamin.

Treatment of cobalamin deficiency is with vitamin B12, which, in the presence of pernicious anemia or malabsorption, is given intramuscularly. Most patients improve with treatment, but improvement may not be evident for a few months and may then continue for years.

Folic Acid (Folate)

Unlike cobalamin, folic acid is present in nearly all foods. Folate deficiency can result from malnutrition (again, especially in alcoholics), malabsorption, or liver disease.

Some prescription drugs, such as phenytoin (to treat epilepsy), barbiturates, and oral contraceptives, interfere with folate absorption and storage. Another drug, methotrexate, which a person may be taking for certain cancers or disorders of the immune system, inactivates folate.

Whether folate deficiency in adults causes either peripheral or central nervous system disease is a matter of debate among scientists. Most findings of deficiency in adults are probably based on inadequately treated deficiency of cobalamin or other vitamins. Low folate levels have been associated with depression and cognitive impairment in the elderly, but nutritional status is often inadequate in such individuals, making cause and effect unclear.

Taking folate supplements during pregnancy prevents the occurrence of neural tube defects such as spina bifida and anencephaly, and the Public Health Service recommends a daily dose of 0.4 mg in women capable of becoming pregnant. (Doses higher than 1.0 mg daily are not a good idea: because of the interaction of folate and cobalamin, higher doses might mask the diagnosis of cobalamin deficiency.)

As with cobalamin, folate deficiency is associated with high blood levels of homocysteine, a risk factor for coronary artery and cerebrovascular disease. Studies are currently under way to determine whether folate and cobalamin supplementation reduces the risk of

stroke or heart attack in people who are not deficient in cobalamin or folate but who have high blood homocysteine levels.

Ascorbic Acid (Vitamin C)

Ascorbic acid is essential in the body's synthesis of collagen and other components of body tissues. Vitamin C deficiency causes bleeding, and neurological disease results from hemorrhage into muscles, peripheral nerves, or the brain. Mega-doses of vitamin C do not seem to produce adverse consequences other than nausea and diarrhea.

Riboflavin, Pantothenic Acid, and Biotin

Multiple vitamin deficiencies are nearly always present in malnourished individuals, and the association of these vitamins with specific symptoms is usually uncertain. The medical literature has described sensory peripheral neuropathy, impaired vision, and deafness with riboflavin deficiency. A rare genetic disorder of biotin dependency produces altered thinking, abnormal eye movements, muscle rigidity, and weakness. These symptoms respond to biotin and reappear if treatment is discontinued.

Fat-Soluble Vitamins

Vitamin A

Several forms of vitamin A are derived from plant and animal tissues. Liver disease and malabsorption both lead to deficiency. Hypothyroidism and diabetes mellitus impair conversion of vitamin A in the body to its active form, and kidney failure or sustained fever reduces the body's stores of the vitamin.

In developing countries, deficiency of vitamin A is a major feature of generalized malnutrition.

Deficiency affects the skin and eyes, producing night blindness, clouding of the eyes' corneas, dry skin, and thickening of oral, nasal,

and respiratory mucous membranes with impaired smell and taste, and lung dysfunction.

Adolescents taking mega-doses of vitamin A for acne (usually more than 40,000 IU daily) develop toxicity, including anorexia, weight loss, dry skin, hair loss, muscle soreness, and raised intracranial pressure, which in turn can cause headache, double vision, and decreased visual acuity.

Vitamin D

In the presence of ultraviolet light, vitamin D is synthesized in the skin and is not required in the diet. Further metabolism in the liver and kidney produces its active form.

Deficiency can result from liver disease and malabsorption, malnutrition, chronic kidney disease, or lack of sunlight. Phenobarbital and phenytoin reduce blood vitamin D levels, and there are hereditary disorders of vitamin D resistance. Vitamin D deficiency causes bone disease— rickets in children and osteomalacia (bony softening) in adults—which in turn can cause spinal cord or nerve root compression with pain, weakness, and sensory loss. Low blood levels of calcium produce muscle spasms (tetany), spasm of the vocal cords with airway obstruction (stridor), seizures, and altered thinking, including psychosis.

Repeated ingestion of large doses of vitamin D (usually more than 50,000 IU daily) produces potentially lethal elevations of blood calcium levels. Symptoms include osteoporosis (bone thinning); kidney stones; calcification of the heart and blood vessels with congestive heart failure and arrhythmia; anorexia, nausea, vomiting, and constipation; and neurological symptoms that include weakness, impaired memory, depression, psychosis with hallucinations, delirium, and coma.

Treatment includes withdrawal of vitamin D, a low-calcium diet, saline, and the diuretic furosemide.

Vitamin E

Vitamin E, which comprises several compounds of a substance called tocopherol, reduces tissue free-radical production.

Deficiency occurs in malabsorption disorders, including the hereditary disease Bassen-Kornzweig syndrome. Symptoms include fatty stool (steatorrhea), acanthocytosis (burr-like deformities of red blood cells), decreased blood cholesterol and triglyceride levels, pigmentary degeneration of the retina with impaired vision, degeneration of the cerebellum and spinal cord (causing ataxia, weakness, and sensory loss), abnormal eye movements, and sensory peripheral neuropathy.

Treatment is with large oral doses of vitamin E; for severely affected patients, the vitamin can be administered by injection.

Trials testing the efficacy of vitamin E in degenerative disorders such as Alzheimer's disease and Parkinson's disease are currently under way. Vitamin E is widely available in health food stores, and very large doses have been associated with impaired blood coagulation, raising the risk of hemorrhage into the brain and other tissues.

Vitamin K

Vitamin K, a group of compounds, is involved in the synthesis of coagulation factors. Deficiency is a feature of liver disease and malabsorption, and, less often, of malnutrition or antibiotic use. The result is bleeding, including intracranial hemorrhage.