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Vitamin Deficiencies

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General Comments on Vitamin Deficiencies

Vitamin deficiencies arise when the diet is inadequate in its content of one or more nutrients or when the body is unable to utilize dietary nutrients adequately. Single nutrient deficiencies are rare these days, because a diet that is suboptimal in one vitamin is nearly always suboptimal in others. Thus, a poor diet tends to have multiple inadequacies. Furthermore, some vitamins are involved in the metabolism of other vitamins, and therefore deficiencies may be interconnected.

A number of factors may serve to intensify the biological effects of a poor diet. For example, exogenous alcohol has specific and selective effects upon vitamin metabolism, interfering with the absorption of some vitamins (e.g., thiamin, riboflavin) and accelerating the metabolic degradation of another (B_6). In addition, a number of medications may affect vitamin metabolism, and at multiple sites. From a practical point of view, laxatives and diuretics, often used for prolonged periods by vulnerable elderly patients with minimal indications, are probably the most common causes of drug-induced vitamin deficiencies.

The concept of risk factors, utilized effectively in the evaluation and prevention of heart disease, needs to be applied to the area of vitamin deficiency. Thus, a patient with alcohol abuse who takes several chronic medications and suffers from malabsorption will have a much enhanced risk of becoming grossly vitamin deficient with a poor diet, and of developing overt deficiency that otherwise might be marginal or subclinical.

A great unknown is the effect of herbal products and so-called alternative/complementary therapies upon vitamin metabolism and on the actions of prescription drugs that, in turn, may affect vitamin metabolism. With large numbers of people consuming a wide variety of products about which there is little information or understanding, a potential exists for developing new forms of malnutrition. We urgently need more information on drug-herbal interactions and their implications for vitamin metabolism.

Several points about the patterns of vitamin deficiency currently emerging in the United States are summarized in Table 64.1.

While the effects of fullblown vitamin deficiencies are well known and have been thoroughly described, the effects of lesser or marginal deficiencies are not as well defined.

TABLE 64.1

Features of Vitamin Deficiencies

1. Dietary vitamin deficiencies tend to be multiple, not single.
2. Clinical evidence of vitamin deficiencies develops gradually, and early symptoms such as fatigue and weakness may be vague, ill-defined, and non-specific.
3. The physical examination cannot be relied upon to make a diagnosis of early vitamin deficiency; classic features such as the "corkscrew hairs" of scurvy are only detectable after profound deficiency has been attained.
4. The rate of development of vitamin deficiencies is highly variable. Water-soluble vitamins may be depleted within several weeks; longer periods are needed for significant depletion of fat-soluble vitamins. Several years are required for clinical manifestations of vitamin B_{12} deficiency unless there are complicating factors, such as ileal resection or inflammatory bowel disease involving the ileum.
5. The impact of dietary deficiencies of vitamins is greatly augmented by the long-term chronic use of certain medications that may affect absorption, utilization, or excretion of vitamins. Chief among these are laxatives and diuretics. These considerations are particularly relevant to older individuals who use the largest number of drugs, use them for the longest duration, and may have marginal diets to begin with.
6. The concept of "risk factors" may be helpful in assessing the factors such as drugs and alcohol that contribute to determining the clinical significance of a given dietary deficiency.

Within recent years, scientists and the general public have been paying more attention to marginal deficiency in attempting to gain the maximal benefits from diet for health. Recent findings suggest that the concept of so-called "normal" needs to be re-evaluated, inasmuch as there may be different risks for disease within the range considered "normal." For example, individuals with serum folic acid levels in the lower part of the normal range have been shown to have significantly elevated serum concentrations of homocysteine compared to those whose folic acid concentrations are in the upper range of normal. With elevated serum homocysteine concentrations emerging as a risk factor for heart disease, these observations suggest that perhaps we should set higher standards and expectations for the normal range.

In the prevention and treatment of vitamin deficiencies, one must approach the patient in a logical fashion and proceed in an orderly direction. Long-term compliance with an appropriate diet and the use of supplements, if indicated, is the goal, but may be difficult to achieve. Some of the points about correction of vitamin deficiencies are summarized in Table 64.2.

TABLE 64.2

Some Considerations in Correction of Vitamin Deficiencies

1. Approach the patient as a whole; ask yourself, how did a vitamin deficiency develop in the first place? What can be done to prevent a recurrence? Are there complicating factors in addition to the diet?
2. Unless there are specific indications of a single nutrient deficiency, such as vitamin B_{12} in pernicious anemia, most malnourished patients will require rehabilitation with multiple nutrients, primarily with diet, and additionally with supplementation, if necessary.
3. Simple steps can often improve a diet significantly, such as discarding old produce, avoiding "fast food" meals on a regular basis, and increasing the intake of fresh fruits and vegetables. In modern nutrition, one speaks of "junk diets" rather than single "junk foods," and the necessity to have moderation and variety.
4. Learn how to read a label from a nutritional supplement bottle so that you can properly instruct your patients. The array of choices of nutritional supplements is bewildering, and patients must learn that more is not necessarily better.
5. Remember that vitamins may behave like drugs and have a defined toxic:therapeutic ratio. Some vitamins, such as vitamins A and D, have a real potential for causing toxicity. B vitamins may also cause problems, as exemplified by the sensory neuropathy resulting from large doses of vitamin B_6.

Vitamin A

Functions

Vitamin A has a wide variety of functions, including specific roles in vision, embryogenesis, cellular differentiation, growth and reproduction, immune status, and taste sensations.

Deficiency

Deficiency of vitamin A is of crucial importance as a worldwide nutritional problem, because the resultant xerophthalmia is a cause of blindness in approximately half a million preschool children each year in the developing countries. In these areas, the diet is composed primarily of such items as rice, wheat, maize, and tubers that contain far from adequate amounts of vitamin A precursors. The World Health Organization and other groups have made great efforts to plan programs that identify people at risk and to institute appropriate preventive measures on a broad scale.

Clinical deficiency of vitamin A may be overt or subclinical. One of the earliest signs of vitamin A deficiency is night blindness, observed in both children and adults. A characteristic sign that is observed later is Bitot's spots, collections of degenerated cells in the outer aspects of the conjunctivae that appear white in color. The development of xerophthalmia follows a defined sequence, leading eventually to keratomalacia, in which perforation of the cornea occurs. This disorder in its end stages is irreversible, but if ocular abnormalities are detected early and treated vigorously, they may be potentially preventable.

Vitamin A deficiency also causes skin disorders in the form of follicular hyperkeratosis. Although characteristic skin changes occur in response to a deficiency of vitamin A, in practical terms one should remember that skin lesions may be caused by other nutrient deficiencies such as zinc, biotin, niacin, and riboflavin.

Children significantly deficient in vitamin A manifest increased incidence of serious and life-threatening infections and elevated mortality rates. It has been recognized that deficient Vitamin A status is a risk factor for the maternal-to-fetal transmission of human immunodeficiency virus; the relative risk of transmission of the virus is fourfold greater in vitamin A-deficient than vitamin A-sufficient mothers.

Vitamin A deficiency in the U.S. is identified largely with certain risk groups: the urban poor, elderly persons (particularly those living alone), abusers of alcohol, patients with malabsorption disorders, and other persons with a poor diet. Vitamin A deficiency is generally found in a setting in which there are multiple vitamin and mineral deficiencies. Special attention must be paid to deficiency of zinc, a frequent finding in alcoholism, as depletion of zinc interferes with the mobilization of vitamin A from its storage sites in liver. This effect is achieved by blocking the release of holo-retinol-binding protein from the liver.

The physician must keep in mind that deficiency of vitamin A in the U.S. may also develop after the long-term use of several medications. Drug-induced nutritional deficiencies in general, particularly those involving vitamin A, occur most frequently among elderly persons, because they use medications in the largest number and for the most prolonged duration, and may have borderline nutritional status to begin with. Among the drugs most relevant to compromising vitamin A status are mineral oil, which dissolves this nutrient; other laxatives, which accelerate intestinal transit and may diminish the magnitude of vitamin A absorption; cholestyramine and colestipol, which bind vitamin

A; and, under certain conditions, neomycin and colchicine. Patients who are consuming olestra, which may possibly interfere with absorption of a number of vitamins, including A, have been advised to take a multivitamin supplement regularly.

Laboratory Diagnosis of Deficiency

The laboratory diagnosis of vitamin A deficiency is based upon the finding of a low plasma retinol; levels below 10 μg/dl signify severe or advanced deficiency. Interpretation of plasma retinol concentrations may be confounded, however, by a number of other factors such as generalized malnutrition and weight loss. Some authorities have preferred to utilize a form of retinol tolerance test, measuring the increment in serum vitamin A levels over five hours following an oral load of vitamin A.

Prevention

Deficiency of vitamin A can be prevented by a diet high in carotenes, which serve as precursors to vitamin A. The carotenes, particularly beta-carotene, are derived exclusively from plant sources, the richest of which are palm oil, carrots, sweet potatoes, dark green, leafy vegetables, cantaloupe, oranges, and papaya. Vitamin A itself (preformed vitamin A) is derived only from animal sources such as dairy products, meat, and fish. The commercial preparations of fish oils are rich, sometimes too rich, as sources of preformed vitamin A.

The nutritional value of dietary sources of vitamin A may be compromised when the food items are subject to oxidation, particularly in the presence of light and heat. Antioxidants, such as vitamin E, may prevent the loss of vitamin A activity under these conditions.

Treatment

Vitamin A deficiency has been treated worldwide with single intramuscular injections of massive amounts (100,000 to 200,000 IU) of vitamin A, repeated at intervals of approximately six months to one year. Such doses have been effective and are associated with remarkably little toxicity, perhaps because body stores are so depleted at the time of therapy. These doses, however, may produce acute toxic symptoms in well-nourished persons.

Clinical vitamin A deficiency in the U.S. can be treated with either beta-carotene, if there is normal body conversion to vitamin A, or vitamin A itself. Daily doses in the range of 25,000 IU of beta-carotene are being consumed by many healthy individuals. The yellowish discoloration of the skin associated with prolonged use of beta-carotene is not believed to be harmful. Vitamin A, in contrast, is quite toxic when ingested in amounts considerably higher than the Recommended Daily Allowances (RDA), especially for prolonged periods. It is probably advisable not to exceed two to three times the RDA for vitamin A in planning a domestic treatment program involving vitamin A administration.

Congenital malformations, a particularly disturbing consequence of vitamin A overdosage, have been reported in women consuming 25,000 to 50,000 IU daily during pregnancy. The lowest dose of vitamin A that would be completely safe as a supplement for pregnant women is not known definitely. Therefore, it is not a good idea for pregnant women to take supplementary vitamin A unless there are specific indications, such as malabsorption, or proven deficiency. Many advisory groups caution that the maximal intake of preformed vitamin A consumed during pregnancy should not exceed 10,000 IU.

At present, there is widespread interest in other therapeutic applications of vitamin A and its derivatives. Large doses of vitamin A have been found to reduce morbidity and mortality rates among children suffering from severe cases of measles. Certain forms of leukemia have been found to respond to derivatives of vitamin A. The therapeutic potential of this vitamin is being expanded greatly in studies of the chemoprevention and treatment of cancer. The toxicity of large doses of vitamin A places important limits on its feasibility in cancer prevention. Attention has turned to beta-carotene and related agents, which in addition to their role as precursors of vitamin A, have strong antioxidant activity and other effects as well. Beta-carotene, however, may possibly pose a risk in heavy smokers in that two studies in this population have shown an actual increase in prevalence of lung cancer when beta-carotene was administered for several years.

Diminished prevalence of certain cancers has been found among people whose intake of fruits and vegetables is high; this finding has been attributable at least in part to the high content of carotenoids in the diet. Many phytochemicals have been found in fruits and vegetables that have potential health benefits. Some data show that a combination of antioxidants (i.e., vitamin E, vitamin C, and beta-carotene) may be more effective than any of these single agents, providing more evidence in favor of moderation and variety in the diet.

Vitamin D

See Section 65 on calcium and Section 61 on calcium and vitamin D in bone health.

Vitamin E

Functions

A generally accepted role for vitamin E is as a scavenger of free radicals, and in this capacity it protects cell membranes from damage. The role of vitamin E as an antioxidant in health and disease has attracted wide interest. It has many other properties as well. Vitamin E is essential for the immune system, particularly T lymphocytes, and has a role in DNA repair. Interest is growing in the effect of vitamin E on inhibiting oxidation of low-density lipoprotein (LDL); oxidized LDL is quite atherogenic. The neuromuscular system and the retina also require vitamin E for optimal function.

Vitamin E may have additional cellular protective effects. There is evidence that this vitamin may protect sulfhydryl groups in enzymes and other proteins. Similarly, stores of vitamin E may be conserved by the glutathione s-transferase system, which utilizes reduced glutathione and serves similar antioxidant functions.

Deficiency

Dietary vitamin E deficiency is relatively unusual in the U.S. under ordinary circumstances, as sources of vitamin E are widely available from the food supply. The recognizable cases of vitamin E deficiency tend to arise in debilitated patients who have had severe and prolonged periods of fat malabsorption, because vitamin E is incorporated into chy-

lomicrons with other products of fat absorption. Any process that interferes with fat digestion and absorption may also impair absorption of vitamin E. Disorders in which symptomatic vitamin E deficiency may develop include cystic fibrosis, celiac disease, cholestatic liver disease, and short-bowel syndrome of any cause.

Major abnormalities of neurologic function are observed in a severe and prolonged vitamin E deficiency state. Patients display areflexia, ophthalmoplegia, and disturbances of gait, proprioception, and vibration. In premature infants, vitamin E deficiency results in hemolytic anemia, thrombocytosis, edema, and intraventricular hemorrhage. There is increased risk of retrolental fibroplasia and bronchopulmonary dysplasia.

In hemolytic anemia, such as that caused by glucose-6-phosphate dehydrogenase deficiency and sickle cell anemia, vitamin E levels in blood tend to be decreased. Inborn errors of vitamin E metabolism have been identified, but are rare. There are severe neurologic abnormalities in this category. In abetalipoproteinemia, there is a defect in the serum transport of vitamin E. A hallmark of this disease is the finding of an extremely low serum cholesterol level together with a very low serum level of vitamin E.

Laboratory Diagnosis of Deficiency

Ideally, the diagnosis of vitamin E deficiency should be made by detailed chromatographic analysis of the various E isomers. In practice, such a procedure is not realistic, and the clinical evaluation usually depends upon a measurement of plasma E alone. Plasma concentrations of vitamin E below 0.50 μg/ml are generally regarded as indicative of deficiency. It has been observed that despite a wide range of dietary intake, the serum variations in vitamin E levels tend to be more limited.

It is important to keep in mind that vitamin E is transported in blood bound to lipoproteins, particularly LDL. In any condition in which the serum cholesterol is abnormally high or low, the vitamin E level will vary accordingly. Therefore, before concluding that anyone is vitamin E-deficient, the plasma level of this vitamin should be evaluated in relation to the prevailing cholesterol concentrations. In addition, an alpha-tocopherol transport protein has been identified recently.

Prevention

Deficiency of vitamin E can be avoided by regular consumption of the many sources of this vitamin in the food supply. The richest sources of vitamin E in the U.S. diet are vegetable oils, including corn, cottonseed, safflower and soybean oils, and the margarines and other products made from these oils. Green, leafy vegetables are also good sources of vitamin E. In evaluating the adequacy of any given dietary regimen, one should keep in mind that losses of the vitamin occur during storage, cooking, and food processing, particularly with exposure to high temperatures and oxygen.

Because vitamin E deficiency frequently occurs as a result of severe intestinal malabsorption, it is essential to identify this condition early and avoid measures that may intensify the degree of malabsorption. For example, cholestyramine (Questran) and colestipol (Colestid), resins used in the treatment of hypercholesterolemia, by binding to the vitamin, may cause some degree of malabsorption of vitamin E and other fat soluble vitamins. Specific supplementation with vitamin E may be needed. The usual vitamin supplement containing 400 IU should be adequate for this purpose.

Treatment

Vitamin E deficiency can be treated satisfactorily. There is a wide margin of safety in the therapeutic administration of the vitamin. Daily doses of vitamin E in the range of 100 to

800 IU can be given safely to nearly all deficient patients. This dosage is higher than that usually found in multivitamin supplements. This dose range can be used appropriately in those patients with vitamin E deficiency diagnosed in association with celiac disease, inflammatory bowel disease, or other chronic and prolonged forms of intestinal malabsorption. In such instances, many other nutrient deficiencies are likely to be found in association with that of vitamin E, and they, too, necessitate treatment.

In the genetic disorders of vitamin E metabolism, such as isolated vitamin E deficiency, doses in the range of 800 to 1000 IU or higher, must be taken. Large doses of vitamin E given therapeutically under these conditions appear to be generally safe. Some investigators have suggested that pharmacologic doses of vitamin E may interfere with the intestinal absorption of vitamins A and K, but there are few data with which to evaluate this potential risk. In addition, there are suggestive reports that doses of vitamin E in excess of 1200 IU per day may possibly interfere with the action of vitamin K and intensify the actions of anticoagulant drugs. Further information is needed on this subject.

Vitamin K

Functions

The best known role for vitamin K is as cofactor for a post-translational modification in a diverse group of calcium-binding proteins, whereby selective glutamic (Glu) residues are transformed into gamma-carboxyglutamic acid (Gla). The best characterized vitamin K-dependent proteins include the four classic vitamin procoagulants (factors II, VII, IX, and X) and two feedback anticoagulants (proteins C and S), all synthesized by the liver.

Gla proteins also occur in several other tissues. Osteocalcin, which contains three Gla residues, is synthesized by the osteoblasts of bone. It is one of the ten most abundant proteins in the body and may play a role in regulating bone turnover. A second protein isolated from bone that is related structurally to osteocalcin is matrix Gla protein. This protein is more widely distributed, and there is now good evidence that this protein is an important inhibitor of calcification of arteries and cartilage. Gla residues provide efficient chelating sites for calcium ions that enable vitamin K-dependent proteins to bind to other surfaces (e.g., procoagulants to platelet and vessel wall phospholipids, and osteocalcin to the hydroxyapatite matrix of bone). The carboxylation reaction is catalyzed by a microsomal vitamin K-dependent gamma-glutamyl carboxylase, which requires the dietary quinone form of vitamin K to be first reduced to the active cofactor vitamin K hydroquinone, vitamin KH2.

In bone, vitamin K achieves gamma-carboxylation of osteocalcin. In addition, vitamin K regulates interleukin-6 production, synthesis of prostaglandin E2, and urinary excretion of calcium. It is not surprising, therefore, that in patients with low dietary intake of vitamin K long-term, the risk for hip fractures is increased.

Deficiency

Isolated deficiency of vitamin K due entirely to inadequate dietary intake tends to be unusual in adults in the U.S., because this vitamin is widely distributed in the food supply. Overt deficiency of vitamin K is more likely to be observed in conditions in which there are significant complicating factors, such as long-term use of broad spectrum antibiotics, and illnesses and drugs associated with fat malabsorption. It is essential to recognize that vitamin K is synthesized by intestinal bacteria and that this source may provide a significant contribution to the supply of the vitamin. Antibiotic treatment will largely eliminate

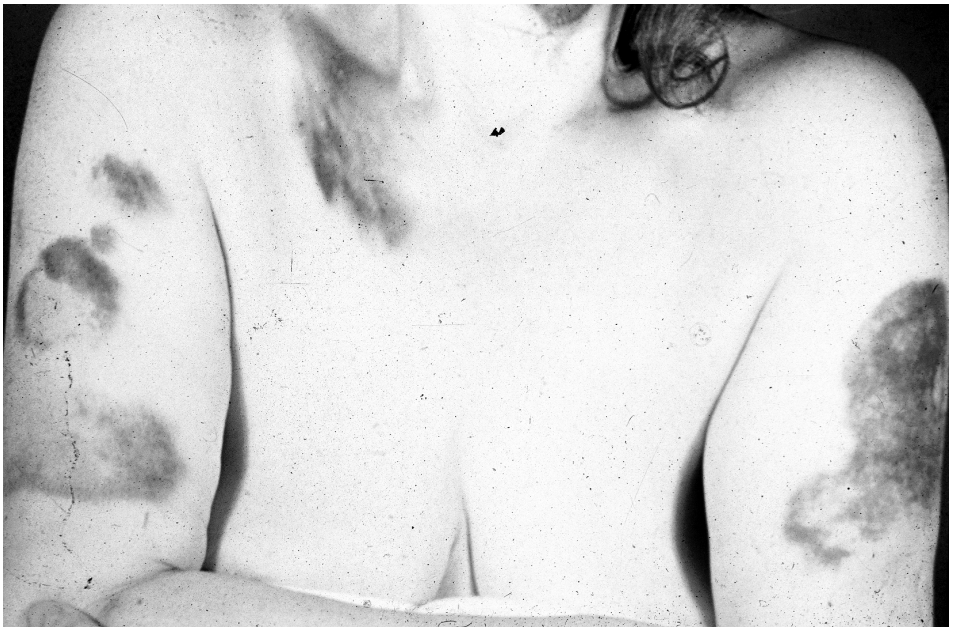

FIGURE 64.1
(See Color Figure 64.1) Patient with severe vitamin K deficiency, illustrating multiple purpuric areas occurring spontaneously. (Photo courtesy of Elaine B. Feldman, M.D.)

these bacterial sources of vitamin K and may have a clinical impact, particularly when treatment is prolonged. One class of antibiotics, the cephalosporins, cause vitamin K deficiency by an entirely different mechanism, namely by inhibiting the vitamin K-dependent hydroxylase.

Severe fat malabsorption is regularly observed as a feature of severe regional enteritis, nontropical sprue, cystic fibrosis, ulcerative colitis, and a number of other disorders. Following extensive intestinal resection, patients are left with a short bowel syndrome, in which fat malabsorption is prominent because of the reduction in intestinal surface area available for absorption and transport.

Vitamin K deficiency with the most serious consequences is that associated with the hemorrhagic disease of the newborn. The pathogenesis of this syndrome derives from (a) the poor placental transport of vitamin K combined with (b) lack of fetal production of vitamin K by intestinal bacteria since the intestinal tract is sterile, and (c) diminished synthesis by an immature liver of prothrombin and its precursors. In adults with vitamin K deficiency, multiple purpuric lesions may be noted (Color Figure 64.1*).

As noted above, dietary sources of vitamin K are widespread in the food supply in the U.S. The highest amounts are found in green leafy vegetables, such as broccoli, Brussels sprouts, spinach, turnip greens, and lettuce. Interestingly, the risk of hip fracture is reported as highest in women who have the lowest consumption of lettuce, which contributes significantly to vitamin K nutrition. Some vitamin K at lower amounts can be found in meat, dairy products, coffee, and certain teas.

Laboratory Diagnosis of Deficiency

Vitamin K in body fluids and in foods can be measured by biological and chemical methods. The vitamin is light sensitive and must be shielded from light during storage

* See color figures following page 992.

and analysis. In practice, functional vitamin K status is assessed indirectly by measurements of serum prothrombin. Clinical vitamin K deficiency should be suspected wherever there is an unusual hemorrhagic tendency.

Prevention

For healthy individuals, dietary vitamin K deficiency should be preventable by maintaining a diet high in green, leafy vegetables. When antibiotics are prescribed long-term, they should be kept to the minimal time period and doses necessary. Efforts should be initiated early to recolonize the gastrointestinal tract through providing live culture yogurt or other sources of normal flora. Similar guidelines should be followed in cases in which drugs causing malabsorption of vitamin K are required. A vitamin supplement containing vitamin K may be advisable. Effective treatment of an underlying disorder of the gastrointestinal tract should be undertaken in a specific fashion where possible, such as a gluten-free diet for nontropical sprue. All of these measures should help to prevent vitamin K deficiency.

Treatment

Treatment of vitamin K deficiency can be accomplished by oral administration of the purified vitamin, consumption of vitamin K-rich foods, or parenteral injection. Water-soluble preparations of vitamin K are available. An oral dose of approximately 500 μg/day should correct vitamin K deficiency, as assessed most simply by measuring serum prothrombin. A poor or inadequate improvement of prothrombin time after vitamin K administration is generally indicative of severe underlying liver disease.

Thiamin (Vitamin B_1)

Functions

The major function of dietary thiamin is to serve as the precursor for the coenzyme, thiamin pyrophosphate, which by the process of oxidative decarboxylation converts alpha-keto-acids to aldehydes. These reactions are an important source of generating energy, and are widely distributed throughout intermediary metabolism. Thiamin pyrophosphate is also the coenzyme for transketolase, which converts xylulose-5-$P0_4$ and ribose-5-$P0_4$ to sedoheptulose-7-$P0_4$ and glyceraldehyde. More recent evidence suggests that thiamin has a role beyond that of a coenzyme in regulating transmission of impulses in peripheral nerves.

Deficiency

The initial clinical presentation of thiamin deficiency is often subtle and nonspecific, comprising anorexia, general malaise, and weight loss. The symptoms, as they progress, are often followed by more intense weakness, peripheral neuropathy, headache, and tachycardia. When thiamin deficiency is advanced, the patient usually exhibits prominent cardiovascular and neurological features.

Cardiac findings include an enlarged heart, tachycardia, edema, and ST-segment and T-wave changes. There is high output failure due, at least in part, to the peripheral vasodilatation. The clinical syndrome has a number of similarities to apathetic hyperthyroidism, with which it is often confused.

The central nervous system findings are those of the Wernicke-Korsakoff syndrome, with vomiting, horizontal nystagmus, ataxia, weakness of the extraocular muscles, mental impairment, memory loss, and confabulation. There may be significant peripheral neuropathy as well.

Laboratory Diagnosis of Deficiency

The diagnosis of thiamin deficiency is based upon the analysis of this vitamin in blood by bioassay or by microbiological, chemical, and functional assays. In practice, urinary thiamin excretion and the erythrocyte transketolase are the most widely utilized assays. Urinary thiamin excretion reflects recent intake, and may be increased after the use of diuretics. The transketolase assay relies upon an indirect measurement of the extent to which the apoenzyme is saturated with its coenzyme, thiamin pyrophosphate. When thiamin stores are depleted, the addition of thiamin pyrophosphate *in vitro* to an erythrocyte lysate produces a large increase in activity. When the percentage increase in activity (activity coefficient) exceeds 15 to 20%, significant thiamin deficiency is diagnosed. Well-nourished individuals have much smaller activity coefficients when tested.

Prevention

Thiamin deficiency can best be prevented by a diet consistently high in meat, grains, peas, beans, and nuts. Treatment of vegetables with baking soda, which is alkaline, a practice often used to enable the bright green colors to be preserved, inactivates thiamin, as does heat.

Intestinal absorption of dietary thiamin is very sensitive to alcohol. A person who drinks alcoholic beverages all day long, but never appears to be intoxicated, is nevertheless at risk for the development of thiamin deficiency. Thiaminases and antithiamin factors in raw fish, seafood, and other food items, significantly break down dietary thiamin and may serve to intensify the effects of a dietary deficiency.

Treatment

Large doses of thiamin (50 to 100 mg) may be administered safely by the parenteral route in the acute syndrome, and the results are often dramatic, with rapid resolution of the nystagmus. Following several days of treatment with doses at this level, treatment with 5 to 10 mg/day is then appropriate. There is little, if any, toxicity when thiamin is given at levels of several times the RDA.

Riboflavin (Vitamin B_2)

Functions

Dietary riboflavin must be converted to its flavin coenzymes, flavin mononucleotide (riboflavin-5′-phosphate, FMN) and flavin adenine dinucleotide (FAD), to fulfill its metabolic functions. Several percent of tissue flavins are bound covalently to proteins, such as monoamine oxidase, and sarcosine and succinate dehydrogenase. The flavin coenzymes

catalyze many different types of reactions, particularly oxidation-reduction reactions, dehydrogenations, and oxidative decarboxylations. Flavin coenzymes are involved in the respiratory chain, lipid metabolism, the cytochrome P-450 system, and drug metabolism.

Riboflavin has antioxidant activity in its role as precursor to FAD, the coenzyme required by glutathione reductase. The glutathione redox cycle provides major protection against lipid peroxides. Glutathione reductase generates reduced glutathione (GSH) from glutathione (GSSG), which is the substrate required by glutathione peroxidase to inactivate hydrogen peroxide and other lipid peroxides. Thus, increased lipid peroxidation is a feature of riboflavin deficiency, and one that is not widely appreciated.

Deficiency

The evolution of dietary riboflavin deficiency may be intensified by diseases, drugs, and endocrine disorders that block riboflavin utilization. The conditions in which such effects are observed include thyroid and adrenal insufficiency, treatment with the psychotropic drugs, chlorpromazine, imipramine and amitriptyline, the antimalarial, quinacrine, and the cancer chemotherapeutic drug, adriamycin. Alcohol ingestion may be a significant cause of riboflavin deficiency by interfering with both intestinal absorption and digestion from food sources.

Clinically, patients with riboflavin deficiency exhibit seborrheic dermatitis, burning and itching of the eyes, abnormal vascularization of the cornea, cheilosis, angular stomatitis, anemia, and neuropathy. A smooth red tongue is classically observed in riboflavin deficiency (Color Figure 64.2), but is not pathognomonic.

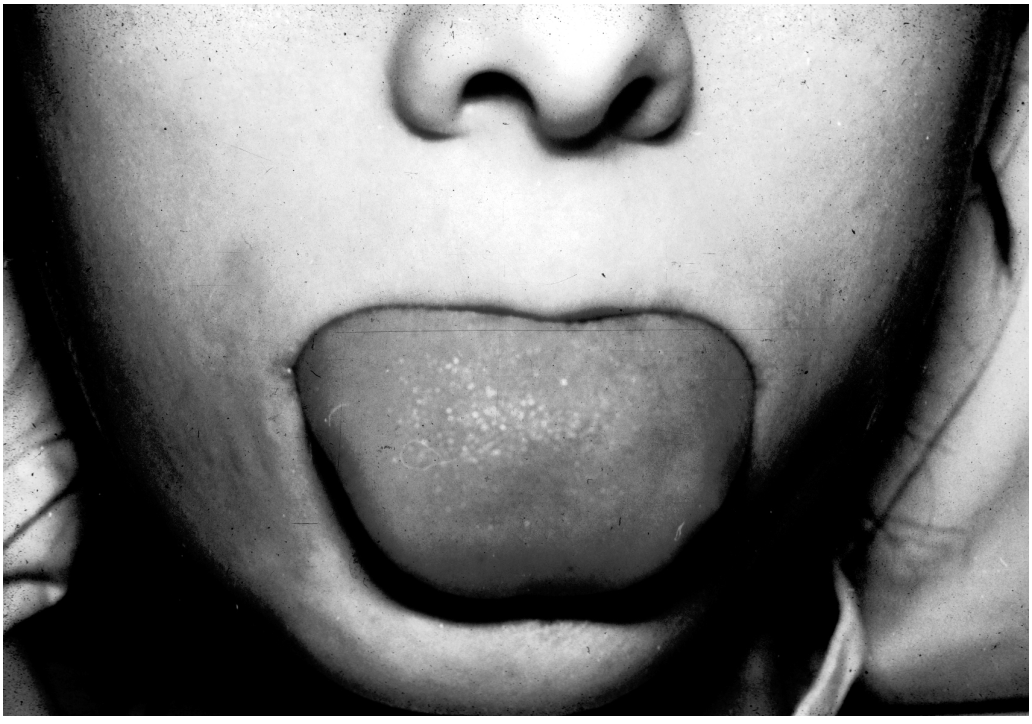

FIGURE 64.2
(See Color Figure 64.2) Patient with classical riboflavin (vitamin B_2) deficiency illustrating pallor, cheilosis and a large, red, smooth tongue. (Photo courtesy of Elaine B. Feldman, M.D.)

Riboflavin deficiency seldom occurs as an isolated entity, and is nearly always detected in association with deficiencies of other B-vitamins.

Laboratory Diagnosis of Deficiency

Riboflavin and its derivatives can be analyzed precisely by high performance liquid chromatography (HPLC) and other techniques which are not generally utilized in clinical practice. Urinary riboflavin excretion is reduced with long-term dietary deficiency, but may be increased acutely after recent intake of the vitamin. Collections have to be made carefully in subdued light and stored in dark bottles because of the light-sensitivity of the vitamin.

A functional test, the erythrocyte glutathione reductase activity coefficiency (EGRAC), measures saturation of the enzyme with its coenzyme (FAD) by the same principle as that used to assess thiamin status with transketolase. An activity coefficient greater than 1.2 to 1.3 indicates some degree of deficiency, with higher levels reflecting more severe deficiency.

Prevention

Riboflavin deficiency can be prevented by maintaining a diet high in meat and dairy products, the major sources of the vitamin in the U.S. Certain green vegetables, including broccoli, asparagus, and spinach, also contain significant quantities of riboflavin, as do fortified cereals. In developing countries, vegetables constitute the major sources of riboflavin.

It should be recalled that because of its heat- and light-sensitivity, considerable amounts of the vitamin can be lost when liquids are stored in clear bottles, when fruits and vegetables are sun-dried, and when baking soda is added to fresh vegetables to maintain color and texture. Under the latter conditions, riboflavin loss is accelerated by photodegradation.

Treatment

Treatment of clinical deficiency can be accomplished by oral intake of the vitamin. Levels greater than 25 mg cannot be completely absorbed as a single dose. This dose level is certainly safe to administer. The parenteral administration of riboflavin is limited by its low solubility. Riboflavin 5′phosphate is more soluble than riboflavin but is not usually available for clinical use.

A theoretical risk involved in treatment with riboflavin is that the vitamin has photosensitizing properties. *In vitro*, phototherapy results in DNA degradation and an increased formation of lipid peroxides. Riboflavin forms an adduct with tryptophan and accelerates its photodegradation. The extent to which these observations have implications for conditions prevailing *in vivo* in humans needs to be elucidated.

Niacin

Functions

The main function of niacin, sometimes referred to as vitamin B_3, is to serve as a precursor of the two coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Both coenzymes catalyze oxidation-reduction reactions, and are involved in a wide variety of reactions in intermediary metabolism. These reactions include glycolysis, lipid, amino acid, and protein metabolism.

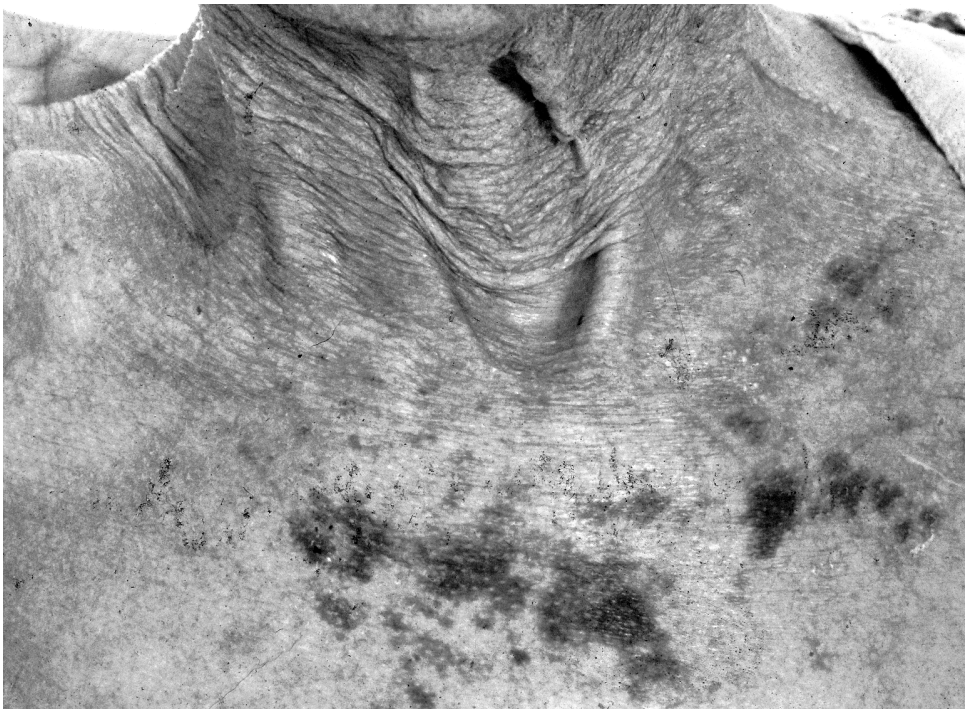

FIGURE 64.3
(See Color Figure 64.3) Patient with advanced pellagra resulting from niacin deficiency, illustrating a dark, scaly eruption over sun-exposed surfaces. (Photo courtesy of Elaine B. Feldman, M.D.)

Deficiency

Dietary deficiency of niacin generally occurs in the presence of other vitamin deficiencies as well. A unique aspect of niacin metabolism is that it is formed from dietary tryptophan. Thus, high quality protein sources tend to protect against niacin deficiency, and poor protein sources that are inadequate in tryptophan, such as corn, tend to accelerate niacin deficiency. Alcoholism may result in niacin deficiency, as will drugs, such as isonicotinic acid hydrazide (isoniazid INH), which interfere with niacin metabolism. The anti-cancer agent, 6-mercoptopurine, may produce severe niacin deficiency. One may also find niacin deficiency in the rare inborn error Hartnup's Disease, and in the malignant carcinoid syndrome in which dietary tryptophan is diverted to the synthesis of serotonin at the expense of niacin.

Early manifestations of niacin deficiency (pellagra) are generally non-specific, with anorexia, weight loss, weakness, and irritability. In later stages of deficiency, the patient may develop glossitis, stomatitis, characteristic scaling, and skin lesions, as shown in Color Figures 64.3 and 64.4. In advanced disease, one may encounter "the four Ds": dermatitis, diarrhea, dementia, and death.

Laboratory Diagnosis and Deficiency

In practice, the diagnosis of niacin deficiency can be established by assay of the urinary excretion of niacin metabolites, specifically N-methylnicotinamide, and less commonly, 2-pyridone. Accurate determinations can be made by HPLC.

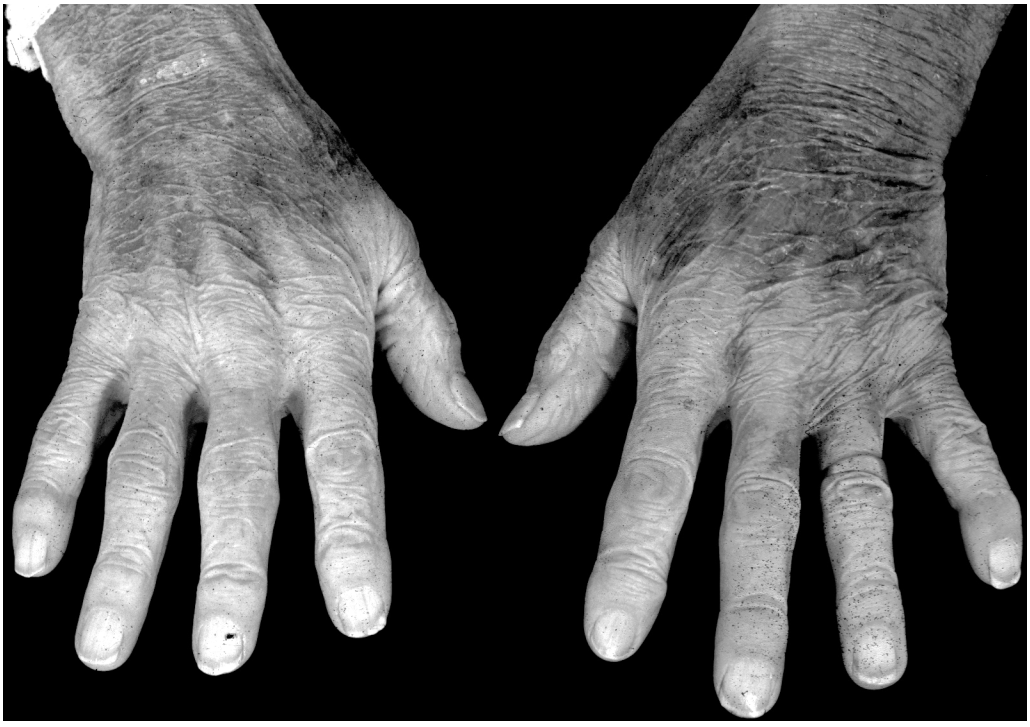

FIGURE 64.4
(See Color Figure 64.4) Hands of a patient with advanced pellagra, illustrating dark, scaly, thickened lesions. (Photo courtesy of Elaine B. Feldman, M.D.)

Prevention

As noted above, the diet needs to be adequate in protein of high biological value that contains tryptophan. Intake of meat and dairy products tends to assure adequate intake of tryptophan. A vegetarian diet may contain adequate amounts of niacin if it is sufficiently balanced and varied.

Treatment

The syndrome of niacin deficiency can be treated with oral administration of the vitamin. Doses in the range of 50 to 150 mg/day of nicotinamide may be recommended to treat severe deficiency, and need to be maintained initially. Improvement is usually noted clinically after only a few days of treatment.

Niacin in the form of nicotinic acid as a drug is a first-line agent for the management of an abnormal serum lipid profile when doses in the range of 1.5 to 6.0 grams are administered daily. Niacin may be effective alone and in combination with other agents in lowering LDL-cholesterol, raising HDL-cholesterol, and reducing serum triacylglycerols (triglycerides). There may, however, be significant side effects noted at this dose range, including worsening of diabetes, abnormalities in liver function tests, elevation of the serum uric acid, and ocular abnormalities. Flushing may be troublesome to the patient, but is often transient. In most instances, the flushing can be minimized by taking a tablet of aspirin shortly before the niacin.

The form of niacin selected is crucial. Nicotinic acid is the form which is effective. Often patients choose niacinamide on their own because it does not cause a flush. Unfortunately, it also will not benefit elevated serum lipid concentrations.

Pyridoxine (Vitamin B_6)

Functions

The role of vitamin B_6 is primarily that of a precursor to pyridoxal phosphate, the coenzyme which participates in a large number of reactions, particularly involving transamination and decarboxylation. In addition, pyridoxal phosphate is involved in side chain cleavage, dehydratase activity, and racemization of amino acids. These reactions relate to gluconeogenesis, lipid metabolism, immune function, cerebral metabolism, nucleic acid synthesis, and endocrine function in relation to steroid hormone action. B_6 deficiency can lead to secondary deficiencies of other vitamins because it plays a role in the pathway leading to synthesis of niacin from tryptophan. B_6, together with B_{12}, folic acid, and possibly B_2, are involved in homocysteine synthetic and degradative pathways.

Although some B_6 is present in the diet in the form of pyridoxal, the majority is in other forms. In plants, B_6 is present largely as pyridoxine, whereas animal sources comprise pyridoxamine as well as pyridoxal phosphate, and other forms.

Deficiency

Like other B vitamins, isolated pyridoxine deficiency entirely on a dietary basis is hardly ever found. In some instances, however, a marginal diet may result in overt deficiency if there are other complicating factors, such as the long-term use of specific pyridoxine antagonists. Two common examples of this are isoniazid and cycloserine, used to treat tuberculosis and generally prescribed for an extended period in order to eradicate the organism. In some individuals a genetic trait may manifest itself, leading to delay in inactivating isoniazid, resulting in their becoming unusually susceptible to developing B_6 deficiency from this drug.

Pyridoxine deficiency is a common feature of chronic alcoholism, found in association with overall malnutrition and inadequate intake of many other vitamins and minerals. An unusual feature of the pathogenesis of B_6 deficiency in alcoholism is that a major effect of alcohol is to accelerate the degradation of pyridoxal into inactive metabolites, particularly pyridoxic acid.

B_6 deficiency is not recognizable as a distinct clinical syndrome. Patients may develop dermatitis, glossitis, cheilosis, and weakness. In more severe deficiency, patients may have dizziness, depression, peripheral neuropathy, and seizures. The risk of kidney stones is increased due to hyperoxaluria. In children, B_6 deficiency may be an important cause of anemia and seizures. Deficiency of B_6 causes a hypochromic, microcytic anemia that resembles the anemia due to iron deficiency.

In a group of rare disorders, called pyridoxine dependency syndromes, large doses of B_6 are required for control. Among these disorders are pyridoxine-dependent convulsions, cystathioninuria, and xanthurenicaciduria.

Laboratory Diagnosis of Deficiency

Vitamin B_6 can be measured directly in blood, with levels less than 50 ng/ml generally considered to represent deficiency. The measurement needs to be interpreted in the light of the patient's diet, as high protein intake depresses plasma pyridoxal phosphate levels, probably because of increased utilization of the coenzyme in protein metabolism.

Urinary tests measure the excretion of metabolites of pyridoxine, most commonly 4-pyridoxic acid. Indirect assessments of vitamin B_6 deficiency can be made using functional assays of the enzymes aspartate or alanine aminotransferase with and without the addition of the cofactor *in vitro*. The principle of this assay is similar to that discussed above for thiamin and riboflavin deficiency. An activity coefficient greater than 1.2 for alanine aminotransferase and 1.5 for aspartate aminotransferase is generally considered to represent vitamin deficiency.

At one time, a specific diagnosis of B_6 deficiency was made by measuring xanthurenic acid after a tryptophan load, inasmuch as B_6 is the coenzyme involved in the transformation. This procedure, although theoretically sound, is somewhat laborious and has largely been abandoned.

Prevention

Vitamin B_6 is widely available in the food supply and is found in vegetables, beans, (especially soy beans), meat, nuts, seeds, and cereals. A diet that is adequate and diversified in these dietary items will generally prevent vitamin B_6 deficiency. It is evident that this kind of diet will prevent deficiencies of the other B vitamins as well. Certain kinds of food processing, particularly heat sterilization, can result in significant losses and reduction of activity of vitamin B_6.

Treatment

Once vitamin B_6 deficiency is diagnosed, it can be satisfactorily managed at a level of 2 to 10 mg/day, which represent doses several times those of the RDA. Vitamin B_6 deficiency during pregnancy should be treated with higher doses in the 10 to 20 mg range because of the increased requirement.

Vitamin B_6 is routinely advised during prolonged treatment with isoniazid, which is a pyridoxine antagonist. In doses of 50 to 100 mg/day, vitamin B_6 has been noted to reduce peripheral neuropathy without apparently lessening efficacy of INH against tuberculosis. In patients with Parkinson's Disease receiving treatment with L-DOPA, too much pyridoxine will interfere with drug action; therefore, these large doses should not be taken as a general rule.

It is important not to exceed certain limits in therapeutic administration of vitamin B_6. Cases of sensory neuropathy have been occasionally noted in patients taking 1 to 2 g per day, but rarely noted when taking only 500 mg/day. The B_6-dependency syndromes can be managed on doses of 100 to 200 mg/day and do not require these megadoses.

Folic Acid and Vitamin B_{12}

See discussion in Section 46.

Vitamin C (Ascorbic Acid)

Functions

Although commonly perceived as a so-called antioxidant, in reality, ascorbic acid serves in both oxidation and reduction reactions, depending upon the prevailing environmental conditions. An important function is that of preventing oxidation of tetrahydrofolate.

Ascorbic acid is involved in collagen biosynthesis, wound healing, immune function, and drug metabolism. It enhances the intestinal absorption of non-heme iron. The vitamin is involved in the biosynthesis of neurotransmitters and carnitine.

Deficiency

Dietary deficiency develops when the diet does not contain adequate amounts of citrus fruits, vegetables, and tomatoes, most commonly among the elderly and the urban poor. Vitamin C deficiency may also arise when there is food faddism or very limited food choices, behaviors that are observed with increased frequency. The classical "tea and toast" diet of the elderly is particularly deficient in vitamin C. The macrobiotic diet may lead to scurvy because of poor sources and the practice of pressure-cooking, which destroys ascorbic acid.

In infancy and childhood, a diet exclusively of unsupplemented cow's milk is deficient in vitamin C and may lead to scurvy. Chronic alcoholism at any age is associated with poor ascorbic acid intake, and if prolonged will greatly increase the risk for scurvy.

The clinical symptoms of vitamin C deficiency develop very slowly, and as with other vitamins are often vague and nonspecific. Patients complain of weakness and fatigue, progressing to dyspnea and lethargy. The characteristic features of scurvy are not observed until the deficiency syndrome is well advanced. Bone and joint pain may occur due to hemorrhages in the subperiosteum. Perifollicular hemorrhages, especially in relation to hair follicles, are observed, as shown in Color Figure 64.5. The hairs may show a corkscrew pattern. Swollen, bleeding gums are observed in advanced deficiency, as shown in Color Figure 64.6. Pallor may be due to the bleeding and the reduction in hematopoiesis. Scurvy results in poor wound healing and secondary breakdown of wounds that had healed previously.

Laboratory Diagnosis

Ascorbic acid can be measured directly in the blood serum or plasma by a variety of chemical methods, most commonly spectrophotometric or fluorometric. Levels of 0.1 mg/dl or lower are generally indicative of vitamin C deficiency. Serum levels may be reduced in many chronic disorders, in smokers, and in some women taking oral contraceptive drugs.

Blood levels tend to segregate in a relatively narrow range in the face of very large differences in dietary intake. Megadoses of ascorbic acid remain almost entirely unabsorbed, and what is absorbed is rapidly metabolized by an efficient hepatic drug-metabolizing enzyme system and, with its low renal threshold, excreted rapidly in the urine.

Prevention

Vitamin C deficiency can be prevented simply by consuming a diet adequate in citrus fruits and vegetables. Consuming orange juice with meals may be a healthy habit that

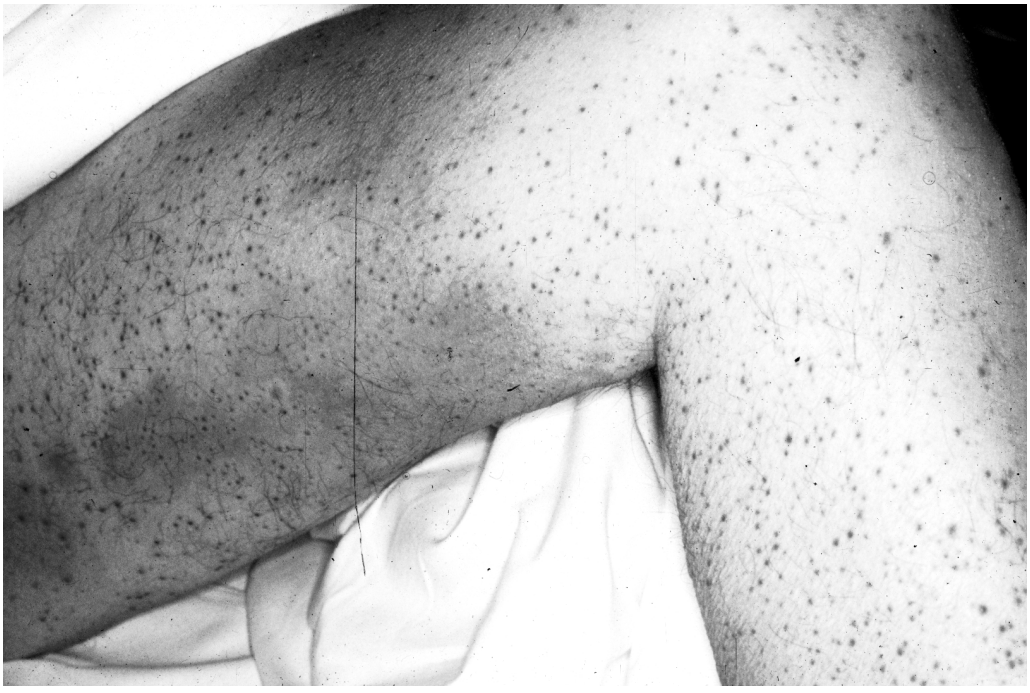

FIGURE 64.5
(See Color Figure 64.5) Leg of an adult patient with severe scurvy, illustrating multiple perifollicular hemorrhages. Some corkscrew hairs are visible. (Photo courtesy of Elaine B. Feldman, M.D.)

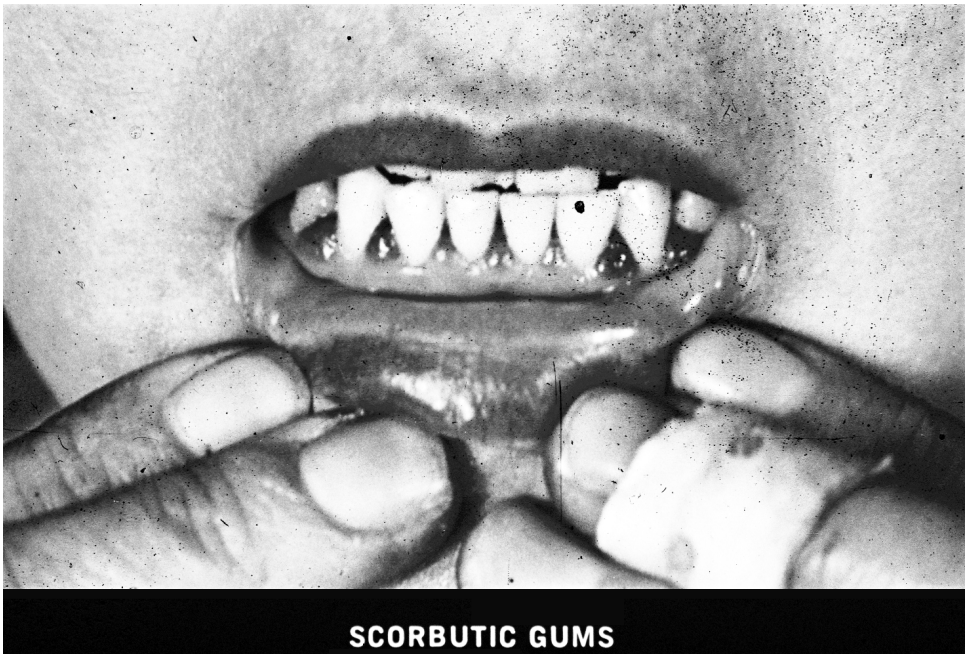

FIGURE 64.6
(See Color Figure 64.6) Mouth and teeth of a patient with far-advanced scurvy showing swollen, bleeding gingiva. (Photo courtesy of Elaine B. Feldman, M.D.)

increases the intestinal absorption of non-heme iron several-fold. Avoiding heating or prolonged storage of foods containing vitamin C can also help maintain adequate stores. Educating people about the potential hazards of a macrobiotic diet, food faddism, and sharply limited food choices should also help to prevent scurvy.

The prevention of scurvy may be accomplished by ingestion of very small amounts of ascorbic acid. Some authorities believe that doses as low as 10 mg/day may be effective. The maintenance of adequate vitamin C status has generally been considered to be in the 40 to 60 mg range, as reflected in the RDA. Recent studies examining the pharmacokinetics of vitamin C and the saturation of tissue stores raise the possibility that larger doses of approximately 200 mg may be optimal.

Treatment

As noted above, doses of ascorbic acid as low as 10 mg/day may prevent scurvy and could achieve benefit in treatment. In advanced cases, a dose range of 100 to 200 mg/day orally may be administered safely and effectively, with a therapeutic benefit evident within a few days. Meat sources containing heme iron are more bioavailable than the non-heme iron present in vegetables. As noted above, efficacy of absorption of non-heme iron can be greatly improved by simultaneous consumption of orange juice.

Megadoses of vitamin C have been given to patients with advanced cancer, and their anticancer efficacy is unproven. Vitamin C has also been advocated to prevent cancer, since its content in fruits and vegetables may be part of the reason that cancer prevalence is reduced in patients who consume several servings a day. There is also a suggestion from some *in vitro* studies that large amounts of vitamin C may not be advisable in terms of possibly accelerating tumor metabolism.

There is some risk for toxicity in doses greater than 1 to 2 g per day in a highly individual fashion. Gastrointestinal upset may occur. Inasmuch as oxalic acid is a direct metabolite of ascorbic acid, the risk of kidney stones theoretically should be increased. The exact prevalence of symptomatic stone formation after ingestion of low doses of vitamin C is not known.

Caution in administering vitamin C should be followed when giving it to individuals with hemochromatosis or those at risk for this disorder, as the intestinal absorption and tissue storage of iron may be increased excessively. Since the gene for hemochromatosis is one of the most common genetic abnormalities known, there may be a risk associated with indiscriminate use of megadoses of ascorbic acid supplements by the general population.

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