

Scurvy in an Unrepentant Carnivore

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GOAL

To outline the recognition and treatment of scurvy, vitamin C deficiency.

OBJECTIVES

1. To describe the biologic role of vitamin C.
2. To discuss the signs and symptoms of vitamin C deficiency.
3. To identify the appropriate prophylaxis and treatment of scurvy.

CME Test on page 52

This article has been reviewed by Michael Fisher, MD,
Professor of Dermatology, Albert Einstein College of Medicine, in June 2000.

For centuries, scurvy, or vitamin C deficiency, decimated crews of sailing ships on long sea voyages and populations deprived of fresh fruits and vegetables during times of war or famine. Today, scurvy is extremely rare in the United States, and its classic findings of perifollicular petechiae, edema and purpura of the lower extremities, corkscrew hairs, and hemorrhagic gingivitis may go unrecognized. We report the case of a man from rural Appalachia who developed typical signs and symptoms of scurvy on two separate occasions, approximately 2 years apart. Both times, the patient underwent an extensive work-up and was diagnosed with numerous other conditions before his vitamin C deficiency was recognized. We discuss the clinical presentation, pathophysiology, diagnosis, and treatment of scurvy, with attention to specific findings that should alert the clinician to this diagnosis.

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Dr. Greer is Professor and Chairman, Department of Dermatology, University of Virginia Health Sciences Center, Charlottesville, Virginia. The opinions expressed herein are those of the authors and do not necessarily represent the views of the sponsor or its publisher. Please review complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects, before administering pharmacologic therapy to patients.

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In 1747, Dr. James Lind performed a landmark experiment in the history of medicine when he demonstrated that eating oranges could prevent sailors from developing a debilitating and often lethal illness on long sea voyages.¹ Scurvy was epidemic not only among sea-farers, but also among populations in wartime and famine that had no access to fresh fruits and vegetables.^{2,3} Lind's discovery led to the British practice of carrying lemon or lime juice on all long sea voyages. It was not until the late 1920s that Albert Szent-Gyorgy and Glenn King, working independently, isolated the substance in citrus fruits that was necessary to prevent scurvy.⁴ This "antiscorbutic" factor was given the name ascorbic acid and is also known today as vitamin C. At the time, it was not known why vitamin C was important, but it was demonstrated to reverse the symptoms of scurvy both in a guinea pig model and in humans.

Today, the physiologic roles of vitamin C are well understood. Vitamin C is a powerful anti-oxidant and reducing agent. It acts as a free radical scavenger, protecting cells from oxidative damage.³ It acts as a cofactor for hydroxylases in collagen, steroid, neurotransmitter, and carnitine biosynthesis by restoring prosthetic iron and copper ions to their reduced states.^{3,5} It protects plasma lipids and low-density lipoprotein from peroxidation, prevents tetrahydrofolate oxidation, and regenerates active (reduced) vitamin E and glutathione. Vitamin C also increases intestinal absorption of non-heme iron, is important for wound healing and is thought to play a role in immunocompetence.^{3,5}

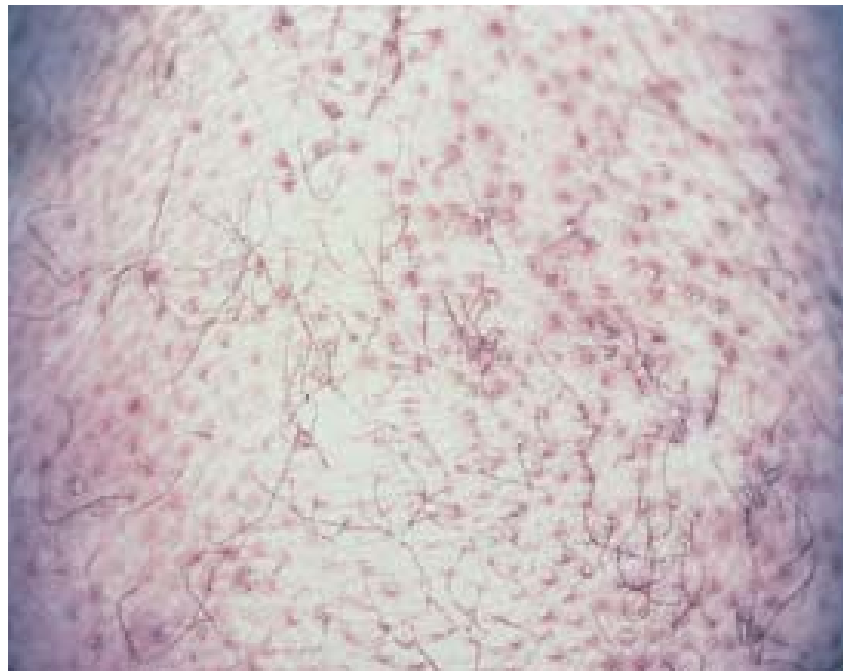


FIGURE 1. Perifollicular hemorrhages and hyperkeratosis in a patient with scurvy.

The most important biologic role of vitamin C is probably its function in collagen synthesis. Collagen, a key component of skin, blood vessels, cartilage, tendons, and bones, consists of a triple-helical protein molecule that undergoes a number of post-translational modifications. Vitamin C is required at the step in collagen synthesis in which proline and lysine residues are enzymatically hydroxylated, because the hydroxylases have prosthetic iron groups that must be in the ferrous state for maximal function.⁶⁻⁸ Vitamin C reduces ferric iron to the ferrous state so that the hydroxylases remain active. Hydroxylation of proline allows the three α -chains of pro-collagen to assemble together as a triple helix, which in turn promotes collagen secretion. Hydroxylation of lysine residues is also a critical step in the formation of mature collagen, because subsequent oxidation of the hydroxylysine residues results in cross-linking of adjacent collagen molecules, providing the basis of its structural stability. Without vitamin C, collagen molecules are inadequately cross-linked and cannot contribute to the tensile strength of skin, blood vessels, and other tissues.⁵

The consequences of vitamin C deficiency can largely be deduced from the vitamin's known biochemical functions. After 1 to 3 months of vitamin C deprivation, when the total body pool declines to about 300 mg, humans begin to develop signs and symptoms of scurvy.⁹⁻¹² The most striking findings are caused by weak blood vessel walls that contain poorly cross-linked collagen. Hemorrhages are common in the skin, resulting in petechiae and purpura, in the joints, causing hemarthrosis, and in the muscles, caus-

ing muscle pain.¹¹⁻¹⁵ Petechiae and ecchymoses are most common on the backs of the legs and are often perifollicular. Other skin changes include lower extremity edema and hyperpigmentation, and development of curly, fractured "corkscrew" hairs. Oral manifestations of scurvy, which do not occur in edentulous patients, include swollen, tender, bleeding gums with loosened teeth and fetid breath.^{11,12,16} Internal bleeding may also occur, and in children, subperiosteal hematomas and even intracerebral hemorrhages may be seen.²

Skeletal changes are observed in growing children who lack vitamin C, because of the important role of collagen in forming the osteoid matrix. Epiphyseal bone growth is disrupted, resulting in abnormal connections between the sternum and the ribs, the so-called "scorbutic rosary," and abnormal jaw and alveolar bone, resulting in loose teeth.¹⁶

Wound healing and resistance to infection are impaired in patients with scurvy, due to the importance of new collagen synthesis in healing wounds and an as-yet poorly defined role for vitamin C in immunocompetence. Patients may develop normocytic or megaloblastic anemia, resulting from a combination of blood lost in hemorrhages, impaired iron absorption and concomitant folate deficiency due to overall poor diet.¹⁷ Dyspnea, pulmonary infiltrates, electrocardiogram changes, hypotension, shock, and even sudden death may occur.^{11,12,18,19} Personality changes, fatigue, and psychomotor retardation are frequently noted in patients with scurvy, and profound depression may occur in chronic cases.²⁰

Case Report

A 54-year-old Caucasian man from rural Appalachia who had no significant past medical history presented to the University of Virginia Medical Center complaining of left lower extremity pain and severe fatigue. The patient had presented to his local physician 14 months earlier, and investigation of his leg pain at that time yielded negative plain films but a positive bone scan. He was treated for a possible arthritic condition with nonsteroidal agents without improvement.

Eight months later, the patient underwent further work-up at another medical center, where plain films again showed only diffuse osteopenia. However, a bone scan and magnetic resonance imaging showed increased uptake in the distal tibia and mid-metatarsal region consistent with possible osteomyelitis. Cultures of a bone biopsy specimen were negative for pathogens, including acid-fast bacilli, fungal, and bacterial organisms. The patient was again sent home on nonsteroidal anti-inflammatory agents. Seven months later, the patient had a significant bleed into his left thigh and knee. Evaluation at his local hospital, including a Doppler ultrasound which was negative for deep venous thrombosis, failed to reveal a cause.

The patient was referred for evaluation by a rheumatologist. He had a history of smoking and of a positive purified protein derivative test. His only medication was Percocet® and he had no known allergies. On examination, the patient was a slender Caucasian man with diffuse hyperpigmentation of both legs and changes consistent with venous stasis along the left medial ankle. Diffuse resolving ecchymosis of the left thigh and distal left extremity were also noted. Peripheral pulses and neurologic examination were normal. Laboratory tests, including complete blood cell count with differential, chemistry panel, urinalysis,

thyroid panel, liver panel, prothrombin time, partial thromboplastin time, erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, and serum protein electrophoresis were unremarkable, with the exception of a borderline macrocytic anemia (hematocrit of 39.6% and mean red blood cell volume of 94.6 fL) with increased red blood cell distribution width (16.7%). His radiologic studies were reviewed, and both his rheumatologist and an anesthesiology pain specialist believed that his presentation was consistent with a diagnosis of reflex sympathetic dystrophy with Sudeck's atrophy of the bone.

Because the patient had unusual skin changes, Dermatology was consulted. Examination of the skin revealed diffuse perifollicular hemorrhages and hyperkeratosis (Figure 1), corkscrew hairs on the abdomen, and hyperpigmentation and ecchymosis of the lower extremities (Figure 2) as described above. In addition, the patient had severe hemorrhagic gingivitis (Figure 3). On further questioning, the patient admitted to a diet consisting only of Bunker Hill canned beef and other cooked foods, with very minimal fresh fruits or vegetables. His constellation of findings was believed to be classic for scurvy and he was discharged on vitamin C supplements (ascorbic acid 500 mg twice a day) with instructions to continue this therapy for life. Within weeks he had made a complete recovery.

The patient was lost to follow-up until approximately 2 years later, when he presented to a new family physician complaining of a painful swelling of the right elbow. He was found to have a 4-cm × 2-cm swelling over the olecranon bursa, from which dark bloody fluid was aspirated. Roentgenograms showed blood and soft-tissue swelling without evidence of fracture. He was given pain medications and sent home.

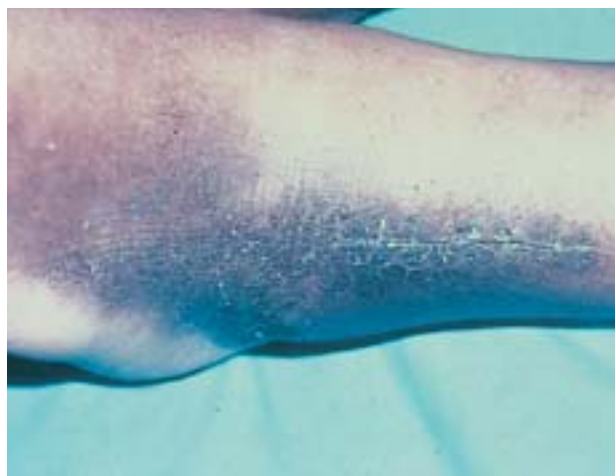


FIGURE 2. Left ankle of patient with scurvy showing hyperpigmentation and scar at site of bone biopsy.



FIGURE 3. Hemorrhagic gingivitis.



FIGURE 4. Hyperpigmentation and confluent purpura of the ankle in patient with scurvy.

He presented to the same physician 3 months later complaining of numbness and tingling of both feet, followed by development of bruising along the length of both legs. He also was noted to have edema of both feet, which progressed to involve the calves. He was referred to a local vascular surgeon for work-up of possible thrombophlebitis. He was found to have normal pulses and normal venous Doppler ultrasound studies, arguing against a vascular etiology of his leg swelling. Two biopsies of the left thigh were performed to rule out vasculitis and both were negative. The patient was advised to wear support hose and elevate his legs, and his family doctor started him on a diuretic.

As the patient continued to have worsening pain, swelling, and purpura of the lower extremities, he was referred to the Vascular Surgery Clinic at the University of Virginia. Evaluation there revealed normal pulses, an ankle-brachial index of 1 (normal), and normal venous Doppler ultrasound and plethysmography. It was believed that his swelling and pain were not of a vascular etiology and he was referred to Dermatology.

Evaluation in Dermatology again revealed intense indurated edema and hyperpigmentation of the lower extremities (Figure 4), perifollicular petechiae and hyperkeratotic papules (Figure 5), corkscrew hairs on the abdomen, and gingivitis. The patient admitted that his diet was still limited to canned beef. He refused to eat fruit because it upset his stomach and to eat vegetables because he found them impossible to chew. He had run out of the prescribed vitamin C supplements many months earlier.

A skin biopsy was taken, which showed changes consistent with scurvy (Figure 6) and blood was sent

for vitamin C levels, which were below the limit of detection (<0.12 mg/dl). The patient was restarted on vitamin C supplements and has not been seen since.

Discussion

Whereas scurvy was once very common in populations without year-round access to fruits and vegetables, it is extremely rare in the United States today. Because vitamin C deficiency has become so rare, it is seldom entertained as a diagnosis even for patients presenting with classic signs and symptoms. Our patient manifested the typical findings of fatigue, muscle pain, bleeding into joints, lower extremity edema and ecchymoses, perifollicular petechiae with hyperkeratotic papules, corkscrew hairs, hemorrhagic gingivitis, and anemia. Yet, he was seen by at least seven physicians (two family doctors, three vascular surgeons, one rheumatologist, and one anesthesiologist) before the correct diagnosis was made. Before he was diagnosed with scurvy, our patient was assigned diagnoses of arthritis, osteomyelitis, reflex sympathetic dystrophy, thrombophlebitis, vascular insufficiency, lymphedema, venous stasis, and idiopathic thrombocytopenic purpura. He underwent an extensive and invasive work-up that included a bone biopsy, and he was treated with numerous ineffectual therapies.

Our patient's case demonstrates that although rare, scurvy does still occur in the United States. Rather than the epidemics that occurred in sailors, soldiers, and explorers of past centuries, most cases today are sporadic and tend to be in socially isolated people, often older men living alone.^{15,17,19} Scurvy has also been reported in the institutionalized elderly, those following



FIGURE 5. Perifollicular petechiae with hyperkeratosis and purpura at skin biopsy sites in a patient with scurvy.

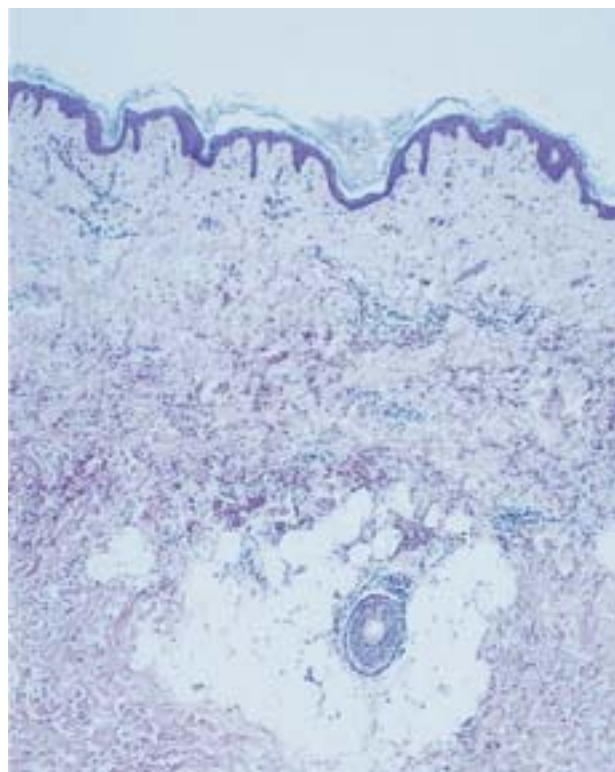


FIGURE 6. Skin biopsy of patient with scurvy showing perifollicular hemorrhage and hyperkeratosis.

strict macrobiotic diets, and in infants who are bottle-fed milk without orange juice supplementation.^{14,17}

The differential diagnosis of scurvy includes other causes of petechiae and purpura, such as vasculitis, platelet disorders (idiopathic thrombocytopenic pur-

pura, thrombotic thrombocytopenic purpura, uremic platelet dysfunction), clotting disorders (warfarin or heparin overdose, liver disease, acquired coagulopathy), embolic disorders (infectious emboli, cholesterol emboli), cryoglobulemia, amyloidosis, and vascular anomalies.¹⁹ In contrast to scurvy, bleeding in these conditions is not typically folliculocentric. Scurvy may also be confused with other causes of lower extremity edema and pain, such as deep venous thrombosis, thrombophlebitis, cellulitis, and venous stasis. The oral manifestations of scurvy may be mistaken for common periodontitis, but the latter condition is generally painless, whereas the hemorrhagic gingivitis of scurvy is quite painful and is only seen in patients with teeth.¹⁶

Diagnosis of scurvy can be made on clinical grounds when a patient with a diet devoid of fruits and vegetables presents with the characteristic signs and symptoms. For confirmation, a vitamin C level of <0.2 mg/dl is diagnostic.²¹ It is important to draw the vitamin C level before any vitamin C-containing supplements are given, since even one dose can normalize serum levels despite a badly depleted body pool. Skin biopsy of a perifollicular hemorrhagic lesion can also be helpful, especially in differentiating scurvy from a vasculitis.¹⁵

Treatment of scurvy is simple and inexpensive and results in dramatic improvement of signs and symptoms. Although 10 mg of oral vitamin C per day is enough to prevent scurvy,^{10,12} it is recommended that patients with scurvy be started on 1 to 2 g/day for the first 2 days, followed by 500 mg/day for the next week.¹⁷ This regimen typically results in a marked decrease in ex-

tremity pain and swelling within days and resolution of purpura within weeks. Because vitamin C metabolism is regulated by saturable absorption from the gut and active excretion in the urine, it is unlikely that these large doses are fully assimilated into the body pool, but they are unlikely to be harmful either.

The maintenance dose (United States Recommended Daily Adult Requirement) of vitamin C is 60 mg for nonsmoking adults and 100 mg/day for smokers, who suffer increased metabolic turnover of ascorbate and other anti-oxidants.^{22,23} Ideally, vitamin C would be obtained from a varied diet, including such excellent sources as citrus fruits, green leafy vegetables, broccoli, peppers, and tomatoes.²⁴ These fruits and vegetables are best consumed raw, as vitamin C can be destroyed by cooking or long storage.¹ For individuals with limited access to these fresh fruits and vegetables or who insist on following diets that exclude good sources of vitamin C, supplementation in the form of vitamin pills is essential.

Although vitamin C supplementation is a simple proposition in principle, it may be a challenge to overcome the socioeconomic, psychologic, or intellectual difficulties that allowed an individual patient to develop scurvy in the first place. Our patient developed scurvy not once, but twice, and suffered needlessly for many months, despite being told explicitly what his diagnosis was and how to prevent it. The most effective way to prevent scurvy in similar patients is likely to be regular medical care with close attention to patient education regarding nutrition.

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