Adult scurvy

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Unlike most animals, which form ascorbic acid by metabolizing glucose, humans require an exogenous source. Vitamin C occurs primarily in fruits and vegetables, and scurvy develops from inadequate consumption of these sources, usually because of ignorance about proper nutrition, psychiatric disorders, alcoholism, or social isolation. The earliest symptom of scurvy, occurring only after many weeks of deficient intake, is fatigue. The most common cutaneous findings are follicular hyperkeratosis, perifollicular hemorrhages, ecchymoses, xerosis, leg edema, poor wound healing, and bent or coiled body hairs. Gum abnormalities, which occur only in patients with teeth, include gingival swelling, purplish discoloration, and hemorrhages. Pain in the back and joints is common, sometimes accompanied by obvious hemorrhage into the soft tissue and joints. Syncope and sudden death may occur. Anemia is frequent, leukopenia occasional. Treatment with vitamin C results in rapid, often dramatic, improvement. (J Am Acad Dermatol 1999;41:895-906.)

Learning objective: At the conclusion of this learning activity, participants should be familiar with the history, pathogenesis, clinical features, and treatment of scurvy in adults.

In 1939, John Crandon, a second-year surgical resident at Boston City Hospital, decided to investigate the effect of vitamin C deficiency on wound healing.[1-4] Believing that such a study should involve at least 3 subjects, he enticed 2 teenagers to join him as paid volunteers in a diet devoid of vitamin C. The experiment soon had only one participant, for after 3 weeks the two youths were spotted drinking orange juice in a restaurant. Crandon persevered, eating only in the hospital cafeteria and a nearby delicatessen and subsisting solely on a regimen of cheese, bread, crackers, eggs, beer, coffee, and chocolate, supplemented by riboflavin, niacin, yeast tablets, and wheat-germ oil. For the first 2 months he also had well-cooked meat and a small amount of cream. This experiment had ominous precedents, for in 1770, William Stark, a 29-year-old British physician, died while conducting similar dietary studies, and many accounts of scurvy described sudden, unexpected deaths.[4]

Using a newly available test to measure levels of vitamin C, Crandon found that it was absent in his plasma at 41 days and in his white cells at 82 days. To test wound healing at that point, on day 90 he underwent a 6-cm transverse incision on his back, with removal of a small sample of muscle. To his disappointment, a biopsy 10 days later revealed normal wound healing. Nevertheless, he remained on his diet. After 3 to 4 months fatigue developed, which worsened as his experiment continued, and he began to let his work slip. He performed surgery all day and was on call every other night. He started taking afternoon naps and became reluctant to see patients in the evenings. At day 134, as he scratched his buttocks and calves, he noticed that his skin felt like sandpaper because hyperkeratotic papules had appeared. At day 155 for the fourth time since beginning his dietary regimen, he donated a pint of blood for money to defray the cost of eating at the delicatessen. His systolic blood pressure dropped from 120 to 90 and never again exceeded 100 during the experiment. At day 162 perifollicular hemorrhages developed over his lower legs, which seemed to increase with protracted standing and subsequently extended to his lower thighs. At day 180 while performing an exercise test, his heart rate reached 190, and, experiencing a sense of imminent death, he collapsed, momentarily losing consciousness. At about the same time a wound from an appendectomy 15 years before began to disintegrate. At day 182 he underwent a repeat incision on his back; the sutures through the fascia held poorly. A biopsy of the site 10 days later showed no healing beneath the skin,

where unorganized blood clot filled the wound, necessitating a drain. At that point, while remaining on his diet, he began receiving daily intravenous vitamin C. A repeat biopsy 10 days later showed normal healing. His experiment thus proved that vitamin C deficiency impairs wound healing and repletion of the vitamin corrects the problem.

Another study, conducted in Sheffield, England in the period 1944-1946, primarily among conscientious objectors, attempted to determine the minimal daily requirements of vitamin C.[5] Part of the trial involved 10 subjects consuming a diet that contained a maximum of 1 mg of the vitamin per day. The earliest detectable change, occurring 120 to 180 days after the experiment began, was hyperkeratosis of the hair follicles, which became hemorrhagic at about 180 to 240 days. The next abnormalities, observed at 210 to 270 days, were swelling and bleeding of the gums, worse in those with preexisting periodontal disease. About the same time the scars of experimental wounds made several weeks earlier, which had healed normally, became red and livid, and newly created wounds showed reduced healing.

Two studies conducted on prisoners from the Iowa State Penitentiary in the 1960s also examined the effects of vitamin C deprivation and its minimal daily requirements. The first began with 6 subjects, but after 54 days 2 prisoners escaped.[6] Perifollicular hemorrhages appeared at days 45 to 52 and follicular hyperkeratosis of the buttocks and lower extremities at 60 to 80 days. Gingival edema and hemorrhage developed from days 43 to 105. Bulbar conjunctival hemorrhages occurred at days 84 to 91. One patient had coiled hairs. These 4 men suffered no serious complications. The second trial included 5 prisoners receiving a diet deficient in vitamin C for 84 to 97 days.[7] In addition to the findings of the first trial, arthralgias, joint effusions, petechial hemorrhages, a large subconjunctival hemorrhage,[8] ankle edema, and dyspnea occurred. The participants also developed features of Sjögren's syndrome, including keratoconjunctivitis sicca, xerostomia, dental decay, and enlarged salivary glands.[9] One subject suffered a bilateral lower extremity neuropathy with sensory and motor findings, attributed to hemorrhage into the sheaths of both femoral nerves.[10] After vitamin C therapy, the neurologic abnormalities resolved in 4 months.

HISTORY

The disease that these experiments attempted to reproduce, scurvy,[11] seems to have been largely unknown, or at least unreported, in ancient medicine, presumably because lengthy separations from the vegetable and fruit sources of vitamin C in the diet were rare.[12] Greek and Roman sailors, for example, stayed close to land, rarely being at sea for the many weeks of vitamin C deprivation necessary for the clinical features to emerge.[12,13] After extended voyages began in the late 15th century, descriptions of the disease became common, although only in the late 16th century did the word "scurvy" first appear in the English language—in Richard Hakluyt's *Principall Navigations, Voyages and Discoveries of the English Nation,* published in 1589. Its provenance remains somewhat uncertain.[14] It apparently derives from an attempt to render into English the French *scorbut,* which comes from the medieval Latin *scorbutus*. This word probably originated from Middle Low German *schorbūk,* in turn from *schoren,* "break," and *būk,* "belly." The etymologic meaning is a "disease that ruptures or lacerates the belly." Conceivably, this derivation could relate to a phenomenon observed in many accounts of scurvy, but especially well described in the voyages of George Anson, a British commodore, during the 1740s in which the disorder was rampant and "a most extraordinary circumstance [occurred]…the scars of old wounds, healed for many years, were forced open again…"[15] A confusing aspect of the word is that the adjective "scurvy," used about the same time, meant "dishonorable" or "contemptible" and derived from an entirely different source—"scurf" meaning "scaly." William Shakespeare, for example, used the word in this sense numerous times throughout his plays.

Among the first descriptions of scurvy was that from the voyage of the Portuguese sailor Vasco da Gama, while traveling around the tip of Africa in 1498. Swelling of the hands, feet, and gums developed in many of his crew. This problem subsequently vanished, apparently as a consequence of eating oranges. When the sickness reappeared later in their voyage, causing numerous deaths, the ill sailors requested oranges again. Both times, the illness occurred only after at least 10 weeks at sea. Subsequently, in the 16th and 17th centuries, explorers from other countries, including Spain, The Netherlands, France, and England, described the remarkable benefits of fruit, especially lemons and oranges, in relieving the symptoms of scurvy. Few, however, realized that these substances could prevent it. One exception was Sir James Lancaster, who took bottles of lemon juice during an expedition to the East Indies in 1601. Unfortunately, this approach did not catch on, and scurvy remained a devastating problem on long voyages throughout the 18th century. A striking example is George Anson's circumnavigation of the world in 1740-1744 when he was

assigned to harass Spanish ships and overseas settlements. The crew returned to England with only 145 of its original members. Four men died from enemy action; more than 1300 succumbed to disease, primarily scurvy. A rare exception to the ravages of this disorder was the group of expeditions in the South Pacific from 1768 to 1776 under the command of Captain James Cook. Scurvy was uncommon in these voyages for several reasons: the sailors were never away from land for more than 17 weeks at a time, they had larger and more varied provisions aboard their ships than most contemporary vessels, and Cook encouraged his crew to gather and eat vegetables and fruits wherever they stopped.

Even before Cook's expeditions, however, James Lind, a Scottish physician, had cogent information about an effective therapy for scurvy. Responding to an outbreak in 1747 aboard HMS Salisbury, the vessel on which he was surgeon's mate, Lind conducted what has been considered the first recorded controlled trial in clinical medicine.[16] He studied 12 men with scurvy, keeping them quartered together and eating the same diet. He assigned two subjects each to 6 different therapies: hard apple cider, elixir vitriol, vinegar, sea water, two oranges and one lemon daily until the supply ran out, and a medicinal paste combined with drinking barley water containing tamarinds. Unlike the others, those who received the citrus fruits were much improved after 6 days, one returning to duty, the other helping nurse the remaining men. When he published these findings as a small part of his Treatise of the Scurvy in 1753 (dedicated to George Anson), Lind concluded that oranges and lemons were the "most effectual remedies for this distemper at sea." He recommended that orange and lemon juice be carried aboard ship to treat scurvy, but his suggestion of nearly boiling the preparations to preserve them would almost certainly have destroyed their vitamin C. Although he recognized that these fruits successfully treated scurvy, he did not conclude that the disease arose from a deficiency of something in the diet that these substances provided. His belief, instead, was that a cold, damp climate caused scurvy. The absence of a reliable, durable preparation of citrus juice, his incorrect theory of causation, and his failure to advocate his ideas forcefully—stating, "the province has been mine to deliver precepts: the power is in others to execute"—resulted in his clinical observations having little impact.

Scurvy continued to be a devastating disease during long voyages, until another Scottish physician, Sir Gilbert Blane, intervened. In 1793 he recommended a daily provision of lemon juice to every sailor on a long trip to the East Indies, and no cases of scurvy occurred. In 1795 he persuaded the Lords of the Admiralty to approve this regimen, and scurvy dramatically declined in the British Navy.

It did not entirely disappear aboard ships during the 19th Century, however, as Richard Henry Dana[17] recalled in his book, *Two Years Before the Mast,* an account of his experience as a sailor in the mid 1830s. During his ship's return to Boston from the coast of California, he describes a problem not previously encountered on the voyage:

> The scurvy had begun to show itself on board. One man had it so badly as to be disabled, and the English lad, Ben, was in a dreadful state, and was daily growing worse. His legs swelled and pained him so that he could not walk…his gums swelled until he could not open his mouth. His breath, too, became very offensive; he lost all strength and spirit; could eat nothing; grew worse every day; and, in fact, unless something was done for him, would be a dead man in a week, at the rate at which he was sinking. The medicines were all, or nearly all, gone; and if we had a chest-full, they would have been of no use; for nothing but fresh provisions and terra firma has any effect upon the scurvy.

In fact, however, most cases of scurvy during the 19th and 20th centuries occurred on terra firma, the most dramatic outbreaks developing when food became scarce because of severe privation, such as the Great Potato Famine of 1845-1848, or warfare, including the American Civil War, the Crimean War, and World War I. The disease also flourished in expeditions that lacked adequate provisions of fruits and vegetables; an estimated 10,000 people died of scurvy during the California Gold Rush, and many suffered from it during Arctic and Antarctic explorations. Another group affected in the late 19th and early 20th centuries was infants, especially in upper class families, who were fed with proprietary food and evaporated or condensed milk, which lacked vitamin C. The most prominent clinical finding was pain in the extremities, which the victims kept so immobilized to prevent discomfort that they sometimes appeared paralyzed. The pain originated from subperiosteal hemorrhage, a finding described by Thomas Barlow in 1884; accordingly, infantile scurvy was sometimes called Barlow's disease.

Attempts to reproduce this disorder in various mammals were unsuccessful until 1907, when a Norwegian scientist, Axel Holst, trying to find an animal model of beriberi, chose the guinea pig for his dietary experiments. He soon discovered that he had produced scurvy instead and asked a pediatrician knowledgeable about infantile scurvy, Theodor Frölich, to join him in his research. They convincingly demonstrated that scurvy was both produced by

Fig 1. Hair shaft abnormalities in scurvy. Some hairs are bent in one or more places, creating the "swan-neck" deformity. Some are coiled into "corkscrew" hairs. These abnormalities probably result from increased disulfide cross-linking of hair keratins.

Fig 2. Perifollicular abnormalities in scurvy, illustrating hemorrhages in a perifollicular distribution. Follicular hyperkeratosis appears in the center of some of the purpuric lesions. Also present are perifollicular, brownish, hyperkeratotic papules resembling keratosis pilaris, a finding typical of scurvy. Some hairs demonstrate the "swan-neck" deformity.

diet—as a consequence of inadequate intake of certain kinds of food—and cured by diet—when scorbutic animals received these foods. In 1912 a Polish chemist, Casimir Funk, proposed that scurvy, along with rickets, pellagra, and beriberi, originated from deficient intake of certain nitrogen-containing compounds with an amine structure that he called "vitamines," short for "vital amines." The word remained, eventually changed to "vitamins," even though the proposed amine nature proved incorrect.

In 1927 a Hungarian scientist, Albert Szent-Györgyi, while investigating a chemical found in high concentrations in the adrenal cortex and also in oranges and cabbages, finally, but unwittingly, isolated vitamin C. He knew that the molecule contained 6 carbon, 8 oxygen, and 6 hydrogen atoms and was related to sugars, whose names end in "ose," but he did not know the precise structure. He proposed the names "ignose," from "ignosco," meaning "don't know," or "godnose," but the editor of the journal to which he submitted his scientific paper did not appreciate such humor, and Szent-Györgyi instead called it "hexuronic acid," since he recognized that the material contained 6 ("hex") carbons and was acidic.[18] Proof that this substance was vitamin C came in 1932 when Szent-Györgyi in Hungary and C. G. King in the United States independently reported its effectiveness in preventing scurvy in guinea pigs.[19] The following year Szent-Györgyi and Norman Haworth, who delineated its precise chemical structure, renamed it "ascorbic acid," meaning a substance effective against scurvy—*a-scorb[ut]ic*.

PATHOGENESIS

Most animals require no exogenous source of ascorbic acid because they derive it from glucose via various enzyme systems.[20] Humans and a few other species, such as nonhuman primates, guinea pigs, the Indian fruit bat, and some birds, lack this capacity, explaining why attempts at reproducing scurvy in various mammals were unsuccessful until Holst chose the guinea pig. Humans get most of their vitamin C from fruits and vegetables, and the percentage of ascorbic acid absorbed from the intestine depends upon the quantity ingested. Small amounts are almost completely absorbed, while the proportion decreases with larger doses. The main route of elimination of ascorbic acid and its metabolites is urinary excretion, which rises with increases in dietary intake.[21] Ascorbic acid is widely distributed throughout the body, with the highest levels in the pituitary and the adrenal glands, where Szent-Györgyi first found it.

Ascorbic acid is necessary for the formation of mature collagen, which comprises 3 polypeptide molecules combined into a triple helix. The polypeptides are initially synthesized in the ribosome as procollagen molecules; lysyl and prolyl residues are catalytically hydroxylated after translation using enzymes requiring ascorbic acid as cofactor. The absence of hydroxyprolyl and hydroxylysyl residues renders the nascent polypeptide unstable and unable to self-assemble into rigid triple helices. This abnormality especially affects blood vessel integrity because of impaired synthesis of basal laminae, media, adventitia, and surrounding connective tissue. The result is perivascular edema, protrusion of endothelial cells into the vascular lumens, and erythrocyte extravasation. This deficient collagen synthesis leads to the hemorrhagic manifestations and poor wound healing characteristic of scurvy.

Some manifestations of scurvy could arise from impairment of the other actions of vitamin C,
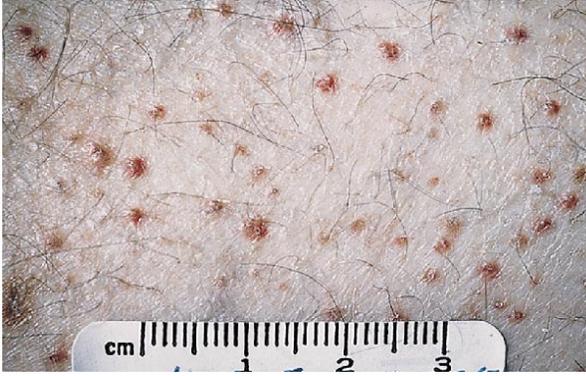
Fig 3. Perifollicular abnormalities in scurvy. In this example, the perifollicular hyperkeratotic papules are quite prominent, with surrounding hemorrhage. These lesions have been misinterpreted as "palpable purpura," leading to the mistaken clinical diagnosis of vasculitis.

Fig 4. Gingival abnormalities in scurvy. The gingival swelling and dusky color just above two of the teeth indicate hemorrhage into the gums of this patient with poor dentition. The gingival abnormalities of scurvy occur only in the presence of teeth, which presumably provide portals of entry for microbes into the gums. One hypothesis suggests that vitamin C deficiency impairs neutrophil-mediated killing of bacteria, leading to chronic gingivitis, which is then complicated by bleeding from the fragile vessels characteristic of scurvy.

although the exact relationships are unclear. It is an enzyme cofactor in the metabolism of tyrosine and the synthesis of carnitine, norepinephrine, and peptide hormones. It increases absorption of iron from the small intestine, and it functions as an antioxidant, reducing harmful free radicals and thereby decreasing damage to lipids, lipoproteins, DNA, protein, and vessel walls.[21]

DIETARY SOURCES OF VITAMIN C AND ADULT DAILY REQUIREMENTS

More than 90% of the vitamin C in Western diets derives from fruits and vegetables, including potatoes, tomatoes, berries, green vegetables, and citrus fruits.[20,21] In general, ordinary cooking of these items reduces their vitamin C content by 20% to 40%; using little water or employing a microwave oven will decrease these losses.[21] Liver and kidney contain ample amounts, but most other meats have little or no ascorbic acid, as do grains, poultry, fish, eggs, and dairy products, unless fortified. Dietary surveys indicate that the average daily vitamin C intake in the United States is about 75 to 85 mg in adults. The actual value may be higher because some processed foods contain ascorbic acid as an antioxidant and because about 40% to 50% of adults in the United States take supplemental vitamins.[21]

The minimal daily requirement of vitamin C to prevent scurvy, based on the British experiments, is 10 mg or less.[5] Opinions, however, differ about what the *recommended* daily intake should be, with values ranging from 30 to 200 mg. The United Kingdom and World Health Organization suggestion of 30 mg rests on the belief that an amount 3 times that necessary to prevent scurvy should provide sufficient safeguards for the population. The United States rec-

ommendation from 1989 of 60 mg is 2 standard deviations above the average intake calculated to provide adequate stores. Certain populations, however, require more vitamin C than others. Tobacco smokers have a metabolic turnover about twice that of nonsmokers, probably because of increased ascorbic acid catabolism. Accordingly, the United States' recommended daily intake for smokers is 100 mg. In pregnancy, because of increased losses to the fetus, guidelines suggest that women take an additional 10 mg daily, and during breast-feeding the advocated increment is 20 to 35 mg. The elderly, however, do not seem to require more vitamin C than younger adults. Some have suggested that the recommended daily intake for all adults should be 100 to 200 mg, primarily because of a possible decrease in cancer with this higher quantity and the correspondence of this value with the amount of vitamin C in a diet containing 5 daily servings of fruit and vegetables, which the Department of Agriculture and the National Cancer Institute endorse.[21]

EPIDEMIOLOGY

In industrialized nations scurvy is rare because ample sources of ascorbic acid are present not only in the diet, but also in vitamin supplements that the general public widely consumes. Still, the disease occurs in certain circumstances even in these countries because, for one or more of several reasons, some people eat inadequate amounts of fresh fruits

Fig 5. Lower extremity abnormalities in scurvy. Patient's foot is edematous and demonstrates ecchymoses, xerosis, and hemorrhagic bullae in the skin. This constellation of findings suggests severe and protracted vitamin C deficiency.

Fig 6. Lower extremity abnormalities in scurvy. In this patient xerosis is present, accompanied by ecchymoses and increased pigmentation from repeated cutaneous hemorrhages. A linear superficial wound covered with hemorrhagic crust has been present for an extended period, indicating impaired wound healing.

and vegetables. One group comprises adults living alone, most commonly men ("bachelor" or "widower" scurvy),[22-25] but sometimes women,[26] who have a deficient intake because of such factors as poverty, poor access to groceries, reclusiveness, dementia, or nutritional ignorance. They mostly prepare their own meals, but those who dine in restaurants do not order fresh fruits and vegetables. Other patients with scurvy avoid these "acid" foods because of purported allergies to them,[27] or because they produce or exacerbate gastrointestinal symptoms, such as dyspepsia, dysphagia, diarrhea, and heartburn.[28-31] Some of these patients have underlying alimentary disorders such as ulcerative colitis,[32] Whipple's disease,[33] peptic ulcers, and gastroesophageal reflux,[34] and, occasionally, advice from clinicians to avoid fruits and vegetables because of abdominal complaints has led to "iatrogenic scurvy."[35] Vitamin C deficiency has also occurred when poor or absent dentition has made consumption of fruits and vegetables difficult.[36] Sometimes people shun these foods just because they do not like their taste,[31] and others because of bizarre dietary beliefs,[37,38] including food fads.[39] Cancer patients may have an increased risk for scurvy because decreased intake of nutrients arises from anorexia or gastrointestinal symptoms caused by their underlying malignancy, chemotherapy, radiation treatment, or depression. In addition, some may receive parenteral nutrition lacking adequate vitamin supplements.[40]

Psychiatric or behavioral disorders can indirectly produce scurvy because the presence of depression, schizophrenia,[41,42] or anorexia nervosa[42,43] may affect the diet that such patients consume. The most

common associated behavioral disorder, however, is alcoholism,[24,25,29,36,40,44-48] which can lead to scurvy for several reasons. Vitamin C is absent from alcoholic beverages, and heavy drinkers often consume little else. Many alcoholics eat poorly and often live alone, with nobody to monitor their diets or prepare their meals. Moreover, alcohol decreases the intestinal absorption of vitamin C.[49]

CLINICAL FEATURES

Victims of scurvy often have dietary deficiencies other than just vitamin C, and many may have other concurrent disorders, such as infections, that could cause some of the clinical abnormalities attributed to scurvy, especially in the older literature. The possible contribution of these other factors led Crandon to perform his study and thus delineate precisely whether vitamin C deficiency, rather than another aspect of malnutrition, altered wound healing. This and the other investigations of experimental scurvy demonstrate that most of the findings reported by such astute clinicians as Lind were, in fact, manifestations of inadequate vitamin C.

Constitutional symptoms

According to Lind, among the first findings in scurvy is "a listlessness to action…a lazy inactive disposition" that degenerates into "a universal lassitude."[50] Crandon noted lack of energy as one of his initial symptoms in experimental scurvy, and exercise testing demonstrated decreased endurance.[1] The Iowa prisoners with experimental scurvy also noted fatigue, especially in the legs, and decreased

exercise tolerance as their first abnormalities.[6] Psychologic studies confirmed evidence of fatigue, depression, and lassitude.[51] Case series of scurvy also report that patients may become resentful, uncooperative, lethargic, and depressed, features that tend to disappear quickly with treatment.[52,53] The origin of these mental changes is unknown, but ascorbic acid is an important factor in neurotransmitter functions in the brain.[54]

Cutaneous abnormalities

Among the most impressive findings in scurvy are cutaneous abnormalities. Lind remarked that in his extensive experience the first indication of the disease is a change in the color of the face to a "pale and bloated complexion."[50] The skin becomes dry and rough, from the development of follicular hyperkeratosis, which was the first dermatologic finding in experimental scurvy.[1,5,6] Biopsy specimens of these lesions demonstrate follicular plugging with soft keratin.[5] In studies of experimental scurvy, the follicular hyperkeratosis predominantly involved the buttocks and legs.[1,5,6] Later a blanching erythema developed around the follicles, and biopsy specimens demonstrated congestion and proliferation of blood vessels.[5]

Lind described another change in the color of the skin, which

> is found covered with several reddish, bluish, or rather black and livid spots, equal with the surface of the skin, resembling an extravasation under it, as it were from a bruise. These spots are of different sizes, from the bigness of a lentil to that of a handbreadth, and larger…They are to be seen chiefly on the legs and thighs; often on the arms, breast, and trunk of the body; but more rarely on the head and face.[50]

These hemorrhagic skin lesions, the most distinctive cutaneous finding in scurvy, usually occur in a perifollicular distribution, especially, as Lind noted, on the legs, where the hydrostatic pressure is highest. On the extremities, they may become more numerous after inflation of a proximal blood pressure cuff.[5] Biopsy specimens demonstrate perivascular and perifollicular hemorrhages, sometimes with chronic perifollicular inflammation and hemosiderin deposits.[5,25,46,55] Electron microscopic findings include discontinuity of the endothelial lining of small venules, ballooned endothelial cells, and a marked decrease in the dermal collagen that normally provides perivascular support.[56] The perifollicular location of the hemorrhages may be from mechanical irritation by movement of hair or because the follicular hyperkeratosis makes that

location more subject to traction and friction than other, smooth, skin surfaces.[56]

Petechiae can occur outside perifollicular sites,[24,53,57] on areas such as the eyelids.[8] Especially in the lower extremities, the cutaneous hemorrhages may become palpable, presumably from extravasation of blood under high hydrostatic pressure. Clinicians have occasionally interpreted this "palpable purpura" as a sign of vascular inflammation and, because of the accompanying rheumatologic symptoms, described below, have erroneously suspected a systemic vasculitis.[28,30,45] These changes occur because of increased fragility in the blood vessel walls, and sometimes numerous petechiae appear after placement of a tourniquet or blood pressure cuff. Cutaneous hemorrhages may be much more extensive, creating large areas of ecchymoses, especially on the legs, sometimes in the absence of perifollicular hemorrhages.[57]

Lind also described leg edema as a manifestation of scurvy:

> Many have a swelling of their legs; which is first observed on their ancles towards the evening, and hardly to be seen next morning: but, after continuing a short time in this manner, it gradually advances up the leg, and the whole member becomes oedematous; with this difference only in some, that it does not so easily yield to the finger, and preserves the impression of it longer afterwards than a true oedema.[50]

Although some cases of edema ascribed to scurvy may have arisen from concurrent thiamine deficiency causing cardiac disease ("wet" beriberi), it occurred in experimental scurvy among the Iowa prisoners.[7] Potential explanations for the swelling include soft tissue hemorrhage, leaking capillaries, or heart failure from severe anemia, which, however, was not present in the cases due to experimental scurvy.[7] Some reports have described a curious "woody edema"[22,52] of the legs, associated with swelling, ecchymoses, pain, and limited motion that may correspond to the latter part of Lind's observations.

Lesions from bleeding may be present in the nails in the form of subungual linear ("splinter") hemorrhages.[28,58] Alopecia develops in some patients, which was seen in association with other features of Sjögren's syndrome in the experiments with Iowa prisoners.[9] Because ascorbic acid is important in the disulfide bonding that occurs with hair formation, scurvy can lead to abnormal body hair. The hair may fracture, coil into a "corkscrew hair," or bend in several places, leading to a "swan-neck deformity." Skin biopsy specimens often demonstrate a coiled hair in its follicle.[5,28]

Evidence of impaired collagen synthesis can be apparent as poor wound healing, and previous scars may soften and thin, as Crandon discovered. Lind described ulcers, primarily on the legs, which occurred from spontaneous opening of previously damaged skin or as a complication of fresh trauma, with even the slightest bruises and wounds causing disruption of the skin surface.[50] The British study of experimental scurvy also reported an accentuation of pre-existing acne, with the papules increasing in size and number, developing a more extensive distribution, and becoming red and hemorrhagic.[5]

In one case subcutaneous nodules appeared on one forearm and both calves; a biopsy specimen disclosed chronic lymphocytic inflammation consistent with a predominantly septal panniculitis, hemorrhage, and hemosiderin-laden macrophages.[41]

Oral findings

Lind described the gingival findings: "their gums…become itchy, swell, and are apt to bleed upon the gentlest friction. Their breath is…offensive; and upon looking into their mouth, the gums appear of an unusual livid redness, are soft and spungy."[50] When patients are edentulous, no gingival abnormalities occur, and they tend to develop most prominently in patients with poor oral hygiene and periodontal disease. The teeth may loosen because of underlying dental disease or secondary absorption of alveolar bone from scurvy itself. The gum findings are most striking in the interdental and marginal gingiva, which become red, smooth, swollen, and shiny.[59] Later the gums appear purplish, sometimes even black and necrotic[5,39]; the marginal epithelium disintegrates, receding from the teeth; and the gingivae often bleed spontaneously or after minor trauma, especially in the interdental papillae. The histologic features include dilated subepithelial blood vessels, which are thin and engorged, and extravasation of erythrocytes into the surrounding tissue in areas of hemorrhage.[39]

Musculoskeletal findings

Lind observed from his vast experience with scurvy that:

> scorbutic people, as the disease advances, are seldom indeed free from…pains…. Some complain of universal pain in all their bones…most violent in their limbs, and small of the back, and especially on their joints and legs when swelled…. [S]corbutic pains in general are very liable to move from one place to another [and] are always exasperated by motion of any sort.[50]

In the British study of experimental scurvy, sudden movement, cough, sneezing, and deep breathing provoked or intensified back pain, whereas discomfort in the extremities tended to be constant and unaffected by movement.[5] The pains may arise in part from hemorrhage into the muscles and other soft tissues, evident on examination as swelling and tenderness of the affected area, often with overlying ecchymoses. Sometimes the discomfort is so severe that the patients cannot walk.[36] Hemorrhage may also occur beneath periosteum, which is quite sensitive to pain.

Another source of discomfort in the extremities is bleeding into the joints, causing hemarthroses, rarely with osteolysis of the adjacent bone.[38] On synovial biopsy the findings are interstitial hemorrhage, some disarray of the vascular basement membrane, and, despite the presence of many large fibroblasts, little collagen formation.[60] Because ascorbic acid is necessary for collagen biosynthesis, a requisite for normal bone formation, scurvy may contribute to osteoporosis,[27] and, theoretically at least, pain in scurvy could occasionally arise from fractures, especially in those with pre-existing abnormal bones, such as postmenopausal women.

Ophthalmologic findings

Scurvy can affect several areas of the eyes. In the studies on Iowa prisoners conjunctival varicosities developed, and hemorrhages occurred beneath both the palpebral and bulbar conjunctiva.[8] Similar events have occurred in spontaneous cases.[60] In the fundus, flame-shaped hemorrhages and cotton-wool spots can develop.[61,62] Other areas of bleeding have included the periorbital area, eyelids, retrobulbar space, and sheaths of the optic nerve, causing either papilledema or optic atrophy.[8,10] In some subjects with experimental scurvy, ocular symptoms arose in association with other features of Sjögren's syndrome. These findings included dryness, erythema, irritation, light intolerance, transient visual blurring relieved by blinking, and stickiness and mattering of the eyes. Those with complaints of dry eyes had decreased lacrimal secretion.[9]

CARDIORESPIRATORY SYMPTOMS

Dyspnea may be present,[53] sometimes because of anemia, which can be severe enough to cause high-output congestive heart failure. Since this symptom occurred in experimental scurvy in the Iowa prisoners, who did not have significant anemia, another mechanism must be responsible in some patients. In one case Cheyne-Stokes pattern of respiration developed, disappearing within 48 hours of vitamin C therapy.[58] In another, lung infiltrates, possibly from leaky capillaries, and pulmonary hypertension appeared, but resolved promptly with treatment.[43]

Syncope[57] and hypotension, occasionally leading to frank shock,[57,58] have occurred, as has sudden death.[57] The account of Commodore Anson's voyage in 1740-1744 describes such events as common, often afflicting those who did not seem critically ill:

[M]any of our people, though confined to their hammocks, appeared to have no inconsiderable share of health, for they [ate] and drank heartily, were chearful, and talked with much seeming vigour, and with a loud strong tone of voice; and yet on their being the least moved, though it was only from one part of the ship to another, and that in their hammocks, they have immediately expired; and others, who have confided in their seeming strength, and have resolved to get out of their hammocks, have died before they could well reach the deck; and it was no uncommon thing for those who were able to walk the deck, and to do some kind of duty, to drop down dead in an instant, on any endeavours to act with their utmost vigour, many of our people having perished in this manner during the course of this voyage.[15]

Lind[50] reported similar events: "They are apt, upon being moved, or exposed to fresh air, suddenly to expire." Such circumstances especially occurred in the terminal stage of the disease:

Towards the close of this malady, the breast is most commonly affected with a violent and uneasy straitness and oppression, and an extreme dyspnoea; accompanied sometimes with a pain under the sternum, but more frequently in either of the sides: while others, without any complaint of pain, have their respiration become quickly contracted and laborious, ending in sudden, and often unexpected death.

The mechanisms for these cardiovascular and respiratory events are somewhat unclear. The decreased blood pressure seems to arise from a defect in the ability of resistance vessels to constrict in response to adrenergic stimuli, as demonstrated in experimental scurvy.[63] This vascular abnormality by itself could lead to syncope, refractory hypotension, and death. Another factor possibly responsible for low blood pressure, chest pain, dyspnea, and sudden death is myocardial hemorrhage, which, although not described in humans, occurs in scorbutic guinea pigs.[64] Cardiorespiratory symptoms and abnormal electrocardiographic findings have developed in some cases of vitamin C deficiency in humans and could be due to myocardial hemorrhage. In the British study of experimental scurvy, a 22-year-old male participant abruptly suffered retrosternal chest pain, dyspnea, cyanosis, and hypotension, accompanied by elevated ST segments

in leads I and II, which led to immediate hospitalization and administration of vitamin C, with resolution of the pain in 9 hours.[5] A second volunteer, a 28-year-old man, suddenly developed constrictive chest pain intensified by deep breathing, a new systolic murmur, and first-degree heart block. With large doses of vitamin C, the murmur and chest pain disappeared in 24 hours, but the block persisted. Another report described ST-segment depression and T wave inversion in two patients with scurvy; in both the abnormalities resolved after 7 days of vitamin C therapy.[65]

Another cardiac complication of scurvy occurred when members of the expedition of the French explorer Jacques Cartier to North America had to spend the winter of 1535-1536 on an island in the frozen St Lawrence river. Deprived of fresh fruits and vegetables, the explorers experienced a large outbreak of scurvy[11]:

[S]ome lost all their strength, their legs became swollen and inflamed, while the sinews contracted and turned as black as coal. In other cases the legs were found blotched with purple-coloured blood. Then the disease would mount to the hips, thighs, shoulders, arms and neck. And all had their mouths so tainted, that the gums rotted away down to the roots of the teeth, which nearly all fell out.

After one man died, an autopsy, performed to discover what might explain this strange disease, demonstrated that "his heart was completely white and shriveled up, with more than a jugful of red date-coloured water about it." Fortunately, a band of Indians showed the explorers how to make a medication from the bark and leaves of a tree, and the sick rapidly recovered. Hemopericardium as a complication of scurvy was later recognized and treated with pericardiocentesis in outbreaks in Russia both in 1847 and during the Crimean War of 1854-1856.[66] Bleeding into the pericardial sac causing cardiac tamponade, therefore, is another potential explanation of dyspnea, hypotension, and death in scurvy.

In most patients who die of this disease, however, autopsies reveal no anatomic abnormalities in the heart,[67] and impaired vasoconstriction to adrenergic stimuli, as discussed above, seems the most plausible explanation.

Gastrointestinal symptoms

Anorexia is common in scurvy, and some patients have gastrointestinal bleeding. On upper endoscopy submucosal hemorrhages have been present anywhere from the distal esophagus to the duodenum.[33,55,68] In two cases repeat endoscopy demon-

strated that the abnormalities disappeared after vitamin C therapy.[33,68]

LABORATORY FINDINGS

In experimental scurvy mild anemia occurred in only one study. In naturally occurring disease, however, anemia is common,[69-71] and its degree apparently correlates with the severity and duration of the scurvy.[69] It may arise from one or more of several mechanisms. Recent hemorrhage into tissue or loss into the gastrointestinal tract is probably responsible for the anemia in some cases. In these, the red cells are normochromic-normocytic, the reticulocyte count is elevated, and bone marrow samples reveal erythrocyte hyperplasia. Such findings, however, are also consistent with hemolysis, and, indeed, the red cell life span may be decreased, as demonstrated by a diminished survival of erythrocytes from normal patients transfused into patients with scurvy.[70] On the other hand, red cells from patients with scurvy survived normally when transfused into nonscorbutic subjects. These findings indicate an extracorpuscular problem in which the milieu in scurvy is unfavorable to the erythrocyte's integrity. The hemolysis is reflected by an increased indirect bilirubin in many patients,[69,71] and repletion with ascorbic acid alone may correct the anemia.[58,69,70]

Since vegetables and fruits that supply the major source of vitamin C also provide the bulk of daily folic acid consumption, a diet deficient in one is commonly deficient in the other. The hematologic result may be a macrocytic anemia due to inadequate folic acid. In addition, because ascorbic acid prevents oxidation of folate to forms that are excreted in the urine, vitamin C deficiency may deplete folate stores by increasing urinary excretion.[72] In some patients with scurvy, therefore, the main or sole cause of the anemia is insufficient folic acid, which, when given alone, will return the hematocrit to normal.[73]

Ascorbic acid increases the absorption of dietary iron, either by reducing it from the ferric to the ferrous state, which is necessary for iron transfer and storage, or by preventing its chelation by phytates or other food ligands.[21] Iron deficiency, however, rarely seems responsible for the anemia in scurvy in the absence of another cause,[70] and iron repletion does not ordinarily correct it.[69]

Other hematologic abnormalities occur in a minority of patients with scurvy. In Crandon's self-experiment the white cells dropped from 5000/mL to a low of 3200/mL and returned to normal after vitamin C repletion.[1] In about one third of clinical cases of scurvy, leukopenia is similarly present.[31,58,69] Platelet number and function, however, remain normal.[73] Sometimes the erythrocyte sedimentation rate is elevated,[5,36,70] but whether this occurs more frequently than in the general population or is related to vitamin C deficiency at all remains unclear.

DIAGNOSIS

The diagnosis of scurvy is primarily a clinical one, based on a dietary history of inadequate vitamin C intake and the various manifestations described above. The combination of follicular hyperkeratosis and perifollicular hemorrhage is pathognomonic and occurs early in the disease. Supporting findings, which usually occur later, are ecchymoses, hairs with corkscrew or swan-neck deformities, and swollen, red or purplish gums in patients who have teeth.

These manifestations of scurvy occur when the body pool of ascorbic acid, normally about 1500 mg, falls below 300 mg.[6] This measurement is impractical, but alternative tests to confirm the clinical diagnosis include plasma or leukocyte ascorbic acid levels. Plasma values are affected by recent dietary intake, while leukocyte levels, which change more slowly, better indicate tissue and total body content. Alternatively, disappearance of the clinical abnormalities with vitamin C repletion establishes the diagnosis without laboratory studies.

TREATMENT

Cures of scurvy have occurred with as little as 6.5 mg of ascorbic acid daily, but a dose that both corrects the deficit and repletes the body stores expeditiously is 100 mg 3 times a day.[75] The manifestations of scurvy tend to recede promptly, sometimes dramatically, and disappear within a few weeks.[5,53,58] Subjective improvement commonly begins within 24 hours,[1] and the lethargy, anorexia, and pain diminish in 2 to 3 days. Joint swelling resolves in a few days.[58] The purplish hue of the skin lesions pales quickly and then subsides in 2 to 4 weeks, leaving areas of brown pigmentation that slowly disappear.[58] The hyperkeratosis decreases in 1 to 2 weeks, and by 4 weeks the hairs have uncurled, returning to their normal appearance. The gums change from purple to red in 1 to 2 weeks, with more gradual resolution of the gingival edema, complete recovery being apparent by 3 months. Except for lost teeth, permanent damage from scurvy does not occur.[75] In those whose anemia is due solely to vitamin C deficiency, the reticulocyte count increases substantially within 10 days, and the hematocrit returns to normal within a few weeks.[55,58]

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CME examination

Identification No. 899-112

Instructions for Category I CME credit appear in the front advertising section. See last page of Contents for page number.

Questions 1-30, Hirschmann JV, Raugi GJ. J Am Acad Dermatol 1999;41:895-906.

Directions for questions 1-30: Give single best response.

1. In a diet totally deficient in vitamin C, the earliest clinical findings occur after a minimum of
   a. 1 week
   b. 2 weeks
   c. 6 weeks
   d. 5 months
   e. 7 months

2. The most important reason for the emergence of descriptions of scurvy in the late 15th century and early 16th century was
   a. clearer recognition of a disease that had been widespread for centuries
   b. extended voyages by sea
   c. a substantial alteration in the European diet because of changes in religious practices
   d. privation in diets of the Europeans because of sustained warfare
   e. the availability of printing, which allowed publication of information previously known but not written down

3. The noun "scurvy" seems to arise from a phrase meaning a disease that
   a. ruptures the belly
   b. causes black spots
   c. irritates the gums
   d. causes pain in the bones
   e. dries the skin

4. The clinician who did a controlled trial of citrus fruits compared with other treatments of scurvy in 1747 was
   a. George Anson
   b. James Cook
   c. John Crandon
   d. James Lind
   e. Gilbert Blane

5. With infantile scurvy, the most prominent clinical finding is
   a. peripheral edema
   b. extensive ecchymoses
   c. painful extremities
   d. xerosis
   e. sore tongue

6. The animal lacking the capacity to derive ascorbic acid from glucose metabolism in which experimental scurvy was first demonstrated is the
   a. rat
   b. chimpanzee
   c. bat
   d. mouse
   e. guinea pig

7. Foods with substantial natural amounts of vitamin C include
   a. fish
   b. eggs
   c. dairy products
   d. potatoes
   e. grains

8. Those who require a larger amount of vitamin C than the normal population are
   a. the elderly
   b. nonsmokers
   c. patients with liver disease
   d. patients with renal disease
   e. women during pregnancy

9. The minimum daily requirement of vitamin C to prevent scurvy is about
   a. 10 mg or less
   b. 30 mg
   c. 60 mg
   d. 100 mg
   e. 150 mg

10. The first symptom most commonly noted in experimental and naturally occurring scurvy is
    a. depression
    b. fatigue
    c. pain in the joints
    d. headaches
    e. abdominal pain

11. The roughening of the skin noted in scurvy is due to
    a. lichenification from scratching
    b. infiltration of the skin by increased collagen
    c. follicular hyperkeratosis
    d. thick scaling
    e. secondary amyloidosis

12. Areas that tend to be most involved with follicular hyperkeratosis are
    a. arms and back
    b. neck and legs
    c. face and neck
    d. buttocks and legs
    e. dorsal feet and hands

13. Perifollicular hemorrhages tend to be most numerous on the
    a. legs
    b. hands
    c. face
    d. trunk
    e. neck

14. Palpable purpura
    a. excludes the diagnosis of scurvy
    b. occurs in scurvy as a manifestation of scorbutic vasculitis
    c. only occurs in scurvy when Sjögren's syndrome is present
    d. may develop in scurvy from extravasation of blood under high hydrostatic pressure
    e. occurs in scurvy and requires corticosteroid therapy

15. Each of the following is a feature of scurvy *except*
    a. alopecia
    b. splinter hemorrhages
    c. corkscrew hair
    d. leg edema
    e. pustules

16. Each of the following is an oral feature of scurvy *except*
    a. large ulcers
    b. offensive breath
    c. swollen hemorrhagic gums in the presence of teeth
    d. loosened teeth
    e. black and necrotic gums in the presence of teeth

17. The musculoskeletal manifestations of scurvy include each of the following *except*
    a. back pain
    b. joint pain
    c. hemarthroses
    d. soft-tissue hemorrhages
    e. inflamed joints

18. The ophthalmologic manifestations of scurvy include each of the following *except*
    a. conjunctival hemorrhages
    b. cataracts
    c. cotton wool spots in the fundus
    d. dry eyes
    e. papilledema from hemorrhage into the optic nerve sheath

19. Plausible explanations of syncope from scurvy include each of the following *except*
    a. myocardial hemorrhage
    b. pericardial tamponade
    c. scurvy-induced bradycardia
    d. hypotension from poor vasoconstrictive response to adrenergic stimuli
    e. severe anemia

20. Plausible explanations for the anemia associated with scurvy include each of the following *except*
    a. concurrent folic acid deficiency
    b. hemolysis
    c. bleeding into gastrointestinal tract
    d. bone marrow aplasia
    e. hemorrhage into soft tissue

21. A hematologic finding in about one third of cases of scurvy is
    a. iron deficiency anemia
    b. leukopenia
    c. thrombocytopenia
    d. monocytosis
    e. eosinophilia

22. A permanent complication of scurvy is
    a. dementia
    b. cutaneous scarring in areas of hemorrhage
    c. peripheral neuropathy
    d. lost teeth
    e. alopecia

23. In patients whose anemia is from scurvy alone, the hematocrit returns to normal in
    a. a few weeks
    b. 3 to 4 days
    c. 1 to 2 days
    d. 3 to 4 months
    e. 6 to 10 months

24. Which of these laboratory tests most accurately reflects the tissue and total body content of ascorbic acid?
    a. Plasma level of ascorbic acid
    b. Leukocyte level of ascorbic acid
    c. Bone marrow level of ascorbic acid
    d. Serum level of ascorbic acid reducing substance
    e. Ascorbic acid level in a skin biopsy specimen

25. Ascorbic acid is necessary for the formation of mature collagen, which exists in the following structure:
    a. double helix
    b. single helix
    c. triple helix
    d. pleated fold
    e. straight, rigid strand

26. The chemist who first isolated vitamin C was
    a. C. G. King
    b. Norman Haworth
    c. Casimir Funk
    d. Theodor Fröhlich
    e. Albert Szent-Györgi

27. The chemist who frst coined the term *vitamine* was
    a. C. G. King
    b. Norman Haworth
    c. Casimir Funk
    d. Theodor Fröhlich
    e. Albert Szent-Györgi

28. The reasons that Lind's experimental evidence about the therapeutic efficacy of citrus fruits had little effect on the incidence of scurvy in the British Navy include each of the following *except*
    a. the stubborn foolish refusal of the British Admiralty to adopt his recommendations

b. the lack of a good preparation of durable citrus juice

c. Lind's weak advocacy of his own views

d. Lind's belief that the cause of scurvy was a cold damp climate

e. Lind's experiment was published as only a small, inconspicuous part of his *Treatise of the Scurvy.*

29. The first person to prove conclusively that vitamin C deficiency causes impaired wound healing in humans was
   a. Richard Henry Dana, Jr
   b. Theodor Fröhlich
   c. Albert Szent-Györgi
   d. Axel Holst
   e. John Crandon

30. The highest levels of vitamin C in the human are in the
   a. pituitary and adrenal glands
   b. pancreas and thymus
   c. liver
   d. heart
   e. cerebral cortex

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Answers to CME examination

Identification No. 899-111

November 1999 issue of the Journal of the American Academy of Dermatology

Questions 1-31, Brown TJ, Yen-Moore A, Tyring SK. J Am Acad Dermatol 1999;41:661-77.

1. e		17. b	
2. a		18. b	
3. c		19. a	
4. e		20. c	
5. c		21. d	
6. c		22. b	
7. c		23. a	
8. a		24. e	
9. b		25. c	
10. d		26. d	
11. b		27. e	
12. a		28. a	
13. c		29. b	
14. d		30. a	
15. a		31. c	
16. b			