

## Summary

- Deficiency of ascorbic acid leads to poor quality collagen
- Hemorrhages and bone abnormalities dominate the clinical picture
- Barlow's disease (infantile scurvy) with periosteal hemorrhage)
- Rapid improvement with vitamin C tablets or fresh fruit and vegetables

## Introduction

Scurvy is a disease caused by lack of vitamin C. The condition was a common ailment aboard European seagoing ships in the early days of world exploration and was a serious problem on long voyages. In 1497, Vasco da Gama, in his epic trip from Portugal to India and back, lost no fewer than 100 of his original crew of 160 to scurvy. Magellan's expedition of circumnavigation of the world (1519-1521) lost 200 of his original crew of 218. Of the 110 crew members of Jacques Cartier's exploration of the St Lawrence river (Canada), 100 were affected during the winter of 1535-1536. A quarter died, the rest recovered with grounded cedar bark, a native Indian remedy. Aboard the ships there was a systematic lack of fresh fruit and vegetables.

In the nineteenth century, scurvy began to occur among infants receiving the newly introduced preserved milk instead of breastmilk or fresh cows' milk. The preserved milk contained adequate carbohydrate, fat, protein and minerals, but the heat used in its processing destroyed the vitamin C, so the infants got scurvy. Nowadays, scurvy only occurs in the event of an unbalanced diet with nutritional deficiency, as in some elderly people and alcoholics. Scurvy is sometimes seen in persistent problematical situations in the tropics (refugees, starvation), certainly in warm and dry regions where there is a lack of fresh fruit and vegetables. In a population living in stable conditions, scurvy is rare.

### Ascorbic acid

For a long time the origin of scurvy was a mystery. Before vitamin C was identified, however, a form of empirical treatment and prophylaxis had been discovered, but the nature of the compound that cured scurvy was not clear. A breakthrough came with the

discovery that guinea pigs could develop scurvy. Guinea pigs, fruit-eating bats and higher primates (Old and New World monkeys, apes and humans) – unlike most mammals – are unable to synthesize ascorbic acid. Lower primates or prosimians, such as lemurs, loris and tarsiers have active L-gulonolactone acid oxidase, and so make their own vitamin C. Humans have an inactivating mutation in this enzyme, which leads to an afunctional pseudogene and therefore the inability to synthesize vitamin C. One could say that the entire human race has an inborn error of metabolism. When the defect in guinea pigs was discovered, scientists had an animal model and an in vivo assay for measuring the antiscorbutic activity of different food products.

It was demonstrated that drying, cooking and prolonged exposure to air destroyed the active ingredient. During his research at Cambridge University in 1928, the Hungarian biochemist Szent-Gyorgyi isolated vitamin C. He isolated the compound from lemons, oranges, cabbages and adrenal cortex. After his return to Hungary, he continued his work on paprikas, as befits a good Hungarian. It turned out that paprikas are very rich in vitamin C. He received the Nobel Prize for Medicine in 1937. He initially proposed to name his crystalline sample “ignose”, indicating its relationship to sugars while at the same time underlining his ignorance of its true nature. The editor of the *Biochemical Journal* where he wanted to publish his findings, did not like jokes and reprimanded him. A second suggestion “godnose” was judged to be equally unacceptable. Szent-Györgyi finally accepted the more prosaic “hexuronic acid”, since the molecule had 6 carbons and was acidic. Haworth suggested the term “ascorbic acid,” acknowledging the antiscorbutic nature of the compound.

Subsequently it became evident that vitamin C occurs in numerous food products. Vegetables such as broccoli and tomatoes, but also potatoes and citrus fruit have large concentrations of vitamin C. Sir Walter Norman Haworth discovered an efficient synthesis method for the preparation of vitamin C based on a carbohydrate precursor. Sir Norman Haworth and Paul Karrer (Switzerland) were jointly awarded the Nobel Prize for Chemistry for their work in 1937.

The name ascorbic acid refers to ‘antiscorbutic’ (from the Low German term for scurvy: *schorbock*). Vitamin C is essential for the production of mature collagen. It is a highly reducing compound and is capable of undergoing reversible oxidation. In consequence, it

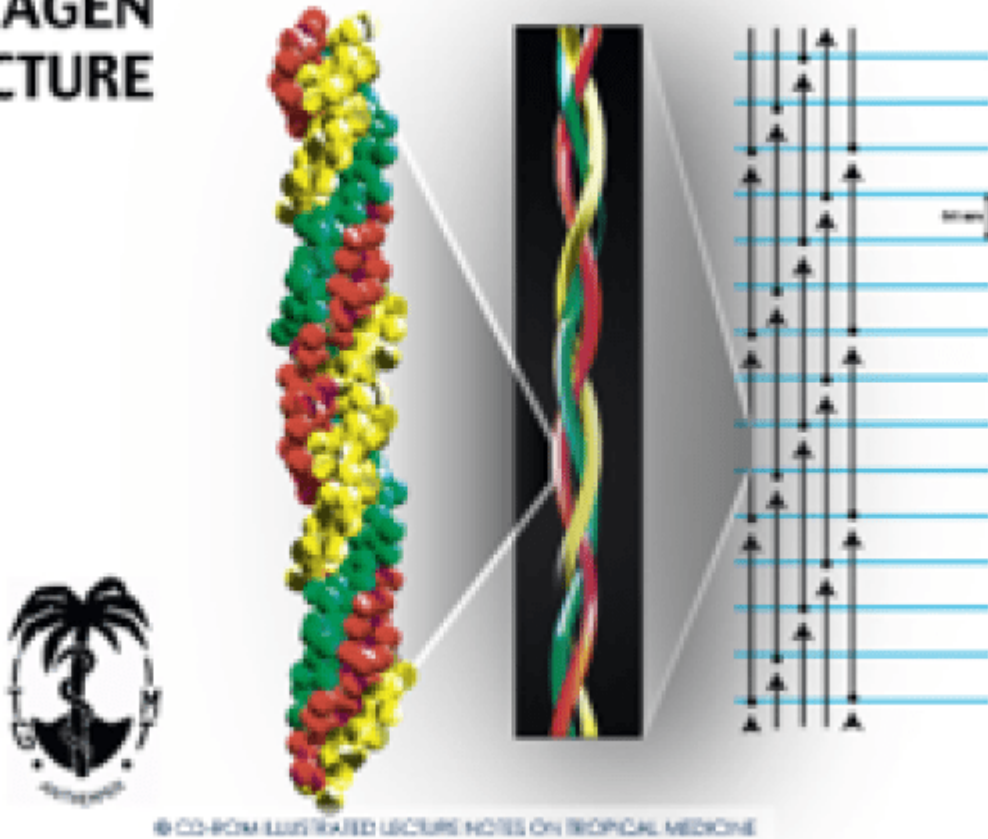
fulfils a role in redox reactions in the body. Vitamin C is the L-enantiomer of ascorbate; the D-enantiomer is not physiologically active. Vitamin C promotes the uptake of iron in the intestine and protects folic acid reductase. Vitamin C regenerates antioxidants such as vitamin E, flavonoids and glutathione. It plays a role in the synthesis of steroids and the production of carnitine.

### Collagen

Vitamin C is important in redox reactions. At least 8 different enzymes use vitamin C as a cofactor (maturation of collagen, production of several peptide hormones and neurotransmitters, synthesis of carnitine). Several symptoms of scurvy can be traced back to defective collagen. Collagen is the commonest protein in the animal kingdom. Large amounts of unusual amino acids are found in collagen: hydroxylysine and hydroxyproline. These are essential for the chemical stability of collagen. The conversion of proline into hydroxyproline is stimulated by the enzyme proline hydroxylase. For this purpose it uses a  $\text{Fe}^{2+}$  ion, which is converted during the reaction into  $\text{Fe}^{3+}$ . This inactivates the enzyme. Enzyme regeneration takes place by an interaction with ascorbate, in which vitamin C is converted into dehydroascorbic acid. For a better understanding of scurvy, we briefly sketch the normal production of the commonest form of collagen. Individual collagen polypeptide chains are synthesized on the ribosomes of the rough endoplasmic reticulum. The strands are released in the lumen of the endoplasmic reticulum as large precursor molecules, the so-called pro- $\alpha$  chains. Signal peptides are still present at front and rear. In the lumen, selected proline and lysine residues are hydroxylized to hydroxyproline and hydroxylysine. Every pro- $\alpha$  chain subsequently combines with two other chains to form a triple-strand helix via hydrogen bridges, the fibrillar procollagen. This is subsequently secreted. Procollagen is converted extracellularly into tropocollagen by enzymatic cleavage (with the exception of collagen IV in the basal lamina). Tropocollagen subsequently develops further into mature collagen. Normal collagen is broken down slowly by extracellular collagenases. In scurvy, defective pro- $\alpha$  chains are formed (the formation of hydroxy-amino acids is disrupted). They do not form a triple helix and are quickly degraded. The consequences are first noticed first in the tissues where collagen turnover is fastest, such as blood vessels. Owing to the gradual loss of the existing collagen, the blood vessels become progressively

fragile.

## COLLAGEN STRUCTURE



Collagen structure. This is disturbed in osteolathyrism and in scurvy (vitamin C deficiency).  
Drawing by JP Wenseleers, copyright ITM

## Aetiology

Primary deficiency is due to an unbalanced diet, i.e. a diet containing less than 10 mg vitamin C per day. There is little agreement on the minimal daily dose to avoid scurvy. Pregnancy, lactation, smoking, surgical procedures, thyrotoxicosis, burns and chronic inflammation increase the body's requirements up to 70-90 mg/day. In achlorhydria and chronic diarrhoea, less vitamin C is absorbed. Ascorbic acid is unstable in the presence of heat and prolonged cooking of food considerably reduces the quantity of active vitamin C. Scurvy is uncommon nowadays but outbreaks can be seen in refugee camps, during famines and occasionally in prisons.

## Clinical aspects

The highest concentrations of vitamin C are found in white blood cells, the lens and the brain. The total body pool of vitamin C is approximately 1500 mg. The excess is excreted. There is a turnover of 3% per day, which gives a half-life of approximately 18 days. This explains the latency period of 3 to 6 months for symptoms to occur after starting a diet without vitamin C.

Ascorbic acid is necessary for the proper formation and maintenance of intercellular material, particularly collagen. In simple terms, it is essential for producing part of the substance that binds cells together, as cement binds bricks together. In a person suffering from scurvy, the endothelial cells of the capillaries lack normal solidification. They are therefore fragile, and haemorrhages take place. Similarly, the dentine of the teeth and the osteoid tissue of the bone are improperly formed. The patient first complains of pronounced fatigue, general debility of slow onset, irritability, weight loss and vague myalgia and joint pain. Sometimes the first symptom is stiffness in the calves, due to local haemorrhages. Because of the pain in the legs, children may present with pseudoparalysis. In many cases they spontaneously adopt an antalgic posture, with bent knees and hips: frog-leg posture as described by Thomas Barlow. This is usually seen in babies born prematurely when they reach about 6-12 months of age if they have been fed deficient artificial food: Barlow's disease or infantile scurvy. Splinter haemorrhages beneath the fingernails may occur as in infective endocarditis. Haemorrhages around the eyes, ears, neck and on the roof of the mouth may occur. Spontaneous bleeding may occur anywhere in the body, including bleeding leading to palpable subperiosteal haemorrhages. Hyperkeratotic hair follicles and perifollicular petechiae (scorbutic purpura) are quasi pathognomonic. Corkscrew hairs is a typical scorbutic feature. The poor cell-binding also explains the poor scar formation and slow healing of wounds manifest in persons deficient in ascorbic acid. Old scars might break open. The gums become swollen, purple and spongy and bleed easily. Often there will be secondary infection. In advanced scurvy, teeth fall out spontaneously. Endochondral bone development ceases because osteoblasts no longer produce osteoid. A fibrous area is formed between diaphysis and epiphysis. The costochondral junctions enlarge. This is clinically palpable as a scorbutic rosary (not to be confused with rachitic rosary). Other symptoms include femoral neuropathy and oedema of the legs. Microcytic hypochromic anaemia may develop as vitamin C is needed to absorb iron.

Sudden cardiac failure and death can occur in a patient with above mentioned symptoms,

even if the person does not appear seriously ill.

## Differential diagnosis

Scorbutic rosary on the thorax and bone abnormalities must be distinguished from rachitic rosary (vitamin D deficiency). Scorbutic gingivitis must be distinguished from other causes such as candidiasis, herpes, trench mouth, syphilis, pemphigus and Behçet's syndrome. Scorbutic haemorrhages must be distinguished from other bleeding diatheses. Subperiosteal haemorrhage with periosteal elevation should be distinguished from congenital syphilis.

## Diagnosis

The vitamin C content in peripheral blood can be measured in specialized laboratories, although plasma vitamin C levels quickly normalize with enteral intake of ascorbic acid and do not reflect tissue levels. A level of less than 11  $\mu\text{mol/liter}$  is diagnostic for scurvy. Measurement in leukocytes – a storage pool for ascorbic acid – is more precise. A capillary fragility test will be positive. When this is measured using the sphygmomanometer, it is called the Hess capillary test. The regular haemostasis parameters (platelets, coagulation times) are normal. Findings on X-rays of the legs include a lucent transverse metaphyseal band with an adjacent dense sclerotic band, metaphyseal spurring and nonspecific evidence of diffuse osteopenia and cortical thinning. Radiographs may reveal periosteal fluid consistent with haemorrhage.

## Treatment

The treatment of scurvy consists of administering extra vitamin C (at least 100 mg three times daily for two weeks) and adjusting the daily diet with plenty of fresh fruit and vegetables. Clinical improvement may be expected within one to two weeks. Chronic gingivitis and extensive subcutaneous haemorrhages take longer to heal. Increased intake of vitamin C with meals can have a manifest effect on the absorption of iron. In many iron-deficient populations, increasing vitamin C intake will help reduce the incidence and severity of iron deficiency anaemia.

### Treatment: historical note on James Lind and Captain Cook

Various therapies were used in ancient times but as long as the cause remained unknown, no rational treatment could be suggested. Some people believed that certain plants could be used as a remedy for scurvy. For instance, *Cochlearia officinalis* (Family: Cruciferae) is known as common scurvy grass. Naval surgeon James Lind was on board the *Centurion*, a British gunship which had been put to sea in 1740 in order to give a hard time to the Spanish. After three years he had gained considerable experience with scurvy. In 1747, he conducted a kind of clinical trial ahead of its time. He had 12 patients with scurvy on board. They were divided into six groups and each group received a different treatment: (1) one glass of cider a day, (2) 25 drops of an elixir of vitriol three times a day, (3) two spoonfuls of vinegar three times a day, (4) half a pint of sea water three times a day, (5) a mixture of garlic, mustard, horseradish and balsam of Peru three times a day, (6) two oranges and a lemon each day. The two men who were given citrus fruit made a spectacular recovery. Cider also brought some improvement, although to a more limited extent. Lind published his findings. In July 1772, Captain Cook set out from Plymouth on board *HMS Resolution* on an expedition that was to last three years. He didn't lose a single member of the crew to scurvy. A paper that he presented on the prevention of scurvy won for Cook the Royal Society's Copley Gold Medal. He ordered the crew to eat sauerkraut twice a week and gave a malt potion and an orange and lemon to everyone who showed the first signs of scurvy. Furthermore he made sure that the ship was provisioned with fresh fruit and vegetables each time they made landfall. He also demanded strict hygiene on board, which was very unusual at the time. The Royal Navy implemented Captain Cook's regimen regarding hygiene and ordered that on voyages lasting longer than two weeks, everyone on board was to be given a spoonful of lemon juice and sugar each day. This mixture was incorrectly described as 'lime juice', and to this day, British sailors are known as 'Limeys'. Unfortunately, limes (*Citrus medica var acidum*) were sometimes used instead of lemons (*Citrus medica var limonum*). Limes contain much less vitamin C than lemons so that fatalities sometimes occurred and the use of lemon juice was regarded with suspicion. After 1860, only lemons were officially allowed for antiscorbutic use. The reason why scurvy was banished from the long-distance sailing ships of the Chinese Ming dynasty (1368-1644) was due to the fact that the crew were regularly given fresh, germinated soya beans to eat, as part of their traditional food. Unlike non-germinated seeds, these shoots are rich in vitamin C. The importance of the absence of scurvy is not to be underestimated, since the voyages

of the Chinese admiral Zheng He (1421) led to world maps, which were obtained by the Portuguese crown and were a crucial element for the major discovery expeditions of Henry the Navigator, opening the world for the West, a fundamental turning point in history.

## Prevention

A sufficiently varied diet containing fruit and green vegetables will prevent the development of scurvy. Prolonged cooking of all food should be avoided. Vitamin C 60-100 mg/day PO provides protection against scurvy. Some people use vitamin C megadoses in the hope of preventing colds and other ailments. There is little evidence to support this but no definitive conclusion has yet been reached.

Vitamin C is metabolized to oxalate. When megadoses vitamin C are consumed on a daily basis, this might facilitate the formation of oxalate kidney stones but there is no consensus on this. Excess ascorbate is normally excreted in the urine, but in patients with renal failure, it is retained and converted to insoluble oxalate and can accumulate in multiple organs.