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LAST UPDATED BY ADMIN ON AUGUST 16TH, 2023

Ectoparasites

LAST UPDATED BY ADMIN ON JULY 15TH, 2022

Fleas

General
Cat flea, Ctenocephalides felis, a vector of Rickettsia felis. Notice the combs, which gives the animal its name.
Fleas are cosmopolitan, wingless insects. They are obligate blood-sucking ectoparasites. They are not strictly adapted to a specific host and on occasions can bite unusual hosts, including humans. Although feeding on less than ideal hosts keeps the fleas alive, it reduces their fertility. The most important jumping fleas are *Pulex irritans* (the human flea), *Ctenocephalides* species (cat and dog fleas), *Xenopsylla cheopis* (Oriental rat flea) and *Tunga penetrans* (sand flea). Adult fleas live 6-12 and sometimes even 24 months. Fertilised adult females lay 3-18 eggs per day. After 2-14 days, depending on moisture and temperature, the eggs hatch to give very active legless larvae. Under favourable conditions, the larvae will pupate and emerge as adult insects. The cocoon is spun from sticky silk, so that a wide variety of substances become attached and provides camouflage. These pupae are therefore very difficult to detect. The pupa stage usually lasts 1 to 2 weeks. Sometimes the adult insect remains in the cocoon for a long time (up to 1 year). Emergence from the cocoon is
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environmentally triggered (e.g. by proximity of a host: CO₂, heat, vibration). This explains why people who move into a house that has been empty for a long time can suddenly suffer numerous fleabites. Adult insects can remain alive for several weeks to months without feeding if the climate is not too harsh. Optimal conditions for their survival is high moisture and temperatures around 20°-30°C. Fleas leave dead hosts and this behaviour is important in the transmission and epidemiology of plague. Body temperature (37°C) inhibits the hatching of eggs and larval development. Reproduction occurs away from the host, on the ground, in cracks and in animal nests.

Muscles do not directly power the amazing jumps of fleas. Muscular tissue reacts too slowly. Instead, muscles are used to build up tension gradually. Fleas do not have wings but for their jumping, they use their wing stumps (their ancestors had wings). A hungry flea can jump up to 600 times per hour during three days. Fleas can jump 20 cm in height and 30 cm in distance. Bites are associated with the injection of saliva and cause a local pruritic skin irritation, principally on the legs. At night bites can occur over the whole body while people are lying down. These insects may be infected with the bacteria causing plague or endemic typhus (Rickettsia typhi) and R. felis. Other organisms can occasionally be transmitted. Fleas also transmit various sorts of minor tapeworms (Dipylidium caninum, Hymenolepis diminuta and possibly H. nana). Occasionally people develop long-lasting red skin lesions after insect bites. In such cases a Köbner’s phenomenon due to psoriasis should be suspected. The original skin lesions themselves can be minimal (e.g. hidden on scalp, ear).

Simple hygiene is often sufficient to keep a house free of fleas. Insecticide resistance is increasing, including resistance to DDT. Organophosphates, carbamates and pyrethroids are used to eliminate flea infestation in a house. Pets can be washed with a shampoo with e.g. malathion or can wear a flea collar, i.e. a collar impregnated with dichlorvos. The latter provides a prolonged local vapour effect in the animal’s fur. It should however be noted that most fleas are not present on the host, but in the bedding, on the ground, etc. For a cat with 25 fleas in its fur, there are some 500 adult insects, 500 cocoons, 3000 larvae and 1000 eggs present on the ground. Flea control should therefore also be directed towards the whole environment not just the animal. Cocoons are relatively resistant to insecticides.

**Fleas, tungiasis**

Tungiasis is a superficial infection of the skin by the sand flea *Tunga penetrans* (sarcopsilla; jigger flea; chique, do not confuse with chigger, which are trombiculid mites). *Tunga trimamillata* is a sand flea species identified in 2002 and seems to be limited to Peru and Ecuador. The lesions it causes are a bit bigger than those of *Tunga penetrans*.  

Institute of Tropical Medicine Antwerp
With a length of about 1 mm (male and unfertilized female), it is the smallest known flea species. Both sexes live on sandy ground and bite birds and mammals, particularly pigs, but also dogs, cats, sheep, goats, cattle, horses, donkeys. Newly hatched insects are very active and the larvae jump around on the ground. They seem to prefer dry sandy ground. The insects don’t do well in humid environments. The insects are a poor jumpers. The fertilized female bores into the epidermis and penetrates deep into the stratum corneum. The soles of the feet, the interdigital spaces and the skin under the nails are particularly affected. Any other part of the body that comes into contact with the ground can be infected (buttocks in beggars, children and lepers). The insect bores mechanically into the stratum corneum with the head innermost and bites onto the dermal papillae. The abdomen of the female swells as a result of the maturation of the approximately 200 eggs. After ten days the flea on average measures 1 cm in diameter. The hindmost abdominal segments are not distended and protrude out as a black central spot, through which excreta and eggs are released to the outside. After the eggs have been expelled the flea dies. The hole fills with fibrin and pus and is gradually re-epidermalised. After 3-4 days larvae emerge on the ground and pupate after approximately a week. The complete cycle takes 2-3 weeks.
Female Tunga penetrans burried in a finger, an uncommon site. Photo Dr Van den Enden © ITM

There is local pruritus and vague pain. In the beginning only a central black dot is visible. Later the lesion is raised, semi-transparent with a central dark spot and an erythematous halo. The number of parasites usually remains limited. However severe infestations with hundreds of sand fleas are found for example in leprosy patients, cachectic patients, alcoholics, in cases of advanced sleeping disease, in mental diseased and handicapped people or in confined communities.

Superinfection can occur during or after the primary infection, but particularly as a consequence of clumsy manipulation to remove the flea, as a result of which it breaks and parts of it remain deeply lodged. Lymphangitis can result as well as septicaemia and gas gangrene with a fatal outcome. Tetanus is a feared complication.

For treatment, the central opening in the stratum corneum is widened with a clean metal needle. The flea is removed and the remaining hole is disinfected. Prevention consists of wearing well fitting shoes instead of walking bare-foot or with wide open sandals. Socks that are left lying on the floor are to be avoided. Local basic hygiene is essential. Regular cleaning of floors using lots of water is strongly
advised, together with removal of pigs from the vicinity of houses.Affected areas of soil may be burned off. Ointment with cresol or lysol protects the feet.

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Lice

General

Lice (singular: louse) have parasitized humans since ancient times. While most primates have only one body lice species, humans have three (pubic, body and hair lice). According to genetic analysis, the common ancestor of headlice was shared by primitive hominids and primates until 6 million years ago. Pubic lice separated about 3 million years ago. Body lice are “only” 650,000 years old (coincides with the start of hominids wearing clothing). Lice have been found on Egyptian and pre-Columbian mummies and even on bodies dug up in Pompei. The Order of lice (Phthiraptera) is divided taxonomically into sucking lice (Anoplura) and chewing lice (Mallophaga), but there are alternative taxonomic classifications. Anoplura only parasitize mammals. Only three species of Anoplura are of regular direct medical importance to humans. These wingless insects are cosmopolitan, obligate haematophages and strictly adapted to their host (there is no animal reservoir). Polyplax spinulosa (Anoplura) is the sucking louse of rats and acts as an occasional vector of murine typhus. Only a single species of Mallophaga (Trichodectes canis) is known to have medical significance. T. canis is the chewing louse of dogs and acts as one of the larval hosts of the dog tapeworm Dipylidium caninum. This insect cannot live on man.

Pubic lice

Pubic lice (Pthirus pubis) do not themselves transmit disease. [The name Pthirus pubis is also used, but in 1987 the International Commission on Zoological Nomenclature decided to keep the original spelling of Pthirus pubis]. They occur on areas of the body with coarse hair (pubic region, perianally, sometimes also on legs, eyelashes, moustache, beard and even armpits and chest). Sometimes they are present on the scalp, including neonates. Sexual contact is the main method of transmission, but is not the only one (e.g. shared clothing). Any transmission involves bodily contact. They cannot live for more than 24-48 hours away from the host. If they are present in children, the possibility of sexual abuse should be taken seriously. A significant and strong correlation between the falling incidence of pubic lice infections and increase in pubic hair removal is observed. The increased incidence of hair removal may lead to atypical patterns of pubic lice infestations or its complete
eradication as the natural habitat of this parasite is destroyed.

Above: Pthirus pubis. Pubic louse. © ITM
Body and head lice

Body and head lice (*Pediculus humanus corporis* and *P. h. capitis*) are two very closely related species (morphologically almost identical) but which occupy different ecological niches. The body louse *P. humanus corporis* lives in clothing and only comes onto the body to suck blood for a short time. The head louse *P. h. capitis* by contrast lives on the scalp and never on the clothing. Mutual fertilisation is possible in the laboratory, but in nature this appears not to occur and they are considered to be different species.

Fertilised females lay 6-9 eggs per day during their life. They live usually for 1 month, maximum 2. The animals are very sensitive to cold. The females attach the sticky eggs to underwear, shirts and trousers. Eggs on clothing cannot survive for more than 4 weeks (usually only 2 weeks). The eggs hatch after 6-9 days. Once hatched, the larvae suck blood five times a day, rapidly returning to the

Above: Pediculus humanus capitis. Head louse. © ITM
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clothing after each meal. Lice avoid light. Once adult, the animals will mate repeatedly. The reason for this is that females have no spermatheca and frequent mating is therefore crucial to build up a population. All in all this means that in optimal circumstances natural populations can increase by 10% per day. This is important in order to understand the dynamics of infections such as epidemic typhus and relapsing fever. Digestion of the blood is rapid. The red blood cells lyse. *R. prowazekii* infects the cells lining the intestine. The intracellular proliferation of *R. prowazekii* causes the insect’s intestine to burst, spreading its contents into the haemolymph. The haemolymph will be stained red. The red colouration can be used in the laboratory to investigate whether a louse is infected with *R. prowazekii*. The louse dies from the infection with *R. prowazekii* and this fact was used previously to investigate which antibiotics were active against this bacterium. The antibiotic that enabled the louse to survive was then studied further. Lice are very sensitive to desiccation so that in dry environments they will not survive. Lice faeces are very dry and powder-like, with a water content of only 2%. The faeces contain a large amount of ammonium, which has an attracting effect on other lice.

*P. humanus corporis* can transmit *Rickettsia prowazekii* (epidemic typhus), *Bartonella quintana* (endocarditis, trench fever) and *Borrelia recurrentis* (epidemic relapsing fever). *R. prowazekii* is fatal for the insect after a few days. It is important for transmission and explains why people with louse borne typhus often have remarkably few lice. *B. recurrentis* proliferates only in the haemocoel of the insect and is transmitted by crushing an infected louse. This explains why “outbreaks” of louse borreliosis are rare unless there are massive numbers of lice. *B. quintana* can survive for up to a year in lice faeces.

The insects on clothing are destroyed by heat. For treatment, clothing is washed at 70°C, steam ironed or sterilised. In emergency situations (epidemic) insecticides are sprinkled (e.g. mixed with talc) between skin and clothing. Malathion or permethrin lotion or systemic ivermectin can be used.

*P. humanus capitis*. This obligate bloodsucking ectoparasite feeds three to six times per day. The female lives one month and can lay up to 300 eggs, also known as nits. The eggs are deposited very close (approximately 1 mm) to the base of the hair and are firmly attached. Given that a hair on the scalp grows about 0.4 mm per day, it follows that virtually all nits found more than 5 mm from the base of the hair are either dead or empty (in practice a figure of 7 mm is taken). The egg shells of the nits are not removed by insecticides. Their presence after therapy sometimes causes anxiety and give rise to the mistaken belief that the insects are resistant.

Larvae and adults suck blood. The irritation from the bites can lead to chronic itching and scratching, possibly with secondary infection (e.g. impetigo) as a consequence. The insects are very dependent
on their host. Even fed adult lice cannot survive for more than a few days (maximum 10) without another feed. They leave a dead person or someone with high fever fairly rapidly.

**Head lice treatment**

There are several options: (1) wet-comb method, (2) topical organophosphate or pyrethroid insecticides, (3) topical dimethicone, (4) systemic ivermectin, (5) topical ivermectin.

**In the wet-comb method** the hair is first washed with a shampoo, followed by application of a hair conditioner to make the hair as smooth as possible. A good louse-comb has teeth 0.2 to 0.3 mm apart. The teeth should have an angular cross-section. After application of the conditioner, the hair is finely combed from the neck towards the front hair-line. The teeth of the comb should be in contact with the skin. After each movement, the comb is cleaned on a piece of white paper. When finished, the hair is rinsed, and combing is started again, this time from the forehead hairline towards the neck. This is done 4 times in a period of 14 days. If living lice are still found after this period, another therapeutic option should be used. The wet-comb method is time-consuming and cumbersome. The success rate varies from 37% to 57%. The advantages are low price, lack of resistance and it can be used when one prefers to avoid topical insecticides (very young children, lactating women). In olden days, shaving the hair very short was sometimes used.

**Topical pediculicides.** In most cases, infestation with lice is treated with insecticides, but head lice have become more and more resistant. Treatment options are organophosphates such as 0.5% malathion [Prioderm®, Radical®] or pyrethroids such as 1% permethrin [Nix®] or depallethrine 0.66-1% in combination with 2.6-4% piperonyl butoxide (ParaShampoo®, Pyriderm®). The contact time should be sufficiently long: at least 10’ for permethrin, 30’ for depallethrine and 12 hours for Malathion. Lotions are better than shampoos as they have a longer contact time with the hair. If after reapplication 7 days later, living lice are still found resistance is likely (reinfestation is also possible).

**Dimethicone 4%** (Silikom®) is applied to dry hair and is rinsed off 8 hours later. This is repeated after 7 days. The idea is to suffocate lice, cutting of the oxygen supply. The cure rate is about 70% with this method, although more study is needed.

**Ivermectin** is a neurotoxin acting on glutamate-gated and gamma-amino butyric acid-gated chloride channels. Oral ivermectin (Mectizan®, Stromectol®) can be used as an alternative or in case of multiresistant lice. A dose of 200 µg/kg is given twice with a 7-day interval. Studies showed a superior efficacy (95%) as compared with topical 0.5% Malathion lotion (85%) applied with the same interval. A 0.5% ivermectin topical lotion can be applied to dry hair, left for 10 minutes then rinsed with water.
Mites

General

Mites are related to ticks, scorpions and spiders. In contrast to insects they do not have antennae and their body is divided into two rather than three parts. Larvae have 6 legs and adult animals 8 legs. Mites tend to be much smaller than ticks. These animals occupy the most diverse ecological niches from Varroa mites which are found in the respiratory tract of honey bees to Demodex mites which colonise the sebaceous glands of human eyelashes. In humans Dermatophagoides pteronyssinus, is known as house dust mite. Sarcoptes scabiei causes scabies.

Some mite larvae belonging to the genus Leptotrombidium (belong to the harvest mites) transmit Orientia (Rickettsia) tsutsugamushi (scrub typhus) in Southeast Asia. Adult mites are of no direct medical importance as they feed exclusively on small invertebrates and insect eggs. A female lays 1-5 eggs per day on moist ground. After the larvae appear, they begin to crawl around actively on the ground, grasses, low plants, etc. Larvae attach themselves to a host when it passes through the vegetation and seek out a piece of skin that is soft, smooth and not too thick (peri-anal, groin, ankles). The very small larvae (150-300 µm) inject saliva and suck up the digested tissues. After 2-10 days the mites fall to the ground and dig themselves in for further development. The ecological habitat of these parasites is strictly defined. Optimal moisture of the soil, the right vegetation and sufficient hosts for the nymphs and adults (arthropods of various kinds), as well as the larvae (mostly rats and mice) need to be present. This results in a very scattered distribution and the existence of mite islands. These are areas where intense transmission of scrub typhus occurs, whereas no infections occur in places only a few kilometers away for instance. Although the potential zoonotic reservoir is not yet completely established, it is important to know that Leptotrombidium mites themselves serve as a reservoir for Orientia tsutsugamushi (transovarial transmission). Transmission of this kind can persist for several successive arthropod generations.

Scabies
Norwegian scabies on a foot of an AIDS patient. Copyright ITM
Norwegian scabies in HTLV-1 patient. Copyright Alexander von Humboldt Institute, Peru.
Scabies, genital nodules. These nodular lesions tend to disappear more slowly than other scabies lesions. Copyright ITM

**Scabies** is caused by *Sarcoptes scabiei*. Morphologically similar mites are found on various animals (in dogs *Sarcoptes scabiei* var. *canis*) but do not permanently infect humans. Cat scabies is caused by *Notoedres cati*. “Milker’s itch” is caused by *Sarcoptes bovis*. *Sarcoptes equi* occurs in horses and riders can suffer an itchy skin disorder from these mites. Scabies mites do not transmit any pathogenic organisms. Adult female *Sarcoptes scabiei* mites measure 400-600 µm, while the smaller males are slightly more than half this size. The cycle from egg to egg lasts 10 to 14 days.

Human-to-human transmission occurs directly or indirectly when hygiene is poor. The majority of mites are found on the wrists and fingers, with smaller numbers on elbows and elsewhere. The face is practically always spared. The mean number of female mites per infected person is 11, most having 1-15 mites. Only 3% of patients have 50 mites or more. The mites dig burrows in the stratum corneum of the skin (1-5 mm per day). These tunnels are clinically very different from larva cutanea...
migrans. A female lays 1-3 eggs per day in her tunnel. Besides the eggs, mite faecal matter (scybala) is present in the tunnels. Larvae appear after 3-5 days. These crawl on the skin surface and many die there. Another 5-6 days later the adult appears which remains in situ if it is female. After becoming an adult and fertilisation by a passing male, the cycle can begin again. Female mites live on a person for 1-2 months. A female can produce up to 40 eggs in her life. Scabies causes pruritus, particularly at night. A definitive diagnosis is not straightforward as the characteristic skin tunnels usually only become visible after secondary infection or eczematous reaction. Scabies may trigger “unusual” impetigo (*Streptococcus pyogenes*). Repeated application of corticosteroid cream can lead to masking: “scabies incognito”.

Scabies provokes a papular, pruritic skin rash. There will be itching at sites where the mites themselves are found (e.g. between the fingers, wrists, elbows, genitalia). The rash is also seen on parts of the body that are not infested by scabies mites. Buttocks, groin, shoulders, arms, calves and ankles can become itchy. In classic scabies, the rash almost never occurs on the head, palms of the hands or soles of the feet. The rash is caused because the patient has become hypersensitive to mite allergens. In a patient who has never been exposed to scabies the rash usually occurs 4-6 weeks after infection. In previously exposed people it occurs much more rapidly, sometimes within just a few days. Despite effective treatment, symptoms and lesions of scabies can persist for weeks (e.g. scabies nodules on the scrotum and penis). Hypersensitivity to the scabies mite does not disappear immediately after the death of the parasite.

Sometimes *Norwegian scabies* occurs (“crusted scabies”). This condition is clinically totally different from classic scabies. A clinical description was first given in 1848 by Danielssen and Boeck in Norwegian leprosy patients. The condition occurs more frequently in immunosuppression e.g. AIDS and in infection with HTLV-1 than in the general population. Drug-induced immunosuppression, long-term topical steroid use and to a lesser extent a mental handicap such as Down’s syndrome increase the risk. In Norwegian scabies there are very numerous mites present in desquamating hyperkeratotic skin crusts. The latter can also occur on the face. The disorder is highly infectious. Sometimes tinea pedis, psoriasis, severe dyshidrosis, hyperkeratotic eczema, contact dermatitis or Darier’s disease (keratosis follicularis; autosomal dominant inheritance) resemble it. In case of doubt, it is sufficient to examine some skin scales after treatment with 10% KOH under a low magnification microscope.

Scabies mites as yet exhibit no resistance to lindane or benzyl benzoate. For treatment, 20-30% benzyl benzoate is used, with which the whole body (except the face) is rubbed twice after washing with soap for 3 days. Lindane lotion (Quellada® = gamma-benzene hexachloride) can also be used but its use has been phased out because of toxicity concerns. This should be repeated after 7 days as the eggs are not killed by only one application. Pyrethroids are effective (e.g. 5% permethrin
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(Zalvor®). Malathion is best used as a lotion not as shampoo. Crotamiton (Eurax®) is also sometimes used but is less effective. Oral ivermectin (Mectizan®) also produces relatively good results, but should preferably be repeated after a few weeks. It is the first choice in Norwegian scabies. Linen and bedclothes are disinfected at the same time by water at >60°C. Washing bedclothes and clothing and ironing them with a steam iron during this period will also help break the cycle of transmission. Without access to a body the mites survive less than 4 days.

Guidelines for elimination of scabies in institutional outbreaks

- change encasings of mattresses, carpet, clothing
- cleaning rooms, furniture, couches
- topical and systemic treatment of patients (permethrin and ivermectin)
- synchronous topical treatment of all contacts with or without skin lesions
- clip nails, brush subungual folds with scabicides
- reduce social contacts, e.g. no reunions in nursing homes
- avoid pets, examine pets
- ten day quarantine of index patient
- caregivers should use gloves and protective clothing, alcohol and handwashing
- evaluate two weeks later for eventual retreatment

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Ticks

General

Ticks are small animals related to mites, scorpions and spiders. Ticks are also known as Metastigmata. Ticks differ from insects. Their bodies are divided into two parts rather than three. Ticks do not have antennae nor wings. The adults have eight legs instead of six. Ticks have 6 legs in the larval stage (nymphs and adult ticks gain a pair of hind legs). Ticks that have climbed onto grass or other plants become aware of their potential host by vibration, warmth, CO₂, moisture and smell (all mammals secrete butyric acid). They remain attached to feathers, fur, skin or clothing, after which they seek a suitable place to suck blood.

There are two types of life cycles. In some species of tick, the larva, nymph and adult remain on the same, individual host not dropping to the ground between stages. In others, the different stages feed
on 2 or 3 different individuals. The host can be identified by the origin of the blood in the tick’s stomach, e.g. by PCR analysis. Ticks with a host change are usually better vectors for pathogenic organisms.

**Tick species**

There are approximately 840 different species of ticks which are classified into 3 families:

- **Argasidae**: argasids or soft ticks, with a tough, leathery skin and a concealed ventrally projecting capitulum (± 170 species). There is no scutum in adult animals. A scutum is a dorsal shield.
- **Ixodidae**: ixodids or hard ticks have a rigid scutum and a capitulum with mouthparts projecting forwards (± 670 species). This capitulum is visible when viewed from dorsal.
- **Nutalliellidae**

**Overview of tick genera in the three families**

- **Argasidae**: *Argas, Ornithodoros, Otobius, Antricola, Nothoaspis*
- **Ixodidae**: *Amblyomma, Aponomma, Boophilus, Cosmiomma, Dermacentor, Haemaphysalis, Hyalomma, Ixodes, Margaropus, Nosomma, Rhipicentor, Rhipicephalus*
- **Nutalliellidae**: only 1 species, rare

**Ticks as vectors**

Ticks are always obligate blood suckers, in contrast to mites which occupy much more varied ecological niches. All ticks need blood to complete each stage of their development. The chelicera dilate the skin, so that the hypostome can be inserted. This hypostome is equipped with barbs to keep them anchored in place and thus permit them to suck blood for several days in case of hard ticks. Many ticks cement their mouth parts to the skin for better attachment. This cement needs to be enzymatically broken down when they detach.

Ticks can be important vectors of various infectious organisms for humans (including protista such as babesias; viruses such as Crimean-Congo haemorrhagic fever or tick-borne encephalitis and bacteria such as *Borrelia, Rickettsia, Ehrlichia/Anaplasma*). Ticks can also transmit diseases in animals: Q fever (*Coxiella burnetii*), theileriosis (*Theileria* sp.), cowdriosis (heartwater, *Cowdria* sp.), dermatophilosis (*Dermatophilus congolensis*, a bacterium), anaplasmosis, babesiosis, sweating sickness (toxin of *H.*
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*truncatum*) and a number of others. The micro-organisms, ticks and their usual natural hosts have developed together over the course of thousands of years with mutual adaptation as a result. As a general rule, the microbes cause little or no damage to the tick and usually persist for the whole of the vector’s life. There is often trans-stadial transmission (from larva to nymph to adult) and sometimes transovarian transmission (from tick to eggs, so the following generation is born infected). The micro-organisms usually have little effect on the natural vertebrate hosts. Many of these warm-blooded animals act as a lifelong reservoir and as an amplifier for both pathogens and ticks. Poorly adapted hosts such as humans, often develop diseases following accidental infection with a pathogenic micro-organism. The term “adaptation” can be open to misinterpretation. It is not the case that the long-term persistence of a pathogen in a specific population automatically entails the reduced virulence of this organism.

A significant obstacle for all ticks in obtaining a blood meal is counteracting the haemostatic system of the host, such as thrombin, factor X and platelet aggregation. Ticks have several antihaemostatic agents which are essential for their survival. These products are present in salivary glands, as expected, but also in eggs and haemolymphs. It appears that their function is not only to prevent blood clot formation in the host and the blood meal, but also regulation of haemolymph coagulation in the tick itself. Besides thrombin-inhibitors, inhibitors of tissue factor and factor X or Xa, tick saliva contains a plethora of vasodilators, platelet inhibitors, fibrin (ogen)olytic agents and immunomodulators.

**Ticks, Argasidae**
Argasids take short (a few minutes) but repeated feeds. After feeding excess water in the blood meal is eliminated partly in the saliva and partly as coxal fluid (e.g. in *Ornithodoros moubata* – syn. *Ornithodorus moubata*). This coxal fluid is secreted by specialised glands between the first and second pairs of legs in the soft tick. *Borrelia duttoni* can be found in this fluid. When this fluid is rubbed into the bite wound an infection can follow. Argasids can cause persistent pruritus at the site of the bite. Some will suck blood from humans if their natural host disappears (e.g. *Argas*
*vespertilionis*, a bat tick). *Argas reflexus* is a tick which came originally from Middle Eastern countries and has now spread throughout Europe and large parts of Asia via the domesticated pigeon, the host for this animal. Other hosts are hens and ducks. The adults can survive for months to years without a blood meal. Humans can be bitten when visiting an abandoned dovecote. The bite is often painful and the skin will swell and redden.

**Ticks, Ixodidae**

**Hard ticks (Ixodidae)** are dispersed world-wide. There are 13 genera, of which *Ixodes*, *Dermacentor*, *Rhipicephalus*, *Haemaphysalis*, *Hyalomma* and *Amblyomma* are the most well-known.

![Hard ticks](image)
The ticks have a hard scutum (dorsal shield) that in the adult male covers the whole back. Males can only suck a limited quantity of blood. The scutum of the female is also hard and cannot distend. It is however smaller so that remarkable distension of the animal’s body is possible when it takes a large blood meal. They feed for 6-12 days. It is very important for the tick that during this period it should
not be noticed by the host. Tick bites are painless, since a component of the tick’s saliva reduces the sensitivity of the receptors in the host’s skin. The males remain on the host for several weeks to months. After the adult female is sated, she falls to the ground in order to lay her eggs. After laying the eggs the female dies. A six-legged larva emerges from the egg and waits for a long time on the ground or on vegetation until a host passes to which it can attach itself. The larva takes one large blood meal over a period of 4 to 6 days.

An eight-legged nymph then develops from the larva, which afterwards develops into an adult animal following a subsequent blood meal (duration 5-8 days). The life cycle of most hard ticks lasts 2 years. The longer the tick remains in place and sucks blood, the larger the quantity of micro-organisms which are transmitted. For example, transmission of Lyme disease is unlikely if the tick is removed rapidly. This is in contrast to the Argasidae, where infections such as relapsing fever can be relatively rapidly transmitted as these animals have a different feeding behaviour. The attachment time needed for transmission of *Borrelia burgdorferi* is much shorter in European ticks than in American ticks.

### Tick paralysis

The saliva of some ticks is neurotoxic and “tick paralysis” can occur. This has been described for 60 different tick species in animals, but only a few are important for humans: in the USA and Canada *Dermacentor variabilis* and *D. andersoni* and in Australia *Ixodes holocyclus*, a marsupial tick. Paralysis occurs in animals (dogs, sheep) and humans. Usually the tick needs to have been present for 4 (2-7) days before the symptoms appear. The neurotoxin is still poorly characterised, but it prevents the release of acetylcholine from the pre-synaptic membrane (cf. botulinum toxin). The condition presents as a flaccid, ascending paralysis with areflexia and with bulbar involvement and ataxia, without neck stiffness and without sensory disorders. Unsteady jerky movements of the limbs and breathing difficulties occur. The paralysis is more pronounced in children younger than 10 years, probably because of their smaller body weight. Evolution towards death is possible (respiratory failure). The disorder can resemble poliomyelitis, but motor involvement is symmetrical. Consciousness is clear. It can also resemble Guillain-Barré syndrome, including the EMG findings. On removal of the tick there is a progressive recovery over the course of the following hours to days.

### Prevention

Prevention of infections transmitted by ticks includes the avoidance of areas where there are ticks. Argasids are often found in mud huts, campsites or places where pigeons or bats nest. It is best not to sleep on the floor and if possible to avoid such places entirely. The use of concrete or plaster in houses diminishes the population of soft ticks. Hard ticks are found in places where domestic or wild
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animals (including birds) congregate, drink, feed or rest. It helps to tuck trousers into socks, wear dark clothing (attracts ticks less) and to wear permethrin or DEET impregnated cloths. A ‘skin-check’ after a walk through dense vegetation is useful.

Removing ticks

Hard ticks are relatively difficult to remove without damaging them. They have barbs on their hypostome (a section of the mouthparts). Tick larvae are small (<1 mm) and colourless before they suck any blood. They should be removed carefully with tweezers, without squashing them. The tick should be grasped as close as possible to the site of attachment in order to minimise the risk of the mouthparts breaking off and remaining embedded in the skin. The broken-off mouthparts of a tick can cause irritation and local infection. They should be scraped out and the wound disinfected e.g. with alcohol or povidone-iodine. It is sometimes claimed that applying vaseline, butter or fat to the animal (interfering with respiration) causes the tick to react by detaching itself from the skin, after which it can be removed more easily. While this does apply to the removal of fly larvae (myiasis), it is less straightforward in ticks. Burning the animal with a cigarette is not indicated: it can cause burns (particularly in children and pets), the tick might burst, thus spreading infectious material, and finally heat encourages the tick to produce more saliva and regurgitation.

Diseases transmitted by ticks

Soft ticks

Relapsing fever: *Borrelia duttonni* via soft ticks such as *Ornithodoros moubata*

Hard ticks

1. Lyme disease: *Borrelia burgdorferi*
2. Rickettsioses: various types such as Rocky Mountain Spotted Fever, fièvre boutonneuse, Queensland tick typhus, Japanese spotted fever, Israeli tick typhus, Siberian tick typhus, Flinders Island spotted fever, Mongolian spotted fever
3. Ehrlichioses and the related anaplasmosis: monocytic (*E. chaffeensis*) and granulocytic (bacteria related to *E. equi*).
4. Arboviral meningo-encephalitis: TBE (FSME and RSSE), Looping ill, Powassan encephalitis, Colorado Tick Fever (= orbivirus)
5. Arboviral haemorrhagic fever: Crimean-Congo HF, Omsk HF, Kyasanur HF
6. Febrile atypical syndrome: Colorado tick fever, Kemerovo tick fever
7. Babesiosis, e.g. Babesia divergens, B. gibsoni, B. microti
8. Tularaemia, caused by Francisella tularensis
9. Tick paralysis: paralysis from neurotoxic substances (e.g. holocycline) in tick saliva

Myiasis

General

Myiasis is the invasion of the body by fly larvae. During this period, the larvae feed on live or dead tissues. Depending on the life cycle of the insect myiasis is obligatory or facultative. In obligatory myiasis, the larvae have to spend part of their life cycle on a living host. Examples are Cordylobia anthropophaga, Dermatobia hominis, Cochliomyia hominivorax, Chrysomyia bezziana and Wohlfarthia sp. In facultative myiasis, the larvae are normally free-living, often on corpses, rotting meat, etc., but are sometimes found on living hosts (e.g. Calliphora, Lucilia, Phormia and Sarcophaga sp.) They can infect wounds and superficial ulcers. Clinically a distinction is drawn between cutaneous, urogenital, nasopharyngeal, ophthalmic and intestinal myiasis. Obligatory intestinal myiasis occurs only in animals, not in humans.

Cordylobia anthropophaga
Myiasis, infestation with the larva of a fly (*Cordylobia anthropophaga*). Copyright ITM
Cordylobia anthropophaga (tumbu fly, ver de Cayor) is a thick brown fly limited to tropical Africa. The larvae are obligate parasites, among others of dogs and humans. The female lays her 100-300 eggs on shaded, polluted ground or on dirty or inadequately washed sheets or clothes with some traces of sweat or urine still on it, laid out on the ground in the shade to dry. The females never lay their eggs on clothing that has been hung up in direct sunlight and also never directly on the skin. The larvae that emerge from the eggs penetrate the epidermis as far as the subcutaneous fatty tissue and develop there for 8 to 12 days. They then crawl out of the skin and fall to the ground where they undergo pupation in 24 hours. The pupae develop into adult flies in 10 to 20 days. The larvae rapidly penetrate the skin without causing any pain. In the first few days, an itchy, painful papule appears which develops over the course of a week into a painful furuncle in the centre of which two black dots (respiratory canals) are visible. The lesions may be few or numerous. The larvae can be pressed out of the skin if their respiration is prevented by coating the lesion with vaseline. One way to avoid
infection is to iron bed linen and clothes on both sides.

**Dermatobia hominis**

*Dermatobia hominis* (ver macaque) occurs in scrubland and woody lowland regions of Latin America. This large (15 mm) blue-grey fly has a remarkable life cycle. During their short life (8-9 days) adult females seize various bloodsucking insects. They then attach 6-30 eggs to the body of these arthropods, which include *Psorophora* mosquitoes and stable flies (*Stomoxys calcitrans*). Cattle flies (*Haematobia irritans* and *H. exigua*) can also act as transport hosts. In some cattle breeding districts they constitute a real plague. The larva of *Dermatobia hominis* develops in the egg. When the transport insect sucks blood the larva feels the higher temperature and breaks out of the egg and drops onto the skin or fur. Subsequently the *Dermatobia* larva penetrates the skin relatively rapidly. The larvae cause rather large cutaneous lesions, often painful and pruritic, few in number and frequently solitary and localised on the head. Development is slow, up to 12 weeks (up to 18 weeks has been reported). Fluid is formed constantly, consisting of the excreta of the larvae, but there is rarely superinfection. If this occurs, cellulitis and lymphangitis can follow. Frequently, the larvae have to be removed surgically (the final size of the larvae is 18-25 mm). A non-invasive technique of removing larvae is based on topical application of Vaseline to cut off their oxygen supply but this does not work very well. Fresh bacon can also be tried, the white part of the raw bacon is laid on the wound for some hours until the larva has attached itself. The bacon should then be lifted up and the larva can be grasped and removed with a rapid movement.
Prevention of *Dermatobia hominis* infections is difficult. The transport host *Haematobia irritans* ("horn fly") principally bites cattle and can be successfully combated by “ear tags” containing a PVC matrix with pyrethroids. They can also bite humans. When these insects form a local plague, they can be controlled in a “low-tech” fashion since *Haematobia irritans* and *H. exigua* obligatorily lay their eggs on fresh cow dung. When this is broken up mechanically, the larvae die. A shepherd with a rake can diminish a local plague and limit the exposure of humans and animals.

**Screw worms**

*Cochliomyia hominivorax* ("New World screw worm"; syn. *Callitroga hominivorax*) is a fly that occurs in Latin America and the Caribbean. It belongs to the Calliphoridae ("blow flies"). It was first described in 1858 by Dr Coquerel, a French army doctor in Cayenne, French Guyana. Many of the prisoners in the penal colony of Devil’s Island had infections in the nose and sinuses. The insect lays its eggs on all types of wounds. The larvae bore deep in the tissues with serious consequences, such as mutilation or even death. Although the species name translates as “man eater”, the insect preferentially plagues cattle. The name “screw worm" refers to the somewhat screw-like appearance of the larvae. They
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have mouth hooks in order to attach themselves firmly. Treatment consists of the mechanical removal of the intact larvae, standard wound care and tetanus prophylaxis. Antibiotics are usually necessary to combat superinfection.

*Chrysomyia bezziana* ("Old World screw worm") strongly resembles *Cochliomyia hominivorax*, but does not lay its eggs on wounds. When larvae invade natural openings (vagina, nose, eyes, mouth), they can cause very painful and serious lesions. The larvae complete their development in humans in 5-6 days, after which they crawl out of the tissues and fall to the ground to pupate. *Chrysomyia megalcephala* is a facultative parasite of humans.

Myiasis. Adult *Chrysomyia bezziana*, dorsal view. Copyright ITM

*Tabanids*
Stinging flies that belong to the tabanids (*Haematopota, Chrysops, Tabanus*) can be mechanical vectors for anthrax and tularaemia (“rabbit fever”). This last infectious disease is caused by *Francisella tularensis*.

**Bed bugs**
There are two main species of bed bugs: *Cimex lectularius* (the common bed bug which occurs world-wide) and *Cimex hemipterus* (the tropical bed bug). In West Africa, *Leptocimex bouetti* attacks man. Bed bugs are insects (4-7 mm) with rudimentary, non-functional wings. This limits their capacity for dispersion. They are not vectors of pathogenic organisms, but are primarily a nuisance because of their behaviour. They suck blood for a short time during the night or at dawn. During the
day the adult insects hide in cracks and crevices. Often dirty brown spots caused by their faeces are found on sheets, walls or floors. Sometimes clusters of hundreds of 1 mm large whitish-yellow eggs can be seen on walls, under wallpaper, etc. After a bite a severe pruritic skin reaction can occur.

Spraying insecticides helps control these animals. The problem of increasing insecticide resistance among bedbugs is getting worse. DEET has a repellent effect, but makes it that blood meals are often interrupted, therefore the insect will bite several times in order to get the same amount of blood. This means that this repellent is less than ideal. Aggressive and total extermination on an infestation is the only solution for infested premises. If this is unfeasible an alternative would be to take oral ivermectin and let the bugs bite the next night. Ivermectin is a neurotoxin for these insects and will kill them.

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**Beetles**

**General**

Although beetles have the greatest wealth of species of all insects, only a few are directly harmful to human health. A few beetles, chiefly belonging to the Scarabaeidae and Tenebrionidae, can be intermediate hosts for worms, such as the tapeworm *Hymenolepis diminuta* (the cause of non-specific abdominal discomfort).

**Blister beetles**

Blister beetles are insects that cause skin lesions by direct contact. They are found on various continents. They contain highly poisonous substances such as cantharidin or pederin. Cantharidin is found in the haemolymph of the beetle and is released when the insect is crushed. A number of insects secrete the caustic fluid via their leg joints when they are disturbed (“reflex bleeding”). In *Lytta vesicatoria* cantharidin is also found in the wing sheath.
Paederus sp. blister beetle. Contact with the animals can result in severe dermatitis or eye inflammation. The insects contain paederin, a blistering agent. Copyright ITM

**Blister beetles toxins**
Dermatitis resulting from contact with blister beetles (Paederus sp.). Copyright ITM, Dr Van den Enden

Dermatitis secondary to contact with a blister beetle, Paederus sp. (fam. Staphylinidae). Contact with the eyes leads to the so-called "Nairobi eye". Copyright ITM

**Pederin**

Pederin is the active vesicant of the short-winged beetle *Paederus fuscipes* and related species. It is a complex non-protein molecule. Pederin is highly toxic, more potent than cobra venom. It inhibits protein synthesis and prevents cell division.

**Cantharidin**

Cantharidin binds chemically to phosphatases 1 and 2A. The toxin is very stable. Dead beetles are still dangerous. Consequently control by means of insecticides does not remove the danger. The toxin
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protects the beetles from predators and is found in the haemolymph and gonads.

**Cantharidin systemic effects**

Sometimes cantharidin is swallowed. The toxin is readily absorbed from the intestine and excreted in the urine. If cantharidin is swallowed to arouse sexual appetite, in an attempted suicide, by accident, with criminal intent or to induce abortion, several symptoms may occur depending on the dose. The initial discomfort begins within 30 minutes. Dysphagia as a result of mucositis with irritation of oral, oesophageal and gastric mucosa is followed by abdominal pain, nausea and vomiting, possibly with blood. Oedema, bleeding and necrosis of the mucosa occur at an early stage. There is intense congestion of the genito-urinary tract, with bleeding in the renal pyelum, ureters and bladder. Bleeding can also occur in the ovaries. Sometimes there is internal bleeding and bruising. Priapism occurs, which was the origin of the use of the substance as an aphrodisiac (Gr. Aphrodite = goddess of love). Diarrhoea occurs, accompanied by leukocytosis, haematuria, renal tubular necrosis, uraemia, shock and coma. Approximately 30-60 mg is sufficient to kill an adult person.

**Clinical aspects**

On skin contact with cantharidin-containing blister beetles, local tissue irritation occurs after a few hours. In intra-epidermal blister formation, redness, oedema and vesicles can appear on the skin. Sometimes there are “kissing lesions” on the elbow or in the hollow of the knee. In contrast, the effect of pederin is not immediately noticeable and only becomes apparent after 1 to 2 days. The erythema is much more severe and can persist for months. On contact with the conjunctiva and/or cornea, *Paederus* sp. cause “Nairobi eye”. This is associated with extensive painful peri-orbital swelling and purulent conjunctivitis. Corneal erosions and blindness can follow.

**Treatment**

For external lesions, the skin should be rinsed copiously as rapidly as possible. After disinfection, silver sulphadiazine cream should be applied. Subsequent care is the same as for a burn. Skin lesions caused by cantharidin practically always heal without leaving scars. An eye that is affected should be rinsed copiously. Afterwards an antibiotic- and steroid-containing eye ointment should be applied (cfr. eye lesions caused by spitting cobras).

There is no specific antidote. Steroids are not effective in controlling the ulcers in the gastro-intestinal tract. Fluid, calcium supplements, analgesics and broad spectrum antibiotics should be given. Gastric
lavage should be carried out and activated charcoal administered. Cantharidin is to a large extent bound to albumin and is not removed by haemodialysis via a charcoal column. Physiological fluid should be administered IV. A blood transfusion might be necessary. Maximum diuresis must be obtained with IV fluid, mannitol and diuretics. No fat should be given orally because it increases the absorption of the toxin.

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Leeches

General

The phylum Annelida is subdivided into three classes: Polychaeta (“bristle worms”, principally marine animals), Oligochaeta (e.g. earthworms) and Hirudinida (“leeches”). Among the latter there is a subclass of Hirudinea (the true leeches) with 12 families. They include terrestrial, freshwater and saltwater species. There are approximately 650 species, but not all of these constitute a problem for humans. Terrestrial (semiterrestrial is a better term) and amphibious species are common in Southeast Asia, the islands in the Pacific Ocean, India and South America. Aquatic species occur worldwide. They are seldom found in low-calcium water. They are good swimmers. Usually victims are people visiting marshy areas or walking in or near slow-moving small brooks or streams.

Leeches bites

On biting leeches introduce vasodilators and hirudin, a very powerful anticoagulant into the skin. The bite causes prolonged painless local bleeding. Once sated after sucking two to five times their own weight of blood they let go and drop to the ground. They feed infrequently. After a large blood meal, the animal can go for over 6 months without feeding. The blood is then digested in the gut over a 100-day period, during which water is extracted and excreted through several pairs of ventrally located nephridia.

Clinical aspects

Leeches can attach to the skin. With the anticoagulant, they also inject a local anaesthetic, so pain is absent. Prolonged wound bleeding can result. Removal of a leech can be facilitated by applying a little alcohol or vinegar. If necessary a burning cigarette may be held near the parasite. No attempt should be made to remove the animals rapidly because the jaws can remain behind. After wound cleaning, local pressure should be applied to stem the bleeding. The bleeding tendency can persist for many
hours, sometimes even up to 2 days. This illustrates the power of the animal’s anticoagulants. Aquatic species can attach to the conjunctiva, nose, nasopharynx, vagina and urethra. When they attach themselves to the epiglottis, trachea or bronchi, serious complications are likely. Internal bleeding, haemoptysis, chronic headache, dysphagia and hoarseness occur. The leeches can be loosened by local application of cocaine or lidocaine. They are removed carefully with a forceps, using a laryngoscope or endoscope. As a rule the leech itself does not transmit any pathogens, although some recent observations from Laos suggest that it might transmit *O. tsutsugamushi*. Wounds can become secondarily infected. *Aeromonas* infections can occur but is rare. Following repeated bites, hypersensitivity can occur. For prevention, protective clothing should be worn. A topical repellent such as dimethyl phthalate or dibutyl phthalate, may be applied.

**Hematology**

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**Sickle cell anaemia**

**General**

Sickle cells are much less flexible than normal erythrocytes. They therefore have difficulty in passing through capillary vessels, the diameter of which is often less than half the diameter of a red blood cell. Janet Watson noted that symptoms appeared in infants only after concentrations of fetal haemoglobin (Hb F) had fallen, establishing the notion of the beneficial effect of Hb F on disease manifestations.

**Sickle cell anaemia, haemoglobin**

**Haemoglobin structure**

Each molecule of haemoglobin consists of a tetramer consisting of 2 pairs of polypeptide chains to which a total of 4 haem groups (one haem group per globin chain) is linked. One molecule of haemoglobin therefore contains 4 proteins. Hb A contains 2 globin chains of one type (alpha) and 2 globin chains of another type (beta. Depending on which 4 chains are present in the haemoglobin...
tetramer, the molecule is given its name.

There are many haemoglobin variants:

**Normal**
- Hb A: alpha2, beta2
- Hb A2: alpha2, delta2
- Hb F: alpha2, gamma2

**Pathological**
- Hb S: alpha2, beta2s
- Hb C: alpha2, beta2c
- Hb E: alpha2, beta2e
- Hb H: beta4 (see alpha-thalassemia)
- Hb Barts: gamma4

**Physiopathology**
Pathophysiology of sickle cell anaemia. Deoxy-haemoglobin S undergoes time-dependent polymerisation. This changes the shape of the red blood cells, which can block the microcirculation.
The normal haemoglobin of a child or an adult are Hb A (97%), Hb A₂ (2%) and Hb F (1%). Hb A contains 2 alpha-chains and 2 beta-chains. If by mutation, the 6th amino acid of the β-chain (glutamic acid, negatively charged) is replaced by a different amino acid (valine, hydrophobic), Hb S is formed. As a result a hydrophobic site is formed on the outside of the folded mutated beta chain. With normal arterial oxygen tension there is no problem and the molecule transports the oxygen. In the capillary bed in the tissues the oxygen is released and deoxyhaemoglobin S is formed. This latter substance has several different properties. In deoxy-Hb S there is a second hydrophobic site on the surface. This
site is concealed in oxy-Hb S. The site is complementary to the first. These two hydrophobic regions adhere to each other, resulting in a kind of polymerization of the deoxyhaemoglobin S molecules. The hydrophobic valine on the surface makes the haemoglobin molecule somewhat less water-soluble if the molecule is not bound to oxygen. The concentration of haemoglobin in the erythrocyte (32-34 g %) does however require a very water-soluble molecule. The deoxyhaemoglobin S molecules start to come out of solution (precipitate). At low oxygen concentrations the deoxyhaemoglobin S molecules adhere to each other, forming long, rigid strands and thus deform the red blood cells making them more rigid. The molecules stick to each other in a definite pattern (like a crystal). This polymerization reaction is relatively slow, giving a “delay time” or $T_d$. The slower the circulation and therefore the longer the time before reoxygenation in the lungs, the more sickling occurs. Usually the transit time of a red blood cell in the microcirculation is less than $T_d$ and a major catastrophe is avoided.

The main variables that affect sickling are the intracellular haemoglobin concentration, pH, the level of oxygenation and the percentage of Hb F. Sickling is accelerated by lack of oxygen, slow blood circulation, acidification and dehydration (a situation which is common with infections). The formation of rigid Hb SS strands is counteracted by Hb F (efficiency of polymerization is reduced). People with high concentrations of Hb F have far fewer symptoms than patients with low Hb F concentrations.

The sickling process also causes damage to various membrane proteins of the erythrocyte, thus promoting adhesion to the vascular endothelium. This makes circulation even more difficult. The degree of adherence is closely correlated to the severity of the disease. If there is inflammation, this “stickiness” can increase even more.

Additional factors play a part in the pathophysiology of sickle cell disease: endothelial cells can be “activated” i.e. they can be induced to express all kinds of molecules on their membrane, after exposure to various inflammatory substances (cytokines, prostacyclin’s, etc). Such cells become “sticky” and promote local haemostasis and possibly thrombosis. There is also an increase in the number of adhesion molecules on the red blood cells. The local production of Nitric oxide (NO) by the damaged endothelium falls.

**Nitric oxide function**

Nitric oxide (NO) produced by endothelial cells causes vasodilatation (effect is concentration dependent). Free haemoglobin in plasma will capture NO, thereby diverting nitric oxide from its homeostatic vascular function.
What are the clinical consequences of sickling?

- Sickle cells rapidly haemolyse. As a result, anaemia occurs: sickle cell anaemia.
- Sickle cells are rigid and obstruct the microcirculation. As a result, small or large infarctions can occur.
- Tissues with poor blood circulation can be infected more easily.
- Due to splenic atrophy, resistance to certain pathogens is reduced.

Geographical distribution

Map sickle cell disease (drepanocytosis). Due to the slave trade, the disease also exists in North America, but is especially common in areas where Plasmodium falciparum is frequent. Copyright ITM
The sickle cell gene occurs in large parts of Africa and to a somewhat lesser extent in the Middle East (Saudi Arabia) and India. In West Africa, 5 to 25% of the population are carriers of the gene. In Central and East Africa, heterozygotes occur with a frequency of from 20 to 40%. If 20% of the population are carriers of the gene, it follows that 1% of newborn children will be homozygous. Through the slave trade the sickle cell gene also found its way to North and South America.

Heterozygous carriers are relatively protected against fatal *P. falciparum* malaria. They are infected just as often, but are less likely to die from the infection. If the malaria parasite is present within the erythrocyte, the red blood cell acidifies slightly. This is enough to promote sickling. Because of the damage to the membrane; potassium flows out of the red blood cell, which is damaging to the parasite and the erythrocyte. The red blood cell is rapidly destroyed, for example in the spleen (heterozygotes have a normal spleen). Since heterozygotes in an endemic malaria area have a longer life expectancy than people with normal haemoglobin, it is thought that this has promoted the occurrence of sickle cell haemoglobin in Africa over the course of evolution. On the other hand, homozygous Hb S people have a very low life expectancy. There will therefore be a genetic equilibrium.

**Sickle cell anaemia, genetics and heredity**

Sickle cell anaemia is a genetically determined disease. A distinction is made between three main groups: homozygotes, heterozygotes and double heterozygotes.

- **Hb SS disease:** classic sickle cell anaemia

- **Hb AS:** sickle cell trait, heterozygote

- **Hb S/Beta^+^-thalassemia; Hb SC:** severe double heterozygote; phenotypical similar as Hb SS

**Heterozygosity (“sickle cell trait”)**

If someone has both a normal gene (from one parent) and a mutated gene (from the other parent), they produces both the normal haemoglobin (Hb A) and also the sickle cell haemoglobin (Hb S). One would expect a heterozygote HB AS to have about 50% haemoglobin A and about 50% haemoglobin S, but for a variety of reasons, the average patient has about 2/3 Hb A and 1/3 Hb S. The person is an asymptomatic carrier and each red blood cell contains both Hb A and Hb S. Such erythrocytes are functionally normal and have the advantage that they provide relative protection against fatal *Plasmodium falciparum* infection. Heterozygotes lead a normal life. But they may well pass the gene
Various subjects | 51

on to their children

Probability per child of having the different haemoglobins:

Parent Hb AA x Parent Hb AS $\Rightarrow$ 50% probability of Hb AA and 50% probability of Hb AS

Parent Hb AS x Parent Hb AS $\Rightarrow$ 25% probability of Hb AA, 25% probability of Hb SS and 50% probability of Hb AS

**Homozygosity**

If a patient has two identical mutated genes (homozygote) they cannot produce Hb A. After birth, the Hb F concentration falls and after 3 to 6 months, the red blood cells contain mainly haemoglobin Hb S. This will lead to sickle cell disease.

**Double heterozygotes**

Certain double heterozygotes can display a sickle cell phenotype.

- haemoglobin SC
- haemoglobin SD
- haemoglobin SO Arab
- haemoglobin S beta thalassemia
- haemoglobin S with haemoglobin New York

Sometimes a child has both a sickle cell gene and also a gene for haemoglobin C. It then has both haemoglobin S and haemoglobin C (Hb SC). Doubly heterozygous people suffer a less serious course of the disease than homozygous sickle anaemia patients. They have a clearly increased risk of eye damage (retinitis proliferans), avascular necrosis of the head of the femur, haematuria and complications during pregnancy (pulmonary infarction and risk of fat embolism after bone marrow infarction).

A little caveat: patient who are homozygous for Hb SS can have Hb A in their blood after a blood transfusion. Don’t be misled by this.
Clinical aspects

It is possible to distinguish two clinical phenotypes of sickle cell disease. The first is dominated by haemolysis and is characterized by severe haemolytic anaemia, leg ulcers (especially lower legs and around ankles) and pulmonary hypertension. The second is dominated by vaso-occlusion incidents, with episodic painful crises, acute chest syndrome, splenic infarction leading to functional asplenia, stroke and avascular necrosis of joints (hip, humerus) predominate.

Vaso-occlusive complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain episodes</td>
<td>In more than 70% of patients.</td>
</tr>
<tr>
<td>CVA</td>
<td>In 10% of children; “silent” lesions with cognitive damage in 50-90%.</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>In 40% of patients, more often in children.</td>
</tr>
<tr>
<td>Priapism</td>
<td>In 10-40% of men. Severe cases lead to permanent dysfunction.</td>
</tr>
<tr>
<td>Liver disease</td>
<td>In &lt;2%. Multiple causes: hep B, C, iron overload.</td>
</tr>
<tr>
<td>Spleen sequestration</td>
<td>In children &lt; 6 years of age. Often preceded by infection.</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>In 6% of pregnant women.</td>
</tr>
<tr>
<td>Skin ulcers (leg)</td>
<td>In 20% of adults</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>In 10-50% of adults (often femur, humerus).</td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>Rare in sickle cell anaemia; in 50% with Hb SC.</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>In 5-20% of adults, often with severe anaemia.</td>
</tr>
</tbody>
</table>

Complications of haemolysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Haematocrit often 15-30%.</td>
</tr>
<tr>
<td>Gallstones</td>
<td>In the majority of adults, usually asymptomatic.</td>
</tr>
<tr>
<td>Red bone marrow</td>
<td>Expansion leads to weakened cortical bone.</td>
</tr>
</tbody>
</table>
**Infectious complications**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Sepsis in 10% of children &lt; 5 years.</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Often by Salmonella or Staphylococcus aureus.</td>
</tr>
<tr>
<td>Escherichia coli sepsis</td>
<td>In adults often originating from infection of the urinary tract.</td>
</tr>
<tr>
<td>Acute aplastic crisis</td>
<td>Due to parvovirus B19. Sudden severe anaemia.</td>
</tr>
</tbody>
</table>

Individuals with sickle cell trait are generally asymptomatic and have no abnormal physical findings. Their laboratory evaluation often shows microcytosis but is otherwise normal with no anaemia, no evidence of haemolysis and no laboratory abnormalities other than haemoglobin AS on haemoglobin electrophoresis. Complications such as splenic infarction, pain episodes and sudden death may be induced by severe hypoxia, severe dehydration, and exertion at the limits of human endurance, e.g. at high altitudes.

Homozygous (Hb SS) children with little Hb F have the clearest symptoms. The symptoms result from haemolysis, thromboses, infections and acute haematological crises. In rural Africa only a few survive beyond puberty. In the first few months after birth the baby is virtually normal (the Hb F concentration is still high). The first problems start at about 3 to 6 months.

**Haemolysis**
Suava Fernand
23-avril 1902
Crâne en brousse (profil)

Figure 3.
“Hair-on-ends” image caused by bone marrow expansion in the diploic space in chronic haemolytic diseases, such as sickle cell anaemia or more commonly in beta thalassemia major. The major trabecular spicules in the diploë are aligned perpendicular to the inner table in an effort to support the soft outer table. Photo ITM
Fish vertebrae in sickle cell anaemia. Marrow expansion makes the vertebrae more susceptible to compression, leading to this diabolo-shape. Copyright ITM

Chronic haemolysis manifests itself as pallor, mild jaundice, dark urine and retarded growth. There is hypertrophy of the bone marrow, which can often be seen in the cranium and the maxillae. But the expansion of the bone marrow is less pronounced than in homozygous ß-thalassemia, possibly because less erythropoietin is produced than expected due to repeated kidney damage. Due to the constant haemolysis and the production of bilirubin; bilirubin gallstones are produced at a very young age (such stones are often not radio-opaque). There is splenomegaly up to about 5 years, afterwards there is atrophy because of the repeated infarctions of the spleen. The expansion of the bone marrow can usually be seen clearly by frontal “bossing”, a pronounced curving of the forehead and by widely spaced teeth in the jaws. On an X-ray of the cranium, small canals in the diploë of the vault of the cranium and are known as a “hair-on-end” appearance (see Fig).

**Acute haematological crisis**

Haematological crises sometimes occur. In children aged from 6 months to 3 years the spleen can sometimes swell acutely (sequestration of blood in the spleen), with sudden anaemia, hypovolemia and shock as a result. Many do not survive this. Due to infections, such as malaria for example, hyperhaemolysis can occur. After certain viral infections (for example parvovirus B19) a period may follow during which the bone marrow does not form any new red blood cells (aplastic crisis). Bone marrow arrest can also occur if there is a marked folic acid deficiency.

**Thrombosis**

Thrombosis is manifested most commonly as episodes of pain but also can produce kidney infarctions (haematuria, papillary necrosis), priapism, atrophy of the spleen, bone necrosis (head of the femur, head of the humerus, metacarpals, vertebrae), cerebrovascular accident (CVA), including the rather rare Moyamoya syndrome (collateral circulation developing around blocked vessels, these collateral vessels are prone to bleeding aneurysm and thrombosis; moyamoya means “puff of smoke” in Japanese referring to the appearance of the collateral vessels on MRI), chronic skin wounds (mainly on the shins) and proliferative retinopathy. Hand-foot syndrome is sometimes the first clinical manifestation. The child then has acutely painfully swollen hands and feet. Chronic damage to the vertebrae leads to biconcave vertebrae (“fish vertebrae”; see Fig) with a typical appearance on X-ray. Due to kidney damage, patients with sickle cell anaemia usually have difficulty in concentrating their urine and are susceptible to dehydration. Hyposthenuria may become evident in childhood as
enuresis. Glomerular sclerosis, manifested by proteinuria, progresses as patients age. Chronic renal failure occurs in up to 5% of patients with sickle cell anaemia. Pulmonary infarctions contribute to acute chest syndrome, with pain, dyspnoea and a poor general condition. Small cerebral watershed infarcts may be clinically silent but produce cognitive defects shown by neuropsychiatric testing. Hemiplegia can result from cerebral infarction. Most patients with brain injury require long term transfusion therapy.

**Eye problems**

Occlusion of small retinal vessels with neovascularization is asymptomatic until haemorrhage occurs within the vitreous. Detachment of the retina, more common in late disease, is a feared complication, and an important cause of blindness, together with occlusion of the central retinal artery. The latter condition is a medical emergency, for which urgent transfusion is imperative.

**Autosplenectomy**

Splenic atrophy in sickle cell anaemia; photo Dr Van den Enden, ITM
Because of the repeated infarctions of the spleen, sickle cell anaemia patients over the age of 5 years no longer have a functioning spleen. Asplenic children are very susceptible to bacterial infections, including pneumococci (i.e. encapsulated bacteria, *Streptococcus pneumoniae*). Osteomyelitis caused by among others, *Salmonella* and staphylococci is common. Often it is difficult to distinguish between pulmonary infarction and pneumonia and between osteomyelitis and bone infarction.

**Acute chest syndrome**

This syndrome consists of a collection of problems, such as acute chest pain, dyspnoea, coughing, fever, hypoxemia, leukocytosis and pulmonary infiltrates, mainly in the inferior lobes. This can develop into a full-blown ARDS (Acute Respiratory Distress Syndrome). Bone marrow infarctions followed by fat and even bone marrow embolism play a part (beware of sickle patients with first pain in limbs, followed by chest problems). Atelectasis also contributes and often develops as a result of hypoventilation that accompanies rib pain and the use of opiates. At autopsy in 75% of fatal cases bone spicules are found in the lung. In 60% of patients with acute chest syndrome, fat-loaded macrophages are found in the broncho-alveolar fluid. Because of the pain in the chest wall, patients are able to breathe less deeply ("splinting") with hypoventilation, atelectasis and perhaps superinfection as a result. Hypoxemia increases the adhesion of red blood cells to the endothelium, via the increased expression of the adhesion molecule VCAM-1 on the endothelium. Breathing in regularly, as deeply as possible, is an important part of treatment ("incentive spirometry"). The patient is asked to breathe in deeply 10 times and to do this every two hours while awake. There is a clear role of opioids in promoting to control pain with careful monitoring to avoid over-sedation and hypoventilation. The administration of oxygen, antibiotics and standard or exchange transfusion completes the treatment. In a good hospital, the mortality of acute chest syndrome is 2% for children and 5% for adults.

**Pulmonary hypertension**

Pulmonary hypertension is a feared complication in chronic and severe haemolytic anaemias, such as thalassemia major, congenital spherocytosis and paroxysmal nocturnal haemoglobinuria. Pulmonary hypertension occurs in about one third of all patients with sickle cell disease. Asplenia increases the circulation of platelet-derived mediators, which promotes pulmonary microthromboses and adhesion of erythrocytes to the endothelium. Haemolysis results in the release of free haemoglobin, which scavenges nitric oxide, causing vasoconstriction.
**Priapism**

Priapism is a persistent and painful erection [Lat. priapus, God of procreation]. It is not associated with sexual stimulation. It is an important complication of sickle cell disease. By adulthood, 90% of males with sickle cell anaemia will have had at least one episode of priapism. The blood that flows into the corpora cavernosa of the penis has difficulty leaving the organ due to venous thrombosis. Because of acidification and hypoxia, sickling of red blood cells increases still further. If priapism persists longer than 4 hours, surgery is definitely required. Persistent priapism (>24 hours) results in fibrosis and impotence. As an initial treatment the patient can be made to go up and down stairs in order to divert blood flow to the leg muscles (the “steal mechanism” principle) or have external compression of the perineum applied, perhaps with ice. General measures such as hydration, (exchange) transfusion and analgesics are necessary. Aspiration and irrigation of the corpus cavernosum with or without saline irrigation is necessary in an episode of priapism lasting more than four hours. The alpha-adrenergic agonist phenylephrine can be injected in the corpora cavernosa, causing blood to leave the corpora cavernosa due to smooth muscle contraction in the penile arteries.

**Diagnosis**

**Laboratory**

A sickling test can be carried out in field laboratories (Emmel’s test). In this, a drop of blood is placed on a glass slide. This is covered with a coverslip and the edges are sealed with some vaseline (to prevent contact with the air). As time goes by and the oxygen in the blood falls further (due to the metabolism of the cells) the red blood cells will sickle. This test can be accelerated by adding a drop of sodium metabisulphite to the blood.
Red blood cells of a homozygote sickle cell anaemia patient undergo dramatic change in shape when oxygen is excluded from their environment (Emmel test). Copyright ITM

**Heterozygotes**

Since normal and mutated beta chains are produced equally rapidly, it may be expected that heterozygotes would have ±50% Hb S and ±50% of Hb A. However, because alpha chains bind more easily to the normal beta chains than the mutated forms, there is a relative excess of mutated beta chains in the tetramers. The excess mutated chains are then destroyed. As a result, most heterozygotes have about 35% Hb S rather than 50%, and about 65% Hb A. The diagnosis of sickle cell trait is established by haemoglobin electrophoresis. If a non-transfused patient with sickle cell disease would have e.g. 65% HbS and about 30% HbA, especially if Hb A2 would be elevated, the suspicion of Hb S/beta-thalassemia would be strong.
Homozygotes

There is severe anaemia (usually Hb 6-9 g%) with considerable reticulocytosis. A blood smear of a homozygote shows many sickle cells, in contrast to that of a heterozygote. The diagnosis can be confirmed by haemoglobin electrophoresis. On electrophoresis it can be seen that most of the haemoglobin consists of Hb S (often more than 80%); the remainder consists of Hb F and Hb A2. Of course, no Hb A can be found. There is often thrombocytosis and leucocytosis.

Treatment

General

Apart from bone marrow transplantation, there is no curative therapy. Hematopoietic stem cell therapy and gene therapy remain possibilities for the future. The suffering of children can be reduced. It is possible to stimulate the induction of haemoglobin F by medication. In contrast with haemoglobin A2 (alpha2 delta2), a minor haemoglobin which is uniformly distributed in all adult red cells, haemoglobin F is found (in normal people) in 0.2 to 7 percent of the adult red cells, and in those cells, it constitutes 14 to 28 percent of the total haemoglobin. They are called “F” cells. Hb F contains gamma chains instead of beta chains (structure alpha2 gamma2). Hb F has a greater affinity for oxygen than Hb A. This helps the fetus to draw oxygen from the mother’s blood. Hb F inhibits the polymerization of deoxy-Hb S. This inhibits the sickling of red blood cells. After birth, the neonate still has more than 50% Hb F in his blood. This explains why very young children are free of sickling crises. After birth the genes for the gamma chains are less active because they become methylated. This is reversible however.

Hydroxyurea is a mainstay in the treatment of sickle cell anaemia. Hydroxyurea (Hydrea®) is a cytostatic drug which was long used in patients with polycythemia vera or chronic myeloid leukaemia, to counter hyperleukocytosis. Another important effect of hydroxyurea is production of nitric oxide (NO), a vasodilator. The anti-sickling activity results from induction of haemoglobin F through activation of a specific promoter for the haemoglobin gamma-chain gene. There is also a reduced expression of adhesion molecules (e.g. VCAM-1, L-selectin), as a result of which red blood cells and neutrophils adhere less easily to the vascular endothelium. Hydroxyurea can be used in prevention (not in an acute crisis). Hydroxyurea reduces the frequency and the severity of the attacks (up to 40% decrease in mortality).
Maintenance treatment

1. Folic acid. The patients have a greater need for this vitamin due to the high demands of the red bone marrow. It is important to check vitamin B12 status, in order not to mask a cyanocobalamin deficiency.

2. Penicillin prophylaxis is given to reduce the number of infectious episodes. Today vaccination with pneumococcal vaccine lessens the importance, but porphylactic penicillin is still recommended to all children with sickle cell diseases till the age of 5 years. Penicillin V 125 mg orally twice daily till the age of 3 years is increased to 250 mg twice daily until the age of 5.

3. Zinc. Up to 20% of sickle cell anaemia patients have persistent leg wounds. Many patients tend to be zinc deficient, possible via excessive renal excretion due renal damage secondary to repeated infarctions in the hypertonic renal medulla. Zinc is a trace element needed for certain enzymes, including some metalloproteases which are important in wound healing. Zinc deficiency makes wounds heal more slowly. Zinc sulphate or zinc acetate per mouth (e.g. 30 mg per day) can help here, but is often given as part of multivitamin supplements (without iron). It is important to mention that prolonged treatment with hydroxyurea can lead to slower healing of leg ulcers.

Additional important measures

1. Immunizations are a cornerstone to prevent infections in sickle cell disease: routine childhood vaccinations are recommended including vaccination against Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae B and hepatitis B. Yearly influenza vaccination is advised.

2. Antibiotics. Every patient must have at home a stand-by broad-spectrum antibiotic such as co-amoxiclav. Azitromycin can be used in case of penicillin-allergy. They should take this at the first signs of infection. The reason for having the antibiotic at home is that patients often live a long way from a hospital and might lose lots of precious time before they are seen by a medical doctor.

3. Malaria prevention is absolutely indicated in an endemic area as infection with this parasite can be fatal.

4. Preventive transfusions are a double-edged sword and are not given routinely. With transfusions the haemoglobin level can be kept at a higher level, which reduces the consequences of anaemia. This also reduces the concentration of Hb S in the blood, thus reducing the risk of complications. However repeated transfusions gradually cause severe transfusion reactions. It is best always to give blood that is low in leukocytes. Since in the long term there will be sensitization to the minor blood groups, the red blood cells in later transfusions will be destroyed very quickly. Slow iron poisoning also occurs, damaging the heart, the liver and some endocrine organs (pancreas, testis). Iron chelation therapy is indicated. In the case of acute aplastic crisis (triggered by infection with
parvovirus B19) and splenic sequestration crisis, transfusions are essential. They are also important in acute chest syndrome. Exchange transfusions are also a therapeutic option.

Hydroxyurea (= hydroxycarbamide, Hydrea®). Usually 500 mg three times daily is given in order to raise the level of haemoglobin F to above 15%. Regular checking of the number of white blood cells is indicated (it is a cytostatic drug). Another side-effect is slower healing of leg ulcers. Pregnancy is a contra-indication. Since the introduction of hydroxyurea in treatment, the quality of life for many patients has improved dramatically. Since the drug is cheap, it is not outside the means of many third-world families and hospitals.

Hereditry should be explained to the parents so that they have the correct information in order to decide whether or not to have another child. If both parents are carriers, the probability of a normal child (Hb A) is 25%, the probability of a healthy heterozygous child is 50% and the probability of a homozygous Hb S child is 25%.

Management of ARDS in sickle cell crisis

The mainstay of treatment for patients with ARDS is supportive care and mechanical ventilation. Although the ventilator can be lifesaving, it can be a source of further lung injury. A crucial intervention in the acute chest syndrome is reduction of the percentage of haemoglobin S in the patient’s blood. One can use “normal” transfusions, but this also increases blood volume and viscosity. Red-cell exchange transfusion avoids this complication. The aim is to reduce the percentage haemoglobin S to well below 30%. The final (desperate) measure is the use of extracorporeal membrane oxygenation (ECMO).

What should be done in the event of a sickle cell crisis?

Antibiotics, transfusions (normal or exchange transfusion), oxygen, pain control with paracetamol-codeine, ibuprofen or morphine analogues are all part of sickle cell crisis management. Sufficient fluid should be administered because the kidneys have difficulty in producing concentrated urine. Often 3 to 4 litres a day are given (adults) if possible orally, otherwise IV. Severe acidosis is best corrected quickly with bicarbonate, although no spectacular results can be expected. In the case of rib or tissue infarctions, and also in chest disorders, it is important that the patient is urged to breathe deeply (10 maximum inspirations) at regular intervals e.g. every two hours. This prevents atelectasis. The polymerizing of Hb S is promoted strongly by dehydration. The higher the salt concentration in the blood, the more quickly the cells sickle. Patients with a sickle cell crisis often have a hypercoagulable
state, thus thromboembolism prophylaxis is essential during hospitalization. This can be done with LMWH's or unfractionated heparin.

What happens if an operation is carried out?

Many homozygous sickle cell patients have to undergo surgery due to complications of their illness (mainly cholecystectomy or orthopaedic surgery) or for other reasons. Perioperative complications are common in patients with sickle cell anaemia. During anaesthesia, the operation itself and in the post-operative phase hypoxia must be avoided. Perioperative hypoxia, tissue hypoperfusion and acidosis can trigger vaso-occlusive crises and cause organ dysfunction (mainly acute chest syndrome and pain crises). Pre-operatively (exchange-)transfusion can be given.

Pregnancy and prenatal care

Pregnant homozygous sickle cell anaemia patients are rare in Africa. In the absence of medical care, mortality for mother and neonate can be as high as 20% and 50% respectively. The most common complications during pregnancy for women with sickle cell disease are hypertension and preeclampsia (14%). It has been suggested that maternal anaemia and placental ischemia may play a role, as slow placental circulation and a high degree of oxygen-extraction promote sickling. A high percentage of the pregnancies result in preterm deliveries (27%) and infants small for gestational age (21%). It is best to keep the mother’s haemoglobin level above 10 gram %, although there is controversy about the use of prophylactic transfusions. It seems logical to reserve transfusions for complications, rather than use them routinely. Hydroxyurea is contra-indicated in pregnancy as it is teratogenic. However, in a small number of cases where hydroxyurea was taken throughout pregnancy, no fetal malformations occurred. During labour and delivery the mother should receive oxygen and should be well hydrated.

Bone marrow transplantation

For patients with severe symptoms, especially severe neurological symptoms or complications, an argument could be made for early bone marrow transplantation if a HLA-identical sibling donor were available. The principal complication of allogeneic stem-cell transplantation (the transplantation of grafts from genetically different donors) is graft-versus-host disease (GVHD), which can occur despite aggressive immunosuppressive prophylaxis, even when the donor is a so-called “perfectly matched” (syn. HLA-identical) sibling. The few patients, mostly children, with sickle cell disease who have undergone bone marrow transplantation after a myeloablative conditioning regimen have become
asymptomatic despite incomplete replacement of their marrow with donor cells (mixed chimerism).

LAST UPDATED BY ADMIN ON JULY 15TH, 2022

Other haemoglobinopathies

Haemoglobin C

Map, distribution of haemoglobin C. Copyright ITM
Hb C is another haemoglobin variant that is common in West Africa. Here the 6th amino acid of the beta chain (glutamic acid, negative charge) is not replaced by a valine but by a lysine (positive charge, basic amino acid), i.e.: (beta6 Glu -> Lys) mutation. Sickling does not occur. Haemoglobin C has no protective effect on P. falciparum infection. The heterozygote state for Hb C is clinically silent. By electrophoretic analysis, 30-40% of the haemoglobin is Hb C and 50-60% is Hb A. People who are homozygous for Hb C (Hb CC) display mild chronic haemolysis, mild to moderate anaemia and mild splenomegaly. On electrophoresis Hb A is absent. There is often microcytosis and there are many target cells and some spherocytes. Cholelithiasis is common. There are rarely major complications. Treatment is not necessary.

**Haemoglobin E**

Above: Map, distribution of haemoglobin E in Southeast Asia. Copyright ITM
Three splice site mutations are known to occur in exon 1 of the beta globin gene. These mutations result in three different abnormal haemoglobins: Malay, E, and Knossos. Haemoglobin E is a very common abnormal haemoglobin in Southeast Asia and India. The mutation GAG to AAG which leads to haemoglobin E, creates an alternate splice site competing with the normal splice site. This results in abnormal haemoglobin production and mild thalassemia in the homozygous state, with a mild microcytic anaemia with a haemoglobin usually above 10 g%. Clinically the affected persons are not ill, although a mild splenomegaly can develop. Electrophoresis reveals approximately 90% Hb E with varying amounts of Hb F.

The heterozygote has a haemoglobin of about 12 g% with microcytosis and an electrophoretic pattern showing Hb E plus Hb A\sub{2} of 20 to 30%. On standard alkaline electrophoresis haemoglobin E co-migrates with Hb A\sub{2}.

When Hb E trait combines with a beta\sup{0} thalassemia mutation, a severe transfusion-dependent (EBeta\sup{0}) anaemia will ensue. EBeta\sup{0} thalassemia patients who undergo splenectomy may stop being dependent on transfusions.

**Glucose-6-phosphate dehydrogenase deficiency**

**General**

In 1926 some people who had been given primaquine (an antimalarial) developed dark urine and haemolytic anaemia. The mechanism was not understood until 30 years later. Adult red blood cells have neither mitochondria nor a nucleus. The cells have no Krebs cycle and meet their energy requirements by glycolysis, an anaerobic process (Embden-Meyerhof chain). This is a very inefficient way of producing ATP, but in this way the erythrocytes do not use the oxygen they transport and the cells are effective carriers of oxygen. By glycolysis a molecule of glucose supplies two ATP molecules and two NADH molecules. By a side-reaction, 2,3 diphosphoglycerate is also produced, a substance that has an important effect on the release of oxygen (see oxygen dissociation curve).

Another metabolic pathway in the cytosol of the red blood cell is the hexose monophosphate shunt (also called the pentose phosphate shunt). The first enzyme in this latter chain is G6PD. The hexose monophosphate chain provides two molecules of NADPH per molecule of glucose. It is the only source of NADPH in the red blood cell.

The normal enzyme is called “type B”.
About 20% of Black people in Africa have “type A+”. This variant is functionally normal, but has a different electrophoretic pattern. “Type A-” has the same electrophoretic characteristics as “type A+”, but has lesser activity. This form is common in Central Africa. People with “type A-” are normally not anaemic. Enzymes with little or moderate activity rarely cause clinically serious problems.

Another important variant is the “Mediterranean type” and is virtually totally inactive. The less active the enzyme, the easier it is for the red blood cell to be damaged by certain chemical substances. Enzymes with very little or no activity are common in people in the Mediterranean basin.

**Clinical aspects**

People with a very low G6PD activity can lead a normal life. In some situations, problems can arise. A crisis begins acutely and symptoms worsen in the course of a week. Jaundice, renal pain, haemoglobinuria and mild splenomegaly occur. Newborn children with G6PD deficiency are at greater risk of kernicterus and phototherapy is sometimes necessary. In many people the haemolysis is self-limiting, even if primaquine, for example, is continued to be administered. Circumstances that can trigger symptoms include:

**The neonatal period (neonatal jaundice).** Severe kernicterus due to G6PD-deficiency-related haemolysis is an avoidable cause of mental retardation. It is possible that the icterus is due to haemolysis combined with impairment of the liver function in these neonates.

A short list of drugs and chemicals that should be avoided by persons with G6PD deficiency includes: primaquine, methylene blue, niridazole, nitrofurantoin, sulfacetamide, sulfamethoxazole, sulfanilamide, sulfapyridine, phenylhydrazine, uropyrine. The administration of such medication is followed, after a 1- or 2-day delay, by falling haemoglobin concentration. Heinz bodies (denatured haemoglobin adherent to the RBC membrane), appear in the early stages of drug administration and disappear as haemolysis progresses.

In sub-Saharan Africa there are few clinically relevant problems, but in the Mediterranean basin severe, even life threatening reactions are more common. Serious infections involving acidosis can cause acute haemolysis. The mechanism by which this occurs is not clear, but leukocytes might damage erythrocytes in their environment by releasing active oxygen species during phagocytosis (cfr production of H2O2 by neutrophils and macrophages).

**Favism.** In the case of severe deficiency, serious haemolysis can occur if fava beans [“Vicia fava”, favism] are eaten or the pollen of the plants are inhaled. The symptoms occur quite quickly after
Various subjects | 70

aerogenic exposure but only develop after 5 to 24 hours after eating fava beans. Divicine and isouramil are oxidants present in this plant and they are normally reduced and inactivated by reduced glutathione. Our knowledge of favism is however incomplete. There is no absolute correlation between G6PD activity and the clinical symptoms. Other factors undoubtedly also play a part. People with “type A-” do not suffer from favism.

Transfusions. Normal red blood cells keep their G6PD activity if they are stored for transfusion. The small amount of activity that G6PD-deficient cells still have, will decrease as time goes by. If this type of blood is transfused into a person who is already ill and who may be receiving potentially haemolysing medication, haemolysis of the transfused blood can occur quickly.

**Diagnosis**

G6PD-deficiency. Heinz bodies are visible in the erythrocytes and consist of denatured haemoglobin.

The morphology of the red blood cells is normal between crises. During a crisis inclusions can be detected in red blood cells (Heinz bodies) by means of a supravital dye such as crystal violet. Heinz
bodies are formed by denatured, damaged haemoglobin. Cells with these inclusions are quickly removed via the spleen. Detection of Heinz bodies is an insensitive test for G6PD deficiency. G6PD activity can be measured directly in a well-equipped laboratory. The simplest quantitative assay measures the reduction of NADP to NADPH in the presence of glucose-6-P and haemolysate. It is important to know that a test might give misleading too high results if performed in less than 2 weeks after a haemolytic episode. Older erythrocytes have less enzyme activity and will be eliminated first after a haemolytic crisis. If the test is then performed on the remaining younger red cells (which have a higher enzyme activity), the activity of the enzyme is overestimated. In a blood smear stained with May-Grünwald Giemsa; Heinz bodies cannot be detected, but one can recognise ‘bite cells’ (keratocytes, blister cells) and dense erythrocytes with irregular outline. In normal people, the activity of G6PD is reduced by half over 120 days (the normal life span of an erythrocyte). It is therefore mainly the older cell population that is affected. This also explains why most clinical episodes are self-limiting (usually about 25% of the cells are haemolysed). It is precisely because of this limited haemolysis that people with, for example, leprosy, can often continue to take dapsone. Reticulocytosis increases after a few days.

For didactic examples of the more unusual blood smears (including G6PD-pathology), see: http://content.nejm.org/cgi/content/full/353/5/498

G6PD-deficiency, methaemoglobinemia and methylene blue

In haemoglobin, iron in haem is present as Fe$^{2+}$. If iron in haem becomes oxidised to Fe$^{3+}$ it is called methemoglobin. This cannot carry oxygen. Normally, the unpronounceable enzyme NADH-dependent cytochrome b$_5$ methemoglobin reductase will reduce methemoglobin to haemoglobin. This is a rather slow process. When methemoglobinemia occurs, one would usually administer methylene blue. However, after administration methylene blue first has to be reduced in the body to its active metabolite leukomethylene blue. It is the leukomethylene blue which will convert Fe$^{3+}$ in haem into Fe$^{2+}$. The conversion of methylene blue to leukomethylene blue is catalysed by NADPH methemoglobin reductase, a reaction requiring NADPH. Because there is an important NADPH-deficit in G6PD-deficient red blood cells, this conversion will not take place, and treatment with methylene blue will not work. What is more, administration of methylene blue in case of important methemoglobinemia is dangerous in case of G6PD-deficiency, because it will increase haemolysis. Methylene blue is an oxidant which will increase the anaemia and the hypoxemia. If one cannot wait for spontaneous improvement, blood transfusion and oxygen administration are warranted.
**G6PD deficiency, hereditary transmission**

The activity level of the G6PD enzyme is genetically determined. The G6PD gene is located on the X chromosome (a man has XY and a woman has XX). A man with a defective gene (hemizygote) and a woman with 2 defective genes (homozygote) are affected. A woman with just 1 mutant gene (heterozygote) is a carrier, but normally does not display any symptoms. She may well pass the defective gene on to her child. Because in women 1 of the 2 X chromosomes is inactivated in each nucleated cell (Lyons hypothesis), a heterozygous woman has 2 populations of erythroblasts and therefore also 2 populations of red blood cells: a normal population and a deficient population. Heterozygous women with a high percentage of deficient cells may become symptomatic. Normal women are therefore genetic chimaeras: some cells contain an active paternal X-chromosome and others contain an active maternal X-chromosome. There are no cells in which both chromosomes are active. Note of course that early precursor cells contain DNA but erythrocytes themselves have no nucleus, and therefore contain no chromosomes or even DNA.

**Oxidative stress**

Oxidative stress is defined as an imbalance between free-radical production and antioxidant protection. There are many varieties, but important ones include the hydroxyl radical (\(^{°}\text{OH}\)), hydrogen peroxide (H\(_2\)O\(_2\)) and the superoxide radical \(O_2^{°-}\), with the \(^{°}\) symbol indicating an unpaired electron. To give a ballpark idea, it is estimated that an average adult human forms 1.7 kilograms of superoxide each year. Each cell in our body produces about 50 hydroxyl radicals each second, one of the most reactive species which exists. It basically reacts instantly with any other molecule, be it fat, protein or DNA which it encounters, thereby damaging it. If there would be no defence against free-radicals, cellular damage would advance at a very fast pace. The cellular defence against free-radicals include antioxidants such as vitamin C and E, glutathione and catalase.

**Hexose monophosphate shunt**

In order to have enough reduced glutathione, a supply of NADPH is needed. The first reaction in the hexose monophosphate shunt produces NADPH. This reaction is catalyzed by the enzyme G6PD. In very general terms it can be said that the hexose monophosphate shunt (= pentose phosphate chain), has two main functions:

- the production of ribose, a component of nucleotides, for e.g. DNA and ATP. In summary, this pathway transforms glucose-6-phosphate into ribose-5-phosphate. However the erythrocyte has
no nucleus nor ribosomes, there is no need for ribose synthesis in these cells.

- the generation of reducing power in the form of NADPH. The pentose phosphate chain reduces NADP+ to NADPH. By oxidising NADPH to NADP+ again, other substances are reduced via a redox reaction. NADPH is an important electron donor (= reducing capacity). The main function of NADPH is to reduce oxidised substances such as glutathione and to allow reductive biosyntheses to take place.

The NADPH/NADP ratio controls the rate of reaction in an autoregulatory manner. In a quiescent state, this ratio is very high and G6PD is nearly completely inhibited. When NADPH is oxidized, as when glutathione is reduced in the glutathione reductase reaction, NADPH is converted to NADP+ and G6PD becomes active, reconverting NADP+ to NADPH.

### Red blood cells and NADPH

Why does G6PD deficiency seem to affect red blood cells especially? Erythrocytes do not have mitochondria therefore red blood cells do not have a back-up system for NADPH production. They have no alternative source of NADPH, as opposed to other cells which have mitochondria. Acetyl-CoA in the mitochondria (entry point for the Krebs cycle) cannot pass through the mitochondrial membrane by itself. If it is bound to citrate it can pass through the membrane. In cells with mitochondria some citrate bound to acetyl-CoA shifts from the mitochondrial matrix to the cytosol, after which the compound is divided again. The citrate therefore acts as a carrier. Citrate is then converted to oxaloacetate and then to malate. Afterwards (malate + NADP⁺) is converted to (pyruvate + CO₂ + NADPH). As a result, even if the hexose monophosphate shunt is functioning poorly, cells with mitochondria can still produce NADPH. The effects of G6PD deficiency are therefore most apparent in the red blood cells (cells without mitochondria).

### Glutathione

Why do we need glutathione? Haemoglobin and many other biological molecules contain many sulphur groups (SH groups = sulfhydryl groups). These are necessary for the molecule to function properly. If these are oxidized, haemoglobin can no longer function as it should. Glutathione is a tripeptide containing cysteine as the second amino acid. This amino acid has a SH group. The reduced glutathione (i.e. with a SH group), converts non-functional, oxidized cysteine disulphide groups (S-S) in other molecules such as haemoglobin into functional SH groups via the enzyme glutathione peroxidase. In this process glutathione itself is oxidized (two glutathione molecules are then bound by a disulphide bridge). Glutathione also reacts with hydrogen peroxide (H₂O₂) and
Various subjects | 74

corrosive organic peroxides. In this way it has an important protective role as an anti-oxidant. If the G6PD enzyme is deficient, no NADPH is formed, neither is any protective reducing glutathione formed and haemoglobin molecules and red blood cell membrane molecules that contain SH groups may be permanently damaged by oxidizing substances. The non-functional, denatured haemoglobin is precipitated in the form of Heinz bodies and the resulting damage to the membrane then leads to haemolysis resulting in moderate, but acute anaemia.

Note on *P. vivax* eradication: In countries attempting to eliminate *P. vivax* infection, the existence of G6PD deficiency is driving the development of a simple, user-friendly point-of-care test for its detection. Today, primaquine and tafenoquine are the only drugs capable to eliminate the hypnozoites in *P. vivax* infections. However, both drugs can provoke a severe haemolytic crisis in a person with G6PD deficiency. Therefore, testing for G6PD deficiency is imperative before these drugs can be administered safely.

**Beta thalassemia**

**General**

In addition to the Mediterranean basin the disease also occurs in Africa, the Middle East, India and Myanmar, Southeast Asia including southern China, Malaysia and Indonesia. There are indications that the high frequency of heterozygous beta thalassemia carriers in the tropics can be explained by a relative protection against the fatal *P. falciparum* malaria (compare with sickle cell trait and G6PD deficiency), but this is controversial.

<table>
<thead>
<tr>
<th>Embryonal Hb</th>
<th>Fetal Hb</th>
<th>Adult Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb Gower 1: zeta&lt;sub&gt;2&lt;/sub&gt;, epsilon&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Hb F: alpha&lt;sub&gt;2&lt;/sub&gt; gamma&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Hb A: alpha&lt;sub&gt;2&lt;/sub&gt;, beta&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Hb Gower 2: alpha&lt;sub&gt;2&lt;/sub&gt; epsilon&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td>Hb A&lt;sub&gt;2&lt;/sub&gt;: alpha&lt;sub&gt;2&lt;/sub&gt;, delta&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Hb Portland: zeta&lt;sub&gt;2&lt;/sub&gt;, gamma&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An average normal adult has Hb A 97%, Hb A<sub>2</sub> 2%, Hb F 1%.

About 150 different mutations have been reported in people with beta thalassemia. About 20 mutations are responsible for 80% of the beta thalassemias. Some are simple nucleotide
substitutions, with missense or nonsense consequences, multiple substitutions, deletions with frameshifts or abnormalities in the promoter. Sometimes something goes wrong with the splicing of mRNA. Within each geographic population there are unique mutations. Individuals who have beta thalassemia major are usually homozygous for one of the common mutations, or heterozygous for one of the common mutations and one of the geographically-unique mutations. All result in reduced synthesis of beta globin chains (beta⁺-thalassemia) or the absence of synthesis of beta globin chains (beta⁰-thalassaemia). Clinically mild forms of beta thalassemia are called thalassemia intermedia, whereas minor forms are non-symptomatic. If the production of both beta and delta chains is diminished, there is delta-beta-thalassemia (a consequence of gene fusion). The imbalance in globin chain synthesis (there are more alpha chains than beta chains) leads to precipitation of alpha chains in the red cell (= inclusion bodies or α-hemichromes), which leads to premature destruction of the cell in the bone marrow or the peripheral blood.

Clinical aspects

Beta thalassemia minor

The heterozygous condition is known as beta thalassemia minor. One beta gene is defective, the other is normal. Fewer beta globin chains than normal are produced but the healthy gene largely compensates for this. There is a typical microcytosis but rarely anaemia. This form is often found by chance and can wrongly be regarded as an iron deficiency.

There is a diagnostic problem for patients suspected to be double heterozygous for Hb E and beta-thalassemia. Hb E and Hb A2 cannot be distinguished in alkaline gel, but diffuse differently in an acid gel. But Hb A and E cannot be distinguished in acid gel. This occurs mainly in people from Southeast Asian origin.

Beta thalassemia major
Beta-thalassemia major. Skull bossing due to expansion of the diploë (red bone marrow in skull). See also “hair-on-ends” aspect by Rx
Beta-thalassemia minor with microcytes and target cells

The homozygous or doubly heterozygous condition is much more serious. The severity depends on which mutation(s) causes or cause the disorder and how many beta globin chains can still be produced. There is therefore a spectrum of clinical severity: thalassemia major or thalassemia intermedia. Patients with thalassemia major are by definition transfusion dependent. The affected infants are normal at first. Newborns still have Hb F, which is not affected in this condition. By the age of 6 to 9 months, the children develop faulty erythropoiesis with anaemia and hypertrophy of the bone marrow, spleen and liver with hepatosplenomegaly. In severe beta thalassemia, erythropoiesis can increase up to 10-fold. The relative excess of alpha globin chains interferes with the normal maturation of the cells in the bone marrow. Ineffective erythropoiesis occurs. There is pronounced haemolysis with considerable splenomegaly. Enlargement of the liver always occurs. Sometimes there are gallstones (bilirubin stones due to the haemolysis). The red bone marrow increases in volume, with swelling of the diploë in the cranial bones, osteopenia and a lowering of the fracture threshold and often microfractures around the main joints. The diploë is the central layer of spongy bone between the two layers of compact bone of the flat cranial bones. The face is often deformed.
somewhat due to cranial bossing and hypertrophy of the maxillae resulting in a mongoloid appearance. Bone marrow expansion can lead to compression of the spinal cord. Extramedullary haematopoiesis can occur, not only in spleen and liver, but also in the posterior mediastinum and even kidneys, leading to local masses which can resemble lymphoma.

There is haemolytic anaemia; microcytosis with normoblasts in the peripheral blood and an increase in the minor haemoglobins (Hb F, Hb A2). Children can survive only with regular blood transfusions and folic acid supplements. Iron overload and infections due to the repeated transfusions are a very real risk. The abnormal accumulation of iron results in dilated cardiomyopathy, endocrine disorders (destruction of the pituitary gland and hypogonadism with impaired sexual development) diabetes, liver disease (often together with hepatitis B and C). Later, restrictive lung disease and pulmonary hypertension can occur (pulmonary hypertension tends to occur in all chronic severe haemolytic diseases).

**Laboratory**

Severe haemolytic anaemia is present, which is accompanied by microcytosis (low MCV), target cells, a high RBC count with a relatively low reticulocyte count considering the severity of anaemia. The high RBC count is a compensation for the low amount of normal Hb in each red blood cell (contrary in iron deficiency where the marrow cannot produce as many RBCs). The Mentzer index is helpful in differentiating iron deficiency anaemia from thalassemia: it is the quotient of the MCV (in fl) divided by the red blood cell count (in millions per µl). If the Mentzer index is less than 13, thalassemia is more likely, if the result is greater than 13, iron-deficiency is more plausible.

On hemoglobinophoresis, a higher level of HbA2 (alpha_2delta_2) is usually found in beta thalassemia patients: the excess alpha globin chains bind to the delta globin chains. Diagnostic confirmation by globin gene testing will be rarely available in the tropics.

**Prevention**

A child born of two heterozygous parents has a 25% probability of being homozygous. There are screening programmes for detecting carriers in Italy, Sardinia, Cyprus and Greece. These are based on MCV and the concentration of Hb A2. Prenatal diagnosis can be carried out with various techniques (e.g. villous chorion sampling carried out in weeks 9-13).

**Therapy**

Non-transfused thalassemia intermedia patients are encouraged to avoid high-iron and iron supplemented foods and are encouraged to drink tea with meals, which decreases iron absorption.
Folic acid is usually given. With beta thalassemia major there is a great need for transfusion. Because of the repeated transfusions, iron overload occurs after a number of years (the time varies). Iron chelation is carried out with deferoxamine (Desferal).

Bone marrow transplantation can be carried out as curative therapy and at present is the only definite treatment. Of course, the bone marrow of an identical twin cannot be used but that of a HLA-DR matched relative can be used.

**Alpha thalassemia**

Alpha genes can be lost through deletion or inactivated by point mutations. If insufficient alpha chains are produced, the condition is known as alpha thalassemia. This condition is very frequent in Asia (from India to China, including Southeast Asia). The disease also occurs in Africa. Since 4 genes code for alpha chains, there are a number of possibilities:

**All 4 alpha genes functional:** normal. Genetic alpha alpha/alpha alpha

**Only 3 alpha genes functional:** silent carrier with no symptoms or signs (thalassemia minima). Genetic alpha alpha/alpha-

**Only 2 alpha genes functional:** silent carrier, often microcytosis (alpha thalassemia minor or alpha thalassemia trait). Genetic alpha alpha/- (= alpha^0 thalassemia) or alpha-/alpha- (= alpha^+ thalassemia). The two genes can either occur on the same chromosome (cis-type) or on each of the pairs (trans-type). Cis-type alpha^0 thalassemia trait tends to be found in individuals of Asian descent, while trans-type alpha^+ tends to run in individuals of African descent. Expert laboratory tests help to distinguish between these two conditions, which is important. If a mother is a carrier of alpha thalassemia, her pregnancy is at risk for Bart’s hydrops fetalis syndrome (worst case scenario), while the worst possible outcome of a pregnancy of a mother with alpha^+ thalassemia is a much milder condition, haemoglobin H disease.

**Only 1 alpha gene functional:** excess of beta globin chains. Genetic alpha/--. The excess beta chains form tetramers and are deposited: \( \beta_4 \) (haemoglobin H). Haemoglobin H is not stable and thermally labile. It contains two reactive SH groups per beta chain. The beta chains in Hb A have only one SH group. This may explain the susceptibility of Hb H to oxidation. The red blood cell inclusions (Heinz bodies = \( \beta \)-hemichromes) can be seen readily with brilliant cresyl blue staining (the same dye as for reticulocytes). The patient is anaemic and there is splenomegaly.
**No alpha genes functional:** the excess of gamma chains leads to the depositing of tetramers composed of four gamma chains: gamma₄ (Barts haemoglobin). Without the alpha globin chains, there can be no fetal or adult haemoglobin which means the red blood cells cannot carry oxygen efficiently throughout the body. Hydrops fetalis with stillbirth is the result. There is an increased risk of toxaemia of pregnancy and of post-partum haemorrhage (hypertrophy of the placenta). The only haemoglobins found in these infants are: Hb Portland (delta₂gamma₂), Hb H (β₄), and Hb Bart’s (gamma₄), and no Hb A, Hb A₂ or Hb F. Electrophoresis of fetal haemoglobins shows about 80% Barts haemoglobin and about 20% Portland haemoglobin (normally only present in the embryo in the first trimester).

**Onyalai**

**General**

Onyalai is a rather mysterious disease, which only seems to occur in central southern Africa (southern Angola and northern Namibia; Kavango and Ovambo territories). Onyalai means “blood blister” in the language of the Kimbundu, an Angolan tribe. Onyalai is a disease of unknown aetiology. Defective nutrition may be the cause. One hypothesis is that a toxin, possibly acting as a hapten, is responsible for this form of thrombocytopenia. The possible etiological role of mycotoxins from contaminated millet, sorghum and/or maize requires further investigation.

**Clinical aspects**

The disease differs clinically, epidemiologically and immunologically from immune (previously idiopathic) thrombocyticpurpura (ITP) It is an acute disease, characterized by the formation of haemorrhagic vesicles and blisters on the palatal and buccal mucous membranes, together with severe thrombocytopenia. This acquired form of thrombocyticpurpura can lead to haematuria and melena. Epistaxis, petechiae and ecchymoses are common, as are subconjunctival bleeding and menorrhagia. Haemorrhage from ruptured bullae, epistaxis or gastrointestinal bleeding can be severe and may cause shock and even death.

**Treatment**

Transfusion of blood and of platelets can be lifesaving. High dose intravenous gammaglobulin may be followed by a rise in the platelet count and cessation of haemorrhage but in general this treatment is disappointing (and expensive). Splenectomy can be considered for patients with
Micronutrient deficiencies

Introduction

Malnutrition refers to deficiencies, excesses or imbalances in a person’s intake of energy and/or nutrients. Malnutrition covers 2 broad groups of conditions. One is ‘undernutrition’—which includes stunting (low height for age), wasting (low weight for height), underweight (low weight for age) and micronutrient deficiencies or insufficiencies (a lack of important vitamins and minerals). The other is overweight, obesity and diet-related noncommunicable diseases (such as heart disease, stroke, diabetes and cancer).

WHO defines malnutrition as follows: Malnutrition refers to a number of diseases, each with a specific cause related to one or more nutrients (e.g. protein, iodine or iron) and each characterized by cellular imbalance between the supply of nutrients and energy on the one hand, and the body’s demand for them to ensure growth, maintenance, and specific functions, on the other.

Consequences of malnutrition

Malnutrition affects people in every country. Around 1.9 billion adults worldwide are overweight, while 462 million are underweight. An estimated 41 million children under the age of 5 years are overweight or obese, while some 159 million are stunted and 50 million are wasted. Adding to this burden are the 528 million or 29% of women of reproductive age around the world affected by anaemia, for which approximately half would be amenable to iron supplementation.

Many families cannot afford or access enough nutritious foods like fresh fruit and vegetables, legumes, meat and milk, while foods and drinks high in fat, sugar and salt are cheaper and more readily available, leading to a rapid rise in the number of children and adults who are overweight and obese, in poor as well as rich countries. It is quite common to find undernutrition and overweight within the same community, household or even individual – it is possible to be both overweight and
micronutrient deficient.

Image: WHO

**Protein-energy malnutrition**

Undernutrition is sometimes used as a synonym of protein-energy malnutrition (PEM). While other include both micronutrient deficiencies and protein energy malnutrition in its definition.\cite{Jones2011-12} The term “severe malnutrition” or “severe undernutrition” is often used to refer specifically to PEM. PEM is often associated with micronutrient deficiency. Two forms of PEM are kwashiorkor and marasmus, and they commonly coexist.
Kwashiorkor

Kwashiorkor is mainly caused by inadequate protein intake. The main symptoms are oedema, wasting, liver enlargement, hypoalbuminemia, steatosis, and possibly depigmentation of skin and hair. Kwashiorkor is further identified by swelling of the belly, which is deceiving of actual nutritional status. The term means ‘displaced child’ and is derived from a Ghana language of West Africa, means “the sickness the older one gets when the next baby is born,” as this is when the older child is deprived of breast feeding and weaned to a diet composed largely of carbohydrates.

Marasmus

Marasmus (‘to waste away’) is caused by an inadequate intake of protein and energy. The main symptoms are severe wasting, leaving little or no oedema, minimal subcutaneous fat, severe muscle wasting, and non-normal serum albumin levels. Marasmus can result from a sustained diet of inadequate energy and protein, and the metabolism adapts to prolong survival. It is traditionally seen in famine, significant food restriction, or more severe cases of anorexia. Conditions are characterized by extreme wasting of the muscles and a gaunt expression.

Undernutrition, hunger

Undernutrition encompasses stunted growth (stunting), wasting, and deficiencies of essential vitamins and minerals (collectively referred to as micronutrients). The term hunger, which describes a feeling of discomfort from not eating, has been used to describe undernutrition, especially in reference to food insecurity.

Micronutrients

Micronutrients are essential elements required by organisms in small quantities throughout life to orchestrate a range of physiological functions to maintain health. Micronutrient requirements differ between organisms; for example, humans and other animals require numerous vitamins and dietary minerals, whereas plants require specific minerals. For human nutrition, micronutrient requirements are in amounts generally less than 100 milligrams per day, whereas macronutrients (carbohydrate, protein and fat) are required in gram quantities daily.

The minerals for humans and other animals include 13 elements that originate from Earth’s soil and
are not synthesized by living organisms, such as calcium and iron. Plants are the primary origin of nutrients for humans and animals and some micronutrients may be available in low levels and deficiencies can occur when dietary intake is insufficient, as occurs in malnutrition.

<table>
<thead>
<tr>
<th>Trace minerals</th>
<th>Vitamins</th>
<th>Essential fatty acids</th>
<th>Essential amino acids</th>
</tr>
</thead>
</table>
| Boron          | Vitamin B complex  
• Vitamin B1 (thiamine)  
• Vitamin B2 (riboflavin)  
• Vitamin B3 (niacin)  
• Vitamin B5 (panthothenic acid)  
• Vitamin B6 group (pyridoxine, pyridoxal-5-phosphate, pyridoxamine)  
• Vitamin B7 (biotin)  
• Vitamin B8 (ergadenylic acid)  
• Vitamin B9 (folic acid)  
• Vitamin B12 (cyanocobalamin)  
• Choline | Alpha-linolenic acid | Histidine |
| Cobalt         | Vitamin A (retinol, retinal, retinoic acid and provitamin A carotenoids (mainly beta carotene)) | Linolenic acid | Isoleucine |
| Chlorine       | Vitamin C (ascorbic acid) | | Leucine |
| Chromium       | Vitamin D (ergocalciferol, cholecalciferol) | | Lysine |
| Copper         | Vitamin E (tocopherol) | | Methionine |
| Iodine         | Vitamin K (phylloquinone, menaquinone complices) | | Phenylalanine |
| Iron           | Carotenoids (alpha carotene, beta carotene, cryptoxanthin, lutein, lycopene, zeaxanthin) | | Threonine |
| Lithium        | | | Tryptophan |
| Manganese      | | | Valine |
| Molybdenum     | | | |
| Selenium       | | | |


There are 4 essential nutrients: essential mineral (nutrient)s, vitamins, essential fatty acids, and essential amino acids. An alternative method of classifying nutrients as either type I or type II. This classification is based on the way in which the body responds to a nutrient deficiency. A type I response is characterised by specific physical signs of deficiency as a result of a reduced tissue concentration of the nutrient. For example, if the diet is deficient in a type I nutrient such as iron, there is an initial consumption of body stores followed by clinical signs characteristic of iron deficiency. The concentration of iron in the tissues is markedly reduced, but there is no effect on growth or body weight. In contrast, a type II response is characterised by reduced growth rate or weight loss in the absence of specific deficiency signs. For example, if the diet is deficient in a type II nutrient like zinc, growth stops, followed by weight loss. Protein and energy (derived from carbohydrates and fat) are classified as type II nutrients.

<table>
<thead>
<tr>
<th>Type I nutrients</th>
<th>Type II nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine</td>
<td>Sodium</td>
</tr>
<tr>
<td>Iron</td>
<td>Potassium</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Zinc</td>
</tr>
<tr>
<td>Calcium</td>
<td>Magnesium</td>
</tr>
<tr>
<td>Selenium</td>
<td>Nitrogen</td>
</tr>
<tr>
<td>Copper</td>
<td>Sulphur</td>
</tr>
<tr>
<td>Manganese</td>
<td>Phosphorous</td>
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<tr>
<td>All vitamins</td>
<td>Water</td>
</tr>
<tr>
<td></td>
<td>Essential amino acids</td>
</tr>
<tr>
<td></td>
<td>Energy (carbohydrates, fats)</td>
</tr>
</tbody>
</table>
Table: Type I and type II nutrients

The type I and II classification is important because it emphasises that poor growth is not caused solely by protein-energy malnutrition but can result from other nutrient deficiencies which may not be recognised and so appropriately treated. Furthermore, it demonstrates the importance of a wide range of nutrients in causing poor growth or weight loss, and therefore the need for a nutritionally balanced diet.

In much of the developed world, such micronutrient deficiencies are rare; this is due to (1) an adequate supply of food and (2) the addition of vitamins and minerals to common foods (fortification). Micronutrient deficiencies are widespread in developing countries and affect approximately 2 billion people worldwide which is equivalent to more than one-third of the total world population. The most common deficiencies are due to lack of iron (anaemia), vitamin A (xerophthalmia) and iodine (goitre and cretinism). Outbreaks of deficiency disorders, which are rarely seen in normal circumstances, have also occurred in emergencies among populations entirely dependent on food aid. These include deficiencies of vitamin C (scurvy), niacin (pellagra) and thiamine (beri beri). The general ration provided in emergencies by agencies like WFP and ICRC are frequently lacking in some essential micronutrients, which means that populations always require other foods (or in some cases micronutrient supplements) to complement the rations. Donor agencies can assist populations to maximise their intake of micronutrient-rich foods by adopting a number of different strategies which, in preferred order, include: promoting the production of vegetables and fruit; providing fresh food items in the ration; adding a food to the ration which is rich in a particular vitamin or mineral; providing fortified foods; and supporting the distribution of nutrient supplements.

Vitamins

Vitamins have a special place in the history of medicine. At the end of the 19th century, it was thought that infectious diseases could explain most of the illnesses of mankind. It took a while to show that nutritional deficiencies were responsible for certain ailments, instead of a particular infection. The study of thiamine deficiency earned its author the Nobel Prize (Eijkman 1929). The research connected with vitamin C was likewise awarded this prestigious prize (Haworth and Szent-Gyorgyi, 1937).

A vitamin is an organic molecule (or related set of molecules) which is an essential micronutrient — that is, a substance which an organism needs in small quantities for the proper functioning of its metabolism but cannot synthesize, either at all or in sufficient quantities and therefore must obtain through its diet. Vitamins can fulfil different biochemical functions. Some function as regulators of cell
and tissue growth and differentiation (e.g. vitamin A), other serve as cofactors/coenzymes (B complex). Vitamin D and vitamin E/C serve as hormone-like regulators of mineral metabolism and antioxidants.

The name vitamin refers to “vital amine” (amine of life), even though not all vitamins (in particular vitamin A) have an amine components. As the word was already ubiquitous by the time it was shown that not all vitamins are amines, the final “e” was dropped to deemphasize the “amine” reference.

Humans must consume vitamins periodically but with differing schedules, to avoid deficiency. Body stores for different vitamins vary widely; vitamins A, D, and $B_{12}$ are stored in significant amounts, mainly in the liver, and an adult’s diet may be deficient in vitamins A and D for many months and $B_{12}$ in some cases for years, before developing a deficiency condition. However vitamin $B_3$ (niacin and niacinamide) is not stored in significant amounts, so stores may last only a couple of weeks. For vitamin C, the first symptoms of scurvy in experimental studies of complete vitamin C deprivation in humans have varied widely, from a month to more than six months, depending on previous dietary history that determined body stores.

A primary vitamin deficiency occurs when an organism does not get enough of the vitamin in its food. A secondary deficiency may be due to an underlying disorder that prevents or limits the absorption or use of the vitamin, due to a “lifestyle factor”, such as smoking, excessive alcohol consumption, or the use of medications that interfere with the absorption or use of the vitamin. People who eat a varied diet are unlikely to develop a severe primary vitamin deficiency. In contrast, restrictive diets have the potential to cause prolonged vitamin deficits, which may result in often painful and potentially deadly diseases.

Well-known human vitamin deficiencies involve vitamin A deficiency, thiamine (beriberi), niacin (pellagra), vitamin C (scurvy), and vitamin D (rickets). These specific deficiencies will be discussed as well as iodine deficiency disorder. The description of other micronutrient deficiencies is beyond the scope of these lecture notes.

Vitamin A deficiency
Summary

- Vitamin A deficiency (VAD) can be caused by insufficient intake through food or by increased need in case of infection
- Leading cause of preventable childhood blindness
- Causes xerophthalmia: dryness of conjunctiva and cornea, Bitot spots, keratomalacia and night blindness
- Is associated with excess mortality
- Treatment with large and repeated doses, lower doses in pregnancy
- Prevention can be achieved with diet change, periodic supplementation and fortification

Epidemiology

Vitamin A deficiency (VAD) or hypovitaminosis A is a shortage of vitamin A in blood and tissues. It is the leading cause of preventable childhood blindness and is related with child mortality. VAD affects about one-third of children under five worldwide and claims the live of more than 500,000 children annually, mainly in Southeast Asia and Africa. An estimated 250,000 to 500,000 children go blind each year due to vitamin A deficiency and half of them die within a year of becoming blind. VAD prevalence in high among pregnant women in many developing countries and contributes to maternal mortality. VAD affects the immune system and infectious diseases such as measles have higher fatality rates. Even subclinical deficiency can be a problem as it may increase child’s risk of developing respiratory and diarrhoeal infections, decrease growth rate (stunting), slow bone development and decrease likelihood of survival from serious illness. Periodic, high-dose vitamin A supplementation is a proven, low-cost intervention which has been shown to reduce all-cause mortality by 12 to 24 percent. Globally, around 65% of all children aged 6 to 59 months received two doses of vitamin A, fully protecting them against VAD. However between 2015 and 2016 vitamin A supplementation coverage dropped by more than half in countries with the highest under-five mortality rates, the countries where it is needed most. This caused an increase of children aged 6 to 59 months left unprotected from 19 to 62 million. Two-thirds of at risk countries have no VAD data of use data that are > 10 years old, challenging vitamin A supplementation programs.

Vitamin A metabolism and pathophysiology

The term vitamin A should be used as the generic descriptor for retinoids exhibiting the qualitative biological activity of retinol. The main molecular structure contains a cyclic part and a non-cyclic chain with 5 double bonds in the all-trans position. A functional group is found at the end of the non-cyclic part which can be an alcohol (retinol), an aldehyde (retinaldehyde), a palmitate
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(retinolpalmitate), etc. The term provitamin A carotenoid should be used as the generic descriptor for all carotenoids exhibiting qualitatively the biological activity of beta-carotene.

Vitamin A is fat soluble and is absorbed in the gut in the chylomicron fraction and then transported via the lymphatics, to the liver. The availability of fats in the intestine will influence the fraction of the available vitamin that will be absorbed. Vitamin A (retinol) is ingested as either retinyl esters or carotenoids and metabolized to active compounds such as 11-cis-retinal, which is important for vision, and all-trans-retinoic acid, which is the primary mediator of biological actions of vitamin A. Once stored in the liver as retinolpalmitate it will be transported to the target organs bound to a protein, the retinol binding protein (RBP). Zinc and an adequate intake of proteins are required for normal production of RBP. Transthyretin (TTR= transports thyroxine and retinol) is a transport protein in the serum and cerebrospinal fluid that carries the thyroid hormone thyroxine (T4) and retinol-binding protein bound to retinol. The liver secretes transthyretin into the blood, and the choroid plexus secretes TTR into the cerebrospinal fluid. If retinol is not needed, it is instead stored in liver stellate cells in the form of retinyl esters.

Rhodopsin, the light-sensitive pigment in rods of the eye, is formed when 11-cis-retinal combines with the protein opsin. Absorption of light energy causes rhodopsin to decompose by a series of photochemical reactions to all-trans-retinal and opsin. As this occurs, a visual signal is transmitted to the central nervous system. Night blindness is an early symptom of vitamin A deficiency. In night blindness, the small amount of light at night does not elicit an adequate response because the amounts of 11-cis-retinal and rhodopsin that can be formed are depressed. Another important function of vitamin A is regulation of growth and differentiation of cells. In the absence of vitamin A: 1) proper stem cell differentiation does not occur; 2) growth and development of embryos are altered; 3) epithelial cellular development with ciliary function is deficient, and the barrier to infection is decreased; 4) cells involved in innate and acquired immune function are decreased; 5) xerophthalmia develops because of abnormalities in corneal and conjunctiva development; 6) normal bone growth and tooth development do not occur, contributing to stunting.

### Vitamin A in skin creams

Companies that produce skin creams often juggle with terms as ‘Pro-retinol A’,... The creams contain pro-retinols (precursors to retinols) that break down to retinol on exposure to the skin. Vitamin A itself is what does all the work. As well as being the precursor to retinal, it is also a chemical messenger, one function of which is to instruct cells to begin multiplying more uniformly, and to produce more elastin and collagen, two protein building materials essential in healthy,
young-looking skin cells.

**Causes of vitamin A deficiency**

Both an insufficient input and an increased need can result in the deficiency. Insufficient intake is seen when following food items are lacking the diet:

- Vegetables: green leafy vegetables – carrots
- Fruits: mango – papaya
- Oils: palm oil

Infections of the gut, malabsorption, worm infestations and particularly giardiasis that provokes steatorrhea decrease vitamin A absorption. Infections can increase vitamin A demands dramatically. Some investigators even calculated the increase during infections in the order of 3000 IU per day. Particularly children with measles are very likely to develop a very fast progressing keratomalacia.

**Recommended daily intake**

<p>| | |</p>
<table>
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<tbody>
<tr>
<td>Adult:</td>
<td>750 µg</td>
</tr>
<tr>
<td>Pregnancy:</td>
<td>750 µg</td>
</tr>
<tr>
<td>Breastfeeding:</td>
<td>1200 µg</td>
</tr>
<tr>
<td>Children:</td>
<td></td>
</tr>
<tr>
<td>&lt; 1 yr:</td>
<td>300 µg</td>
</tr>
<tr>
<td>1-4 yr:</td>
<td>250 µg</td>
</tr>
<tr>
<td>4-6 yr:</td>
<td>300 µg</td>
</tr>
<tr>
<td>7-9 yr:</td>
<td>400 µg</td>
</tr>
<tr>
<td>10-12 yr:</td>
<td>575 µg</td>
</tr>
<tr>
<td>13-15 yr:</td>
<td>725 µg</td>
</tr>
</tbody>
</table>

Note: 1 IU = 0,3 mcg retinol
There is a very strong association of vitamin A deficiency with malnutrition (PEM). Both are diseases of the poorer people of the population and of the deprived. They will have an overall lower food intake but particularly of meats and milk products, sources rich in vitamin A and of oils and fats, which are necessary for the vitamin A absorption. These children will also have more frequent infections, increasing their demands and interfering with the absorption at the level of the gut. Once their serum protein levels decrease like in severe malnutrition the necessary enzymes for absorption and transportation to the target organs will diminish further aggravating the deficiency.

**Clinical aspects**

VAD is an important contributing factor in mortality which is still very high in the majority of the third world countries. This can for a large extend be explained by the role vitamin A has in maintaining the immunological response and the differentiation and maintenance of epithelial surfaces, like the skin, bronchi, gut and genito-urinal tract, which are more prone to invasion by bacteria in a vitamin deficiency state. A higher frequency of diarrhoea, ARTI (acute respiratory tract infection) and otitis media have been noted. These effects are present well before there are overt clinical signs at the level of the eye.

**Xerophthalmia**

Although xerophtalmia literally means (xeros= dry ; ophthalmos = eye) dryness of the eye and is used as such by the ophthalmologists, it is used in a broader sense in the public health context of vitamin A deficiency. Here it means all lesions, internal and external, attributable to the deficit of vitamin A: dryness of conjunctiva and cornea, Bitot spots, keratomalacia and night blindness. Xeroderma is another expression of xerosis.

The natural course of the disease progresses from night blindness to dryness of the cornea, sometimes with Bitot spots, to keratomalacia, although many children will not pass through this sequence. In a community where children have eye signs, there will be many other children who are vitamin A deficient but who have completely normal eyes and vision. Children with eye signs due to VAD are only the ‘tip of the iceberg’ explaining why community approaches to control VAD are important. Some eye signs reflect long-standing VAD, whereas other eye signs reflect severe, acute, sudden-onset VAD. A child who is vitamin A deficient, but who does not have eye signs, may develop immediately corneal ulcers as a result of infections or diarrhoea. Children with any of the eye signs of VAD are at high risk of dying.
Night blindness

- Nyctalopia or night blindness is not always perceived because it is a subjective sign; on the one hand and because its perception is very much influenced by the availability of electricity on the other hand. The child has an inability to see in poor lighting conditions like those which prevail at the end of the day when the evening is setting. A longer adaptation of vision to the dark is needed, like when one is getting from a light to a darker environment. Children will usually not complain and mothers should be asked if they stumble over objects in the house in the evening or that their children can’t find the parents anymore in the house in the evening. The child might become less active and may be fearful of moving around. Night blindness is quantifiable through a dark adaptation test, but it is difficult to evaluate objectively in children.

**Historical note: Xerophthalmia and Vitamin A**

The Eber’s Papyrus describes night blindness in ancient Egypt. Physicians treated the condition by squeezing the “juices” of a grilled lamb’s liver into the eyes of afflicted patients. In 1971, George Wolff speculated that these topically applied “drops,” rich in retinol, probably drained into the lachrymal sac, where they were absorbed into the systemic circulation and thereby reached the retinal cells. Perhaps that was the case, but Alfred Sommer observed the treatment of a young boy in rural Indonesia that was described in exactly the same fashion, but provided a more direct explanation for the way in which “liver juices,” applied topically, could reach the back of the eye. At the conclusion of the ceremony, after juice from a goat liver had been squeezed onto the boy’s eyes, the traditional healer fed the child the remaining liver! The healer did not consider eating the
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liver part of the treatment; he fed the child the liver so as not to waste precious food.

Modern concepts of xerophthalmia date from the early 1800s, when dogs that were “starved” on sugar and distilled water developed perforating corneal ulcers resembling those in “ill-nourished infants”. One hundred years elapsed before investigators realized that these changes were caused by lack of a specific nutrient “fat soluble A”, present in the lipid fraction of milk, eggs, butter and cod-liver oil, and -as provitamin A carotenoids- in dark-green leafy vegetables and certain coloured fruits. Bloc -studying the growth and development of children in a Danish orphanage, noted that vitamin A-deficient children were far more likely to develop urinary tract infections, grew less and were less likely to develop xerophthalmia, and that vitamin A treatment cured the condition. By 1928, Green and Mellanby dubbed vitamin A the “anti-infective factor”.

In 1932 Ellison administered daily vitamin A to one-half of the cases of measles admitted to the Grove fever hospital outside London. Those given vitamin A had only half the case-fatality rate of those restricted to standard therapy.

Vitamin A was finally crystallized in 1937.

Conjunctival- and corneal xerosis

VAD causes squamous metaplasia and keratinization in the eye. Conjunctival xerosis can be difficult to detect. One can see a slight wrinkling of the conjunctiva. In corneal xerosis glands in the conjunctiva no longer function normally, leading to loss of tears and mucous with an increased risk for infections. The light reflex of the cornea loses its well-defined appearance and becomes mottled and hazy. The cornea becomes dry, less translucent and more opaque.

Bitot spots are unpainful, triangular, whitish, pearly coloured spots, usually found on the lateral side of the conjunctiva, which are pathognomonic for VAD. They consisting of keratin accumulations, often intermixed with an overgrowth of Corynebacterium xerosis, which result from epithelial (squamous) metaplasia: the conjunctival cells become more like skin than a mucous membrane. The white foamy deposits can be wiped away partially, but they don’t disappear completely, even when the deficiency is reversed.

Corneal ulcer and keratomalacia

If the acute VAD is not treated promptly, the cornea can become ulcerated and melt away. The
liquefaction necrosis of the cornea varies from small ulcerations to softening and rupture of the cornea, with resulting loss of anterior chamber fluid and collapse of the eye. Keratomalacia indicates that more than one-third of the cornea is affected. In just a few days the cornea can be completely destroyed and secondary infection is common. As long as there is no superinfection, there is no pain or redness. The end result is corneal scarring, staphylomas (bulging of a badly damaged cornea) or phthisis bulbi (a shrivelled up eye). Children with keratomalacia are often malnourished, but previously healthy appearing children can develop keratomalacia following measles infection or diarrhoea. It is important to screen young children from the same family and community.

**Diagnosis**

**Clinical**

In low resource settings the diagnosis of individual patients is usually made clinically. Fundus examination can be useful to detect xerophthalmic fundus, which is more present in adults. Small white spots are found on the retina. This moderate form of VAD (night blindness, conjunctival dryness) will disappear after 2-4 days of treatment without leaving any lesions or sequelae.

**Plasma levels and Hepatic reserves**

The problem with measuring plasma retinol levels is that they only change after a prolonged period of vitamin deficit, due to the buffering action of the liver. Their use is limited to research evaluations of vitamin A deficiency and of very little practical use in real life situations. Hepatic reserves can be determined with a liver biopsy, which is only done on an experimental and research basis. The reserves can be estimated: after administration of a small dose of retinol (1.800 IU) the plasma retinol levels are measured again and compared with the retinol concentrations before the administration. If the concentration increases by more than 20 % then this indicates reserves are low.

<table>
<thead>
<tr>
<th>Plasma retinol</th>
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<tbody>
<tr>
<td>&gt;= 30 mcg/100 ml</td>
<td>Normal</td>
</tr>
<tr>
<td>30-20 mcg/100 ml</td>
<td>Mild deficiency</td>
</tr>
<tr>
<td>20- 10 mcg/100 ml</td>
<td>Associated with night blindness, Bitot spots Moderate deficiency</td>
</tr>
</tbody>
</table>
Impression cytology

Impression cytology is a technique to detect the degree of metaplasia of the conjunctiva. The lack of differentiation and the decrease or absence of goblet cells is looked for. It is not a routine diagnostic test.

Vital staining

Vital staining detects the degree of conjunctival metaplasia by putting dye (Lissamon green or Bengal rose) on the conjunctiva. This method lacks specificity.

Treatment

The presence of clinical signs of vitamin A deficiency should be considered an emergency. The most urgent are those infants with corneal signs. Large and repeated doses are therefore given. Associated illnesses should always be treated.

In an endemic zone, all children with PEM and measles need vitamin A treatment.

Treatment dosage

<table>
<thead>
<tr>
<th>Children &lt; 1 yr</th>
<th>Children &gt; 1 yr and adults except pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td>100.000 IU immediately</td>
<td>200.000 IU immediately</td>
</tr>
<tr>
<td>100.000 IU after 24 hrs</td>
<td>200.000 IU after 24 hrs</td>
</tr>
<tr>
<td>100.000 IU after 14 days</td>
<td>200.000 IU after 14 days</td>
</tr>
</tbody>
</table>

Below one year or below 8 kg the dose is half of the dose delivered in the vitamin A high dosage capsules. These contain 6 drops; to administer throw away three drops and give the remainder.

Although teratogenic in animals, a clear correlation between ingestion of large doses of vitamin A and
congenital malformations has not been established. As a precautionary measure, pregnant women should not receive large doses of vitamin A due to the possible teratogenic effect. Smaller doses up to 10,000 IU per day are safe. A total dose of 200,000 IU should be aimed at. Lactating women should receive 200,000 IU in the first month postpartum. One month after delivery again smaller doses up to 10,000 IU per day are preferred. This because one month after delivery there is the possibility of recurrent pregnancy.

Xerophthalmia is treated with topical antibiotics and padding of the eye. Topical steroids should be used with caution. Corneal grafting and conjunctival reconstruction using a flap are out of scope for most settings where VAD is prevalent.

**Prevention**

“Appropriateness” is a basic premise for vitamin A intervention. Two conditions dictate whether a program, designed to prevent vitamin A deficiency, is appropriate:

- A substantial segment of the population is “at risk” of developing clinical or biochemical vitamin A deficiency of sufficient severity to be considered of Public Health importance.
- The problem is serious enough to warrant the diversion of scarce resources toward a program to control vitamin A deficiency versus other preventable diseases or community projects within the country.

Currently vitamin A prophylaxis is approached through one of the three major intervention strategies:

1. A change in diet directed toward achieving a continuous intake of vitamin A rich foods.
2. Administration of a single, large dose of vitamin A administered on a periodic basis.
3. Fortification of an appropriate dietary vehicle with vitamin A.

**Change in dietary intake**

Different strategies have been applied to increase dietary intake. Promotion of breastfeeding is effective in entirely breastfed children, provided the mother has adequate daily intakes of vitamin A. They have a lower prevalence of mild and severe xerophthalmia during early childhood. Nutritional education, kitchen gardening programs, larger scale agricultural programs and income generating programs are possibilities to achieve a higher vitamin A intake. Diet adaptation is the most sustainable solution and avoids the risk of hypervitaminosis. This approach de-medicalizes a food related condition. Challenges can be the availability of vitamin A rich products. These products must
also be culturally accepted and land suitable.

**Distribution of large dose vitamin A capsules**

Large doses of 200,000 IU are distributed at regular intervals, most frequently every six months. The seasonal distribution approach is used to protect children in the higher prevalence seasons, reduces cost while maintaining the same impact. There are three possible delivery strategies: the ‘medical’ or ‘therapeutic’ approach, which offers treatment to children who present to a health facility with an illness episode. They will be given a dose of vitamin A according to a set of pre-set criteria of high risk of developing vitamin A deficiency. The ‘targeted’ distribution covers groups within the larger general target population; e.g., residents of a high prevalence neighbourhood, those attending mother and child health clinics, etc. The ‘universal’ distribution in which all pre-school children and not pregnant lactating mothers in a prescribed region are dosed at prescribed intervals by single or multipurpose workers in the community.

**Vitamin A fortification**

Fortification of Mono-sodium Glutamate in the Philippines and of sugar in Guatemala has been highly successful. Other possible vehicles are wheat and milk. Vitamin A is light- and heat sensitive so it must be protected from light and stored in a cooler environment. The success of this type of program depends on the identification of a suitable vehicle, which has to be consumed by all and particularly the population at risk, and in a continuous and constant fashion. Fluctuations between people and in time should be as small as possible. The cost of the program on a national scale is usually high enough to raise the question as to who is going to bear it; the government, the industry or the consumer. Disagreement over this last point has led to the discontinuation of some fortification programs.

**Vitamin A toxicity**

**Acute hypervitaminosis**

Ingestion of large dose can give rise to transient signs and symptoms of toxicity, which are self-limiting and completely reversible. No deaths have been reported after the ingestion of the doses used in treatment and prevention. Intracranial pressure rises giving rise causing headaches and a bulging fontanel in young children. Nausea, vomiting, dizziness, headaches have been described in adults. Desquamation of the skin, bone pains and hair loss can occur in the following days.
**Chronic hypervitaminosis**

Ingestion of large doses on a regular basis can lead to hepatitis, cirrhosis, hair loss, dry scaling skin, hyperpigmentation, hyperostosis and bone pains, hepato-splenomegaly and anaemia. It is therefore recommended not to exceed a daily intake of 3000 µg (10,000 IU) in children and 7500 µg (20,000 IU) in adults. Why does the liver get damaged in chronic hypervitaminosis A? The liver gets a double blood supply: arterial via the arteria hepatica and venous via the portal vein. The blood vessels branch until they form a capillary-like network, the so-called liver sinusoids. These vessels are rather different from ordinary capillaries and containing large fenestrations. They do not rest upon a basal membrane but are surrounded by reticuline fibers. The sinusoids contain, apart from vascular endothelial cells, also Kupffer cells, monocyte-derived phagocytes. Outside the sinusoids is the space of Disse (German anatomist, Joseph Disse; 1852–1912). This space contains the microvilli of hepatocytes as well as Ito cells (syn. stellate cells; Japanese physician Toshio Ito: 1904–1991). Ito cells store fat and fat soluble vitamins, like vitamin A. Excessive intake of vitamin A leads to pathologically enlarged Ito cells. When damaged, Ito cells can change into an activated state. These are responsible for secreting collagen scar tissue. This leads to fibrosis, cirrhosis and portal hypertension.

**Rickets**

**Summary**

- Vitamin D in food: sequentially converted in the skin (sunlight), liver and kidneys
- Calcitriol needed for mineralization of osteoid and calcium uptake in the intestine
- Deficiency in children (epiphyseal plate still open) leads to rickets
- Deficiency in adults (epiphyseal plate closed) leads to osteomalacia
- Irregularly frayed, wide, cup-shaped distal ulna and radius, rachitic rosary, hypocalcaemia
- Pseudofractures, bone deformities, gait disturbance
- Rapid recovery after deficiency correction, except if end-organ resistance
- Do not confuse rickets with rickettsiosis
Rickets: Historical Note

For centuries, rickets – despite being common – was a mysterious disease. In 1650, Francis Glisson, a Cambridge physician published in Latin a treatise on rickets titled “De Rachitide.” Glisson’s treatise addresses the clinical features of rickets in a scientific tone, but lapses into medieval mysticism while discussing the aetiology of rickets. Glisson ascribed the aetiology of rickets to “cold distemper, that is moist and consisting of penury or paucity of and stupefaction of sprits.” Despite his affirmation of mysticism in the cause of rickets, Glisson was convinced that rickets was neither contagious nor heritable. Glisson’s suggested treatments for rickets included: cauterity, incisions to draw out bad humours, blistering and ligature of soft wool around the limb to retard the return of blood. For correction of bony deformities, Glisson proposed splinting and artificial suspension of the affected infant: “The artificial suspension of the body is performed by the help of an instrument cunningly made with swathing bands, first crossing the breast and coming under the armpits, then about the head and under the chin, then receiving the hands by two handles, so that it is a pleasure to see the child hanging pendulous in the air, and moved to and fro by the spectators. This kind of exercise is thought to be many ways conducible in this affect, for it helped to restore the crooked bones, to erect the bended joints, and to lengthen the short stature of the body.”

After Glisson’s discoveries, no advances were made in the study of rickets for 2 centuries. At the turn of the 20th century, rickets was rampant among the underprivileged infants residing in industrialized cities of North in the United States and several polluted cities in Europe. In 1919, Edward Mellanby, an English physician, conducted the earliest definitive experimental study exploring the role of diet in the aetiology and treatment of rickets. Puppies between 5 and 8 weeks of age were exposed to 1 of 4 natural diets. All 4 diets were rachitogenic after a variable period of exposure. Rickets was severe and developed easily in dogs that grew well on the rachitic diets. Neither yeast (antineuritic vitamin) nor orange juice (anti-scorbutic vitamin) hindered the development of rickets. Various foods were added to the rachitic diets and their effect on development of rickets was studied. Foods rich in fat-soluble vitamin A (cod-liver oil, butter, and whole milk) were able to prevent rickets. Mellanby postulated, “It therefore seems probable that the cause of rickets is a diminished intake of an antirachitic factor which is either fat-soluble A, or has a somewhat similar distribution to fat-soluble A. Mellanby’s work clearly established the role of diet in the cause of rickets.

McCollum was now confronted with same question faced by Mellanby, whether fat-soluble A was anti-rachitic by itself or if there was another substance with specific anti-rachitic function with
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similar distribution as fat-soluble A. McCollum and Mellanby were aware of F. G. Hopkins’ report that oxidation destroyed fat-soluble A. Mellanby found oxidized butter fat had lost its anti-rachitic effect, but similarly treated cod-liver oil still retained its protective action against the development of rickets. Mellanby stated “this difference can be explained by the fact that cod-liver oil contains greater quantity of antirachitic vitamin than butter, or that the destructive change takes longer time, or whether some other explanation must be sought. McCollum and his coworkers were soon able to explain the preservation of anti-rachitic function in oxidized cod-liver oil. Unlike Mellanby, they chose to explore the anti-xerophthalmic and anti-rachitic functions of oxidized butter fat and oxidized cod-liver oil. They chose “diet 3143,” which was adequately restricted with regard to fat-soluble A to cause severe rickets but still able to prevent the onset of xerophthalmia, to induce rickets in rats. Using the “line test,” the anti-rachitic potency of several fish liver oils, vegetable oils, and butter fat were tested. Oxidized cod-liver oil had lost its anti-xerophthalmic function, but still retained its calcium-depositing properties. Untreated coconut oil had no anti-xerophthalmic property, but had minimal anti-rachitic function. McCollum and his coworkers concluded that the anti-rachitic substance found in certain fats was distinct from fat-soluble vitamin A and its “specific property was to regulate the metabolism of the bones.” In the sequence of discovery of vitamins, the newly discovered antirachitic substance was the fourth; hence it was called vitamin D.

In 1890, addressing the aetiology of rickets, Palm studied the relationship between incidence of rickets and its geographical distribution and concluded that rickets was caused by lack of exposure to sunlight. Palm was able to point out that, despite a superior diet and relatively better sanitary condition, infants residing in Britain were more at risk for rickets than infants living in the tropics. Exposure to plenty of sunshine, which was the norm for infants residing in the tropics, was responsible for their protection against rickets. Palm recommended “systematic use of sun-baths as a preventive and therapeutic measure in rickets.”

The bridging of the knowledge that photosynthesized vitamin D and vitamin D in cod-liver oil were similar was responsible for the eventual conquest of rickets. By the 1930s, the use of cod-liver oil in the treatment and prevention of rickets became common place. The eventual public health prevention initiative of fortification of milk with vitamin D led to eradication of rickets.

Vitamin D metabolism and calcium homeostasis

Vitamin D is present in food as a fat-soluble provitamin. Vitamin D is regarded as a sterol, although the B ring of the molecular steroid skeleton is open. A photochemical conversion and two hydroxylations take place in the body before the final form is reached. The absorption of vitamin D is determined by the fat content of the food; by the proper functioning of the pancreas (lipase) and by the presence of sufficient bile. After absorption in the intestine, the provitamin is first transported to the skin, where a photochemical conversion takes place via ultraviolet light. Vitamin D₃ (= cholecalciferol = calcioi) is formed. This compound can also be produced via UVB radiation from an endogenous precursor, 7-dehydrocholesterol or pre-vitamin D₃. Sunlight breaks the B ring of the cholesterol structure to form pre-D₃. Pre-D₃ then undergoes a thermal induced rearrangement to form...
D₃. Continued irradiation of pre-D₃ leads to the reversible formation of lumisterol and tachysterol (isomers of pre-vitamin D₃) which can revert back to pre-D₃ in the dark. Vitamin D₃ is subsequently bound to a carrier protein and transported to the liver, where an initial hydroxylation takes place with the formation of 25-OH-D₃. In the kidneys, 25-OH-D₃ (calcidiol) is further hydroxylated to the metabolically much more active form 1,25-(OH)₂-D₃ (calcitriol). A similar hydroxylation takes place in the placenta. Extra-renal synthesis of 1,25-(OH)₂-D₃ may occur in pathological conditions, such as sarcoidosis and other granulomatous disorders.

It is important to maintain calcium concentrations at a constant level to preserve a normal neurological function, muscular contractility and bone mass. In the extracellular compartment calcium is always in equilibrium with phosphate. Their product has to remain constant, otherwise the calcium-phosphate complexes will precipitate. If calcium increases, phosphate will decrease. The biggest reservoir of those two minerals is the bone. When the calcium concentration drops, the parathyroid glands secrete the parathyroid hormone PTH. This stimulates the production of 1,25(OH)₂D. The receptor of 1,25-(OH)₂-D₃ is located in the cytoplasm of the cell. After binding, the complex migrates to the cell nucleus where (as a transcription factor) it mediates the expression of various genes. As a result of this (1) the active absorption of calcium in the intestine is stimulated, (2) the loss of calcium through the kidneys is decreased (resorption is stimulated) with increase in phosphate excretion and (3) bone cells (osteoclasts) are stimulated to resorb bone minerals and release calcium in the extracellular compartment. As a result of this the calcium concentration will rise and the secretion of PTH decrease.

**Rickets, causes**

Rickets and osteomalacia develop when there is insufficient vitamin D, when its metabolism is disturbed or when the tissues are resistant to its activity (e.g. mutation of the vitamin D receptor). By following the metabolic chain that leads to the active 1,25-(OH)₂-D₃ the various causes of osteomalacia/rickets can be visualized. For instance, the food may contain too few precursors. If there is insufficient fat in the diet, or there is insufficient bile and the fat is not absorbed (steatorrhoea), a deficiency of fat-soluble vitamins (ADEK) will occur. Prolonged treatment with cholestyramine is a risk factor. Insufficient exposure to sunlight is also an aetiological possibility. Dark-skinned people residing for a long time in the northern hemisphere are a high-risk group. This also applies to those who wear protective clothing and people who spend most of their time indoors (elderly people and Islamic women and children are high-risk groups). For instance, rickets/osteomalacia is not uncommon in Indian and Pakistani immigrants in Britain. A lack of direct sunlight and calcium (chelation of calcium by the phytates in their traditional diet and low intake of milk) contributes to the problem. There are several diseases that may be associated with vitamin D deficiency, such as chronic renal failure (lack
of 1-25-(OH)$_2$D$_3$ and hyperparathyroidism), hypoparathyroidism, genetic diseases such as hereditary hypophosphataemia, or vitamin D-resistant rickets.

<table>
<thead>
<tr>
<th>Clinical nutrition and bone disease</th>
<th>Rickets, osteomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>Rickets, osteomalacia</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Scurvy</td>
</tr>
<tr>
<td>Copper</td>
<td>Fractures (in premature infants with parenteral nutrition)</td>
</tr>
<tr>
<td>Calcium</td>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>
### Vitamin D content of food (µg/100 g)

**Cereals**
- Grain, flours, starches 0

**Milk & milk products**
- Cow’s milk 0.01-0.03
- Human milk 0.04
- Dried milk 0.21
- Cream 0.1-0.28
- Cheese 0.03-0.5
- Yoghurt Trace-0.04

**Eggs**
- Whole 1.75
- Yolk 4.94

**Fats and oils**
- Butter 0.76
- Cod liver oil 210
- Margarines and spreads* 5.8-8.00

**Meat & meat products**
- Beef, lamb, pork, veal Trace
- Poultry, game Trace
- Liver 0.2-1.1

**Fish and fish products**
- White fish Trace
- Fatty fish Trace-25
- Crustacea & molluscs Trace

**Vegetables** 0

*Added during production (Vitamin D₂).

Source: Holland et al 1991
Table: Vitamin D content in foods

**Pathophysiology**

Osteomalacia refers to a disorder in which there is abnormal bone mineralization and the ratio of mineral to matrix is diminished due to an excess of unmineralized osteoid. This in contrast to osteoporosis where there is a reduction in quantity of bone mass per unit of volume. Osteomalacia in children is known as rickets, and because of this, use of the term “osteomalacia” is often restricted to the milder, adult form of the disease.

Crystallization of minerals in osteoid requires adequate concentrations of ionized calcium and phosphate. Vitamin D influences these levels after its dihydroxylation into calcitriol (hepatic position 25 and renal position 1). When concentrations are too low crystallization does not proceed normally. Vitamin D disrupts mineralization because it normally regulates and enhances the absorption of calcium in the intestine. A lack of vitamin D causes plasma calcium concentrations to fall. Low plasma calcium levels stimulate parathyroid hormone (PTH). PTH raises calcium concentration but also increases renal clearance of phosphate. When phosphate decreases below a critical level, mineralization cannot proceed normally. On top of this, hypophosphatemia causes a disturbed apoptosis of chondrocytes, leading to an excess of unmineralized osteoid.

Rickets in the strict sense of the term is a disease caused by any interference with the process of enchondral bone formation (calciumphosphate deposition in cartilaginous bone), the cascade of events normally taking place in the epiphyseal growth plates and resulting in gain in length of long bones. In children, the abnormalities are clearest in the areas of most active growth, i.e. the epiphyses. In chronic deficiency there is resorption of trabecular and cortical bone, which is not compensated by mineralization of osteoid. Adequate treatment with vitamin D causes a rapid reversal of this situation. Normal enchondral bone formation is resumed. In adults, the changes are similar but are not limited to the extremities of the long bones. As a consequence, the skeleton will be affected in its two main functions as the mechanical support for the other organs and the major reservoir of calcium to serve a large array of physiologic functions.

**Clinical aspects**

The clinical picture is one of bone deformities ranging from mild signs to very distinctive bone deformities. Clinical and radiological bone lesions predominate in the areas of rapid bone growth, namely the long bone epiphyses and the costochondral junctions. Thus the clinical manifestations are most striking at the time of greatest velocity. The maximum frequency of signs is usual found between 4-12 months with most of the signs seen in children below 18 months. Bone changes, visible
on X-rays, precede clinical signs, becoming evident in the 3rd or 4th month of life (more common 6-9 months)- sometimes even at birth if the mother is severely vitamin D deficient. Bone changes in rickets are most evident at the distal ends of the radius and ulna. The bony ends lose their sharp, clear outline. They are cup-shaped and show a spotty or frayed outline. Later, the distance between the ends of the radius and ulna and the metacarpal bones appears to be increased because the noncalcified ends are invisible on the X-ray. This increase in the width of the epiphyseal cartilages can also be seen at the distal extremities of the tibia and fibula (“erlenmeyer deformity”). As healing begins, a thin white line of calcification appears at the epiphysis, becoming denser and thicker as calcification proceeds. Kyphoscoliosis may develop and walking is delayed. Older children and adolescents experience walking as painful and in extreme cases develop bowlegs or knock-knees.

Maternal osteomalacia leads to changes in the bones of the foetus and even to tetany or seizures in the newborn (hypocalcaemia). Young infants with vitamin D deficiency are restless and sleep poorly. They have reduced mineralization of the skull (craniotabes = “wasting of the skull) and frontal bossing can be seen. On the thorax, palpable lumps develop at the costochondral junctions: costochondral beading (rachitic rosary). Harrison’s groove, corresponding to the costal insertion of the diaphragm, may be present.

In adults, osteomalacia occurs particularly in the vertebrae, pelvis and legs. Fine lines appear in the cortex: ribbon-like areas of demineralization, the so-called pseudo fractures or Looser’s lines. Histologically they consist of focal accumulations of non-calcified osteoid. Preferential localizations for pseudo fractures are the lateral edge of the scapula, femur neck, medial femoral shaft, ribs and ramus pubis. Looser’s lines are usually symmetrical, extending perpendicularly to the cortex; are manifestly shorter than the diameter of the bone and display no callus formation. As the bones soften, body weight may cause bowing of the long bones, vertical shortening of the vertebrae and flattening of the pelvic bones, which narrows the pelvic outlet. This may subsequently cause difficulties in childbirth.

Rickets: clinical signs in babies

1. Aspecific restlessness and irritability
2. Head sweating
3. Skeletal signs (ricketsial thoracic rosary at 6-9 months of age). Disturbed bone maturation with wide epiphyseal plates and fraying of metaphysis. Frontal bossing and soft osseous borders of cranial vault (craniotabes) with or without widened fontanelles.
4. Delayed teething, enamel hypoplasia and numerous caries
5. Hypotonia: muscle flabby or muscle cramps (eventual seizures, tetany, laryngeal spasms)
6. Higher risk of upper respiratory tract infections due to muscle weakness and thoracic cage
deformities
7. Anaemia (von Jacksch-Luzet syndrome) due to marrow space fibrosis. If severe, extramedullary production of red cells in liver and spleen can lead to hepatosplenomegaly

Human breast milk contains very little vitamin D (approx 25 IU per litre). Prolonged breast feeding by mothers who don’t take extra vitamin D, followed by sudden switch to milk formula (containing lots of phosphate) can precipitate overt hungry bone syndrome, sometimes presenting with signs of acute or subacute hypocalcemia (e.g. convulsions).

**Diagnosis**

In the blood there is approximately 500 times more 25-OH-D$_3$ present than 1,25-(OH)$_2$-D$_3$ and the half-life of 25-OH-D$_3$ is 15-45 days, constituting a factual reservoir of the vitamin. As a consequence, serum level of 25(OH)D is the laboratory test ordered to indicate whether or not a person has vitamin D deficiency or insufficiency. The half-life of 1,25-dihydroxyvitamin D is short (4 to 6 hours). The levels of this compound can remain normal (or even raised) even when a person may be vitamin D deficient, depending on the activity of the 1-alpha-hydroxylase that converts 25-hydrovitamin D to 1,25-dihydroxyvitamin D, which in turn depends on the current blood concentration of calcium, phosphate and parathyroid hormone. Measuring the active form of vitamin D (1,25-dihydroxyvitamin D) lacks utility in the routine evaluation of suspected vitamin D deficiency.

In healthy people, normal levels are 25 to 40 ng/mL (62 to 100 nmol/L) for 25-OH-D$_3$ and 20 to 45 pg/mL (48 to 108 pmol/L) for 1,25-(OH)$_2$-D$_3$. In nutritional rickets and osteomalacia, 25-OH-D$_3$ levels are very low.

Hypophosphatemia and high serum alkaline phosphatase are characteristic. Calcium is low or normal, depending upon the effectiveness of parathormone (secondary hyperparathyroidism) in restoring serum calcium to normal.

It is also considered reasonable to treat at-risk persons with vitamin D supplementation without checking the level of 25(OH)D in the serum, as vitamin D toxicity is very rare.

**Differential diagnosis**

A review of the patient’s history may suggest nutritional problems. Rickets must be distinguished from infantile scurvy (cfr. scorbutic rosary), congenital syphilis (serologic tests) and from
chondrodystrophy (large head, short extremities, thick bones; normal calcium, phosphate and alkaline phosphatase levels). Frontal bossing can be a sign of congenital lues, hemolytic anemia (thalassemia’s, sickle cell disease), Hurler syndrome, achondroplasia). Yaws (= Pian = Framboesia) can give rise to sabre tibia. Osteogenesis imperfecta, cretinism, congenital dislocation of the hip, hydrocephalus and poliomyelitis should be readily distinguishable. Tetany must be distinguished from convulsions due to other causes. Vitamin D-resistant rickets may be caused by severe renal damage, as in chronic renal tubular acidosis (e.g. Fanconi’s syndrome or X-linked hypophosphataemia). Osteomalacia must be distinguished from other causes of bone decalcification, such as hyperparathyroidism, senile or postmenopausal osteoporosis; osteoporosis of hyperthyroidism, steroid use, Cushing’s syndrome and atrophy of disuse.

**Treatment**

The World Health Organization defined an “International Unit” of vitamin D₃ as 0.025 micrograms (or one microgram = 40 IU).

Treatment usually consists of vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol), in addition to dietary advice and sunlight exposure. While there is evidence that vitamin D₃ raises 25(OH)D blood levels more effectively than vitamin D₂, other evidence indicates that D₂ and D₃ are equal for maintaining 25(OH)D status. Treating vitamin D deficiency depends on the severity of the deficit. An initial high-dosage treatment phase until the required serum levels are reached, is followed by the maintenance of the acquired levels. The lower the 25(OH)D serum concentration is before treatment, the higher is the dosage that is needed in order to quickly reach an acceptable serum level. The initial high-dosage treatment can be given on a daily (1000 IU for newborns, 1000 to 5000 IU for 1-12 months old infants and 5000 IU for patients older than 1 year) or weekly basis or can be given in form of one or several single doses orally or intramuscular (200,000 IUI), especially when there are concerns about compliance. Maintenance supplementation of 400 IU per day is recommended, with double doses for premature infants, dark-skinned infants and children residing in areas of limited sun exposure.

It is important to make sure that the children are receiving enough calcium. A daily intake of 800 mg in infants and children, and 1 g in adults, is the required minimum during the first month of treatment. Milk and dairy products can easily supply this, but when this does not seem possible, calcium supplementation must be provided.

The first radiological signs of healing will appear after 2-4 months.
**Vitamin D intoxication**

When accidental or intentional high doses of vitamin D are taken, the clinical picture is dominated by hypercalcaemia. The rate at which the symptoms develop depends upon the dose and duration of excess vitamin D intake. The first symptoms are anorexia, nausea, vomiting, polyuria, polydipsia and pruritus. Polyuria is secondary to a massive increase of urinary calcium excretion. Complications consist of metastatic calcifications (nephrocalcinosis!) and renal failure.

Patients sometimes complain of eye irritation. Physical examination may reveal a bandlike grey-white opacity across the corneal surface: band keratopathy. Treatment consists of stopping further administration of vitamin D and giving corticosteroids. Urinary acidification is recommended. Diuretics serve no useful purpose. Bisphosphonates such as pamidronate (an osteoclast inhibitor) may be used in extreme cases.

**Prevention**

With the major source of vitamin D derived from the skin, exposure to sunlight is the best prevention. In high latitude countries, supplements or fortification may be needed. Human breast milk is deficient in vitamin D (1.0 µg/L = 40 IU/L), whereas fortified cow’s milk contains ten times as much. Breastfed infants should therefore be given a supplement of vitamin D (400 IU/day) from birth to 6 months, at which time they are given a more diversified diet. Large doses of 200,000 IU (5 mg) can also be given every 3 months. This dose is not always well absorbed. The safest is to give daily small doses. Bottle feeds have already adjusted levels of vitamin D. Food fortification of margarine and cow’s milk has eradicated rickets in Europe and the United States.

The elderly are a particular group at risk. Many older people stay indoors most of the time and get very little exposed to sunlight. The can develop demineralization of the bone with bone pains and fractures. Daily supplements can be necessary.

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**Beriberi**

**Summary**

- Thiamine = vitamin B1, water-soluble, heat-labile
Deficiency caused by lack of thiamine intake
Deficiency caused by thiaminases
Symptoms may develop acutely
Dry beriberi: peripheral neuritis with paralysis and loss of sensation
Wet beriberi: high-output heart failure
Cerebral beriberi: ophthalmoplegia, mental confusion, ataxia
Infantile beriberi: aphonia, areflexia and heart failure
Diagnosis by empirical treatment

Thiamine

Thiamine (Vitamin B1) is an essential micronutrient with dual co-enzymatic and non-co-enzymatic functions. It is involved in carbohydrate and branched-chain amino acid metabolism; as well as in the production of neurotransmitters, myelin, and nucleic acids. There is also evidence that thiamine plays a role in immune and anti-inflammatory processes and gene regulation. Thiamine is a water-soluble, heat-sensitive and very unstable vitamin which is present in many foods: meat, grain products, potatoes, beans, nuts and yeast. The richest sources are cereal grains and pulses. Green vegetables, fish, meat, fruit and milk all contain useful quantities. The refining of sugar, rice and grain products reduces the thiamine content. Whole grain rice requires more chewing and is heavier, but polishing of brown rice (removal of the dry outer layer) reduces the content of vitamin B1 to practically zero. Thiamine resists temperatures up to 100°C, but it tends to be destroyed if heated further (e.g. if fried in a hot pan or cooked under pressure). It is often washed away with the cooking water, which can be avoided by preparing food with just the amount of water that will be absorbed in cooking, or by using water that is left over in soups or stews. Cassava contains only about the same low quantity as polished, highly milled rice. It is surprising that beriberi is not common among the many people in Africa, Asia and Latin America whose staple food is cassava, although underdiagnosis might play a role. Some nutrients contain thiaminases which have the ability to break down vitamin B1 in the food: raw fish, coffee and tea leaves. Certain plants, such as bracken (especially the young fern fiddleheads) contain thiaminases and are consequently toxic (cfr. the disease called “staggers” in horses eating these ferns). This thiaminase is destroyed by cooking. The uptake of thiamine takes place in the proximal small intestine. A small amount is stored in muscle tissue. In Asian countries such as China, Indonesia, Japan, Malaysia, Myanmar, the Philippines and Thailand beriberi used to be a major cause of morbidity and mortality in those whose diet consisted mainly of rice. In contrast, people in many parts of the Indian subcontinent were relatively protected from beriberi because they consumed mainly parboiled rice, which conserves enough thiamine.
Fig: Thiamine is a co-enzyme in the conversion from pyruvate to acetyl-CoA and in the conversion of alpha-ketoglutarate to succinyl-CoA. Non availability of thiamine leads to lactic acidosis.
Thiamine pyrophosphate (= thiamine diphosphate) is the co-enzyme of several enzymes of carbohydrate metabolism:

1. Pyruvate dehydrogenase, which is needed to convert (decarboxylate) pyruvate to acetyl CoA (Krebs cycle).
2. Transketolase: involved in the pentose phosphate pathway. This pathway generates NADPH which is essential for reductive biosynthesis, e.g. production of myeline.
3. 2-Oxo-glutarate dehydrogenase (= alpha ketoglutarate dehydrogenase), needed for the Krebs cycle.
Various subjects

Thiamine is important for neural cell membranes and it has a modulating function in neuromuscular transmission.

**Beriberi, historical overview**

At the end of the 16th century, the first reports emerged of a new disorder in the Far East. In Indonesia this disease was called beriberi. The etymology of the word is not clear. Dr. Jacobus Bontius reported that beriberi is similar to the local name for sheep, and was believed to refer to the peculiar gait of that animal. Together with Nicolaas Tulp from Holland (cf. the painting “The Anatomy Lesson of Dr. Tulp” by Rembrandt, 1632) he gave the first European description of the disease. In Hindi, the term ‘bharbari’ means swelling; in Arabic the term ‘burh’ means shortness of breath; and ‘bahri’ means marine. In Singhalese, ‘bhayree’ means weakness. Beriberi was found to be a ravaging disease which occurred with varying frequency. This was dramatically illustrated in 1883 when a training ship of the Japanese navy sailed to Hawaii via New Zealand and South America for over nine months. Of the crew of 376 sailors and officer cadets, 169 fell ill with beriberi and 25 died of the disease. On the recommendation of the Japanese medical officer Takaki, a different diet was used, with more meat, fish, barley and beans and less rice on a new voyage with the ship Tsukuba that was undertaken the following year. On this voyage there were only 14 cases of beriberi and no fatalities. Takaki observed that beriberi was common among low-ranking crew who were often provided free rice and thus ate little else, but not among crews of Western navies, nor among Japanese officers who consumed a more varied diet. These findings prompted the Japanese Navy to change its staple diet. More barley was used instead of rice, with a drastic reduction of beriberi as a result. However, the physicians of the time concluded that it was not the different diet that was responsible but the improved hygiene. During the Russian-Japanese war of 1904-1905, no fewer than 90,000 cases of beriberi were diagnosed in Japanese soldiers.

The disease occurred in communities that ate white rice, but not in all individuals and the disorder was also seen (to a lesser extent) outside rice-growing areas. The Dutch doctor Christian Eijkman, who won the Nobel Prize in 1929, was working in Indonesia and he used chickens as an animal model for beriberi. He noticed the symptoms of beriberi in some chickens used in his laboratory when their feed had been altered for a few months. During that time, chickens in the laboratory had been fed leftover rice from military rations, until a new cook refused to allow military rice to be fed to civilian animals. Rice was then purchased from another source, and the birds soon
During the months that the chickens developed beriberi, the feed had been polished rice, and when the birds’ diet was switched back to unpolished rice, the birds recovered in a few days. Eijkman surmised that polished rice lacked a dietary component found in unpolished rice, and that beriberi was caused by depriving the body of this component, which he called “the antiberiberi factor”. Subsequently, Eijkman was able to prove that the disease was not caused by blood contamination, respiratory metabolism, perspiration, or seasonal or temperature variation. He suspected the disease was caused by an unknown bacteria. The Polish researcher Casimir Funk isolated the antiberiberi factor and established that it was an amine. He coined the term ‘vitamin’ for ‘vital amine’. As a result of his discovery, research into deficiency diseases gained momentum. It wasn’t until 1936, however, that the correct chemical structure of the antiberiberi factor was finally revealed. Funk was sure that more than one substance like Vitamin B1 existed, and in his 1912 article for the Journal of State Medicine, he proposed the existence of at least four vitamins: one preventing beriberi (“antiberiberi”); one preventing scurvy (“antiscorbutic”); one preventing pellagra (“antipellagric”); and one preventing rickets (“antirachitic”).

**Rice bran and thiamine**

Rice bran is a tiny covering membrane that entirely encloses brown rice. It comprises several thin layers. On the outside of the kernel is the fused testa-pericarp (seed coat and fruit wall) and immediately below is the aleurone layer, which is rich in fat and protein. This layer plays an important role in the germination of rice. When an intact grain of rice is exposed to a moist environment, the central core of the grain (embryo) absorbs water. As a consequence, the embryo secretes a plant hormone (gibberellin) that diffuses into the aleurone layer. This layer subsequently secretes amylase, which converts the starch in the endosperm (‘the grain’) into sugars that can then be absorbed by the embryo. The endosperm is rich in starch but poor in thiamine and other compounds. The embryo and the bran, on the other hand, are rich in proteins, fats and thiamine. The high oil content of bran makes it subject to rancidification, one of the reasons that it is often separated from the grain before storage or further processing. Bran is often heat-treated to increase its longevity. In white rice the bran and embryo have been removed, as a result of which the rice becomes rancid less quickly but is also deficient in thiamine. When brown rice is steeped in water and partly cooked (parboiled) before preparation, the thiamine in the aleurone layer is able to diffuse into the starchy endosperm. When the rice is then polished, the grain still contains some of the vitamin. This is why beriberi was absent in those regions where the people ate parboiled rice. Parboiling makes it easier to remove the husk but a lot of people don’t like the rather musty taste that this treatment gives the rice. In most cultures this thin membrane is removed without parboiling by mechanical polishing, beating or shaking.
Causes

Thiamine in the human body has a half-life of 18 days and is quickly exhausted, particularly when metabolic demands exceed intake. A biochemical deficiency can become apparent rather quickly, even after just 7 days. The course of the disease is usually somewhat slower. A daily intake of 1 mg of thiamine is sufficient for a moderately active man and 0.8 mg for a moderately active woman. Pregnant and lactating women may need more. FAO and WHO recommend an intake of 0.4 mg per 1,000 kcal for most persons. Deficiency may develop in alcoholics, elderly people, malabsorption, use of diuretics, prolonged administration of antacids, dialysis, folate deficiency, diets with a high content of refined grain products lacking fruits and vegetables and ingestion of thiaminase-containing food. Refugees, victims of famine, prisoners and alcoholics are especially at risk for beriberi.

Because thiamine is involved in carbohydrate metabolism, a person whose main supply of energy comes from carbohydrates is more likely to develop signs of thiamine deficiency if their food intake is decreased. With a deficient diet, clinical complaints often develop in strong young males because they have a high glucose metabolism. Increased thiamine consumption may develop in seriously ill patients, hyperthyroidism, pregnancy, lactation and fever. Chronic malabsorption (chronic diarrhoea) leads to reduced uptake. Clinically particular attention should be paid when people are at risk of deficiency and are temporarily receiving no food (persistent vomiting, hyperemesis gravidarum). Especially when a glucose solution is administered quickly by intravenous injection and the metabolism suddenly has to cope with additional substrate, symptoms of acute deficiency may be induced. In practice such a situation can arise when a confused alcoholic with suspected hypoglycemia is admitted to hospital and a sudden deterioration of the clinical condition is observed after glucose administration.

In infants, refeeding syndrome is a potentially fatal complication of SAM management, especially when the introduction of food is too fast. Rapid initiation of nutritional rehabilitation also increases intracellular thiamine turnover which, on a background of pre-existing low whole body thiamine status, can precipitate the onset of true thiamine deficiency and may contribute to the mortality linked with refeeding syndrome.

Clinical aspects

The energy used by the nervous system is derived entirely from carbohydrate, and a deficiency of thiamine blocks the final utilization of carbohydrate, leading to a shortage of energy and lesions of the nervous tissues and brain. Deficiency causes degeneration of peripheral nerves, the thalamus, mammillary bodies and the cerebellum. The cerebral blood flow is markedly reduced and vascular
resistance is increased. The heart may become dilated, muscle fibers become swollen, fragmented and vacuolized with interstitial spaces dilated by fluid. Vasodilation occurs and can result in oedema in the feet and legs. Arteriovenous shunting of blood increases and eventually high-output heart failure may occur.

Deficiency signs may initially be very limited. Muscular cramps and paraesthesia may develop. Tiredness is already present but is often camouflaged: deficient patients often do normal activities with less movement. Anaesthesia over the shin is one of the first clinical signs. In more severe deficiencies, cardiovascular problems may develop (Wet beriberi). This concerns a high-output heart failure with peripheral pitting oedema, low peripheral resistance, warm extremities, full pulse, “pistol shot” heart tones, swollen neck veins, slight cyanosis and lactate acidosis. Quick deterioration with sudden death may occur. When neurological symptoms are prominent, this is called ‘Dry beriberi’. This term indicates a mixed motor-sensory neuropathy with pain, paraesthesia, hyporeflexia and muscle atrophy. Nocturnal muscular pain in the calves may develop. The symptoms are more pronounced in the legs than in the arms. Frequently the patient is unable to get up from the squatting position without assistance and wrist drop or drop foot can develop. Patients often succumb due to infectious complications (TB, decubitus) when they become bedridden.

Acute Wernicke’s syndrome manifests by horizontal nystagmus, ophthalmoplegia with diplopia, fever (dysfunction of the hypothalamus), ataxia, confusion and coma. Frequently there are autonomous disorders, both sympathetic hyperactivity with tremor and agitation and hypoactivity with hypothermia and low blood pressure. Acute cerebellar ataxia may develop. During alcohol abstinence with simultaneous thiamine deficiency an acute delirium tremens may develop. Retrograde amnesia, confabulation, psychosis and learning difficulties are signs of Korsakoff’s syndrome (psychosis). This develops in 80% of Wernicke patients.

Infantile beriberi is manifested by aphonia, areflexia and heart failure. Breast-fed babies of thiamine-deficient mothers – who often have no overt signs – become restless between 2 and 5 months of age, cry frequently (a loud piercing cry) and often refuse breastfeeding. They soon become debilitated and cry soundlessly. Soshin beriberi, a fulminating form of congestive heart failure with cyanosis and oedema; lactic acidosis is also documented in infants. Administration of thiamine IV results in very rapid recovery, often with noticeable improvement in less than 24 hours. Due to the non-specific presentation, thiamine deficiency is often overlooked or misdiagnosed as typhoid fever, sepsis, malaria, pneumonia or decompensated congenital cardiomyopathy in infants.
Diagnosis and treatment

The diagnosis of thiamine deficiency is initially a clinical one. A practical and easy test to determine the thiamine status does not exist. Since the vitamin is cheap and not toxic if suspicious of deficiency a trial of therapy is reasonable. A high level of clinical suspicion should be demonstrated in the following situations: suspicion of infantile beriberi; unexplained neurological signs, encephalitis, and cardiac failure; early clinical deterioration after initiation of feeds in malnutrition; sepsis (including in SAM); severe burns; major trauma; hypoxia; and unresponsive lactic acidosis. In acute situations a dose of 100 mg thiamine is administered IV. It is best to add 2 ml of a 50% magnesium sulphate solution, since magnesium is a cofactor for transketolase an associated hypomagnesaemia is frequently observed. The clinical response in heart failure is usually very dramatic and fast. Improvement can already be observed just a few hours after administration. The patient is subsequently treated with 20 mg thiamine daily together with a multivitamin and efforts are made to eliminate the cause of the deficiency (diet, including avoidance of thiaminases, treatment of alcoholism, absorption problems, antiemetics, etc.). Central lesions usually do not fully recover. In the case of peripheral neural lesions, the degree of recuperation depends upon the duration and severity of the damage.

Prevention

A balanced diet, sufficiently rich in vitamins, is essential. Food supplements may be given to high-risk groups. An unbalanced diet (e.g. based on polished rice) should be avoided. Lactating mothers in endemic regions should preferably take thiamine.

Thiamine deficiency in alcoholics

Although classical beriberi is uncommon in industrialized countries, thiamine deficiency is by no means a rarity. It is prevalent in the alcoholic population worldwide. Alcoholism is an increasingly prevalent condition, and several clinical features previously believed to be due to chronic alcoholic intoxication are now known to be the result of nutritional deficiencies. The most common of these conditions is probably alcoholic polyneuropathy, which has similarities to neuritic beriberi and is believed to result mainly from thiamine deficiency. Alcoholics who get much of their energy from alcoholic drinks often consume insufficient food and do not get adequate amounts of thiamine and other micronutrients. They may develop a peripheral neuritis, which can influence both the motor and the sensory systems, often affecting the legs more than the arms. The various manifestations include muscle wasting, abnormal reflexes, pain and paresthesia. These symptoms often respond to treatment with thiamine or B-complex vitamins taken orally.
Another condition resulting from thiamine deficiency in alcoholics is Wernicke-Korsakoff syndrome. Wernicke’s disease is characterized by eye signs such as nystagmus (rapid involuntary oscillation of the eyeball), diplopia (double vision arising from unequal action of the eye muscles), paralysis of the external rectus (one of the muscles of the eyeball) and sometimes ophthalmoplegia (paralysis of the muscles of the eye due to lesions in the nuclei of cranial nerve III and VI). It is also characterized by ataxia (loss of coordination of body movements) and mental changes. Korsakoff’s psychosis involves a loss of memory of the immediate past and often elaborate confabulation which tends to conceal the amnesia. Korsakoff syndrome (KS) is a late neuropsychiatric manifestation of Wernicke encephalopathy (WE). They are two different syndromes, each representing a different stage of the disease. Wernicke encephalopathy (WE) is an acute syndrome requiring emergent treatment to prevent death and neurologic morbidity. Korsakoff syndrome (KS) refers to a chronic neurologic condition that usually occurs as a consequence of WE. It is now generally agreed that any distinction between Wernicke’s disease and Korsakoff’s psychosis in the alcoholic patient may be artificial; Korsakoff’s psychosis may be regarded as the psychotic component of Wernicke’s disease. This view is supported by the fact that many patients who appear with ocular palsy, ataxia and confusion, and who survive, later show loss of memory and other signs of Korsakoff’s psychosis. Similarly, psychiatric patients with Korsakoff’s psychosis often show the stigmata of Wernicke’s disease even years after the illness. Pathological evidence also indicates the unity of the two conditions.

That Wernicke-Korsakoff syndrome is caused by thiamine deficiency and not by chronic alcohol intoxication is shown by the fact that the condition responds to thiamine alone, even if the patient continues to consume alcohol. Of overriding importance in this syndrome is the rapid occurrence of irreversible brain damage; early recognition and treatment are therefore vital. A patient suspected of having the syndrome should immediately receive 500 mg of thiamine by injection (500 mg IV 3x/d for 3 days followed by 250 mg IV/IM per day for 4 days), even before a definitive diagnosis is made.

**Prevention**

The prevention of Wernicke-Korsakoff syndrome calls for considerable public health ingenuity. Several possible measures have been suggested:

- the “immunization” of alcoholics with large doses of thiamine at regular intervals (the development of a suitable depot carrier to reduce the frequency of these injections would be very helpful);
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· the fortification of alcoholic beverages with thiamine;

· a provision by public health authorities that thiamine-impregnated snacks be made available on bar counters.

The cost of any of these measures would almost certainly be less than the present enormous expenditure on institutional care of those who have suffered from Wernicke-Korsakoff syndrome.

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Pellagra

Summary

- Disease caused by lack of vitamin PP (niacin) or tryptophan
- High risk if unbalanced maize based diet
- 3 D’s clinical signs: dermatitis, diarrhea and dementia
- Treatment by nicotinamide supplements/vitamin B complex and a balanced diet

Introduction

For many years, chiefly in regions where maize is the staple diet, a condition has been known which was characterized by cutaneous, mucosal and neurological abnormalities. This condition is known as pellagra. The disease derives its name from an old Italian description. It had been established that prisoners on a prolonged diet consisting solely of maize developed a skin problem. The etymology of the word is based on the Italian “pelle” (skin) and “agra” (rough). In the 18th century the inexpensive polenta, based on maize meal, was a staple of many rural regions of Italy. It was initially thought that the disease was caused by a fungal toxin in the food. In 1796, Dr Casper Casal, of Oviedo (Spain), described the disease mal de la rosa. The illustration in his work shows manifest skin lesions of the neck. Since that time, this symptom has been known as Casal’s necklace.

Pellagra, historical note

In the early 20th century, pellagra was a major problem among the poor Southerners of the USA.
The work of the American scientist Joseph Goldberger represented a milestone in the history of epidemiology when he discovered that orphans whose diet consisted mainly of maize with molasses developed pellagra and that others (who had a more varied diet) were not affected by the disease. None of the staff ever contracted the disease (they had the first choice of the food). He injected himself and several volunteers with blood from pellagra patients. Not one of them developed the disease. Even eating faecal matter of the patients (!) was likewise unable to induce the disease in these intrepid volunteers, which was a strong argument against an infectious origin. After milk, eggs and meat were put on the menu of the orphanages, pellagra disappeared. A controlled experiment at a State Prison Farm in Mississippi manifestly demonstrated that pellagra only develops after living on an unbalanced diet. An animal model was developed using dogs that were fed on maize and subsequently developed so-called ‘black-tongue’.

In 1937 Conrad A. Elvehjem an agricultural chemist at the University of Wisconsin, discovered that nicotinic acid cures black tongue. It was discovered that the disease has its origins in a deficiency of a compound present in small quantities in food. The compound was designated as vitamin PP (pellagra preventing factor). Sometimes the term vitamin B3 is used. The identification of pellagra as a deficiency disease was not evident. There were sometimes apparently contradictory data. Early in the 20th century, for instance, pellagra was rife in the maize-eating population of Romania. Paradoxically, however, their maize contained more niacin than the food of the indigent population of India, where pellagra did not occur. The explanation was only discovered later when it became clear that maize contained very little tryptophan and that much of the niacin in maize is present as a bound form called niacytin (which is not absorbed in the intestine). The reason why pellagra did not occur in the indigenous maize-eating population of Central America was found to be based on the fact that they used alkali in the preparation of their maize meal, which released niacin from niacytin. They also had a more varied diet, which included a lot of beans (i.e. another food that contains niacin). It should be noted that white bread contains much less niacin than maize, but the niacin in maize is not fully available because it is in a bound form.

The highest prevalence in recent times has probably been in southern Africa, where conditions for some agricultural and industrial workers until 1994 were not unlike those in the southern United States between 1900 and 1920. A report from South Africa suggested that 50 percent of patients seen at a clinic in the Transvaal had some evidence of pellagra, and that the majority of adults admitted to the mental hospital in Pretoria had the disease. Pellagra regrettably has also been widely reported in refugee camps and in famine situations where maize has been the relief food and relief agencies have given too little attention to providing a balanced diet or adequate micronutrient intakes.
Niacin

Niacin is also known as nicotinic acid, although the latter term is avoided in order not to evoke an association with tobacco and thus make people suspicious. The amide is likewise active (nicotinamide). Niacin is absorbed from food in the stomach and small intestine. A small quantity of niacin is produced endogenously from tryptophan, an essential amino acid. Food that is rich in tryptophan and deficient in niacin will not give rise to clinically manifest deficiency. Alcoholics and people with hyperthyroidism are at higher risk of contracting pellagra. The conversion from tryptophan to niacin is more difficult in people with vitamin B2 (riboflavin) and B6 (pyridoxine) deficiency.

Niacin is required for adequate cellular function and metabolism as an essential component of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). NAD and NADP are the active forms of niacin and are coenzymes for many dehydrogenases that play an important role in glycolysis, protein and amino acid metabolism, pyruvate metabolism, pentose biosynthesis, generation of high-energy phosphate bonds, glycerol metabolism, and fatty acid metabolism. In case of deficiency, all sorts of cell functions become deranged. High energy requirements (brain) or high turnover rate (gut, skin) organs are most susceptible to deficiency.

Aetiology

On average, a person needs approximately 20 mg niacin on a daily basis. Primary pellagra may be caused by niacin and/or tryptophan deficiency in the diet. A generally poor balance of amino acids in the diet could also give rise to pellagra. For instance, pellagra frequently affects people who eat sorghum (millet) as a staple food. This grain crop contains high concentrations of leucine. Although this grain contains adequate tryptophan, excessive concentrations of leucine interfere with tryptophan metabolism and subsequent niacin synthesis. Zein the main protein in maize (= corn) – which is the staple food in many parts of the world- contains very small amounts of tryptophan. Niacin in maize is chemically bound and is not absorbed in the intestine unless the food is treated with alkalis as lime water. An example of the latter is the tortilla. Food products that contain large quantities of niacin are liver, kidney, groundnuts and yeast and, to a lesser extent, wheat and green vegetables. The bioavailability of niacin from meat, milk, beans and eggs is excellent.

Secondary deficiency may develop in persistent chronic diarrhoea with malabsorption, liver cirrhosis and alcoholism and in the event of prolonged parenteral nutrition being given without vitamin supplements. During treatment with isoniazid (INH) the drug is substituted for nicotinamide in the synthesis of NAD. The resulting molecule is inactive. In prolonged treatment with INH (tuberculosis) it
is possible for iatrogenic induced pellagra to be provoked. On top of that, INH tends to bind to vitamin $B_6$ and reduce niacin synthesis, since $B_6$ (pyridoxine) is a required cofactor in the tryptophan-to-niacin reaction. There are also several situations where tryptophan metabolism is disrupted. For instance, pellagra may develop in carcinoid syndrome due to the conversion of tryptophan into serotonin (5-hydroxytryptamine). Beware the cluster abdominal pain, diarrhoea, flushing, variable blood pressure, pulmonary valve stenosis and intermittent wheezing in carcinoid syndrome.

**Clinical aspects**

Clinically, the disease is identified by the so-called classical three Ds: dermatitis, diarrhoea and dementia. Mucositis should also be added to these characteristic symptoms. The symptoms may develop alone or in combination. People suffering from pellagra usually appear poorly nourished with weakness and underweight.

Skin lesions occur symmetrically on areas of the skin exposed to sunlight, such as the face, the back of the hands, the neck, the forearms and exposed portions of the leg. Patients initially present with deepening of the pigmentation. The hyperpigmented areas lose the oily sheen of healthy skin and become dry, scaly and eventually cracked. There is usually a definite line of demarcation between these lesions and the healthy skin, and this line can be felt as the affected area is rough to the touch. The skin condition may remain static, heal or progress. If it progresses, desquamation commonly occurs; there may be deep cracking and fissuring and the skin becomes thick and rough; occasionally the skin may blister. The blisters contain a colourless exudate. In white subjects the skin lesions initially look like the erythema of sunburn. In both black and white patients, the lesions of pellagra produce burning sensations and pain when exposed to the direct rays of the sun, just as sunburn does in a person with pale skin.

The most conspicuous is a sharply defined symmetrical, desquamating rash in the neck (Casal’s necklace) and on the forearms. A butterfly-shaped rash may appear on the face, which must be distinguished from skin abnormalities in SLE patients. Secondary infection may develop, including wound myiasis. Skin lesions may be associated with acute intertrigo with erythema, maceration and abrasion; superinfection may develop in the predilection areas (folds of the groin, genitals). Pellagra sometimes occurs without skin lesions (**pellagra sine pellagra**).
Casal’s necklace
Pellagra dermatitis with hyperpigmentation, drying, cracking and fissuring of the skin

Mucositis develops in the mouth, vagina and urethra. A red tongue and stomatitis are characteristic of acute deficiency. The tip and edges of the tongue are the first to be affected. This is followed by a generalized painful, burning glossitis, with swelling of the tongue and hypersalivation. Lip and tongue ulcers may develop. The area around the parotid duct orifice may become necrotic (the area opposite the molar teeth). Deeper mucosae may be affected, with sore throat and oesophageal damage with dysphagia and abdominal pain. Some patients report loose stools but these complaints are not usually predominant. Caution: chronic malabsorption in itself may induce niacin deficiency. Gastrointestinal hyperemia, ulceration and proctitis may lead to bloody diarrhoea. When angular stomatitis is present this usually indicates an associated riboflavin deficiency (vitamin B2).

Neurological symptoms are due to an organic encephalopathy. Psychosis may occur with sleep and memory disorders, anxiety, agitation, rapid irritability, disorientation, confusion and confabulation (compare this with Wernicke-Korsakoff’s syndrome in thiamine deficiency). Mania, delirium, paranoia
and depression occur in later stages of the disease. At one time many pellagra patients were incarcerated in mental institutions. Muscular rigidity may develop together with a cogwheel phenomenon, hyperreflexia and a positive Babinski’s sign. In the motor cortex, lysis of Betz’s cells and to a lesser extent, lysis of Purkinje’s cells are found. In the spinal cord, the posterior columns are chiefly affected (proprioception tracts; cfr vitamin B12 deficiency). In peripheral nerves there is myelin degeneration, but to what extent this overlaps with the findings in beriberi is unclear (nutritional deficiencies are often mixed). Post-mortem examination may reveal cardiac, adrenal gland, liver and spleen atrophy.

**Dracula and Pellagra**

Dracula was not the first time a vampire appeared in literature, but it’s truly the book that established vampires as a horror staple. The question is, where did the author Bram Stoker gain inspiration for the vampiric flaws and habits of Dracula? The origins may be surprising.

In 1735, pellagra was a newly recognized disease in Europe. In the 18th and 19th centuries, a big change to the European diet occurred – Corn. Corn is a crop that originated in the Americas, domesticated by Native Americans over the course of many generations. Corn could produce more calories per acre than traditional European staple crops, and corn cultivation slowly spread. However, corn is lacking in many vital nutrients. Where corn cultivation went, pellagra was soon to follow.

To societies with little medical knowledge, pellagra was a spooky illness indeed. People with pellagra (called pellagrins) developed a hypersensitivity to sunlight. Avoidance of sunlight is a classic vampire trait and one of the foremost symptoms of pellagra. The tongues of pellagrins became swollen and beefy red. Lips became red and cracked. The reddened mouth and tongue might have led to suspicions of blood drinking. In Dracula, the count himself is described as having very red lips. Mental problems also plagued pellagrins. The lack of niacin led to degradation of the neurons, causing dementia in sufferers. Insomnia is a fairly common symptom of this, leading pellagrins to adopt the vampire-like habit of staying awake into the night. Increased levels of irritability and aggression occurred as well. Did this lead their neighbours to fear attack from red-lipped people in the dead of night?

Death was the end result of pellagra for many unfortunate people in those times. After one person died from pellagra their family members might have appeared to be wasting away due to sustained supernatural attack. In traditional vampire folklore, the vampire returns night after night
to slowly drain its victim of life. However, the real reason for entire families declining was the result of shared poor dietary conditions. If one family member died from pellagra, it was likely that the other family members were sickened as well.

When Bram Stoker researched for Dracula, he delved into the folklore of the communities most affected by pellagra. With this in mind, it doesn’t seem like a coincidence that Stoker’s description of vampires bears resemblance to the symptoms of pellagra. Vampire legends may have arisen as an explanation for a frightening illness that people back then encountered every day. So what’s the best way to defeat a vampire? Maybe it’s time to put away the crosses and holy water and instead feed the vampire some chicken and eggs.

**Diagnosis**

When all symptoms and signs are present; the clinical diagnosis is simple. In most cases there are only a few symptoms present. Especially in non-endemic settings the linkage of the different symptoms can be very challenging contributing to an additional “D”: delay in diagnosis. The diagnosis is confirmed by measuring serum niacin or the urinary excretion of N’-methylNicotinamide (NMN). NMN excretion of <0.8 mg/day suggests niacin deficiency. Patients with pellagra also have increased urinary excretion of coproporphyrins. In clinical practice a successful trial of therapy will confirm the original diagnosis.

**Treatment**

As there is seldom a deficiency of only one vitamin, treatment should include a polyvitamin preparation in addition to a balanced diet. The diet should contain at least 100 g per day of good protein (if possible, meat, fish, milk or eggs; if not, groundnuts, beans or other legumes) and should be high in energy (3 000 to 3 500 kcal per day). Specifically for pellagra, nicotinamide (precursor of niacin) is given as a supplement in a dose 300 mg daily using divided doses. If niacin itself were to be administered, the patient would complain of flushing, paresthesia and a burning sensation. If no oral supplement can be given (severe stomatitis, severe diarrhoea, uncooperative patient), 100 to 250 mg can be injected SC twice daily. In the acute phase the patient should avoid exposure to sunlight. Pellagra is often a very gratifying disease to treat. Violent, almost uncontrollable mental patients can become normal, rational, peaceful human beings within a few days of taking a few tablets of nicotinamide. In persons with severe skin lesions, a sore mouth and severe diarrhoea with frequent watery stools, dramatic improvements occur within 48 hours. The skin redness and pain on exposure to sunlight improves; pain in the mouth abates and eating becomes a pleasure for the patient; and most gratifying for the patient, the intractable diarrhoea disappears. Neurological improvement is
rather slow.

**Prevention**

A balanced diet is essential for prophylaxis and reliance on maize as the sole staple food should be discouraged. In some countries flour is systematically enriched with extra niacin. Niacin tablets should be administered in prisons and institution in areas where pellagra is endemic and to refugees in famine relief.

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**Nicotinic acid and hyperlipidemia**

Nicotinic acid has been in use as a lipid-lowering drug for several decades. It is effective in lowering low-density lipoprotein (LDL)-cholesterol, triglycerides, and lipoprotein (a), and in increasing high-density lipoprotein (HDL)-cholesterol. All these effects are pronounced, and at present greater increase of HDL-cholesterol cannot be obtained by any other drug. Patients with hypertriglyceridaemia/low HDL-cholesterol despite being treated with a statin, are the most suitable candidates for being treated with this drug. However, more recent studies have delivered disappointing results, leading to the conclusion that no further benefit is achieved by adding niacin to existing statin therapy in patients with high cardiovascular risk. Moreover, in these studies, several adverse effects of the treatment were observed and niacin for hyperlipidemias is not recommended anymore.

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**Scurvy**

**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 Laurence 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-gulunolactone 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 synthetize 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: hydroxyllysine 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 Fe$^{2+}$ ion, which is converted during the reaction into 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 endoplasmatic 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. This is disturbed in osteolathyism 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 µmol/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.
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.

Iodine deficiency disorders

Summary

- Iodine deficiency disorders (IDD) are most prevalent in mountainous, alluvial plains and areas far away from oceans due to low iodine intake
- About 2 billion people in the world have low iodine intake
- Cretinism is only the tip of the iceberg of IDD manifestations
- Iodine deficiency is the most frequent cause of avoidable mental retardation
- Goitrogenous factors like thiocyanate and selenium deficiency contribute to goiter formation
- Neurological cretinisme is irreversible
- Myxoedematous cretinisme can be reversed when treated early
- Prevalence of endemic goiter, urinary iodine concentrations, TSH dosage and prevalence of cretinism determine endemcity of IDD
- Salt, water or oil are used for iodine fortification

Introduction

Iodine is an oligo-element that is present in the human body in a very small quantity (15 to 20 mg for adults). Its only known function is as essential element in the production/composition of the thyroid hormones T3 and T4. These hormones have a specific role in the metabolism of all cells of the
organism and in the growth process of most organs, in particular the brain. In a situation of iodine shortage, thyroid hormone synthesis and availability is reduced, with numerous health consequences. In the past the deficiency was called “endemic goitre”, related to the most prominent sign of the deficiency “the goitre”, but the health problems due to iodine deficiency are far more important than goitre alone. It is now replaced by “iodine deficiency disorders” or “IDD”.

Epidemiology

At present there are no exact figures on the prevalence iodine deficiency disorders available: in 1990 it has been estimated that among the 1572 million people in the world exposed to iodine deficiency (28.9 % of the world population), 11.2 million were affected by overt cretinism, the most extreme form of mental retardation due to the deficiency and that another 43 million people were affected by some degree of mental impairment. It therefore appeared that iodine deficiency was the leading cause of preventable mental retardation. A WHO report of 2007 concludes that global progress in controlling iodine deficiency has been made, but still 2 billion people (of which 266 million school-aged children) have insufficient iodine intake. This report warns that more than adequate or even excessive iodine intake in 34 countries.

Although present in 95 countries, the problems due to iodine deficiency occur most in mountainous regions: the mountain chains of the Himalayas, the Andes (where the neurological form is dominant), the mountainous regions of Vietnam, etc. Regions that are situated at a low level, far away from the oceans, like the central part of the African continent (where the myxoedematous form is dominant) and to a lesser degree the European continent, are also affected as well as the high plains of China and Australia. The groups with the highest risk for iodine deficiency are in order of importance the fetus, the newborn, the pregnant and nursing woman, the young child. The prevalence increases with age until puberty, and is higher among women than among men.

The real problem of the iodine deficiency, from a public health point of view, is not goitre itself, but the mental retardation secondary to the thyroid deficiency that is present in fetal life and in the beginning of postnatal life. The socio-economic consequences (high number of disabled, learning difficulties in children, infant death in children with cretinism) are quite important and they are a real obstacle to the development.

Aetiology
1. Low iodine intake

Several arguments confirm that iodine deficiency is the main cause of the observed problems: there is an inverse relation between the prevalence of goitre and the urinary excretion of iodine over 24 hours, used as an indicator of iodine intake. The correction of the iodine deficiency decreases the prevalence of endemic goitre, cretinism and of hypothyroidism.

Low iodine intake can be explained by 2 phenomena:

Geography

A soil that is poor in iodine produces water and foods, poor in iodine. The ocean is the essential reservoir for iodine. The iodized ions are oxidized in elementary iodine on the surface of the water by the sunlight. The iodine is volatile and diffuses in the atmosphere and returns to the soil by rain. So it’s brought along by rivers, running water and melting ice. The poorest soils in iodine are found in mountainous regions: these were covered by the glaciers of the Quaternary and because these melted the underlying iodine was swept away with the erosion. Most mountainous districts in the world have been or are still endemic goitre regions. The disease may be seen throughout the Andes, in the whole sweep of the Himalayas, in the Alps where iodide prophylaxis has not yet reached the entire population, in Greece and the Middle Eastern countries, in many foci in the People’s Republic of China, and in the highlands of New Guinea. The iodine content of the drinking water is low, as is the quantity of iodide excreted each day by residents of these districts.

Non-mountainous regions, far away from the oceans can have poor iodine concentrations in their soils. Plants absorb iodine from the ground, plants are eaten by animals and plants and animals are eaten by humans, so the iodine concentration in food is often a good reflection of the distance from the sea. Examples of iodine deficient low-land regions are the belt extending from the Cameroon grasslands across northern DRC and the Central African Republic to the borders of Uganda and Rwanda, Holland, Central Europe and the interior of Brazil.

Last, a wash-away effect in soils that are regularly flooded can be seen, like the alluvial plains in deltas of big rivers.

Isolation

Food diversity and the mobility of the populations bring along a spontaneous reduction of the prevalence of the endemic goitre. Isolation leads to poor food exchanges and diversification. The phenomenon of opening isolated regions, observed in the last decades, explains as much of the decrease in the prevalence of IDD as the iodination campaigns. It is also the reason for the observed
spontaneous historical reduction of the prevalence of IDD in most countries.

2. Goitrogenous factors

The role of additional factors playing a role the aetiology of IDD has been suspected because goitre exists in regions where the iodine intake is adequate. The additional role of goitrogens from food origin or in the environment has been looked into and has been proved in a number of regions in the world.

Thiocyanates inhibit the iodine pump and increase the renal clearance of iodide. They are derived from manioc, in a variable quantity that depend on the nature of the soil, the type of cassava that is cultivated, the way of preparation and consummation of cassava. DRC, Mozambique and Indonesia are countries where thiocyanate can be found. Thiocyanate is derived from intestinal breakdown linamarin – a cyanogenic glycoside – from cassava and its conversion to thiocyanate by the liver. Thiocyanate is a competitive inhibitor of the Na/I symporter in thyroid follicular cells. A reciprocal relationship exists between iodide and thiocyanate in that increasing amounts of iodide protect increasingly against the thiocyanate derived from the cassava. It now seems well established that cassava may contribute to the severity of endemic goitre and probably the incidence of endemic cretinism, but there are many severe endemics where cassava is not eaten. In these regions, it is possible that other goitrogens in the local food may contribute to the effects of a prevailing iodine deficiency. Thiocyanate may cross the human placenta and affect the thyroid of the fetus.

Thiourreas act on the level of the oxidation and metabolism of iodine in the thyroid.

3. Selenium deficiency

It has been shown that selenium deficiency may have profound effects on thyroid hormone metabolism and possibly also on the thyroid gland itself. In this situation the function of type I deiodinase (a selenoprotein) is impaired. Type I deiodinase plays a major role in T4 deiodination in peripheral tissues like kidney, liver and gut. It has been shown that when in an area of combined iodine and selenium deficiency, only selenium is supplemented, serum T4 decreases. This effect is explained by restoration of type I deiodinase activity leading to normalization of T4 deiodination and conversion to T3, while T4 synthesis remains impaired because of continued iodine deficiency. Selenium deficiency also leads to a reduction of the selenium containing enzyme glutathione peroxidase. Glutathione peroxidase detoxifies H$_2$O$_2$ which is abundantly present in the thyroid gland as a substrate for the thyroperoxidase that catalyzes iodide oxidation and binding to thyroglobulin,
and the oxidative coupling of iodotyrosines into iodothyronines. Reduced detoxification of $\text{H}_2\text{O}_2$ may lead to thyroid cell death. Elevated $\text{H}_2\text{O}_2$ levels in thyrocytes may be more toxic under situations of increased TSH stimulation such as is present in areas with severe iodine deficiency. Finally decreased availability of glutathione peroxidase impairs thyroid hormone synthesis in the thyroid gland, a fact that could also contribute to decreased T4 synthesis. Selenium deficiency certainly plays a role in the aetiology of the type of myxedematous endemic cretinism seen in Central Africa but does not by itself constitute a cause of endemic goitre. Extensive epidemiological data collected in China indicated that all selenium-deficient areas were IDD-endemic areas. However, the reverse is not true: IDD can be very severe in many selenium-rich areas.

**Iodine needs**

The physiologic needs are equal to the hormonal quantity of iodine that is produced every day. This means 50 to 100 µg/day for an adult. The quantity starts increasing in puberty certainly among women. Among the girls of 11 to 12 years a slight increase in the volume of the thyroid body is not rare (transitory hypertrophy).

<table>
<thead>
<tr>
<th>RECOMMENDED INTAKE</th>
<th>ug/day</th>
<th>8 µg/kg</th>
<th>5 µg/100ml of milk</th>
<th>7 µg/100 kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 6 months</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 - 12 months</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - 10 years</td>
<td>60 – 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 11 years</td>
<td>100 - 115</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pregnancy – lactation</td>
<td>125 - 150</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table: Recommended daily intake of iodine (µg/day)

**Pathophysiology**

**Goitre**

Because of a deficiency of iodine, the synthesis of the thyroid hormones is reduced. A low level of thyroxin in the blood stimulates the hypophysis to free TSH. This results in a hyperplasia of the cells of the thyroid gland with increase in thyroid volume (goitre). This in turn makes a higher captivation
of circulating iodine possible. If the normal production of thyroid hormones cannot be maintained, hypothyroidism appears.

However, efficient adaptation to iodine deficiency is possible in the absence of goitre as demonstrated in nongoitrous patients in endemic goitre areas such as New Guinea and the Congo. Moreover, adequate adaptation to iodine deficiency has been demonstrated in areas of severe iodine deficiency in the absence of endemic goitre. This clearly indicates that goitre is not required for achieving efficient adaptation to iodine deficiency. Rather in these conditions, efficient adaptation to iodine deficiency is possible thanks to a high iodide trapping capacity but with only a slight enlargement of the thyroid. At this stage, the characteristic hyperplastic picture includes abundant parenchyma, high follicular epithelium and rare colloid.

On the contrary in large goitres, the major part of the gland is occupied by extremely distended vesicles filled with colloid with a flattened epithelium. The mechanism responsible for the development of colloid goitre is not fully understood but it does not appear to be TSH hyperstimulation. It must be the consequence of an imbalance between thyroglobulin synthesis and hydrolysis, i.e. secretion. In these conditions, iodide is diluted while thyroglobulin is in excess, resulting in a lesser degree of iodization of thyroglobulin and consequently a decrease in iodothyronine synthesis and secretion. Hydrolysis of large amounts of poorly iodinated thyroglobulin will result in an important leak of iodide by the thyroid and enhanced urinary loss of iodide, further aggravating the state of iodine deficiency. Therefore, large colloid goitres in endemic iodine deficiency represent maladaptation instead of adaptation to iodine deficiency because they may produce a vicious cycle of iodine loss and defective thyroid hormones synthesis.

**Iodine deficiency in the fetus**

The fetus and the newborn are more sensitive than the adult to the effects of low levels of circulation thyroid hormone seen in iodine deficiency or goitrogenous substances. There is an immaturity of the adaptation mechanisms and iodine reserves are small. The period of growth, pregnancy and lactation increases the needs and make the individual more vulnerable.

The human brain develops during its fetal life until the end of the third life-year. Consequently an iodine and/or thyroid hormone deficiency during this critical period of life causes irreversible changes in the development of the brain. Iodine deficiency in the fetus is the result of iodine deficiency in the mother. The consequence of iodine deficiency during pregnancy is impaired synthesis of thyroid hormones by the mother and the fetus. An insufficient supply of thyroid hormones to the developing brain may result in mental retardation.
The physiologic role of thyroid hormones can be defined as to insure the timed coordination of different developmental events through specific effects on the rate of cell differentiation and gene expression. Thyroid hormone action is exerted through the binding of T3 to nuclear receptors which regulate the expression of specific genes in different brain regions following a precise developing schedule during fetal and early postnatal life. The T3 which is bound to the nuclear receptors is primary dependent on its local intracellular production from T4 via type II deiodinase and not from circulating T3.

Figure: Ontogenesis of thyroid function and regulation in humans during fetal and early postnatal life
Brain growth is characterized by two periods of maximal growth velocity. The first one occurs during the first and second trimesters between the third and the fifth months of gestation. This phase corresponds to neuronal multiplication, migration and organization. The second phase takes place from the third trimester onwards up to the second and third years postnatally. It corresponds to glial cell multiplication, migration and myelinization. The first phase occurs before fetal thyroid has reached its functional capacity. It is now largely agreed that during this phase, the supply of thyroid hormones to the growing fetus is almost exclusively of maternal origin while during the second phase, the supply of thyroid hormones to the fetus is essentially of fetal origin. Thyroid hormones are transferred from mother to fetus both before and probably after the onset of fetal thyroid function, contrasting with the previous dogma that this transfer is minimal or does not exist. Nuclear T3 receptors and the amount of T3 bound to these receptors increase about six to tenfold between 10 and 16 weeks, also before the secretion of hormones by the fetal thyroid. This transfer is decreasing but persists during later gestation. Up to 30 % of serum T4 in cord blood at birth could be of maternal origin.

Clinical aspects

The term Iodine Deficiency Disorders (IDD) refers to all the ill-effects of iodine deficiency in a population that can be prevented by insuring that the population has an adequate intake of iodine. These effects are listed in in the table below.

<table>
<thead>
<tr>
<th>Fetus Abortions</th>
<th>Stillbirths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td></td>
<td>Increased perinatal mortality</td>
</tr>
<tr>
<td></td>
<td>Endemic cretinism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonate Neonatal goitre</th>
<th>Neonatal hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endemic mental retardation</td>
</tr>
<tr>
<td></td>
<td>Increased susceptibility of the thyroid gland to nuclear radiation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Child and goitre</th>
<th>Adolescent (subclinical) hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Impaired mental function</td>
</tr>
<tr>
<td></td>
<td>Retarded physical development</td>
</tr>
<tr>
<td></td>
<td>Increased susceptibility of the thyroid gland to nuclear radiation</td>
</tr>
</tbody>
</table>
Adult goitre with its complications

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired mental function</td>
</tr>
<tr>
<td>Spontaneous hyperthyroidism in the elderly</td>
</tr>
<tr>
<td>Iodine-induced hyperthyroidism</td>
</tr>
<tr>
<td>Increased susceptibility of the thyroid gland to nuclear radiation</td>
</tr>
</tbody>
</table>

Table: The Spectrum of Iodine Deficiency Disorders, IDD, Adapted from Hetzel, Laurberg et al.; Stanbury et al.

**Goitre**

Goitre is an increase in thyroid volume of four to five times that can cause aesthetic problems or compression of the oesophagus and trachea. Goitre can be associated with hypothyroidism, but also Iod-Basedow (not to be confused with Basedow’s disease which is the same as Graves’ disease) hyperthyroidism can occur in a patient with an endemic goitre due to iodine deficiency relocates to an iodine-abundant geographical area. Cancer is a rare complication of goitre.

**Cretinism**

Cretinism exists in two extreme forms, but most presentations are intermediate forms. Neurological cretinism is be secondary to a state of maternal and fetal hypothyroidism supervening in the beginning of fetal life. The child is euthyroid but presents with spastic diplegia (symmetrical paralysis), deaf-muteness, strabismus and serious mental retardation. This condition is irreversible. Myxedematous cretinism is the long-term consequence of a permanent, earlier unknown hypothyroidism; it begins during the fetal or neonatal period if mothers are deprived of iodine during the later process of pregnancy. Myxedematous cretinism has a picture of hypothyroidism with important stature and variable mental retardation. This condition can still respond to thyroid hormone replacement therapy and early detection and treatment is crucial to safeguard the baby’s prognosis. The mental deficiency is the iceberg of which cretinism is only the top. Retardation of intellectual development was noted in up to 5% of the total population in an endemic zone. This makes iodine deficiency the most frequent cause of avoidable mental retardation. These people often have a\Clinically and biologically euthyroid aspect since the retardation is a\Consequence of a transient hypothyroidism during the critical phase of the cerebral development which resolved spontaneously.
Iodine deficiency in the neonate

Miscarriages are more frequent in iodine deficient regions. An increased perinatal mortality due to iodine deficiency has been shown in DRC from the results of a controlled trial of iodized oil injections alternating with a control injection given in the latter half of pregnancy. There was a substantial fall in infant mortality with improved birth weight following the iodized oil injection. Low birth weight of any cause is generally associated with a higher rate of congenital anomalies and higher risk of death throughout childhood. Apart from mortality the importance of the state of thyroid function in the neonate relates to the fact that the brain of the human infant at birth has only reached about one third of its full size and continues to grow rapidly until the end of the second year. The frequency distribution of IQ in apparently normal children in such conditions is shifted towards low values as compared to matched controls who were not exposed to iodine deficiency during the critical period of brain development because of correction of the deficiency in the mothers before or during early gestation. More globally, in a meta-analysis of studies on neuromotor and cognitive functions in conditions of moderate to severe iodine deficiency, iodine deficiency resulted in a loss of 13.5 IQ points at the level of the global population.

Iodine deficiency in the adult

A high degree of apathy has been noted in populations living in severely iodine deficient areas. This may even affect domestic animals such as dogs. It is apparent that reduced mental function due to cerebral hypothyroidism is widely prevalent in iodine deficient communities with effects on their capacity for initiative and decision making. This indicates that iodine deficiency can be a major block to the human and social development of communities living in an iodine deficient environment and constitutes a major teratogen at the community level. In addition to this impact to brain and neurointellectual development, iodine deficiency at any period in life, including during adulthood, can induce the development of goitre with mechanical complications and/or thyroid insufficiency. Another consequence of longstanding iodine deficiency in the adult but also in children is the development of hyperthyroidism, especially in multinodular goitres with autonomous nodules. It is now accepted that hyperthyroidism is one of the disorders induced by iodine deficiency.

Treatment

The prolonged administration of iodide or of T4 reduces the volume of goitre. Surgical treatment is rarely indicated. Unfortunately, these individual treatments are frequently impossible to apply on the whole population because of the magnitude of the problem and of the lack of medical infrastructure. The logical medical attitude is to focus all efforts on the prevention. The principle is simple: the
prevention of iodine deficiency = a regular and stable iodine administration.

**Prevention**

**Diagnosis of endemicity**

Several factors can be taken into consideration when determining and quantifying the endemicity of the problems related to iodine deficiency:

1. **Prevalence of endemic goitre**

   Its determination is based on the percentage of people with a goitre in a specific population. During field inquiries, the best method consists in examining the whole population of the region. In case of difficulties, it is allowed to limit these inquiries to children from 6 to 12 years. By palpation, a thyroid is considered goitrous when each lateral lobe has a volume greater than the terminal phalanx of the thumbs of the subject being examined. However, palpation of goitre in areas of mild iodine deficiency has poor sensitivity and specificity. In such areas, measurement of thyroid volume by ultrasound is preferable.

   **Classification**
<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No palpable or visible goitre.</td>
</tr>
<tr>
<td>Grade 1</td>
<td>A goitre that is palpable but not visible when the neck is in the normal position (i.e. the thyroid is not visibly enlarged). Thyroid nodules in a thyroid which is otherwise not enlarged fall into this category.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>A swelling in the neck that is visible when the neck is in a normal position and is consistent with an enlarged thyroid when the neck is palpated.</td>
</tr>
</tbody>
</table>

   Revised classification of goitre according to WHO/UNICEF/ICCIDD

2. **Dosage of urinary iodine**

   It is difficult to measure precisely the food iodine content. When in nutritional balance, the intake of iodine equals the urinary excretion of iodine. Urinary iodine excretion is a good marker of the very recent dietary intake of iodine and therefore is the index of choice for evaluating the degree of iodine
deficiency and of its correction. Iodine concentrations in casual urine specimens of children or adults provide an adequate assessment of a population iodine nutrition, provided a sufficient number of specimens is collected. Twenty four hours samples are difficult to obtain and are not necessary. Relating urinary iodine to creatinine is expensive and unnecessary. However the median urinary iodine is often misinterpreted. Individual iodine intakes and therefore a spot urinary iodine concentration are highly variable from day-to-day, and a common mistake is to assume that all subjects with a spot UI <100 μg/L are iodine deficient.

For epidemiological studies, the population distribution of urinary iodine is required rather than individual levels. Because the frequency distribution of urinary iodine is usually skewed towards elevated values, the median is considered instead of the mean as indicating the status of iodine nutrition.

<table>
<thead>
<tr>
<th>Median urinary iodine (μg/l)</th>
<th>Iodine intake</th>
<th>Iodine nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>Insufficient</td>
<td>Severe iodine deficiency</td>
</tr>
<tr>
<td>20-49</td>
<td>Insufficient</td>
<td>Moderate iodine deficiency</td>
</tr>
<tr>
<td>50-99</td>
<td>Insufficient</td>
<td>Mild iodine deficiency</td>
</tr>
<tr>
<td>100-199</td>
<td>Adequate</td>
<td>Optimal</td>
</tr>
<tr>
<td>200-299</td>
<td>More than adequate</td>
<td>Risk of iodine-induced hyperthyroidism following introduction of iodized salt in susceptible groups</td>
</tr>
<tr>
<td>&gt; 300</td>
<td>Excessive</td>
<td>Risk of adverse health consequences: iodine-induced hyperthyroidism, auto-immune thyroid diseases</td>
</tr>
</tbody>
</table>

Table: Epidemiological criteria for assessing iodine nutrition based on median urinary iodine concentrations in school-aged children

3. TSH dosage (thyroid stimulation hormone)

TSH level in the serum are elevated in cases of iodine deficiency. However difficulties are often encountered in obtaining venous blood samples in populations due to apprehension about blood collection and operational difficulties. Therefore these measurements are not routinely recommended in routine assessment and monitoring. In spite of the difficulties in blood collection, it has to be kept in
mind that the final objective of correction of iodine deficiency is not only to increase the access of the population to iodized salt and to normalize the urinary iodine concentration but mostly to normalize thyroid function tests. Elevated serum TSH, unless exceptional pathological situations, indicates an insufficiency in the saturation of the T3 receptor in the brain, whatever the level of serum thyroid hormones. Therefore, elevated serum TSH constitutes an indicator of the potential risk of iodine deficiency on brain development. Serum T4 and T3 are less specific indicators of iodine deficiency because they are modified usually only in conditions of at least moderate iodine deficiency. Moreover these levels are largely influenced by age and sex. Elevated serum T3 in spite of low serum T4 is considered as a protective mechanism to most parts of the body, except the brain, where T3 is produced locally and not derived from the circulating T3.

The use of whole blood from finger pricks spotted on filter paper cards can be used at least for the measurement of serum TSH as indicators of thyroid hyperstimulation. A frequency distribution of serum TSH in neonates shifted to high values is a particularly sensitive index of the risk of potential damage of the developing brain due to iodine deficiency. In normal conditions, less than 3 % of neonatal TSH are above the critical threshold of 5 mU/L whole blood. However because of technical and financial limitations the use of this variable has been recommended only in countries and areas where a program of systematic neonatal hypothyroid screening is already implemented.

4. Prevalence of cretinism

The study of the prevalence of cretinism can be completed by a study of the light forms (deaf muteness) when necessary. The prevalence of the cretinism can be up to 10 % of the whole population in certain regions.

Criteria on the intervention level

An operational definition of endemicity based on the experiences and a consensus between the experts has been refined and allows identification of the need for interventions in a formal manner. A zone is arbitrarily defined as affected by endemic goitre when more than 10 % of the children between 6 to 12 years suffer from goitre.

<table>
<thead>
<tr>
<th>Iodine Deficiency</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
</tr>
</thead>
</table>
Number of cases of goitre among school children

<table>
<thead>
<tr>
<th>Visible goitre</th>
<th>Total goitre</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 %</td>
<td>20-49 %</td>
</tr>
<tr>
<td>&gt; 10 %</td>
<td>10-19 %</td>
</tr>
<tr>
<td>5-9 %</td>
<td>1-5 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinary iodine (median, µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevalence of cretinism</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 %</td>
</tr>
</tbody>
</table>

Indicators of iodine status at population level

In case of suspicion of endemic disease a fast inquiry on the prevalence among school children from 6 to 12 years old will give a first approximation of the magnitude of the problem. The consultation of a specialist is recommended for the following stages which will consist in refining the endemicty diagnosis and in deciding if an intervention is a good idea and what sort of intervention is needed.

**Intervention strategies**

1. Iodized salt

The iodination of salt is one of the most simple, least expensive and most efficient measures, in nutrition as well as in public health. It was used for the first time in 1917 in the United States. Since then its efficiency has been recognized in several countries: Guatemala, Argentina, Brazil, and Switzerland. It is a simple technology with an ignorable risk for toxicity. Iodine is added to the salt under the form of potassium iodide or, in humid tropical regions, potassium iodate because of its increased stability. The proposed concentration varies between $1/25,000$ and $1/100,000$ in function of certain criteria like the consummation of salt by the population and the severity of the deficiency. The cost averages 0.20 US$/person/year and the efficiency of the program depends on:

- the control and monitoring of the iodine quantity
- the resistance of the producers of salt
- the geographical distribution of the production sites
- the distribution in the risk zones
- the accessibility of the iodized salt and the by-passes

Iodized salt is considered as the most appropriate measure for iodine supplementation. The advantage of supplementing with iodized salt is that it is used by all sections of a community
irrespective of social and economic status. It is consumed as a condiment at roughly the same level throughout the year. Its production is often confined to a few centres which means that processing can occur on a larger scale and with better controlled conditions. However this is often not the case in developing countries.

The packaging of the iodized salt is very important. Jute bags have been used extensively but in humid conditions salt absorbs moisture. The iodate dissolves and will drop out of the bag if it is porous with a heavy loss. This has been found to reach 75% over a period of nine months. To avoid this waterproofing is required, achieved by a polythene lining inside the jute bag or else a plastic bag. The additional cost of a plastic bag (50-80% more) would be justified by reduced losses and their resale value.

2. Iodination of water

Water is really a good means of transportation with a large distribution and it is easy to adjust. There are no negative effects and costs are moderate. It can be done by iodizing the water distribution system or wells with slow release capsules. As salt, it is a daily necessity and thus the iodization will reach the most vulnerable groups.

3. Iodized oil

An iodized oil supplementation program is necessary when other methods have been found ineffective or can be considered to be inapplicable. Iodized oil can be regarded as an emergency measure for the control of severe IDD until an effective iodinated salt program can be introduced. Spectacular and rapid effects of iodized oil in reducing goitre can be expected. Iodized oil can be given in injections (Lipiodol®) or orally. Protection of an oral dose is around one year, that of an injection four to five years.

The possibility of linking up an iodized oil program with childhood vaccination and antenatal care has been considered in the past. Diversification and modification of food habits in endemic zones is another preventive measure, but is challenging as it often requires importation of sea food to remote areas.

Monitoring

In the countries that have begun iodized salt programs, sustainability is a major focus. These
programs are fragile and require a long-term commitment from governments. In several countries where iodine deficiency had been eliminated, salt iodization programs fell apart and iodine deficiency recurred.

The indicators used in monitoring and evaluating IDD control programs include:

1) Indicators to monitor and evaluate the salt iodization process (Process indicators)
2) Indicators to monitor the impact of salt iodization on the target populations (Impact indicators).

The impact indicators include in order of priority the determinations of urinary iodine, of the prevalence of goitre and of the serum levels of TSH and thyroid hormones. It is now considered that iodine deficiency has been eliminated from one particular country when the access to iodized salt at household level is at least 90 %, together with a median urinary iodine of at least 100 μg/L and with less than 20 % of the samples below 50 μg/L.

**Side effects of iodine supplementation**

The effect of iodine on the thyroid gland is complex with a U shaped relation between iodine intake and risk of thyroid diseases as both low and high iodine intake are associated with an increased risk. It is stated that normal adults can tolerate up to about 1000 μg iodine/day without any side effects. However this upper limit of normal is much lower in a population which was exposed to iodine deficiency in the past. The optimal level of iodine intake to prevent any thyroid disease may be a relatively narrow range around the recommended daily intake at 150 μg.

The possible side effects of iodine excess are as follows:

1. Iodide goitre and iodine-induced hypothyroidism

When the iodine intake is chronically high, as for example in coastal areas of Japan and China due to the chronic intake of seaweeds rich in iodine such as laminaria or in Eastern China because of the high iodine content of the drinking water from shallow wells, the prevalence of thyroid enlargement and goitre is high as compared to normal populations and the prevalence of subclinical hypothyroidism is elevated. The mechanisms behind this impairment of thyroid function are probably both iodine enhancement of thyroid autoimmunity and reversible inhibition of thyroid function by excess iodine (Wolff-Chaikoff effect) in susceptible subjects. However, this type of thyroid failure has not been observed after correction of iodine deficiency, including in neonates after the administration of huge doses of iodized oil to their mothers during pregnancy.
2. Iodine-induced hyperthyroidism

Iodine-induced hyperthyroidism (IIH) is the main complication of iodine prophylaxis. It has been reported in almost all iodine supplementation programs. Iodine deficiency increases thyrocytes proliferation and with the development of multifocal autonomous growth. These nodules become autonomous and can result in hyperthyroidism after iodine supplementation. A multicentre study conducted in seven African countries, including Zimbabwe and Congo showed that the occurrence of IIH in the last two countries was due to the sudden introduction of poorly monitored and excessively iodized salt in populations which had been severely iodine deficient for very long periods in the past. The conclusion of the multicentre study was that the risk of IIH is related to a rapid increment of iodine intake resulting in a state of acute iodine overload.

It thus appears that IIH is one of the Iodine Deficiency Disorders. It appears to be largely unavoidable in the early phase of iodine supplementation. It affects principally the elderly with long lasting autonomous nodules. Its incidence reverts to normal or even below normal after one to ten years of iodine supplementation.

3. Iodine-induced thyroiditis

Another possibility is the aggravation or even the induction of autoimmune thyroiditis by iodine supplementation. However, no large surveys have been performed which have analyzed the impact of large scale programs of iodine supplementation on the occurrence of clinically significant iodine-induced thyroiditis with public health consequences on thyroid function.

4. Thyroid cancer

Although in animal studies the chronic stimulation of the thyroid by TSH is known to produce thyroid neoplasms, in humans correction of iodine deficiency rather decreases the risk of and morbidity from thyroid cancer.
Summary

- Acute hypertonic paraparesis
- Cyanide intoxication caused by badly processed bitter cassava (manioc)
- Other factors such as deficiency of sulphur-containing amino acids seem to be important

Definition

Konzo is characterised by an epidemic acute isolated and symmetrical hypertonic paraparesis, which is permanent but non-progressive. The condition is to date only known in poor regions of Africa. In the Yaka valley konzo means “bound legs”, a good description of the hypertonic gait. This is the name used in Congo and is now the official term for this motor neuron disorder.

Epidemiology

Two large epidemics have been reported, each of more than 1000 cases. The first was in the Bandundu region in Congo (1936-37) and the second in the Nampulla province of Mozambique (1981). Outbreaks that are related to households living in absolute poverty that have sustained themselves for weeks or months on insufficiently processed bitter cassava, have been reported from 6 countries: Congo (esp Bandundu region), Mozambique, Tanzania, the Central African Republic, Cameroon and Angola. The total number of reported cases up to 2009 was 6788, but most cases are never reported and there are estimates of 100,000 cases in DRC alone. The majority of cases of konzo occur in the dry season, chiefly during a long drought. Sporadic cases of konzo also occur. Children who are being breastfed are not affected. Familial clustering is common.

Aetiology

The aetiology of konzo has not yet been fully clarified. At present a toxic/nutritional aetiology is assumed. There is an epidemiological connection between konzo and eating bitter cassava. Nevertheless, konzo only occurs in 1% of the cassava consuming population. Consumption of bitter cassava is a precondition, but not in itself sufficient to induce konzo. Cassava contains very little sulfur and shortage of sulfur-containing amino acids are probably contributory, since these are essential for the detoxification in the body of cyanide to thiocyanate, which is removed in the urine. People of the same ethnic group living only 5 km away from those with konzo might have a near zero konzo prevalence which is related to different protein intake through fish or bushmeat. It is possible that as yet unidentified components also play a role. Due to its clinical similarity to neurolathyrism, a search for the neurotoxin beta-ODAP was performed but turned up negative. Epidemics coincide with
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periods of food shortage, drought, intense trading in cassava and war. These are circumstances in which people may be inclined to shorten the long preparation which bitter cassava requires. If shortcuts are taken to process the cassava quickly, large amounts of cyanogens may remain in the food. The disorder is regarded as a form of cyanide intoxication, although the final word on this has not yet been spoken.

Cassava

Cassava originated in South America and was first cultivated by the Maya in Yucatán. It was introduced in Africa by Portuguese traders from Brazil in the 16th Century and around the same era it arrived in Asia with Portuguese and Spanish ships. There are various species, all belonging to the Euphorbiaceae: *Manihot esculenta*, *M. aipi* and *M. utilissima*. Over the last 400 years, the plant has become a staple for millions of Africans, especially those in areas with marginal land where few other crops survive. Cassava is known by several names in tropical and subtropical countries: manioc, yuca, mandioca, Brazilian arrowroot. It is named tapioca when it is dried to a powdery extract. Food items such as the gelatinous porridge “fufu” in West- and Central Africa and the bammy of Jamaica come from cassava. Cassava is a woody shrub and is extensively cultivated as an annual crop for its edible starchy tuberous root, a major source of carbohydrates. The young leaves and shoots may be eaten as vegetables (“saka saka”). Cassava is the third-largest source of food carbohydrates in the tropics, after rice and maize. It is a major staple food in the developing world, providing a basic diet for over half a billion people. It is very drought-tolerant and grows on marginal soils where other crops do not grow well. It is usually harvested after 18 months. Cassava roots are poor in protein, but the leaves are a good source of protein rich in lysine. The cassava roots, when they are still attached to the stalk, remain good for many months if stored under the earth. Once harvested deterioration begins quite quickly. There is an unwanted conversion of starch to sugar and a number of enzymatic reactions occur which cause discoloration of the product and reduces its value. Bacterial and fungal deterioration also occur. Drying the roots to a moisture content of less than 14% prolongs their storage life considerably.

Apart from its nutritional value, cassava has several other uses: alcoholic beverages made from cassava have distinct local names (cauim and tiquira (Brazil), kasiri (Guyana, Suriname), impala (Mozambique), masato (Peruvian Amazonia chicha), parakari or kari (Guyana), nihamanchi (South America) also known as nijimanche (Ecuador and Peru), ó döi (chicha de yuca, Ngābe-Bugle, Panama), sakurá (Brazil, Suriname), tarul ko jaarh (Darjeeling, Sikkim, India)); ethanol biofuel made from cassava is increasingly used in China; cassava serves as a good roughage source for ruminants such as cattle and manioc starch diluted in water can be sprayed over clothing before
Ironing to stiffen collars. It was claimed that cassava has anti-cancer activity but a report from the American Cancer Society states that “there is no convincing scientific evidence that cassava or tapioca is effective in preventing or treating cancer”. Nigeria is the world’s largest producer of cassava producing 57 million tons or 21% of the world total, while Thailand is the largest exporter of dried cassava.

There are “sweet” and “bitter” varieties, indicating the absence or presence of toxic cyanogenic glucoside levels, respectively. In particular the bitter form survives well under dry conditions. Bitter cassava produces up to 1 g/kg of cyanide, especially during prolonged dry seasons. This is 50 times more than the sweet variety. The more toxic varieties of cassava are a fall-back resource (a “food security crop”) in times of famine or food insecurity in some places. Farmers often prefer the bitter varieties because they deter pests and animals. If large amounts of bitter cassava are eaten for long periods, without special precautionary measures being taken to remove the toxin from the plant, and if there is a deficiency in sulphur-containing amino acids Konzo results.

**Pathophysiology**

The capacity to produce toxic hydrogen cyanide is present in more than 2000 plant species, classified into over 100 plant families. In all cases the HCN is not stored as such in the cells. The plant produces complex molecules, generally glucosides (e.g. amygdalin) but also some lipids. From these, HCN can enzymatically be released. The enzyme that accelerates this reaction is physically separated from the cyanogenic substance. If the plant is crushed and its structural integrity is threatened, the enzyme comes into contact with the cyanogenic substance and the reaction can then take place. It can be assumed that the cyanide is intended to protect the plant from damage.

In cassava, above mentioned process is mirrored as follows. The bitter varieties contain large amounts of the two cyanogenic glucosides linamarin and lotaustralin, in a ratio of 10 to 1. Linamarin is found in vacuoles in the cytoplasm. The concentrations are highest in the peel. Linamarase, the enzyme which breaks down linamarin, is found in the cell wall. When the cells burst (accidental crushing of the plant, being eaten by insects or during processing), the linamarin comes into contact with linamarase. This enzyme splits linamarin into glucose and acetone cyanohydrin. The latter spontaneously releases acetone and HCN. This reaction may be accelerated by the cassava enzyme hydroxynitril lyase. Once HCN has been produced, it spreads in the air as gas (boiling point of HCN =25.7°C).

Cyanides are rapidly acting toxic substances. Cyandide (CN⁻) inhibits cellular respiration by binding to
the trivalent iron (Fe$^{3+}$) of cytochrome oxidase, a component of the mitochondrial electron transport chain. This impairs the energy-generating function of the mitochondria, leading to cell death.

Cyanide (CN$^-$) is normally converted in humans to the less toxic thiocyanate (SCN$^-$) by the enzyme rhodanase (also written as rhodanese). This is a mitochondrial enzyme which is widely present throughout the human body, with the highest concentrations in the liver and kidneys. Thiocyanate is the chief metabolite of cyanide. Thiocyanate itself has a goitrogenic effect if there is a shortage of iodine in the diet. The body uses sulphur-containing amino acids to render cyanide harmless. If the diet is deficient in sulphur, cyanide will be converted to cyanate (OCN$^-$), which induces neurogenerative disease in both animals and humans. The cells which are most affected are Betz’ cells in the motor cortex.

**Clinical aspects**

Konzo begins abruptly, without prodromal signs. In 90% of cases the onset of symptoms takes less than one day. The initial symptoms are described as tremor, cramps, a heavy feeling and/or weakness in the legs, a tendency to fall down and difficulty remaining upright. There is a visible hypertonic gait when walking or running. Occasionally there will be lower back pain, blurred vision, speech difficulties and/or paraesthesia of the legs, but they disappear within a month. During the first two days the majority of patients have general muscular weakness and are confined to bed. Hypertonicity is present from day one. Flaccid paralysis of the limbs does not occur. Since this is an upper motor neuron disorder, very brisk reflexes are found in the legs and Babinski’s sign is present. Pronounced clonus occurs, or may be triggered by physical examination, e.g. dorsiflexion at the ankle joint. Later there is a slight partial improvement. Finally the affected person develops a stable hypertonic paraparesis, which persists for the remainder of life, or might improve a little. After onset the neurological signs remain constant or improve minimally if no further cyanide is ingested, unlike for example HTLV-1 infection in which further deterioration takes place. Some sufferers will later have a second attack with deterioration of their condition, possibly with dysarthria, abnormalities of eye movement, hypertonicity of the arms.
Differential diagnosis

Lathyrisim is a neurological disease cause by eating large quantities of the Lahyrus grain that has high concentrations of the neurotoxin β-oxalyl-L-α,β-diaminopropionic acid (ODAP). It causes paralysis due to upper motor neuron damage. It is mainly seen in Bangladesh, India, Nepal and Ethiopia. Tropical spastic paraparesis has symptoms similar to konzo, but the onset is much slower. Polio can be easily distinguished as it provokes an asymmetrical flaccid paralysis.

Chronic, low-level cyanide exposure can lead to the tropical ataxic neuropathy (TAN) that manifests with polyneuropathy, ataxic gait, optic atrophy and sensory deafness. It was first described by Osuntokun among the Ijebu speaking Yorubas in south western Nigeria in 1968. Till today TAN remains an enigmatic disease with no effective treatment. The exact pathogenesis remains unresolved, and several factors have been proposed including malnutrition, vitamin B deficiencies,
malabsorption, poor protein consumption, chronic cyanide and nitrile toxicity, with a strong geospatial endemic prevalence in areas of cassava cultivation.

Motor neuron disease

The term “motor neuron disease” includes disorders in which (1) both the upper and the lower motor neurons are affected (amyotrophic lateral sclerosis), (2) disorders in which only the lower motor neurons are abnormal (spinal muscular atrophies, post-poliomyelitis, Guillain-Barré syndrome, botulism, trauma) and (3) disorders of exclusively the upper motor neurons (neurolathyrism, konzo, hereditary spastic paraplegia, primary lateral sclerosis, stroke, multiple sclerosis, cerebral palsy, trauma).

Symptoms of upper motor neuron disease (= lesion above the anterior horn cell of the spinal cord or the motor nuclei of cranial nerves): muscle weakness, spasticity, clasp-knife response, Babinski sign present, increased deep tendon reflexes
Symptoms of lower motor neuron diseases (= lesion in nerves distal from the anterior horn of the spinal cord or lesion in fibres from the cranial motor nuclei to the muscles): muscle paresis or paralysis, fasciculations, hypotonia, hyporeflexia, muscle wasting

Diagnosis

The following criteria are used for the diagnosis of konzo:

1. A visible symmetric hypertonic gait when walking or running
2. The onset of the disease takes less than one week and then remains stable
3. Bilateral brisk knee and Achilles tendon reflexes without signs of vertebral lesions
4. Eating bitter cassava and no consumption of grass peas (Lathyrus sativus)

Urinary concentrations of thiocyanate and linamarin are elevated. The patient is HTLV-1 negative.

Treatment

There is no known etiological treatment for konzo. Treatment with sodium thiosulphate (Na$_2$S$_2$O$_3$), a cyanide antidote, gave disappointing results. A good and varied diet, high dose multivitamins and physical rehabilitation with walking aids are advised. Since the sufferers have no cognitive defects, affected children should be encouraged to continue their education. Some children have been
operated with an elongation of the Achilles tendon which improved the position of the foot but the long term outcome remains uncertain.

**Prevention**

Konzo is not a large public health problem when Africa is regarded as a whole. It is, however, a real problem in the communities affected and of course for the individual patient. The message should be that (1) konzo is not infectious in order to avoid sufferers becoming socially isolated, (2) cassava should be processed correctly without missing out any steps (shortcuts in processing are to be avoided), (3) a varied diet is important. Including maize (corn) flour when making porridge, or including other sulphur-containing food product, such as onions in the diet, is advised; but food habits take a long time to change. The tubers can be made safe by correct processing. As a first step the cells should be burst in order to bring the linamarin into contact with the endogenous glucosidase. In a second step (drying or heating) cyanohydrin is converted to hydrogen cyanide which then evaporates (this is faster at a higher temperature). One of the following precautionary measures should be taken when preparing cassava:

- Fermenting by immersion in water, followed by drying in the sun or cooking, (sufficient time necessary, usually 3 days or longer if the water is cold)
- Grating and fermenting of fresh pulp followed by drying with heat (3 days needed).
- Direct drying of the roots in the sun (less effective)

**Snakes**

**Summary**

- Not all snakes are venomous
- Often dry bites by venomous snakes
- Vipers: primarily haemorrhages and necrosis
- Elapids: primarily paralysis and necrosis.
- No arterial tourniquet.
- Pressure-immobilisation technique during transport (neurotoxic snakes)
- Antivenom if symptoms of envenomation
- Neostigmine + Atropine if paralysis
• Potential side effects of antivenom (anaphylaxis, serum sickness)

**Description**

There are around 2700 snake species, including around 375 venomous snakes with medical relevance. Of the latter, around 200 are potentially lethal. The biotopes vary greatly: from the arctic circle to the equator, and from sea level to 5000 m in elevation. Venomous snakes are not found in Chile, Madagascar, New Zealand, Hawaii and New Caledonia. In Belgium there are a very small number of indigenous vipers (*Vipera berus* = common European adder), ringed snakes (*Natrix natrix* or grass snake) and smooth snakes (*Coronella austriaca*). The last two are not venomous.

It is estimated that at least 421,000 envenomings and 20,000 deaths (figures may be as high as 1,841,000 and 94,000 resp.) occur annually worldwide. The highest burden of snakebites is in South Asia, Southeast Asia and sub-Saharan Africa. People most at risk are agricultural workers and children. One of the most frequently bitten people are drunken young men harassing a snake.

The majority of snake-bite victims seek traditional treatment and may die at home unrecorded. The amount of disability (permanent sequelae due to snakebites) is unknown and underreported. Although it is more common in rural areas, snakes can be present in town areas (e.g. in India). Snake bites have been recognized as a neglected disease by WHO.
Crotalus atrox, the Western diamondback rattle snake. Photo Protherics, used with permission
Juvenile *Elaphe situla* snake (Leopard snake), not venomous. This escaped (?) specimen was found in the middle of a main street in Antwerp, Belgium. Illegal breeding of protected species is common.

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**Biology of snakes**

Snakes are quasi-cylindrical reptiles without limbs. They move using a concertina movement, rectilinear, curvilinear, via “sidewinding” or by a combination of these methods. There are even 5 species of “flying” (gliding is a better word) snakes. In snakes, the left lung is atrophic, except in boas. The right lung can have an extension in the throat, which is important for the animal because there is airway compression when it swallows large prey. In general, the length of the lung is about one-half of the total body length, although in seasnakes the lung is longer. In reptiles, the nostrils come out in the mouth cavity (there is no palate to separate the mouth cavity from a nasal cavity). They can breathe through their mouth if it is empty. A full mouth blocks respiration. They can tolerate apnoea for a fairly long time, because as poikilothermic animals they have a rather low oxygen demand. By exhaling quickly some snakes can produce a hissing noise (cf. the puff
Description, scales and colour

**SNAKE: terminology head scales**

The scales on the head of a snake are rather constant within a species and are used for taxonomic identification. Adapted from "The Encyclopedia of Snakes by Chris Mattison"
Examples of Batesian colour and shape mimicry in Central American snakes. The left snake in each pair and the outermost snakes of the triple cluster are dangerous Micrurus species. The snakes on the right side and the central of the 3 snakes are non-venomous Pliocerus sp. The similarity is striking. Drawing adapted by ITM, from original.

Stripes and/or spots can act as a camouflage, breaking up the visual outline against the surroundings. A harmless snake can imitate a venomous one when both live in the same environment, i.e. Batesian mimicry (1861, Henry Walter Bates, English naturalist). In this way predators avoid the snake, if they have learned earlier that an animal with such coloration is dangerous.

**Description, heat sensors and Jacobson´s organ**

Most snakes have poor hearing and limited visual acuity. By contrast, in the roof of their mouth they possess an extremely sensitive organ, known as a Jacobson´s organ. It consists of two
openings lined with sensory cells. The animal flicks out its forked tongue and brings it back into the mouth, inserting the tips into the two openings of Jacobson’s organ. The tongue brings molecules from the environment into the organ. In this way the snake can sense its environment.

Snakes are very good at perceiving vibrations, e.g. of the ground. Some people use this as a means of prevention, by regularly beating a stick on the ground in front of them when they walk in an area with venomous snakes.

Description, food and body heat

All snakes are carnivorous. Because they do not have to continually maintain their body at a constant temperature, their food intake requirement is a good deal lower than that of warm-blooded animals. Because chronic “constipation” is most pronounced among sit-and-wait predators – animals for which body weight is of great importance – some people assume that these snakes make good use of the extra weight (3 to 22% of their body weight is faecal material). These animals lie still on the ground and use their heavy intestine as a counterweight in order to be able to strike more quickly with the mouth. Since the environment of the snake is so important for the animal, it is not unusual for a snake to lie at night on a path or road, where the temperature is somewhat higher than in nearby vegetation. Obviously this increases the chances of an accidental bite being suffered by a night time walker. In order to conserve heat, they can roll themselves up (small surface/weight ratio). This is also important to limit transcutaneous loss of water. In cold regions snakes can hibernate, individually or in a group. Many snakes have a limited territory. After having bitten somebody, a snake can generally be found within a rather small radius around the site of the incident, even after several hours.

Description, venom gland
Jacobson’s organ in the roof of the mouth of a snake is covered with chemosensory cells. The tongue will bring chemicals from the environment in contact with the epithelium. Nerves connect the organ to the olfactory lobes of the brain.
Snakes. The structure of the fangs differs between taxonomic groups. Copyright ITM

Colubrids have a modified salivary gland (Duvernoy’s gland), which discharges near the fangs at the
rear of the mouth. The venom is slowly introduced into the prey via capillary action. Therefore, in order to get sufficient venom into the tissues, a long contact period is necessary. However, this occurs only exceptionally in humans. This explains why most bites by colubrids are harmless. This also explains why occasionally envenomations are described by snakes that traditionally are regarded as non-venomous. In elapids and vipers, in contrast the venom glands consist of the uppermost labial salivary glands. They can be actively emptied by the musculus constrictor glandulae, so that the animals can actively and very quickly inject venom, or even spit venom (several meters).

**Description: jaws, fangs and teeth**

The left and right sides of the jaws can move independently of one another. This makes it possible to swallow large prey, yet the animals cannot chew. Snakes have no sternum, so that a large ingested prey does not constitute a mechanical obstacle when it is being swallowed (some prey have a diameter which is greater than the resting diameter of the snake).

In snakes, the teeth are not so firmly attached to the top/inner side of the jawbones (so-called “pleurodont dentition”). This makes it possible for the teeth to be easily replaced throughout a snake’s lifetime. The teeth break off easily. This influences the biting behaviour. Thus vipers bite, inject venom and release again in rapid succession, because a struggling prey could cause injury or break the teeth.

A temporomandibular joint is a purely mammalian characteristic that is not found in snakes. In snakes, the joint between lower and upper jaw is formed by the os articulare at the bottom and the os quadratum (quadrate bone) at the top.

**Infections transferred via snakes**
Pentastomiasis. Armillifer armillatus causes porocephalosis in humans. This tongue worm normally infects snakes. Copyright ITM

C-shaped calcifications due to infection with Armillifer armillatus, a tongue worm. Pentastomiasis is also known as porocephalosis. Photo ITM

Pythons can be infested by tongue worms (Pentastomida) such as *Armillifer armillatus* in Africa or *A. moniliformis* in Asia. These parasites live in the lungs of the reptiles. The eggs in the snake’s sputum can infect humans, e.g. through contamination of drinking water or when a snake is prepared as food. Porocephalosis (syn. pentastomiasis) is the result. In general, infection leads to asymptomatic crescent-shaped calcifications in the abdomen. Living parasites are rarely found elsewhere (e.g. subconjunctival). Gnathostomiasis (infection with the nematode *Gnathostoma spinigerum*) can also follow consumption of undercooked snake meat. A larva migrans syndrome or a very serious eosinophilic meningo-encephalitis can then develop. *Spirometra* sp. can be transferred via snakes
(also via frogs) and cause sparganosis, whereby the immature cestode can be found in the eye. These worms can survive for up to nine years in humans.

**Taxonomy**

**Introduction**

The classification is important because a certain correlation exists between snake family and pathology. This correlation is not absolute. Studying the fangs in the mouth of a dead snake which has been brought in can help determine the treatment. However, it is better to be cautious when doing this (the bite reflex can continue for over 1 hour after death even after decapitation). It can be useful to have on hand a number of photos or a poster illustrating most of the snakes in the surrounding area. On the basis of these pictures, a patient can sometimes indicate which animal has bitten him or her.

**Table 1: Examples of venomous snakes**

<table>
<thead>
<tr>
<th>Snake family</th>
<th>Species - some examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elapidae</strong></td>
<td>Cobra’s, including spitting cobra’s (<em>Naja</em>), coral snakes (<em>Micrurus, Micruroides</em>)</td>
</tr>
<tr>
<td></td>
<td>Kraits (<em>Bungarus</em>), Mamba’s (<em>Dendroaspis</em>), <em>D.polylepis</em></td>
</tr>
<tr>
<td></td>
<td>Sea snakes</td>
</tr>
<tr>
<td></td>
<td>Elapidae: A large and diverse Family of exclusively venomous snakes, covering all continents (except Antarctica) and several major oceans, these snakes have well developed fangs towards the front of the mouth, which can deliver often highly potent venom, produced in paired venom glands.</td>
</tr>
<tr>
<td><strong>Viperidae</strong></td>
<td>Subfamily Viperinae “Old World” and Subfamily Crotalinae (Pit Vipers)</td>
</tr>
<tr>
<td></td>
<td>Russell’s Viper, Puff viper, Gabon Viper, rhinoceros -horned viper (<em>Bitis</em>)</td>
</tr>
<tr>
<td></td>
<td>Bush Viper (<em>Atheris</em>), Echis carinatus</td>
</tr>
<tr>
<td></td>
<td>Viperidae: A large and diverse Family of exclusively venomous snakes, covering most continents (except Australia and New Guinea, Antarctica), with a highly evolved fang structure. The fangs are at the front of the mouth, attached to a mobile maxilla, enabling the fang to fold away against the roof of the mouth, thus permitting longer fangs compared to head size.</td>
</tr>
</tbody>
</table>
### Various subjects

<table>
<thead>
<tr>
<th><strong>Colubridae</strong></th>
<th><strong>Dispholidus typus</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>This is the largest Family of snakes, generally considered non-venomous and distributed globally. However, a few species have evolved fangs towards the back of the mouth, which deliver venom from venom glands.</td>
<td>(Boomslang) – sub-Saharan Africa</td>
</tr>
<tr>
<td><strong>Thelotornis (Twig Snake)</strong></td>
<td><strong>Thelotornis</strong> (Twig Snake)</td>
</tr>
<tr>
<td><strong>Atractaspididae</strong></td>
<td><strong>Atractaspis microlepidota</strong></td>
</tr>
<tr>
<td>A small Family of exclusively venomous snakes, found only in Africa and the Middle East, characterised by their side-striking fangs and unique venom components (sarafatoxins), only a few species of which appear able to significantly envenom humans.</td>
<td>(Burrowing Asp)</td>
</tr>
</tbody>
</table>

### Taxonomy, vipers (Viperidae)

Vipers and pit vipers have very long hollow fangs in the front of the mouth. When the mouth is closed the fangs lie folded up against the roof of the mouth. Vipers are slow, heavy snakes and are generally “sit-and-wait” predators. They move flat over the ground. One does not expect vipers to be present among tree branches for example. Venomous European vipers have vertical pupils. Non-venomous snakes in Europe have round pupils.

**Daboia russelli**

Russell’s viper (*Daboia russelli = Vipera russelli = “tic-polonga”) is one of the most dangerous Asian snakes. This nocturnal animal is often lethargic and will avoid dense jungle. It can hiss loudly through its large nostrils. There are 5 subspecies, which is important because antivenom from one country is often not effective on the local subspecies in another country. The symptomatology too will depend on the subspecies: pituitary haemorrhages and chemosis in Burma and southern India, anticholinesterase-resistant neurotoxicity in India and Sri Lanka; haemorrhages with all subspecies.

**Bitis arietans**

The puff adder (*Bitis arietans*, la vipère heurtante) gives rise to considerable problems in Africa. They can strike very quickly.

**Bitis nasicornis**
Bitis nasicornis belongs to the vipers. The exact function of the horns on the snout of this snake is not clear. Copyright ITM

**Vipera berus (Common viper or adder)**

Vipera berus, the common European adder or common European viper, is a venomous viper species that is extremely widespread and can be found throughout most of Western Europe and as far as East Asia. Known by a host of common names including common adder and common viper, adders have been the subject of much folklore in Britain and other European countries. They are not regarded as especially dangerous; the snake is not aggressive and usually bites only when alarmed or disturbed. Bites can be very painful, but are seldom fatal.
Vipera Berus distribution in Europe

**Bitis gabonica**
Bitis gabonica is also known as the Gaboon viper. Most animals have typical markings. Copyright ITM
*Bitis gabonica* is also known as the Gabon viper. Most animals have typical markings. Copyright ITM

**Echis carinatus complex**

The saw-scaled vipers are among the most important venomous snakes in the world, it is estimated that they are responsible for 50% of the global mortality caused by snakes.

**Taxonomy, pit vipers (Crotalidae)**

The pit vipers or Crotalidae get their name from the presence of two pits at the front of the head, about halfway between the eyes and the nostrils. These contain infrared sensors with which the animal can better locate its prey.

**Agkistrodon sp.**
Pit viper: Agkistrodon piscivorus, also known as Mocassin. Courtesy of Protherics

_Crotalus sp._
Pit viper: Agkistrodon piscivorus, also known as Mocassin. Courtesy of Protherics

Crotalus atrox, the Western diamondback rattle snake. Photo Protherics, used with permission
Rattlesnakes belong to the genus *Crotalus* and *Sistrurus*. When a rattlesnake administers a venomous bite to a human being, it injects 25-75% of its venom. It takes on average 3 weeks for the venom supply to be entirely replenished. Rattlesnakes have a typical tail structure. The rattle is used when the snake feels threatened. In this situation, the snake will raise its head and front part of the body, as well as the rattle and hold the body in an S-shape, ready to strike. The North American *Crotalus cerastes* is also called the “sidewinder”, referring to the way it moves. There are several desert snakes which demonstrate this behaviour.

**Taxonomy, burrowing vipers or Atractaspididae**

These animals (mole vipers or burrowing vipers) were earlier classified among the Viperidae, but currently form a separate family with over 50 species. They are primarily found in Africa. They are rather small animals, although some individuals can be as long as 1 meter. They live primarily underground. Bites are rare, but can have serious consequences. The hollow fangs can be moved sideways, even without opening the mouth. The venom of *Atractaspis engaddensis* contains an extremely powerful cardiotoxin, the so-called “sarafotoxin”, a word deriving from the Hebrew “Saraf ‘En Gedi” (saraf meaning ‘snake’, En Gedi refers to an oasis in the Judea desert in Israel).

**Taxonomy, Elapidae**

This family includes the cobras, mambas, kraits and coral snakes (Gr. Elaps: snake). The venom produces primarily local necrosis and paralysis. Elapids have moderately short, immobile fangs on the maxillae, at the front of the mouth. They cannot be folded backwards as in vipers. Often these snakes have small teeth behind the fangs and sometimes there is a small diastema.

**Cobras**

A cobra often raises its head and neck when it is threatened. The animals are characterised by the typical “hood”, the widening of the neck caused by spreading its cervical ribs when threatened. The king cobra (*Ophiophagus hannah*) is a very large Asian elapid, which eats other snakes. Some African and Asian cobras can spit venom.
Coral snakes

Elapids also live in the New World: the coral snakes. They often have a beautiful colour pattern. A mnemonic device for the colour bands in North America: “red on yellow, kill a fellow; red on black, venom lack”. This phrase does not work in other geographical areas.

Bungarus sp.: Kraits

Often the animals are distinctly passive during the day. At night, however they are active and they sometimes enter houses and bite. People with krait bites generally experience remarkably little local pain.
**Dendroaspis sp. : Mambas**

Mambas are only found in sub-Saharan Africa. These venomous snakes are notorious. They belong to the genus *Dendroaspis*: *D. polylepis* (black mamba), *D. viridis* (Western green mamba), *D. angusticeps* (Eastern green mamba) and *D. jamesoni* (Jameson’s mamba).

**Australian elapids**

The fauna of Australia is complex, and differs in many ways from the fauna on other continents. The medical relevant Australian snakes belong to the elapids.

**Taxonomy, sea snakes or Hydrophiidae**

The taxonomical classification is controversial, but these animals can be classified among the Elapidae or be grouped in their own family. Taxonomically they are broken down into the Hydrophiinae (real sea snakes) and the Laticaudinae (sea kraits). In some taxonomic diagrams these groups get the status of family: Hydrophiidae and Laticaudae.

**Taxonomy, Colubridae**

The name derives from the Latin “coluber”, which means snake. Only a few are genuinely dangerous. They have short small fangs on the maxillae at the back of the mouth so that they have to open their mouth very wide (170 to 180°) to inject venom. They also require a long contact period to introduce enough venom into the bite wound. Colubrids are often kept as pets, e.g. *Elaphe* sp. (rat snakes) or *Lampropeltis* sp. (king snakes, milk snakes). The boomslang (*Dispholidus typhus*) in southern Africa is another dangerous colubrid, yet bites by this animal are quite exceptional. Haemorrhages are the most obvious symptom after a bite by a boomslang.

**Taxonomy, Boidae**

The Boidae include boas and pythons. Constrictor snakes such as the anaconda, boas and pythons are not venomous. Boas are viviparous snakes from the New World and pythons are oviparous snakes from the Old World. Because they must be able to hold their body in small-diameter loops, they have short vertebrae. When they are wrapped around their prey, what makes them so deadly is not that they squeeze so hard, but rather that they can very effectively resist attempts to stretch. Every time the unfortunate prey exhales, the snake contracts a little bit more, and prevents the prey from
inhaling. After this has been repeated a few times, the prey simply suffocates.

**Distribution**

As far as native venomous snakes are concerned, only vipers are found in Europe.

In Africa there are elapids, vipers and colubrids.

The most important snakes in America are the pit vipers and several coral snakes.

In Asia, all families are represented (but not all genera).

A number of elapids live in Australia.

Problems with venomous sea snakes are limited to coastal areas of Asia and Australia.

Imported exotic pet snakes can be responsible for bites, especially in affluent countries.

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**Viper populations in Belgium**

There are three isolated wild viper populations in Belgium: the largest one in Brecht (Groot Schietveld), and much smaller populations in Kalmthoutse Heide and in the Visbeekvallei (Lille).

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**Distribution of the most important snakes**

It is useful to have an idea of which major venomous snakes can be found where.

In **Southeast Asia** Russell’s viper (Daboia russelli), Echis carinatus, the habus and the Malayan pit viper (Calloselasma rhodostoma) are the most important.

In **Africa** the saw-scaled vipers (*Echis carinatus* complex), the puff viper (*Bitis arietans*) and to a lesser extent cobras and mambas are important.

In **South and Central America** the cascabel (*Crotalus durissus terrificus*), jararaca (*Bothrops jararaca*) and fer-de-lance (*Bothrops atrox*) are the most important venomous snakes. Bites by the notorious bushmaster (*Lachesis muta*) are actually quite rare.
In **North America** the various rattlesnakes (*Crotalus* sp. and *Sistrurus* sp.) are the most important, with *Crotalus atrox* (Western diamondback) heading the list. Mocassins (*Agkistrodon* sp.) and coral snakes (*Micrurus* and *Micruroides*) are statistically less important.

**Coastal areas in Southeast Asia and Northern Australia:** sea snakes such as *Pelamis*, *Laticauda* sp, *Enhydrina* sp.

**Australia:** Brown snake (*Pseudonaja* sp), black snake (*Pseudechis*), death adder (*Acantophis*), Taipan (*Oxyuranus*), tiger snake (*Notechis*).

**The five medically most important snakes in the world are:**

<table>
<thead>
<tr>
<th>Snake family</th>
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<tbody>
<tr>
<td><em>Echis carinatus</em> complex</td>
</tr>
<tr>
<td><em>Bitis arietans</em></td>
</tr>
<tr>
<td><em>Daboia russelli</em></td>
</tr>
<tr>
<td><em>Daboia russelli</em></td>
</tr>
<tr>
<td><em>Calloselasma rhodostoma</em></td>
</tr>
<tr>
<td><em>Bothrops atrox</em></td>
</tr>
</tbody>
</table>

**Snake venom**

**Snake venom, composition**

Snake venom is a complex mixture of enzymes, toxins and all sorts of smaller molecules. The most important components are the substances with a cytotoxic effect, neurotoxins and the factors leading to bleeding tendency. Some toxins have multiple effects.

**Snake venom, necrosis**
Various subjects | 183

Mode of action of phospholipase A1, A2, C and D on cell membrane phospholipids. Several snake venom components have phospholipase A2 activity. Copyright ITM

Enzymes which help the snake to digest its prey are often cytotoxic for man. Proteolytic enzymes have a trypsin-like activity. Hyaluronidase splits acidic mucopolysaccharides and promotes the distribution of venom in the extracellular matrix of connective tissue. Snake venom often contains various phospholipases A2. These are esterolytic enzymes which break down membrane phospholipids. This causes cellular membrane damage (“lyso”, lysis: destroy). Certain venom components have phospholipase C activity. In humans, all these enzymes cause oedema, blister formation and local tissue necrosis.

Myotoxins are present in sea snakes and Australian elapids, as well as in Bothrops, Crotalus, Naja and
certain colubrids (*Philodryas* sp). They bind to potassium or calcium channels on muscle membranes and provoke massive rhabdomyolysis.

**Snake venom, paralysis**

Neurotoxins are divided into several subgroups. The venom of all elapids contains alpha-neurotoxins. They act on the post-synaptic nicotinic acetylcholine receptors of the motoric end-plate. With regard to their activity on the neuromuscular junction, the alpha-neurotoxins can be compared with curare or with the autoantibodies in myasthenia gravis. They block the stimulus transmission from nerve cell to muscle and cause paralysis. The postsynaptic effects are reversible with antivenom and neostigmin.

Neurotoxic snake venom with presynaptic and postsynaptic components. Neuromuscular junction with acetylcholine and inhibition of acetylcholinesterase by neostigmine. Copyright ITM
A second subgroup are the presynaptic beta-neurotoxins. They inhibit recycling of acetylcholine and augment the action of the presynaptic alpha-neurotoxins. Presynaptic neurotoxins inhibit the fusion of the vesicles containing acetylcholine, with the nerve’s membrane of the neuromuscular junction. Neostigmin will not be effective in these cases.

Snake venom, blood coagulation

Some components of certain snake venom interfere with blood coagulation. The diversity is staggering. It seems that nearly every step of the coagulation cascade, as well as the fibrinolysis mechanism can be activated or inhibited by one or other component in snake venom.

Clinical aspects

Bites by venomous snakes are not always accompanied by venom injection and symptoms of envenomation (so-called “dry bites”). Dry bites occur in 50 to 80% of bites. The interval between bite and possible death can vary greatly. In general it can be said that death comes most quickly after cobra bites and most slowly after viper bites. A 24-hours observation period after a snake bite without envenomation symptoms is recommended before a patient can be discharged with clear advice about alarm signs that require readmission.

Inappropriate pre-hospital treatment, such as prolonged arterial tourniquet, incisions at the bite site and sustained aspiration by suction pumps; can cause major complications. Clinical effects of venomous snake bites include vomiting, pain at the bite site and anxiety. This anxiety can lead to dizziness, sweating, shortness of breath or hyperventilation (not to be confused with neurotoxicity). Further, there are a number of specific problems:

Local cytotoxicity
The patient was bitten by Bothrops atrox, a venomous South American pit viper. Extensive skin necrosis for which skin grafts are needed. Copyright Alexander von Humboldt Institute, Peru.
Local cytotoxicity is characterised by local swelling and blister formation. Later necrosis can develop which can be promoted by arterial thrombosis, inappropriate tourniquet use and local excess pressure in the tissues. A compartment syndrome is probable if the tissue pressure amounts to >30 to 40 mm Hg. This is rare. Prophylactic fasciotomy is not recommended. Local necrosis is primarily encountered
with vipers, pit vipers and some elapids. Wound infections are not unusual and can aggravate local necrosis. Sometimes fangs or teeth break off and remain in the wound. Most tissue destruction develops in the first 3 days. Chronic ulceration, osteomyelitis or arthritis can follow a snakebite.

**Cardiovascular toxicity**

Cardiovascular toxicity can occur with viper bites. Hypotension can result from vasodilatation, extravasation, haemorrhages and direct myocardial toxicity. Venom-induced shock leads to a combination of hypotension, lactic acidosis, haemoconcentration and hypoproteinemia. The venom of mole vipers includes so-called “sarafotoxins”, peptides which strongly resemble mammalian endothelins and provoke profound vasoconstriction, including the coronary arteries. On the other hand, vasodilatation can occur due to ACE inhibition. Historically, the first angiotensin-converting enzyme inhibitor was discovered in the venom of a South American venomous snake, Bothrops jararaca. This formed the basis for developing captopril, the prototype of a very important class of drugs (Lasker Award 1999). The effect of some components of certain snake venom is comparable to an overdose of captopril, with serious hypotension as a consequence.

**Haemostasis disturbances**

Haemostasis disturbances are primarily seen with vipers, pit vipers, Australian elapids and colubrids. The haemorrhagic tendency manifests itself as minor subcutaneous haemorrhages, bleeding gums, epistaxis, haematemesis, melena and/or bleeding from venipuncture sites. Haemorrhages in the adrenal gland and pituitary gland are found with bites by the Russell’s viper. This last symptom can be compared with Sheehan’s syndrome (post-partum pituitary necrosis). An acute Addison crisis can follow; which must be treated with steroids. Panhypopituitarism, secondary hypogonadism and diabetes insipidus can be late consequences.

**Neurotoxic effects**

Neurotoxic effects are a characteristic of elapids and sea snakes. The venom of the rare “berg adder” (*Bitis atropos* in South Africa and Zimbabwe) is also neurotoxic, which is highly exceptional for a viper. Gradually ptosis develops, with vision impairment and eye muscle paralysis (ophthalmoplegia) and mydriasis. Afterwards hoarseness, dysphagia and pharyngeal paralysis develop producing drooling of saliva. The patient can sometimes have difficulty sticking out his or her tongue. Weakening of the neck muscles means the patient can appear to have a “broken-neck symptom”. When the patient is drawn up by the hands from a supine position to 45°, the head hangs backwards if there is neck
muscle paralysis. Ultimately the patient develops respiratory paralysis.

Neurotoxicity must be distinguished from the symptoms caused by anxiety. Some people who believe that they have been bitten by a snake (even if this is not the case), will hyperventilate, resulting in perioral or diffuse paresthesiae or rigidity and tetany of the hands (decrease of the free plasma Ca\(^{++}\)-concentration due to respiratory alkalosis). Others experience dizziness or syncopal tendencies including vasovagal syncope. A few people will become agitated, possibly with a series of bizarre complaints.

**Muscle toxicity**

Severe muscle pains and myoglobinuria develop. Cardiac arrhythmia can occur as a result of hyperkalaemia. Hyperkalaemia results as a result of rhabdomyolysis with the additional consequence of acute renal failure.

**Renal toxicity**

Kidney toxicity is often multifactorial. Hypotension/shock, diffuse intravascular coagulation with intrarenal micro-thrombi, myoglobinuria and haemoglobinuria are major causes of kidney damage. Myoglobinuria as a result of rhabdomyolysis can cause acute tubular necrosis. Myoglobin is filtered through the glomeruli and causes renal vasoconstriction and tubular injury. The urine is dark and will test positive for blood. Massive haemolysis causes a similar picture. Another cause of renal failure is immune complex nephritis following administration of antiserum.

**Eye lesions**

Eye lesions can occur when a snake spits venom in the eyes (spitting cobras). The snake can spit its venom over distances of up to 3 meters. Burning pain, itching, oedema and eyelid spasms develop. In more than 50 % of cases there are corneal erosions, sometimes leading to blindness. After rinsing copiously with a non-irritating liquid, a local anaesthetic can be given to stop the pain and the blepharospasms. Afterwards an eye ointment containing antibiotics is applied. In case of bites by Burmese Russell’s vipers, chemosis can develop (conjunctival oedema), sometimes combined with subconjunctival haemorrhages. Chemosis reflects a generalised increase in vascular permeability and has a poor prognosis. Due to this increased capillary permeability, periorbital oedema, facial oedema and serous effusions can develop.
Clinic: rule of thumb

<table>
<thead>
<tr>
<th>Local necrosis</th>
<th>vipers, pit vipers, elapids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paralysis</td>
<td>elapids and sea snakes</td>
</tr>
<tr>
<td>Haemorrhages</td>
<td>vipers, pit vipers, colubrids, Australian elapids</td>
</tr>
</tbody>
</table>

However, there are exceptions to this rule of thumb:

e.g. *Naja nigricollis* (black-necked cobra): only haemotoxic

e.g. *Crotalus durissus terrificus*: primarily neurotoxic

e.g. *Bitis atropos* (“berg adder“): primarily neurotoxic

Prognosis after snakebite - example

<table>
<thead>
<tr>
<th>Chance of envenomation symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rattlesnake bite</td>
<td>80%</td>
</tr>
<tr>
<td>Sea snake bite</td>
<td>20%</td>
</tr>
<tr>
<td>Russell’s viper bite</td>
<td>50%</td>
</tr>
<tr>
<td>Malayan pit viper</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Mortality**

* Crotalus durissus terr. 75% if untreated; 12% with antiserum
* Echis carinatus 20% if untreated; 3% with antiserum
* Dendroaspis polylepis almost 100% lethal if untreated

**Local necrosis**

* Echis carinatus 9%
* Bitis arietans (puff viper) 36%
<table>
<thead>
<tr>
<th>Snake Species</th>
<th>Interval Between Snakebite and Death</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Naja nigricollis</em> (cobra)</td>
<td>71%</td>
</tr>
<tr>
<td><em>Naja naja</em> (cobra)</td>
<td>8h (1/4-60h)</td>
</tr>
<tr>
<td><em>Crotalus</em> species (rattlesnakes)</td>
<td>16h (2h-26h)</td>
</tr>
<tr>
<td><em>Bungarus caerulus</em> (Indian or common Krait)</td>
<td>18h (3h-63h)</td>
</tr>
<tr>
<td><em>Vipera berus</em> (European viper)</td>
<td>34h (6h-60h)</td>
</tr>
<tr>
<td><em>Vipera (Daboia) russelli</em> (Russell´s viper)</td>
<td>40h (1/4h-9 d)</td>
</tr>
<tr>
<td><em>Calloselasma rhodostoma</em> (Malayan pit viper)</td>
<td>60h (5h-10 d)</td>
</tr>
<tr>
<td><em>Echis carinatus</em> (saw-scaled viper)</td>
<td>5 d (1-41 d)</td>
</tr>
</tbody>
</table>

**Treatment**

**Initial**
Australian compression and immobilization technique used in neurotoxic snake bites. A large (minimum 15 cm) elastic bandage is used. Peripheral arterial pulsations should remain present. The optimum pressure under the bandage lies probably between 55 and 70 mm Hg. Adapted from Wilderness Medicine 4rd edition, Mosby.
Victims are often afraid of dying. This anxiety must be reduced which is best done by showing a professional approach. The bitten body part should be immobilised, ideally with a splint as for a broken limb. Immobilisation reduces absorption of the venom, which delays systemic effects. A tight elastic bandage is wrapped around the bitten limb (slower lymph flow). It is important to use a large (15 cm) elastic bandage, tight enough to impair spread of venom, but not too tight in order to avoid interfering with oxygenation. If a bite by a cytotoxic snake is involved, this might be contraindicated, as necrosis could increase locally. For immobilisation the elastic bandage and the splint are of equal importance. They must be applied as soon as possible. A tourniquet is not useful and can aggravate the injuries through ischaemia. The sudden removal of a tourniquet in the case of cobra bites can cause an acute worsening of the symptoms (situation e.g. soon after arrival in the hospital). Dangerous procedures such as incision, sustained suction pumps on the skin, amputation of a finger, prolonged tourniquet, etc. should be avoided. The commercial “Extractor” device consists of a syringe and a vacuum cup. If used within three minutes after the bite, it can remove up to 2-30% of the venom (the device remains on the site for 30 minutes). However, the negative pressure of almost 1 atmosphere also causes massive oedema. Whether there is a clinical benefit is not established (it might be counterproductive). Quickly sucking out (< 3 minutes after the bite) the bite wound can remove up to 50% of the venom, but the usefulness of this has not been demonstrated. With eye injuries, immediate and copious rinsing with any non-irritating liquid is indicated. If possible and if this can be done without danger, it is best to bring the dead snake along for identification (note carefully: the bite reflex continues long after death, even after decapitation!). Attempting to kill the snake is dangerous and could lead to further bites. Correct species identification is often difficult, but it is of course important to have an idea of the family to which the animal belongs.

Treatment upon arrival in hospital

A plasma expander and corticosteroids such as methylprednisolone must be available. Antivenom is given as indicated (see below). In case of vomiting an anti-emetic can be administered. Adrenaline (adult 0.5 ml of 0.1 % SC or IM ; for a child 0.01 ml/kg) can be used against angioedema. Endotracheal intubation may be required. If shock and inadequate response to 1 to 2 litres of IV-Ringer or 0.9% saline solution (adult dose), IV albumin is administered. Albumin remains in the bloodstream longer. No salicylate derivatives (aspirin) should be used for painkilling, due to the risk of haemorrhage. Tetanus vaccination must not be overlooked. Take blood for full blood count and cross matching (check for thrombocytopenia, spherocytosis, schistocytes, anaemia). Coagulation parameters must be determined if possible. In under-equipped labs it is often impossible to perform conventional coagulation tests. Yet it is essential to determine whether there are blood coagulation problems. For this 2 ml of blood is taken in a dry clean glass tube. Normally blood coagulates and forms a clot within 15 minutes. If the blood has still not clotted after 20 minutes, then there is a
haemotoxin present. This simple test can be repeated. If there are coagulation problems, antivenom should be given, if needed followed by or simultaneously with cryoprecipitate or fresh frozen plasma. The thrombocytopenia which often develops is sometimes not corrected by antivenom.

**Treatment if respiratory paralysis**

In case of respiratory paralysis, the patient must be artificially ventilated. On average this lasts 1 to 4 days if no antiserum is given, but longer periods of paralysis do occur. Neostigmine - an acetylcholinesterase inhibitor - ensures that more neurotransmitter is present, so more stimulus transmission can take place. In this way, neostigmine reduces the effect of certain types of neurotoxins (cobra, mamba). For an adult 0.02 mg/kg and for a child 0.04 mg/kg is injected IM. Afterwards a neostigmine maintenance dose can be infused. Unpleasant side effects (diarrhoea, intestinal cramps, excessive salivation, sweating) are attributable to stimulation of the parasympathetic nervous system (muscarinic receptors). In order to prevent this, the anticholinergic atropine as antidote (0.6 mg IV every 4 hours) is also given. Atropine is a competitive inhibitor of the muscarinic receptors with constipation, dry mouth and mydriasis as side effects.

**Treatment of hyperkalaemia**

Hyperkalaemia occurs primarily in sea snake bites with severe rhabdomyolysis (see above). In case of cardiac arrhythmia, 10 ml 10% calcium gluconate IV can save a life. This does not reduce the kalaemia, but counters the effects of potassium on the heart. Treatment is coupled with 250-500 ml of a 10% glucose-infusion together with 10-20 units of fast-acting insulin. Sodium bicarbonate can also be given. Salbutamol or albuterol (b₂-agonists) can be administered via inhalation to lower the kalaemia, since they also cause a potassium shift to intracellular. In case of persistent hyperkalaemia, peritoneal or haemodialysis is necessary.

<table>
<thead>
<tr>
<th>Hyperkalaemia - treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium gluconate</td>
</tr>
<tr>
<td>Insulin + glucose</td>
</tr>
<tr>
<td>NaHCO₃</td>
</tr>
<tr>
<td>beta₂-agonist, salbutamol</td>
</tr>
<tr>
<td>Kayexalate (no clear data on efficacy)</td>
</tr>
</tbody>
</table>
Treatment with antivenom

Stock of antisera in the Antwerp Zoo. Snake antivenom. In 2007, FAV-Afrique was available via this Zoo. Copyright ITM

Antivenom, to whom?
To whom should antivenom (antiserum) be administered? The presence of “fang marks” – wounds caused by the fangs – is not per se an indication since dry bites also leave “fang marks”. Many bites from nonvenomous or mildly venomous species result in discrete local tissue swelling. When the offending snake cannot be identified, giving antivenom for this situation will result in many patients
receiving antivenom unnecessarily. Antivenom is administered to patients with local symptoms of envenomation, such as progressive important swelling, intense pain in and around the bite wound, haemorrhages which are difficult to stop, blister formation and/or when there are signs of systemic effects of the venom (muscle paralysis, blurred vision, difficulty in speaking, diffuse haemorrhages, respiratory problems, pulmonary oedema, shock, prolonged coagulation times). Antivenom is still useful up to more than one week after the bite. It is never too late to administer antivenom if there are symptoms of envenomation.

Antivenom, dose
The initial dose of antivenom to be administered to a victim is subject of debate. In clinical practice, the severity of the symptoms will determine the amount of antivenom given to a specific patient. For example: one vial of any Indian polyvalent antivenom represents only 4.5 or 6 mg of total neutralising capacity, depending upon the offending snake species. Each vial neutralises a minimum of 6 mg of Naja naja venom and Daboia russelli venom and 4.5 mg of Bungarus caeruleus venom and Echis carinatus venom. But a Russell viper injects an average of 63 mg of venom in a bite. If one would give 2 vials as loading dose, one can expect to neutralise about 20% of the venom. In this case, the loading dose should be around 10 vials. Even “low-dose” strategies recommend a minimum of 6 vials as a starting dose. The objective of additional antivenom is to neutralise any circulating unbound venom that was not neutralised by the initial dose. In hemotoxic bites, the dose is repeated if coagulation is not restored after 6 hours. The liver requires 6 hours to restore clotting factors. Additional antivenom before this period is potentially unnecessary. In case of neurotoxic bites, the antivenom can be repeated after 1 or 2 hours if the patient has not improved or if his condition is worsening. True reversibility of neurotoxic envenomation (detaching tissue-bound post-synaptic neurotoxins) is only possible within the first 1 or 2 hours. After that period, the role of antivenom is to neutralise unbound venom. Patients paralysed due to destruction of the presynaptic nerve terminals will respond much less to antivenom.

The treatment with antivenom is effective for problems of blood coagulation, shock and specific neurotoxicity. For other problems (nephrotoxicity, local necrosis and some paralyses) the effect is a great deal less spectacular. Note: the same dose of antivenom is required in children, as the amount of venom injected is the same as in adults.

Antivenom side effects
Antivenom which is prepared from horse serum, contains foreign proteins and frequently produces side effects. Anaphylaxis (IgE-mediated type I reaction), anaphylactoid reactions (not IgE-mediated, but via complement activation through protein aggregates in the antivenom) and serum sickness (immune complex or type III reaction) can develop. Anaphylaxis risk is higher in a patient who has previously been treated before with antivenom (e.g. a snake hobbyist bitten on different occasions). Soon after administration, ±20% of the patients develop itching, urticaria, fever, cough, tachycardia, nausea and/or vomiting. Sometimes there are quite serious bronchospasms. Antihistamines do not reduce the incidence or seriousness of these symptoms, in contrast to a low dose of adrenaline (0.25 ml SC of a 1/1000 solution). Most clinicians currently advocate no routine prophylaxis, but will have
adrenaline, corticosteroids and antihistamines drawn up, so they are ready to treat an early reaction.

Serum sickness as a result of immune complexes develops in 30 to 90% of the patients. It manifests itself after 5 to 24 days (average 7 days). The frequency depends on the dose of antivenom administered. Fever, itching, joint pain and periarticular swelling, lymphadenopathy, mononeuritis multiplex and immune complex nephritis with albuminuria characterise this disorder. If serum sickness develops, steroids are given for 5 days.

Examples of antivenom:

**CroFab®** (= earlier **CroTAb®, Protherics Inc.**) was approved in October 2000 by the American FDA. The product includes Fab fragments against 4 North American venomous snakes: *Crotalus atrox* (Western Diamondback rattlesnake), *Crotalus adamanteus* (Eastern Diamondback rattlesnake), *Crotalus scutulatus* (Mojave rattlesnake) and *Agkistrodon piscivorus* (Cottonmouth). This antiserum covers via cross-protection virtually all pit vipers in North America and several in Central America.

**ViperaTAb®** is a monovalent antiserum that is used for bites by *Vipera berus*.

**ViperFav®** (Aventis Pasteur Merieux) is a polyvalent, yet narrow-spectrum F(ab’)₂ antivenom against *Vipera berus, V. ammodytes* and *V. aspis*.

**Venom detection kit**

In Australia there has existed for many years a detection kit to identify venom and determine the snake species (Commonwealth Serum Laboratories). This is based on a two-step enzyme immunoassay in which the wells in the ELISA plate are coated with antibodies against the various types of snake venom. Using a swab some venom is taken from the bite wound (in a person or a pet) and identified. This makes it possible to use specific antivenom. However, this method still has to be further developed for other parts of the world. A positive “venom detection kit” result per se is no indication for antivenom. The results must always be interpreted in the clinical setting.

**Monitoring antivenom therapy**

When an adequate quantity of antivenom has been given, the following response can be expected:

1. The patient rapidly feels better.
2. Gum bleeding stops within 15 to 30 minutes.
3. The coagulation test (20´ test) normalises within 3-9 hours, but the clinical haemorrhages stop much earlier.
4. The blood pressure normalises within an hour. Cardiac arrhythmias disappear.
5. Neurotoxic effects begin to disappear within 30 minutes; complete recovery takes much longer. Bites by kraits and sea snakes (presynaptic venom) improve slowly.
6. Active haemolysis and rhabdomyolysis stop within several hours. Urine afterwards returns to its normal colour.

**Indications to repeat antivenom administration:**

1. Persistence or recurrence of non-coagulability after 6 hours or new bleeding after 1-2 hours.
2. Worsening neurotoxic or cardiovascular signs after 1-2 hours.

**Treatment of complications**

Supportive therapy is necessary (fluid balance, analgesics, transfusion). Blood pressure, pulse, respiration, muscle functions, central venous pressure, urine production, blood coagulation and circumference of the bitten body part (leg, arm) must be monitored. Wound infections including tetanus must be prevented and combated.

In case of compartment syndrome, fasciotomy should only be considered in extreme cases (tissue pressure >40 mmHg). It often does more harm than good. With local necrosis, operative intervention is necessary (wound debridement, skin grafts, amputation). Deep abscesses can develop and must be drained. After the acute episode scars are likely. Skin grafts might be needed. A Volkmann’s ischaemic contracture of the forearm can occur and requires intensive physiotherapy to regain some function. Kidney failure can sometimes make (peritoneal) dialysis necessary. Strict fluid balance monitoring should be introduced in order to avoid any overload. With heavy myoglobinuria or haemoglobinuria an infusion of mannitol (200 ml of 20% over 20´) may be given and alkalisation of the urine is advised. An adequate hydration of the patient must be maintained. Muscle rest is obligatory if rhabdomyolysis is suspected.

**Shock**

Shock can be the result of anaphylaxis, direct vasodilatation due to the venom, cardiotoxicity with or without arrhythmia, hypovolaemia (fluid shift to extravascular and/or internal/external bleeding), respiratory failure, acute Addison crisis or sepsis. Plasma expanders under continuous control of the central venous pressure (watch carefully for pulmonary oedema), dopamine and steroids may be
necessary.

**Errors in evaluation/treatment of snakebite**

1. Not thinking of a venomous snake bite when confronted with a swollen ecchymotic limb
2. Cryotherapy and/or incision of the wound
3. Insufficient immobilisation of a bitten limb
4. Not looking for fang marks
5. Not keeping in mind that envenomation can change over the course of time, with clinical deterioration as a result
6. Only giving vasopressors to support the blood pressure, without giving IV fluid
7. Forgetting to check coagulation repeatedly
8. Delaying antivenom treatment if signs of envenomation are present, or thinking that it is too late to give antivenom
9. Administering a too low dose of antivenom
10. Not having adrenaline ready on stand-by
11. Applying an arterial tourniquet for a prolonged period
12. Performing a fasciotomy when not needed

**Prevention**

It is very rare for a snake to be spontaneously aggressive. Snakes tend to note the presence of a person through detection of vibrations. If given the chance they generally flee as a person approaches. Never attempt to corner a snake. Many bites occur when people are attempting to kill the animals. The risk of a snakebite increases if the victim is drunk, reckless or imprudent. However, people can accidentally tread on a snake on a path at night or in a field. More than 50% of venomous snake bites are on the feet or lower legs. Wearing sturdy, high-topped footwear in areas with increased risk is recommended. Some snakes follow their prey (generally small rodents) all the way into houses, and can bite a sleeping victim if they are surprised. Control of rats and mice around houses is not only beneficial in itself; but also reduces the number of snakes attracted to the area. The grass around the house must be kept short. There are specific high risk environments and professions. This encouraged the development of various experimental vaccines. Naturally they do not protect against the bite itself, but are designed to reduce mortality and morbidity. Sleeping under a bednet protects against snakebites, especially in these areas where snakes tend to enter houses when looking for their prey.

To the question whether people routinely need to carry preventive antivenom when travelling in
remote areas, the answer is “no”. The chance of incurring a venomous snake bite with envenomation is low. Furthermore antivenom is not a harmless product, it is expensive and must be stored in specific conditions. Taking a couple of elastic bandages along is recommended. These can also be used for other purposes.

**Antisera: useful information**

- MAVIN (Münich Antivenom Index) available via: http://www.toxinfo.org/antivenoms/
- http://www.who.int/bloodproducts/snake_antivenoms/en/
- For Belgium: Antigif centre Brussels: tel 070.245.245. Usually antivenom against European vipers (Viperfav) should be available.

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### Scorpions

#### General

Today there are around 1400 species of scorpions, although estimates of the exact number vary widely. All scorpions are venomous, but only a minority twenty five or so are potentially lethal for humans. Scorpions do not bite. Stings by scorpions are fairly common. Every year, more than 1 million cases of scorpion envenomation are reported worldwide. However most clinical reports emphasize the serious cases and systematically overestimate the danger these creatures pose. In endemic areas, people don´t go to a doctor for minor stings. Fatal stings are essentially limited to Mexico, Brazil, Trinidad, northern Africa, South Africa, the Middle East and India. It is primarily children and patients suffering from a respiratory and/or cardiovascular condition who run a high risk of complications.

#### Biology

Scorpions are the most primitive members of all Arachnida. Their sting is used to kill prey, for defence against aggressors and in some species it also has a role in the courtship display. Some scorpion species are long (*Hadogenes troglodytes* up to 21 cm), others are heavy (*Pandinus imperator*, also called the Emperor scorpion; *Heterometrus* sp.), while others are small (*Microtityus waeringi*, adult 12 mm). All scorpions are exclusively carnivorous. A scorpion first grasps its prey
(generally insects) with the pedipalps. If the prey is not immediately overpowered, they sting it by bending the tail forwards over the body. The venom is actively injected. The scorpion releases gastrointestinal juices over the prey in order to liquefy it and later suck it up. They consume only the body fluids and liquefied tissues of their prey. A meal can last several hours. Some species are cannibalistic.

Because many scorpions live in dry environments, they have become adapted to minimize loss of water. This is made possible in part by a watertight cuticle based on chitin. This has unusual optical characteristics. Scorpions fluoresce with a greenish colour under long-wave UV light. This makes them easy to spot at night with the aid of a UV lamp. The reason for this fluorescence is unclear.

Taxonomy

Taxonomy, families

**Buthidae**: virtually all medically important species belong to this family. However, it includes nearly one-half of all scorpion species (around 600 known species). Buthidae have a triangular central plate, whilst the other families have a pentagonal sternum.

**Bothriuridae**: unimportant

**Chactidae**: unimportant

**Diplocentridae**: unimportant, except for *Nebo hierichonticus*

**Scorpionidae**: unimportant, except for *Hemiscorpio lepturus*

**Vaejovidae**: of limited importance. *Vaejovus* sp. and *Hadrurus* sp. can cause painful stings; but the effect is always local and limited.
Tityus serrulatus. Yellow scorpion endemic in parts of Latin America. Copyright ITM
Scorpion. Parabuthus granulatus, from Namibia. With special thanks to Prof Verdonck, Kortrijk.

**Distribution**

Virtually all lethal species belong to the Buthidae family. These animals are found primarily but not exclusively in dry areas. In the Buthidae family, the medically important and dangerous genera have the following distribution:

<table>
<thead>
<tr>
<th>Genus</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Androctonus</em></td>
<td>from Morocco and Senegal eastwards to India</td>
</tr>
<tr>
<td><em>Buthus</em></td>
<td>Mediterranean, Middle East and East Africa</td>
</tr>
<tr>
<td><em>Hottentotta</em></td>
<td>Northern Africa and the Middle East</td>
</tr>
<tr>
<td><em>Leiurus</em></td>
<td>East Africa and the Middle East</td>
</tr>
</tbody>
</table>
### Parabuthus
- From Sudan to South Africa

### Mesobuthus
- India, Southern and Central Asia

### Tityus
- South America

### Centruroides
- USA, Mexico, Central America

The most important species are:

- *Buthotus tamulus*
- *Leiurus quinquestriatus*
- *Androctonus crassicauda (and A. australis)*
- *Tityus serrulatus*
- *Centruroides suffusus*

## Scorpion venom

Scorpion venom is a mixture of various active substances, but generally the neurotoxins are the most important. The neurotoxins are small proteins. Alpha neurotoxins inhibit the closing of sodium channels, without interfering with the opening potential. They lead to a strong membrane depolarization and hence, neuronal excitation. In a second phase loss of excitability is possible. Beta neurotoxins open Na\(^+\)-channels. Sodium is primarily an extracellular ion, and is necessary inter alia for maintaining an electrical voltage difference across the cell membrane. When the Na\(^+\)-channels open, sodium flows into the cell which depolarises the membrane. The nerves fire non-stop. The clinical effects of alpha and beta neurotoxins are similar. There follows a massive release of neurotransmitters, both acetylcholine and noradrenaline from nerve endings and adrenaline from the adrenal medulla. The main part is formed by the catecholamines, thus sympathetic effects usually outgo the parasympathetic effects.

Scorpion venom also contains serotonin, which contributes to local pain.

## Clinical aspects

### General

Most scorpion venoms contain little or no cytotoxic enzymes, so that a sting produces little local
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...tissue damage. An exception to this is the cytotoxic venom of *Hemiscorpius lepturus*, a scorpion from Iran. Their stings are characterized by erythema and purpuric and bullous lesions that resolve, but in about 20% of cases there is delayed localized necrosis. Companion features include nausea, vomiting, fever, minor autonomic effects, direct haemolysis with haemoglobinuria and acute kidney injury that might necessitate dialysis. Bites by loxosceles spiders can mimic a similar clinical syndrome.

There are four factors which play a role in defining eventual symptoms: the quantity of venom introduced and its toxicity as well as the size and medical condition of the victim. Many scorpions without medical interest have venom that can kill a mouse, but when introduced into human beings only produces symptoms analogous to those of a bee sting. If there is an allergy to this venom, anaphylaxis can follow and death can result from a sting of even a “harmless” scorpion. Stings without injection of venom do occur (“dry” stings).

**Local effects**

Rapidly developing pain at the site of the sting is characteristic. Swelling and local redness are often limited but can be quite serious. Local necrosis is exceptional. Local paraesthesias can occur. Several South African scorpions can squirt venom up to one metre away. If this comes into contact with the cornea, chemical keratitis with burning pain develops.

**Systemic effects**

There are 3 main mechanisms of action: adrenergic (sympathic) excess, cholinergic (parasympathic) excess and neuromuscular excitation. The adrenergic effect results in tachycardia and hypertension as well as mydriasis, agitation, seizures and myocarditis. The cholinergic effects are bradycardia and hypotension, vomiting, transpiration, salivation, lacrimation, miosis and bronchial spasms with excess secretions. The neuromuscular excitation can lead to oculomotor abnormalities, visual disturbances, muscle spasms and eventually paralysis. Complications are cardiac arrhythmias, myocardial depression with pulmonary oedema, hypotension and shock. Death can be caused by respiratory failure or by coma and multiple-organ due to shock.

Symptoms can either develop quickly, within ten minutes, or – more rarely – slowly, after only 24 hours. More and more, doctors use a clinical gradation:

degree 1 : local effects only
degree 2: autonomic excitation, agitation and anxiety

degree 3: pulmonary oedema, hypotension and cardiogenic shock, severe neuromuscular excitation

degree 4: multi-organ failure, coma, seizures, end-organ failure secondary to hypotension

Evolution from degree 1 to degree 4 can occur very quickly (sometimes within half an hour). Generalized fatigue with muscle stiffness and weakness, anxiety and restlessness are frequent. The tendon reflexes are hyperactive. Sometimes fasciculations, tremors and/or clonus develop.

Other complications from scorpion stings include pancreatitis, rhabdomyolysis, diffuse intravascular coagulation and priapism.

Children are generally very restless, with crying and shouting, agitation, shaking, twisting and swinging of their limbs. The child cannot sit still. Mortality depends largely on age. Children, the elderly and people with a serious pre-existing medical condition have a substantially higher risk of death than adults.

**Diagnosis**

The diagnosis is essentially clinical. Due to the quick and intense local pain, the scorpion is often noticed. Yet the typical victim is someone who is usually stung at night in the foot, outdoors, possibly when he/she has moved a stone or some wood. People are also stung in the morning when they try to put on a shoe in which a scorpion is hiding. Occasionally in North Africa men are stung in the genitalia when they urinate against an object while squatting. The laboratory often shows leukocytosis, hyperglycaemia and a transient increase of the pancreatic and cardiac enzymes. The ECG can display temporary ischemic deviations. Investigations should focus on potential complications of scorpion envenomation.

**Scorpion stings, differential diagnosis:**

- Spider bite by *Latrodectus mactans* (black widow). The bite of the female spider produces little local reaction, contrary to bites by *Loxosceles reclusa*, yet is characterized by marked abdominal muscle rigidity, pain and excessive sweating. Dysphagia, sialorrhea, vision impairment and generalized hyperesthesia are generally absent with these spider bites. In South America, bites by *Phoneutria* spiders need to be considered.
- Overdoses of neuroleptics, anticholinergics or tricyclic antidepressants. Generally these products...
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do not produce excessive salivation and there is no local pain.
- Organophosphate poisoning causing inhibition of acetylcholinesterase, leading to a buildup of acetylcholine. These insecticides also cause agitation, restlessness, muscle weakness, muscle fasciculations, hypersalivation, diarrhoea, miosis, transpiration, tachycardia and respiratory difficulties. However there is no pain.
- Tetanus, botulism, diphtheria, meningitis and encephalitis can cause similar symptoms.
- Neurotoxic snakebite.
- Thyroid storm, carcinoid or pheochromocytoma.

Treatment

Patients with systemic symptoms must be hospitalized for 24-48 hours, preferably in an intensive care unit. Cardiac arrhythmia, hypertension and respiratory problems must be monitored. The airways must be kept open. Administration of oxygen and artificial respiration can be necessary.

Pain relief with powerful analgesia is often required. Local application of ice can reduce the pain, but may not be tolerated due to hyperaesthesia of the skin. Opiates should be avoided because of the danger of respiratory depression. Sometimes simple infiltration of the sting site with 2% xylocaine (i.e. lidocaine without adrenalin) can reduce the pain. The general management is aimed at neutralising the effects of the overstimulation of the autonomous nervous system. Hypertension is counteracted by giving the vasodilator prazocin (alpha-blocker, Minipress®) or nitroglycerin if there is pulmonary oedema. Atropine is sometimes used as a parasympatholytic agent, but can aggravate orthosympathic symptoms, so usually it is preserved for bradycardia associated with hypotension. In case of neuromuscular incoordination or convulsions diazepam IV should be given. Inotropes (e.g. dobutamine) and diuretics (furosemide) are indicated if there is heart failure. Hyperthermia requires cooling and salicylates.

Most cases improve without antiserum within 9-30 hours (except for pain and paresthesias). In the event of severe envenomation, death frequently occurs within 6 hours after the sting. When systemic symptoms or autonomic excitations is present, IV antiserum is recommended. It should be diluted and administered in an IV infusion over 20-30 minutes. The dose is not age-dependent. Antivenom is expensive and guidelines often suggest and that its use should be restricted to cases of severe envenomation. However, once severe envenomation has developed, the administration of antivenom may be less effective, since its primary therapeutic action is to bind toxins; it does not reverse established pathophysiological injury, such as excess levels of catecholamine, pulmonary oedema, and cardiogenic shock. Antisera are good for neutralizing neuromuscular effects but have little effect on pain or paraesthesias. A type III hypersensitivity reaction can develop after administering the
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antiserum (horse, donkey or goat serum; see treatment of snakebites). Type I reaction (anaphylaxis) is exceptional. Tetanus vaccination must be checked.

**Antitoxin:**

<table>
<thead>
<tr>
<th>Region</th>
<th>Antitoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA and Mexico</td>
<td>anti-<em>Centruroides</em></td>
</tr>
<tr>
<td>South America</td>
<td>anti-<em>Tityus</em></td>
</tr>
<tr>
<td>South Africa</td>
<td>anti-<em>Parabuthus</em></td>
</tr>
<tr>
<td>Maghreb</td>
<td>anti-<em>Androctonus</em> and anti-<em>Buthus</em></td>
</tr>
<tr>
<td>Egypt and Israel</td>
<td>anti-<em>Leiurus</em> (also active against Androctonus crassicauda)</td>
</tr>
<tr>
<td>India</td>
<td>anti-<em>Mesobuthus</em></td>
</tr>
</tbody>
</table>

**Prevention**

Firstly, reduction of the places of shelter and the food supply of the scorpions. Insecticides are only effective in the sense that they eliminate the prey of scorpions. There is often insufficient contact between the body of the scorpion and the insecticides to be directly toxic. Natural enemies of the scorpions include cats and solpugids (alias camel spider). Of course, a house cat is no guarantee that there will be no scorpions in or around a house. It is recommended to clear away junk, loose wood etc. (fewer hiding places). The same applies for certain types of vegetation (e.g. *Opuntia* cactus hedges in northern Africa). Cracks and crevices in and around the house must be sealed. In endemic areas it is best to always shake out shoes before putting them on and to examine clothes and blankets before using them. It is prudent to also check the toilet before use. At night, scorpions can easily be detected with an UV-light.

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**Spiders**
Summary

- *Loxosceles* (violin spiders): cytotoxic. Local pain, skin necrosis, rarely systemic symptoms
- Mygalomorph spiders: fine urticarial hairs. Itching and eye damage. Respiratory problems
- Funnel-web spiders: Neurotoxic and local pain
- *Phoneutria* (banana spiders): local pain and systemic reactions

General

The subphylum of the Chelicerata includes 4 classes: Euryptera (extinct), Pycnogonida (sea spiders), Merostomata (horseshoe crabs) and Arachnida. The latter includes animals such as spiders, scorpions, mites and ticks. The name “Chelicerata” refers to the modified mouth parts (chelicerae). Spiders form the order of the Araneida (id. Araneae) within the Arachnida. The number of spider species is estimated to be 30,000 to 34,000. There are only a small number of spiders which are potentially harmful for human beings. The reason for this is that most species simply have too little venom or their fangs are too short to penetrate human skin. The venom of some spiders is only active against their natural prey and has no effect on human beings. Finally for some species the probability of spider-human contact is very low. Mortality as a result of spider bites is very low compared to snakebites, although there is a moderate morbidity (globally > 10,000 each year).

Some spiders are large. The record is held by *Theraphosa leblondi*, the Goliath bird spider from Guyana. A giant specimen had a body length of 10 cm, a leg span of 26 cm and fangs of 25 mm. Some species have a limited geographical range (e.g. *Atrax robustus* in a limited part of Australia, *Phoneutria nigriventer* in Brazil), yet others are quasi cosmopolitan. There have been repeated instances of spiders, originally endemic in one area accidentally being introduced into another area where they had not been naturally present. In 2003, there was a notorious incident where *Latrodectus mactans hasselti* (black widow) was accidentally introduced in Hasselt, Belgium. Knowledge about spider bites is limited and incomplete, given that bites are often not noticed immediately (including that of the black widow) or because the spider was not identified.

Spiders produce various types of silk for different purposes, such as for the web, winding around prey or eggs, “droplines” to make possible a hasty exit, for dissemination (“balloon riding” via a filament that is carried along by the wind), as a nuptial gift. Fibroin and sericin are produced in separate silk glands. Not all spiders produce webs. Some hunting spiders rely on their vision and speed to capture their prey.
Venom glands and venom

Most spiders have venom glands. The venom glands lie either in the chelicerae or at the front of the cephalothorax. The venom duct leads to the fangs, which are located at the end of the chelicerae. The venom is injected into the natural prey but is also used to defend against predators. After having killed the prey, the spider releases digestive juices over it and afterwards sucks up the liquefied mush. Spider venom has various purposes. Spiders which hunt, such as *Loxosceles* and *Phoneutria*, have neurotoxic / proteolytic toxins in their venom. Spiders which make webs generally have weaker venom, except for *Latrodectus*. Some bird spiders have urticarial hairs which, when lost by the animal, can irritate skin, conjunctivae and the mucous membrane of the mouth. Similar irritating hairs are also found in other animals, such as some caterpillars (e.g. procession caterpillar) and various adult butterflies.

Species, clinical and treatment

**Loxosceles**

*L. reclusa* (violin spider, brown recluse spider in North America) and *L. laeta* (South America) are the most familiar and notorious. They have a beige-brown colour with a dark spot in the form of an upside-down violin dorsally on the cephalothorax (the “violin” points to the rear of the abdomen).
There are three pairs of eyes (dyads), one in front and the others on the sides. In nature they can be found under stones, logs, etc., but the animals also often enter houses and thrive in this environment (they are “synanthropic”). They are often found there in large numbers. In South America *L. laeta* is known as the “araña de los rincones” [“rincón” = corner], which refers to this peridomestic character. In so far as their psychology is understood, spiders only bite when they feel threatened. They live 1 to 3 years.

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Loxosceles spider bite. The venom can provoke skin necrosis. Copyright Alexander von Humboldt Institute, Peru

The venom of *Loxosceles* sp. is primarily cytolytic and haemolytic. Clinically, a bite results in initial pain followed by mild skin irritation. After 6 hours or so the pain intensifies. There are local vasospasms and ischemia develops. An itching oedema with a red halo and purple centre develops. A
central bulla can form. This can evolve into a necrotic wound which nevertheless remains limited to the skin. A bite by *Loxosceles reclusa* can produce significant skin wounds, with necrosis and tissue loss. Underlying muscle tissue is not affected. A deep scar can remain. Occasionally there are systemic reactions with haemolysis and anaemia, clotting disorders, kidney failure and, in exceptional cases death. The patient can develop chills and fever, macular rash, joint pain, nausea and vomiting. Treatment is essentially symptomatic. Tetanus prophylaxis must not be overlooked when local necrosis is present. When a patient is seen soon after a bite, dapsone 50-100 mg twice per day can be given, in order to limit the necrosis. It is best if G6PD-deficiency is excluded first. The efficiency of dapsone is not clear however. The wound should not be debrided too quickly (wait up to 2 weeks). Sometimes a skin graft may be necessary. When kidney failure or clotting disorders occur, the patient should be hospitalised. Anti-Loxosceles antiserum exists, but is usually not available.

**Latrodectus**

![Latrodectus hasselti](image)

Latrodectus hasselti. Australian black widow spider. Notice the red mark on the abdomen. Photo by Aart Noordam with special thanks to Arabel.
Latrodectus mactans. North American black widow spider. A red mark, sometimes diabolo-shaped, can be seen on her round ventral abdomen. Photo by Gilbert Loos with special thanks to Arabel.

These spiders, also known as black widows, have a very wide geographical distribution. The common English name refers to the habit of the female to eat the male after inseminating her. There are no natural wild populations of black widows in central and northern Eurasia (yet), although accidental introduction of exotic species occasionally happens. E.g. introduction in Belgium was first seen in 1967 in Tervuren, in 1999 *L. hasselti* was found in Bree (near Hasselt, of all places! What’s in a name?) and another introduction (*L. mactans*) was detected in August 2009 in Antwerp. Specialists recognize *Latrodectus mactans* (North American black widow), *L. hasselti* (Australian black widow) and *L. m. tredecimguttatus* (Southern Europe, including Italy; South America; spiders carry several (“13”) pigment spots). At least 3 other species exist. *L. mactans* often bears a typical red hourglass-shaped spot on the abdomen. Only bites by female black widows are potentially dangerous. The fangs of the male are too small to penetrate human skin. Australia has probably the highest rate of latroductism per capita in the world. Unlike loxoscelism, neurotoxicity plays a central role with latroductism. The initial bite feels like a pinprick, but direct local tissue damage at the bite site is
generally absent or insignificant. The venom contains several substances, the most important of which is alpha-latrodectin (= alpha-latrotoxin), a neurotoxin that triggers an increased release of neurotransmitter at nerve endings. This results in a presynaptic depletion of neurotransmitter vesicles. Acetylcholine, noradrenaline, dopamine, glutamate and enkephalin systems are all sensitive to the toxin. This release followed by depletion of acetylcholine at neuromuscular junctions leads to fasciculations and muscle spasms, followed by flaccid paralysis and risk of respiratory arrest.

Sometimes painful muscle rigidity (primarily abdominal -“pseudo-appendicitis”- but without the specific focal tenderness or rebound pain) can occur. Other symptoms are hypertension, sweating, tremor, headache, malaise, vomiting, fever, general weakness, patchy muscle paralysis (sometimes with ptosis), excessive salivation, photophobia and priapism. Mortality in published series varies from 5 to 12% but these numbers are likely to be an overestimate due to case selection. Pets such as cats can easily be killed by female black widows.

Mild cases with limited signs and symptoms tend to resolve spontaneously over hours to days. The pain however can be very intense. If pain predominates, analgesics (including opiates) may be necessary and sometimes are insufficient. In more severe cases (usually within 12 hours, but sometimes up to days after the bite), benzodiazepines (diazepam) can be used against muscle spasms and to reduce the abdominal pain. Hypertension which does not improve after pain control sometimes requires the vasodilator IV nitroprusside or nifedipine. Antivenom can be given in serious cases, including priapism, but is rarely available. Full recovery might take several weeks. Respiratory or cardiac support is very rarely needed. Neostigmine for counteracting acetylcholine depletion has been proposed but never been proven to help.

**Atrax and other funnel-web spiders**

In Australia there are 35 species of funnel-web spiders. They have a funnel-shaped web, often with triplines to detect their prey. *Atrax* species are large, aggressive spiders. The most notorious is the Australian *Atrax robustus* or Sydney funnel-web spider. The venom of the spider includes a neurotoxin with potentially fatal consequences for humans. The fangs can be up to 5 mm long and can penetrate a fingernail. The spider makes its web under stones, logs, hedges, near vegetation and fences. Clusters of up to 150 animals have been found. With this species, the bite of the male spider is much more serious than that of a female spider and is justifiably highly feared. The venom includes the small protein robustoxin, a unique presynaptic neurotoxin. The venom interferes with the release of the neurotransmitters noradrenaline and acetylcholine at the level of the motor and autonomous nerves.
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A bite by *Atrax* is followed by intense pain. This is probably due to the mechanical damage and the acidic pH (4.5) of the venom. No dermal necrosis results. In serious cases there follows a rapidly progressive neuromotor syndrome which can be fatal within two hours. Initially there is local piloerection and muscle fasciculation. These symptoms become generalised with tingling sensations around the mouth and tongue and lip spasms. Within a half hour they are followed by marked hypertension, tachycardia, 2nd degree AV block, hyperthermia, haemoconcentration and coma with increased intracranial pressure. Copious sweating, excessive salivation, lacrimation, diarrhoea and muscle cramps follow. Asphyxia can lead to death. If the patient survives, there follows hypotension and intermittent apnoea after one or two hours, possibly with pulmonary oedema. This too can be fatal. Muscle enzymes (CK) can rise substantially. Children are at higher risk than adults.

Shortly after a bite it is recommended that a splint and a lymphatic tourniquet (“pressure immobilisation technique“) should be applied. In this way the systemic resorption of the venom is slowed down and the patient can be transferred to a hospital. Antitoxin has been available in Australia since 1981 (Funnel Web Spider Antivenom, CSL, Australia). Oxygen, mechanical respiration with PEEP, atropine (against bronchorrhea and excessive salivation) and short-acting antihypertensives should be used depending on the symptoms. Since acute stomach dilatation can develop, nasogastric aspiration must be performed.

**Phoneutria**

These aggressive South American spiders are nocturnal hunters which do not weave webs. They often hide in bunches of bananas, hence their popular name. *Phoneutria* is unusually aggressive and tends to bite several times at the same site in quick repetition.

The venom is a complex mixture with several neurotoxic components. It acts on both the peripheral and the central nervous system. A bite is followed by sharp pain and then by tachycardia, hypertension, hypothermia, profuse sweating, excessive salivation, nausea and vomiting, priapism and dizziness. Death can occur within 6 hours and is generally attributable to respiratory arrest. A polyvalent antiserum (anti-Loxosceles and anti-Phoneutria) can be given through local infiltration and IV administration.

**Lycosa**
Wolf spiders belong to the Lycosidae family. They are nocturnal hunters which generally do not spin webs. Earlier it was believed that they hunted in groups, hence the popular name. Wolf spiders include species with a moderately cytotoxic venom. The best known is the European tarantula (Lycosa tarantula). Its bite was earlier deemed to provoke tarantism in the victim, a syndrome characterised by stupor and a wish to dance. Possibly this refers to the consequences of Latrodectus bites, rather than Lycosa itself, since the latter only causes local pain, swelling and erythema. Tetanus vaccination, painkillers and local disinfection suffice for bites by these animals.

**Bird spiders and their relatives**

“Bird spiders” belong to several genera. Some people keep them as “pets” although several species are protected under the CITES convention (Convention on International Trade in Endangered Species).
Several American genera of bird spiders have fine urticarial hairs. The density amounts to 10,000 fine hairs/mm². When the animals feel threatened they rub with their legs over their back, detaching the fine urticarial hairs which are armed with small barbs. These can be released by the thousands and cause persistent itching when they come into contact with the skin and work their way under the surface. Penetration into the cornea or inhalation can lead to serious consequences. When handling these animals, wear gloves and safety glasses, avoid rubbing your eyes and wash carefully after manual contact. Bites by these spiders cause local pain and swelling, whether or not followed by lymphangitis. The treatment is symptomatic. Beware of the fact that urticarial hairs are also present on exuvia (shed skin), even when preserved in alcohol!

**Chiracanthium**

*Chiracanthium* species are notorious for their annoyingly painful bites. A bite is followed within 30 minutes by local itching and redness. Sometimes this can evolve to local necrosis. Systemic effects include (rather rare) nausea and abdominal pain, as well as headache. The treatment is symptomatic. Besides black widows and wolf spiders, the only European spiders which should really be handled carefully are *Chiracanthium* species (Clubionidae) and the water spider *Argyroneta aquatica*. 
Pre-travel consultation

In the last decade, a major increase in international travel has been seen. Each year, more than a billion international tourist arrivals are counted. 15-65% of those experience some sickness and 5-15% need to seek medical care. About 1/100.000 travelers die during their journey. Of travel related deaths 50% are due to accidents (car, drowning, ...), 40% due to a cardiovascular event, 9% secondary to neoplasms or other underlying diseases and only 1% due to an infectious cause.

A pre-travel consultation is a perfect example of preventive medicine. It is more than delivering vaccinations and prescribing antimalarial pills. The aim of a pre-travel consultation is to inform the traveler about potential health risks while travelling and to discuss possible interventions (like vaccinations, antimalarial pills).

Taking a glance at the above figures, the importance of safe travel vehicles with seat-belts cannot be underestimated: this advice might be much more cost-effective than any pre-travel vaccine given. Making sure that people with underlying conditions travel in their best possible health-status is also of major importance.

Possible health risks depend on several factors:

- The traveler: pre-existing conditions, risk behavior, vulnerable travelers like the elderly, pregnant and young children
- Destination
- Type of travel: expat, backpacking, cruise...
- Special activities: diving, high altitude, biking...

Each pre-travel consultation should include:

- Discussion about pre-existing conditions: is the traveler fit enough for this travel? What about travel insurance? Especially in case of vulnerable travelers, the risks of traveling should be discussed. In any case, it is always a shared decision, but sometimes, the traveler may want to postpone the travel or to change the destination after being informed. E.g. people who have a contra-indication for yellow fever vaccine, pregnant women may not go to a country with an...
ongoing Zika virus outbreak.

- **Prevention of travel-related infectious diseases**
  - **Malaria risk**: is there malaria, which precautions to take? Only mosquito bite prevention or also prophylactic antimalarial drugs? Continuous malaria pills or only during shorter periods (“on demand”) when entering a higher-risk region (e.g. South-East Asia)? No preventive measure protects 100%, so in case of fever up to 3 months after return, malaria needs to be ruled out.
  - **Risk for other diseases transmitted by mosquitos?** Think of dengue, chikungunya, zika, Japanese encephalitis…?
  - **Travelers diarrhea**: how to prevent, what to do when diarrhea occurs, whether or not to prescribe antibiotics, when and how to take them?
  - **Sexually transmittable diseases**: always to be discussed when people travel without their partner. Take condoms! Even though it is generally not “planned”, many travelers have sex occasionally while traveling.
  - **Other infectious diseases**: schistosomiases, larva migrans, tunga penetrans, ...
  - **Vaccinations:**
    - **Mandatory vaccines?**
      - Yellow fever: this vaccine is subject to the International Health Regulations. Proof of vaccination – written down in the” yellow vaccination card”- can be a requirement for entry in some countries. Since 1/7/2016 the vaccination is lifelong valid, however, for some people, the duration of protection might not be lifelong: a single reinforcing vaccination is recommended when returning to an endemic region.
      - Meningitis ACW135Y (pilgrimage to Mekka)
      - Polio in Afghanistan and Pakistan if staying longer than 4 weeks
    - **Are standard vaccinations updated?**
      - tetanus-diphtheria-whooping cough;
      - measles
      - hepatitis B when risk behavior or social volunteer work or medical sector
      - What about flu and Covid-19 vaccination in vulnerable travelers?
    - **Travel-related vaccines:**
      - Hepatitis A,
      - Japanese encephalitis
      - Tick-borne encephalitis
      - BCG: seldom necessary, but sometimes mandatory in young children of expats (in e.g French Lycee or American Lycee). In some European countries, this vaccine is not available anymore.
References:

Guidelines can change in each country; the Belgian Guidelines can be found on the website www.wanda.be from the Institute of Tropical Medicine. Wanda is also available as an App: all information is offline available.

ALWAYS USE THE LATEST UPDATE!!! ESPECIALLY YELLOW FEVER RECOMMENDATIONS AND RECOMMENDATIONS ABOUT MALARIA CHANGE!

International guidelines:

WHO guidelines of travel medicine: http://www.who.int/ith/en/

CDC yellow book (cave malaria guidelines are very “American” and in Europe we prescribe usually less frequently anti-malarial pills): http://wwwnc.cdc.gov/travel/yellowbook/2016/table-of-contents

Polio recommendations: http://www.polioeradication.org/

General information

Travel medicine: Travel medicine 3rd edition, Keystone

General information about vaccines: Vaccines, 6th edition, Plotkins

Info about travel equipment, survival: Field guide to wilderness medicine, P S Auerbach, 4th edition

Ongoing epidemics: Promed: http://www.promedmail.org/, CDC, ECDC

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