

## Summary

- Chronic infection with *Mycobacterium leprae*
- Bacteria multiply in the macrophages and Schwann cells of peripheral nerves
- Clinical spectrum: from tuberculoid (paucibacillary) to lepromatous (multibacillary)
- Thickened nerves with neuritis: trophic, motor and sensory disturbances
- Neuropathy leads to paralysis, trophic ulcers, blindness, mutilations
- No central nervous system lesions
- Skin: numb white area with elevated edge (tuberculoid) to diffuse infiltration with nodules (lepromatous).
- In lepromatous leprosy also involvement of deeper tissues (testes, tongue, eyes, etc.)
- Diagnosis: clinical, modified Ziehl staining of smears (skin lesion, nose, earlobe)
- Treatment of leprosy with dapsone, rifampicin and clofazimine
- Leprosy reactions: type 1 (change in immunologic defence) and type 2 (immune complex)
- IRIS reaction possible in HIV patients within 4 months of starting HAART

## General

Hansen's disease, or leprosy, was previously present in most parts of the world. Now, it is a problem in regions of extreme poverty. The number of registered cases is falling: 5.37 million in 1985, 3.1 million in 1992, 1.8 million in 2000, 249,007 in 2008, and 174,087 new cases in 2022, according to WHO. At the end of 2022, the prevalence was estimated at 154,459 cases, and more than half came from India. There are probably as many patients who have not yet been diagnosed. The number of severe infections (with disability) is decreasing, reflecting earlier detection. It is hoped that the general incidence of the infection will be below 1/10,000 soon. A prevalence of less than 1/10,000 is regarded as the goal for eliminating leprosy as a public health problem, this is not the same as eradicating the disease. By 1999, 80% of all leprosy cases occurred in 6 countries: India, Brazil, Bangladesh, Indonesia, Myanmar and Nigeria. HIV-infected patients usually die of infections caused by faster-growing bacteria (e.g., tuberculosis) and not from the slow-growing *Mycobacterium leprae*. The AIDS epidemic has, therefore, had little effect on the incidence of leprosy, but immune reconstitution after starting HAART can lead to florid lesions in a patient who has subclinical asymptomatic leprosy. The illness is characterized by skin and nerve lesions, which, together with progressive tissue destruction, causes mutilation.

Resistance to dapsone became a significant problem around 1980. Thus, combination therapy has been used since that time.

### Historical note

Due to the mutilations which can occur in leprosy, since ancient time there has been a lot of prejudice and stigmatization. Sufferers were usually banished from the community. Apart from the physical handicap, the emotional, economic and social consequences were often very severe. The hypothesis was that leprosy was a hereditary disease and/or a punishment from God. One argument in favour of hereditary transmission or rather against the hypothesis of leprosy being an infectious disease was the result of transmission experiments, in which Dr Daniel Danielssen in Bergen, Norway, injected himself and four helpers with material obtained from skin nodules from leprosy patients, without further consequences. The pathogen of this chronic disease was discovered in 1873 by the Norwegian Gerhard Henrick Armauer Hansen. At that time there were several thousand leprosy sufferers in Norway. Following the example of John Snow (see Cholera) he followed the course of each illness over time. Families of which the members lived physically close together had a higher incidence of the disease, compared to families of which the members lived apart. In this way he came to the idea that this could be an infectious disease. In 1871-72 he observed small vague intracellular rods in skin nodules. This information was published in 1873. A staining method was discovered in 1880 by the German Albert Neisser. The pathogen proved to be a bacterium: *Mycobacterium leprae*. It was the first time that a bacterium had been considered responsible for causing a human disease. Regrettably, Dr Hansen carried out an unethical experiment, in which he introduced material from a leprosy nodule into the cornea of another person in an attempt to prove its infectious nature. He was suspended from practicing for life by the courts.

In 1873 Jozef de Veuster, better known as Father Damian arrived on Molokai in the Hawaiian archipelago. There he found 800 leprosy patients who were living in miserable conditions. He decided to stay and to devote the rest of his life to improving the fate of his fellow human beings. In 1876 he developed lesions on his arms and back (an illustration of the long incubation period). In 1881 he developed nerve pain and in 1883 his left foot lost all sensation. He died on 15th April 1889.

## Mycobacterium leprae

*Mycobacterium leprae* is an obligate intracellular, slow-growing acid-fast bacillus (0,5 x 3-8 µm). On Gram-staining, it is Gram-variable. The *Mycobacterium leprae* genome project sequenced the entire genome in 2001. The genome is relatively small (3,27 Mbp) and contains about 1600 genes and more than 1100 pseudogenes. In comparison, *Mycobacterium tuberculosis* contains about 4000 genes. This seems to imply massive gene decay in the leprosy bacillus and the absence of critical enzymatic pathways, thereby requiring host parasitism for survival.

### Biological information

Do not confuse *Mycobacterium leprae* with *Mycobacterium lepraemurium*, a natural pathogen of rats and mice. The disease caused by *Mycobacterium lepraemurium* is sometimes used as a model for human leprosy. In 2008, *Mycobacterium lepromatosis* was identified (analysis of 16s rRNA gene) as a related but distinct mycobacterium which might be responsible for diffuse cutaneous leprosy and Lucio's phenomenon in humans. Additional research still has to identify the place in the overall pathology of the disease.

Phenolic glycolipid-1 (PGL-1) is a glycolipid in the capsule of *Mycobacterium leprae*. PGL-1 contains an antigenically distinct trisaccharide unit that is not found in any other bacteria. PGL-1 makes up to 2% of the total bacteria mass, suggesting that the function of the sugar chains may be related to functions unique to *Mycobacterium leprae*. PGL-1 binds to laminin-2, which facilitates PGL-1 binding to the basal lamina of axons on Schwann cells and the resulting invasion of the cells. This might explain the neurotropism of these bacteria. Because this invasion can occur even when the bacteria are dead, the invasion seems not to be driven by the bacteria, but by passive interaction between glycolipids in the capsule of the cell wall and molecules in the basal lamina of Schwann cells. If this binding can be blocked, a new therapeutic avenue may become possible. However, laminin-2 is also present in the basement membrane of other tissues. The basement membrane in muscle is composed of laminin, type IV collagen, entactin/nidogen and heparan sulphate proteoglycan. One major component of the basement membrane in muscle is laminin-2, which is composed of a heavy chain laminin a2 and two light chains, b1 and laminin g1. Other factors must also play a role in the fact that *Mycobacterium leprae* has a predilection

for neural tissue.

It has long been suspected that leprosy has a strong genetic component. A leprosy susceptibility locus on the long arm of chromosome 6 (region q25-q26) was discovered in 2003/4. This DNA stretch included the Parkinson's disease gene *PARK2* and the co-regulated gene *PACRG*. The *PARK2* gene is expressed by human Schwann cells and macrophages, which are the primary host cells of *Mycobacterium leprae*.

### Mycobacterial culture

It has not been possible to date to culture the bacterium in vitro, which has made research extremely difficult. This can be circumvented to some extent by making use of animal experiments. However, the bacterium multiplies very slowly (generation time 12 days). It was assumed that the bacterium had a preference for cooler parts of the body. In 1960 the American Charles Shepard (CDC) discovered that it is possible to culture the bacterium in the footpads of mice (average 30°C). In this way it was possible to obtain 10<sup>6</sup> bacteria from each footpad. More severe infection could be obtained by using immune deficient mice (e.g. athymic nude mice). It became possible to test the efficacy of drugs against the mycobacterium. In 1971 Waldeman Kirchheimer and Eleanor Storrs discovered that the nine-banded armadillo, *Dasypus novemcinctus*, could also become infected. This species was selected because it has a low body temperature (approximately 34°C) and a primitive immune system. The animal develops a generalized infection with involvement of the internal organs, especially the liver and spleen. After intravenous inoculation, between 10<sup>10</sup> and 10<sup>12</sup> mycobacteria per gram of tissue can be obtained (chiefly from the liver and spleen). In this way it became possible for researchers to analyse large amounts of proteins and DNA, which accelerated research. Latest data suggest that in South America armadillos might function as a natural reservoir for this infection but more study is required, clarification of this would be very important regarding the possibility of eventual eradication of the disease.

## Transmission

Humans form the reservoir. Infection with *M. leprae* is possible in chimpanzees, Rhesus

monkeys, mangabey monkeys and wild armadillos, but the epidemiological importance of this is unknown and is probably very small. Further research is required to understand its significance. In 2011 genetic analysis showed that in some cases in the Southern USA, leprosy might be acquired from infected armadillos. Leprosy, in such cases, can be considered as a zoonosis.

The transmission route (or routes) is (are) not known with certainty. There is probable transmission via nasal secretions from humans with multibacillary leprosy. Unlike chronic skin wounds, the affected nasal mucosa in these patients contains large quantities of bacilli. *Mycobacterium leprae* is identified in the oral mucosa of paucibacillary and multibacillary leprosy patients. Speaking, coughing and sneezing produce aerosols (droplet clouds). The most crucial port of entry is probably the lungs: the bacteria are breathed in. Direct contact is probably of much lesser importance. Long-term close contact with leprosy sufferers increases the risk of infection. Nevertheless, most cases occur without known contact with leprosy patients. The risk of the disease for leprosy health workers is minimal. Leprosy is possibly a highly infectious disease with low disease expression. Most people exhibit no symptoms after infection while others have brief cutaneous lesions. The susceptible individuals are in the minority: fewer than 10 % of infected people become ill. In hyperendemic regions, the proportion of people with symptoms is not more than 4 %, and the ratio is usually smaller (1/1000). Transplacental infection in untreated multibacillary pregnant patients has been described but is rare (in approximately 1% of the children in this situation).

### Leprosy epidemic?

Leprosy epidemics do not occur, although a single unusual exception has been recorded. In 1912 a woman with leprosy arrived in the Oceanic island state of Nauru. This had presumably never happened before. In 1920 the first secondary case was diagnosed in the indigenous population. In 1924 there were 284 cases in a population of 1250 people. In 1929 there were 438 cases (34% of the population), after which the incidence decreased. More than 90% of the lesions were tuberculoid and deformities were rare. The extent to which genetic inbreeding within an immunologically naive population was important in this case, has not been investigated. (Compare with the ravages caused by measles in isolated island dwellers when they were first contacted by Western seafarers; see also the results of

smallpox in the Aztec kingdom after the arrival of Cortez in the 16th century).

## Physiopathology

It is assumed that after inhaling the bacterium multiplies within macrophages and Schwann cells (myelin-producing cells around peripheral nerves) and spreads very slowly. This occurs chiefly at the relatively cooler superficial body parts: the skin, superficial nerves, eyes, nasal mucosa and testicles. *Mycobacterium leprae* seems to be a thermophobic germ. Very rarely (in lepromatous patients), the bacteria spread to the deeper tissues (lymph nodes, muscles, bone, and even kidneys). The central nervous system is never affected. Nystagmus, ataxia or the presence of Babinski's sign cannot be attributed to leprosy. The human body defends itself against this mycobacterium employing specific defense cells (lymphocytes). Few bacteria and a strong Th1 immunity response characterizes tuberculoid leprosy. Patients with lepromatous leprosy have lesions with many bacteria and a strong Th2 immunity (with reciprocal repression of the Th1 response). If the Th1 reaction is strong, there are few bacteria and well-defined granuloma. If minimal, the bacteria can multiply virtually unhindered and granuloma formation diminishes. The reason why a person develops a Th1 or Th2 response to *M. leprae* is not yet clear. In lepromatous cases, the high bacillary load leads to an abundance of mycobacterial antigen, leading to immune complexes bound to antibodies. These circulating immune complexes bind complement to opsonize them and facilitate phagocyte uptake.

## Leprosy classification

The symptoms vary greatly. This has led to considerable confusion in the past. A fundamental breakthrough was achieved by Ridley and Jopling (1962, 1964). They concluded that the patient's cellular defences determine the clinical expression. They proposed a classification for the disease with tuberculoid leprosy at one extreme and lepromatous leprosy at the other and a spectrum of borderline (B) forms in between

**TT <-> BT <-> BB <-> BL <-> LL**

In practice, this classification is complex and requires high expertise and experience. Even

so, consensus is difficult to reach in a single patient. Some classification schemes include polar forms (TTp and LLp). The WHO promoted a simpler, more straightforward pragmatic division into paucibacillary and multibacillary forms for operational reasons and accepted in 1987 (pauci = few; multi = many). If at least 1 acid-fast rod is found, the patient is referred to as multibacillary. A disadvantage of this very simple classification is that if the microscopy is poorly executed, a multibacillary case may be classified as paucibacillary and will then remain under-treated. Therefore, WHO has harmonized pauci- and multibacillary leprosy treatment in 2018, recommending the same 3-drug regimen for both presentations. The only difference is the treatment duration. Leprosy can be classified on clinical grounds only. Patients with 1 to 5 skin lesions and maximally 1 trunk nerve affected are considered paucibacillary. If more than 5 skin lesions or more than 1 trunk nerve are involved, the patient is regarded as multibacillary.

**Paucibacillary:** Indeterminate, TT, BT (with no acid-fast rods on the smear)

**Multibacillary:** BT with bacteria visible on a smear, BB, BL, LL

#### The Ridley-Jopling classification reflects the cellular resistance of the patient:

A patient with the tuberculoid form (TT) has high cellular resistance. There are few bacteria, the lesions are localised, and the patient is not very infectious. If leprosy bacillus antigen (lepromine) is injected into the skin, the lymphocytes react strongly. A local reaction is observed. The lepromine test is positive in this case. The reaction is read after 28 days (Mitsuda reaction): diameter > 5 mm is highly positive (cf. Mantoux reaction in tuberculosis). An earlier reaction (Fernandez reaction: 48 hours) can also be read but it is non-specific. There is no cross reaction between Mantoux and the lepromine test. There is quite a poor correlation between the Fernandez and Mitsuda reactions.

There is little immunological resistance in lepromatous form (LL). There are countless bacilli and the lesions are diffuse. Patients are infectious for their environment. The lack of resistance is reflected in the negative lepromine test. The patient produces antibodies but these are not protective.

## Clinical aspects

### Indeterminate leprosy

Most infections do not give rise to symptoms (only to a positive lepromine test). After infection, there is an incubation period of 2-15 years (the mycobacteria multiply slowly). If the patient does not recover spontaneously, a transient indeterminate lesion appears. It consists of one or more grouped hypopigmented non-pruritic macules, which are well delineated. On white skin, they are red or hyperpigmented. There will rarely be any reduction of sensitivity (hypo-aesthesia). Sometimes, somewhat reduced sweating is seen. Nerves never become thickened at this stage. Bacilli are practically never found in this lesion. After the initial lesion, there is evolution towards recovery or towards one of the forms in the spectrum TT - LL, which usually occurs within 2 years. Approximately 75% of indeterminate leprosy cases recover spontaneously. This indeterminate stage is often not diagnosed. Some indeterminate leprosy infections can be diagnosed on clinical grounds alone, especially in family members of an untreated leprosy patient. In other situations, diagnosis is often only possible via histology.

### Tuberculoid leprosy

In tuberculoid leprosy, there are only one or a few asymmetrical skin spots on not more than two body parts. They are sharply delineated, sometimes with a slightly elevated border and central healing. There are often papules on the edge. The lesion is rather hypopigmented (on dark skin) or erythematous (on white skin), and sensitivity is lost. First, the sensitivity to temperature decreases, then the sense of touch, then pain and finally, deep sensitivity. There is hair loss, and the skin is dry. One or two peripheral nerves are affected (thickened) at the areas of predilection or in the region of the skin lesion.

The consequences of neural dysfunction appear early (muscle weakness and atrophy, reduced sensitivity to pain, sense of touch and sweating). Paralysis is common. It sometimes occurs before the loss of sensitivity. There is no direct involvement of other tissues. Leprosy is the only infectious disease which causes thickening of the nerves. Purely neurological involvement also sometimes occurs without skin abnormalities (= neural leprosy). This slow form of neural dysfunction stands in sharp contrast to the swift neurological damage that

occurs during leprosy reactions. In leprosy, autonomic symptoms such as bladder or bowel problems, postural hypotension, impotence, etc, are rare. Patients with amyloidosis tend to have pronounced autonomic neuropathy.

## **Peripheral neuropathy, mononeuritis multiplex and polyneuropathy**

Peripheral neuropathy, mononeuritis multiplex and polyneuropathy

Most cases with leprosy present with skin and neurological signs. However, pure neuritic leprosy also occurs. In the tropics, leprosy should therefore be considered in the differential diagnosis of any peripheral neurological symptom. This tends to be predominant axonal (lower amplitudes on EMG), probably due to intraneuronal oedema with compression of the axons, but occasionally accompanying demyelination is found (slower conduction speed on EMG). Here the differential diagnosis becomes much more difficult and sometimes can only be reached on nerve biopsy.



Indeterminate leprosy, small lesion on left upper arm. The lesion was initially treated for suspected mycosis. Copyright ITM



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Tuberculoid leprosy, hypopigmented skin lesion. Photo Dr Brouwers. Copyright ITM

An individual peripheral nerve can become damaged by direct trauma, invasion by a tumor,

but also via entrapment e.g., carpal tunnel syndrome, repeated compression, such as prolonged leaning on an arm in a particular position (N. radialis) or repeated pressure, e.g., at the level of the fibula head while seated on the ground (N. fibularis).

The peripheral nerve damage in leprosy (outside of leprosy reactions) is due to a slow-evolving mononeuritis multiplex, i.e., dysfunction of individual named peripheral nerves. Evolution is much faster in leprosy reactions, which can lead a clinician astray, especially if skin lesions are few. Sometimes the distinction between polyneuropathy with typical symmetrical distal gloves and stocking distribution is unclear. The differential diagnosis of mononeuritis multiplex is vast. Many systemic diseases associated with mononeuritis multiplex cause nerve damage by affecting the vasa vasorum.

Inflammation of these structures should be looked for in a biopsy when vasculitis is possible. Mononeuritis multiplex occurs in several forms of vasculitis (polyarteritis nodosa, Granulomatosis with polyangiitis, systemic lupus erythematosus, livedoid vasculopathy), other connective tissue diseases (mixed forms), anti-phospholipid antibody syndrome, cryoglobulinemia, sarcoidosis, amyloidosis, diabetes and as a paraneoplastic entity. Nerve lesions secondary to chronic hypereosinophilia will orient the clinician in a very different direction. Neuropathy due to diphtheria occurs about a month after infection, mainly demyelination of motor fibers, e.g., of motoric cranial nerves, leading to visual symptoms. Lyme disease can give acute neuritis, and so will usually not enter the differential diagnosis.

### Peripheral neuropathy differential diagnosis

Lepromatous leprosy is a cause of peripheral neuropathy, leading to glove-and-stockings parasthesia. The differential diagnosis is large: many cases of polyneuropathy are secondary to metabolic disturbances and intoxications, ethanol being the prime example. Some metabolic diseases can be interpreted as auto-intoxication, e.g. uraemia. The clinician has to consider diabetes mellitus, hypothyroidism, vitamin 12 deficiency, dry beriberi (thiamine deficiency without cardiac failure), dysglobulinemia including multiple myeloma and Waldenström macroglobulinemia, primary and secondary amyloidosis, chronic hepatitis, heavy metal intoxication (lead, arsenic, thallium, mercury), solvents (hexacarbon solvents and CS<sub>2</sub>), buckthorn toxin (used as tea), chronic ethylene oxide poisoning. Check

for possible side-effects of medication, such as isoniazid (vitamin B6 antagonism), vincristine, cisplatin, nitrofurantoin. Rarely mononucleosis, typhoid fever and mumps are mentioned as causes but the pathogenesis here is unclear. Guillain-Barré syndrome is an acute ascending inflammatory demyelinating polyradiculoneuropathy and in its acute form the distinction with leprosy is straightforward. Chronic inflammatory demyelinating polyneuropathy (CIDP) however is more difficult. It resembles a chronic form of Guillain-Barré and can occur in isolation or in AIDS. A paraneoplastic origin of polyneuropathy is often difficult to prove early in the disease (lung, pancreas, ...) but as times passes, the presence and identity of the tumour will become clear. CIDP is a chronic progressive or relapsing symmetric sensorimotor disorder, leading to generalized thickening of the brachial and lumbar plexi and peripheral nerves (including sciatic nerves and others), as can be demonstrated on whole body magnetic resonance neurography. A number of hereditary conditions can lead to neuropathy, e.g. porphyria, Tangier's disease (genetic disorder of cholesterol transport), Bassen-Kornzweig syndrome (vitamin E deficiency due to abetalipoproteinemia), Fabry's disease (lysosomal storage disease: check family history and look for corneal opacities and spoke-like cataracts), Refsum's disease (phytanic acid accumulation often with deafness and retinitis pigmentosa). Hereditary polyneuropathies such as the different types of Charcot-Marie-Tooth (early drop-foot, hammer toes and peroneal atrophy with thin "stork legs" with familial clustering), Déjerine-Sottas (more rapid and severe than "classic" Charcot-Marie-Tooth), Friedreich's disease and hereditary pressure neuropathy fall need the assessment of a specialist in neurology. Finally, many polyneuropathies are idiopathic.

### Nerve thickening

Leprosy is the only infectious disease which causes nerve thickening. Nerve thickening may also occur in rare non-infectious disorders such as certain forms of primary amyloidosis of the nerves and inherited muscular and nervous diseases. Déjerine-Sottas disease is a rare form of hypertrophic neuritis which usually leads to severe disability in childhood. Here, the skin is normal. In some cases of Charcot-Marie-Tooth disease (hereditary sensorimotor neuropathy type I), hypertrophic neuritis occurs. In Refsum's disease, an autosomal recessive familial disorder, there is a defect in the degradation of phytanic acid, which sometimes causes thickening of nerves, together with cerebellar ataxia, progressive deafness, heart problems, skeletal deformations, retinitis pigmentosa and dry skin

(ichthyosis). Neurofibromatosis can also be included in the differential diagnosis (including café-au-lait patches). Traumatic injury may sometimes cause local thickening, as may amyloidosis. Chronic inflammatory demyelinating neuropathy can lead to generalized diffuse thickening of plexi and peripheral nerves, as mentioned above. The technique to demonstrate this in a non-invasive way is whole-body magnetic resonance neurography using diffusion-weighted whole body imaging with background signal suppression (DWIBS) is at the onset of the second decade of the 21st Century only available in a few medical centres in the West.



Tuberculoid leprosy, hypopigmented skin lesion. Photo Dr Brouwers. Copyright ITM



Multiple well demarcated hypopigmented skin lesions in leprosy. Photo Dr Brouwers, Copyright ITM

## Borderline leprosy

Patients with borderline leprosy have lesions that fall between the tuberculoid and lepromatous forms. Multiple skin lesions exist, and nerve lesions are common. Three types of borderline leprosy are described: borderline tuberculoid, mid borderline and borderline lepromatous leprosy. The spectrum varies from >3 well-defined, dry, firm and rough, anaesthetic, asymmetric lesions with autonomic dysfunction (loss of hair and sweat) in borderline tuberculoid leprosy towards more generalized, ill-defined, smooth, shiny and soft, non-anaesthetic, symmetrical lesions without autonomic dysfunction in borderline lepromatous leprosy.

## Lepromatous leprosy



Lepromatous leprosy, photo Cochabamba, Bolivia



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Multibacillary leprosy, numerous hypopigmented skin patches. ©ITM

There are countless disseminated macules and/or skin nodules, with blurred outlines sometimes joining to form larger plaques. There is no central healing tendency and no hypopigmentation, although sometimes a “copper colour” is present. The infiltrated skin nodules exhibit less or no anesthesia, but numbness develops in the hands and feet. The infiltration may lead to diffuse skin thickening, chiefly of the ears, lips and forehead (“lion’s face” in LLp). In Mexico, the diffuse variety of leprosy is sometimes called “pretty leprosy” (lepra bonita) because it tends to iron out the wrinkles in the skin, restoring a youthful appearance to the patient.

Infiltration of the mucosa leads to chronic rhinitis with epistaxis, septum perforation and destruction of the nasal cartilage. The tongue is thickened, and there may be hoarseness. The upper incisors become loose and often drop out. There is often loss of the eyebrows (madarosis) and eyelashes. The central portion of the forehead (frontalis muscle) is more affected than the lateral portion. This sign is quite characteristic of leprosy and was first described by Monrad-Krohn. The sensory loss on the forehead can be quite marked (since the skin is relatively cold), but at the hairline, there tends to be an abrupt increase in the sensitivity to pinprick. Testicular atrophy leads to gynecomastia.

The nerves are not severely thickened, but the involvement of the nerves is extensive, generalized, gradual and symmetrical. The consequences of this loss are evident later in the disease, and sensory dysfunction, rather than motor defects, are foremost. Deep tendon reflexes are preserved for a long time, distinguishing this disease from many other neuropathies (except amyloidosis). Vibration sense and position sense remain intact for a long time. With the progression of the disease, the motor branches of small nerves are invaded so that there are distal atrophy, especially in the hands.

## Clinical aspects, specific problems

### Blindness

**Blindness** can occur in tuberculoid as well as in lepromatous leprosy. Blindness may be caused by:

1. Involvement of the facial nerve. This causes peripheral facial paralysis. Most often, the zygomatic branch is affected, and the eye can no longer close (lagophthalmia), which leads to drying out of the cornea. The patient attempts to draw the eyes upwards under the eyelids to moisten them. The lower eyelid may exhibit paralytic ectropion. Artificial tears may prevent corneal dehydration. Sometimes, the eyelid needs surgical correction to prevent blindness.
2. Involvement of the supra-orbital branch of the trigeminal nerve leads to an insensitive cornea. The patient does not feel dehydration or the presence of dust, resulting in keratitis. Artificial tears, as used in sicca syndrome, may be beneficial. The patient should be taught to consciously blink “” (“Think blink””).
3. Infiltration of the eye by countless bacilli with possible formation of lepromas (nodules full of bacteria). The latter only occurs in lepromatous leprosy.
4. Iridocyclitis, for which eye drops with steroids are indicated. It is seen in lepromatous leprosy. Cataract formation and phtysis bulbi are late complications.
5. Beware of glaucoma in patients treated with cortisone for leprosy reactions, as cortisone can increase intraocular pressure. Topical cortisone administered as eyedrops is more dangerous than systemic cortisone.

## Mutilations

Mutilations may occur due to:

1. Paralysis with muscular atrophy and contractures.
2. Loss of sensitivity leads to not noticing wounds or burns and maintaining postures that would otherwise be painful.
3. Failure of autonomous nerves resulting in trophic skin disturbances. Dry skin with cracks occurs.
4. Untended wounds with secondary infections may lead to chronic ulceration. Tissue destruction and bone resorption lead to mutilation of the fingers, hands, toes and feet. Most mutilations can be avoided. E.g., to avoid claw hands, the patient should passively stretch their fingers daily.
5. Direct destruction of tissues, e.g., the nose. Bone lesions in LL are often more attributable to direct destruction than to bacterial infiltration. Injuries are made worse by anesthesia, superinfection, atrophy and ankylosis following disuse. The phalanges of fingers (dactylitis)

and toes are most frequently affected, shorten gradually and become thinner due to lateral bone resorption.



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Multibacillary leprosy. Ulcus penetrans on foot. Copyright ITM



Multibacillary leprosy, hand mutilation. Copyright ITM



Leprosy with mutilations of the feet. Bone destruction is clearly visible on this X-ray. Notice to so-called pencil shape of some affected phalanges. Copyright ITM



Leprosy. Foot ulcer.

## Leprosy reactions

The host's immune responses to the leprosy bacillus create some of the pathology associated with the disease. Reactions in leprosy can occur before, during or after treatment, though they are most often seen in the months following treatment. Beware: A leprosy type 1 reaction has nothing to do with the hypersensitivity-anaphylactic type I reaction.

### Type 1 or reversal reactions

Lesions caused by a change in the immunologic defense of the patient are called type 1 reactions. These reactions may be triggered by: treatment, pregnancy, inter-current illness or vaccination or are sometimes due to spontaneous changes in immune defense. Polar tuberculoid or lepromatous forms are generally immunologically stable and do not develop

type 1 reactions (only the 3 borderline stages are unstable). In the central part of the clinical spectrum, there are fluctuations in the number of bacilli and in the patient's resistance. If the patient's immunity increases, many leprosy bacilli will be destroyed. The body may react strongly to proteins released from these dead bacilli. This type of reaction (previously called an **upgrading reaction**: increase in cellular immunity towards TT) may cause damage to the body itself. Existing skin lesions become inflamed, discolored, red and painful. [Signs of inflammation of the leprosy patches are only found in leprosy reactions]. There will rarely be new lesions. Paralysis may occur quickly with a sudden increase in size and tenderness. Treatment of such a reaction must be swift to limit the damage: anti-inflammatory therapy (aspirin, indomethacin, corticosteroids), immobilization of the affected body part and sometimes decompressive nerve surgery. The leprosy therapy is not discontinued. Side effects of steroid therapy include Cushing's syndrome with weight gain, moon facies, steroid acne, osteoporosis, gastritis, diabetes and steroid cataract.

Sometimes, the immune response may be reduced. Nowadays, this is seldom seen with combination therapy. Progressive leprosy lesions develop (previously called a **downgrading reaction**: decreased cellular immunity towards LL). They take a less dramatic course than upgrading reactions.

## Type 2 reactions

Patients with LL and BL have almost no cellular defense against the leprosy bacillus. They do produce many antibodies, but these are not protective. The antibodies may precipitate in the body through immune complexes and cause a different set of lesions (type III hypersensitivity reaction). This type of reaction is called a type 2 leprosy reaction. It is also called Erythema Nodosum Leprosum (**ENL**). ENL shows a high relapse tendency. Leprosy reactions are an important cause of mutilation. These reactions appear as sudden new red, painful skin nodules on the legs and arms, which may form sterile pustules or ulcers. The symptoms are usually generalized, such as fever and general malaise, accompanied by muscle and joint pain, proteinuria, inflammation of the eyes and, swelling and pain in the nerves, acute epididymo-orchitis. Approximately half of LL and BL patients develop ENL a few months after beginning chemotherapy. Patients with TT are spared this complication.

Differentiation between type 1 and 2 reactions is not always easy, nor is the distinction between leprosy reaction and disease relapse. For treatment of Type I and Type II reactions, see the chapter on treatment.



Lepromatous leprosy with leprosy reaction type 2. Copyright ITM



Lepromatous leprosy with leprosy reaction type 1 in the face. Copyright ITM

### Lucio's phenomenon

In 1852, Lucio and Alvarado described a necrotizing skin reaction associated with non-nodular diffuse leprosy. Lucio's phenomenon occurs in diffuse lepromatous leprosy (*Lepra bonita*) and can be considered an extreme type II reaction. It occurs in untreated patients and is mainly known from Mexico and other countries in Central America. It is characterized histologically by ischemic necrosis of the epidermis as a result of necrotizing vasculitis of small blood vessels whose endothelium is massively invaded by *Mycobacterium leprae*. Clinically, one can recognize eruptions of crops of small erythematous lesions with central necrosis. The eschar may be shed, revealing ulceration, with eventual scar formation.

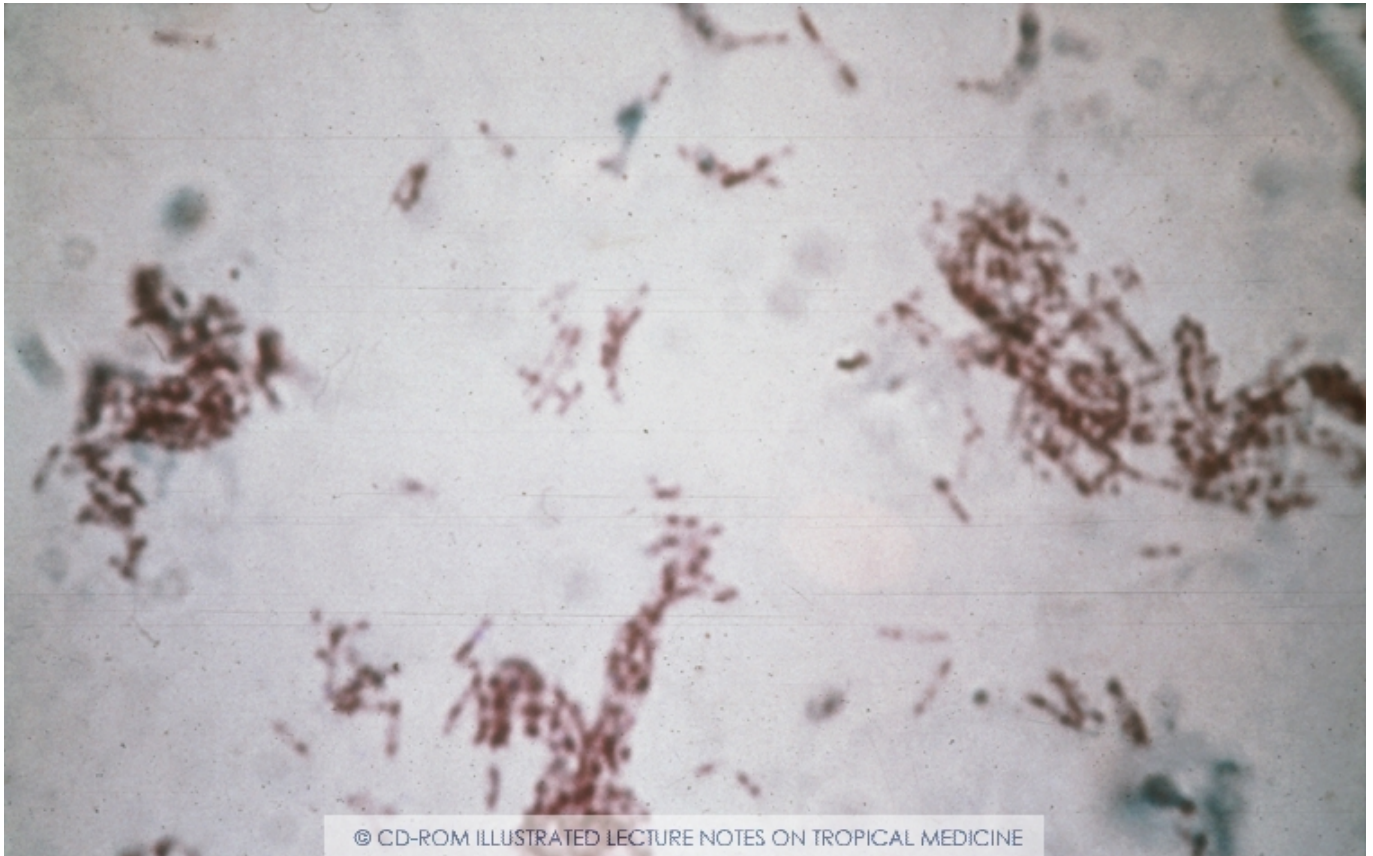
Large painful haemorrhagic skin infarcts and vasculitis lesions can occur. The resultant ulcers are large with undermined edges and necrotic bases. Smears from the bases generally show large numbers of acid-fast bacilli. This condition is treated with wide surgical excision with skin grafts. The ulcers will not be cured by chemotherapy alone.

## IRIS reaction in HIV patients

In the first decade of the 21st century, antiretroviral medication became more widely available in developing countries. In the first four months of therapy, there is a danger of immune reconstitution syndrome (IRIS). The rapid recovery of cell-mediated immunity triggers an immune response to foreign antigens. This presents with the first, often dramatic manifestation of an existing subclinical infection or the deterioration of existing lesions. Acute reactions in leprosy lesions can result in severe skin inflammation, ulceration and rapid loss of nerve function. The patient might mistake the HAART as responsible for leprosy symptoms. Strange at first sight, but prolonged immunosuppressive therapy may be necessary while the patient's immune system recovers from the suppression by HIV.

## Diagnosis

### General



Lepromatous leprosy, skin biopsy. Numerous acid-fast mycobacteria are visible. They typically cluster in globi (small groups), which is strongly suggestive for this disease.

The diagnosis of leprosy is based on clinical and microscopic examination. Leprosy cases are often cared for by specialized teams, previously more so than nowadays. The role of the first-line health workers should not be underestimated: recognizing the illness and following up with the patient (leprosy reactions, eyes, wounds, foot care).

There are 3 cardinal signs for leprosy diagnosis. At least 1 of the 3 must be present to make the diagnosis of leprosy in an endemic area:

1. Anesthesia over the skin lesions
2. Enlargement of peripheral nerves with or without tenderness with evidence of nerve damage: loss of sensation, muscle paresis or paralysis of hand, feet or eyes
3. Demonstration of *Mycobacterium leprae* in the skin smears

## Clinical aspects

The reason for an initial consultation is often the observation of painless traumas, burns or chronic skin abnormalities. Sometimes the initial presentation is an acute problem, e.g., ENL triggered by pregnancy, delivery, concomitant illness or vaccination.

### Skin lesions

1. Check the texture, color, hair growth, sweating. Anhydrosis occurs quite early due to trophic and vasomotor disturbances (chiefly in tuberculoid leprosy). Loss of hair occurs, and the skin is often atrophic. However, edema also occurs, even progressing to elephantiasis of the feet and legs.
2. Loss of eyebrows and eyelashes (madarosis) in lepromatous leprosy.
3. Macules, papules, plaques or nodules. A leprosy macule is never completely colorless, has never been present since birth and does not flake or itch unless there is a leprosy reaction.
4. Open wounds are complications, not primary signs.

## Diminished sensitivity (numbness)

Examining sensitivity reliably is not easy. Use two basins with cold and hot water, a cotton wool ball, a feather, and a needle. A tuning fork of 128 Hertz can be used for proprioception. One technique for testing feet sensitivity is using a Semmes-Weinstein monofilament. This monofilament is a supple thread of artificial material, such as nylon, mounted on a holder. The thread is pressed perpendicularly against the foot until it assumes a C-shape. In this way, a standardized pressure can be created. If the patient does not feel this, there is neuropathy leading to an increased risk of foot ulcers. When the soles of the feet are hyperkeratotic, the test is more difficult to interpret. When seeing a patient suffering from sensory loss, one has to try to detect an underlying pattern during the neurological examination. Typical patterns include:

1. Mononeuropathy, when isolated, damages an individual nerve, affecting the sensation in the area of the nerve.
2. Mononeuritis multiplex. Similar to mononeuropathy but, several peripheral nerves are affected.
3. Polyneuropathy in a glove-and-stocking distribution of impairment. The longest nerves tend to be involved first in metabolic or toxic causes, e.g., diabetes, or alcohol.
4. Dermatomal distribution. Sensory loss corresponds to the cutaneous distribution of a spinal nerve root, stressing the importance of knowing the dermatomes.
5. Sequence of failure:  $t^{\circ}$  > fine touch > pain > deep pressure.

## Thickening of superficial nerves

Examine and palpate peripheral nerves systematically. Some of the most important are the supraorbital nerve (above the eye socket), great auricular nerve (in the neck, arises behind the sternocleidomastoid, ascends, curving diagonally across that muscle, and courses forwards and upwards), the ulnar nerve (at the elbow), median nerve (ventral side of the wrist) radial nerve (the superficial branch at the wrist), lateral peroneal nerve (the knee, at the head of the fibula), posterior tibial nerve (behind the medial malleolus) and near a skin lesion.

## Neural dysfunction

1. Painless wounds, risk of burns due to the lack of pain sensation.
2. Peripheral facial paralysis with the risk of eye lesions due to lagophthalmia with cornea drying.
3. Trigeminal nerve involvement with risk of eye lesions due to insensitivity of the cornea. Test with a cotton wool stick.
4. Atrophy of the thenar (common digital nerve) and hypothenar eminence.
5. Claw hand with atrophy of the interossei (ulnar nerve). Reminder: there are seven interosseous muscles, 3 palmar (adduction of fingers) and 4 dorsal (abduction of fingers). They assist the lumbrical muscles to bend the metacarpophalangeal joints and extend the interphalangeal joints. They are all innervated by the ulnar nerve. An excellent clinical test for these muscles is to spread and then adduct the fingers. A sheet of paper between the adducted fingers must be firmly held. Froment's sign tests for palsy of the ulnar nerve, and more specifically, the action of adductor pollicis. To perform the test, a patient is asked to hold a piece of paper between the thumb and his flat palm. The paper is then pulled away. If the ulnar nerve is intact, the patient can maintain and hold the paper without difficulty. In the case of ulnar nerve palsy, this will be difficult. The patient might compensate by flexing the flexor pollicis longus of the thumb (flexion of the DIP joint of the thumb), a muscle innervated by the median nerve.
6. Opposition of the thumb. If the median nerve is affected, the m. abductor pollicis brevis, the m. flexor pollicis brevis and the m. opponens pollicis become dysfunctional, and opposition of the thumb is compromised.
7. Wrist drop (radial nerve). Dorsal wrist extension is weak or not possible.
8. Foot drop (fibular nerve = peroneal nerve). Heel gait is not possible.
9. Claw toe (paralysis of flexors) and loss of sensation at sole of foot (posterior tibial nerve). The patient cannot walk on his or her toes.

Painful peripheral neuropathy can also occur: leprosy is not always a painless disease! Gabapentin and especially pregabalin (Lyrica®) are helpful against neuropathic pain. Pregabalin is active on calcium channels that are central to neuropathic syndromes. In general, pregabalin is preferred over tricyclic antidepressants and anti-epileptic drugs.

## Electromyography

Nerve-conduction studies provide two basic measurements. The first is of the total number of units that respond on either the motor or the sensory side. The total sensory or total motor potential (sensory action potentials and motor action potentials) indicates the number of axons that have reached their destination and are still functioning. In axonal neuropathies,

such as those due to vincristine, alcoholism, diabetes or uraemia, an early reduction in sensory action potential is recorded from the distal parts of the extremities. Amyloid neuropathy gives similar results. The second measurement is of the conduction velocity which reflects Schwann-cell or myelin function. It is a measurement of preservation of saltatory conduction down the nerve fibre. A few diseases affect primarily myelin in the peripheral nerves, e.g. Guillain-Barré syndrome and its variants. Chronic pressure, such as in carpal tunnel syndrome, leads to pressure lesions and can result in prominent slowing of the conduction velocity. Mixed lesions are common. In leprosy, conduction velocities are reduced in a spotty fashion.

## Microscopy

### Acid fast bacilli in smear

Preferably, several smears should be taken from the ear lobes, forehead, chin, buttock and from the raised edge of active skin lesions. The latter is sometimes forgotten. The skin is pinched between the thumb and finger of one hand. Make a small incision with the other hand (5 mm long, 2 mm deep) using a scalpel, scrape a little tissue away, then smeared onto a slide (slit-skin smear). Try not to include any blood in the smears. Smears are also sometimes made from the nasal mucosa.

The smears are stained with a modified Ziehl-Neelsen stain (e.g., Kinyoun stain). It is a cold stain. Discoloration is with a low concentration of acid (1% HCl). The mycobacteria are less acid-fast than *Mycobacterium tuberculosis* and bleach too much with standard Ziehl-Neelsen, which uses more concentrated acid. *M. leprae* is a weak Gram-positive or Gram-neutral acid-fast bacillus measuring  $0.3 \times 2-7 \mu\text{m}$ . The bacteria are often grouped in clusters (globi). The

hydrophobic character of the waxy mycobacterial capsule plays a part here.

The morphological index has increasingly been abandoned. It is the percentage of live bacteria to the total number of bacteria. For this, 200 free-lying bacteria are examined. Live bacteria are homogeneously stained. Dead bacteria have a granular staining pattern. The resorption of dead bacilli into the tissues is very slow (1 log decrease per year). The presence of acid-fast bacilli in a treated patient does not necessarily mean the therapy has failed. The morphological index is a better measure of recovery than the bacterial index. The disappearance of bacteria during treatment can be partly attributed to the loss of their acid-fast nature. In some biopsies that test negative with the Fite-Faraco stain, bacteria can still be detected using Gomori methenamine-silver staining.

Ridley proposed the bacterial index. He developed a logarithmic scale from 0 to 6+. Using an oil-immersion objective, the scale is based on the average number of bacilli per microscopic field. Infections with a high bacterial load usually take 5-8 years from the beginning of therapy before the bacterial index is negative. [A rule of thumb is 1+ per year].

<b>Bacterial index</b>	
0	0 bacilli in 100 oil-immersion fields
1+	1 to 10 bacilli per 100 fields
2+	1 to 10 bacilli per 10 fields
3+	1 to 10 bacilli per field
4+	10 to 100 bacilli per field
5+	100 to 1000 bacilli per field
6+	> 1000 bacilli per field

## Biopsy

If the smears are negative, a skin biopsy is performed, which must penetrate the subcutaneous tissue. The biopsy should preferably contain a superficial nerve branch (hypodermic). In multibacillary leprosy, there is a zone of healthy tissue between the superficial epidermis and the infiltration with bacilli in deeper dermis. This does not apply to tuberculoid leprosy. The linear distribution of an infiltrate consisting of neutrophils and vacuolated macrophages follows nerves and blood vessels. The foamy characteristic of the histiocytes is an important clue. Bacilli in a tissue biopsy can most easily be detected with a modified Ziehl stain (Fite-Faraco stain). *Mycobacterium leprae* stains poorly with Ziehl on sections from paraffin tissue blocks. The acid fastness may be restored by impregnating the tissue segments with peanut oil or turpentine beforehand. In TT, it will rarely be possible to detect acid-fast rods, but the diagnosis can be made based on typical histological appearance (non-caseous granulomas around a nerve branch). In indeterminate leprosy, minimal nonspecific chronically inflamed infiltrate around nerves, blood vessels and skin nodes. Bacilli are very seldom present in indeterminate leprosy, and generally, none are found. A sural nerve biopsy can be performed when the diagnosis is unclear. The presence of neutrophils and edema of the papillary dermis is also an essential clue to a Type 2 reaction. Type 1 reactions, by contrast, are lymphocyte-rich.

### Lepromine

Lepromine is not used as a diagnostic aid for the individual patient. In the time before armadillos could be used, lepromine was prepared from skin nodules from multibacillary patients. It was called lepromine H (human), with 160 million bacilli/ml as standard. At present lepromine is prepared from armadillos and is known as lepromine A (armadillo). Both human and armadillo lepromine contain varying amounts of tissue. A more purified preparation is Dharmendra lepromine, which is used in India. This produces a weak Mitsuda reaction. Sometimes another purified version is used, called Convit's soluble antigen.

## LTT

Lymphocyte transformation tests have been developed. They are more specific than

lepromine tests. It was observed that many healthy people who had had contact with lepers reacted positively in this test, unlike people who had not been exposed to leprosy. This is an argument for the hypothesis that leprosy is highly infectious but has a very low disease expression.

## Serology

Antibodies can be detected using serology, but this produces many practical problems. One of the better-studied antibodies is called phenolic glycolipid-I antibody (PGL-I). The titers are proportional to the bacillary load. Newly lepromatous patients are always positive, but the diagnosis can be made simpler. Up to 50% of tuberculoid patients are negative in this test. At present, the technique (ELISA or dipstick assay) is abandoned more and more. Leprosy sufferers often have circulating auto-antibodies so that their plasma often gives false-positive results for various other disorders (e.g., positive RPR or VDRL suggesting syphilis). Cross-reactivity with *Leishmania* is described as an important differential diagnosis in regions where both diseases are endemic. The cerebrospinal fluid in leprosy is normal.

## PCR

inherent problems with this technique due to contamination in the laboratory, the results from various studies must be interpreted with caution. In many people, positive PCR results from nasal swabs (e.g., 33% in contact persons in the same household and 20% of persons who work with leprosy sufferers) are found. There may be indeed many asymptomatic carriers. As in many diseases, PCR is gaining importance in diagnosing leprosy.

### Culture

If there is doubt concerning resistance, an in-vivo culture can be carried out in research centers (injection in the food-pad in mice). The inoculated test animals then receive food mixed with various concentrations of dapsone, rifampicin or clofazimine. Maximum growth of the resistant bacteria is reached in approximately 6-9 months. To bypass the problems associated with experimental animals, attempts are being made to develop in-vitro techniques. Using in-vitro radiorespirometry ( $^{14}\text{CO}_2$  production from  $^{14}\text{C}$ -labelled palmitinic

acid) as in the Bactec or Buddemeyer systems, an attempt can be made to measure the metabolism of the bacteria, and in future it should be possible to use this to examine the viability of the mycobacteria, e.g. during treatment. These techniques have no place in daily clinical practice. It must be stated that no long term in-vitro cultivation technique is available.

## Differential diagnosis

Initially, the differential diagnosis must take into account a large number of other diseases. Fixed drug eruption, morphea (localized scleroderma), dermatophytosis, dermal filariasis, eczema, scars, nodular cutaneous leishmaniasis, post-kala azar dermatitis and keloids may exhibit clinical similarities.

**Diffuse cutaneous leishmaniasis** often resembles lepromatous leprosy and can be similar to cutaneous lymphoma (mycosis fungoides).

**Lobomycosis** or Lobo's disease is rare and occurs almost exclusively in the Amazon and Orinoco basins, although some cases have been known from Surinam and Central America. The disease is caused by a fungus, *Loboa lobo*, and may be clinically very similar to lepromatous leprosy or keloids. The diagnosis is with a skin biopsy.

**Systemic lupus erythematosus** (SLE) may be mistaken for leprosy. Skin and mucosal lesions of lupus erythematosus discoides, necrobiosis lipoidica (check for hyperglycemia) and porphyria cutanea tarda (lesions chiefly on the hands and face, where exposed to the light) may pose diagnostic problems.

**Neurofibromatosis** (Recklinghausen's disease) sometimes causes a problem in differential diagnosis. [In neurofibromatosis type 1, 100% of the children have café au lait patches before they are 2 years old, 70% have freckles in the skin folds (axilla), and 90-100% of patients also have hamartomas in the iris (Lisch's nodules) as well as neurofibromas by the time they are 20 years old. In the rarer type 2 (NF2), café au lait patches only occur in 1%, and the freckles are absent. In NF2, the peripheral nerves may develop schwannomas, but in these patients, acoustic neurinomas are the most common.

**Annular skin lesions** which are similar to tuberculoid leprosy may also occur in tinea corporis, cutaneous sarcoidosis (lupus pernio), granuloma annulare, granuloma multiforme, syphilis, actinic granulomas and Jessner-Kanof 's lymphocytic skin infiltration (pseudolymphoma; etiology unknown). A Sutton's naevus is generally easy to recognize (ring-shaped depigmentation with central hyperpigmentation).

**Annular psoriasis** is characterized by the presence of thick scales that usually exhibit symmetrical distribution, with enlarged blood vessels in the dermis. There may be pustules or pitting of the nails and/or arthropathy. Köbner's phenomenon may occur.

**Granuloma annulare** is more challenging to differentiate. It is a benign skin disorder characterized by a granulomatous inflammatory process, which manifests itself in a ring or annular configuration of papules. The lesions usually occur in the region of a joint (the hands, elbows) but may also occur elsewhere. There is no neural dysfunction. An aetiological association with sunlight is assumed, but this is only one hypothesis. Most lesions (75%) heal spontaneously in 1-2 years. It is possible that granuloma multiforme is a variant of granuloma annulare. Biopsy is usually central to the diagnosis. Given the strong similarity to leprosy and since granuloma multiforme is regularly seen and treated as leprosy, it is advisable to study a number of photographs of people with this disorder, or better still, the patients themselves, in order to become familiar with the clinical picture.



Systemic lupus erythematosus with butterfly rash on the face. This patient was wrongly diagnosed as having leprosy and treated as such for one year before the correct diagnosis

was made. Photo prof Gigase, copyright ITM.

**Pityriasis alba** is an eczema variant (slightly scaly, on skin exposed to light). Gibert's pityriasis rosea is another condition that is easier to differentiate.

**Pityriasis versicolor** (Gr. "pityron" = bran; refers to the light skin scaliness) is a widespread skin infection with a fungus: *Pityrosporum ovale* (yeast stage) or *Malassezia furfur* (mycelium stage). This lipophilic fungus forms the tyrosinase inhibitor azelaic acid from sebaceous fats, a substance that inhibits melanin synthesis, explaining the white appearance of the skin spots. Account must be taken of the fact that depigmented skin spots can also be caused by damage to the melanocytes (pigment cells) after an ordinary infection, wound or burn (post-inflammatory hypopigmentation).

**Vitiligo** is easy to differentiate because most depigmentation is complete (never complete in leprosy) and the texture of the skin with this condition is otherwise normal)

**Endemic treponematosis and syphilis** (the differential diagnosis is often difficult here). It is important to know that people with leprosy often have a false positive VDRL (screening for syphilis). TPHA [the *Trepanoma pallidum* haemagglutination test] permits differentiation.

**Trichoepithelioma** is a condition resembling leprosy with numerous rounded, skin-coloured, firm papules and nodules. It is a benign tumor originating in the hair follicles.

There are not many neuropathies where temperature and pain sensation are diminished while sparing vibration and position sense, as well as sparing deep tendon reflexes. In these cases, one should consider **primary amyloidosis** and **syringomyelia** (lesion of the crossing fibers of the central grey matter of the spinal cord) in the differential diagnosis. Less than 10% of leprosy cases develop secondary amyloidosis. Patients with primary/hereditary amyloidosis usually have pronounced autonomic neuropathy from the onset, with episodic diarrhea, impotence, decreased sweating, postural hypotension and other evidence of impaired vasomotor control.

## Treatment

Before discussing the antibiotic treatment of leprosy, it is essential to mention that the following steps are critical in the management of Hansen's Disease:

1. Assess nerve damage severity and duration
2. Treat type 1 and type 2 reactions
3. Manage neuropathic hands and feet. Surgery can have an essential role in mitigating mutilations and neuropathic lesions
4. Educate the patient about the disease and adverse effects of medication
5. Explain the psychological issues that accompany leprosy
6. Address the stigma of leprosy

Because of the increasing resistance to dapsone, in 1982, the WHO proposed using only combination regimens. With modern therapy, the infectivity falls very swiftly (in a few weeks). People are being cared for more and more in their home environment. This requires vast efforts in follow-up. Rehabilitation, orthopedic aids, good shoes and eye care are crucial. Surgical reconstruction, tendon transplantations etc., have their place but require specialized physicians. Instructing patients, chiefly concerning checking wounds and foot hygiene, is very important. Prompt treatment of wounds can prevent much suffering.

### Historical note

In the past, leprosy sufferers were strictly avoided or isolated in a leprosarium. This completely disrupted the social lives of the people affected. Patients hid themselves and withdrew from care.

Dapsone was first synthesised by Fromm and Whitmann in 1908, but it was used exclusively in veterinary medicine for streptococcal mastitis. In 1941 it was discovered that Promin® (sodium glucosulphone) PO and IV could produce an improvement in leprosy. Diasone, another sulphone, was better tolerated but was later replaced by dapsone. The first cases of dapsone resistance were reported in 1964. In the '60s the efficacy of clofazimine was discovered. In 1965 the activity of thalidomide in ENL was ascertained. In the late '60s and early '70s rifampicin was developed and this exhibited

exceptional efficacy.

## Typical regimens

### **Paucibacillary leprosy (TT and BT)**

For 6 months

Rifampicin 600 mg/once per month under supervision Clofazimine 300 mg/once per month under supervision and Clofazimine 50 mg/day without supervision

Dapsone 100 mg/day without supervision

Then keep under supervision for a further 2 years for late leprosy reactions and any relapse.

### **Multibacillary leprosy (smear-positive BT, BB, BL and LL)**

For 1 year Rifampicin 600 mg/once per month under supervision

Clofazimine 300 mg/once per month under supervision and Clofazimine 50 mg/day without supervision

Dapsone 100 mg/day without supervision

Then, keep under supervision for 5 years (or life-long in LL).

These regimens are usually quickly accepted and have little toxicity. Relapses seldom occur (< 5% after several years).

## Dapsone

The anti-leprosy activity of this sulphone was ascertained in the '40s and until 1980 it was often used in monotherapy (initially IM, later PO). It is safe during pregnancy. Dapsone

(=DDS; Diamino Diphenyl Sulphone) is a slow-acting bacteriostatic product. It is swiftly absorbed from the intestine and undergoes enterohepatic circulation. A steady-state serum concentration is reached approximately eight days after beginning the treatment. It has a half-life of 28 hours and can be taken once daily. Dapsone resistance is presently spread world-wide. Dapsone is generally well tolerated.

#### 1. Pharmacological predictable adverse reaction to dapsone

- peripheral neuropathy
- hemolytic anemia (even if there is no G6PD deficiency)
- methaemoglobinaemia with nonspecific nausea, vomiting, fatigue, dizziness, weakness, headache

2. Allergic/idiosyncratic reaction: the dapsone hypersensitivity syndrome. This usually starts within 6 weeks after beginning dapsone. If there is no alternative, desensitization may need to be carried out. Symptoms:

- hepatitis with icterus
- eosinophilia
- fever
- skin eruption, including exanthema, pustular lesions and even Stevens-Johnson syndrome
- lymphadenopathy
- agranulocytosis
- nephritis
- pneumonitis

- hypothyroidism

#### Other medical uses of dapsone

Dapsone is also used in the treatment and prevention of *Pneumocystis jirovecii*, in the treatment of toxoplasmosis, in dermatitis herpetiformis, in *Loxosceles* bites (see the chapter “spiders”) and several other rare disorders. Dapsone is contained in Lapdap® and Maloprim®, agents for malaria prophylaxis.

## Rifampicin

Rifampicin (Rifadin®, Rimactan®) (id. Rifampin) is a highly active but expensive bactericidal agent. It interferes with the synthesis of nucleic acids by inhibiting DNA-dependent RNA polymerase. Due to its high sterilizing activity and the slow growth of *M. leprae* it can be given once monthly if combined with other drugs. This reduces the cost and toxicity significantly without compromising efficacy and makes supervision of adherence easier. Rifampicin sometimes causes liver damage. See also tuberculosis. It may be used during pregnancy, although there are isolated reports of congenital deformities. Spina bifida and hare lip were observed in the progeny of rodents when the product was administered at high doses during pregnancy.

## Clofazimine (Lamprene®)

Clofazimine is a weak bactericidal agent. It has anti-lepromatous and anti-inflammatory properties. This lipophilic drug is best taken after a meal for better absorption. It accumulates slowly in the skin, where it may cause dryness and hyperpigmentation. The latter may sometimes cause stigma in patients. The urine, tears and sweat are also stained red. Sometimes, there is nausea. In rare cases, there is severe enteritis with paralytic ileus. The tissue half-life is very long (70 days). If clofazimine is used in type 2 leprosy reactions, the effect is usually only noticeable after 4 to 6 weeks. Clofazimine passes the placental barrier and is present in breast milk. Neonates may then also exhibit hyperpigmentation. It is probably safe during pregnancy.

## Other

In 1987, it was discovered that minocycline, ofloxacin (Tarivid®) and clarithromycin (Biclar®) possess bactericidal properties against *Mycobacterium leprae*. The therapeutic place of all these drugs in the treatment of leprosy still needs to be determined. They may be used if, for example, rifampicin is not tolerated. Shorter therapies (single dose and 6 weeks) are being studied but have been abandoned due to too many failures in follow-up.

## New experimental regimens

Monthly treatment with rifampin 600 mg, minocycline 100 mg and moxifloxacin 400 mg (RMM) is a promising treatment being studied.

## Pregnancy and lactation

There is very little data on leprosy and pregnancy. During pregnancy there is progressive reduction of the cellular resistance, but humoral immunity is probably stimulated. In theory fewer type 1 reactions would be expected during pregnancy. On the other hand, type 2 reactions may be more frequent. Possibly, there is an increase in the bacillary load in untreated patients. Since the disease may become worse during pregnancy, the medication is continued unchanged. The use of thalidomide for leprosy reaction type II during pregnancy is, of course, forbidden.

## Neuropathic pain in leprosy

Leprosy patients often suffer from neuropathic pain. Carbamazepine (can be used but can result in a lupus-like syndrome. Pregabalin is approved for chronic neuropathic pain (leprosy, diabetes, shingles). It can be administered orally, for example, 150 mg in the morning and 300 mg in the evening.

## Treatment of leprosy reactions

## Treatment of type I leprosy reactions

Treatment of such a reaction must be swift to limit the damage: anti-inflammatory therapy (aspirin, indomethacin, corticosteroids) and immobilization of the affected body part. The leprosy therapy is not discontinued. Contrary to tuberculosis, prolonged steroid use does not seem to increase the risk for severe leprosy nor to re-activate asymptomatic infections.

## Treatment of type II leprosy reactions with erythema nodosum leprosum

The treatment of ENL consists of analgesics, clofazimine (which also has anti-inflammatory characteristics) at higher doses than normal leprosy therapy (100 mg 3 times daily for 1 to 3 months). However, it is a slow-acting drug, corticoids systemically and if necessary eye drops. If needed, the fast-acting drug thalidomide can be used (Softenon®, 100 to 400 mg/day for 10 days, then reduced to 50-100 mg daily). **Methotrexate** seems a good alternative in patients with poor response to steroids who cannot take thalidomide or had poor response to thalidomide.

Thalidomide is not an immunosuppressive but is immune-modulating drug. It changes the balance of several cytokines. For example, it is an antagonist of TNF-alpha and increases the action of IL-2. Contraception is mandatory during the use of thalidomide (men and women) since it is highly teratogenic, probably due to interference with angiogenesis in the fetus, not due to induction of mutations. It causes phocomelia, heart, ear and eye abnormalities, autism and embryopathy.

Thalidomide was officially taken off the market in 1961. In 1965, Dr Jacob Sheskin, an Israeli dermatologist discovered fortuitously that thalidomide in leprosy patients improved ENL. In 1998, thalidomide was approved by the FDA for treating ENL and in 2006, for treating multiple myeloma.

Thalidomide is now used in erythema nodosum leprosum and some immunologically mediated diseases, such as refractory mucosal aphthosis (common in AIDS), Behçet's syndrome, severe erythema multiforme and severe prurigo nodularis (Hyde's disease). Apart

from teratogenicity, side effects include peripheral neuropathy (risk higher when the cumulative dose is greater than 20 grams), somnolence, constipation, nonspecific skin rash and dizziness.

### Lenalidomide

Lenalidomide (Revlimid) is a 1:1 racemate and chemically related to thalidomide. It is studied in myelodysplastic syndromes. About two thirds of patients with the 5q- syndrome (myelodysplasia with anaemia and thrombocytosis) benefit from lenalidomide. At present it is used in Kahler's disease (multiple myeloma). It might replace thalidomide in the future for certain indications. Lenalidomide is 50,000 times more potent than thalidomide in inhibiting tumour necrosis factor-alpha.

Because of its resemblance to thalidomide, it is contra-indicated in pregnancy. Its place in leprosy reactions is not yet clear today.

### Cyclosporin A in leprosy

Cyclosporin A acts primarily to suppress T-cell activation, especially the CD4-Th1 helper cell, which play a central role in reversal reactions. Such reversal lesions contain high numbers of CD4-lymphocytes, especially Th-1 helper cells. This is in contrast with ENL, where an influx of CD4-Th2 cells and deposition of immune complexes occurs. Prednisone remains the drug of choice in reversal reactions, but in case of failure, cyclosporin A can be used as an alternative.

## Prevention

Basic hygiene is important for staff and patients: washing hands, wearing a mask if the patient has rhinitis, and wearing gloves to take samples. *Mycobacterium leprae* is found in breast milk, but this is not sufficient reason to stop breastfeeding. It is thought that infectivity quickly drops to zero after the start of combined chemotherapy. Examination of the people in contact with leprosy patients is indicated. The risk of leprosy in the family of lepromatous patients is 5-8 times higher than in the general population.

Since 2020, WHO recommends prophylaxis with a single-dose rifampicin (SDR-PEP) for both household and social contacts. The protective effect in preventing leprosy is 55-60% with a higher efficacy when combined with BCG vaccination at birth. In the case of contact with multibacillary patients, check-ups for 5 to 7 years, once per year, including looking for the “numb spot”, are advised.

Due to the complex bacterial cell wall combined with the difficulty of cultivating *M. leprae* in vivo, no suitable antigen for vaccine production has been found today. BCG vaccination provides partial protection.