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REVIEW ARTICLE

Recent advances in diagnostic and treatment of infectious disease leprosy

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ABSTRACT

Being classified as a chronic disease than an acute infectious one, leprosy is associated with long lasting complications regarding immunology, disability and deformity. Throughout history, the leprotic person is always barred from society. It is caused by *Mycobacterium leprae,* acid-fast bacteria having a long incubation period. The aim of this review is to educate people about the transmission and symptoms of this disease. Moreover to provide information regarding the pathophysiology as well as pathogenisis of leprosy or better known as Hansen's disease. Aftermost mentioned is the treatment as well as the WHO recommended multidrug therapy regimens for leprosy.

Key words: Leprosy, Hansen's disase, Pathogenesis, Mycobacterium leprae.

INTRODUCTION:

Leprosy, commonly known as Hansen's disease (HD), is a persistent infectious disease which is cause by the bacteria Mycobacterium leprae and Mycobacterium lepromatosis, an acid-fast, rod-shaped bacillus. Primarily infections are without symptoms and normally remain for 5 years to as long as 20 years. The disease mostly infiltrates the skin, peripheral nerves, mucosa of the upper respiratory tract and also the eyes. Leprosy is curable and treatment provided in the early stage averts disability. This may result in a sort of ability to feel pain and thus loss of parts of extremity due to repetitive injuries. Weakness and poor eye sight might also be present. [1] The skin lesions and deformities can be extremely disfigured and the reason that infected individuals historically were measured outcasts in many cultures. Although human-to-human transmission is the primary source of infection, three other species can carry and transfer M. leprae to humans: chimpanzees, mangabey monkeys, and nine-banded armadillos. The disease is termed as chronic granulomatous disease, related to tuberculosis, because it produces inflammatory nodules (granulomas) in the skin and nerves over time. [2] Leprosy continues to be a challenge to health worldwide, with about 250,000 new cases has been detected every year. Inspite of widespread implementation of effective multidrug therapy (MDT), leprosy has not been eliminated. A third of newly diagnosed patients has nerve damage and may develop disabilities, although the fraction varies according to numerous factors, including level of self-care. Women who develop leprosy persist to be especially disadvantaged, with rates of late diagnosis and disability enduring high in this subgroup. Leprosy was not a specified disease in the Millennium Development Goals, but improvement in the other areas they cover, such as education and levels of poverty will also helps leprosy patients and services. [3] Recent advances in basic science have improved our knowledge of the disease. Variation in the cellular immune response is the basis of a range of clinical manifestations. The introduction of MDT has appreciably contributed to a decrease in the occurrence of the disease. However, leprosy control activities, including monitoring and avoidance programs, must be maintained. [4] Approximately 219,000 new cases of leprosy were identified worldwide during 2011, happening mainly in Africa, Asia and South America. Control of leprosy has improved significantly over the last 20 years due to national campaign in various countries around the world. [5]

History of leprosy:

Unluckily, the history of leprosy and its interaction with man is one of most suffering and misunderstanding task. The latest research proposed that atleast as early as 4000 B.C. folks had been infected with M. leprae, although the first known written reference to the disease was found on Egyptian papyrus in about 1550 B.C. The disease was well known in ancient China, Egypt, and India, and there are several references to understand the disease in the Bible. Because the disease was badly understood, slow to show symptoms, and had no known treatment, many cultures thought the disease was a curse or punishment

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from the Gods. In 1873, Dr. Hansen discovered bacteria in leprosy lesions; signifying leprosy as an infectious disease, not a hereditary disease or a punishment from the Gods. Because of Hansen's discovery of M. leprae, researches were made to find treatments that would stop or eliminate M. leprae; in the early 1900s to about 1940, oil from Chaulmoogra nuts was used with questionable efficacy by injecting it into patients' skin. Currently, there are numerous areas (India, East Timor) of the world, where the WHO and other agencies (for example, the Leprosy Mission) are functioning to decrease the number of clinical cases of leprosy and other diseases such as rabies and schistosomiasis that occur in remote regions. [2] Hansen's disease (leprosy) is not highly transmissible, is very treatable, and, with early diagnosis and treatment, is not disable. Compiled statistics disclose that Hansen's disease (leprosy) is rare in the U.S. There are currently about 6,500 cases; about 3,300 require active medical management. [6]

Causes of leprosy:

Agent: *Mycobacterium leprae*,s an acid-fast, rod-shaped gram-positive bacillus. [7]

Mycobacterium leprae:

M. leprae, an acid-fast bacillus is an important human pathogen. In addition to humans, leprosy has been observed in ninebanded armadillo and three species of primates. The bacterium can also be grown in the laboratory by injection into the footpads of mice. Mycobacterium is known for their disreputably slow growth. With the replication time of 14 days, M. leprae has not yet been successfully cultured in vitro. *M. lepromatosis* is a newly identified mycobacterium which is described to cause disseminated leprosy whose significance is still not clearly understood [8]. Leprae shows red when a Ziehl-Neelsen stain is used. M. leprae and M. lepromatosis are the causative agents of leprosy. An intracellular, acid-fast bacterium, *M. leprae* is aerobic and rod-shaped, and is bounded by the waxy cell membrane coating characteristic of Mycobacterium species. [9]

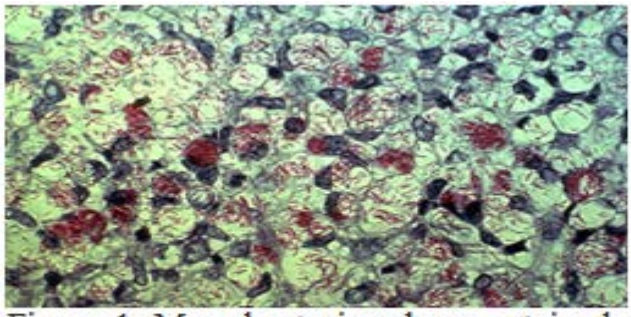


Figure 1: Mycobacterium leprae stained with Ziehl-Neelsen carbolfuchsin [10]

Transmission:

The accurate mechanism of transmission is not well understood, while person to person spread via nasal droplets is believed to be the main route. Large amounts of M. leprae organisms have been found in the nasal secretions of people with untreated lepromatous leprosy. Leprosy is one of the slightest infectious diseases, because:

• Over 99% of the population has adequate natural immunity;

• Over 85% of the clinical cases are non-infectious, and

• An infectious case is render non-infectious within one week, most often after the very first dose of treatment. [11]

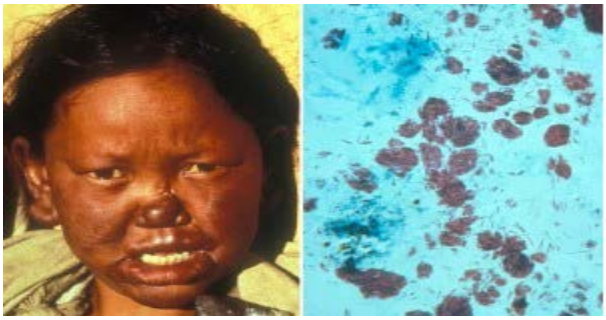


Figure 2: Transmission of leprosy

As a result, the skin, nose, ear lobes, certain peripheral nerves, and the slightly cooler anterior part of the eye are more likely to be affected by leprosy. [12]

Several other reasons of transmission of disease:

1. Person to person- leprosy transmitted from person to person through infected respiratory droplets;
2. Parents of someone with leprosy;
3. Children of someone with leprosy;
4. Brothers or sisters of someone with leprosy;
5. The extent of exposure;
6. Genetics;
7. Environmental conditions. [8]

This is difficult to examine experimentally because M. leprae cannot be cultivated in vitro and proofs can only be obtained indirectly through epidemiological studies. Only 5-10% of the population is vulnerable to develop the disease. The assault rate among close contacts is around 5%. Lepromatous and borderline cases are infectious while indeterminate and tuberculoid are considered as non-infectious. The disease is not hereditary but a genetic vulnerability may be inherited as shown by the aggregation of cases in some families.[13] The modes of transmission of leprosy is uncertain but, like tuberculosis, the infection is considered to be spread by the respiratory route because lepromatous patients harbour

bacilli in their nasal passages. The bacterium accumulates principally in the extremities of the body where it resides within macrophages and infects the Schwann cells of the peripheral nervous system. [14]

Signs and Symptoms:

The bacteria that cause Hansen's disease grow slowly. It may take 2-10 years before signs and symptoms appear. Symptoms largely affect the skin, nerves, and mucous membranes (the soft, moist areas just inside the body's openings). The disease can cause:

- Skin lesions that may be faded/discolored
- Growths on the skin
- Thick, stiff or dry skin
- Severe pain
- Numbness on affected areas of the skin
- Muscle weakness or paralysis (particularly in the hands and feet)
- Eye problems that lead to blindness
- Enlarged nerves (mainly those around the elbow and knee)
- A stuffy nose
- Nose bleeds
- Ulcers on the soles of feet

Since Hansen's disease affects the nerves, loss of feeling or sensation may occur. When loss of sensation occurs, injuries (such as burns or fractures) may unobserve. One should always try to avoid injuries. But, if one experience loss of sensation due to Hansen's disease (or another cause), may not feel pain that can warn harm to the body. So, take extra caution to ensure that body is not injured. [15] Leprosy mainly affects the skin and the nerves outside the brain and spinal cord, i.e. the peripheral nerves. It may also hit the eyes and the thin tissue lining the inside of the nose. The main symptom of leprosy is disfiguring skin sores, lumps, or bumps that do not go away after several weeks or months. The skin sores are pale-colored.[16]

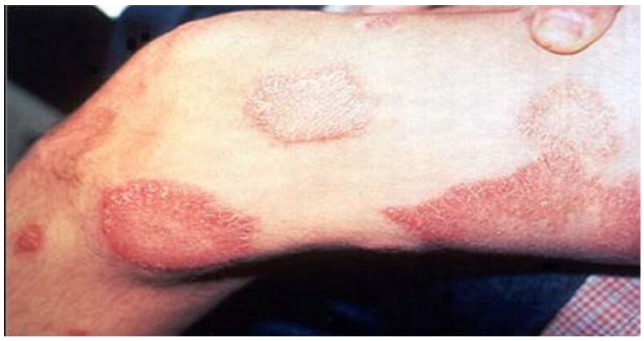
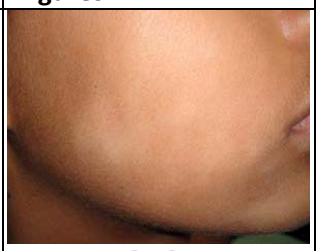
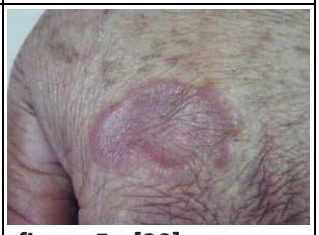
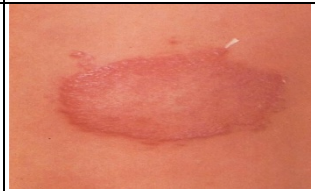
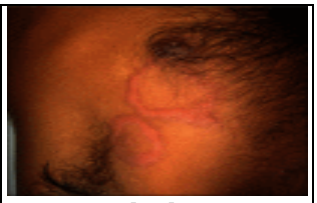
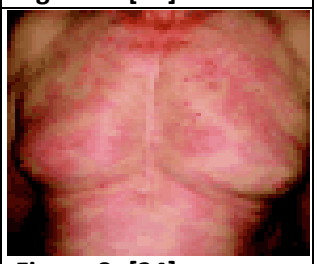
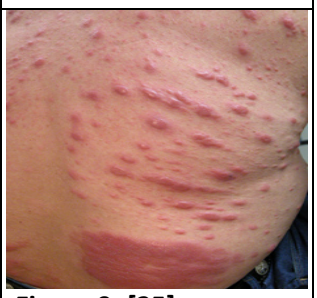


Figure 3: Signs and Symptoms [17]

Table 1: types of leprosy

Types	Causes	Symptoms	Diagnosis	Figures
Indeterminate leprosy	A benign form, relatively unstable, seldom bacteriologically positive. These cases may evolve toward lepromatous form or the tuberculoid form, or may remain unchanged indefinitely.	A benign form, Unstable, seldom bacteriologically positive.	Physical examination, bacteriological examination, Skin lesion (dark skin is hypopigmentation, lesion) are macular or infiltrated, sensory loss,	 **Figure 4: [18]**
Tuberculoid leprosy(paucibacillary leprosy)	Few bacilli present, increased CMI, usually localized with discretely demarcated lesions, early in nerve involvement; may heal spontaneously in 1-3 years.	Severe pain, Muscle weakness, hands, feet, Skin stiffness and dryness, Loss of fingers and toes, Eye problems.	Skin lesion (dark skin is hypo pigmentation. [19] lesion are macular or infiltrated, sensory loss,anesthetic (lose pain, tactile and termic sensation).[8]	 **figure 5:. [20]**
Borderline tuberculoid leprosy	Bacilli present and CMI unstable.	Lesion like tuberculoid but small, Less nerve enlargement, Revert to tuberculoid.	Lesions like tuberculoid leprosy, nerve enlargement, this form may persist.	 **Figure 6:. [22]**

Mid-borderline leprosy	Bacilli present and CMI unstable.	Reddish plaques, Moderate numbness, Swollen lymph glands.	Asymmetrically distributed reddish plaques, moderately anesthetic, regional adenopathy	 **Figure 7:.[23]**
Borderline lepromatous leprosy	Bacilli present and CMI unstable.	Many lesions with flat lesions, Raised bumps, Plaques, and nodules, Sometimes numb.	Skin lesions with macules, papules, plaques, and nodules, sometimes with or without anesthesia; the form may persist, regress or progress to lepromatous lepros.	 **Figure 8:.[24]**
Lepromatous leprosy (granuloma formation) or (multibacillary leprosy)	Many bacilli present,decreased cell-mediated immunity (CMI), diffuse skin lesions.[7]	Skin lesions, Nasal symptoms, Thinning of eye – brows, eyelashes, skin on face, Laryngitis,Swelli-ng of the lymph nodes. [21]	Diffuse infiltration, macules, papules and nodules. pale macules, Alopecia, limb weakness.[8] a loss of sensitivity, an enlarged nerve.19]	 **Figure 9: [25]**

Clinical feature of leprosy:

Leprosy affects mainly the skin, superficial peripheral nerves, the eyes, and certain organs (e.g., the testicles). A dispersed skin condition is often the reason patients seek care, although they may also complain of numbness and other types of paresthesia or general signs such as fever and weight loss. Lepromatous leprosy is measured to be at the dynamic, progressive, systemic, and infectious end of the spectrum. Bacteriology will be positive and the Mitsuda reaction (intradermal lepromin test) will be negative due to the absence of specific cell-mediated immunity.[26] Leprosy is characterized by one or more of the following cardinal features listed below-

a) Hypopigmented patches.

b) Partial or total loss of cutaneous sensation in the affected areas (earliest sensation affected being light touch).

c) Presence of thickened nerves.

d) Presence of acid fast bacilli in the skin or nasal smears.

The clinical diagnosis is not made unless at least one of the cardinal signs is present. [27]

Table: 2

Clinical features	**Tuberculoid**	**Borderline tuberculoid**	**Borderline lepromatou**	**Borderline**	**Lepromatous**
Skin					
Infiltrated lesions	Defined plaques, irregular plaques, healing centres	Polymorphic, partially raised edges, satellites	Papules, odules, punched-out centres	Diffuse thickening	Diffuse thickening
Macular lesions	Single, small	Several, any size	Multiple, all sizes, bizarre	Innumerable, small	Innumerable, confluent
Peripheral nerve lesions	Solitary, enlarged nerves	Irregular enlargement of several large nerves, asymmetrical pattern	Many nerves involved, symmetrical pattern	Late neural thickening, asymmetrical anaesthesia and paresis	Slow, symmetrical 'glove-and-stocking' anaesthesia.[27]
Lepromine test	Strongly positive	Weakly positive	Negative	Negative	Negative. [27]

The clinical features of the disease are resolute by the host response to *M. leprae*. Patients commonly present with skin lesions, numbness or weakness which is caused by peripheral nerve involvement or more rarely a painless burn or ulcer in an anaesthetic hand or foot. [28]

Pathophysiology:

M. leprae, an acid- fast bacillus is a main human pathogen and known for their notoriously slow growth. Schwann cells are main target of M.leprae leading to injury of nerve, demyelination and subsequent disability. It has been shown that M. leprae can attack Schwann cells by a specific laminin binding protein of 21kDa in addition to PGL-1, a major unique glycoconjugate on the M. leprae surface, binds laminin-2, which explain the weakness of the bacterium for peripheral nerves. The detection of the M.leprae-targeted Schwann cells receptor, dystroglycan (DG), acting a major role for this molecule in early nerve degeneration. The direct bacterial ligation of M.leprae to neuregulin receptor induce demyelination, ErbB2 and Erk1/2 activation, and subsequent MAP kinase signalling a proliferation.[26] Beginning of Leprosy is insidious. It affects nerves, skin and eyes. It may also affect mucosa (mouth, nose, and pharynx), testes, kidney, voluntary/smooth muscles, reticulo-endothelial system and vascular endothelium. Bacilli enter inside the body usually through respiratory system. It has low pathogencity, only a small proportion of infected people develop signs of the disease. Bacilli start multiplying slowly (about 12–14 days for one bacterium to divide into two) within the cells, get liberated from the destroyed cells and enter other unaffected cells. [29]

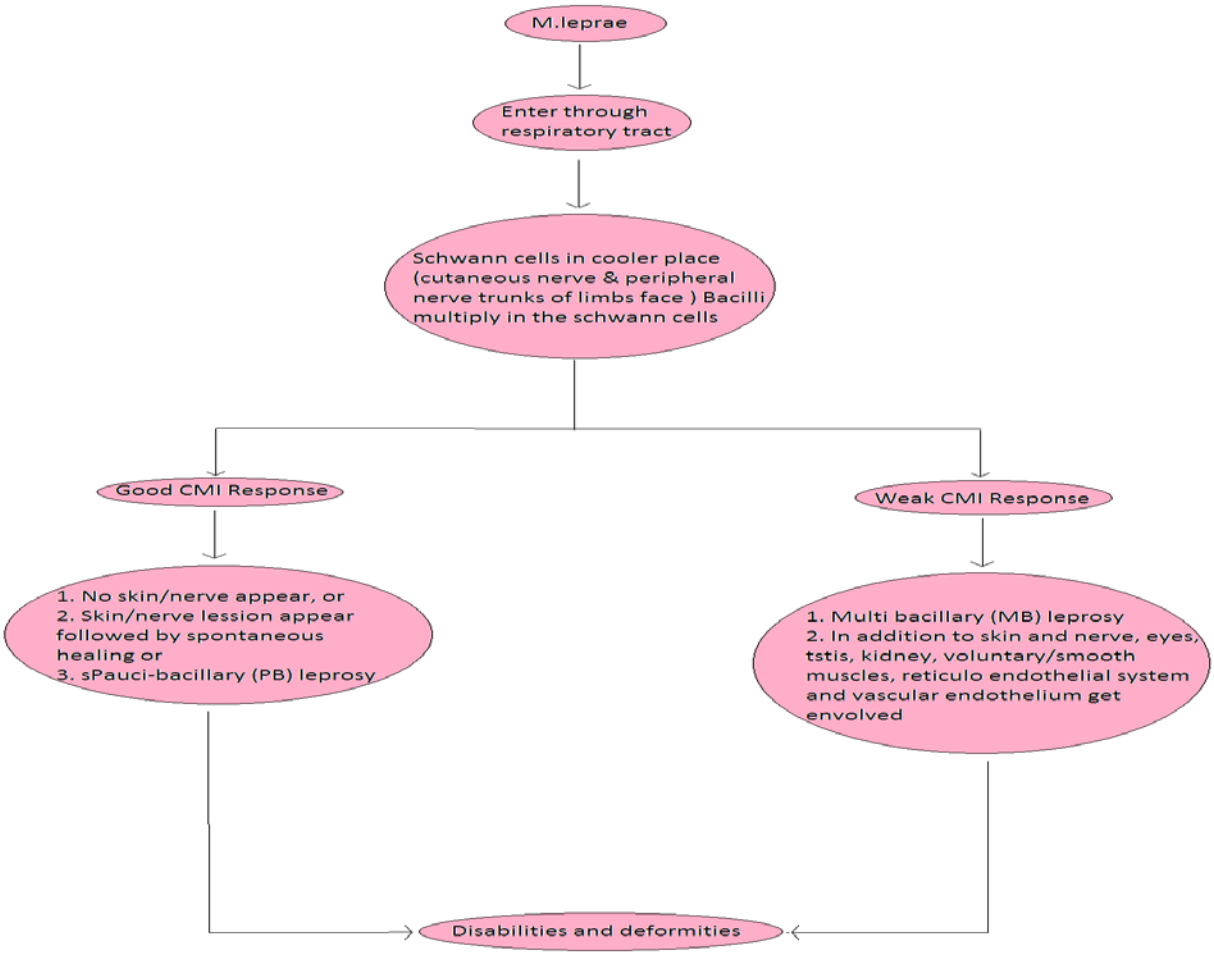


Figure 10: Pathogenesis of leprosy

In Persons with strong Cell Medicated Immunity (CMI), granuloma formation occurs in cutaneous nerve that swells and gets destroyed. Often only a few fascicles of the nerve are infiltrated but inflammation within the epineurium that causes compression and destruction of unmyelinated sensory and autonomic fibers. Myelinated motor fibers are the last to get affected producing motor impairment. Severe inflammation may effect in caseous necrosis within the nerve. Clinical manifestation of sensory loss occurs when nearly 30% of the sensory fibers

are destroyed. Good CMI successfully confines the disease to the nerve Schwann cell resulting in occurrence of pure neural leprosy. M. leprae may escape from nerve to adjacent skin at several time and cause classical skin lesion(s). Regions of the skin with relatively higher temperature such as axilla, groin, perineum and hairy scalp are usually spared.

In persons with depressed CMI, bacilli entering the Schwann cells multiply unchecked and destroy the nerve. Also, bacilli liberated by infected and destroyed cells are engulfed by histiocytes. Histiocytes with bacilli inside them become wandering macrophages. Bacilli multiply within these macrophages and travel to other tissues, through blood, lymph or tissue fluid.[30] Most people are resistant to infection with *M. leprae*; however, certain genotypes are increasingly predictable as risk factors for leprosy. Both human leukocyte antigen (HLA) and non-HLA alleles have been linked to susceptibility to infection. A recent genome wide association study in eastern China allied variant genes in the NOD2 signaling pathway with susceptibility to infection with *M. leprae*. [31]

DIAGNOSIS OF LEPROSY:

Using some new information about specific sequences of M. leprae, several gene probes and gene amplification systems confirming diagnosis and monitoring treatment have been developed. Among these, polymerase chain reaction (PCR)-based methods have been useful in confirming the diagnosis in paucibacillary leprosy (where few bacilli are present). [32]

The diagnosis of leprosy is simple but it requires ability to differentiate skin lesions and recognize nerve involvement. Diagnosis based on an anaesthetic patch is likely to miss about 30% of the MB cases. Paramedical workers in the field need to be trained to identify at least two cardinal signs of leprosy: Anaesthetic skin lesions and Enlarged Nerves. This involves training, supervising and monitoring primary health care staff as well as offering refresher training .[33] The exact diagnosis of leprosy is of fundamental importance to all aspects of leprosy epidemiology, case management and the prevention of disability. The diagnosis and classification of leprosy have traditionally been based on the clinical examination, frequently with additional information from skin-smears. Histopathologic examination, inoculation of the mouse foot pad, serologic tests, skin testing and PCR have been largely confined to research studies. [34]

Neurological examination exposed that they were indeed totally anesthetic (light touch, pinprick, and temperature). Palpation of peripheral nerves for pain or enlargement, with particular attention paid to the elbow's ulnar nerves, was not relevant. The patient denied that she had ever had a diagnosis of leprosy. The differential diagnoses might include tumid lupus erythematosus; Jessner lymphocytic infiltration; and erythema annulare centrifugum, deep type. [35] The diagnosis of leprosy is based on the demonstration at least two of the first or three cardinal signs enumerated below or the last one independently.

1) Characteristic skin lesions- The essential characteristic of lesion of tuberculoid and indeterminate leprosy in a dark skin is hypopigmentation, macular or infiltrated, with sensory loss. In light skins the lesions are copper coloured or erythematous. The lesions of lepromatouas leprosy show one or more of characteristics features such as diffuse infiltration, macules, papules and nodules.

2) Sensory loss- This may be of individual skin lesions or of an area of the skin supplied by a peripheral nerve.

3) Thicked nerves at the sites of predilection- e.g the ulnar nerve immediately above the ulnar groove; the posterior tibial nerve behind the medical malleolus; the lateral popliteal nerves as it winds round the neck of the fibula; the radial cutaneous nerve at the wrist; the facial and greater auricular nerves; and the median nerve proximal to the flexor retinaculum. In addition, cutaneous branches associated with a lesion may be enlarged.

4) The presence of acid – fast bacilli in slit-skin smears- The appearance of skin lesions is very often characteristic and unaided sometimes sufficient to suggest the diagnosis. A long history of disease, a slow and insidious onset combined with absence of irritation and itching, is highly suggestive of leprosy but not diagnostic unless they are supported by at least one of the other signs, i.e., sensory loss, thickened nerves, or acid – fast bacilli in the skin smears. The diagnosis should be established after a detailed clinical examination, bacteriological examination, and only when signs and symptoms are clear and unequivocal**. [36]**

Use of recent technologies in leprosy diagnostics

Development of newer techniques and improvement and modification of old techniques for diagnosis of leprosy are now being undertaken. Demonstration or localization of *M.leprae* and its antigens in the lesions further increases the specificity as well as sensitivity of diagnosis. Use of Cuper May's fluorescent method, immunoperoxidase technique with anti BCG polyclonal antibodies, demonstration of PGL-1 antigen. Tissue level localization of antigens of *M.leprae* using more specialized polymerase chain reaction (PCR) and RTPCR, technique have markedly increased the sensitivity . PCR methodology is now being developed to detect presence of a small number of *M.leprae* its DNA/RNA in the skin smears. They can serve as an important/sensitive tool in

timely diagnosis and classification. [37] This technique has been applied not only to skin biopsy samples, but also to several different types of specimens such as skin smears, nerves, urine, oral or nasal swabs, blood, and ocular lesions. The PCR test was specific and detected M. leprae DNA in biopsies from leprosy patients.[38]

LEPROMIN TEST:

This measures the cell-mediated immunity (CMI). Autoclaved M. leprae are injected intradermally into the forearm, the result is read in 48-72 hours (Fernandez reaction) and 3-4 weeks (Mitsuda reaction) later. The Fernandez reaction indicates the degree of delayed-type hypersensitivity (DTH) and the Mitsuda reaction indicates CMI. The Mitsuda reaction is not diagnostic as it is positive in normal individuals not exposed to M. leprae and negative in lepromatous leprosy. [39]

TREATMENT OF LEPROSY:

The World Health Organization provides a multidrug treatment regimen that targets the Mycobacterium leprae bacillus which causes leprosy. Several investigational drugs are available for the treatment of drug-resistant M. leprae. Future directions in leprosy treatment will focus on: the molecular signaling mechanism M. leprae uses to avoid triggering an immune response; prospective studies of the side effects experienced during MDT; recognition of relapse rates post-completion of designated treatments; combating multidrug resistance; vaccine development; development of new diagnostic tests; and the implications of the recent discovery of a genetically distinct leprosy-causing bacillus, Mycobacterium lepromatosis. [40] Primarily affecting skin, mucous membranes and nerves. It is more prevalent among the lowest socio-economic strata. In India, the National Leprosy Control Progromme was launched in 1955, and was change to National Leprosy Eradication Programme (NLEP) in 1982, with the use of multidrug therapy (MTD), India has achieved elimination of leprosy as a public health problem (prevalence rate <1 case per 10,000 population) in December, two polar types-lepromatous (LL) and tuberculoid (TT) with 4 intermediate form borderline (BB), borderline lepromatous(BL), borderline tuberculoid(BT) and intermediate(I) of the disease are recognized .

For operational purposes, leprosy has been divided into:

1) Paucibacillary leprosy (PBI) (Non infectious): This includes TT, BT, I, and Polneuritics.

2) Multibacillary leprosy (MBL) (Infectious): This include LL, BL,and BB. [41]

Table 3: Drugs Used in Leprosy

Drugs	Mechanism of action	Actions	Adverse effects	Uses	Dose
Dapsone	Dapsone inhibits the incorporation of PAPBA into folic acid.[42]	Leprostatic,inhibit growth of many other bacteria.	Mild heamolytic anaemia,nausea and vomiting,fever, pruritis,rashes,	Leprosy, pemphigoid (an autoimmune blistering disease of skin and mucous membranes), ulcerative colitis[45]	100 mg/day
Rifampicin	Rifampin inhibits DNA dependent RNA synthesis.	Highly effective,acts on bath intra & extracellular organisms,resistance develops.	Hepatotoxicity ,gastrointestinal disturbances,flu like syndrome,CNS symptoms,hypersensitivity reaction.[43]	Leprosy,tuberculosis ,brucellosis.multibacillary leprosy in combination with dapsone and rifampicin	600 mg/monthly
Clofazimine	It have bactericidal effect on *Mycobacterium leprae* ; it inhibits mycobacterial growth with binds preferentially to mycobacterial DNA.	Leprostatic , exerts anti-inflammatory effects in the control of erythema nodosum leprosum reactions.	Discoloration of the hair, cornea, conjunctiva, tears, sweat, sputum, faeces and urine also occurs. Gastrointestinal bleeding, gastrointestinal toxicity, hepatitis or jaundice, and mental depression.	the treatment of lepromatous leprosy complicated by erythema nodosum leprosum reactions ,skin ulceration [44]	50 mg/daily

Ethionamide	Ethionamide disrupts mycolic acid synthesis.[44]	More toxic, more expensive, Resistance develops.	Liver dysfunction, toxic hepatitis, gastrointestinal disturbance, allergic reaction, alopecia, dermatitis [46]	Treatment of multibacillary leprosy, Hepatotoxicity.	250mg/ day

A number of different antibiotics (including Dapsone, Rifampin, Clofazamine, Fluoroquiolones, Macrolides, and Minocycline) are used to kill the bacteria that cause the disease. More than one antibiotic is often given together. Aspirin, Prednisone, or Thalidomide is used to control inflammation.[46]

Table 4: modified who – recommended multidrug therapy regimens in leprosy

S.NO.	Types of leprosy	Monthly supervised drug treatment	Daily self-administered drug treatment	Duration of treatment
1.	Paucibacillary	Rifampicin 600mg	Dapsone 100mg	6 months
2.	Multibacillary	Rifampicin 600mg Clofazimine 300mg	Clofazimine 50mg	12 months
3.	Paucibacillary Single-lesion	Ofloxacin 400mg Rifampicin 600mg Minocycline 100mg	Dapsone 100mg	Single dose[47]

The recommended length of treatment is 2 years or until they become smear negative**.** Then they should be examined at least once a year (clinical examination, skin smear) for 5 years. Never use Rifampin alone or Rifampin+Dapsone without a third bactericidal drug to avoid Rifampin resistance. [48]

Lepra Reactions

So-called reactions in leprosy are clinically evident, immunologically mediated inflammatory conditions occurring during the course of the disease in about 50% of patients. These manifestation of leprosy are due to the immunologic response of the host to the bacilli. They are mainly of two types.[49] Reactions are the main cause of nerve damage and disability in
leprosy so it is important that you are able to recognise them. The swelling can affect
the skin patches, the nerves, the eyes and, in a few cases, the internal organs. Inflammation of a skin patch can be uncomfortable, but it is not usually very serious (unless it is near the eye).[50]

Type I Reaction

It is a delayed type of hypersensitivity reaction, i.e. type-IV. It is usually see in boderline leprosy. Antigens from breaking down lepra react with T lymphocytes leading to quick change in cell mediated immunity. Clinically a number or all skin lesions become erythematous, edematous, warm to touch and affectionate. Necrosis with supervening ulcerations may also occur. Rapid swelling of one or more nerves due to acute neuritis may lead to motor deficit. [51]

Type 2 reaction

Erythema nodosum leprosum ENL occur in MB (LL type) patients first occurs later in the course of treatment. In relation to Lepra Reaction, it is important to memorize that the two types of Immunity are involved - "Humoral Antibody Response" and "Cell Mediated Immunity". On the other hand, a temporary raise in the reversal reactions (type 1) has been noted in MB leprosy patients in their first year of MDT. Type 2" reaction may also be accompanied by severe eye problems, mainly Iritis which may be confused with conjunctivitis. The testes (cooler) may be swollen and extremely tender. There may be soften of the bones,particularly in hands, feet and tibiae. Muscle pain (Myositis) and inflammation of the joints give the impression of severe rheumatism. These reactions respond satisfactorily to predonisolone along with thalidomide or CLF.[52]

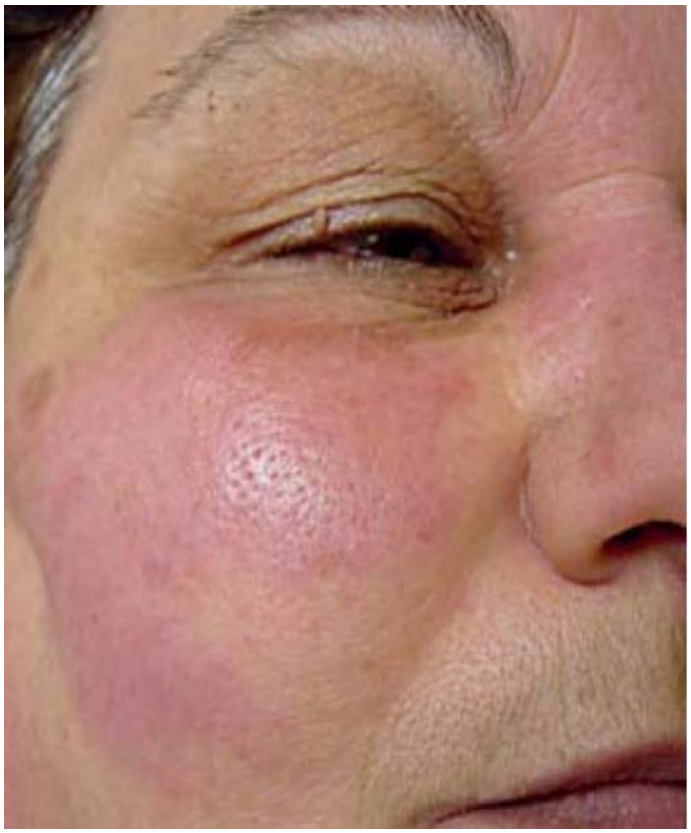


Figure 11: type 1 reaction: erythematosus plaque on the face and

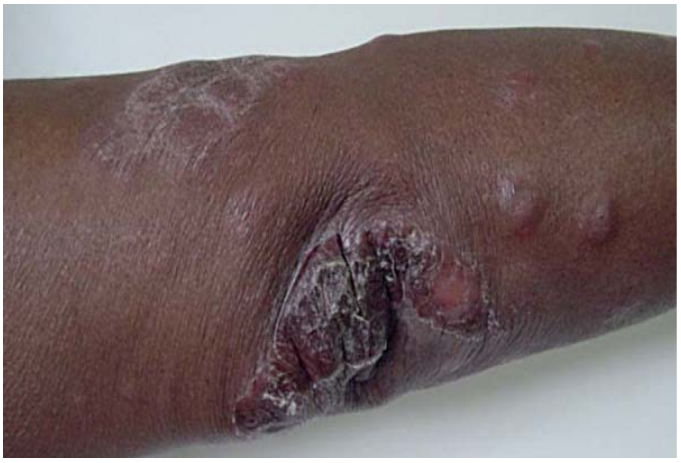


Figure 12: type 2 reaction: erythema nodosum leprosum: inflammatory nodules in the upper limb [18]

AYURVEDIC TREATMENT OF LEPROSY

Traditional medicines are widely used throughout the world. As the name implies, these treatments are a part of the traditions of each country that have been handed down from generation to generation.[53] It has a long tradition of traditional medicinal systems including AYUVEDA, UNANI, SIDDHA and TIBETAN systems with inexhaustive treasure of medicinal plants useful in the remedy of various ailments.[54]

Table 5:

Sl. no.	Botanical name	Family	Vernacular name	Part of plants	medicinal use
1.	*Fumaria indica*	Fumariaceae	Pittpapra	Root decoction	skin disease and leprosy
2.	*Bidens pilosa* Syn. *Biternata*	Asteraceae	Ara-kajhar/ Samsa	Leaf paste on	leprosy [54]

It is one of the oldest diseases known to mankind. In India, leprosy has been known since ancient times as kushtha rog, Light skin patches with loss of sensation, Thickening of nerves. As the disease progresses, there is a breakdown of the skin with the formation of ulcers, a likelihood of the hands and feet to be affected by trauma or burns, especially since they experience no sensation in the affected region. This results in deformities of the hands and face. Also, the nerve supply to muscles can be affected resulting in foot drop, claw toes etc. [55]

Herbal medicine (or "herbalism") is the study and use of medicinal properties of plants. The Pen Tsao lists 365 medicinal plants and their uses - including Ephedra (the shrub that introduced the drug ephedrine to modern medicine), hemp, and chaulmoogra (one of the first effective treatments for leprosy). [56]

Hydnocarpus wightiana/ **Chaulmoogra Oil and the Treatment of Leprosy**

Chaulmoogra oil entered Western medicine only in the nineteenth century, but it had been used in the East against leprosy and various skin conditions for many hundreds of years. In the woods he was directed by the gods to a tree with a large fruit with many seeds. He was told to eat the seeds, which he did, and was thereupon cured of leprosy. The oil was long used in traditional Ayurvedic medicine in India for the treatment of leprosy and various skin conditions.[57] chaulmoogra is given intravenously (iv) for leprosy.leprosy used in chemical found in chaulmoogra seed.[58]

Figure: 13: Chaulmoogra plant [58]

Table 6: List of Herbal Plants Which Is Used In Treatment of Leprosy

S.No	PLANTS NAME	Family	Part(s)used	Medicinal use
1.	Azadirachta indica/neem	Meliaceae	Leaf, bark ,seed	Leprosy
2.	Melia azedarach	Meliaceae	Leaf, bark ,seed	Leprosy
3.	Abrus precatorius	Papilionatae	Leaf, bark ,seed	Leprosy
4.	Achyranthes aspera	Amranthaceae	Leaf	Leprosy
5.	Tinospora cordifolia	Menispermaceae	Stem	Leprosy [59]

FOLLOWING PLANTS ARE USED TO TREAT LEPROSY

Azadirachta indica [60] Momordica charantia[61] Garlic(allium sativum)[62]

Figure 14: PLANTS USED IN LEPROSY TREATMENT

CONCLUSION AND FUTURE PROSPECTS

As mentioned above in this review, leprosy is not highly transmissible and is almost treatable, but being a worldwide disease it still affects about quarter of a million people every year. Advancement in clinical treatment has led to better understanding of the disease. Improvement in services and education as well as eradication of poverty will also help leprosy patients. The causes, types, sign and symptoms as well as treatment of the disease are well known hence passing of the

information to the public will improve awareness. As this review covers almost every aspect of the disease, such tools can be very useful in understanding the history of leprosy, the present scenario, as well as the future research advances towards better management of the disease.

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