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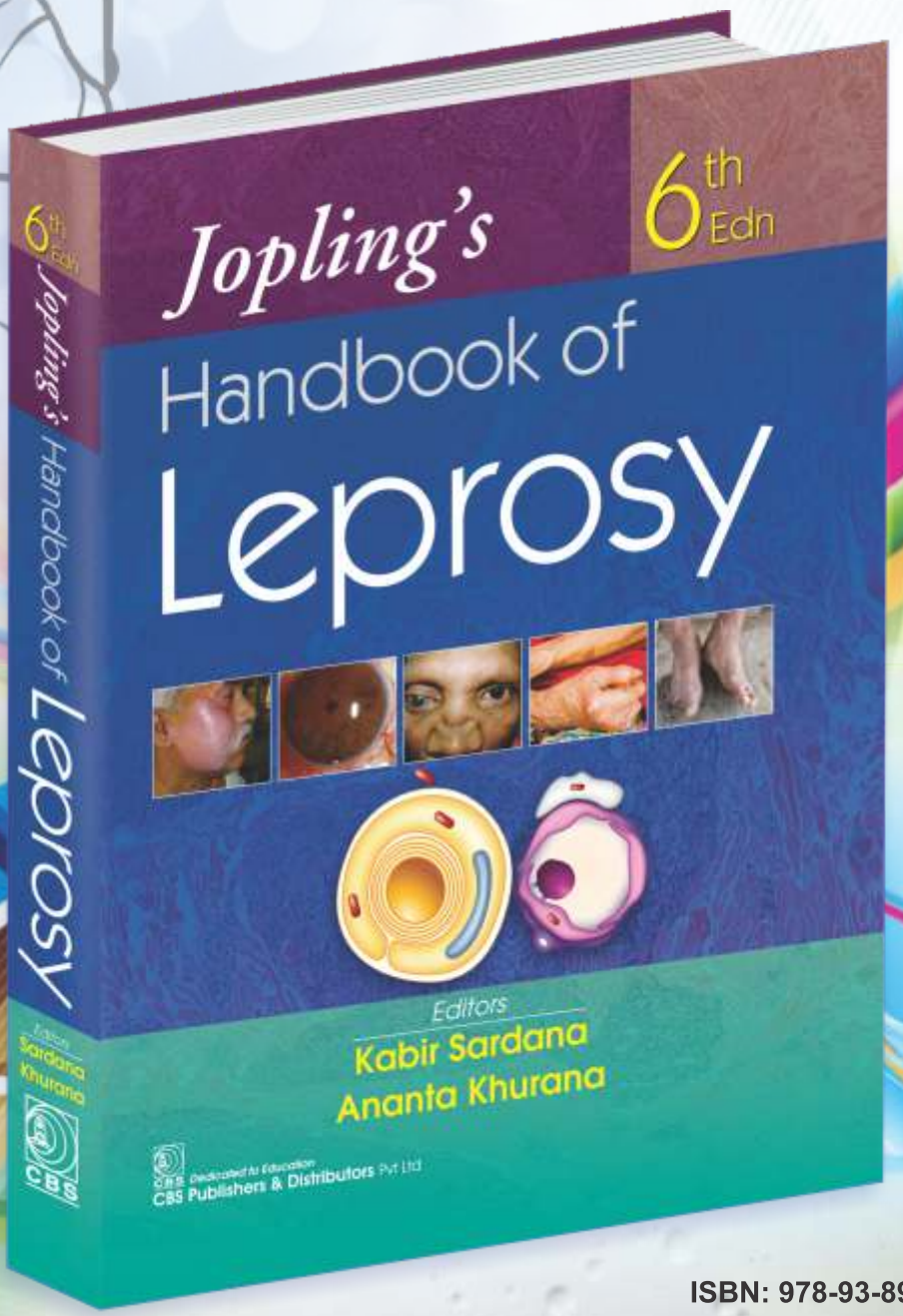

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Jopling's 6th Edn

Handbook of Leprosy

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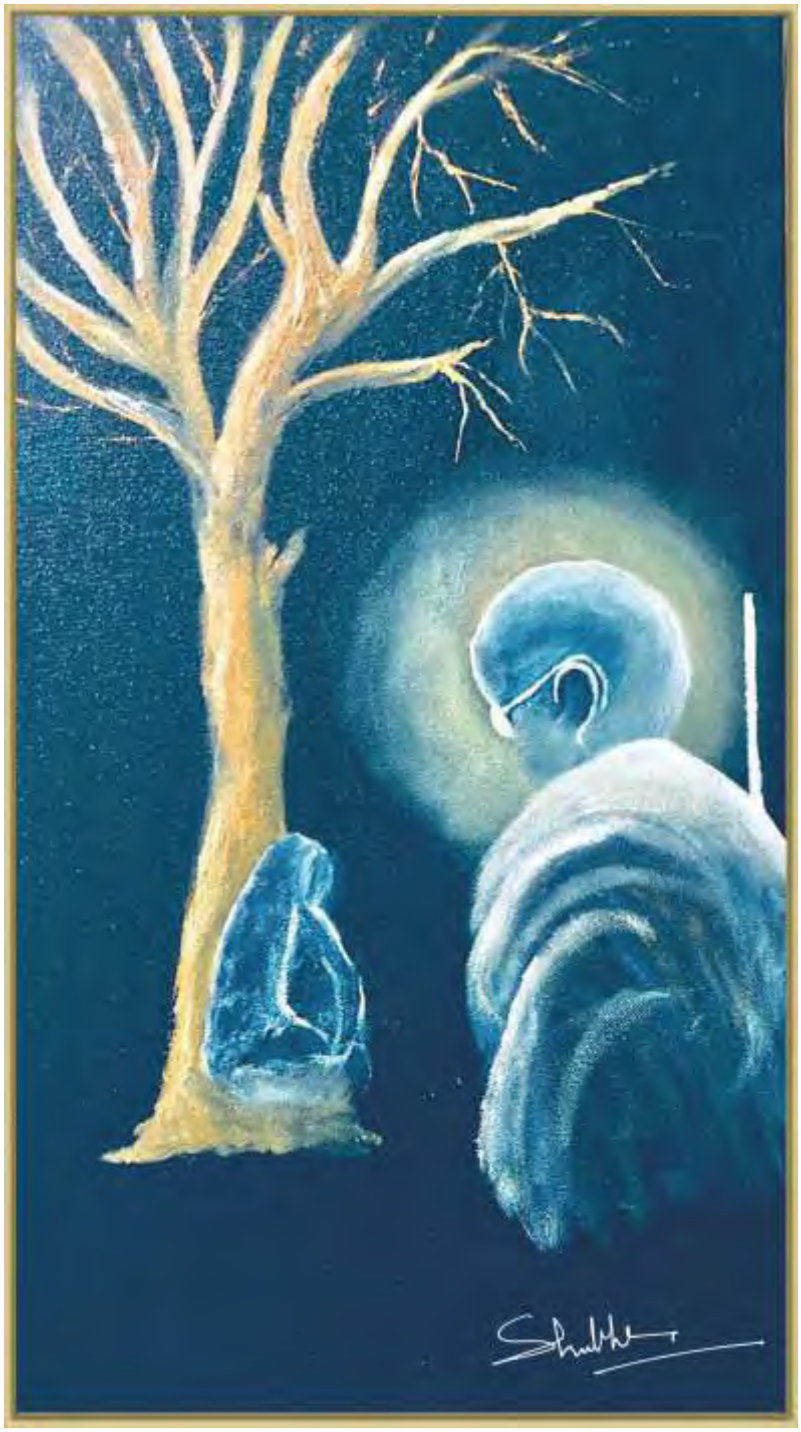
to

Mohandas Karamchand Gandhi



who devoted his life to the care and rehabilitation of leprosy patients.

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Contents

Preface to the Sixth Edition

Jopling's Handbook of Leprosy has been read and referred to by generations of dermatologists across the country and outside and is probably one of the most acclaimed texts on leprosy. The 6th edition comes after a huge gap of 24 years from the last edition. The 5th edition had been reprinted 14 times from 1996 till 2019, with no additions/changes in text. The aim of this edition was to retain the original concepts and the clinical content of the previous editions and in addition updating the book with the enormous advancements made since, while keeping the text concise and the book handy and easy to read. The reader will note that the original table of contents has been enlarged encompassing the additions to the text.

Most of the classical text on clinical leprosy from the previous editions is retained and a section on special scenarios has been added. The major changes in 6th edition include an updated review on immunopathogenesis of disease which has seen several advancements over past two decades. From a simplified view on involvement of humoral and cell-mediated immunity at the two poles as detailed in the last edition, this edition incorporates the established and proposed immunopathogenetic mechanisms and deals with the complexities of the topic in a simplified manner with representative schematic diagrams. The diagnosis section includes the classical descriptions from the 5th edition with added text on newer methods. The second part of the diagnosis chapter comprehensively covers aspects on histopathology of leprosy in detail. Reactions are covered separately and include recent treatment concepts. Resistance in leprosy is now a reality and a summary of the topic with a section on its clinical relevance has been included. The treatment of leprosy has undergone some significant changes since the last edition and this has been thoroughly updated, even though we feel some changes in treatment have been hasty and could have waited for longer follow-up data. We have added a drug formularly which summarizes the essential aspects of the drugs used not only in treatment of leprosy but also in reactions. The second section under treatment covers the concepts of chemoprophylaxis and immunoprophylaxis in leprosy and provides the reader a review of all important work done on these aspects so far and gives them insight into concerns remaining and future directions. The section ends with a brief segment on immunotherapeutics, the majority of work on which has been done in India.

It is an accepted reality that while MDT has been successful for multiple reasons, a proportion of cases suffers from disability and the management of this domain is largely relegated to ancillary branches. We believe that this is a crucial aspect and we have tried to present a concise summary of diagnosis and management of neural involvement and the consequent deformities. The section on differential diagnosis provides an illustrated review with large portions of original text retained and many photographs added.

We believe a book of leprosy should have contributors who see and manage cases and not just those who interpret data which is a mechanical and abstract way of tackling

a disease. This accounts for our contributors who range from dermatologists, physicians, scientists, rehabilitation experts and those who have worked on core aspects of the disease. Some of our contributors have doubled up both as contributors and reviewers and we are grateful to Dr M Hogeweg and Dr Cynthia Butlin for their efforts.

A big thanks to the fabulous team at CBS Publishers & Distributors, especially to Mr YN Arjuna Senior Vice-President—Publishing, Editorial and Publicity, Mrs Ritu Chawla General Manager—Production, Mr Vikrant Sharma and Mr Tarun Verma for the dedicated reformatting, Mrs Baljeet Kaur for the artistic depiction and image balancing, Mr Neeraj Prasad for cover design and to Mr Ananda Mohanty and Mr Khirod Sahoo for the meticulous proof reading; all of whom have been tolerating our efforts and the delays for the last one year!

We hope the updated *Jopling's Handbook of Leprosy* proves to be useful for postgraduates, academicians, practitioners and field workers alike and helps in understanding and tackling this ancient disease.

Kabir Sardana
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Preface to the First Edition

For a long time I have been impressed by the demand for information on leprosy from all sections of the medical and nursing professions, and I have attempted, in this Handbook, to give the basic facts about the disease and its management as clearly and conscisely as possible. During my visit to leprosy centres in Africa in 1968, I noted the responsible work undertaken by paramedical workers and their eagerness to do it well; I have particularly in mind the medical assistants in-charge of rural clinics or travelling in Land-Rovers as members of mobile medical teams, and I hope that these workers and their counterparts in other developing regions will find in this volume the help they need.

As regards the medical profession, I hope that this Handbook will give the student and general practitioners a better understanding of leprosy, and will also have an appeal to the specialist on whom the diagnosis of the disease may fall, especially the dermatologist and the neurologist.

I would like to thank my son-in-law, Mr David Dartnall, for the drawings and diagrams, and I am grateful to Dr Colin McDougall and Dr Tin Shwe for helpful criticism and advice.

WH Jopling, 1971

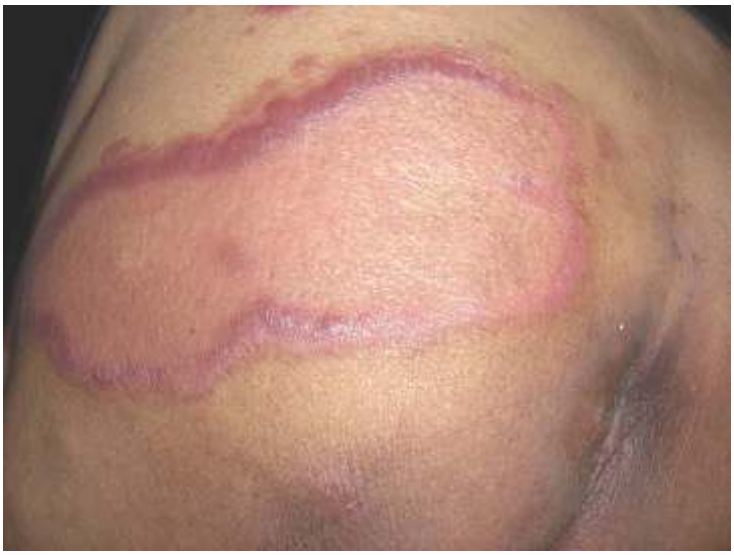


Fig. 2.11: An annular plaque seen in the borderline spectrum of leprosy

4. *Punched-out Lesions*

These are characteristic of the borderline type and are erythematous plaques with vague outer edges and a punched-out central portion also likened to a "hole-in-cheese" / "Swiss cheese" appearance (Fig. 2.12). The edge of the "punched-out" portion is distinctly palpable and clear cut. Some degree of anesthesia will be found on testing the lesions.

5. *Bizarre Lesions*

These take the form of raised bands or of geographical lesions (Fig. 2.13) (like the contour of a map). Some degree of anesthesia will be present.

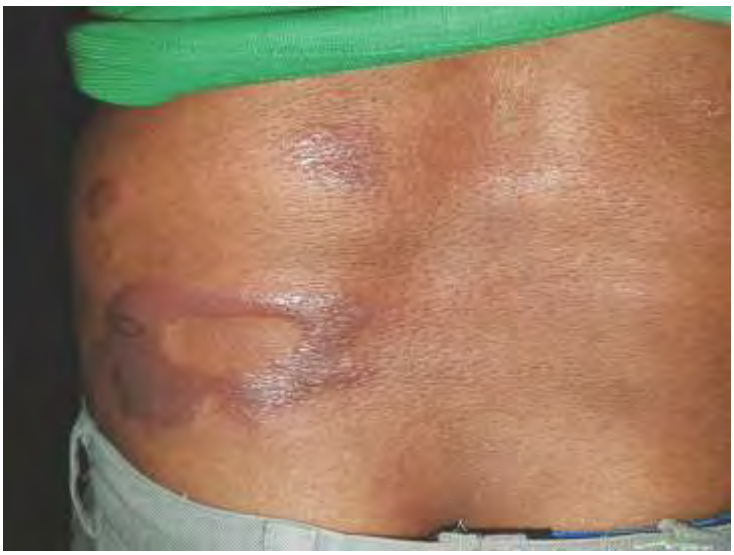


Fig. 2.12: BB Hansen annular plaque with a "Swiss cheese" appearance

2.2 RELAPSE, REACTIVATION, REACTION AND REINFECTION

C Ruth Butlin

NATURAL HISTORY OF TREATED LEPROSY

When a person has leprosy, some of the clinical manifestations are a direct result of bacterial multiplication in his body (what one might call "active signs of infection"), but many of the more prominent manifestations are a result of an immunological inflammatory response to the bacterial antigens. The latter can occur in absence of viable bacteria, so may be seen before, during or after effective chemotherapy. These inflammatory phenomena, which we call lepra reactions, include type 1 reactions, type 2 reactions/erythema nodosum leprosum (ENL) and acute neuritis.

Active signs of infection in untreated cases include congestion of nasal mucosa with bleeding, diffuse infiltration, madarosis, lepromatous nodules, hypopigmented or erythematous skin patches with or without impaired sensation, thickening of peripheral nerve trunks and gradual impairment of nerve function in extremities. A positive skin smear does not necessarily indicate active infection since it takes much longer for the bacterial debris to be cleared from the body than it does to kill the bacteria, however, an increasing bacteriological index (BI) in sequential smears from the same area does indicate bacterial multiplication. A reactional episode is not by itself a sign of active infection.

These concepts are difficult for patients to understand and may confuse some clinicians who are unfamiliar with the natural history of leprosy disease.

The normal response to an appropriate course of chemotherapy is a rapid improvement (within weeks) in any nasal symptoms, followed by gradual subsidence of infiltration and lepromatous nodules (over many months), and a slow healing in any skin patches (shown by them becoming flatter and less well-defined, with partial recovery of former pigmentation and sometimes of sensation). If the smear was positive initially, there will be a fall in BI over several years. If serial biopsies were done, histology would show, in lepromatous cases, increasingly foamy cells replacing macrophages stuffed with AFBs, and in borderline or tuberculoid cases, granulomas becoming less well organized and being slowly replaced by fibrous tissue (Job).[1]

Hence, one should not expect to see complete resolution of all signs of infection in every case by the end of a standard MDT course, lasting 6 or 12 (or even 24) months. The clinical appearance cannot be taken as a criterion for "cure" and the decision to stop chemotherapy is taken on the basis of completing a full course within the set time period. Clinical signs of previous infection will continue to subside after cessation of MDT. Reactional episodes may occur months or years after release from treatment and do not signify a need for extending/repeating the chemotherapy course.

Recording and Reporting in Leprosy Control Programmes

In the context of a national programme, one must distinguish and report separately to authorities, "new cases" (never before treated), returned defaulters who are restarting treatment, and relapse cases who need a second course of treatment. However, large numbers in each of these categories have different implications for a control programme: A high proportion of defaulters is suggestive of poor service at clinic level, whereas

manifestation of disease. It is not known what triggers this "awakening" of persisters, timing and frequency of relapses.

It is impossible to state accurately the probability of relapse after a course of chemotherapy since what evidence is available is not consistent. There have been many attempts to quantify the risk, but published estimates differ widely and cannot easily be compared (because they differ in the measurements reported, in the criteria for classification and for diagnosis of relapse, in the duration of chemotherapy and of follow-up and because local background prevalence may affect results). Commonly quoted figures are 0.1% per annum (p.a.) for PB cases and 0.06% p.a. for MB cases. Several authors have shown that those with initial BI > 3.0 + (or BI of > + 4.0 at end of chemotherapy) are at higher risk of relapse. Some researchers believe that the relapses occur earlier after shorter courses of rifampicin-containing chemotherapy.[10] There have been suggestions (based on case series) that relapse is more likely during pregnancy or in the postpartum period, than in non-pregnant women, though this has not yet been confirmed by any community studies. A selection of the more useful publications from leprosy control programmes and research studies is shown in Table 2.13.

Table 2.13: Relapses after MDT

Reference	*Previous chemotherapy*	*Number of subjects observed*	*Person years at risk (PYAR)/ maximum duration or mean follow-up period*	*% subjects relapsed*	*Relapse rate per thousand (PYAR)*	*Timing of relapses, if given*
WHO 1995[11]		20,000	9 years	0.77%	Not given	
Norman 2004[12]		173	16.4 +/– 1.83 years	2 = 1.16%	0.007/thousand PYAR	At 14 and 15 years after release from treatment (RFT)
Becx-Bleumink 1992 (3)[4]		2379	Mean 4.7 years, (range 2.5–6.0 years)	24 = 1%	2.4/thousand PYAR	
WHO 7th exp-cttee, 1998[13]		Not given	Not given	0.1% each year	Not given	
Ali 2005[14]		356	16 years	3 = 0.84%	0.86/thousand PYAR	
Girdhar 2000[15]	**24 months or more MB MDT for MB cases**	301 260	1085 PYAR 2–8 yr follow-up • 980.2 PYAR • 2–8 yr follow-up	12 = 4% 20 = 8%	0.11/thousand PYAR 0.20/thousand PYAR	
Gebre 2000[5]		256	• 1091 PYAR • Mean 4.3 years. Max 8 years	None	None	
Cellona 2003[16]		500	• 5368 PYAR • Mean 10.8 years	15 = 3%	0.028/thousand pyar	

(Contd.)

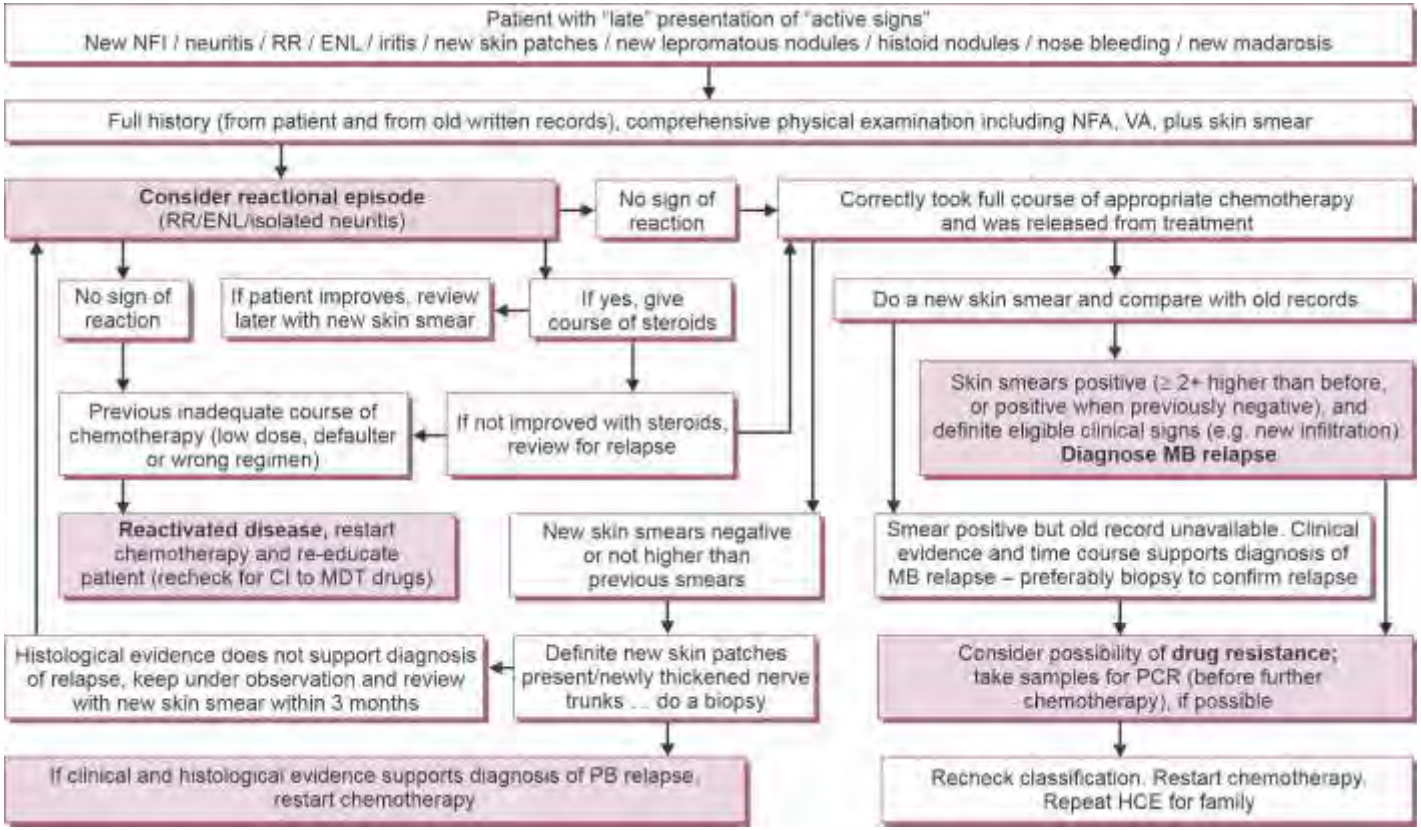


Fig. 2.30: Algorithm of facilitate differentiating relapse from reaction/re-activation in leprosy

NFI: Nerve function impairment; VA: Visual acuity; HCE: Household contact examination; RR: Reversal reaction; CI: Contraindication

Table 2.16: Differentiating late reactions (ENL) from relapse in treated leprosy cases*		
	Type 2 reaction	*Relapse*
Which patients (original classification)	• BB, BL or LLs • Only smear positive MB cases	• BT, BB, BL or LL • Cases who were originally • PB may downgrade to MB forms on relapsing (e.g. BT to BL)
Timing	• Whilst still smear positive • Predominantly within 5 years of diagnosis • Episodic	• Usually >2 years after completing chemotherapy • Progressive
Onset of new lesions	Rapid	Gradual
Old skin lesions	No change in diffuse infiltration	Increased area, more nodular
Course	• Recurrent "crops" of new erythematous skin nodules which spontaneously subside in 2–3 days leaving a "bruise-like" mark or may "blister" leaving a shallow erosion. • Each episode may subside after a few days/weeks.	Skin nodules persist and increase, infiltration extends
Sites of new lesions	Many parts of body can be affected by inflammation, but rarely see epistaxis due to ENL reaction.	Infiltration predominantly on face/ears, extensor surfaces, back. Lepromatous nodules predominantly around ears, on face, near elbows, wrists, knees and ankles; also, on palate.
Character of new lesions	• Inflamed subcutaneous nodules, or tender thickening of nerves/spontaneous nerve pain/acute nerve function impairment. • Circumcorneal inflammation and eye pain. Acute orchitis. • Pain in bones and joints.	• Diffuse infiltration, superficial firm non-tender nodules which do not blanch on pressure, non-painful thickening of nerves, gradually progressive neural impairment. • Lepromatous pannus/pearls in painless eye. • Stuffiness of nose and bleeding.
Constitutional symptoms	• Usually malaise, peripheral edema, high fever, anorexia. • Often neutrophil leukocytosis. • High ESR/CRP	• No constitutional symptoms • May be mild anemia, otherwise blood picture normal
Response to steroids	Usually improvement within a few days	If improves, it is only temporary
Skin smear	• BI same as previous one or less. • Bacteria appear fragmented	• BI higher than previous smear. • May see solid-staining rods.

*Based on table in a guide to leprosy control, WHO, 1988 **(p. 42)**.

Case reports of leprosy in young infants[5] suggest a vertical mode of transmission from mothers to fetus via placenta or via breastfeeding, although it is uncommon. In infants, the most likely route of transmission are skin-to-skin contact with mother and through nasal droplets if the mother has not yet had chemotherapy. The chances of air-borne infection due to close proximity during breastfeeding is low if the mother is on treatment or has already completed multidrug therapy (MDT).[18] Acid-fast bacilli resembling *Mycobacterium leprae* have been detected in the breast milk, but the viability is uncertain.[19] Also, there is no evidence that orally ingested *Mycobacterium leprae* can cause leprosy. Thus, breastfeeding by women who are on MDT is safe for infants.[18]

CLINICAL PRESENTATION AND DIAGNOSIS

There are certain differences between adult and childhood leprosy (enumerated in Table 2.18). When a child is infected with *Mycobacterium leprae*, he/she will either *not* develop leprosy, or *will* develop indeterminate leprosy. This can either self-resolve, remain stationary or may progress to a determinate type. In a leprosarium in the Philippines, of the total 2000 children examined, 470 had symptoms of leprosy and were treated. Amongst those who had doubtful leprosy (and were untreated) and

Table 2.18: Differences between childhood and adult leprosy

	Adult leprosy	*Childhood leprosy*
Age	15 years and above	0–14 years, most commonly involved is 9–14 years
Incubation period	Long (12–13 years)	Short. Few weeks to 10–12 years
Bacillary load	Usually multibacillary	Usually paucibacillary
Most common type of leprosy	Can be borderline or lepromatous	Usually indeterminate Single skin lesion is more common followed by 2 to 3; more than 4 skin lesions are rare
Self-resolving skin lesions	Uncommon	Common in children. With the development of immunity as the child grows, the skin lesions can self-resolve
Pure neuritic, histoid and Lazarine leprosy	Can be the presentation in adults	Rarely reported
Reactions and relapses	Both type 1 and type 2 lepra reactions are common. Relapses too can occur	Reactions are usually rare, and more common in older children with multibacillary disease. ENL and relapses are uncommon
Deformities	Common	Rare
Histology	Granuloma formation is an indication of effective build-up of cell-mediated immunity, commonly observed in adult skin and nerve biopsies	Well defined granulomas are usually rare

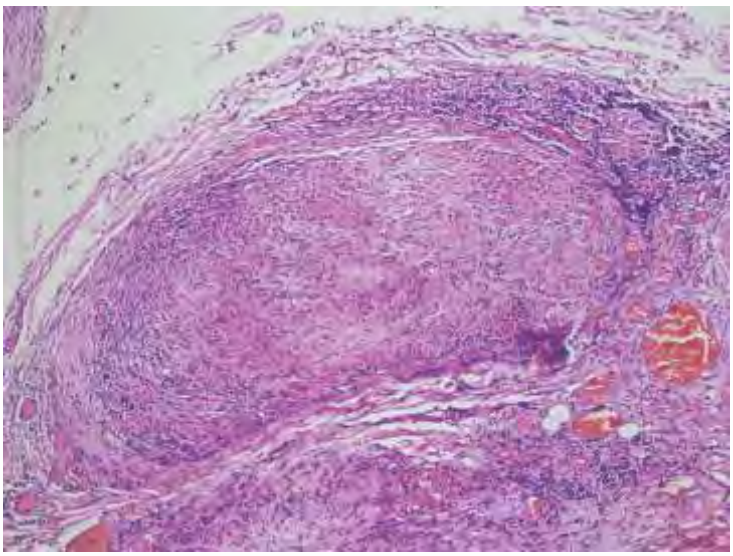


Fig. 2.49: Chronic tubercular leprosy. Transverse section of nerve biopsy showing a nerve fascicle showing marked endoneural fibrosis, along with few vague epithelioid cell granulomas and mild endoneural lymphocytic infiltrate. Epineural lymphoid infiltrate is also present

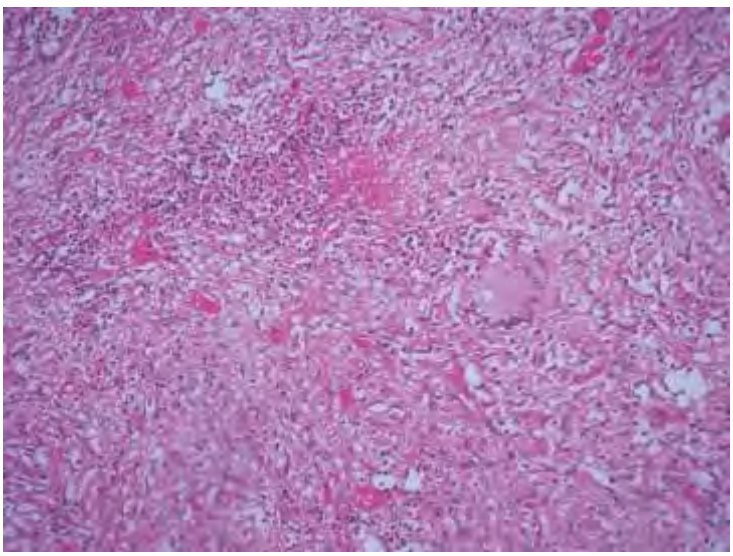


Fig. 2.50: Borderline lepromatous leprosy in type 2 lepra reaction. Nerve biopsy showing endoneural infiltration by foamy macrophages, along with few epithelioid cells and a few giant cells. Features of type 2 reaction such as focus of necrosis, nuclear debris and neutrophilic infiltrate are also identified

conduction velocity and increased latency.[1] These findings usually precede the clinically apparent nerve function impairment (NFI) and can detect subclinical neural involvement. However, a study comparing combination of nerve palpation with Semmes-Weinstein (SW) monofilament testing and voluntary muscle testing (VMT) showed comparable efficacy to NCS in detecting nerve damage.[19]

Recently, development of high frequency (15–20 MHz) ultrasonography (HRUS) has made visualization of nerves easier and cost-effective in comparison to magnetic resonance imaging (MRI). This technique provides information about exact site and size of nerve thickness, morphological variations in nerve trunk such as texture, pattern of fascicles and vascularity.[20, 21] This is very important in diagnosis of PNL and also in identifying reactions in PNL as increased vascularity and edema of nerve trunk signifies neuritis. A diagnostic algorithm has been illustrated in Fig. 2.51.

Complications and Sequelae

As with other types of leprosy nerve involvement, PNL may also produce complications like sensory and motor impairments, trophic changes and ulcerations and deformities such as claw hand or foot drop (which may be the initial presentation of PNL in neglected cases).[4, 22] Another significant complication of PNL includes nerve abscess which may be single or multiple in same or different nerve trunks.[23, 24] Another rarely reported entity in PNL is segmental necrotizing granulomatous neuritis (SNGN) which presents as nodular lesions of varying sizes along the nerve trunk.[25]

Over time, PNL can progress to the other clinical forms of leprosy including indeterminate, BT and BL spectrum.[26] This has been noted in approximately 15–35% of patients within 2 years of diagnosis of PNL,[27] while a few of them may develop cutaneous lesions during the multi-drug therapy (MDT). Moreover, cutaneous lesions

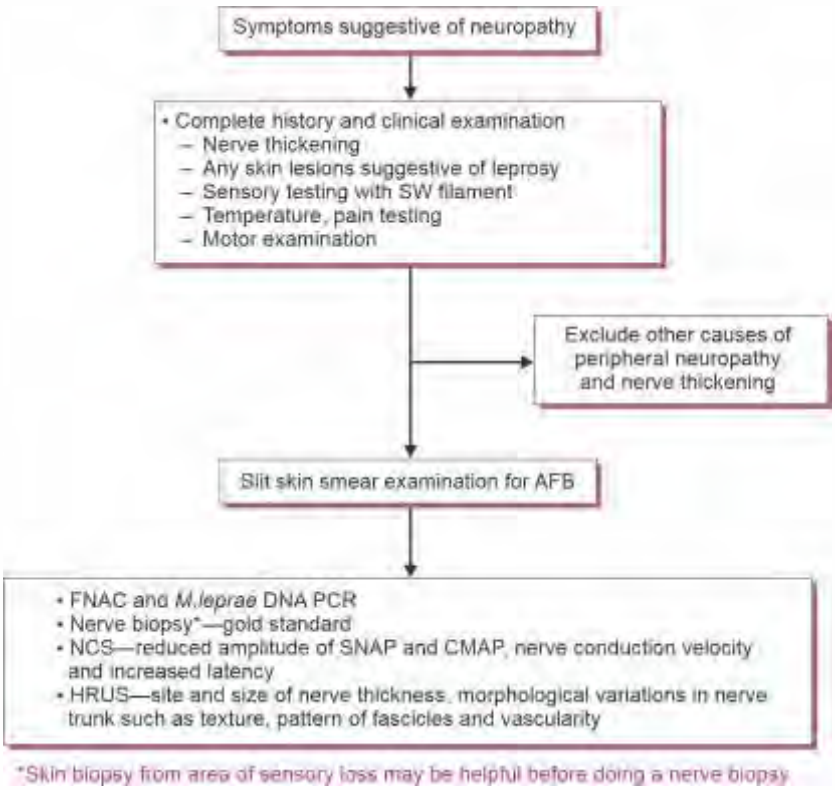


Fig. 2.51: An algorithm depicting diagnostic approach for pure neuritic leprosy
NCS: Nerve conduction study, HRUS: High-resolution ultrasound

Ziehl-Neelsen Method of Staining M. leprae in Smears

The term 'acid-fast' refers to the capacity of the bacillus, when stained with a red dye (carbol fuchsin), to retain its red color when treated with acid. Tubercle and leprosy bacilli are alcohol-fast as well as acid-fast, and a mixture of acid and alcohol is used in the standard method of staining—the Ziehl-Neelsen method. However *M. leprae* is less acid- and alcohol-fast than *M. tuberculosis* is and this fact is of practical importance when it comes to applying the Ziehl-Neelsen method of staining, for if it is used in leprosy in the same manner as in tuberculosis, it is likely that bacilli will not be found for the simple reason that the leprosy bacilli will have been decolorized and therefore will not be identifiable under the microscope. This problem is overcome by having a weaker acid-alcohol mixture and by leaving it in contact with the slide for a shorter time. In a properly stained skin smear, the leprosy bacilli appear bright red and everything else takes the color of the counterstain used. If stained smears are treated with pyridine, the bacilli lose their red color; this is known as pyridine extractability,[2] and distinguishes *M. leprae* from all other pathogenic mycobacteria (*M. vaccae* and *M. phlei* have been shown to lose their acid-fastness when extracted with pyridine,[3] but these are nonpathogenic mycobacteria). There are many minor modifications of this method, each as good as another in the hands of an experienced technician, and the method described here is a reliable guide (Fig. 3.1a to d):

Fig. 3.1a to d: Procedure of slit skin smear making and Ziehl-Neelson staining. (a) Materials required beforehand to perform the procedure; (b) Hold the skin firmly between the thumb and index finger to drive out the blood; (c) Heat the carbol fuchsin (while avoiding boiling the solution) until a greenish yellow sheen is achieved; (d) The stained smear after rinsing off the carbol fuchsin with water (*Courtesy*: Dr Aastha Aggarwal, Dr Diksha Agrawal)

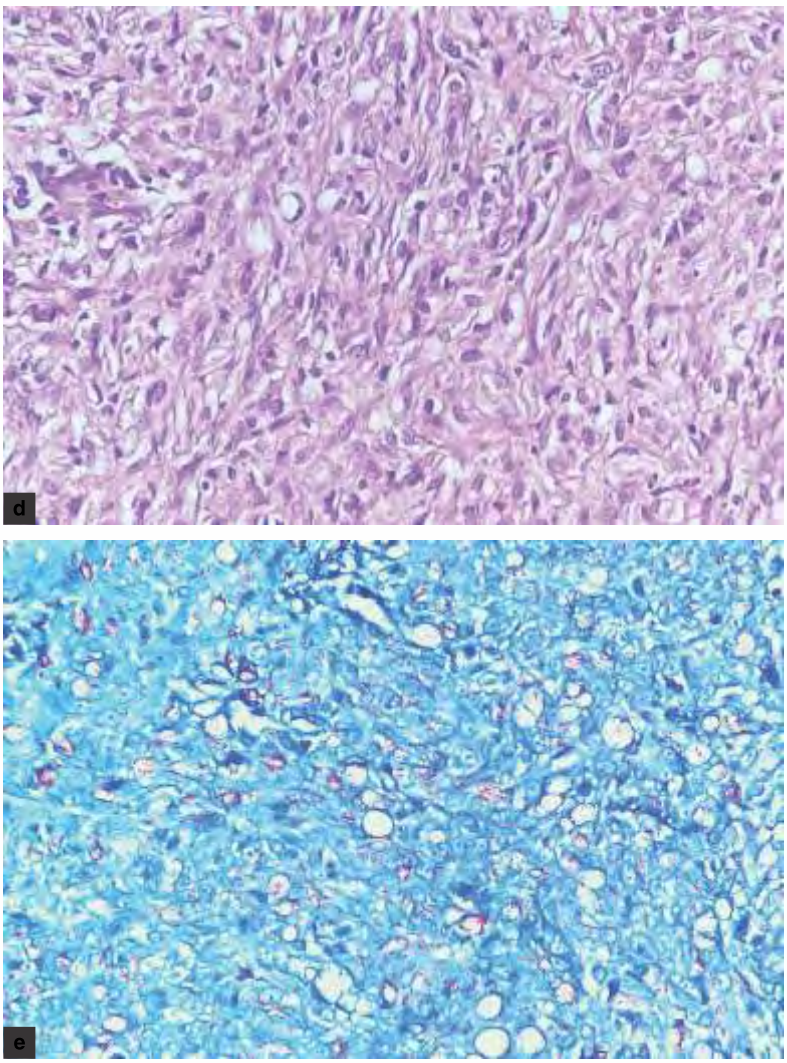


Fig. 3.10: (d) Higher magnification showing oval to spindle cells arranged in fascicles, a few cells showing foamy cytoplasm (H & E, ×400); (e) Fite stain showing many solid staining acid-fast bacilli arranged in clumps (Fite, ×1000) (*Courtesy*: Dr Purnima Paliwal)

REACTIONS IN LEPROSY

A. Type 1 Reaction (T1R)

Lockwood et al have considered histological diagnosis of T1R in the setting of two of the following features—granulomas with extra and intracellular edema, dilated vascular channels, separation of dermal collagen, evidence of an intense delayed-type hypersensitivity response with acute damage to dermal nerves and granuloma (Fig. 3.11).[10] But it is pertinent to point out that there are discrepancies between clinical and histopathology features in patients manifesting leprosy reactions.[10–12] Dermal edema, considered as an important feature of reaction may be missed if there is a delay between the onset of reaction and time of biopsy.[12,13]

Table 4.1: Microbiology of *Mycobacterium leprae*

Ultrastructure
Rod-shaped bacilli, 1–8 μm long, 0.3 μm diameter.

Cell Wall and Capsule[14]
- *Cell wall core*: Complex of long-chain fatty acids (mycolic acids) linked to arabinogalactan, which is further attached to peptidoglycan.
- *Lipoglycans and glycolipids*: LAM, PDIM, PIM, cord factor/dimycolyl-trehalose and sulfolipids; noncovalently attached to the plasma membrane through their GPI anchors; extend to exterior of cell wall.
- *Phenolic glycolipid 1* (*PGL-1*): A unique glycolipid found only in *M. leprae*; important immunological functions.
- *Cell wall proteins*: Structural and nutrient uptake function.

Cell Membrane
- *Lipids*: Mainly phospholipids
- *Proteins*: MMP-I and MMP-II

Generation (Doubling) Time[15]
- Slow; 12–13 days in footpads of mice during the logarithmic phase
- For the entire period from inoculation to the early plateau phase, the average is 20–40 days
- Logarithmic phase is preceded by a lag phase of 60–90 days

Cultivation in Animal Models
- Uncultivable in microbiological culture media or in cell culture systems
- Nine banded armadillo (*Dasypus novemcinctus*): Ideal core body temperature of 32°–35°C; disseminated infection in susceptible animals
- Mouse foot pad (MFP) inoculation:[16] Most favorable inoculums size: 5000 bacilli; Minimal infectious dose: 50–500 bacilli (Shepherd, 1971)[17]/5 bacilli (Welch, 1980);[18] growth peaks at approximately 10^6 bacilli within 5–6 months and then enters a plateau phase. In immunodeficient strains such as thymectomized and irradiated mice, congenitally athymic nude mice and SCID mice, prolific *M. leprae multiplication continues*, reaching up to 10^{10} bacilli in each foot pad.[19–21]

Viability Assays
- Molecular: Reverse transcriptase (RT)—PCR of 16S rRNA[22]
- MFP inoculation
- Morphological index
- Fluorescent vital dyes: Fluorescein diacetate (FDA) and Ethidium Bromide (EB), rhodamine 123 (R-123)/EB, SYTO9 and propidium iodide
- Metabolic profiling: ^{3}H-purine/pyrimidine uptake, mass spectrometry to measure Na^+/K^+ ratio, ATP content, PGL-1 synthesis
- Radio respirometry: ^{14}C-labeled palmitic acid oxidation

LAM: Lipoarabinomannan, PDIM: Phthiocerol dimycocerosate, PIM: Phosphatidyl-myoinositol; MMP: Major membrane protein.

GENETIC SUSCEPTIBILITY TO LEPROSY

Twin studies, familial clustering and segregation analyses studies have suggested that host genetics play an important role in susceptibility to leprosy.[23–25] Further, following infection, the development of different clinical forms also is based on the genetic makeup of an individual which regulates the type of immune response.[26]

Genetic polymorphisms in components of the innate and adaptive immune response have been shown to be important susceptibility/protection factors in different populations. Important among these are summarized in Table 4.2. TLR and complement

Table 4.2: Summary of literature on association of leprosy with genes related to innate immune response and cytokines[26,29,30–58]

S. No.	*Gene*	*Protective polymorphisms (population studied)*	*Polymorphisms associated with susceptibility to leprosy (population studied)*
1.	*TLR1*	• I602S/rs5743618, 602S/SS/rs5743618 (Indian) • I602S/SS/rs5743618 (Turkish) • N248S/SS/rs4833095 (Bangladesh; ENL)	• N248S/SS/rs4833095 (Bangladesh) • N248S/SS/rs4833095 (Brazilian) • N199N/rs3804099 (Ethiopian, T1R)
2.	*TLR2*	–	**Susceptibility to T1R:** N199N/rs3804099 (Ethiopian)
3.	*TLR4*	A299G/rs4986790-T390I/rs4986791 Ethiopian	–
4.	*NOD2*	• Protection from disease *per se*: rs8057341, rs2111234, rs3135499, rs8057341-genotype AA, rs8057341-al-lele A (Brazilian) • **Protection from T1R:** rs2287195, rs8043770, rs7194886, rs1861759 (Nepalese)	• Susceptibility to leprosy *per se*: rs12448797, rs2287195, rs8044354, rs8043770, rs13339578, rs4785225, rs751271, rs1477176, rs1131716 (Nepalese) • rs9302752, rs7194886 (Chinese) • **Susceptibility to ENL:** rs8044354, rs17312836, rs1861759, rs1861758 (Nepalese) • Susceptibility to reactions: rs751271 at NOD2, rs2069845 (Brazilian)
5.	*PARK2*		• rs9347684, rs9346929, rs4709648, rs12215676, rs10806765, rs6936373, rs1333957, rs9365492, rs9355403 (Indian) • PARK2_e01 (-2599) allele T, rs1040079 (allele C) (Brazilian) • PARK2_e01 (-2599) allele T, rs1040079 (allele C) (Vietnamese)
6.	*PARK2/PAR-CRG*		• rs6915128, rs10945859, rs9347683, rs10806768 (Indian) • rs6915128, rs10806768, rs1333955, • rs1333955 (Vietnamese) • rs1333955 (Brazilian)
7.	*VDR*	*TaqI*"Tt"rs731236 (Indian)	• *TaqI*"tt"rs731236(Brazilian) • *TaqI*"TT"rs731236 (Mexican) • *TaqI*"tt"rs731236, *TaqI*"TT"rs731236, • Fok-I/rs2228570 (Nepalese; susceptibility to T1R) • *TaqI*"Tt"rs731236 (Indian) • Fok1"ff" and Taq1"tt" (Indian)
8.		–	• Genotype 22 and 23 (Brazilian) • INT4/469 + 14 (Indonesian; PB) • 3-UTR/1729 + 55del4 (Malian; MB) • 274 C/T (Brazilian; TT)

(*Contd.*)

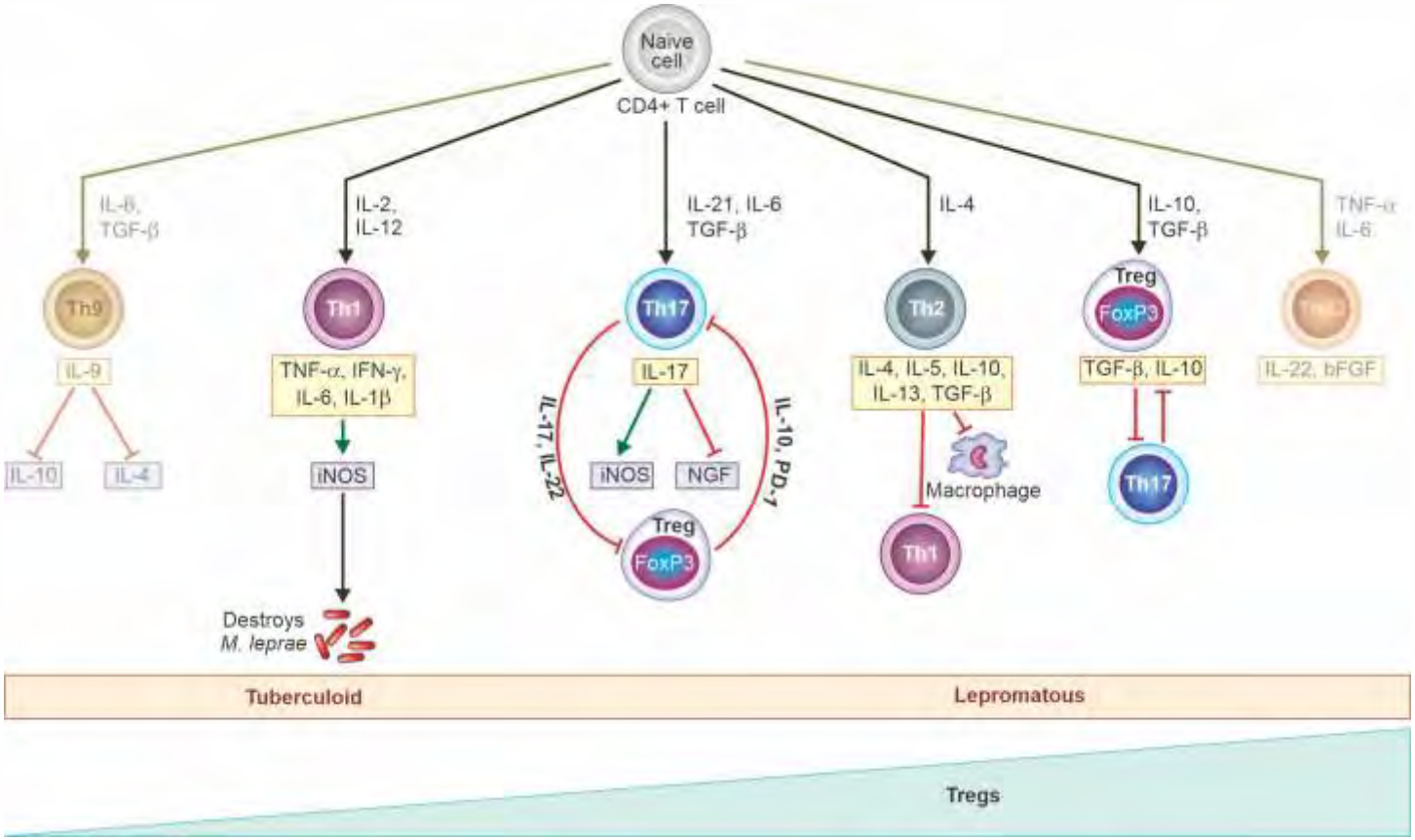


Fig. 4.3: The T helper profiles across the spectrum of leprosy. Note the reciprocal relationship between Th17 and FoxP3+ Treg cells. The role of Th9 and Th22 is not well delineated in leprosy (Treg: T regulatory; NGF: Nerve growth factor; iNOS: inducible nitric oxide synthase; bFGF: basic fibroblast growth factor)

4.4 *M. LEPRAE* AND NERVE INJURY

Kabir Sardana, David Scollard

M. leprae is the only bacterium that infects nerves and Schwann cells (SC) and produces a range of clinical manifestations—from a silent neuropathy to rapidly damaging acute neuritis. Multiple factors can predict nerve damage in both the normal disease process and in reactions and an understanding of this is crucial as leprosy is largely a neural disease. *M. leprae* interacts specifically with the mature glia of the human peripheral nervous system (PNS), i.e. Schwann cells, and *not* the glia of the CNS (oligodendrocytes or astrocytes), and thus the clinical presentation mainly involves the peripheral nerves.[1, 2]

The effect of the bacilli can be broadly divided into a *direct* effect and *an indirect* effect which is largely mediated by the immune response. While the direct mechanism of nerve damage in leprosy is attributed to the ability of *M. leprae* to bind and infect SC and is predominantly found in multibacillary (MB) forms, the indirect mechanism of nerve involvement is commonly observed in paucibacillary (PB) forms, where the immune response of the host plays the predominant role.[3, 4]

The route of entry is believed to be via the respiratory mucosa (*see Chapter 4, Section 4.2*) and from there the bacilli may cross the basement membrane and the underlying connective tissue in order to reach the blood vessels.[5] *M. leprae* can then spread hematogenously and reach skin and peripheral nerve trunks in an asymmetrical fashion.

1. DIRECT DAMAGE

Scollard et al[6] described the invasion of nerves by *M. leprae* occurs via the colonization of the endothelial cells of the blood and lymphatic vessels in the epineurium. This vascular and lymphatic colonization increases the risk of nerve ischemia and facilitates the invasion of *M. leprae* into macrophages residing in the epineural layer.[7] This vascular route of invasion enables *M. leprae* to cross the impermeable perineural sheath and reach the endoneurium, thus leading to the invasion and proliferation of mycobacteria within SCs, which form the primary target of *M. leprae* in peripheral nerves (Fig. 4.4). SCs provide a safe niche for survival of the bacillus, protected from the host immunity due to blood nerve barrier. Differentiated SCs have a high bacterial retention capacity promoting replication and colonization. The bacillus thus initially inhabits the SC without causing much damage, thus facilitating its own survival. It later takes advantage of the plasticity of SCs (ability to dedifferentiate into an immature phenotype) for furthering bacterial colonization and spread.[8]

The direct action of *M. leprae* on the SCs can cause nerve damage. The nonmyelinated Schwann cells (SCs) are highly susceptible to *M. leprae* colonization, whereas myelinated SCs are naturally resistant to the mycobacterial invasion (Fig. 4.5).[8] The clinical translation of this explains the earlier loss of thermal sensation which is mediated by unmyelinated C type fibers.[10] In the endoneurium, *M. leprae* can bind to SC basement membrane, specifically to its basal lamina[11] (Fig. 4.5). While the basal lamina is composed of various elements, the most important is the laminin 2 isoform, which is formed by assembly of three subunits of laminin chains—the β_1, γ_1, and α_2 chains. Of these components, a specific subcomponent-G domain of the laminin α_2 chain **(α_2LG)** determines the neural affinity of *M. leprae* (Fig. 4.6).[12] Surface molecules of *M. leprae*,

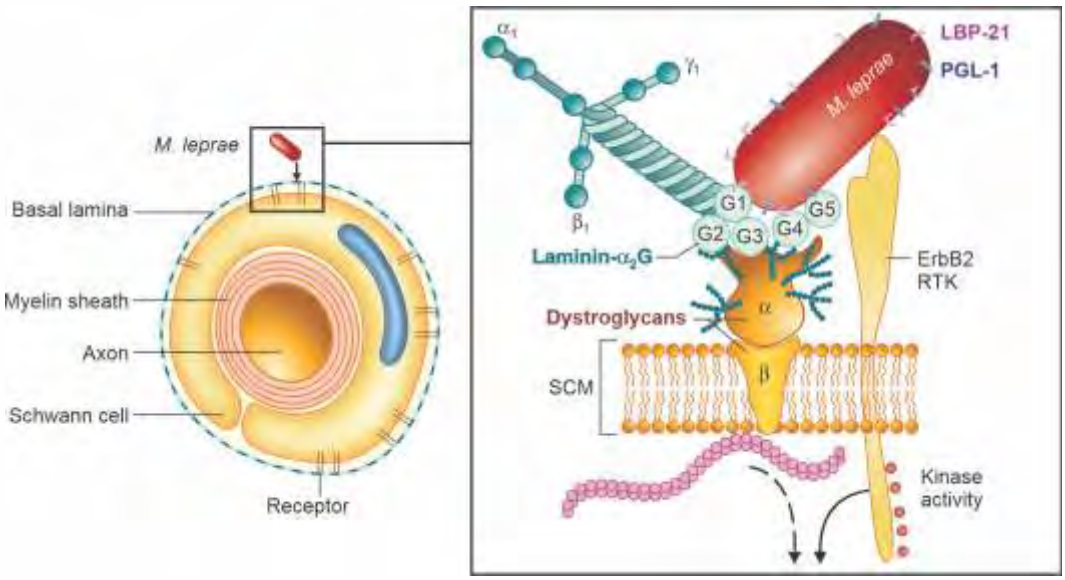


Fig. 4.6: Schwann cell receptors α/β-dystroglycan and receptor tyrosine kinase ErbB2 serve as receptors for *M. leprae* on the Schwann cell membrane (SCM) in an α_2LG domain dependent and independent manner (LBP-21: Laminin-binding protein 21; ErbB2 RTK: ErbB2 receptor tyrosine kinase; PGL-1: Phenolic glycolipid 1)

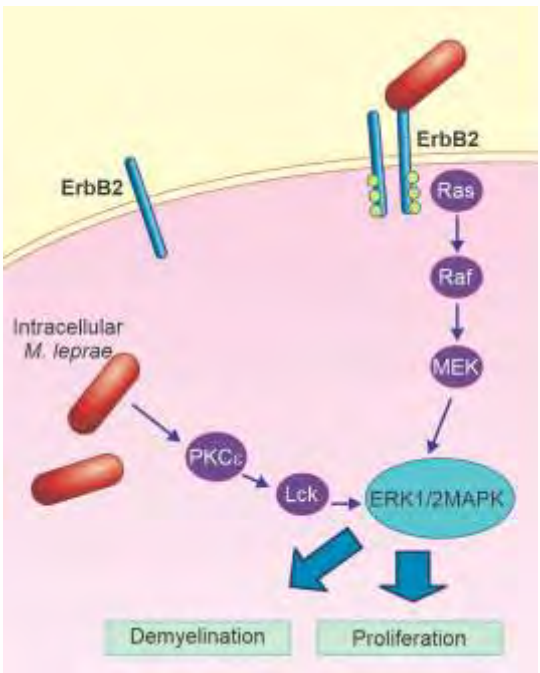


Fig. 4.7: Schematic showing the activation of ERK1/2 MAPK signaling pathways by *M. leprae*. The bacilli bind to ErbB2 receptor which via the Ras-Raf-MEK-ERK pathway induces Schwann cell demyelination and proliferation. Intracellular *M. leprae* induces proliferation of nonmyelinated Schwann cells through a different route to ERK that involves PKCε and Lck (ERK: Extracellular signal-regulated kinase)

4.5 IMMUNOPATHOGENESIS OF REACTIONS

Ananta Khurana, Kabir Sardana

The reactional episodes mark periods of acute intense tissue damage in an otherwise chronic course of the disease. A brief summary of the immunopathogenesis of reactions covering the salient aspects are given below and depicted in Figs 4.8 and 4.9.

TRIGGERS

Factors which trigger the development of reactions are still not completely known. Most reactional episodes occur while the patients are on multi-drug therapy (MDT), although *de novo* presentation with reactions is also common.[1] It is hypothesized that the antigen that becomes available to the immune system by killing of the bacteria during antibiotic treatment gives rise to overactivation of the immune system, which attempts to clear these bacterial antigens, leading to an inflammatory state, especially in those with high bacillary load at initiation of MDT.

Type 2 reaction (T2R) mostly develops in patients with lepromtous leprosy (LL) and a BI of ≥4.[2] Pregnancy, lactation, puberty, intercurrent infection, vaccination, surgery and psychological stress are the proposed risk factors for T2R, but these have not been confirmed in prospective studies. Coinfections are more frequently associated

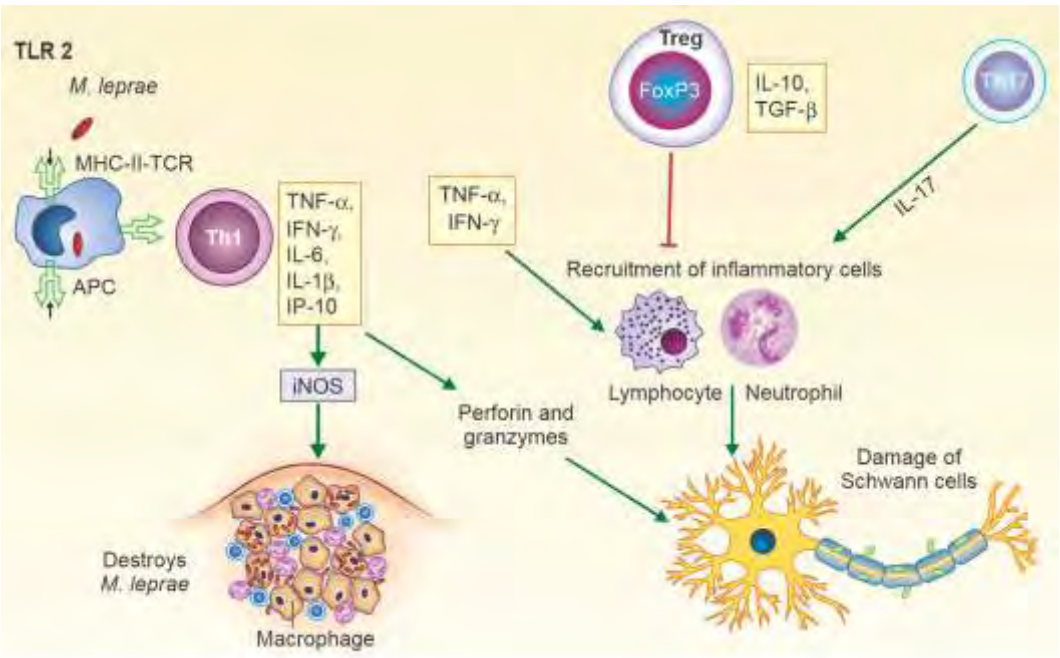
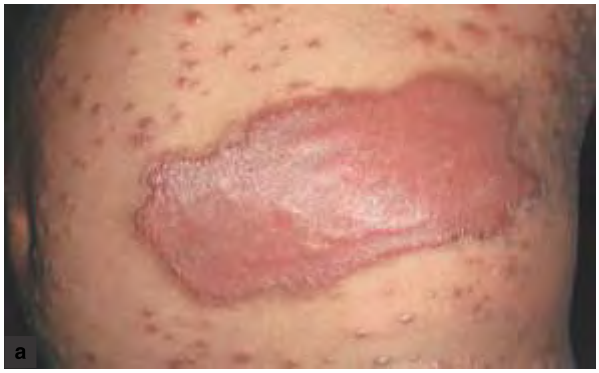


Fig. 4.8: Type 1 reaction occurs in a setting of a prominent Th1–Th17 immunity at baseline, with a shift towards Th1-Treg predominance during the reactional state. The role of Tregs here is to control the excessive immune damage mediated by the proinflammatory cytokines released into the tissues. There is a resultant destruction of bacilli, tissue inflammation and nerve damage (*see* text and Box 4.2 for details)



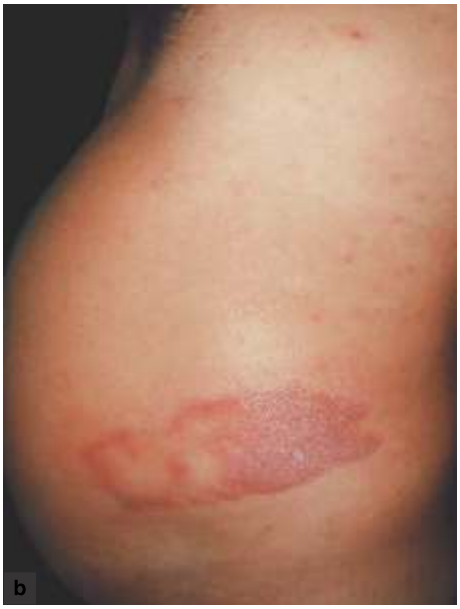
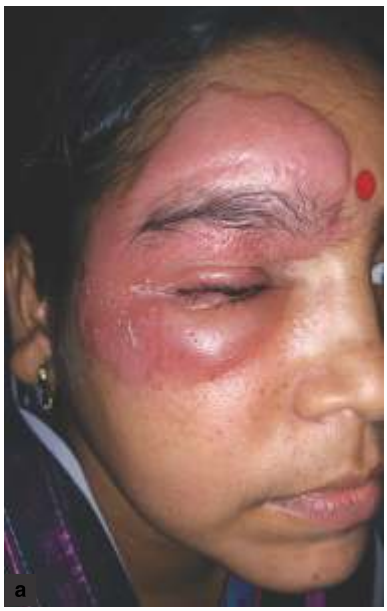


Fig. 5.5: (a) The patient has a visible annular edematous plaque with multiple barely visible papules which showed a BI of 5 with globi. A diagnosis of BB downgrading to LLs was made. The downgrading reaction was apparent at a later date, (b) when the papules were histologically confirmed as LLs establishing the downgrading reaction (*Courtesy*: Dr Jaison A Barreto, Sao Paulo, Brazil)

Severe reactions may be accompanied by systemic illness, characterized by low grade fever, malaise and anorexia. Another associated manifestation is edema of hands, feet, or face (Fig. 5.6); sometimes all three sites are involved, or, rarely, one foot or one hand. Tenderness of palms and soles is often present, and may sometimes herald an upgrading reaction.

Neuritis is the most important part of a T1R and may be seen concomitantly with skin involvement or even independently; possibly reflecting hypersensitivity to different antigens of *M. leprae* as mentioned before.[41,42] This takes the form of rapid



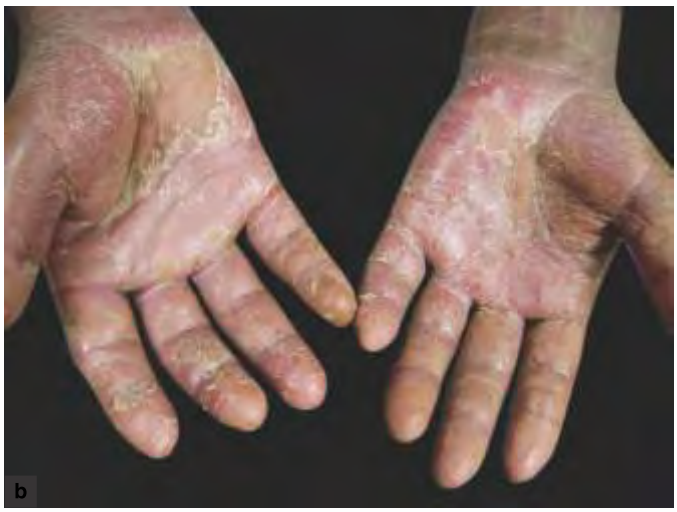


Fig. 5.6: (a) A type 1 reaction with intense signs involving the facial plaque—a candidate fit for oral steroids; (b) BT Hansen plaque on the palms with type 1 reaction

ACUTE EXACERBATIONS

Acute exacerbation of the disease is seen mainly in very advanced lepromatous patients with nodular and plaque-like lesions. Clinically the lesions undergo ulceration, that mimic a reaction but are exemplified by a lack of associated systemic features which are seen in ENL[8] (Fig. 5.13a and b). Histologically, there are small localized areas of necrosis in the middle of a large sheet of macrophages eliciting a localized infiltration of neutrophils. Vasculitis is rarely seen. The macrophages contain a relatively large load of AFB with many solid staining organisms which helps to differentiate acute exacerbation from ENL. It seems that there is a sudden localized burst of bacterial multiplication which outgrows the macrophage population resulting in localized necrosis and acute inflammation. Continuing the MDT seems the most useful measure.

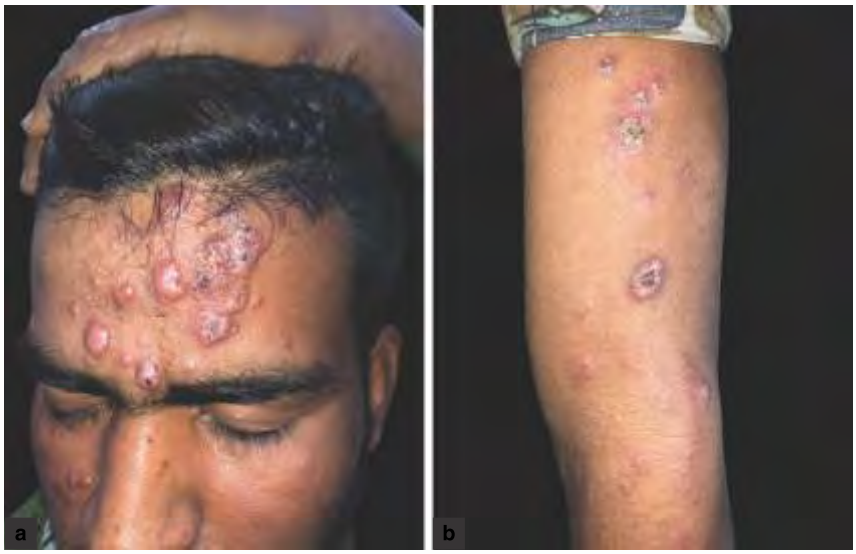


Fig. 5.13a and b: Acute exacerbation in an advanced untreated case of lepromatous leprosy with ulcerating nodules and plaques over face and arm. The slit smear showed a BI of 6+ with globi

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CHAPTER

6

Drug Resistance in Leprosy

6.1 DRUG RESISTANCE

Mallika Lavania, Utpal Sengupta

INTRODUCTION

Drug resistance is clinically assessed when there is a decrease in the effectiveness of a medication and usually means that the pathogens have "acquired" a mechanism leading to reduced response to a drug.[1–4] Currently, leprosy control is mainly based on World Health Organization (WHO) recommended multi-drug therapy (MDT).[5,6] It has been noted earlier that any therapeutic control measure of disease with antibiotics may lead to emergence of drug resistance.[1–7] Therefore, a surveillance mechanism should be in place for detecting the appearance of drug resistance in the community. Inability to deal with emerging resistance with appropriately tailored drug regimens will defeat the whole purpose of chemotherapy.

Global Epidemiology of Drug Resistance

In 2008 WHO started a surveillance network with six countries where leprosy is endemic (Brazil, China, Colombia, India, Myanmar and Vietnam), and subsequently a total of 19 countries participated in this sentinel surveillance.[5] In a recent WHO report, overall, 8% strains were found to have resistance conferring mutations. The average rate of rifampicin resistance among all leprosy cases was 3.8%, while in relapsed cases the resistance rate was 5.1% (secondary resistance) and in new cases the rate was 2.0% (primary resistance). Similarly, dapsone resistance was seen in 5.3% with secondary and primary resistance rates of 6.8% and 4% respectively. Ofloxacin resistance was seen in 1.3% with secondary and primary resistance rates of 1.7% and 1% respectively.[5] Further, the multi-drug resistance levels were low (20 of 154 resistant cases being resistant to both rifampicin and dapsone, to ofloxacin and dapsone but none to all three drugs or against both rifampicin and ofloxacin).[4,5]

Types of Drug Resistance

Drug resistance in leprosy may be primary or secondary. Primary resistance refers to infection with a strain of *M. leprae* which is already resistant to a drug in a treatment-naïve case. Drug-resistant *M. leprae* mutants in this scenario having been acquired from an infection source containing drug-resistant leprosy.[8] These cases typically present as new cases which are not responding to standard MDT regimen.[9] Secondary

Table 6.1: WHO recommendations for resistance testing in leprosy	
New cases Inclusion criteria	Only *smear-positive* MB cases with a bacillary index (BI) **>2+** are to be tested as these have a higher chance of a positive PCR
Retreatment cases	To detect secondary resistance, all retreatment leprosy cases have to be tested with the exception of transferred in cases unless they are considered at risk for AMR due to irregular treatment
Testing for drugs	PCR+ sequencing for *folP1*, *rpoB* and *gyrA* gene mutations
Samples	• 2 slit skin smear samples of the lesion with a BI ≥2+ should be taken, with the ear lobe being the preferred sampling site together with the most prominent skin lesion *OR* • 1 skin biopsy (e.g. 4 mm punch biopsy) should be taken from a prominent lesion with a BI ≥2+

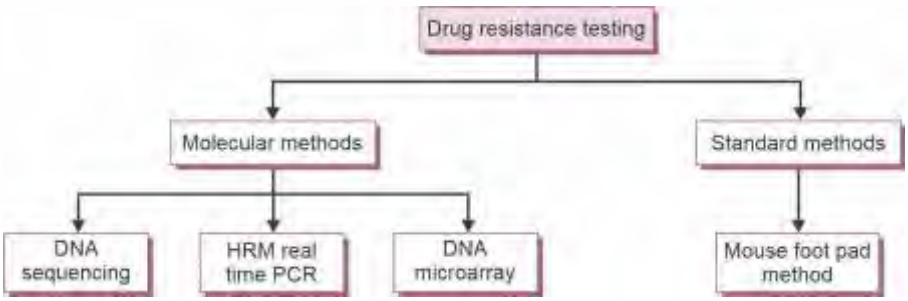

Fig. 6.2: Various techniques used for drug susceptibility testing

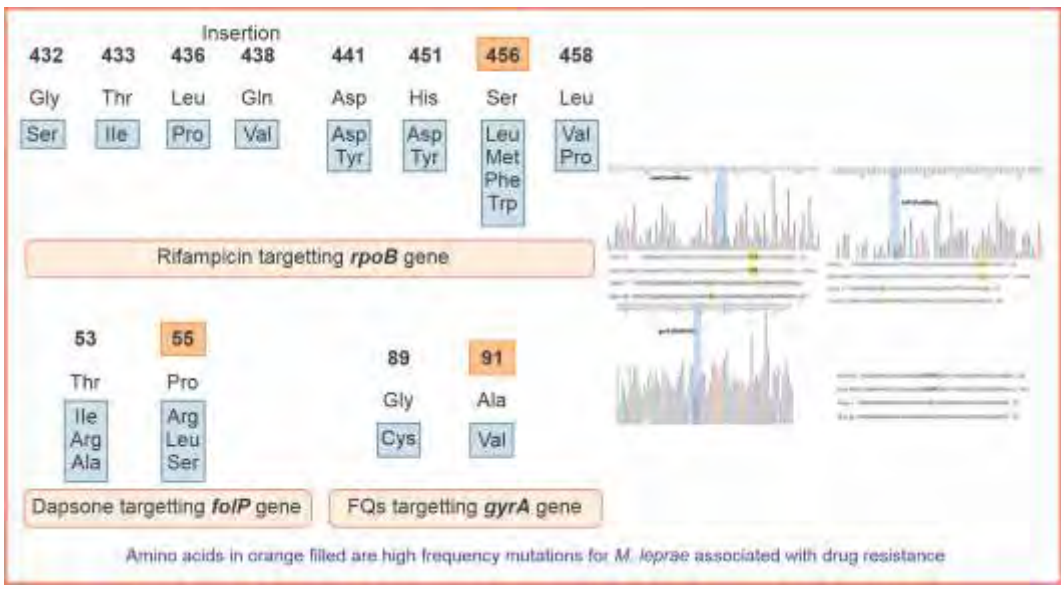

Fig. 6.3: A depiction of multi-drug resistance by qPCR

1. Clofazimine

Drug class	• Antimycobacterial • **MIC:** Unknown, multiplication of *M. leprae* is inhibited by feeding mice 0.0001 g% clofazimine in their diet
Mechanism of action/ pharmacokinetics	• Unknown; Postulated mechanisms (acts on outer membrane): – Interaction with respiratory chain → redox cycling → oxidation of reduced clofazimine → reactive oxygen species (ROS), H_2O_2 → interference with ATP production → cell death. – Interaction with membrane phospholipids → antimicrobial lysophospholipids → interference with K^+ transport → interference with ATP production → cell death. – It is weakly bactericidal against *M. leprae* and antimicrobial activity can be demonstrated in humans only after continuous exposure for about 50 days. • 70% absorbed after oral administration, t½ = 70 days, serum levels 0.5 µg/mL (exact half-life is difficult to determine because the drug seems to be excreted more rapidly from some tissues than others); excretion is via sebum, sweat, feces and urine. • *Resistance*: Only inconclusive isolated reports of resistance so far.
Dosage	• **Leprosy treatment:** 300 mg once a month, to be administered under supervision and 50 mg daily, to be self-administered • **ENL:** 100 mg 3 times a day for one month, subsequent dose reductions are required; may take 4–6 weeks to attain full effect. A recent RCT has found that the drug's role in ENL might be overrated.
Drug interaction	None of significance
Side-effects	• **GIT:** Nausea,abdominal pain, appetite ↓, weight ↓ Side-effects seen only with >100 mg (in 25% of such patients), subacute intestinal obstruction if 100 mg TDS given for >3 months • **Eye:** Dry eye, eye discoloration • **Skin:** Hair color changes (reversible), xerosis (due to anticholinergic action), skin discoloration (including areas exposed to light) due primarily to a drug-induced reversible ceroid lipofuscinosis (localized to lesions; disappears on stopping the drug in 6–12 months), red discoloration of body fluids • **Others:** Headache, lymphadenopathy, splenic infarction, depression or suicide.
Pregnancy	Category C; MDT continued • Clofazimine crosses the placenta, though the kinetics remain to be elucidated. • Hyperpigmentation of the neonate that resolves gradually is reported in humans. • Three neonatal deaths reported. Rodent studies are generally reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically, embryotoxicity and intrauterine growth retardation were noted.

Table 7.7: Major clinical trials on single dose rifampicin (completed and ongoing)

Trial/authors	*Place*	*Participants*	*Intervention*	*Results*	*Remarks*
COLEP trial (Moet et al, 2004)[13]	Bangladesh	21, 711 close contacts of 1037 patients with newly diagnosed leprosy	SDR or placebo given to close contacts (household, first and second neighbor and social contacts) in second months of starting the index case on treatment	• 91/9452 contacts in placebo group and 59/9417 in SDR group developed leprosy • Overall a 57% reduction in incidence of leprosy using SDR in the first 2 years. There was no additional effect after 4 and 6 years.[14] However, total difference in incidence between the 2 arms remained statistically significant showing that no apparent access cases were observed in the SDR arm within 6 years after the intervention • Number needed to treat (NNT) to prevent a case of leprosy among contacts was 297 • Protective effect for BCG (given at infancy) was 56% in the placebo arm and 53% in the rifampicin arm	SDR mainly effective in contacts of paucibacillary leprosy and contacts: 1. Who were not closely related to the index patient; (maximum benefit in neighbor of neighbor and social contact group rather than household contacts) and had lowest risk profile as per intake data 2. Female contacts 3. Who were seronegative for *M. leprae* specific PGL-1 antibodies at intake 4. Without a BCG scar 5. Ages 10–14 and 20–29 The combined effect of SDR with BCG given at infancy showed a protective effect of 80%
MALTALEP (Richardus et al, 2019)[16] (To assess prevention of new leprosy cases among contacts in the first year after BCG vaccination)	Bangladesh	14, 988 contacts (household and next door neighbors) of 1552 new leprosy patients randomized into the SDR – arm (n = 7379) and the SDR + arm (n = 7609)	SDR+ arm: BCG vaccination followed by SDR 8–12 weeks later. SDR– arm: BCG vaccination alone given	• SDR+ arm: 19 new leprosy cases in first year and 29 in second year • SDR– arm: 27 new in first year and 24 in second year • Reduction in incidence of leprosy in SDR+ compared to SDR– was 42% (nonsignificant; p = 0.148) in the first year	• To what extent SDR suppresses excess leprosy cases after BCG vaccination is difficult to establish because many cases appeared before the SDR intervention. • Thus, BCG vaccination followed by SDR cannot be recommended as a routine intervention in leprosy control

(*Contd.*)

8.2 OCULAR COMPLICATIONS AND MANAGEMENT

Kabir Sardana, Ananta Khurana, Margreet Hogeweg

While there are myriad ocular complication described[1–4] (*Section 2.1*) here we intend to focus on the common treatable ocular disorders. In the present era the most important cause of blindness in leprosy patients is not due to leprosy but due to age-related cataract.[3,4] Reasons why these patients have not been operated vary, but important reasons are the stigma towards leprosy, poverty and lack of guardian or transport. Thus, more than "cosmetic surgeries" early diagnosis and treatment of cataract must be encouraged.[3,4]

1. Reactions

- Acute iritis
- Acute episcleritis
- Acute scleritis

We will discuss primarily acute iritis while the other complications are uncommon and are listed in Box 8.4.

Acute Iritis[5,6]

Leprosy-related acute iritis occurs only in multibacillary (MB) patients and is considered to be a surrogate marker of ENL reaction. Acute iritis may recur at any time, unrelated to disease activity or systemic ENL reaction.

In the differential diagnosis of acute red eye in a leprosy patient, all other common conditions causing an acute red eye should be considered. These include acute conjunctivitis (where a topical antibiotic may be used), corneal foreign body and injury, corneal ulcer and acute glaucoma. In addition, the use of high doses of clofazimine for ENL reaction may also cause red eyes (Figs 8.3 and 8.4).

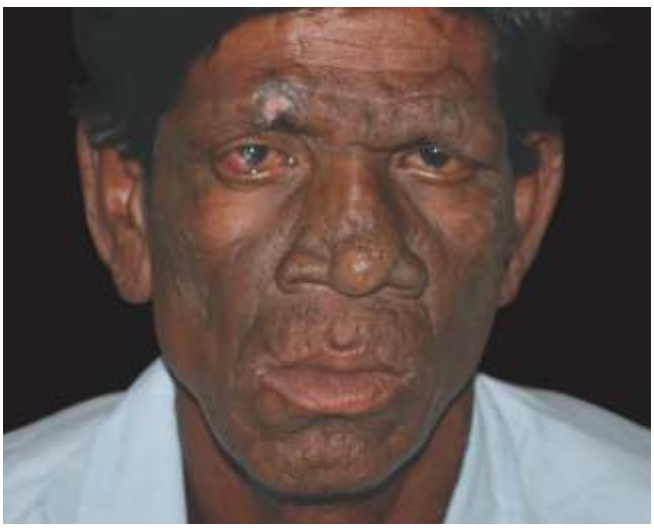

Fig. 8.3: LL Hansen with diffuse infiltration, nodules, madarosis, deformed nose and red eyes (due to clofazimine) (*Courtesy*: Dr Karthikeyan Govindasamy)

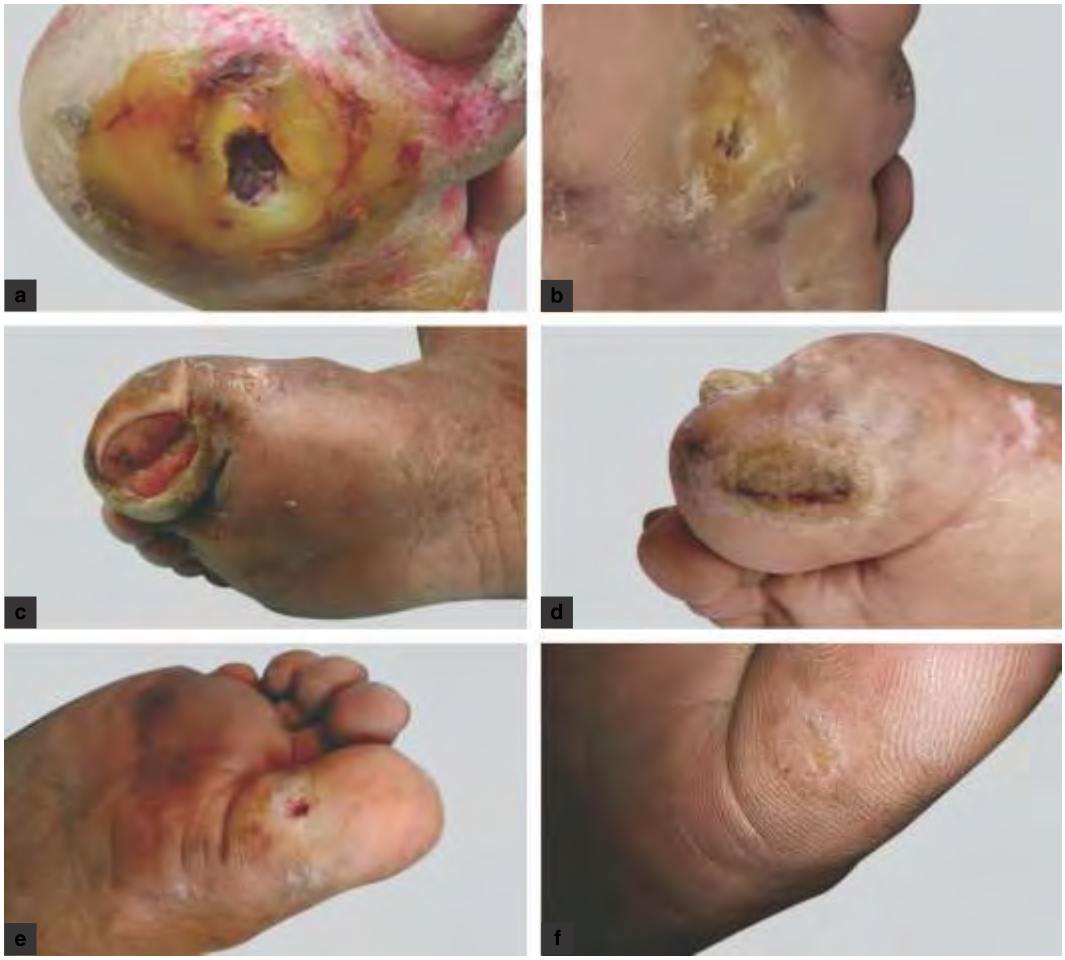

Fig. 8.24: (a) Trophic ulcer on plantar surface at baseline; (b) Trophic ulcer on plantar surface after 4th sitting of PRF; (c) Trophic ulcer on big toe at baseline; (d) Trophic ulcer on big toe after 6th sitting of PRF; (e) Trophic ulcer on big toe at baseline; (f) Trophic ulcer on big toe after 3rd sitting of PRF (*Courtesy*: Dr Konchok Dorjay)

4. *Recurrent Plantar Ulceration*

While the most common cause for recurrence is lack of use of proper footwear and excessive walking, other implicated causes include: (a) Poor quality of scar and (b) excessive pressures because of a deformity. In some cases, breakdown of the scar and recurrence of ulceration occurs because of circulatory insufficiency and such cases need corrective surgery.

The interventions needed include scar revision and deformity correction. Some cases may need posterior tibial neurovascular decompression which relieves the pressure on the artery, improves the blood flow and brings about the healing of the ulcer. It is important to impress on the patient that corrective surgery for recurrent plantar ulceration is not a substitute for protected use of the foot and that, in fact, the practice of foot care is even more essential after such surgery.

The newer thermoplastic material[5] like Orfit® is commonly used by occupational therapists to make a custom-made static gutter splint quickly. The material is dipped in hot water, made pliable and cool so as to not produce scalds when applied and is fitted into the desired position and allowed to cool. Once hardened, it is retained in position with Velcro straps (Fig. 8.62). The material that is dipped in warm water to make the desired type of splint (but hard one, nonelastic and nonflexible). The self-adhesive Velcro is used to keep it in position.

c. ***Adductor band:*** It is a simple circular splint made of rexin, felt lining and Velcro at the sides (Fig. 8.63a) and can be wrapped around proximal phalanges keeping all fingers in adduction (Fig. 8.63b). It helps correct early abduction deformity with steroid therapy or after nerve decompression surgery.

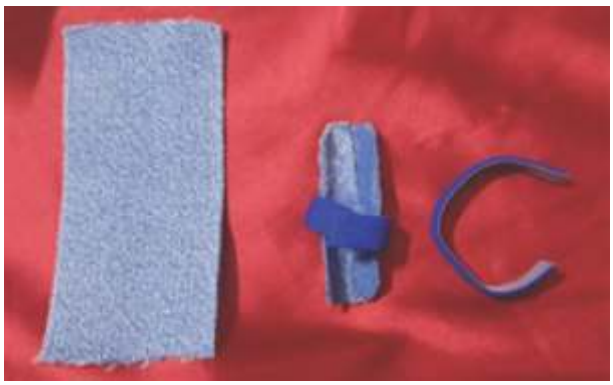

Fig. 8.62: Making splint on the spot with Orfit® material (*Courtesy:* Mr Mukesh Doshi, OT, Nanavati Hospital)

Fig. 8.63a: Adductor band splint to wrap around the base of all four fingers

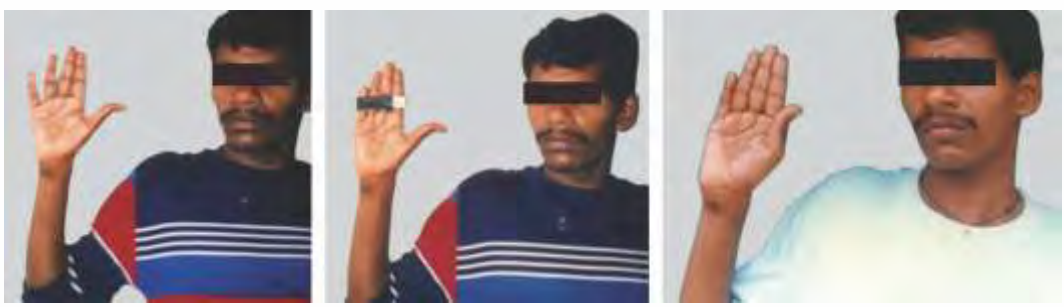

Fig. 8.63b: Early deformity supported with adductor band; with continued therapy helping in recovery

- Advise to be cautious in handling hot or sharp objects. This can be done by insulating the objects or tools with the help of cloth or soft materials or by use of gloves (Fig. 8.71c and d).
- Rest the wounds to prevent progression. This is especially important for plantar blisters/ulcers. This can be achieved by walking with the help of crutch or canes.
- Advise to perform regular exercise to prevent damage to the joints (contractures).
- Avoid sitting cross legged
- Use of footwear with soft insoles such as microcellular rubber (MCR) and rigid outer soles needs to be worn daily (Fig. 8.71e).
- The footwear needs to be inspected daily for excessive wear and tear or for the presence of any embedded sharp objects.

Fig. 8.71: (a) Foot care: Soaking feet in water; (b) Scraping the callosities; (c) Hand care: Protecting anesthetic hands from possible minor injuries by padding of rough surfaces; (d) Hand care: Using tongs to prevent accidental burns while cooking; (e) Foot care using shoes with soft microcellular rubber (MCR) insoles and tough outer soles

Table 10.3: Surface markings for palpation of nerve trunks

Nerve trunks palpated in leprosy	*Cutaneous nerves seen/palpated in leprosy*
Ulnar (ulnar groove on medial epicondyle of humerus) With elbow in flexion, the medial epicondyle is identified; the ulnar nerve is palpated *behind* and *above* it	Supra orbital (junction of medial one-third and lateral two-thirds of supraorbital ridge)
Radial (radial groove below insertion of deltoid muscle) Hold forearm with right hand in pronation and elbow in flexion. Roll the nerve in the groove in the humerus posterior to the deltoid muscle insertion	Supratrochlear (medial to supraorbital nerve)
Median (middle of wrist under flexor retinaculum) Hold the wrist in slight extension with the left hand. Roll across the center of the wrist. The enlarged nerve is palpable proximal to the wrist under the palmaris longus tendon	Infraorbital nerve (medial part of inferior orbital margin)
Posterior tibial (between medial malleolus and tendo-Achillis)	Zygomatic branch of facial (VII) nerve (zygomatic arch)
Common peroneal/lateral popliteal (below lateral aspect of knee along neck of fibula) Ask patient to flex knee and feel above and behind the head of the fibula. The first bony prominence is the head of fibula. The nerve can be traced behind the knee and can be felt even when not enlarged	Greater auricular (junction of upper one-third and lower two-thirds of sternocleidomastoid muscle)
	Supraclavicular (medial one-third and lateral two-thirds of clavicle) Radial cutaneous (anatomical snuffbox)

A diagrammatic depiction of the innervation of the palm and sole is shown in Fig. 10.2.

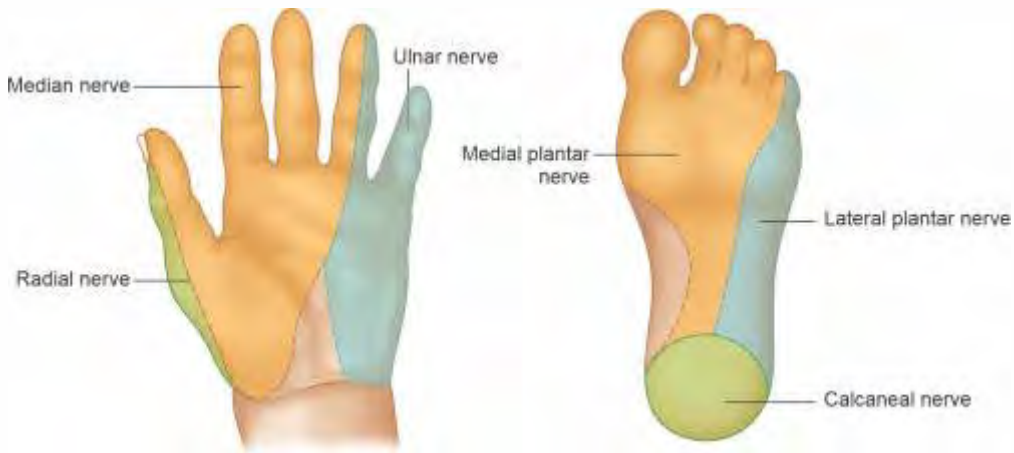

Fig. 10.2: Sensory innervation of palm and sole

Table 10.6: Tests for nerves supplying various hand muscles *(contd.)*

Nerve	*Muscle*	*Test*	*Interpretation*	*Disability*
	Interossei and medial two lumbricals	Ask patient to flex MCP joints of fingers against resistance	Inability to do so	Ulnar claw hand (hyperextension of MCP and flexion of IP joints)
	Palmar interossei	**Card test:** Patient to place hand with palm up on table with fingers extended and adducted → firm paper card inserted into web space and patient to try and grasp it against resistance	Inability to hold the card (Fig. 10. 13)	Guttering of interosseous spaces **Wartenberg's sign:** Little finger subtly abducted—earliest sign of ulnar nerve involvement.
Median	Abductor pollicis brevis	**Pen test:** Patient to rest hand on table and asked to touch a pen held above the palm (Fig. 10.14)	Inability to do so	**Ape thumb deformity:** Thumb lies flat in plane of hand
	Abductor pollicis brevis	• Ask patient to keep hands with thumbs pointing towards each other (Fig. 10.15) • Ask the patient to hold his arms close to his body with elbows bent and palms facing each other • Ask him to move the thumbs away from the palm towards each other	Inability to hold them in that position for at least 30 seconds	–
	Opponens pollicis	Stabilize hand with own hand. Patient asked to touch fingertips with thumb against resistance	Inability to do so	–
	Flexor digitorum superficialis and flexor digitorum profundus (lateral half)*	**Oschsner's clasping test** • Clasp both hands	Index finger remains straight and does not flex	**Pointing index/ Benediction sign**
Radial	Extensors of wrist joint	**Wrist up test:** Close fist and dorsiflex wrist joint against resistance	Inability to do so	Wrist drop

*Affected in high median nerve palsy; not commonly seen in leprosy.

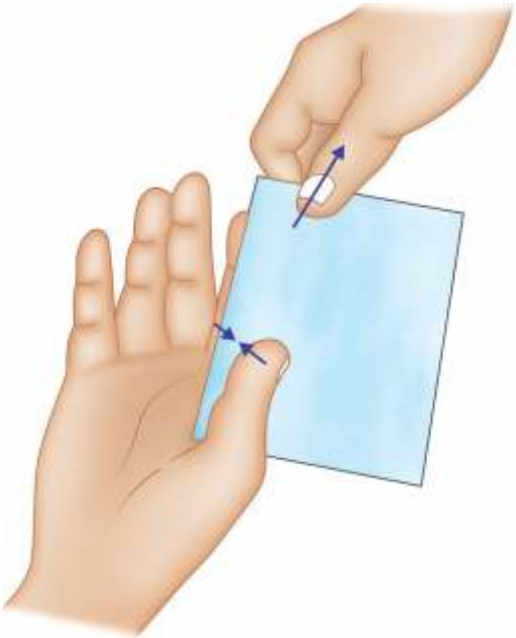

Fig. 10.12: Froment's sign while doing book test for adductor pollicis (ulnar nerve)

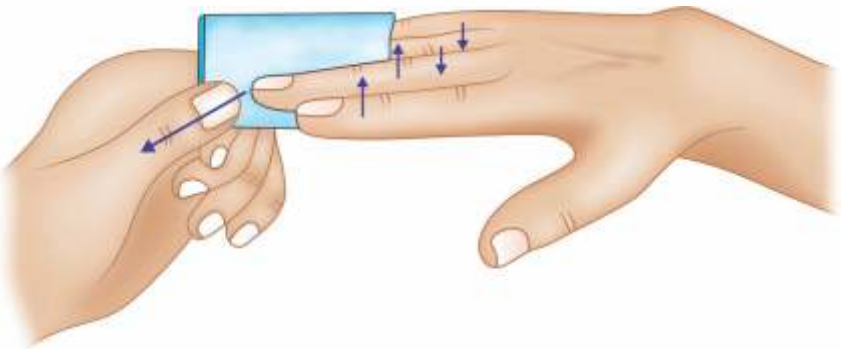

Fig. 10.13: Card test for palmar interossei (ulnar nerve)

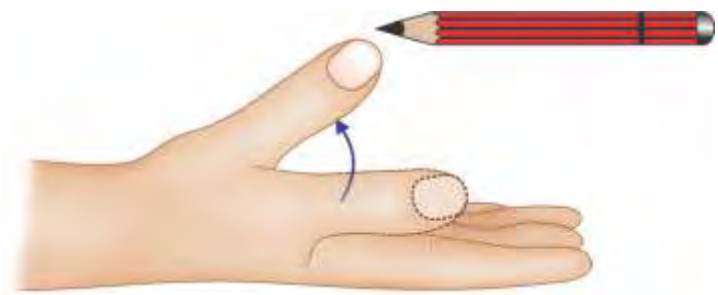

Fig. 10.14: Pen test for abductor pollicis brevis (median nerve)