LEPROSY

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LEPROSY

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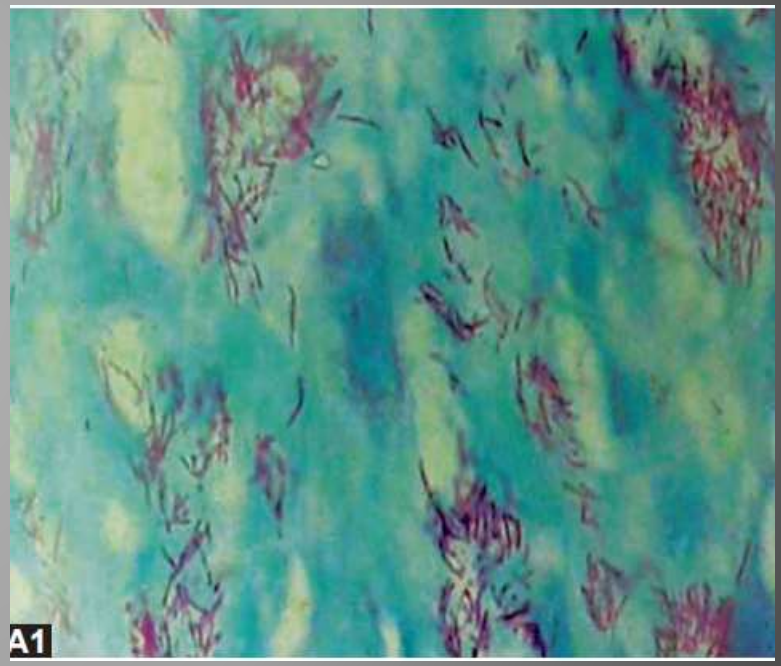
INTRODUCTION:

- Leprosy is a chronic infectious disease caused by Mycobacterium leprae.
- Long incubation period – 5 to 7 years
- Source of infection – Humans (Infected patients, silent carriers)
- Acid fast, gram positive bacillus, Obligate intracellular pathogen



DEFINITION OF A CASE OF LEPROSY

- Three cardinal signs which form the basis for the clinical diagnosis of leprosy:

1. Hypopigmented or reddish skin lesions with definite loss or reduction of sensations.
2. Thickened peripheral nerves with impairment of sensations in the area supplied
3. Acid-fast bacilli in the skin smear

TRANSMISSION OF LEPROSY

- M. leprae discharged during coughing or sneezing may get airborne as droplets and cause infection.
- Hematogenous spread from the initial bacilliferous lesion in the nasal mucosa occurs in those unable to mount a protective immune response.
- Oral cavity lesions, saliva
- Dermal – Transepidermal elimination of M. leprae from infectious nodules
- Predilection of initial lesions on exposed or trauma prone areas – skin as a portal of entry and exit of leprae bacilli.

WHO/NLEP CLASSIFICATION OF LEPROSY

	Characteristic	*PB (Pauci Bacillary)*	*MB (Multi Bacillary)*
1	Skin lesions	1 - 5 lesions	6 and above
2	Peripheral nerve	No nerve / only one nerve involvement	More than one nerve
3	Skin smear	Negative at all sites	Positive at any site

Table 15.1: Characteristics of Ridley-Jopling classification*

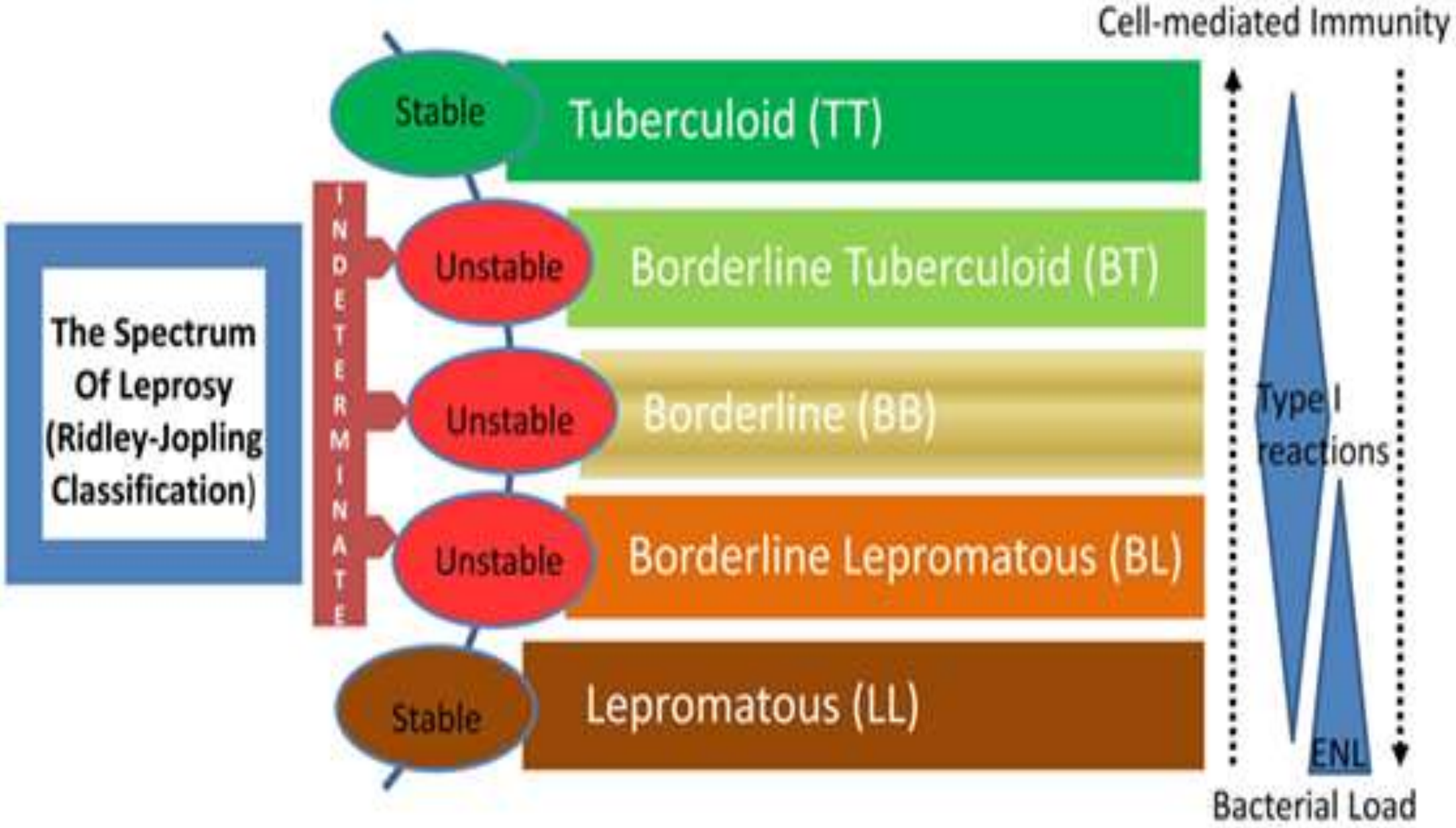
Observation	*TT*	*BT*	*BB*	*BL*	*LL*
Number of lesions	Usually single (up to 3)	Few (up to 10)	Several (10–30)	Many, asymmetrical (>30)	Innumerable, symmetrical
Size of lesions	Variable, usually large	Variable, some are large	Variable	Small, some can be large†	Small
Surface	Very dry, scaly, lesions look turgid	Dry, scaly, lesions look bright and infiltrated	Dull/slightly shiny	Shiny	Shiny
Sensations in lesions	Absent	Markedly diminished	Moderately diminished	Slightly diminished	Minimally diminished, not affected
Hair growth in lesions	Absent	Markedly diminished	Moderately diminished	Slightly diminished	Not affected initially§
AFB in lesions	Nil	Nil or scanty	Moderate in number	Many	Plenty, including globi
Lepromin reactivity	Strongly positive (+++)	Weakly positive (+ or ++)	Negative/weakly positive	Negative	Negative

Abbreviations: TT, tuberculoid; BT, borderline tuberculoid; BB, borderline borderline; BL, borderline lepromatous; LL, lepromatous; AFB, acid-fast bacilli.

* Compartmentalization of the features is not very stringent. All these features occur in various combinations as the disease progresses.

† Presence of large lesions indicates downgrading of the disease from higher spectrum.

§ In disease of long standing—almost all body hair are lost.


Cell-mediated Immunity
The Spectrum Of Leprosy (Ridley-Jopling Classification)
INDETERMINATE
Stable
Tuberculoid (TT)
Unstable
Borderline Tuberculoid (BT)
Unstable
Borderline (BB)
Unstable
Borderline Lepromatous (BL)
Stable
Lepromatous (LL)
Type I reactions
ENL
Bacterial Load

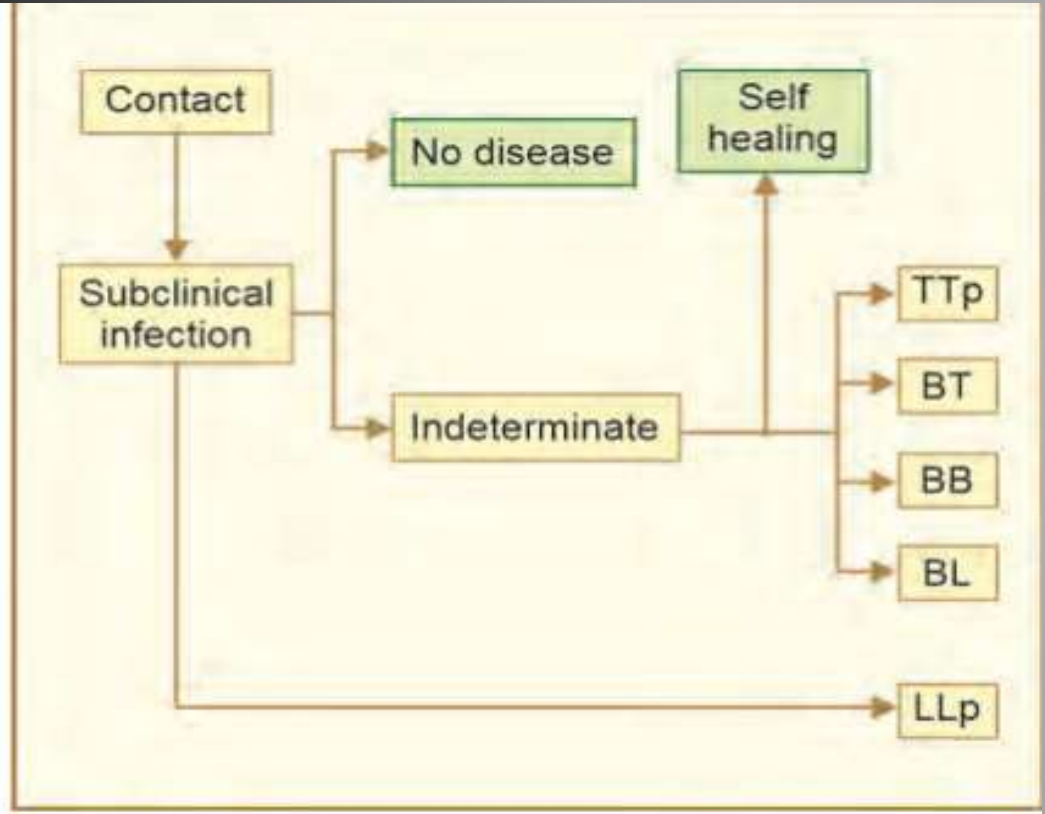


Fig. 2.4: Evolution of leprosy depicted on a straight line spectrum[26]

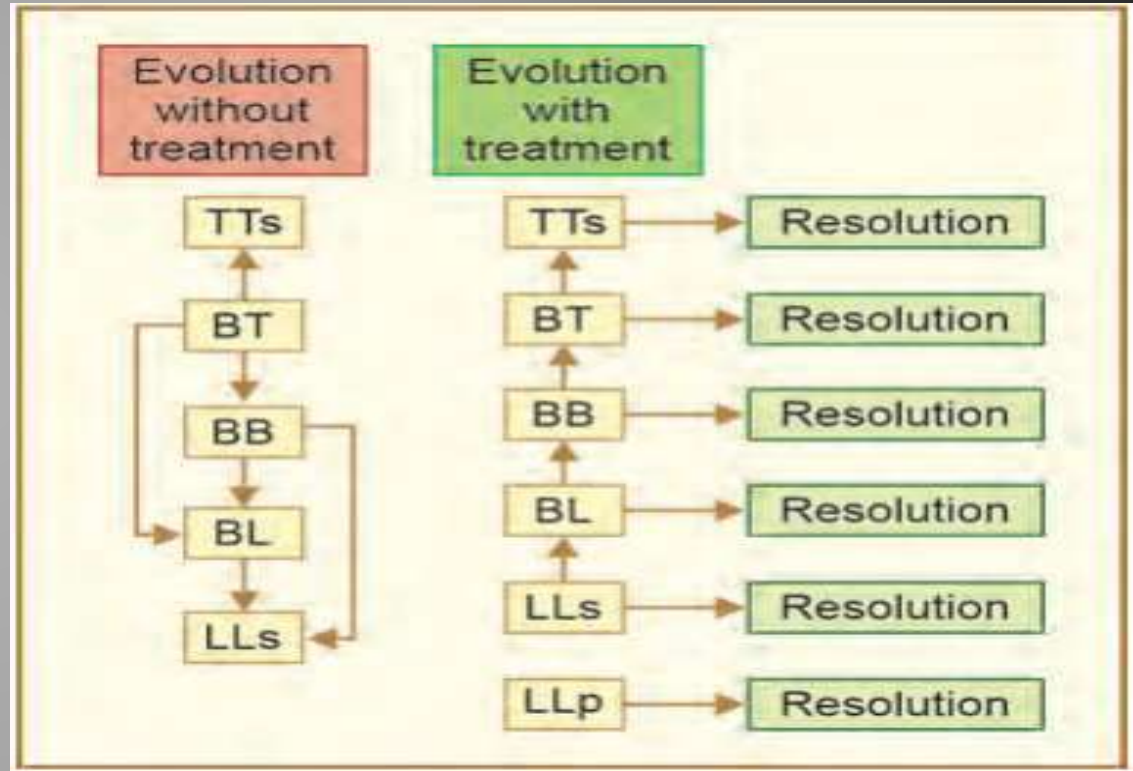
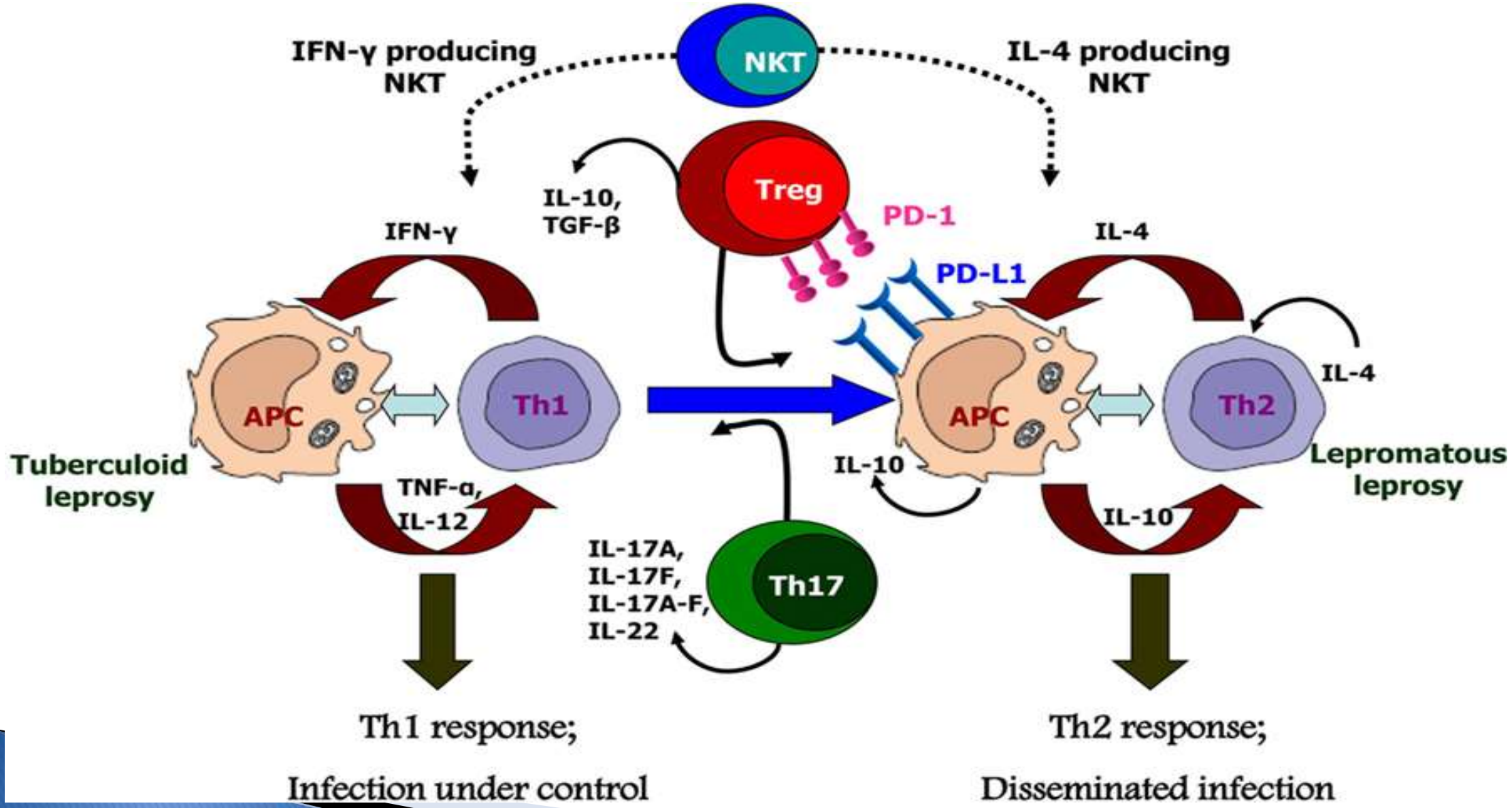
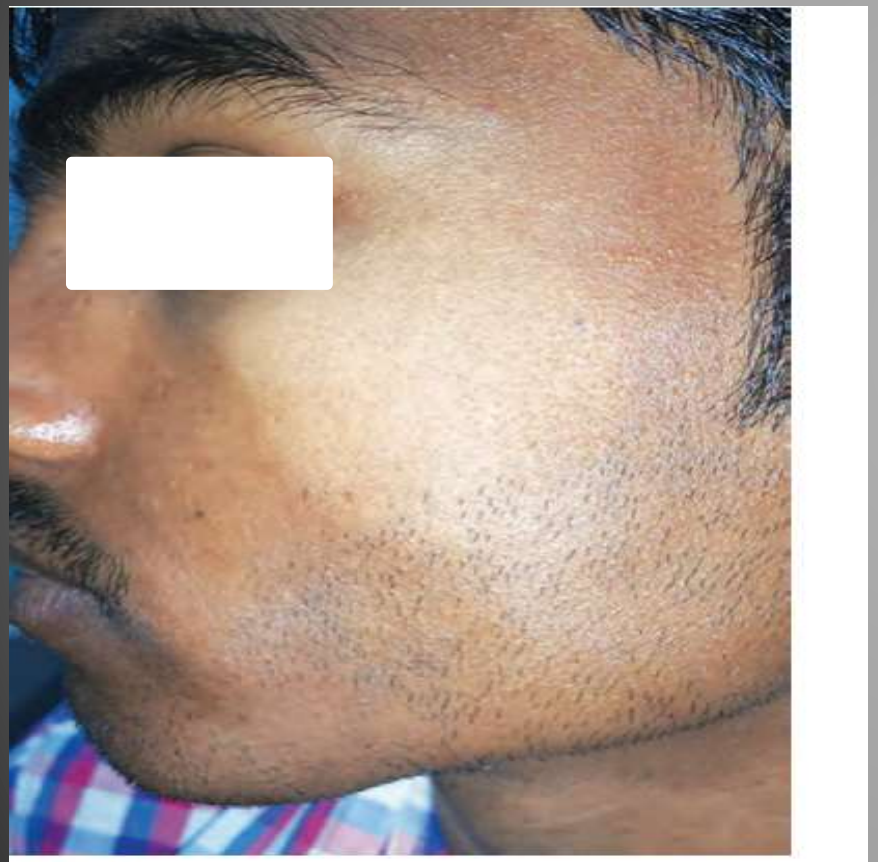


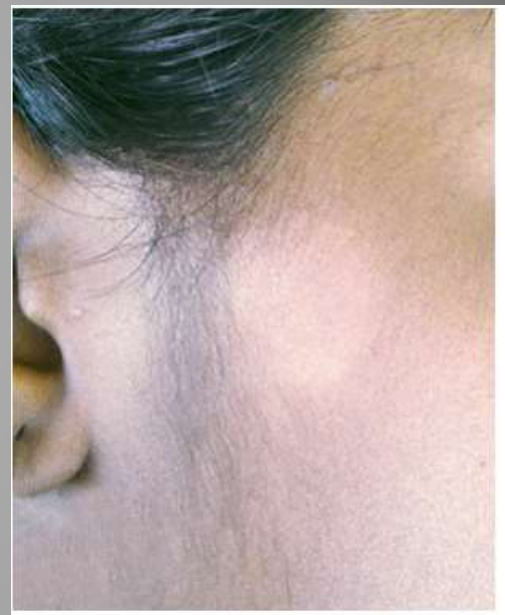
Fig. 2.5: Evolution of disease with and without treatment[26]


IFN-γ producing NKT
NKT
IL-4 producing NKT
IL-10, TGF-β
Treg
PD-1
PD-L1
IFN-γ
IL-4
APC
Th1
APC
Th2
IL-4
Tuberculoid leprosy
TNF-α, IL-12
IL-10
Lepromatous leprosy
IL-10
IL-17A, IL-17F, IL-17A-F, IL-22
Th17
Th1 response;
Infection under control
Th2 response;
Disseminated infection

INDETERMINATE LEPROSY



2.7: Macular lesion of indeterminate leprosy



.14: Ill-defined patch of indeterminate leprosy

TUBERCULOID (TT) LEPROSY

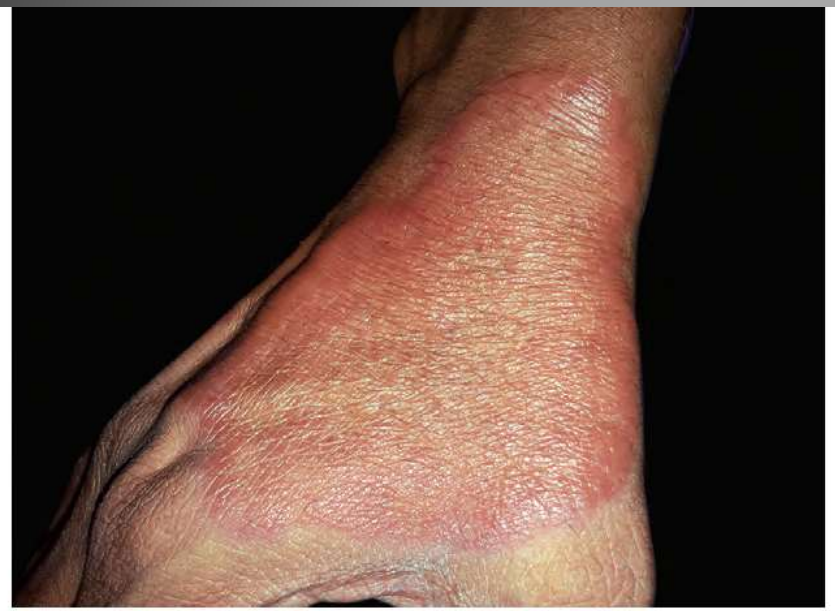


Fig. 2.8c: TT leprosy: Note the well-defined border with peripheral elevation and central flattening (saucer right way up)

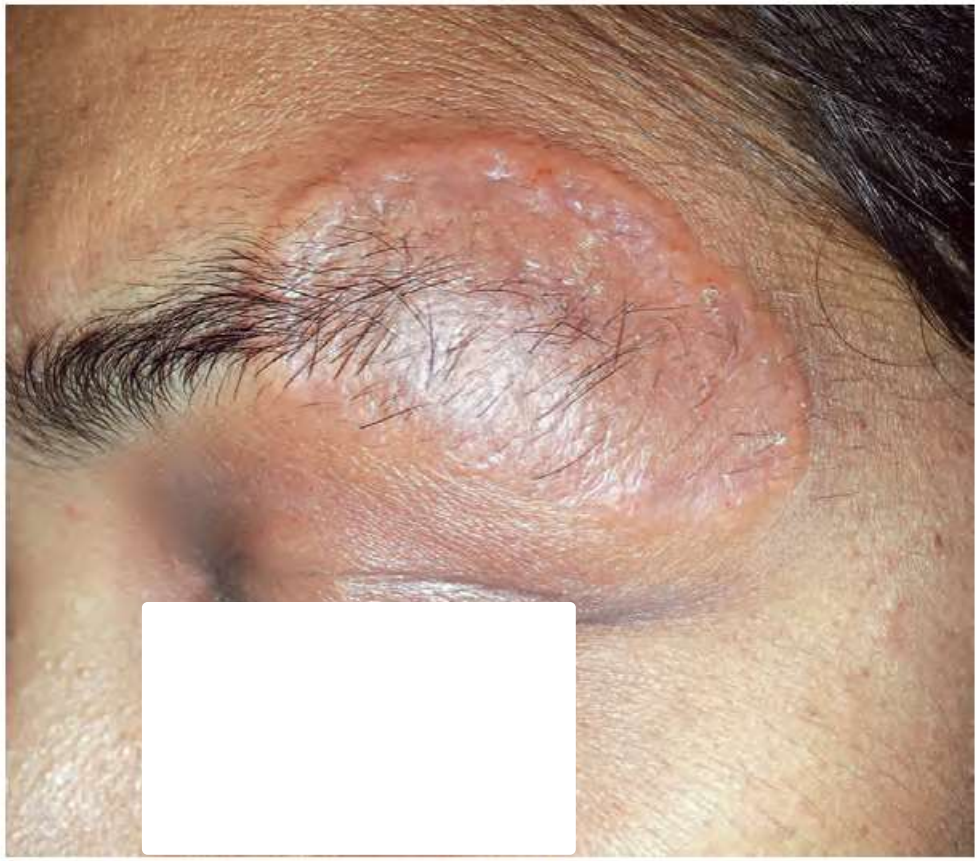


Fig. 2.8e: TT: "Saucer type" lesion with loss of hair on the lesion

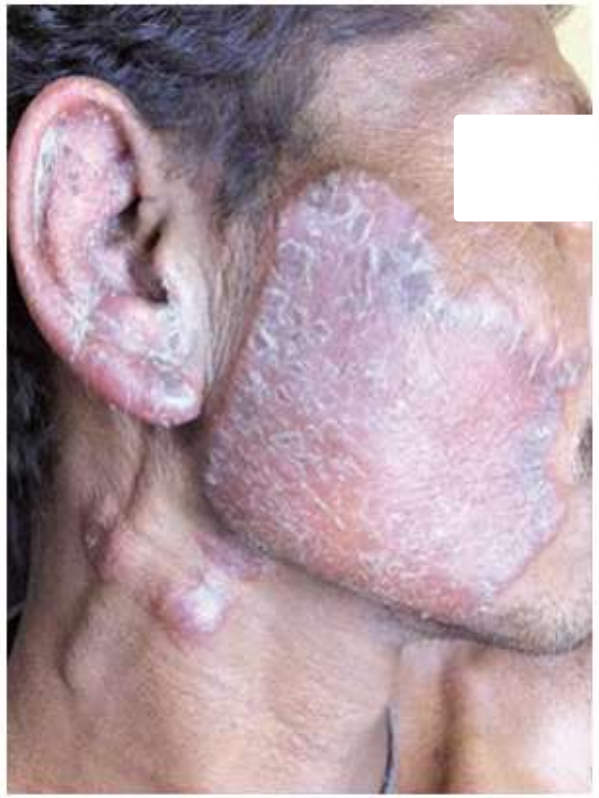
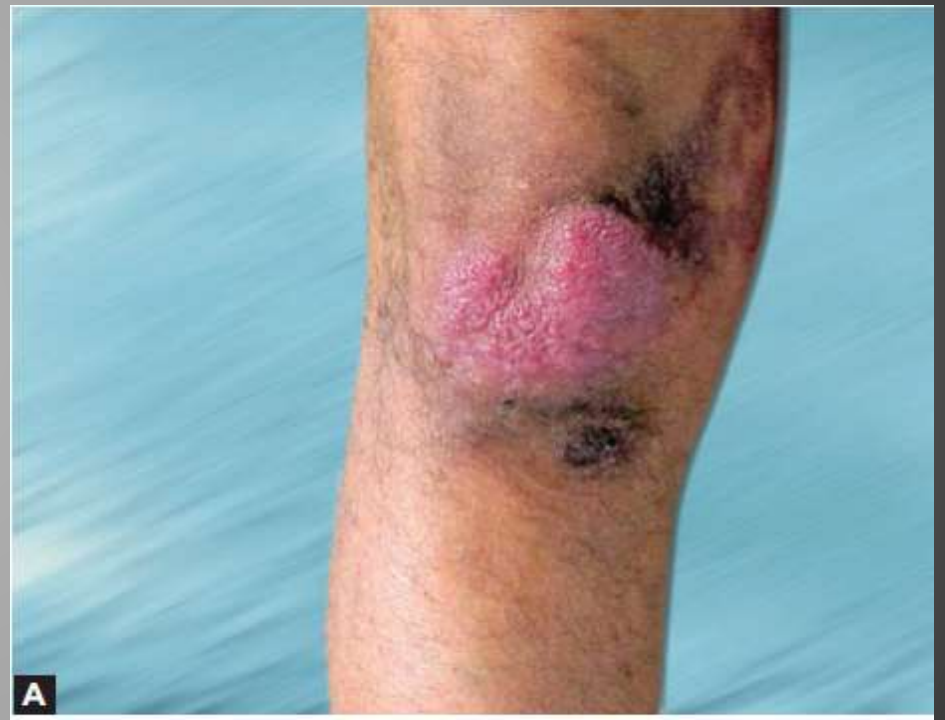


Fig. 14.15: Well-defined, raised outer border of a TT lesion ending abruptly; while the inner margin is ill-defined, sloping and waning toward the center. Enlarged, nodular great auricular nerve and involvement of ear is noted



Figs 15.2A and B: (A) Tuberculoid leprosy plaque

BORDERLINE TUBERCULOID

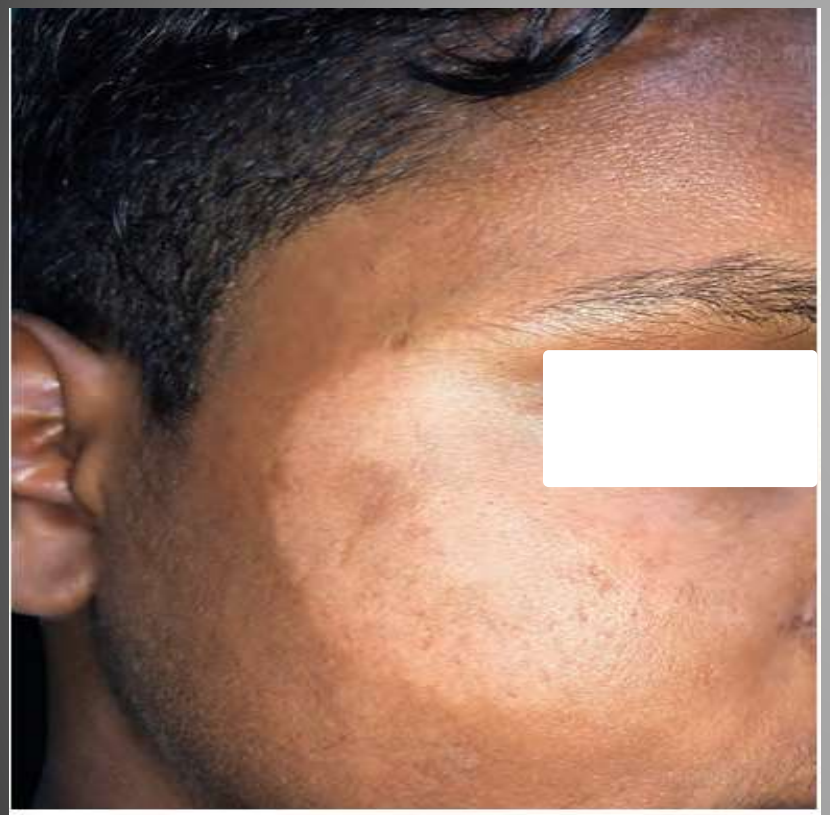


Fig. 2.31: Hypopigmented plaque of BT leprosy over the face in a child

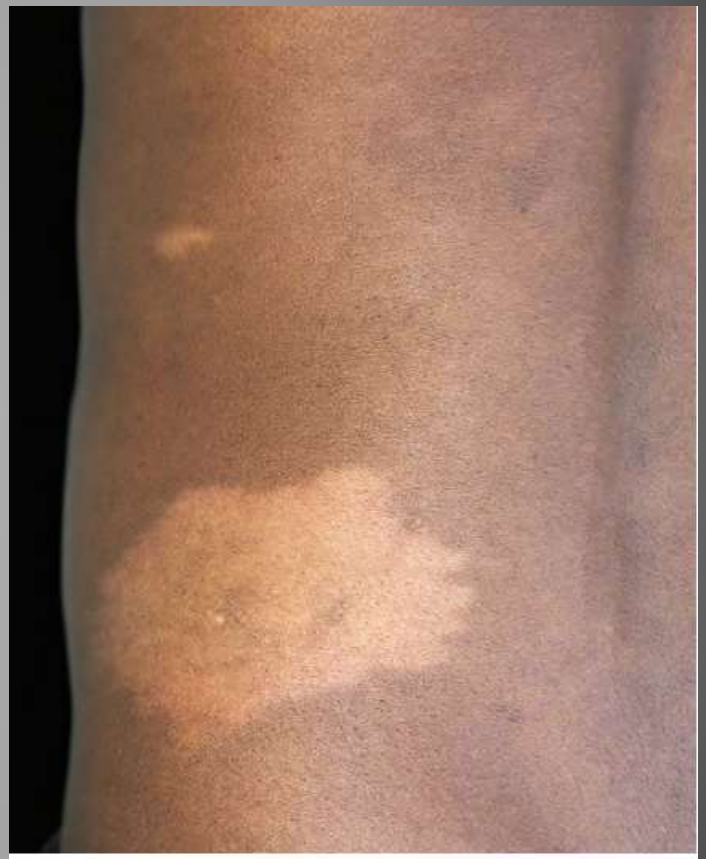
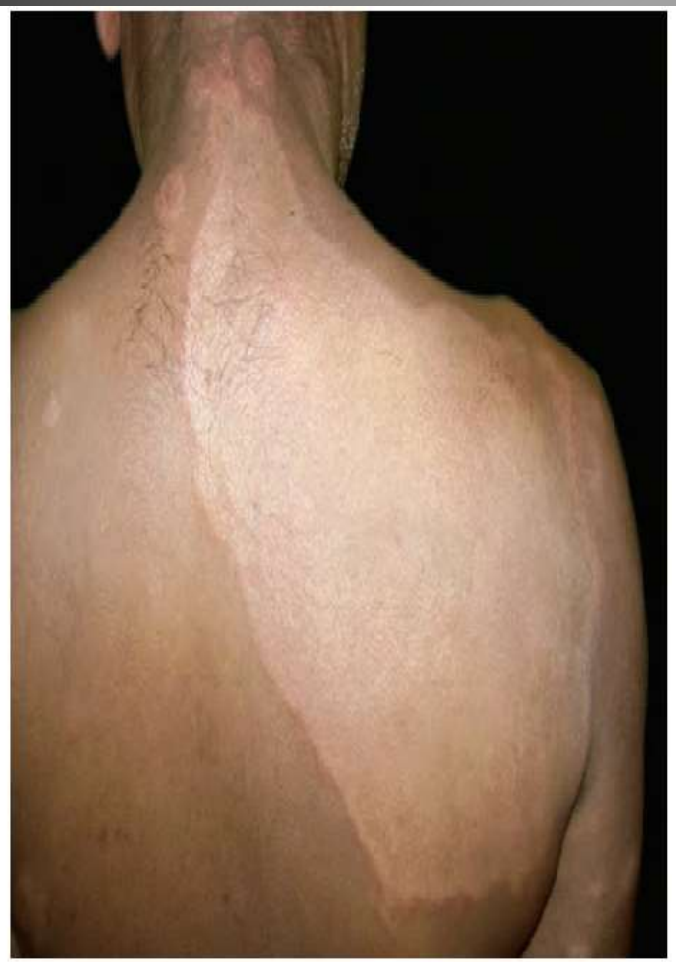


Fig. 2.32: Hypopigmented macules over the trunk in a childhood case of BT leprosy



BT: A large plaque encompassing the back and upper shoulder with "satellite" lesions

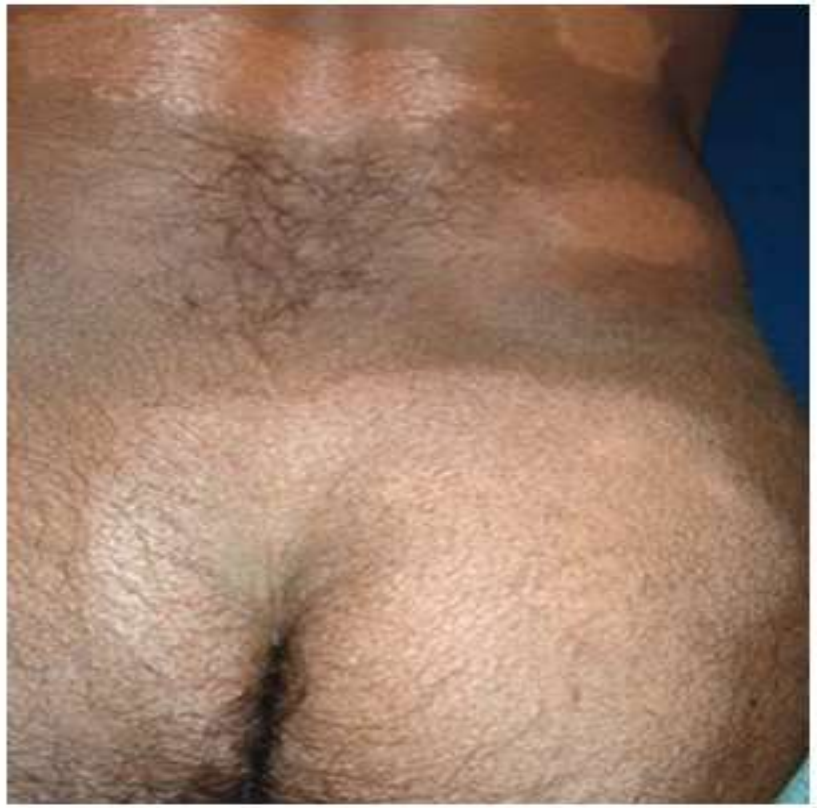


Fig. 14.17: Large patches of BT leprosy with pseudopodia and satellite lesions

MID BORDERLINE LEPROSY (BB)

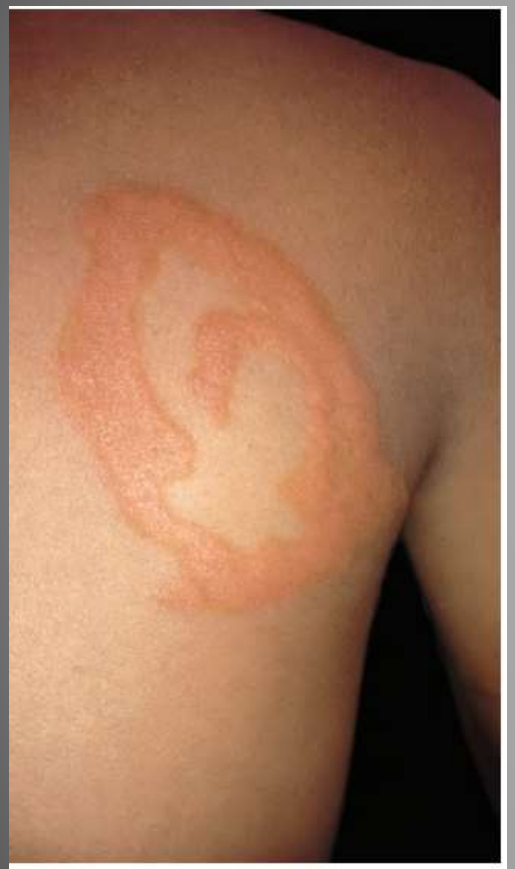
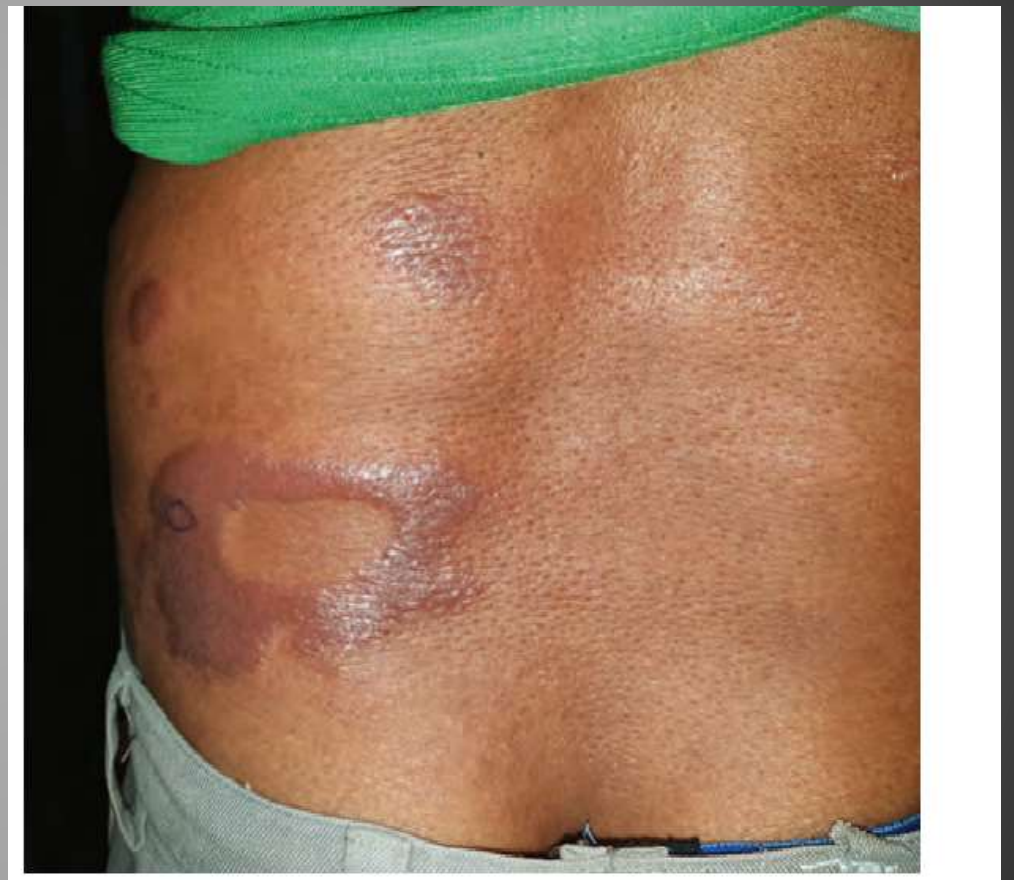
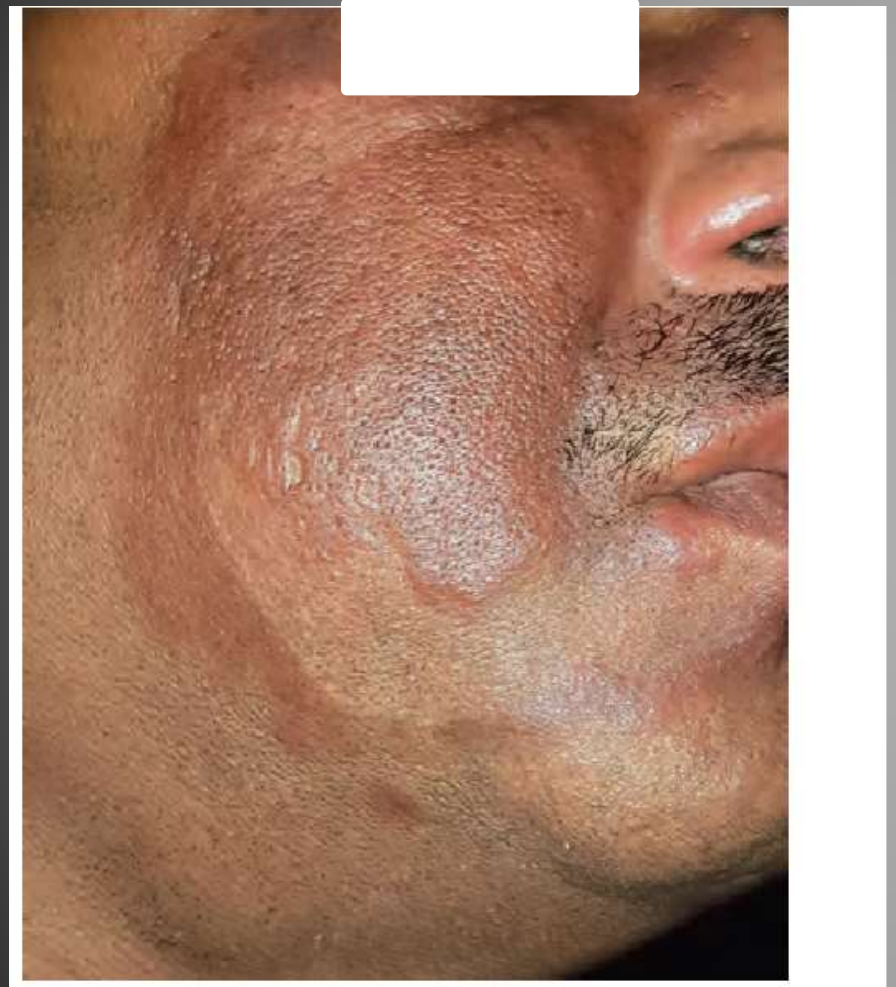


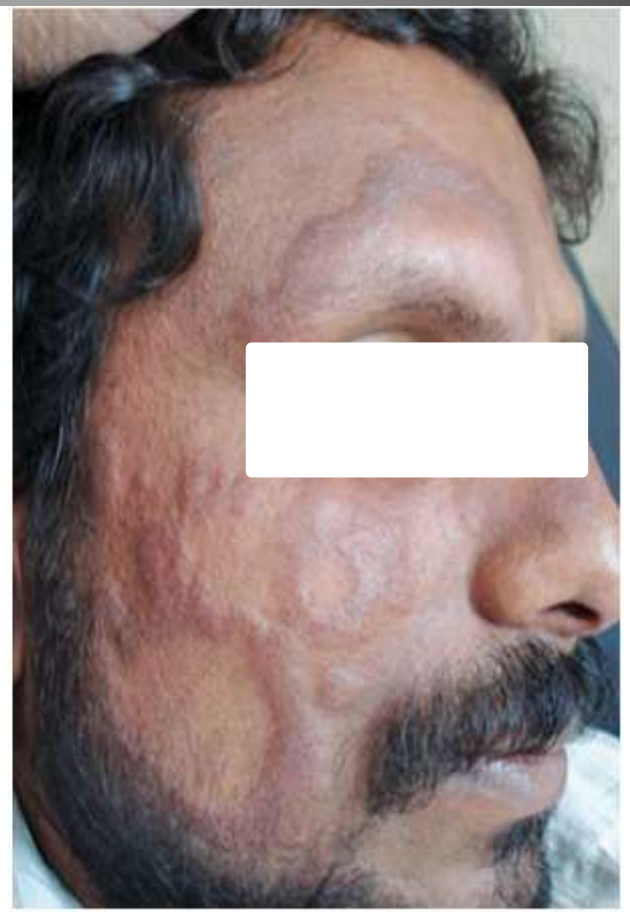
Fig. 2.34: Classic annular skin lesion of mid- borderline (BB) leprosy



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

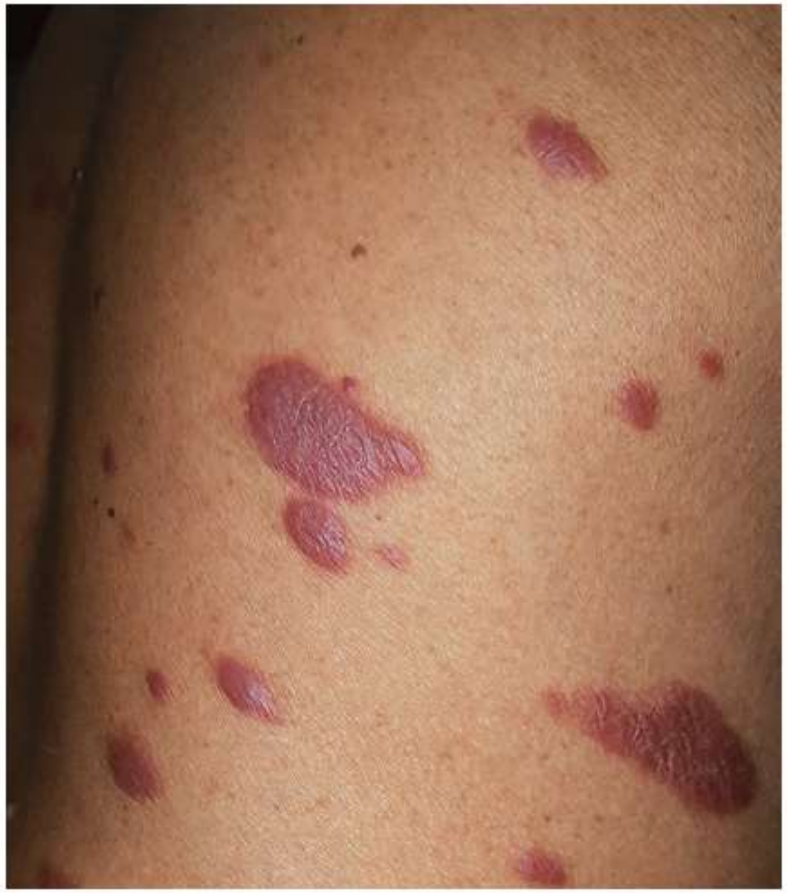


2.13: "Geographical bizarre" lesions on the face



ig. 14.16: Annular BB lesion with punched-out inner border and outer border sloping down to the surrounding skin

BORDERLINE LEPROMATOUS LEPROSY (BL)



"Inverted saucer" lesions with central infiltration described in BL leprosy

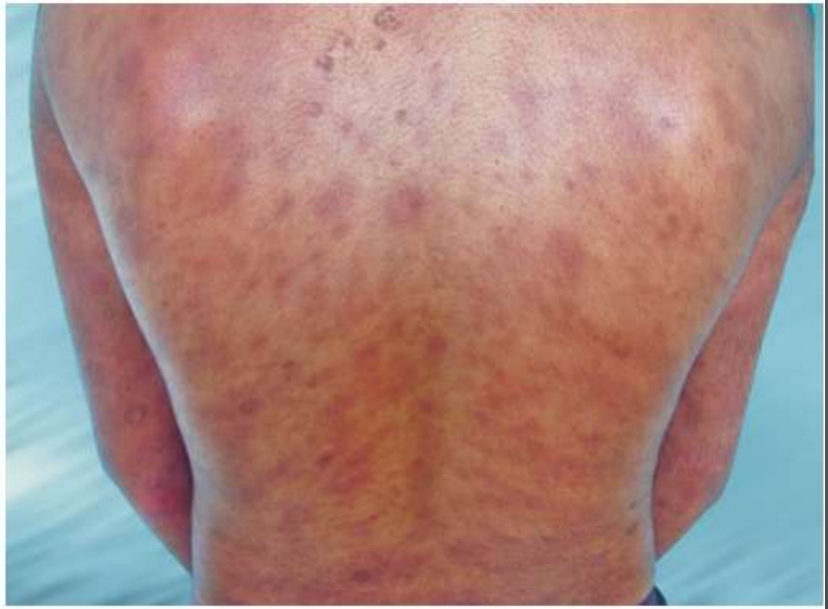


Fig. 15.10: Borderline lepromatous—multiple small papules and plaques on the back

LEPROMATOUS LEPROSY

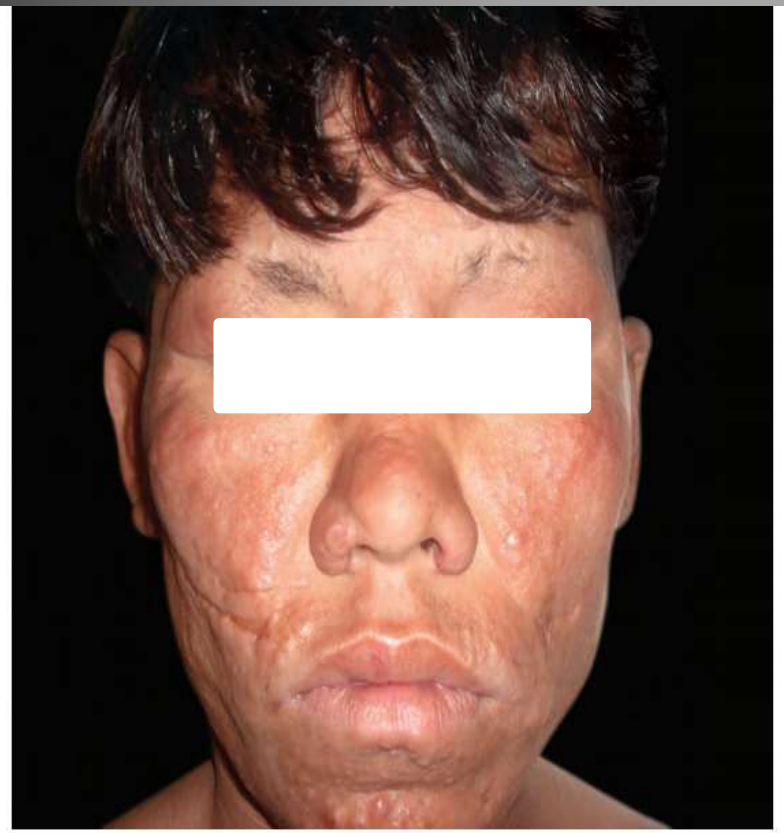


Fig. 2.17b: LL: A patient with diffuse infiltration, madarosis and nodules (the so-called "Leonine facies")

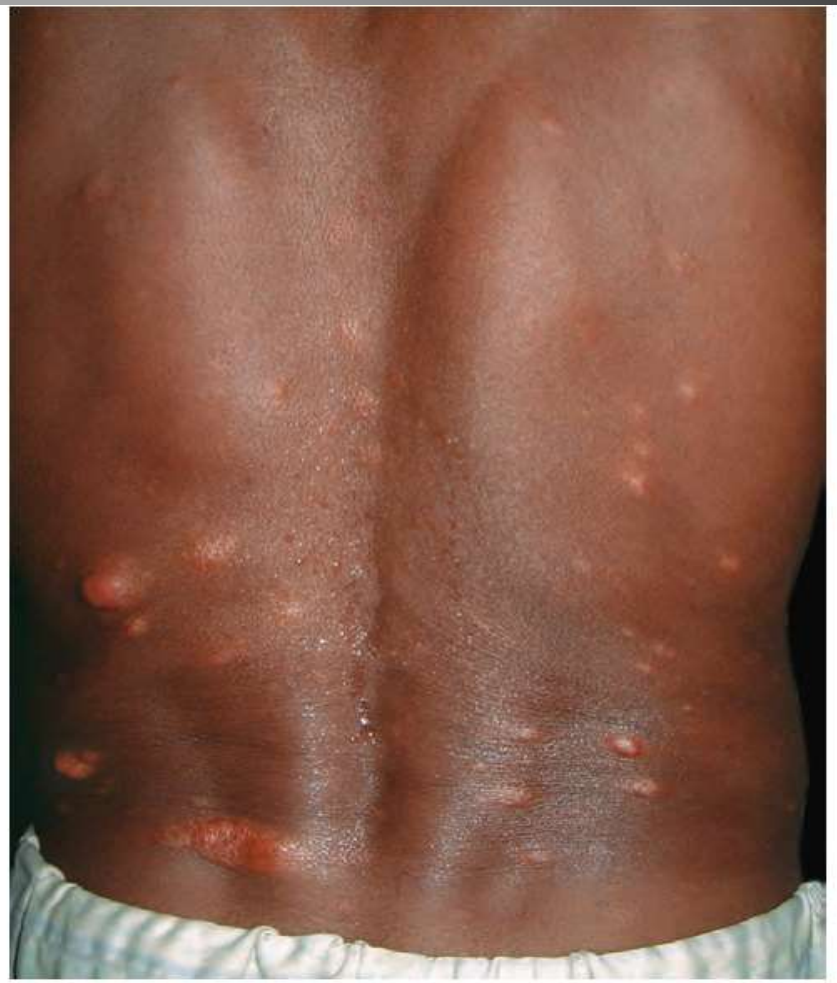


Fig. 2.17a: Papules and nodules in a case of LL

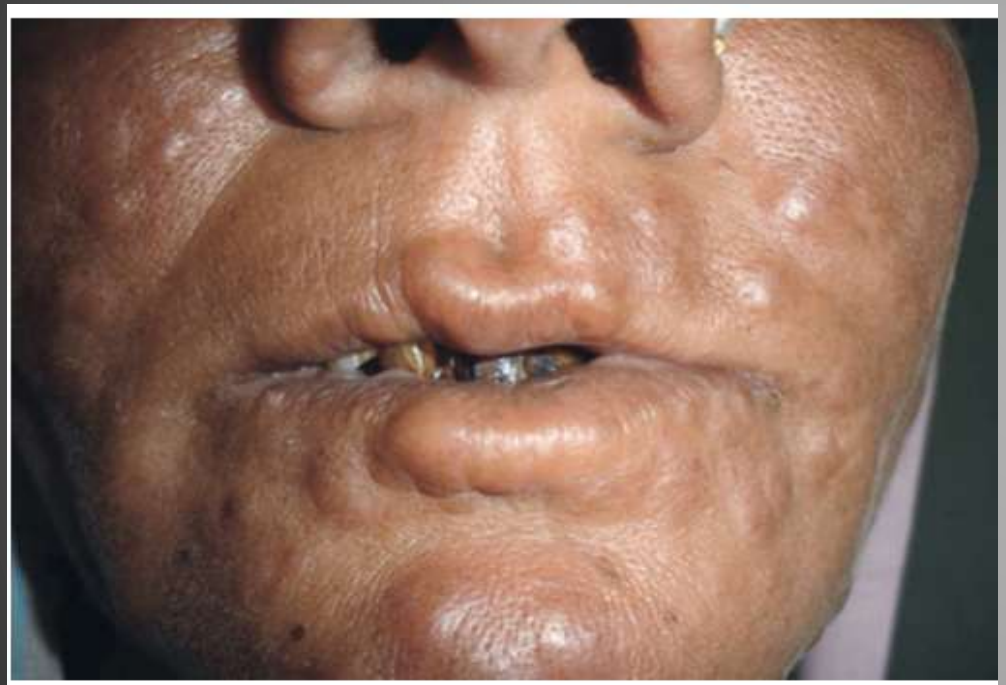
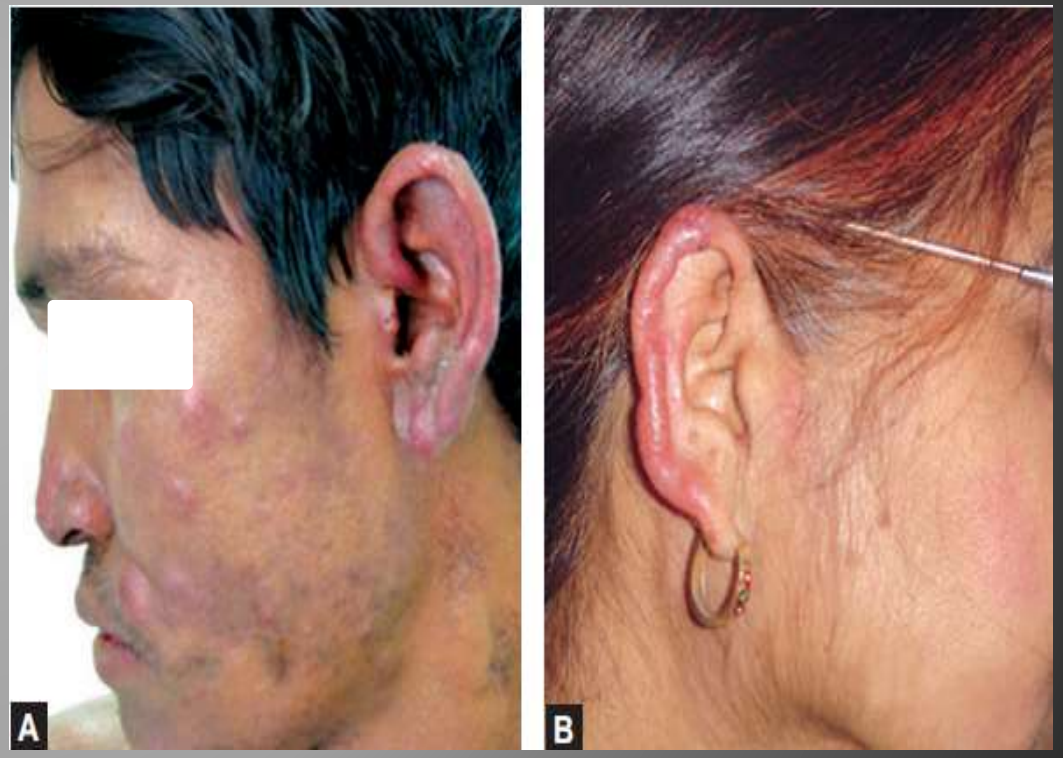


Fig. 14.33: Nodular infiltration of lip in LL leprosy



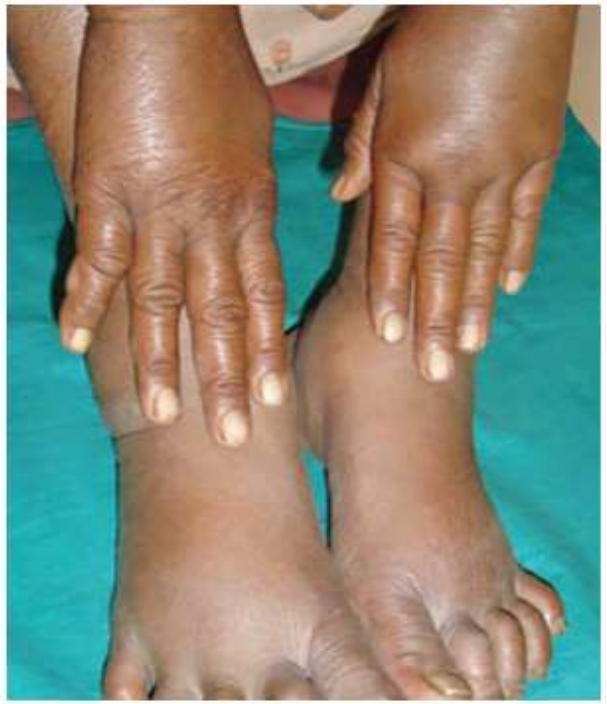


Fig. 14.1: Edema of hands and feet in a patient with untreated lepromatous leprosy

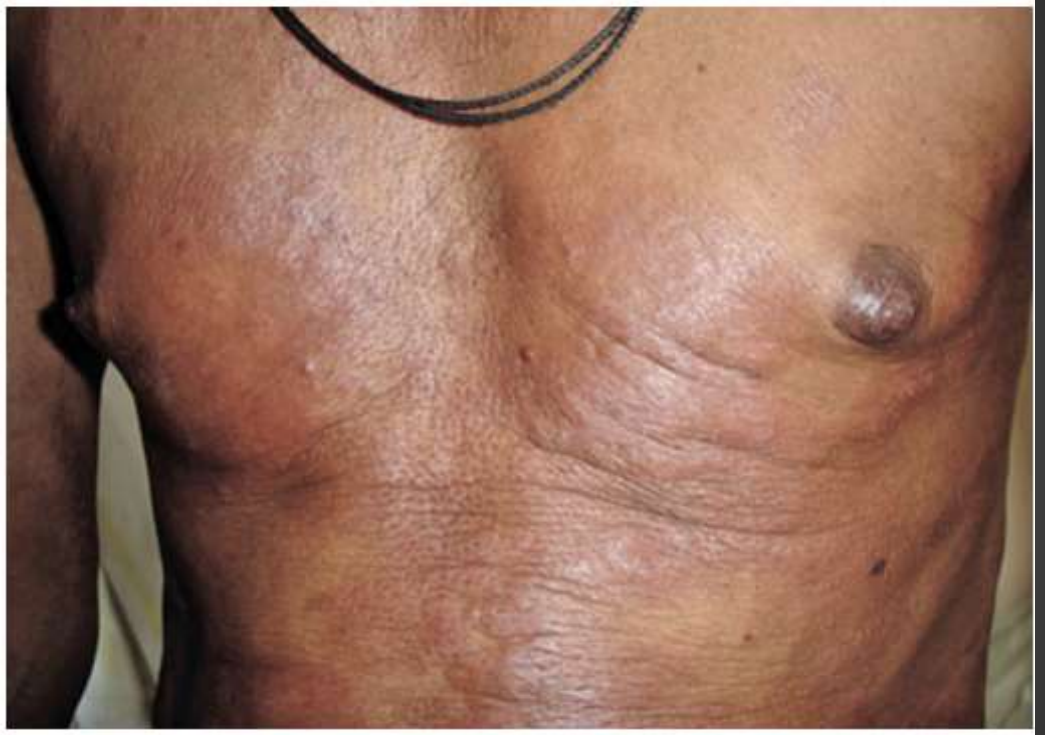
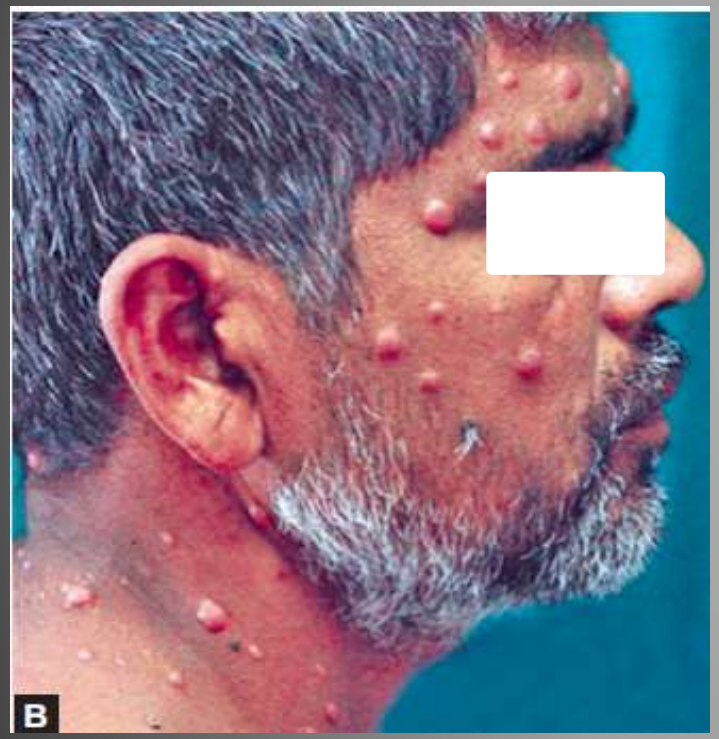


Fig. 14.7: Bilateral gynecomastia in a patient with untreated LL

HISTOID LEPROSY



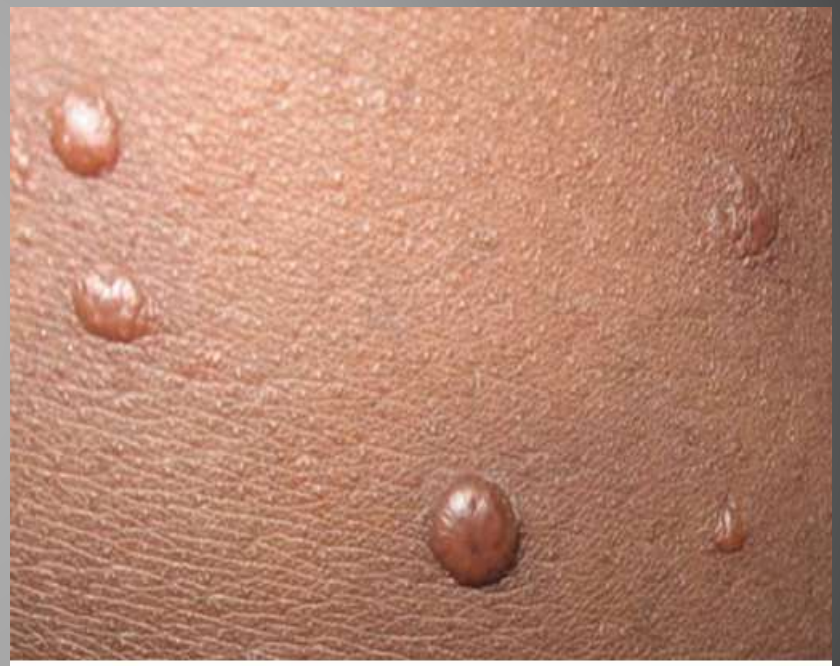


Fig. 14.20: Skin-colored, dome-shaped, shiny nodules of histoid leprosy, located on normal-looking skin

- Deformities of face
  - Deformities of hands and feet
    - Neuropathic ulceration

	Specific deformities	Motor paralysis	Anaesthetic
FACE	Loss of eyebrows Nasal deformity Hanging ear lobes Sagging face	Lagophthalmos Facial palsy	-
HANDS	Reaction hand or frozen hand Twisted finger Intrinsic plus fingers.	Claw hand Wrist drop Paralysed thumb	Shortening of digits Mutilation Contractures
FEET	-	Claw toes Foot drop Neuropathic plantar ulceration	Neuropathic disorganisation of foot Neuropathic plantar ulceration

DEFORMITIES IN LEPROSY

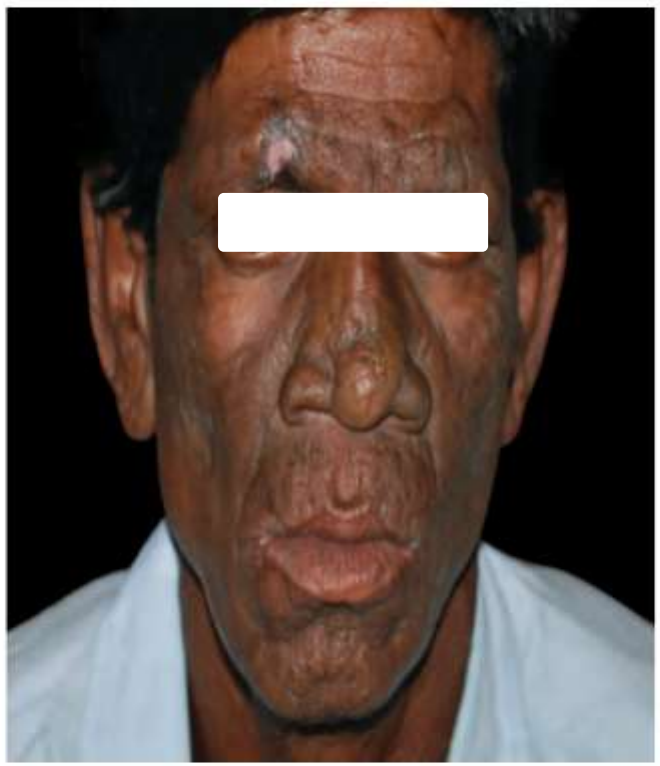


Fig. 8.3: LL Hansen with diffuse infiltration, nodules, madarosis, deformed nose and red eyes

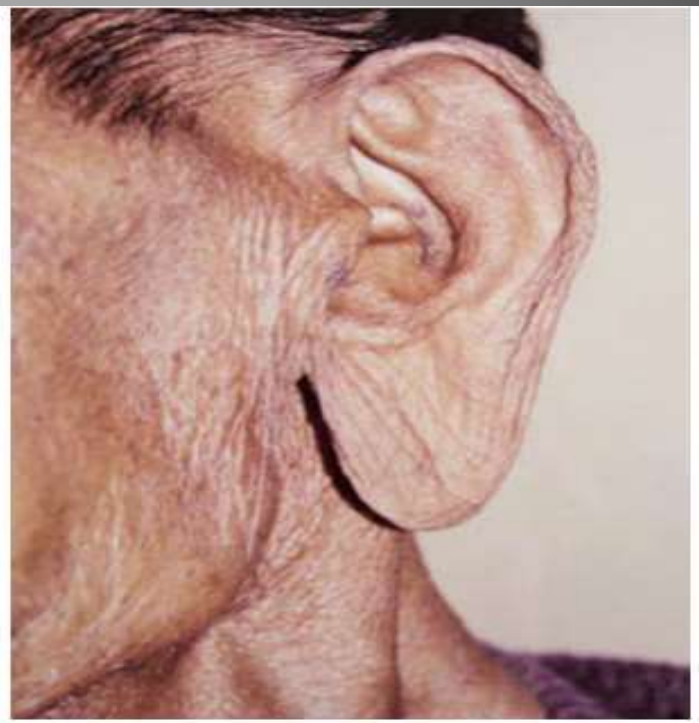


Fig. 14.6: Buddha ear

Fig. 8.9b: A patient with left complete claw hand and trophic changes in the distribution of the median nerve of the right hand

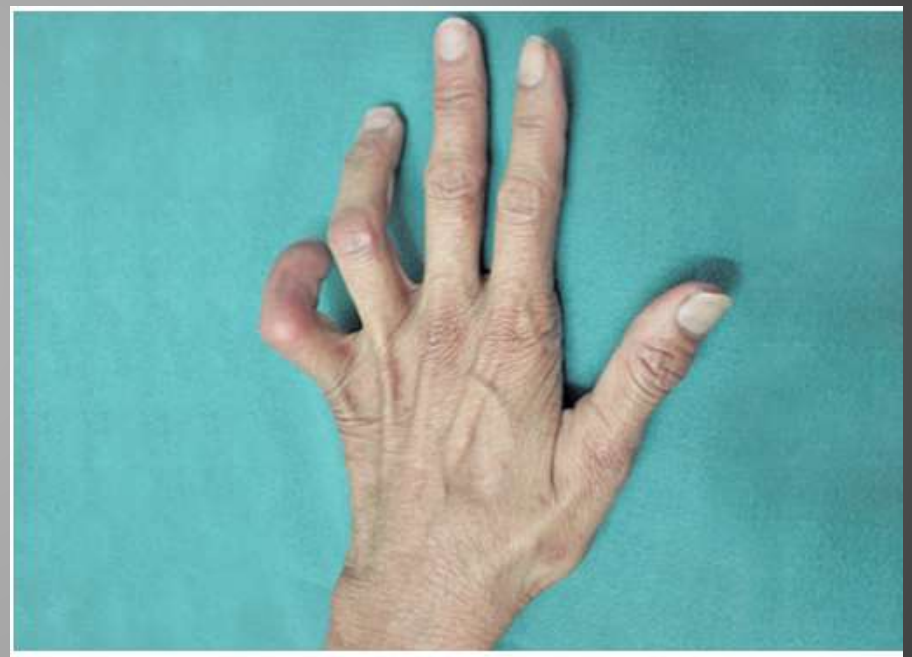


Fig. 14.48: Partial or ulnar clawhand

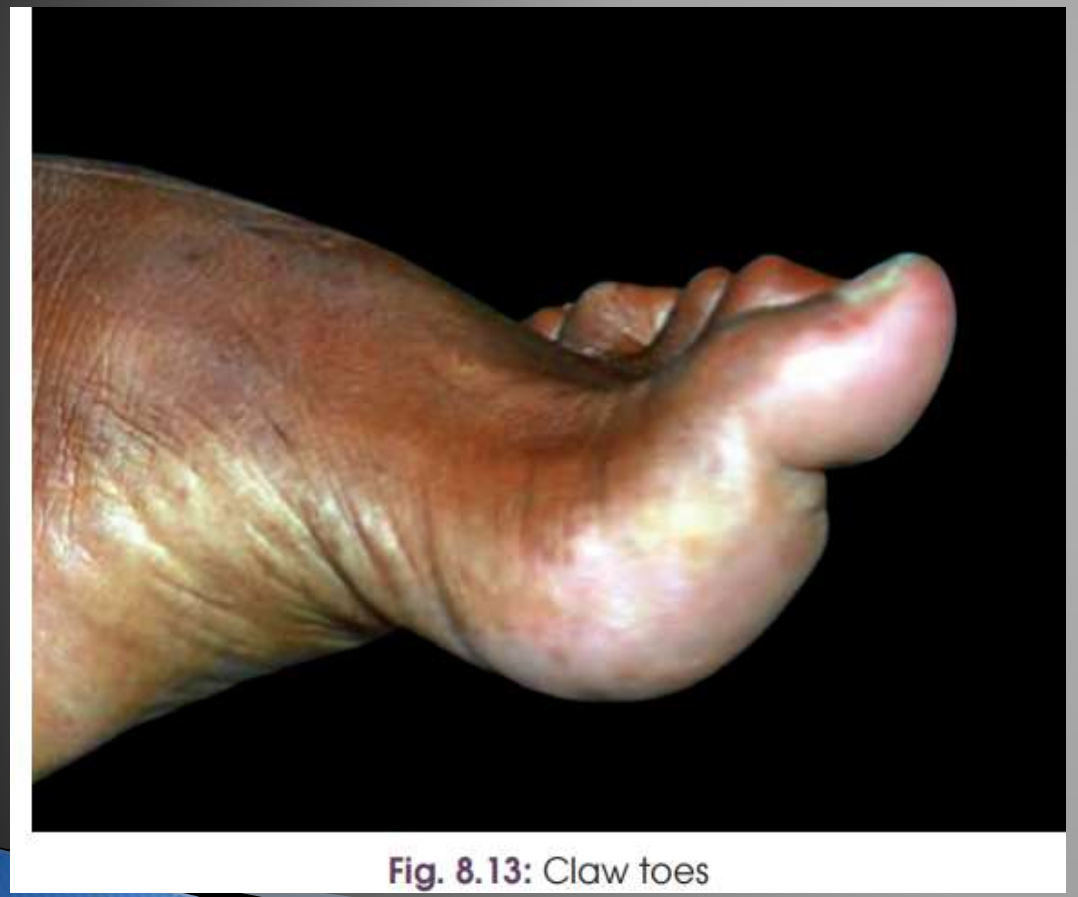


Fig. 8.13: Claw toes

6a: Left-sided facial palsy with lagophthalmos and Bell's phenomenon

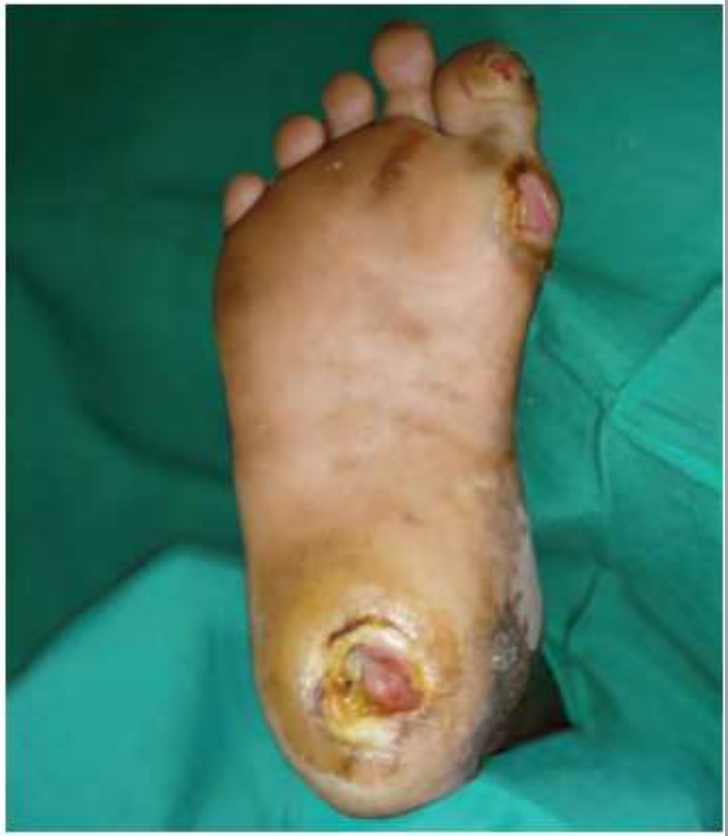
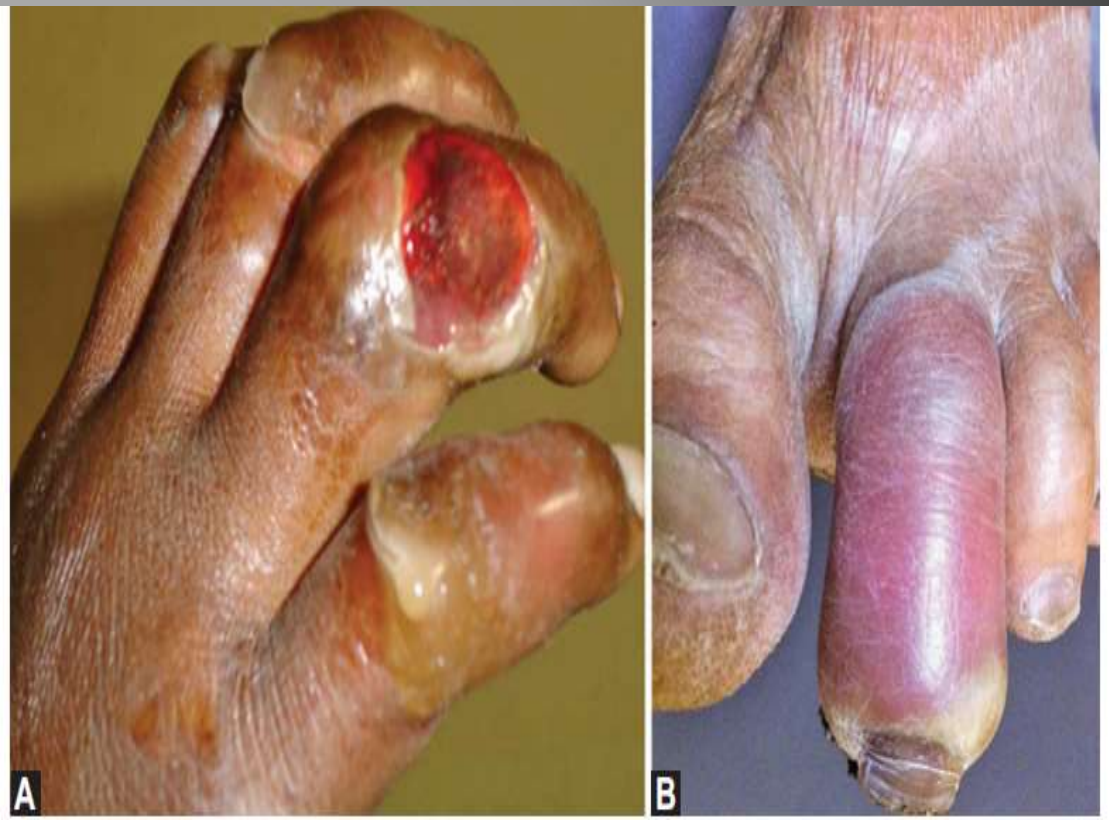


Fig. 8.21: Acute plantar ulcer



Figs 14.51A and B: Dactylitis involving fingers (A) and toe (B). Note the blistering and ulceration of the skin on fingers

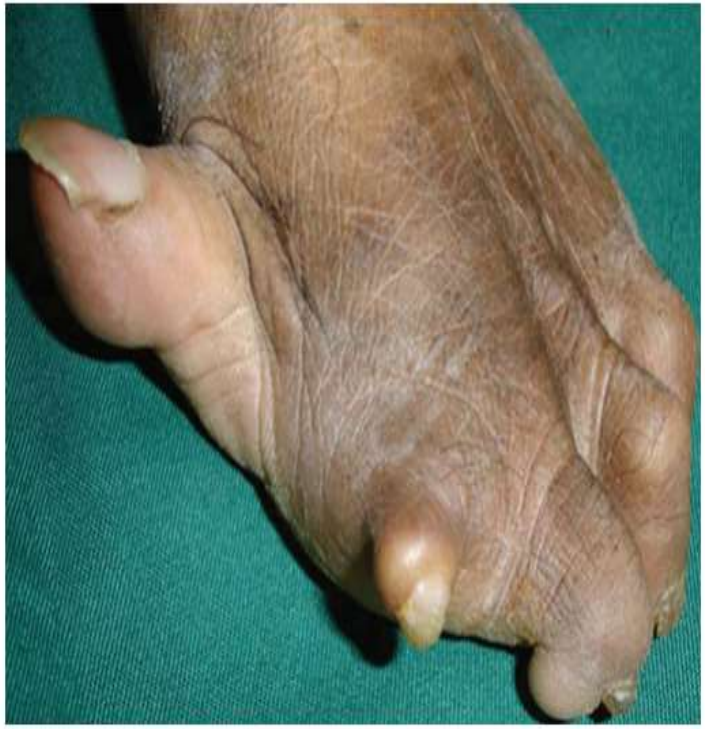


Fig. 14.54: Resorption of digits

REACTIONS IN LEPROSY

- Reactions are acute inflammatory episodes superimposed on the relatively uneventful usual course of leprosy.

- Type 1 lepra reactions:- Downgrading
  Upgrading

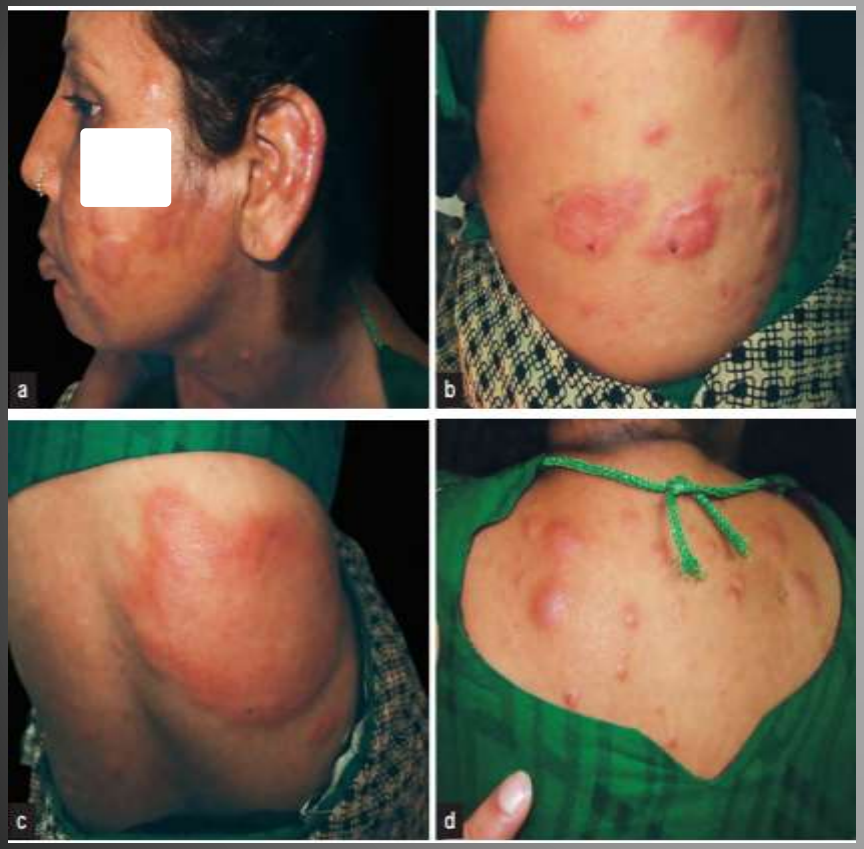
(Reversal reactions)

- Type 2 lepra reaction- Erythema Nodosum leprosum (ENL)

Table 5.1: Type 1 upgrading and downgrading reaction

	Upgrading (reversal) reaction	*Downgrading reaction*
Onset	Reversal reaction usually occurs during the first 6 months of therapy in BT and BB patients, but longer intervals have been observed in BL patients	It is seen either in patients on *no* treatment or who have *interrupted* treatment
Cause	Alteration in CMI (↑)	Alteration in CMI (↓)
Features	• Some or all of the existing leprosy lesions show signs of acute inflammation (pain, tenderness, erythema and edema) • Necrosis and ulceration occur in severe cases • Lesions desquamate as they subside • New lesions *might* appear occasionally	Lesions worsen and the morphology of the existing lesions and new lesions becomes more lepromatous
Nerve	Neuritis is often *marked*	Neuritis is *less* marked
Histology	In reversal reaction, there is edema, reduced bacilli and increased defensive cells such as lymphocytes, epithelioid cells and giant cells	There is increase in bacilli and defensive cells are replaced by macrophages
Treatment	Steroids are needed in most patients	Usually just continuing the MDT suffices; if steroids needed, response occurs with *lower* doses than upgrading reaction

TYPE 1 REACTION



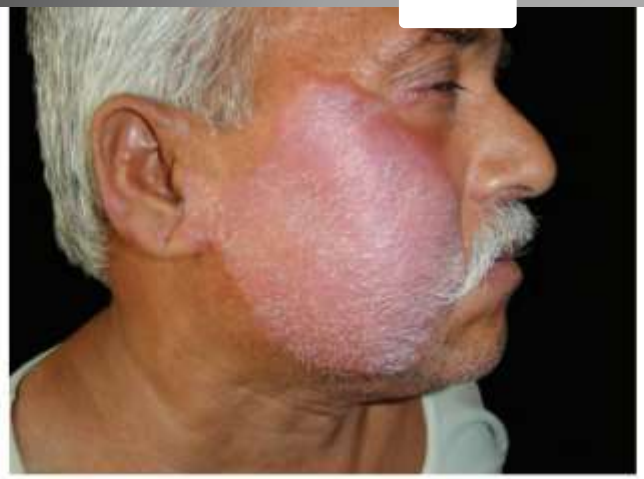
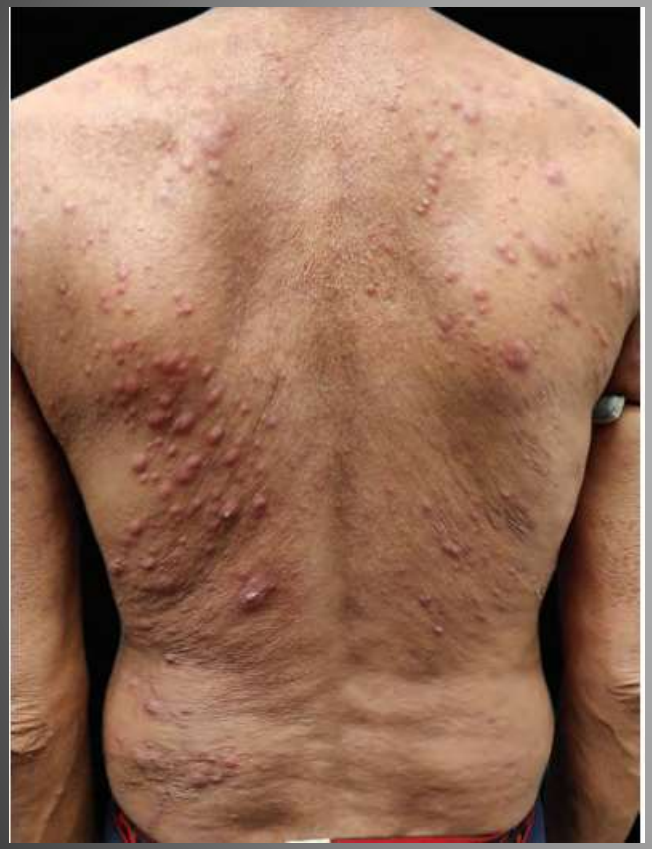
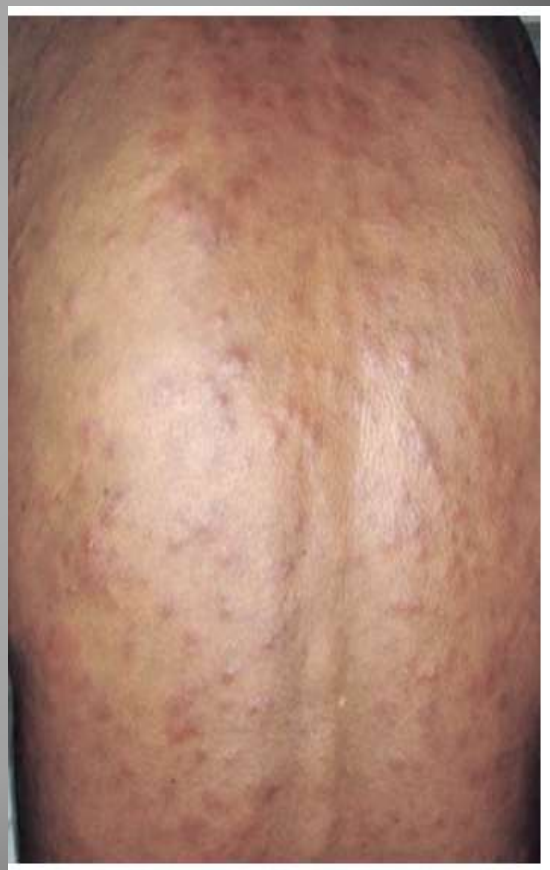


Fig. 5.2a: BT Hansen with marked edema in a plaque during a type 1 reaction

TYPE 2 LEPRA REACTIONS

- Type 2 reaction can cause inflammatory reaction in any organ invaded by the lepra bacilli.
- Present as crops of erythematous, partially blanchable, warm, tender papules or nodules, superficial or deep seated, bilaterally symmetrical.
- They are usually seen to involve the face, arms, thighs, palms and sole





g. 14.21 Nodules of erythema nodosum leprosum

Table 5.2: Systemic involvement in type 2 reaction	
Organs involved	*Signs and symptoms*
Joints	Polyarthritis or polyarthralgia
Lymph nodes	Tender generalized lymphadenopathy (especially femoral)
Eyes	Uveitis (iritis and iridocyclitis), glaucoma and blindness
Organomegaly	Hepatosplenomegaly—may be tender
Genitalia	Orchitis and epididymitis
Kidneys	Glomerulonephritis, acute tubulointerstitial nephritis and amyloidosis which can progress to chronic kidney disease
Bone	Dactylitis, periosteitis
Muscles	Myalgia, myositis
Nerves	Neuritis

MANAGEMENT

- INVESTIGATIONS :-

1. Skin biopsy from lesion, anaesthetic area
2. Slit skin smear examination for acid fast bacilli
3. Nerve biopsy (Pure neuritic Hansens)
4. Nerve conduction study

TREATMENT

Table 7.3: MB-MDT for MB cases

	Dapsone	*Rifampicin*	*Clofazimine*
Adult 50–70 kg	100 mg given daily	600 mg given once a month under supervision	50 mg daily and 300 mg given once a month under supervision
Child 10–14 years*	50 mg given daily	450 mg given once a month under supervision	50 mg alternate day and 150 mg given once a month under supervision

Table 7.4: MB-MDT for PB cases

	Dapsone	*Rifampicin*
Adult 50–70 kg	100 mg given daily	600 mg given once a month under supervision
Child 10–14 years*	50 mg given daily	450 mg given once a month under supervision

Table 2.20: Treatment of leprosy in children

	Paucibacillary MDT (6 months)	*Multibacillary MDT (12 months)*
0–9 years	Rifampicin 10 mg/kg monthly, supervised	Rifampicin 10 mg/kg monthly, supervised
	Dapsone 2 mg/kg daily	Dapsone 2 mg/kg daily
		Clofazimine 6 mg/kg monthly supervised and 1 mg/kg daily
10–14 years (<40 kg)	Rifampicin 450 mg monthly, supervised	Rifampicin 450 mg monthly supervised
	Dapsone 50 mg daily	Dapsone 50 mg daily
		Clofazimine 150 mg monthly, supervised and 50 mg every other day
Blister pack	Blue kit (Fig. 2.43)	Yellow kit (Fig. 2.42)
>14 years	Rifampicin 600 mg monthly, supervised	Rifampicin 600 mg monthly, supervised
	Dapsone 100 mg daily	Dapsone 100 mg daily
		Clofazimine 300 mg monthly supervised and 50 mg daily
Blister pack	Green	Red

Fig. 2.42: MB MDT blister pack for children (yellow kit)

Fig. 2.43: PB MDT blister pack for children (blue kit)

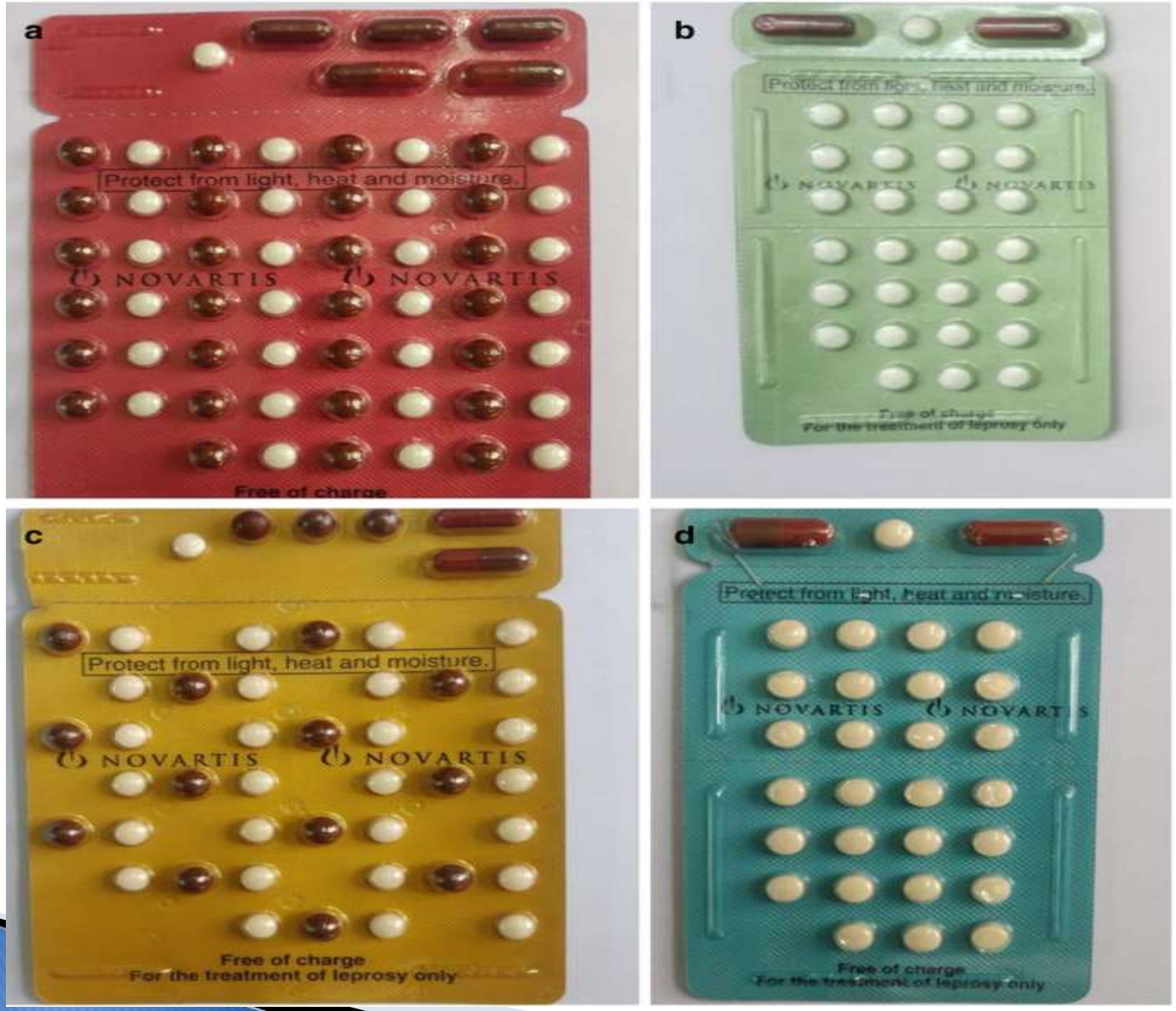

a
Protect from light, heat and moisture.
NOVARTIS
NOVARTIS
Free of charge
b
NOVARTIS
NOVARTIS
c
Protect from light, heat and moisture.
NOVARTIS
NOVARTIS
Free of charge
For the treatment of leprosy only
d
NOVARTIS
Free of charge
For the treatment of leprosy only

Table 7.6: Treatment of drug-resistant leprosy (WHO)

	Treatment	
Resistant type	*First 6 months (daily)*	*Next 18 months (daily)*
Rifampicin resistance	Ofloxacin 400 mg* + minocycline 100 mg + clofazimine 50 mg Ofloxacin 400 mg* + clarithromycin 500 mg + clofazimine 50 mg	Ofloxacin 400 mg* or minocycline 100 mg + clofazimine 50 mg
Rifampicin and ofloxacin resistance	Clarithromycin 500 mg + minocycline 100 mg + clofazimine 50 mg	Clarithromycin 500 mg or minocycline 100 mg + clofazimine 50 mg

*Ofloxacin 400 mg can be replaced by levofloxacin 500 mg or moxifloxacin 400 mg.

Mycobacterium leprae

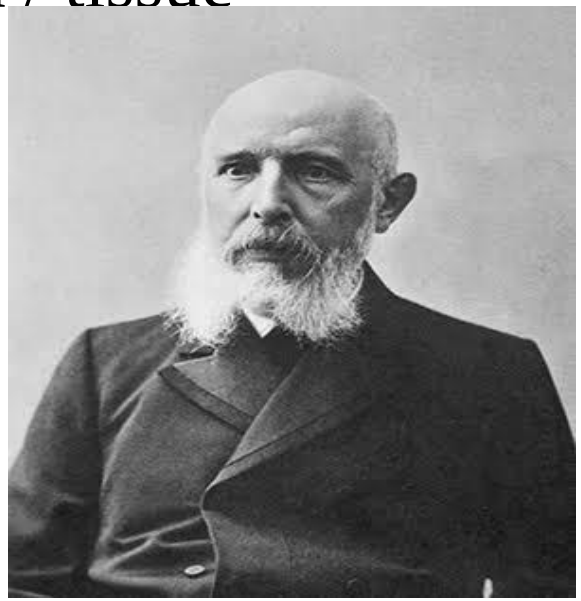
Dr Amaiye Gaonkar

3rd year Junior resident

Department of Microbiology

Introduction

- Mycobacterium leprae causative agent of leprosy
- Discovery of lepra baccili by G.H. Armauer Hansen
- Not cultivable in artificial culture media / tissue culture
- Generation time – 12-13 days
- Incubation period – 3-5 years



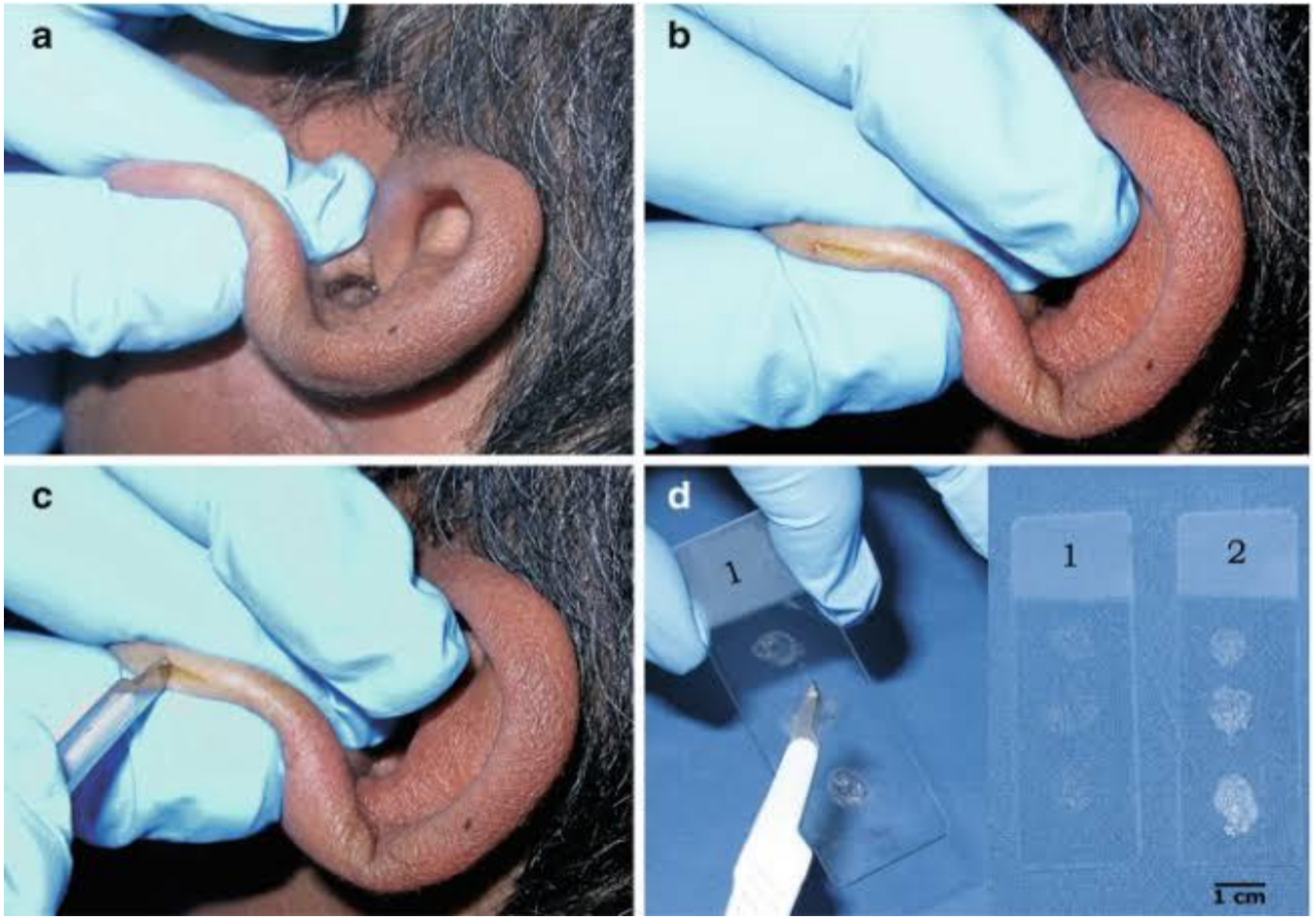
- Obligate intracellular, strict aerobe
- Non motile Non sporing
- Less acid fast – can resist 5% sulphuric acid
- Bacilli are bound together by lipid like substance called glia and entire mass is globi
- Parallel rows of globi gives cigar bundle appearance

Smear Microscopy

- Specimen collection
  - 6 sites – sample to be collected
  - Four from skin (forehead , cheek, chin, buttock)
  - ear lobule
  - nasal mucosa by nasal blow / scrapping

- Slit skin smear
- technique to collect the skin and ear lobe specimen
- Edge of the lesion is preferred
- Nasal specimen
- Nasal blow – early morning mucus specimen blown on clean cellophane sheet
- Nasal scrapping – scrape nasal septum to remove a piece of mucous membrane

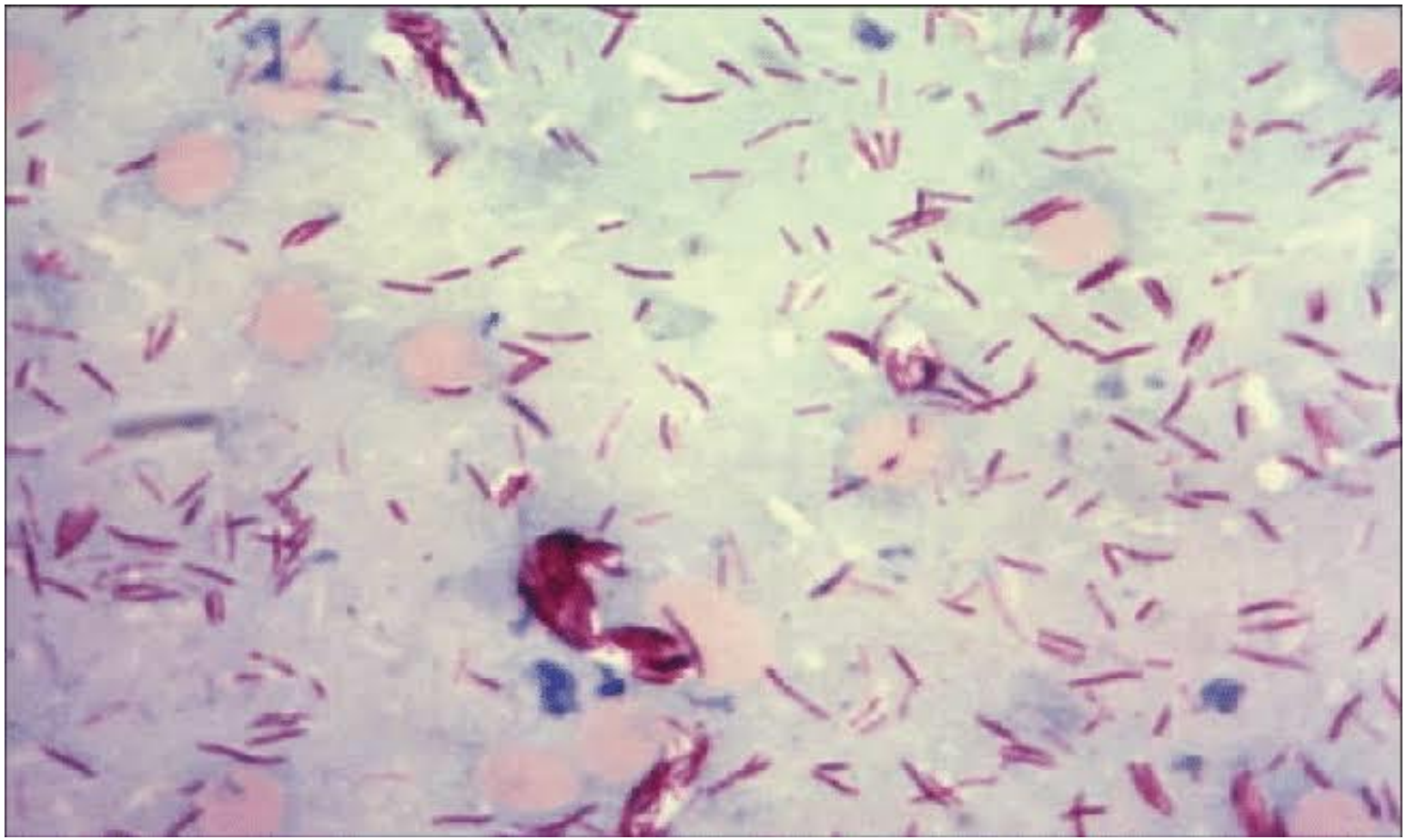
Slit skin smear



Microscopy

- Ziehl – Neelson technique – 5% suphuric acid for decolorization
- red acid fast bacilli are seen
- Arrange singly or groups (cigar bundle appearance)
- Bound together by glia to form globi
- Globi are present inside foamy macrophage – foamy cells or virchows lepra cells

Red Acid fast Lepra bacilli



❖ Bacteriological index

- Total number of bacilli (live + dead) seen per oil immersion field.

- ❖ Morphological index

  percentage of uniformly stained bacilli out of total number of bacilli counted.

  adv- better marker to monitor treatment.

Grading of smear

- Based on number of bacilli per oil immersion field
- 1-10 bacilli in 100 OIF = 1+

  1-10 bacilli in 10 OIF = 2+

  1-10 bacilli per OIF = 3+

  10-100 bacilli per OIF = 4+

  100-1000 bacilli per OIF = 5+

  > 1000 bacilli per OIF = 6+

Mouse foot pad inoculation

- Inoculating specimen into into food pad of mice keeping at 20.C for 6-9 months
- nine banded armadillo can be used
- Advantage : 10 times more sensitive ,detecting drug resistance, viability of bacilli.

Lepromin test

- Demonstrates the delayed hypersensitivity reaction and intact CMI against lepra antigen
- 0.1 ml of lepromin antigen is injected intradermally to inner forearm
- Reading taken at two occasions- 48 hrs and 21 days

Early reading or fernandez reaction

- Induration surrounded by erythema is produced at the site of inoculation within 24-48 hours
- Red area of >10 mm diameter is positive
- Indicates – past exposure to lepra bacilli

Late reading or Mitsuda raction

- Positive test indicated by a nodule formation

  > 5mm size at the site of inoculation which ulcerates later on

- Late reaction is against the bacillary component of the lepra antigen
- Indicates patient cell mediated immunity is intact.

Lateral flow assay

- Based on immunochromatography test
- Detects anti- M.leprae PGL-1 IgM Ab in serum
- Adv : Low cost ,light weight , portable, no expertise technician required for processing

Antibody Detection

- FLA-ABS – Fluorescent leprosy antibody absorption test
- detects M. leprae specific antibodies irrespective of duration and stage of disease
- Sensitivity – 92%
- Specificity – 100%

ELISA

- Detects IgM antibodies to Phenolic glycolipid-1 (PGL-1) antigen of M.leprae

  sensitivity - Lepromatous Leprosy- 95%

  - Tuberculoid Leprosy – 60%

Polymerase chair reaction

- Rapid and high sensitive and high specific test
- Amplifying the M. leprae targeted sequence such as 18kDa, 16srRNA and RLEP with PCR.
- Drug susceptibiliy to rifampicin can be tested.

HistoPathological findings in Leprosy

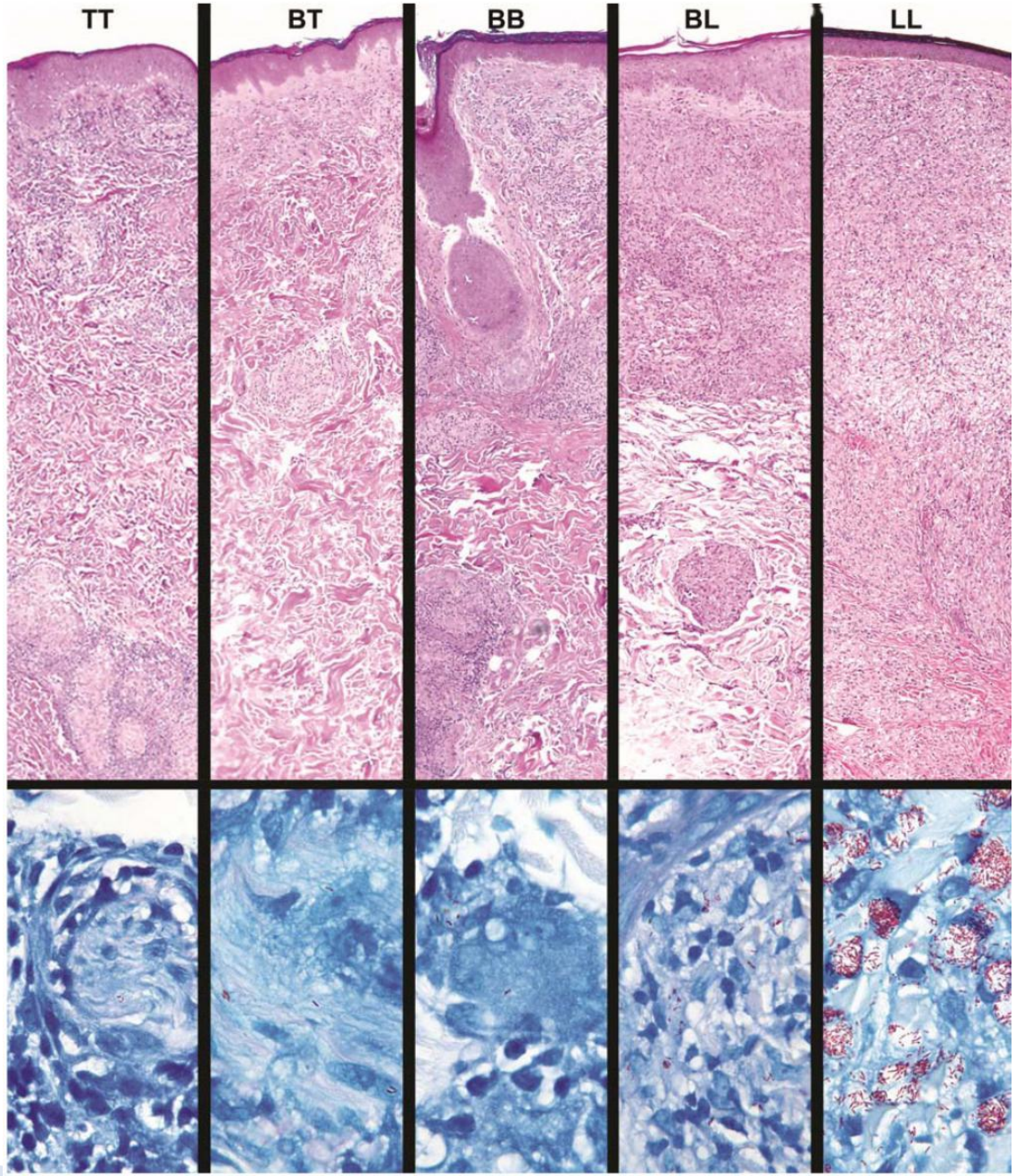
Dr. R.G.W. Pinto
Professor and Head of Department of Pathology GMC
Ex Dean Goa University
Ex Dean GMC
President Asian Society of Cytopathology
Chairman International Affairs Committee
India's Representative to International Academy of Cytology
and EFCS(European Federation of Cytology Societies)

Dr. Cheryl Gonsalves
Junior Resident Pathology

Classification of leprosy

WHO	Ridley-Jopling
Paucibacillary	tuberculoid ("TT"), borderline tuberculoid ("BT")
Multibacillary	midborderline or borderline ("BB")
Multibacillary	borderline lepromatous ("BL"), and lepromatous ("LL")

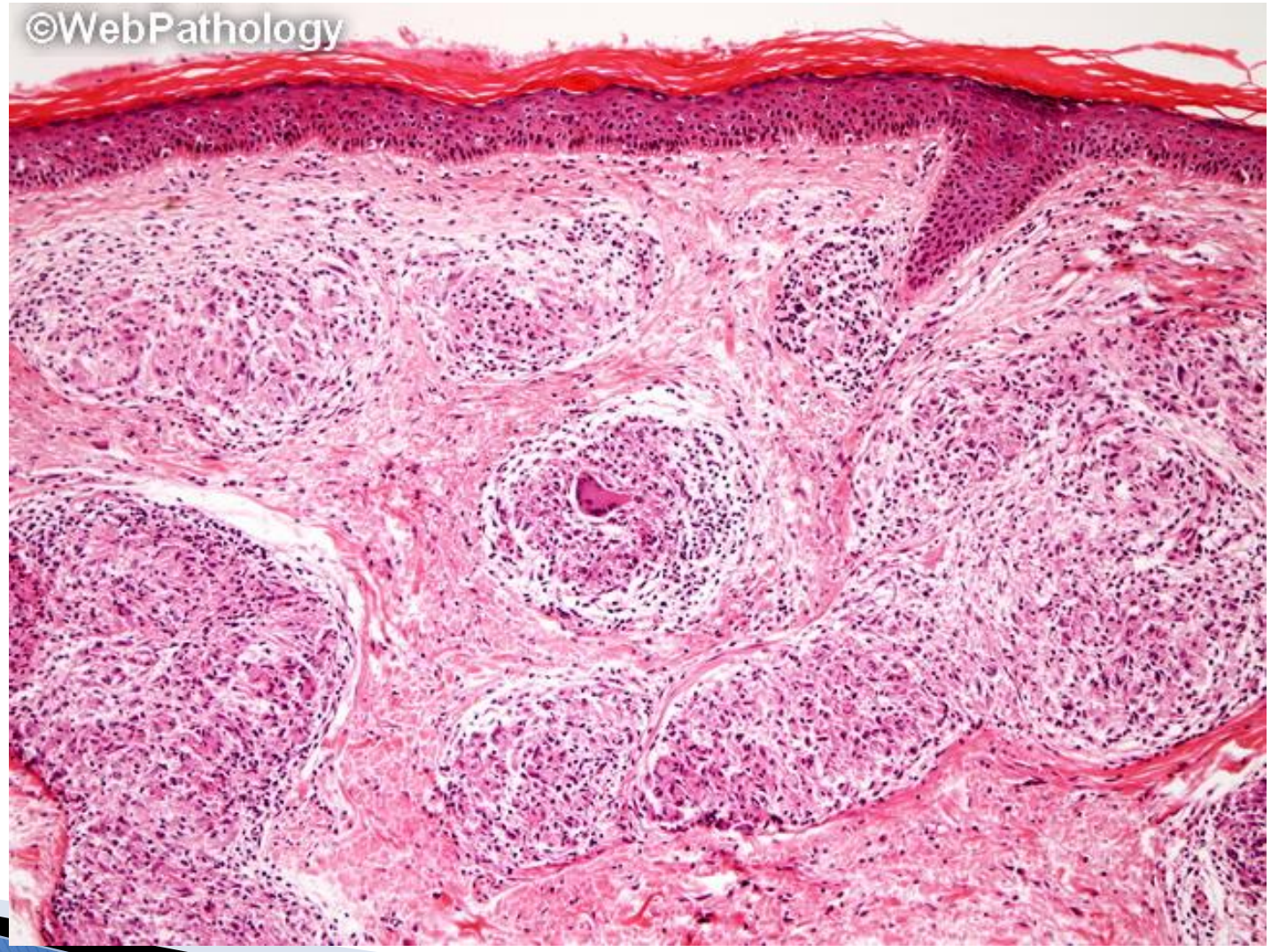
Microscopic findings in Leprosy



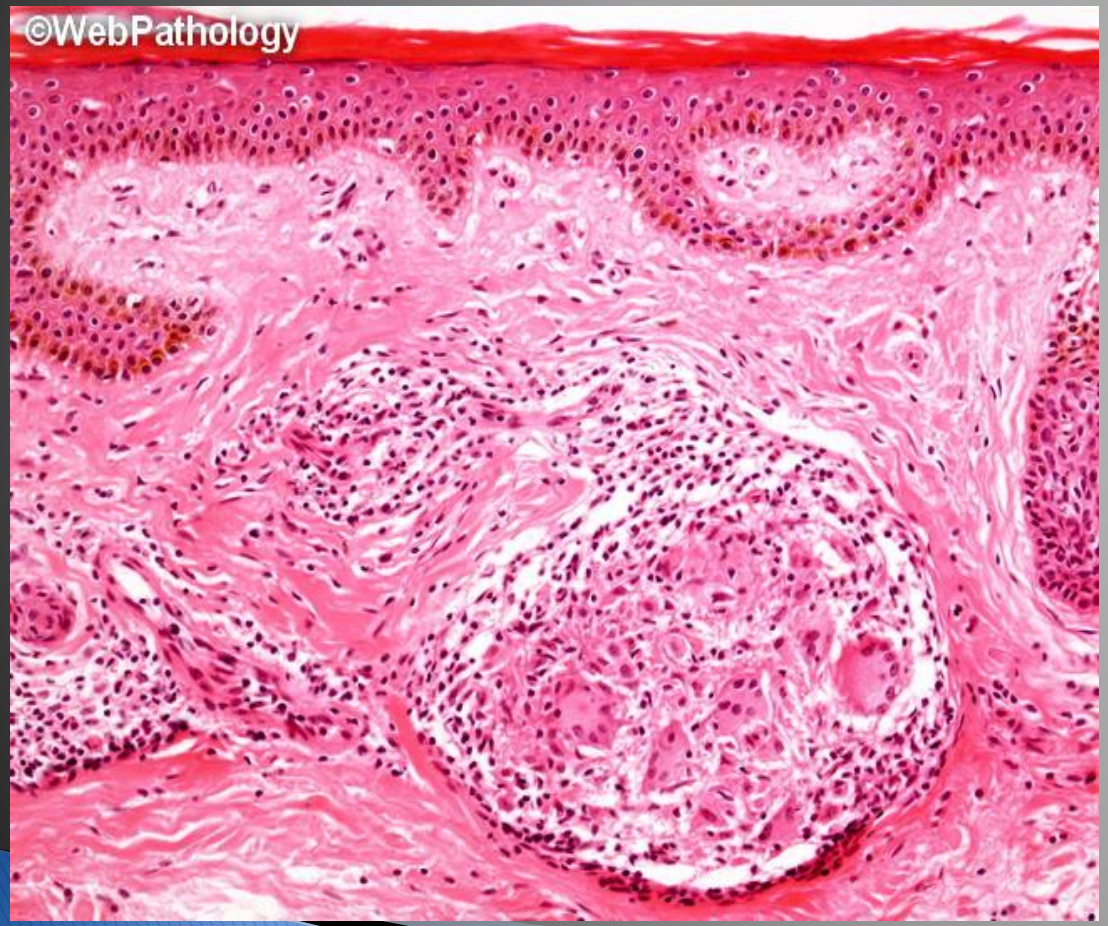
Tuberculoid leprosy

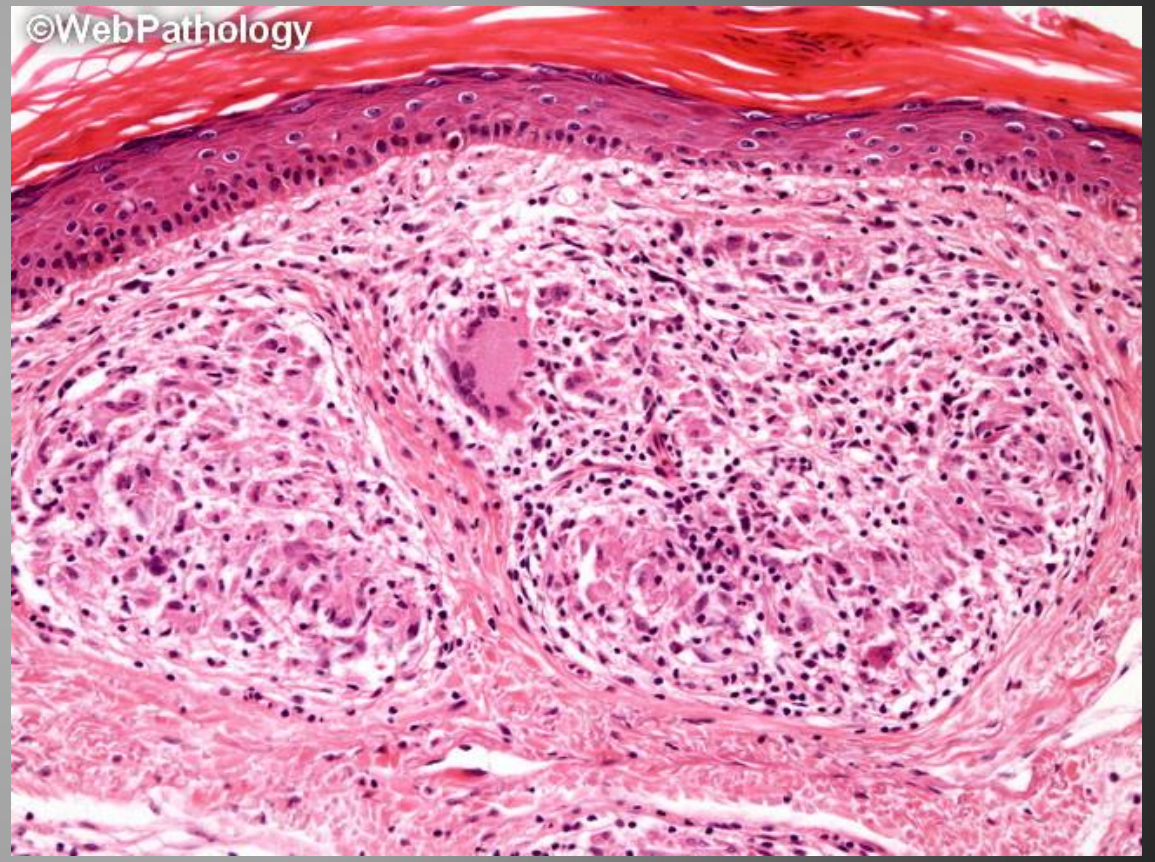
- Well formed, circumscribed and non caseating granulomas.
- Granulomas are composed of epithelioid cells(modified macrophages), langhans giant cells and lymphocytes.
- Absence of Grenz zone: Granulomas in the dermis extend to the basal layer of the epidermis (without a clear/Grenz zone).
- Fite- Faraco stain generally does not show lepra bacillus, hence the name “paucibacillary” leprosy.
- Perineural inflammation by lymphocytes.
- Strong T cell immunity is responsible for granuloma formation without lepra bacilli.

Microscopy



Microscopy

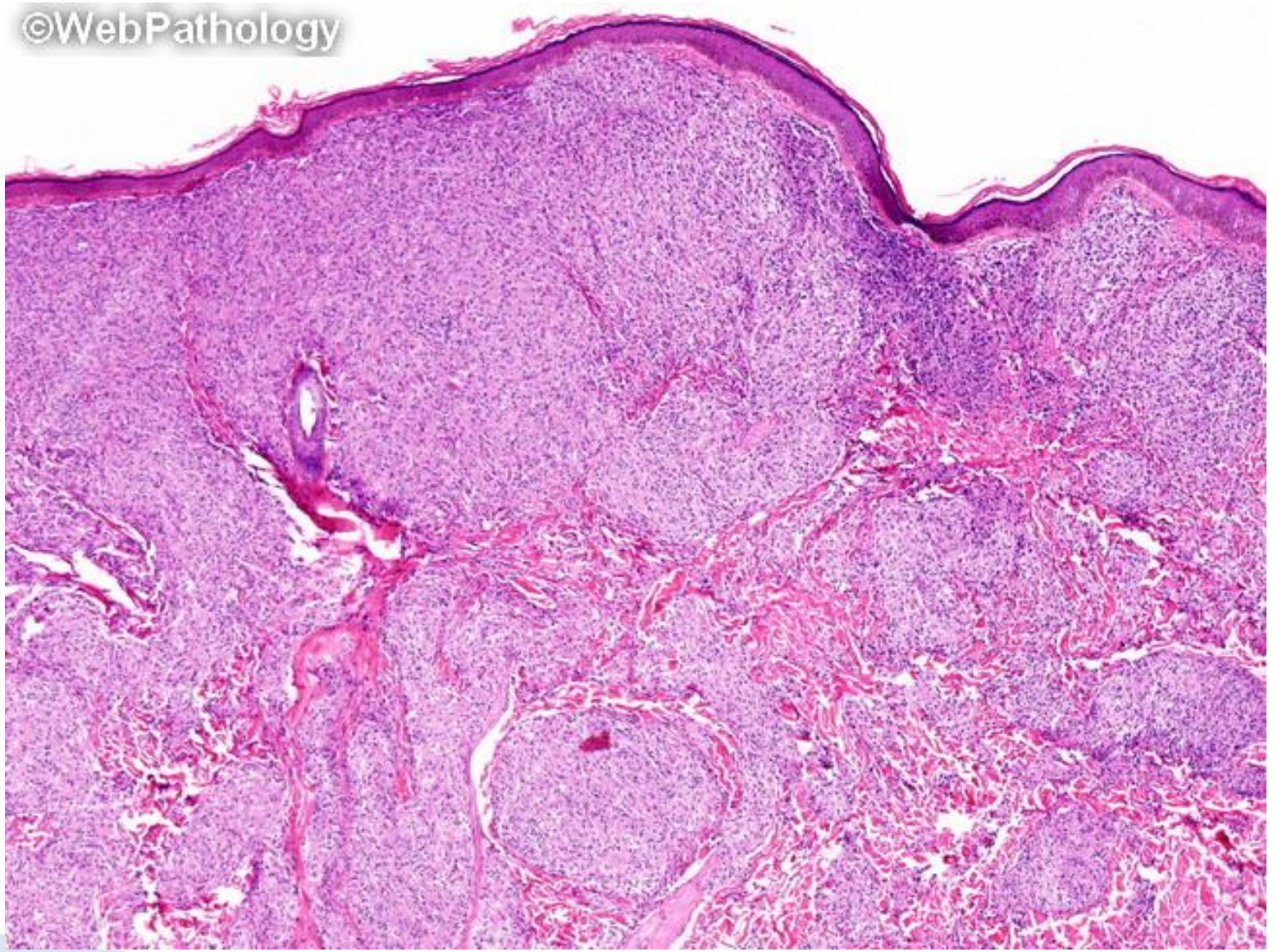




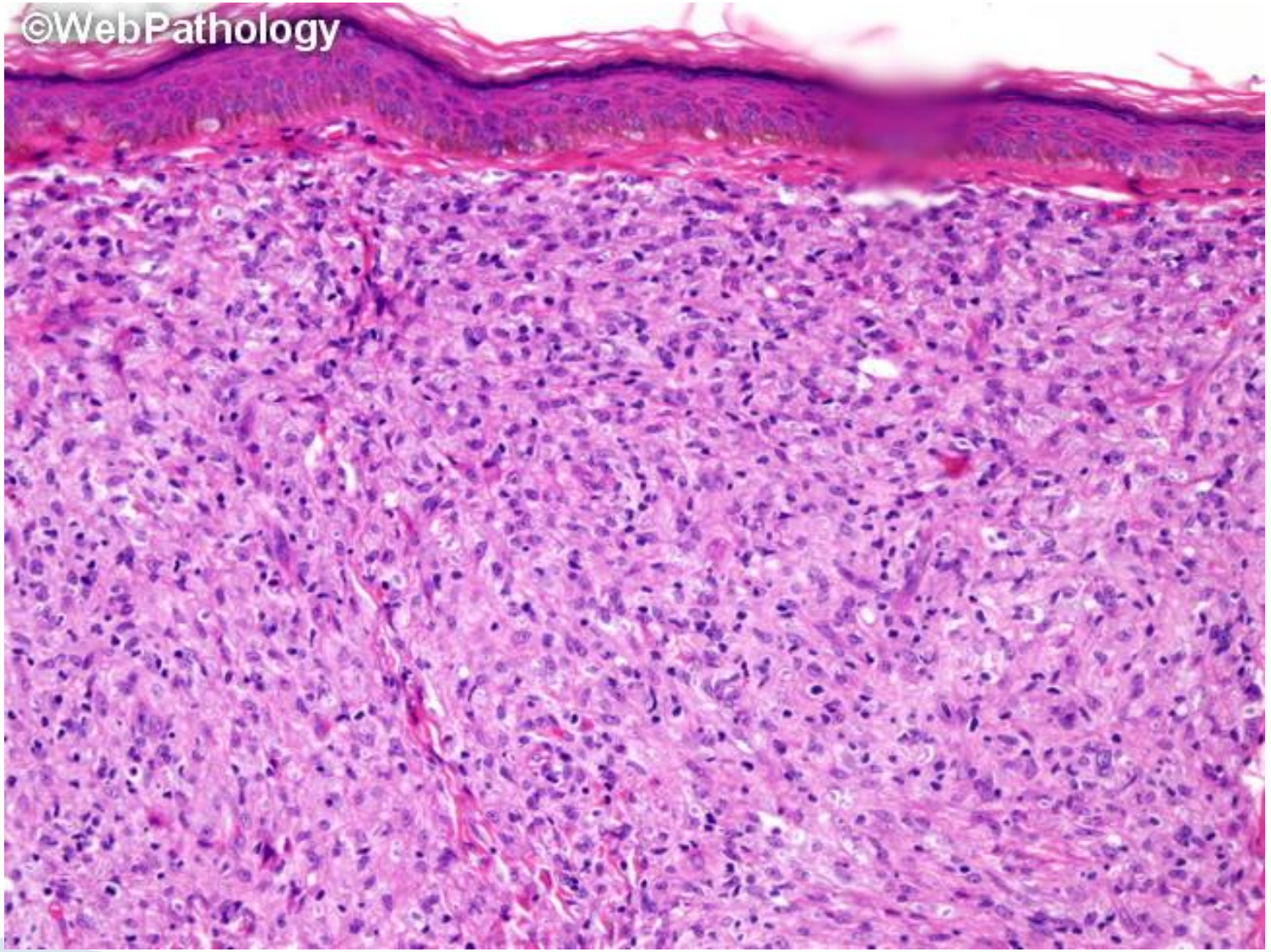
Lepromatous leprosy

- Nodular lesions which contain large aggregates of lipid laden foamy macrophages (lepra cells, Virchow cells), filled with aggregates (globi) of acid fast lepra bacilli.
- Epidermis is thinned and flattened (loss of rete ridges) over the nodules.
- Grenz (clear zone): It is a characteristic, narrow, uninvolved dermis (normal collagen) which separates the epidermis from nodular accumulations of macrophages.
- Fite-Faraco stain shows numerous lepra bacilli within the foamy macrophages. They maybe arranged in a parallel fashion like cigarettes in a pack.
- Due to the presence of numerous bacteria it is also referred to as multibacillary.

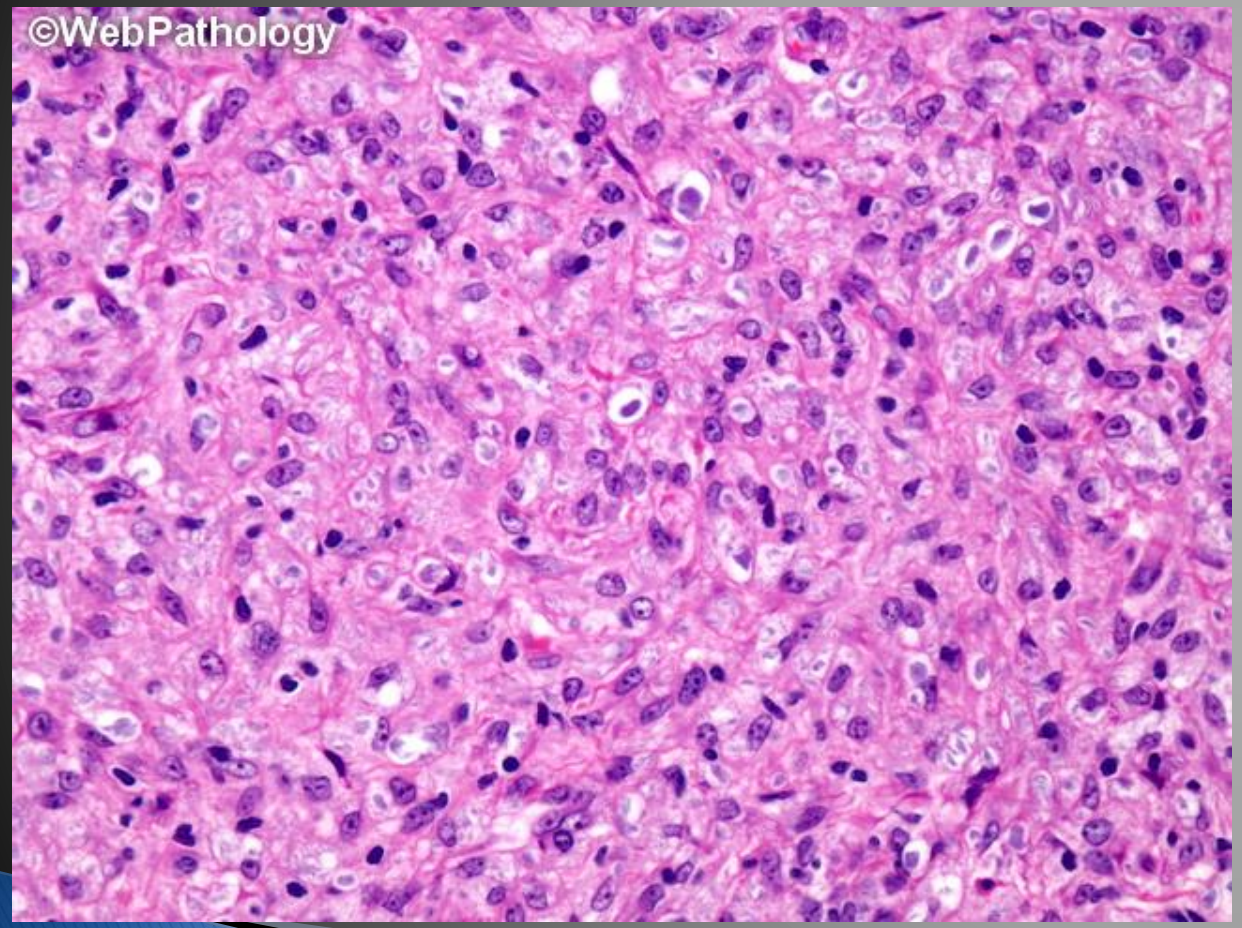
Microscopy

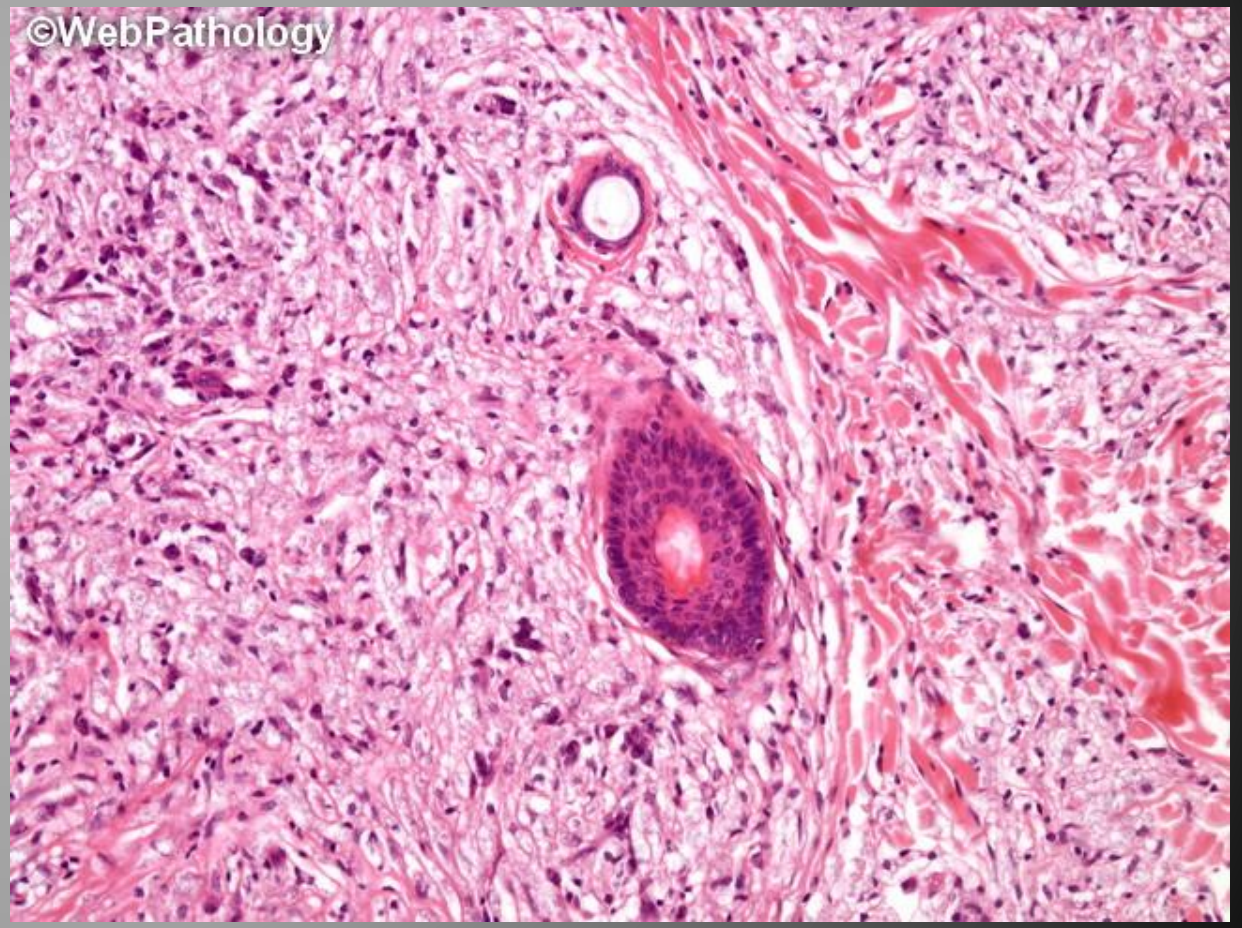


Microscopy

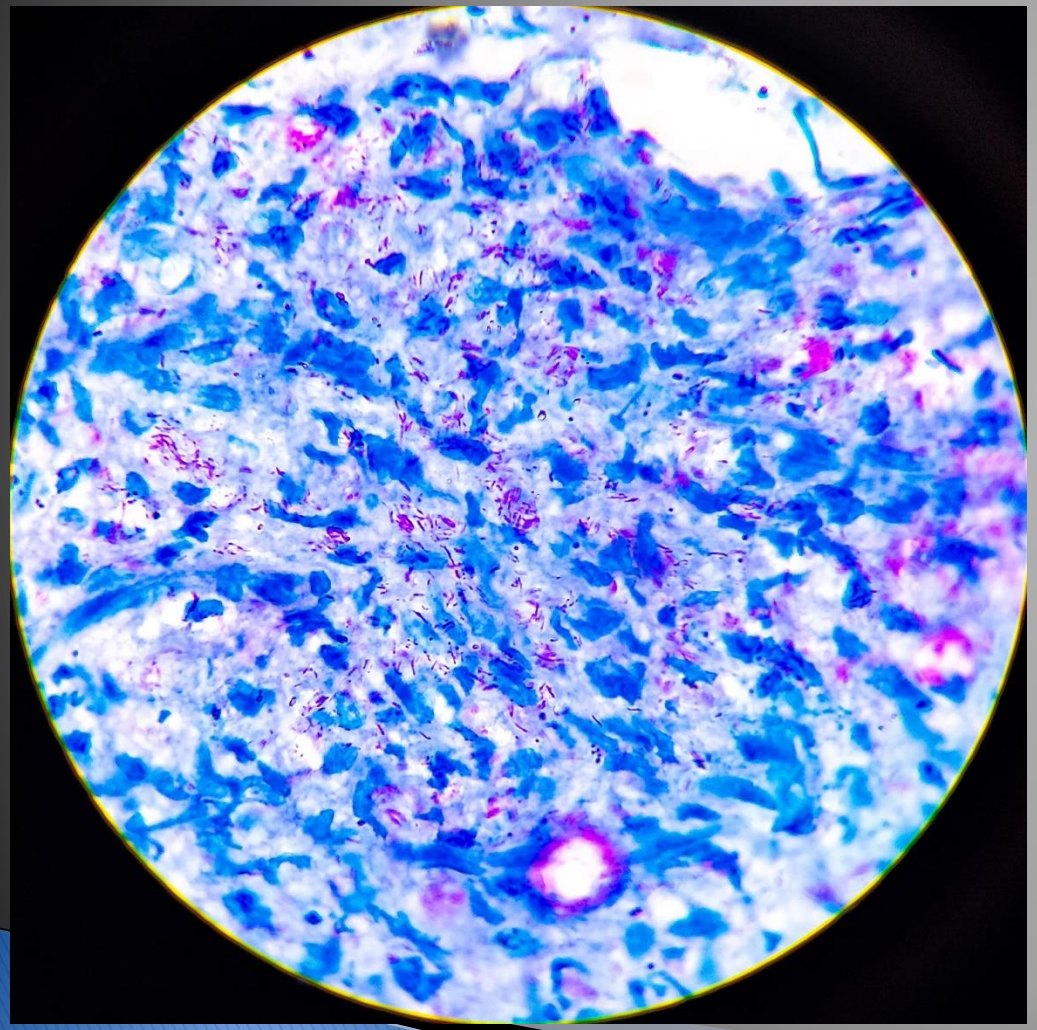


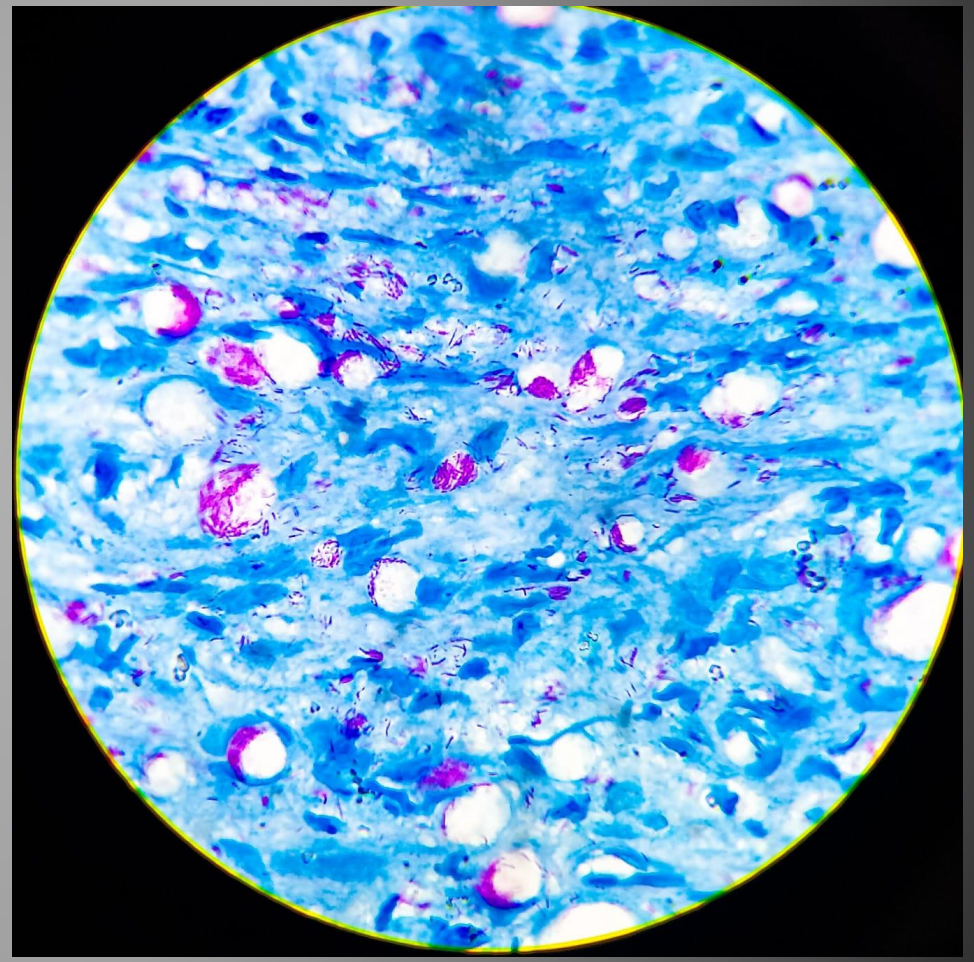
Microscopy





Acid Fast Staining





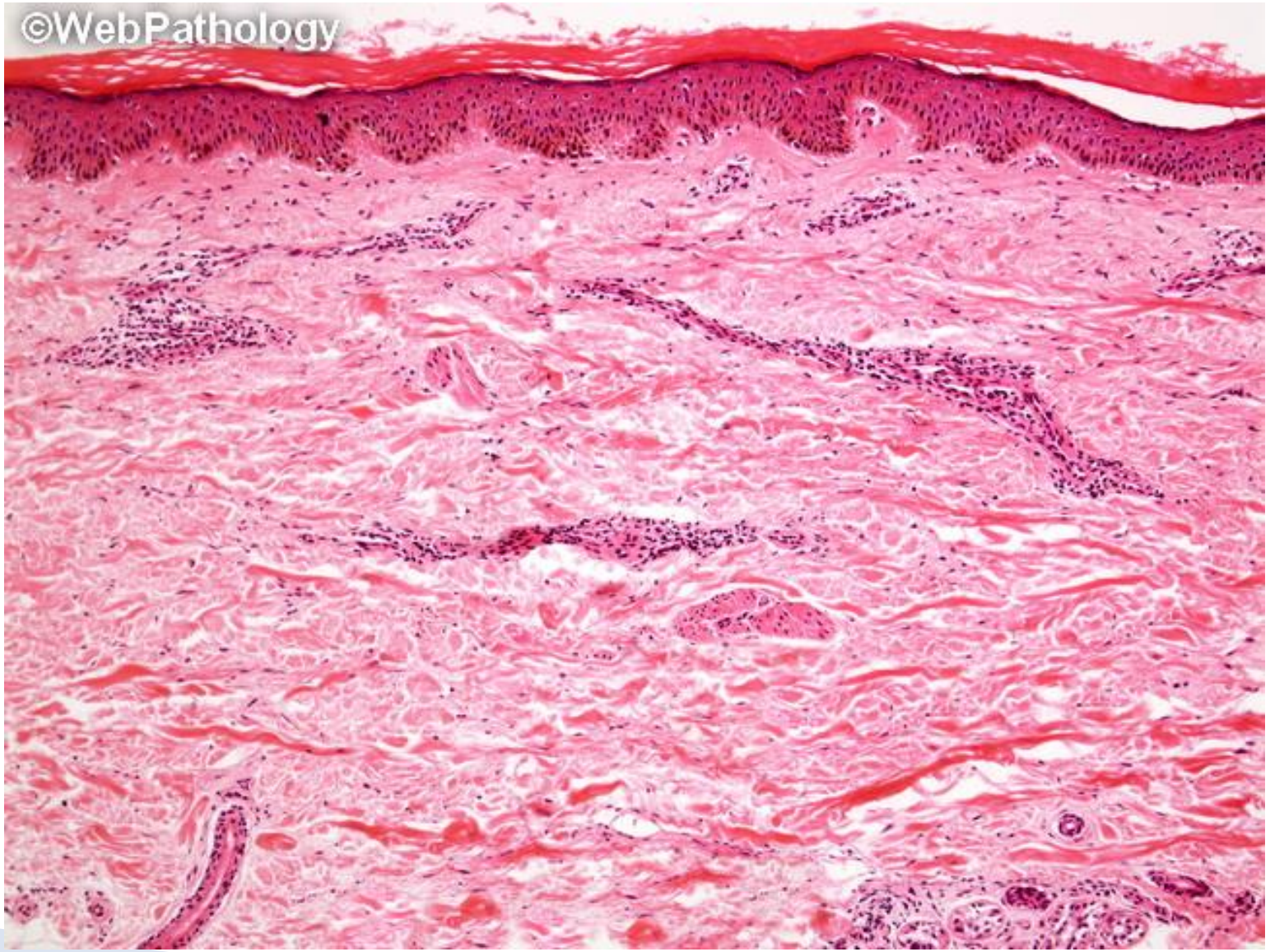
Borderline leprosy

- 1. Borderline Tuberculoid (BT)
- 2. Borderline Lepromatous (BL)
- 3. Mid- Borderline (BB)

Borderline Tuberculoid (BT)

- It shows epithelioid cells and numerous lymphocytes with a narrow clear subepidermal zone.
- Lepra bacilli are few and found in nerves.

Microscopy



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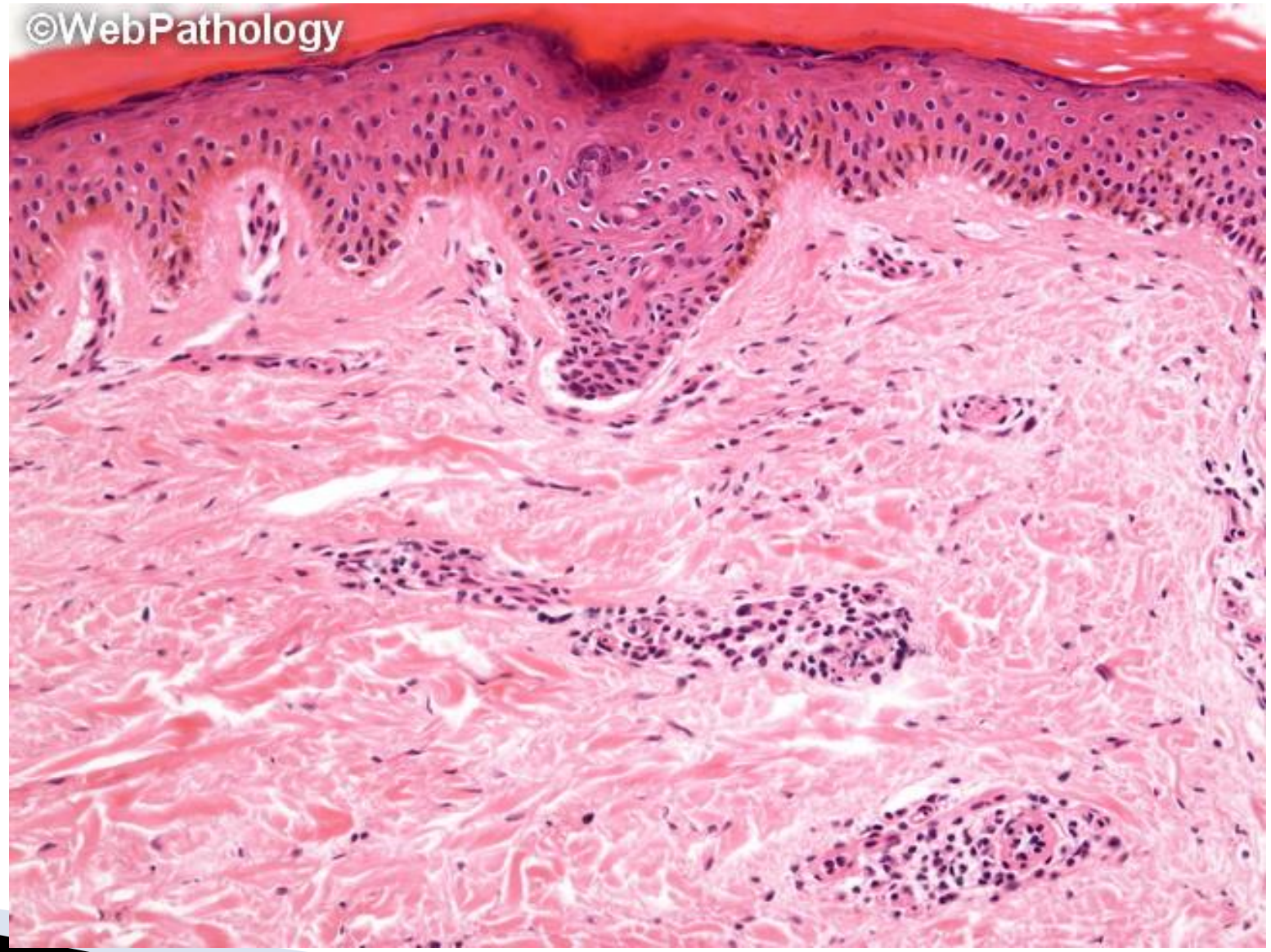
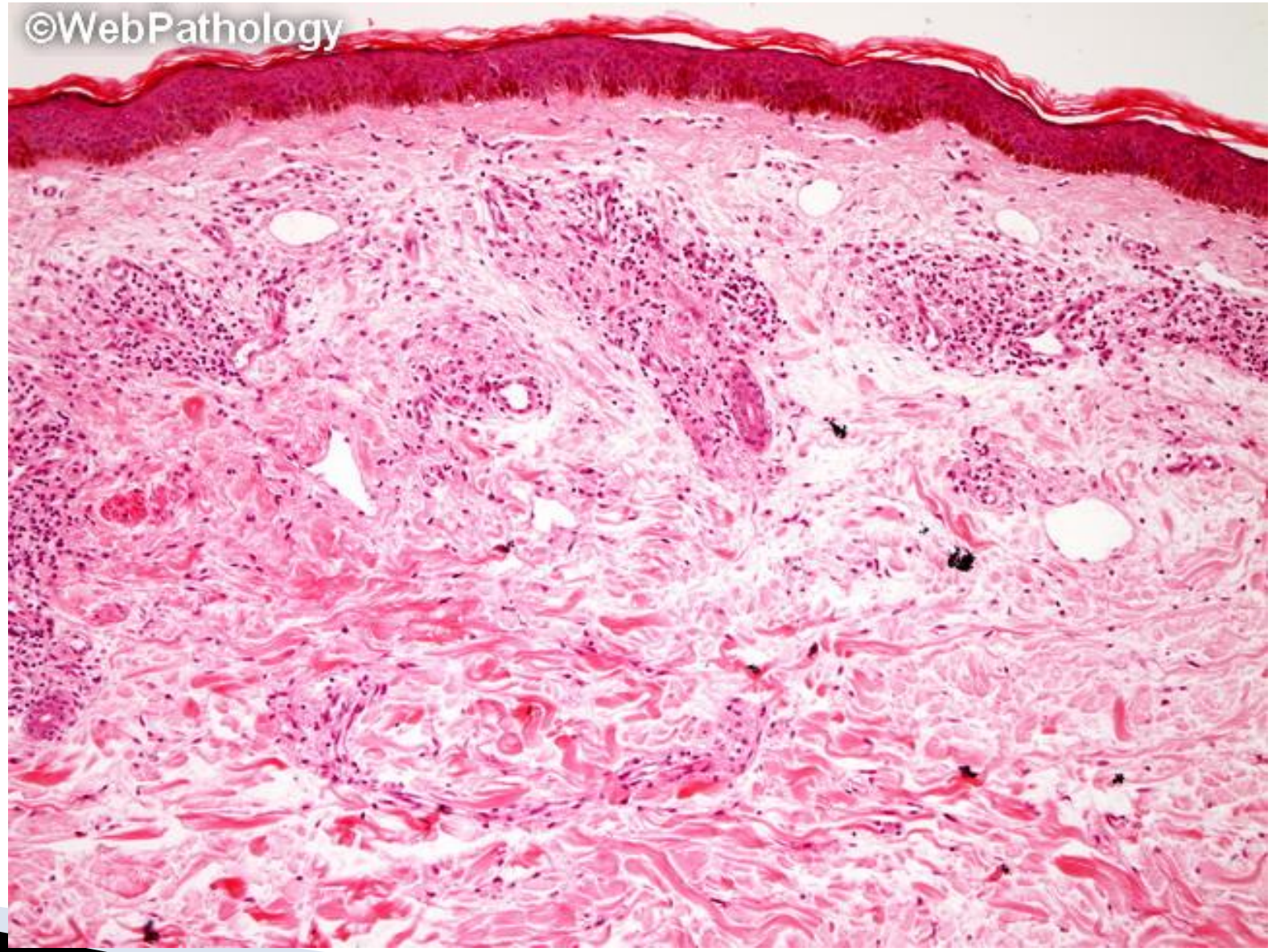


Borderline Lepromatous (BL)

- It shows predominantly histiocytes, few epithelioid cells and lymphocytes.
- Numerous lepra bacilli are found.

Microscopy



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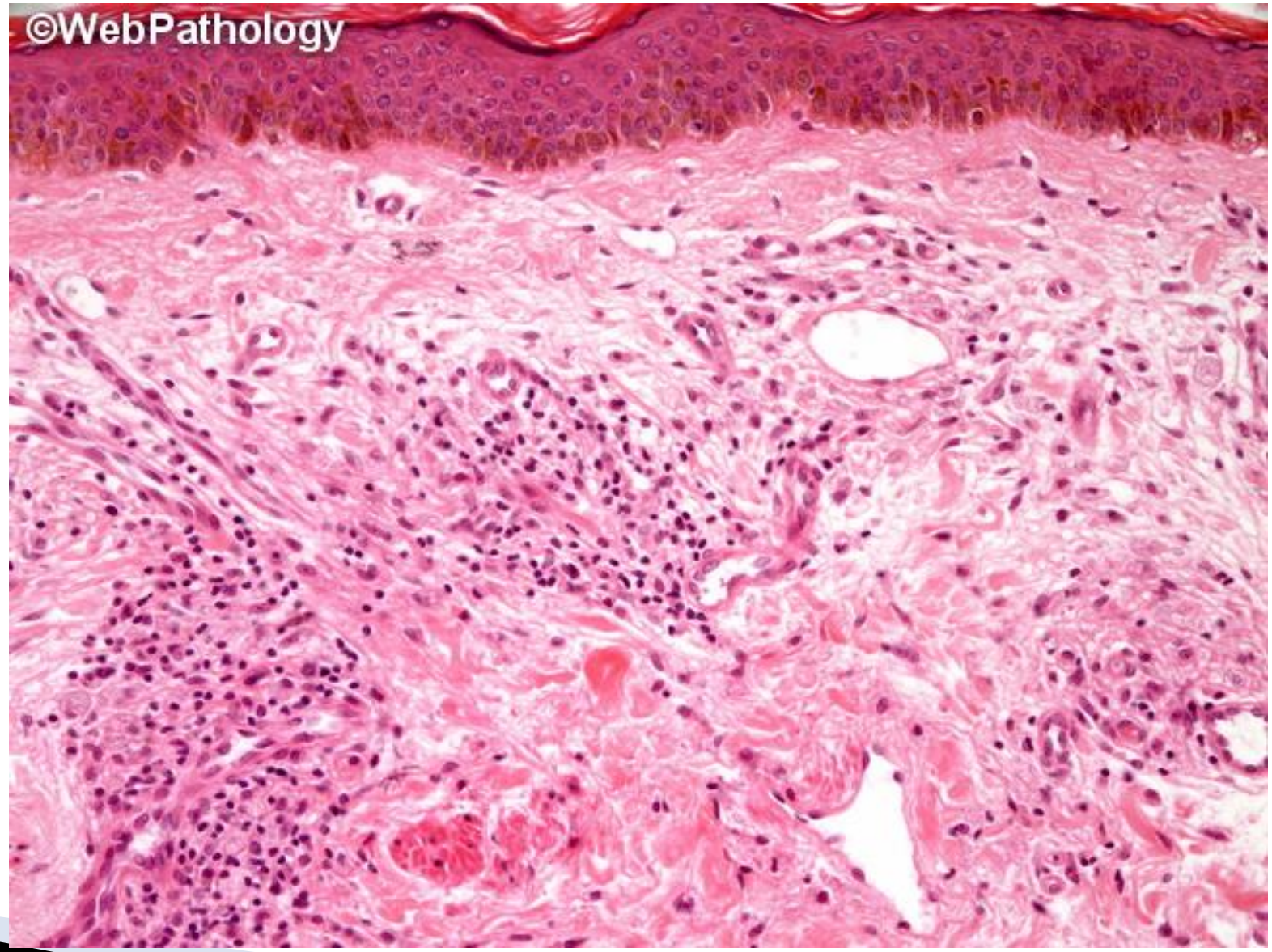
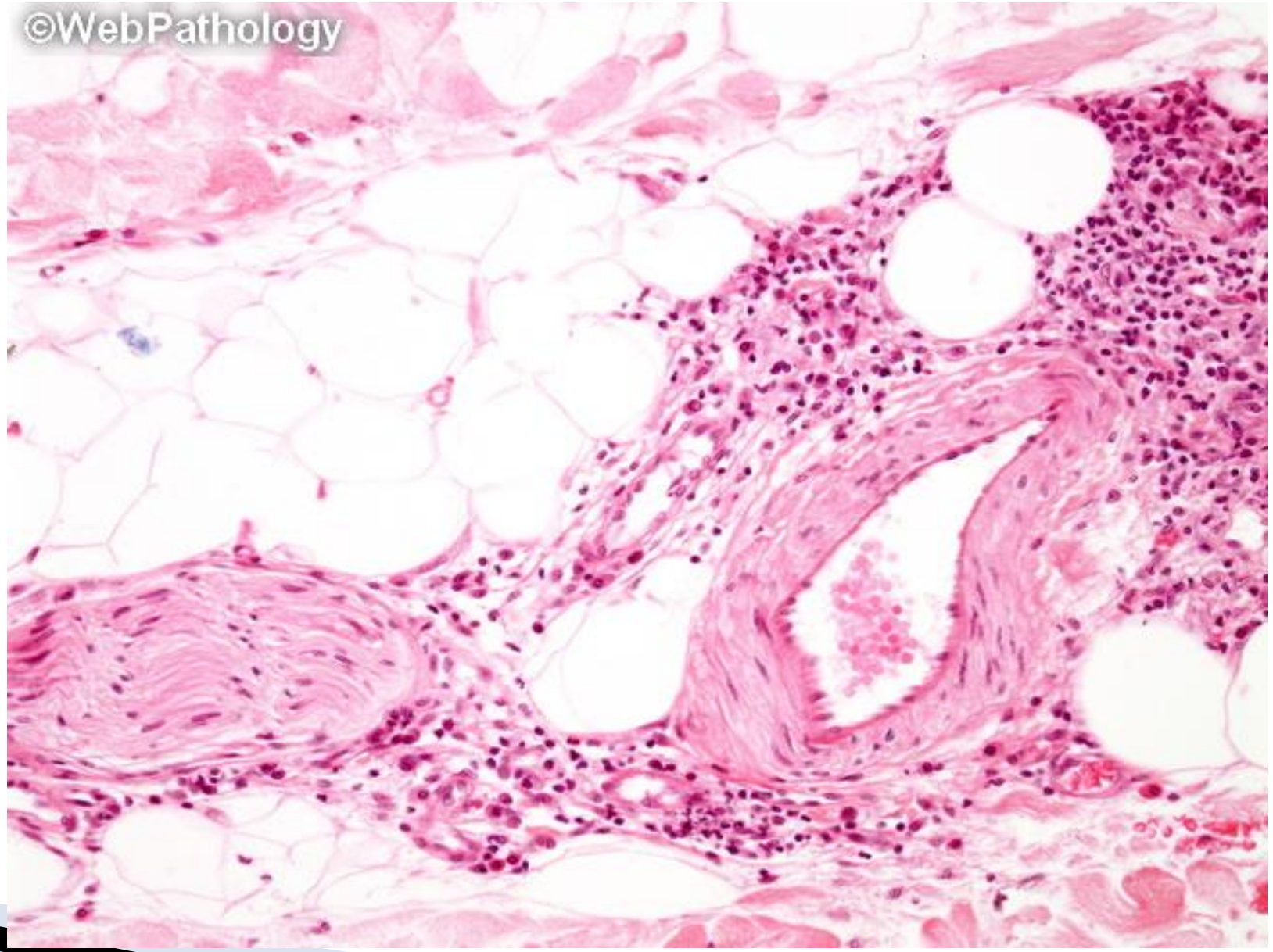


Microscopy



Mid- Borderline (BB) or Dimorphic form

- It shows sheets of epithelioid cells without any giant cells.
- Few lymphocytes are found in the perineurium.
- Lepra bacilli are seen mostly in nerves.

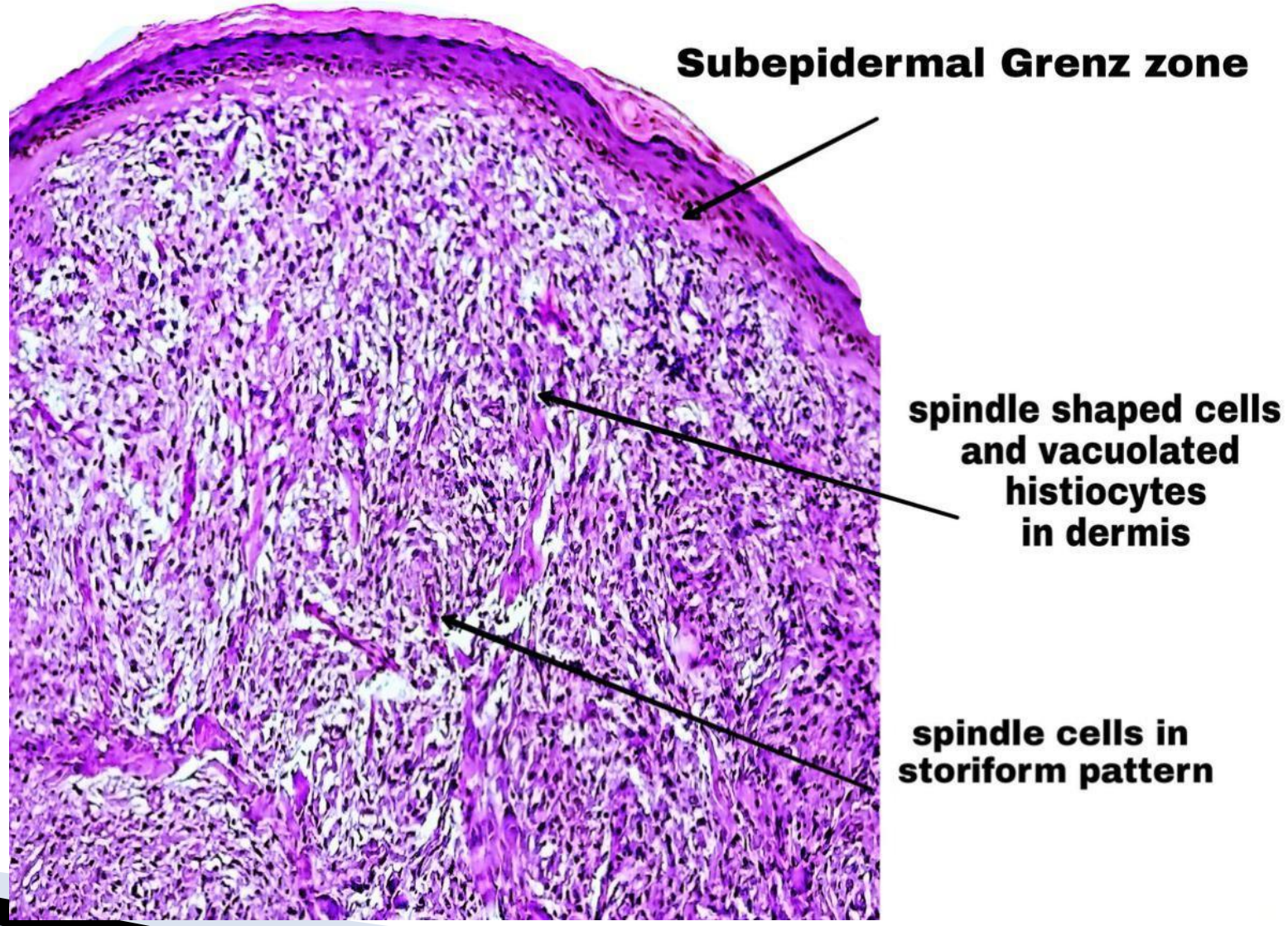
Indeterminate leprosy

- Microscopically, features are non specific and few findings help in suspecting leprosy.
- These include:
- 1. Local infiltration of lymphocytes or mononuclear cells surrounding the skin adnexa (eg. Hair follicles and sweat glands) or around blood vessels.
- 2. Involvement of nerve (if seen strongly favours the diagnosis)
- 3. Finding of lepra bacilli (which confirms the diagnosis).

Histoid leprosy

- It shows spindle cell proliferation with storiform pattern suggestive of fibrous histiocytoma.

Microscopy


Subepidermal Grenz zone
spindle shaped cells and vacuolated histiocytes in dermis
spindle cells in storiform pattern