

Mycobacterial infections

Bacterial persistence, host immunity, granulomatous inflammation and tissue injury

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Explain why mycobacteria are acid-fast and persist intracellularly.
- Trace the Th1–macrophage response from inhalation to granuloma.
- Recognize primary, postprimary and disseminated tuberculosis.
- Select investigations for active versus latent tuberculosis.
- Differentiate tuberculosis, NTM disease and the leprosy spectrum.

Three major mycobacterial disease groups

An acid-fast genus; Markedly different reservoirs, host responses and organ distributions.

Tuberculosis

M. Tuberculosis complex; Human
pulmonary/systemic infection



Nontuberculous mycobacteria

Environmental species;
Opportunistic pulmonary and
disseminated disease



Leprosy

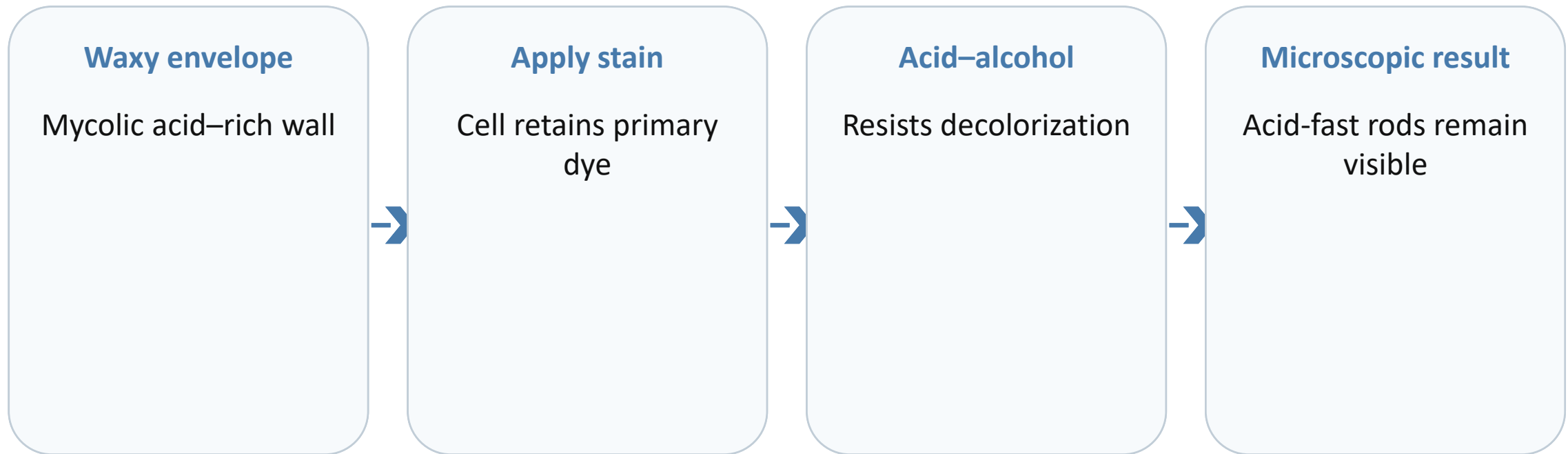
M. Leprae / M. Lepromatosis;
Skin and peripheral nerves

Mycobacteria: Structural identity

- Slender aerobic rods that may form straight or branching chains.
- Waxy cell envelope is enriched in unusual glycolipids and lipids.
- Mycolic acids underlie retention of acid-fast stains despite acid–alcohol decolorization.
- They are weakly gram-positive; Routine Gram stain is not their defining laboratory feature.

Why acid-fast staining works

This is a physicochemical staining property, not a species-level identification test.



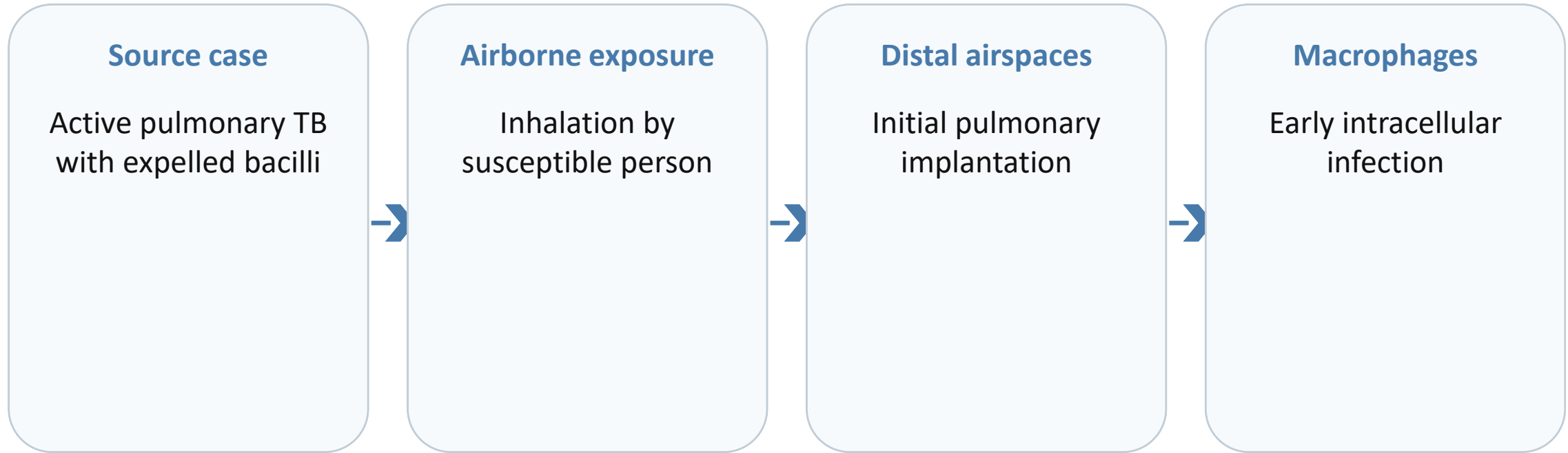
Acid-fastness is not species identification

- A positive acid-fast smear demonstrates acid-fast organisms in the sampled material.
- Different mycobacterial species require further microbiologic or molecular identification.
- Culture and molecular testing establish organism identity and inform susceptibility.
- A negative smear cannot reliably exclude disease in low-burden or immunocompromised cases.

Tuberculosis: Core definition

- Chronic pulmonary and systemic infection, usually caused by *M. Tuberculosis*.
- In humans, infectious pulmonary cases release bacilli in sputum.
- Spread occurs mainly through airborne organisms from people with active disease.
- The clinical outcome is shaped by host cell-mediated immunity.

Airborne transmission to alveolar macrophages



M. Bovis: A distinct ingestion route

- Unpasteurized milk from infected cattle can transmit M. Bovis.
- Oropharyngeal and intestinal tuberculosis may follow contaminated milk exposure.
- This route is uncommon where milk pasteurization is routine.
- It remains relevant where bovine tuberculosis and unpasteurized dairy coexist.

Contexts favoring tuberculosis transmission

- Poverty and crowded living conditions facilitate exposure.
- Prisons, homeless shelters and long-term care settings are relevant examples.
- Transmission risk depends on exposure to infectious individuals.
- Host susceptibility additionally determines progression after acquisition.

Conditions associated with progression

These factors raise susceptibility; They do not prove active tuberculosis.

Immune-related

- HIV infection / advanced immunodeficiency
- Glucocorticoids or transplant immunosuppression
- Tumor necrosis factor inhibitors

Other clinical contexts

- Diabetes mellitus and chronic renal failure
- Silicosis or other chronic lung disease
- Malnutrition, alcohol use and debilitating illness

Infection is not the same as active disease

Latent infection

- Immune response to mycobacterial antigens
- No clinical evidence of active tuberculosis
- Viable bacilli may persist for decades

Active tuberculosis

- Organism-associated tissue disease
- Pulmonary or extrapulmonary manifestations
- May be transmissible when bacilli enter airways

Outcomes after first exposure

Primary infection

Bacilli proliferate
before adaptive
response



Immune containment

Th1-activated
macrophages restrict
replication



Persistent focus

Fibrocalcific lesion
may harbor viable
bacilli



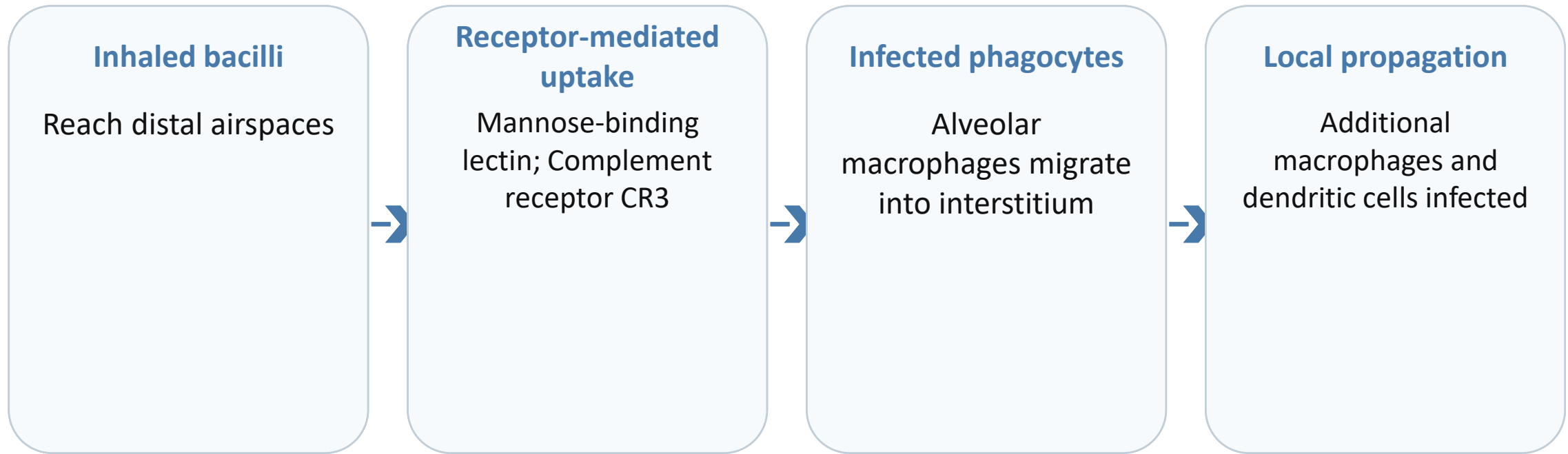
Later reactivation

Loss of host
resistance permits
disease

Containment and damage are linked

- Th1 cells activate macrophages to control M. Tuberculosis.
- The same cellular response produces granulomas and caseous necrosis.
- Effective containment often leaves limited residual tissue damage.
- Dysregulated or sustained inflammation may produce cavities and impaired lung function.

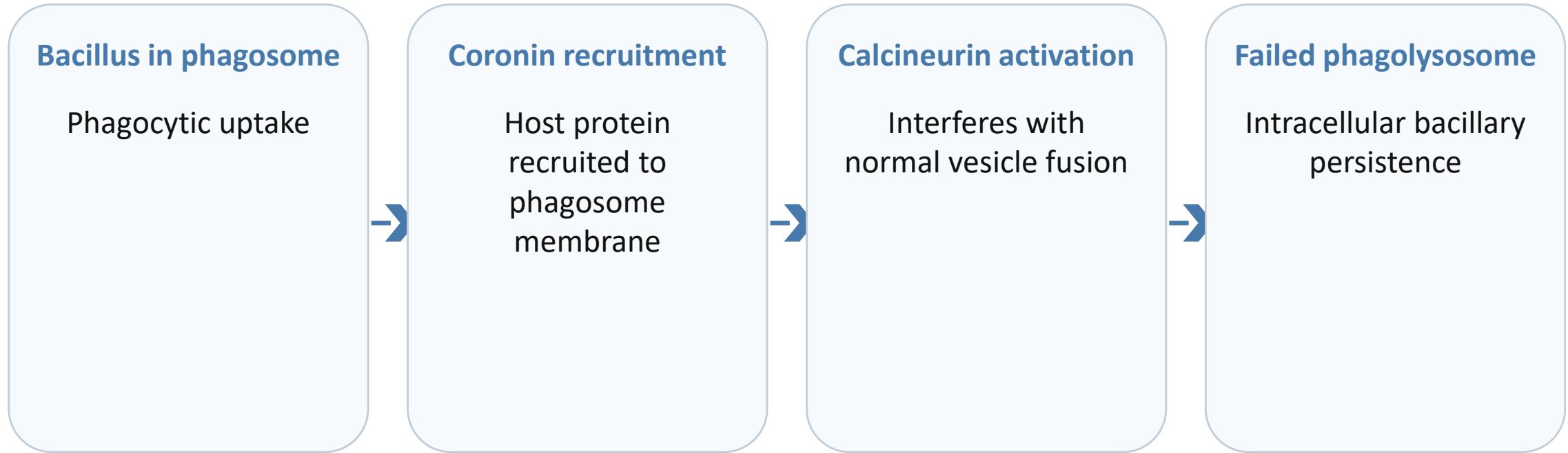
Phase 1: Bacillary entry into macrophages



Macrophage uptake does not ensure microbial killing

- M. Tuberculosis enters phagocytic vesicles within macrophages.
- It interferes with phagosomal maturation and lysosomal fusion.
- Bacilli thereby avoid the destructive environment of an effective phagolysosome.
- This intracellular refuge permits replication before acquired immunity develops.

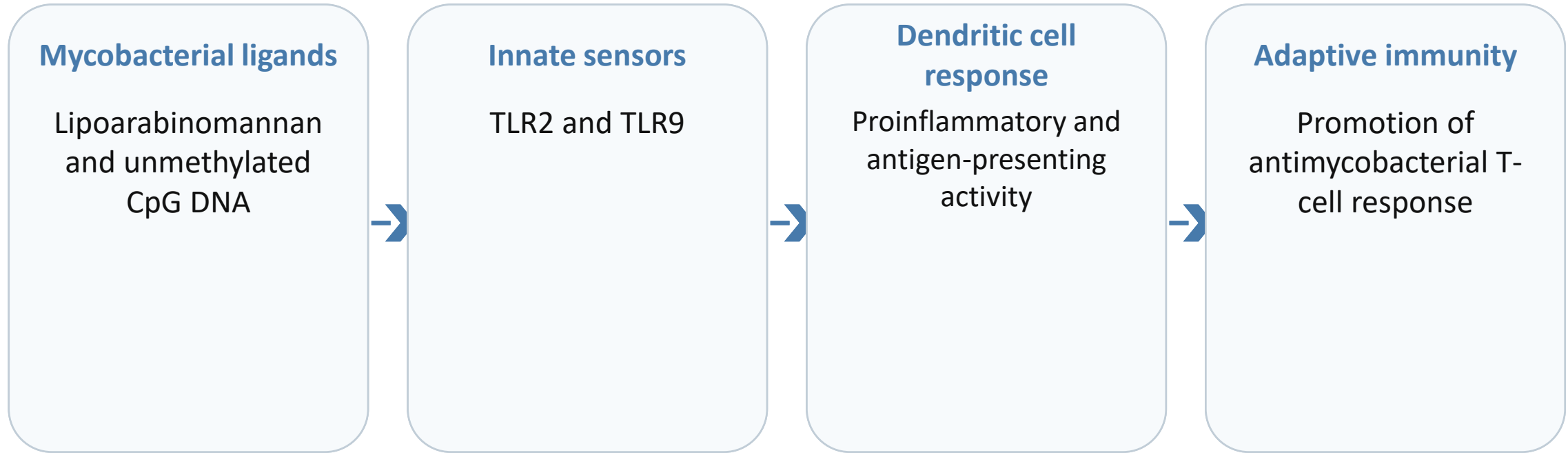
Phagosome–lysosome blockade



The initial weeks may be clinically silent

- Before effective T-cell immunity, bacilli multiply within alveolar macrophages.
- Early transient bacteremia can seed multiple distant sites.
- Most immunocompetent hosts are asymptomatic or experience mild flu-like symptoms.
- Subsequent immune containment usually prevents clinically overt dissemination.

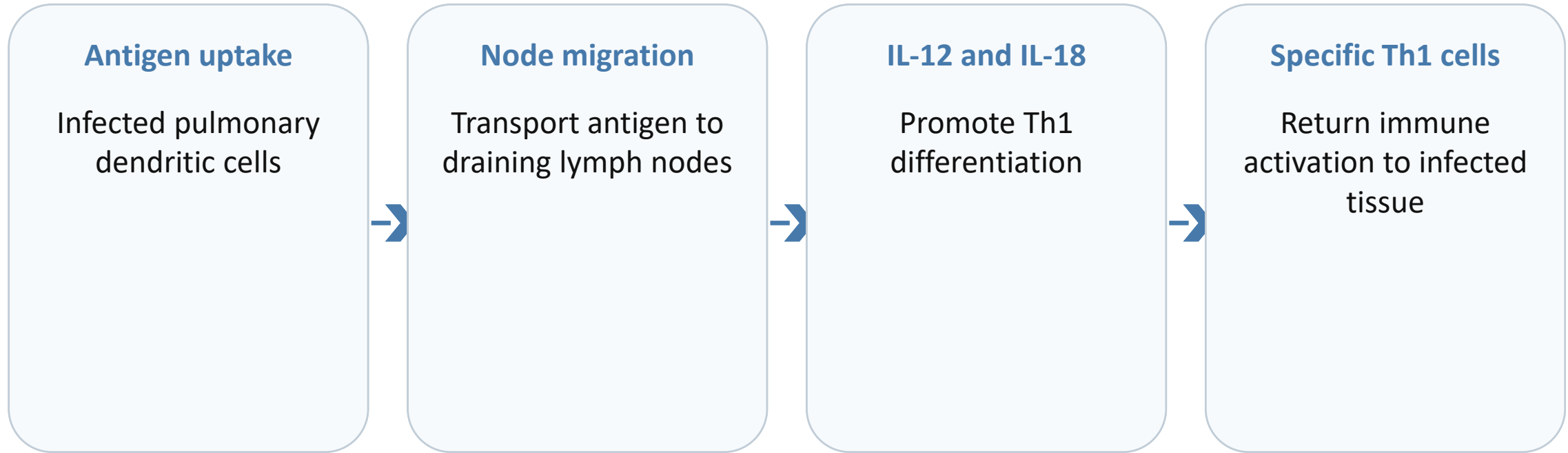
Innate recognition of mycobacteria



Neutrophils are not uniformly protective

- M. Tuberculosis can infect neutrophils and resist their killing.
- After intracellular replication, infection can lead to neutrophil death.
- The resulting inflammation is distinct from the later organized Th1 granuloma.
- In NTM infection, neutrophil products may worsen preexisting lung injury.

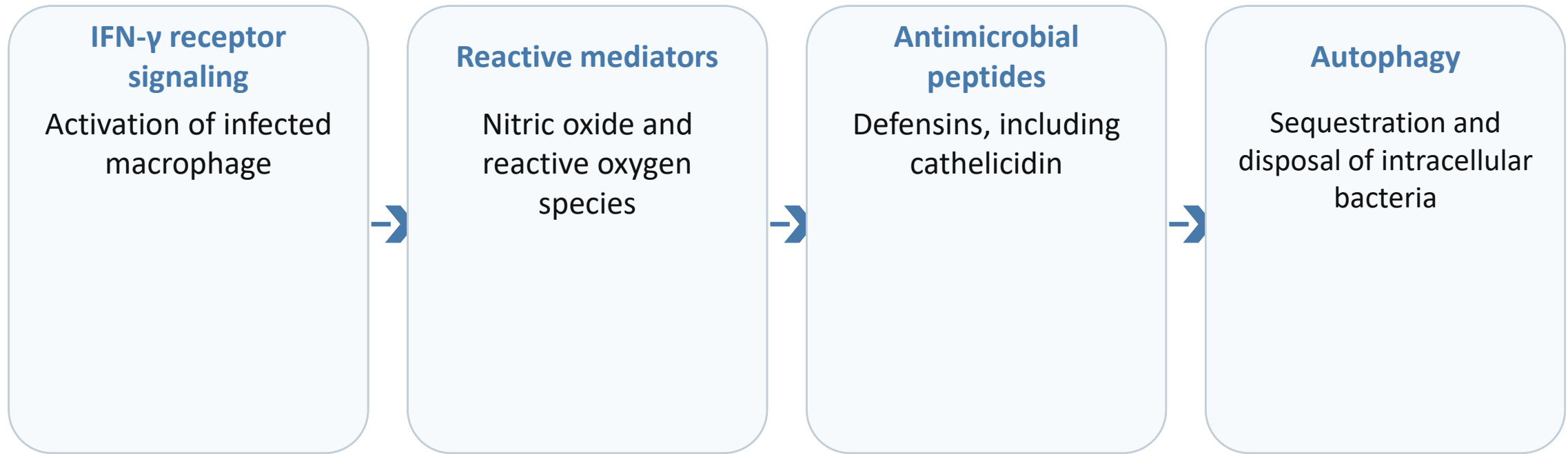
Dendritic cells initiate the Th1 response



Th1 immunity becomes effective after a delay

- In a previously unsensitized host, the Th1 response emerges at about 3 weeks.
- Antigen-presenting cells produce IL-12 and IL-18.
- Th1 cells secrete interferon- γ (IFN- γ).
- IFN- γ is the critical activator of antimycobacterial macrophage effector functions.

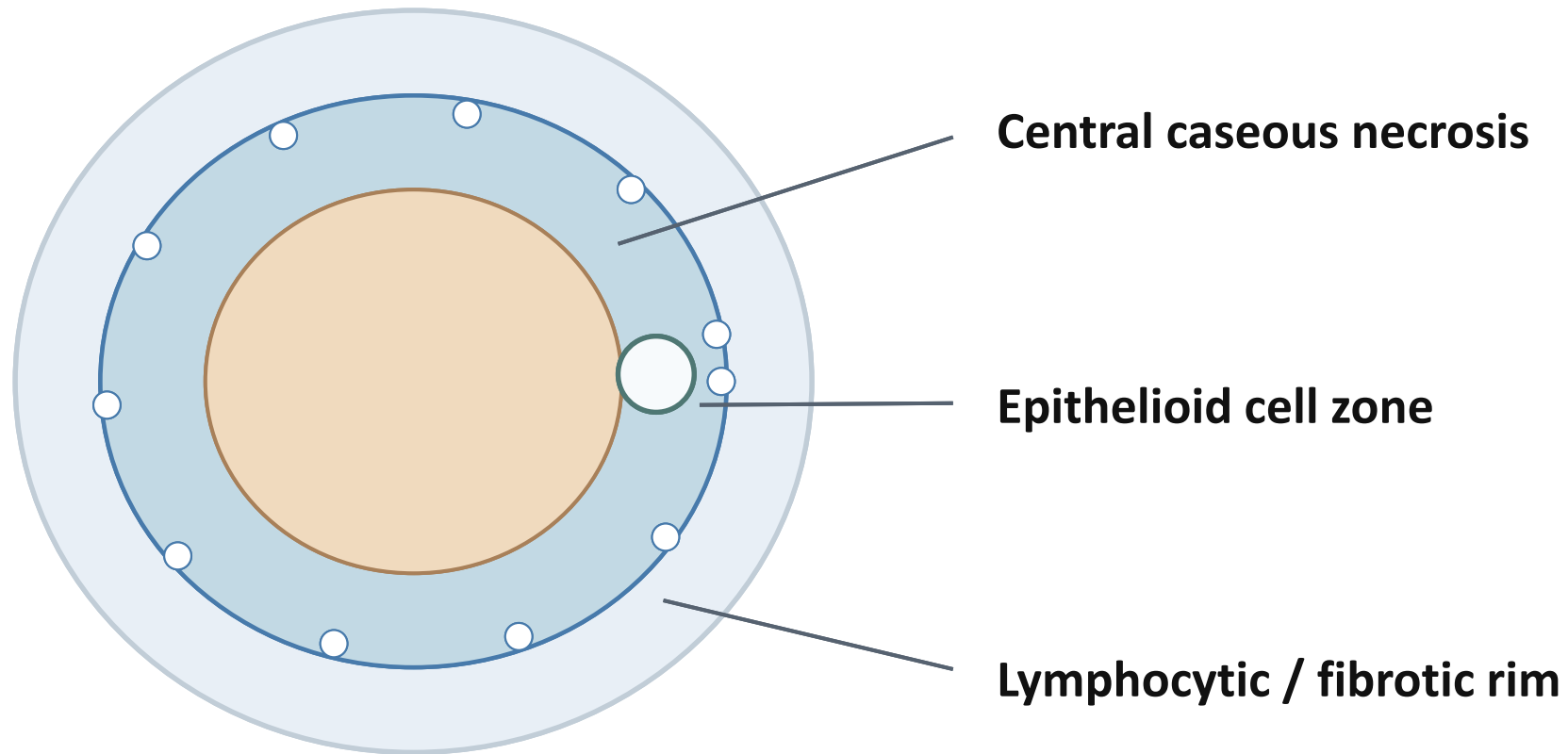
IFN- γ : Macrophage killing mechanisms



Activated macrophages build granulomas

- IFN- γ -stimulated macrophages become epithelioid histiocytes.
- Epithelioid histiocytes aggregate into organized cellular foci.
- Some macrophages fuse to form multinucleated giant cells.
- Lymphocytes and fibrosis develop around the lesion over time.

Granuloma: An organized cellular barrier

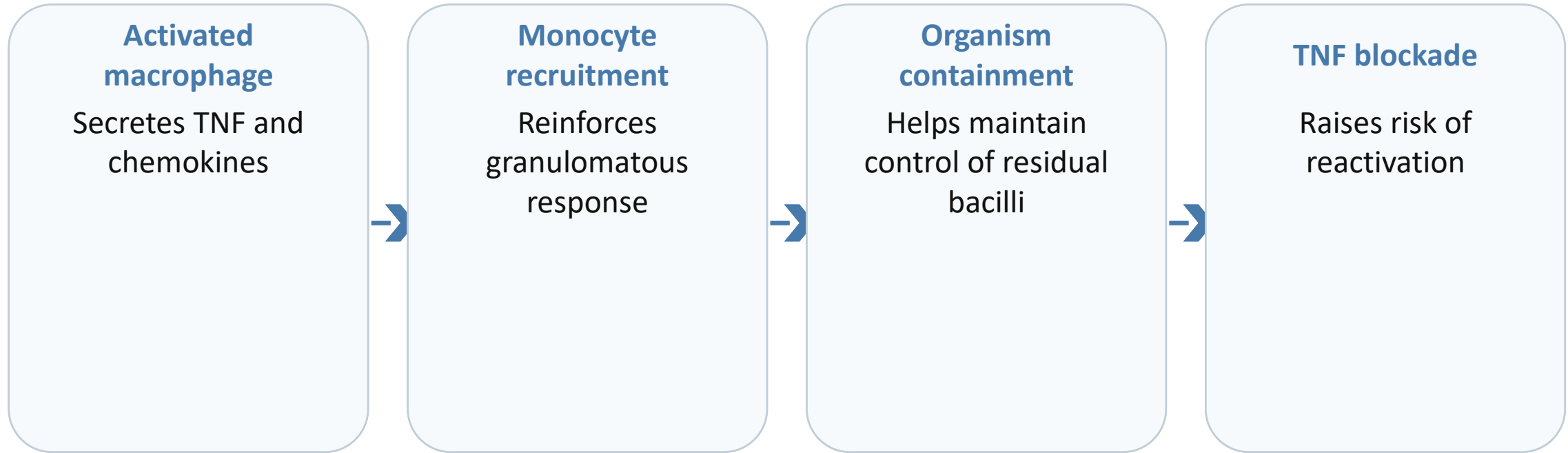


Schematic, not histology

Caseation reflects immune-mediated injury

- Granuloma formation contains organisms but does not completely eliminate them.
- Ongoing cellular inflammation may generate central caseous necrosis.
- Necrotic tissue can subsequently liquefy and communicate with a bronchus.
- Cavity formation promotes further airway spread of infectious bacilli.

Tumor necrosis factor sustains containment



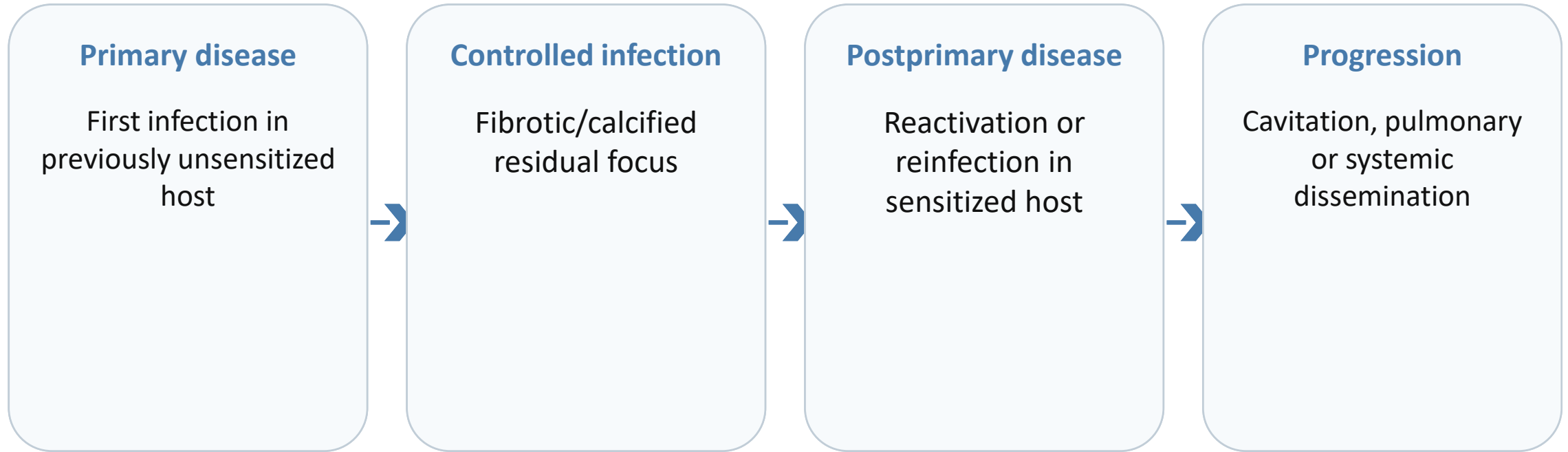
Why immunosuppression changes morphology

- Impaired Th1 signaling weakens activation of bactericidal macrophages.
- Bacillary proliferation can become extensive while granulomas are poorly formed.
- Tissue sections may contain numerous bacilli even without classic tubercles.
- Extrapulmonary and disseminated infection become more frequent.

Mendelian susceptibility to mycobacteria

- Rare inherited defects impair IL-12 / IFN- γ host-defense pathways.
- Examples include loss of IL-12 receptor β 1 function.
- Affected patients may develop severe tuberculosis.
- Even normally low-virulence mycobacteria or BCG vaccine strains can cause disease.

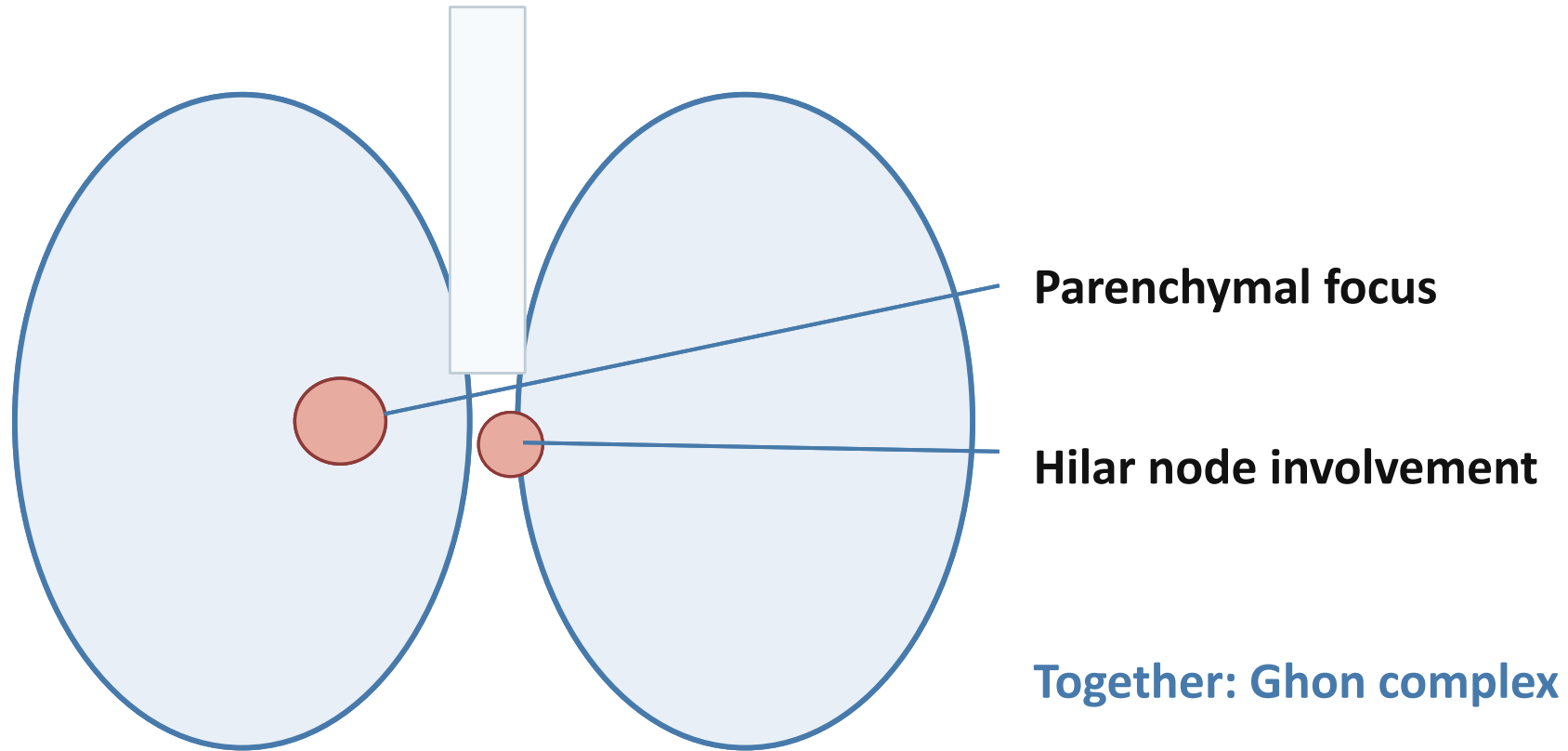
A spectrum of pulmonary tuberculosis



Primary tuberculosis begins subpleurally

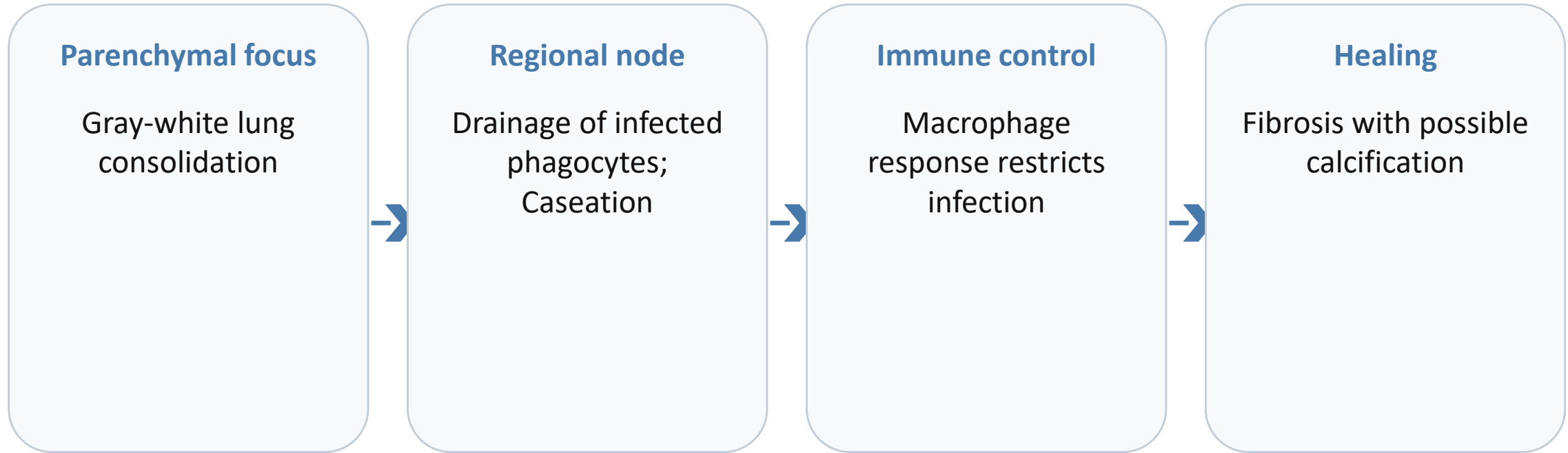
- Inhaled organisms usually implant in distal airspaces.
- Typical site: Lower upper lobe or upper lower lobe, close to pleura.
- A discrete gray-white inflammatory focus forms as immunity develops.
- The focus often develops central caseous necrosis.

Ghon focus and Ghon complex



Schematic lung-location diagram

The Ghon complex evolves with immunity



Fibrocalcific healing does not guarantee sterilization

- Most primary infections are controlled by cell-mediated immunity.
- Granulomas gradually fibrose; Calcification may make lesions visible radiologically.
- Dormant bacilli can persist within some healed lesions.
- Loss of resistance may reactivate these foci many years later.

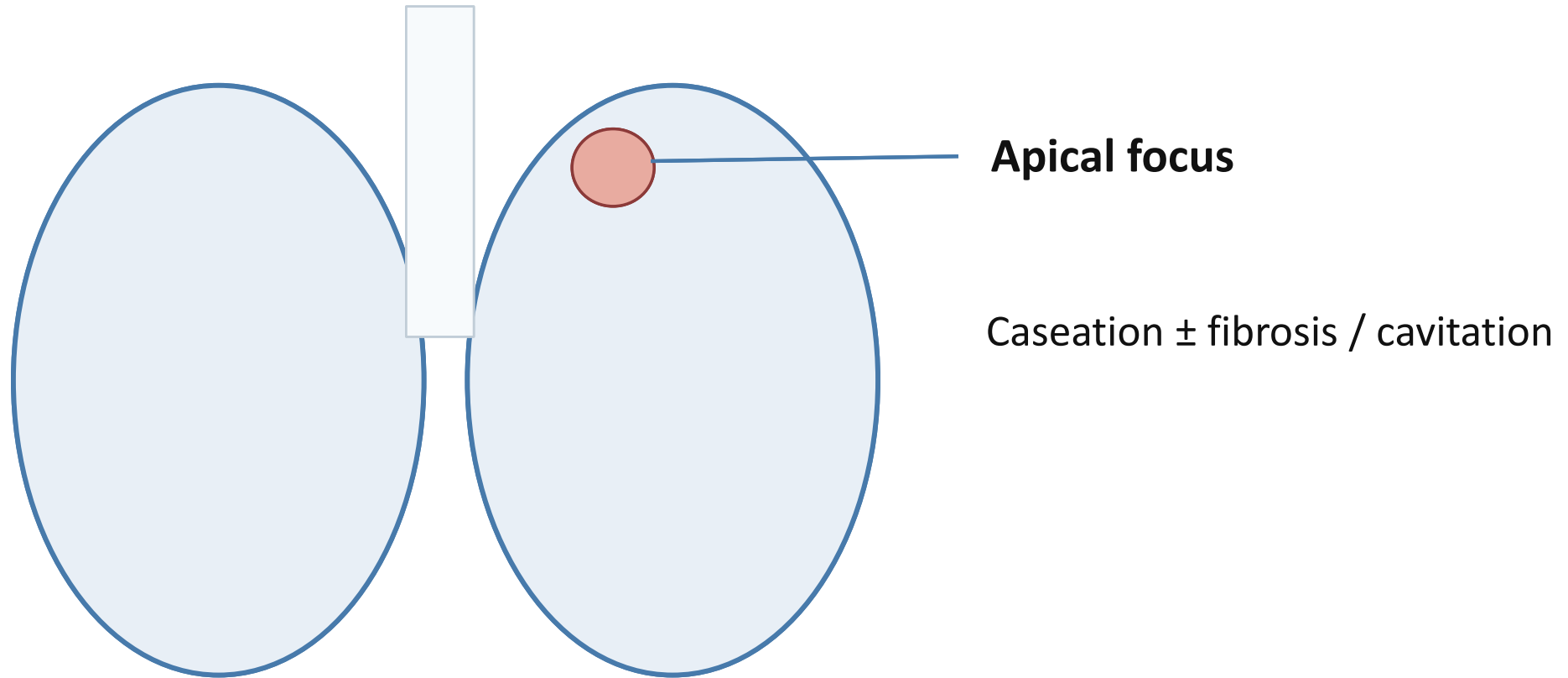
Progressive primary tuberculosis

- A minority of newly infected people develop clinically important primary disease.
- Lobar consolidation may resemble acute bacterial pneumonia.
- Hilar lymphadenopathy and pleural effusion are relatively prominent.
- Hematogenous spread can cause meningitis or miliary tuberculosis.

Postprimary tuberculosis arises in a sensitized host

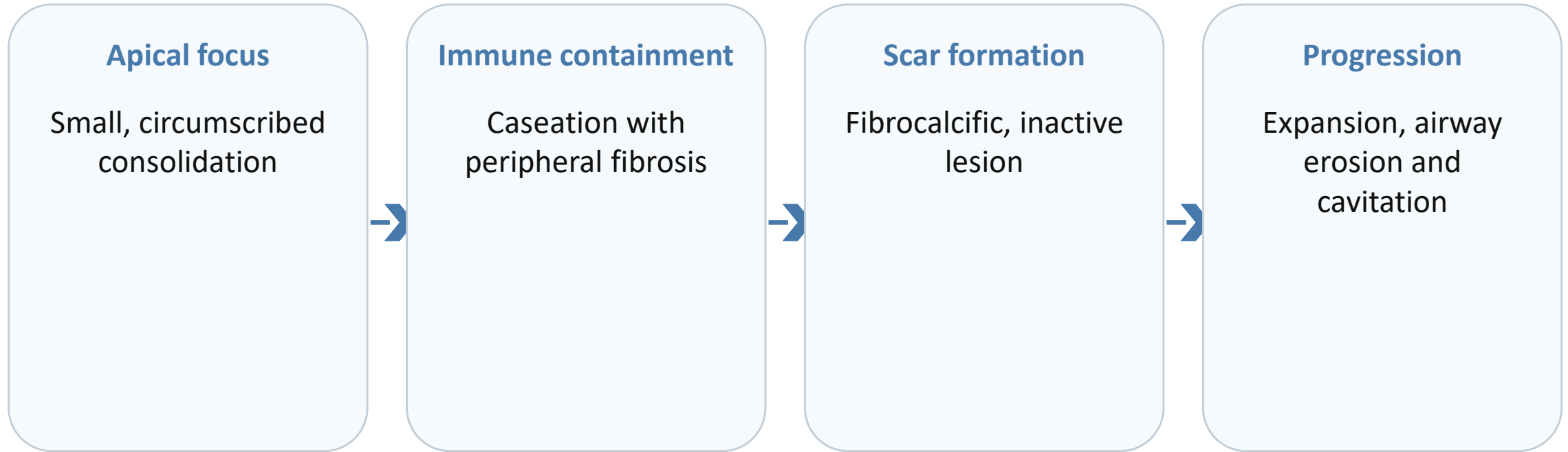
- May follow reactivation of persistent organisms after months or years.
- Reinfection also contributes where tuberculosis exposure is common.
- Preexisting hypersensitivity produces rapid local inflammatory injury.
- The initial focus classically favors the apical lung.

Apex-predominant postprimary disease



Schematic lung-location diagram

The secondary focus can heal or progress



Cavitation: A structural consequence of necrosis

Coalescent caseation

Necrosis of infected
lung parenchyma



Airway erosion

Caseous material
drains into bronchus



Irregular cavity

Poorly walled off by
fibrous tissue



Bacilli in sputum

Greater opportunity
for transmission

Why cavitory tuberculosis produces hemoptysis

- Progressive necrotizing lesions erode nearby bronchi and vessels.
- Vascular injury allows blood to enter the bronchial tree.
- A cavitory patient may expectorate bacilli-rich sputum.
- Persistent cavities and fibrotic healing can distort lung architecture.

Primary and postprimary tuberculosis

Feature	Primary	Postprimary
Host	Previously unsensitized	Previously sensitized
Typical location	Subpleural middle lung zones	Upper-lobe apex
Lymph nodes	Prominent hilar involvement	Less prominent early
Progression	Consolidation / pleural effusion	Cavitation more typical
Potential sequel	Fibrocalcific Ghon complex	Apical scar or progressive cavity

Clinical onset can be indolent

- Localized secondary infection may initially be asymptomatic.
- Constitutional symptoms include malaise, anorexia, fever and weight loss.
- Low-grade remittent fever and night sweats are characteristic presentations.
- Cytokines produced by activated macrophages contribute to systemic illness.

Pulmonary symptoms reflect lesion progression

- Cough and increasing sputum accompany pulmonary progression.
- Sputum may evolve from mucoid to purulent.
- Hemoptysis suggests tissue or vascular destruction.
- Pleural involvement can cause pleuritic chest pain and effusion.

Histology: Tuberculoid granulomatous reaction

- Microscopic tubercles contain epithelioid histiocytes.
- Multinucleated giant cells are commonly present.
- Lymphocytes and fibroblasts form a peripheral rim.
- Granulomas may be necrotizing or nonnecrotizing.

Noncaseating granulomas do not exclude tuberculosis

- Tuberculous lesions do not invariably contain demonstrable caseous necrosis.
- Histologic pattern is influenced by lesion stage and host immune competence.
- A granuloma pattern alone is not species-specific.
- Acid-fast stains and microbiologic evaluation remain indicated when tuberculosis is plausible.

High bacillary load may coexist with weak granulomas

Cell-mediated immunity preserved

- Organized epithelioid granulomas
- Caseation may be prominent
- Few detectable bacilli in late fibrotic lesions

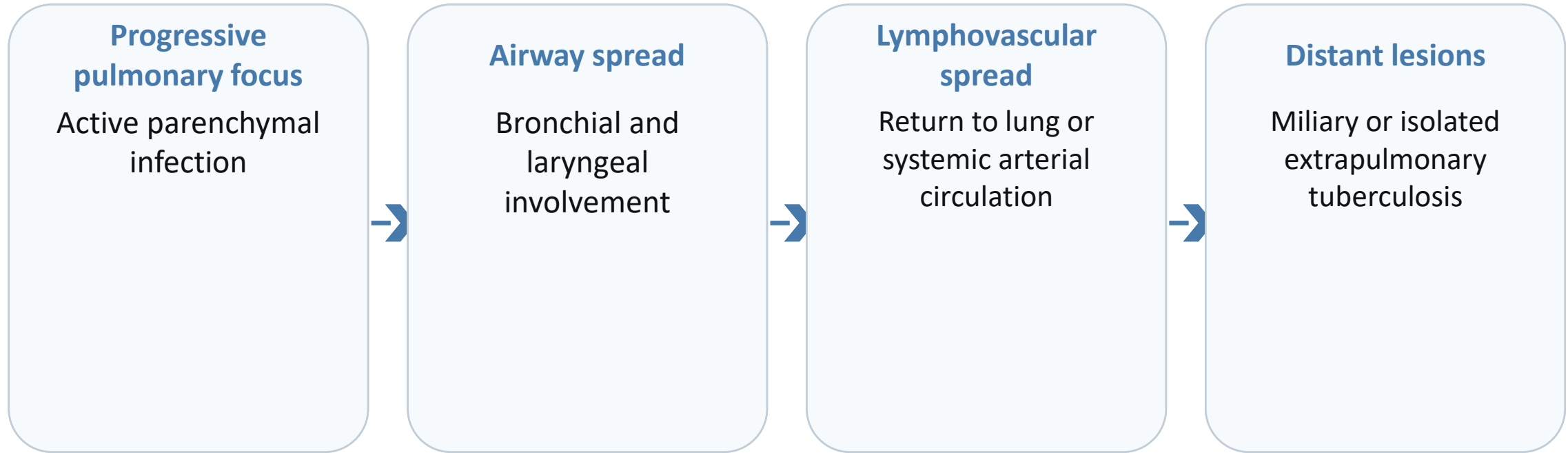
Severe immune compromise

- Poorly organized or absent granulomas
- Macrophages may harbor numerous bacilli
- Dissemination and atypical distribution more likely

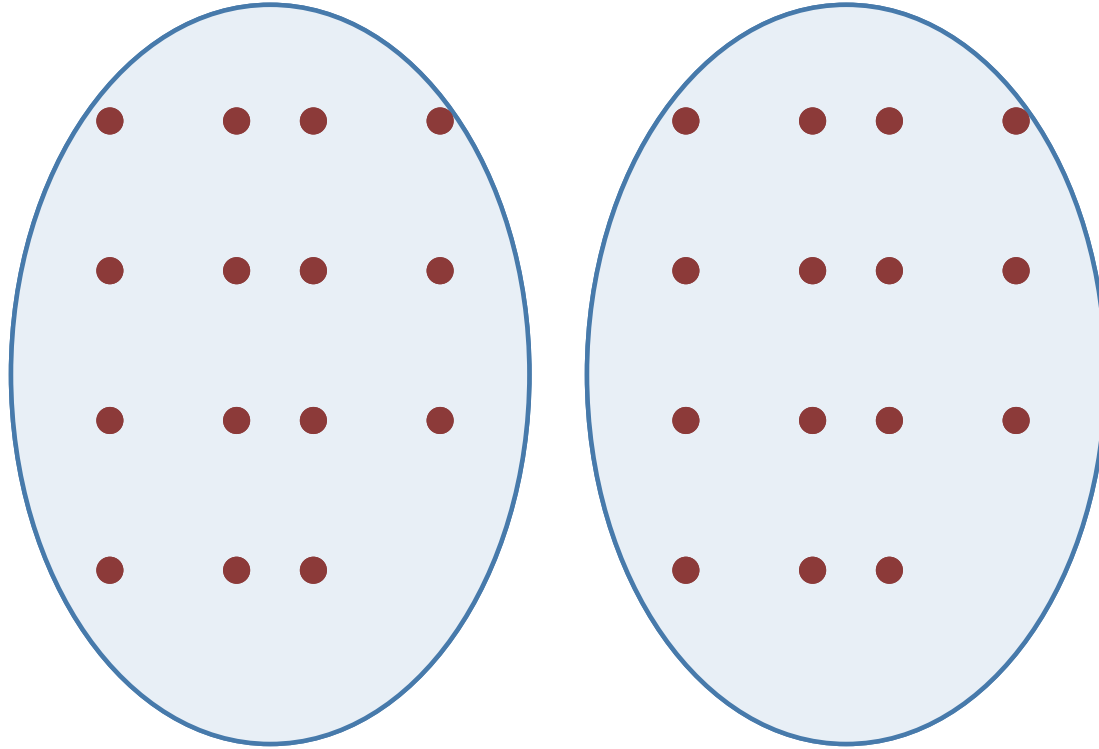
Acid-fast stain interpretation in tissue

- Acid-fast bacilli may be found in early exudative or caseous lesions.
- Late fibrocalcific lesions often have very low demonstrable bacillary burden.
- A stain-negative granuloma does not rule out tuberculosis.
- Correlation with culture or molecular assays is needed for pathogen identification.

Airway, lymphatic and bloodborne dissemination



Pulmonary miliary tuberculosis

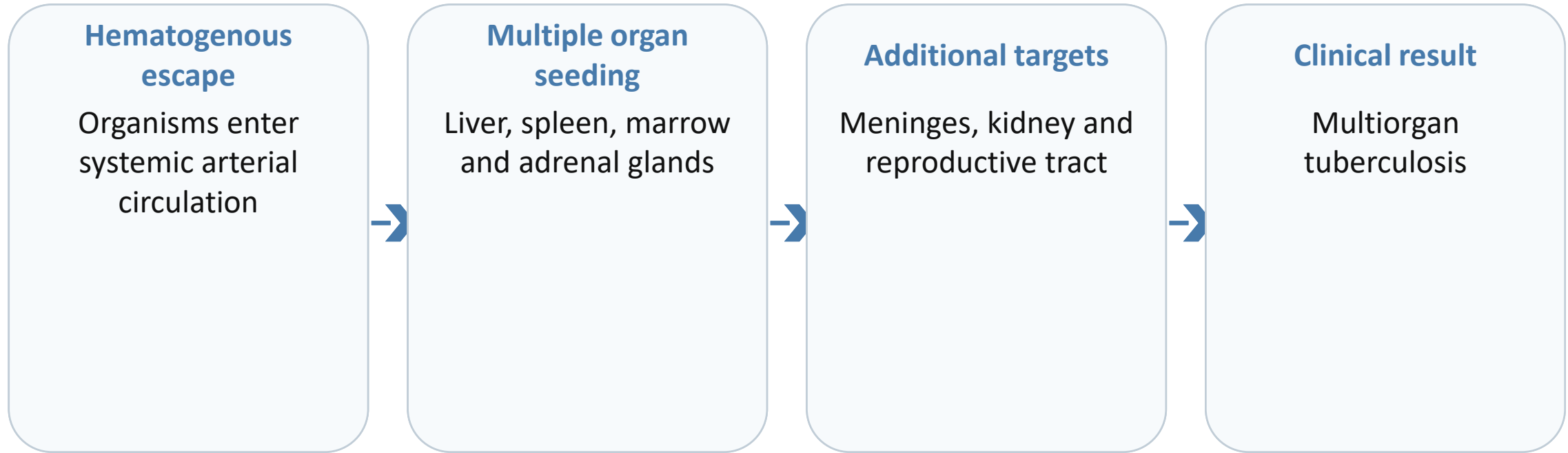


**Widespread tiny
parenchymal foci**

Unlike one dominant cavitary
focus, miliary disease
distributes numerous lesions
through the lungs.

Schematic, not radiology or gross pathology

Systemic military dissemination



Extrapulmonary tuberculosis can dominate presentation

- Hematogenous seeding can establish isolated organ disease.
- Meningeal infection produces tuberculous meningitis.
- Osteomyelitis, genitourinary lesions and adrenal disease may occur.
- The presenting complaint may not be respiratory.

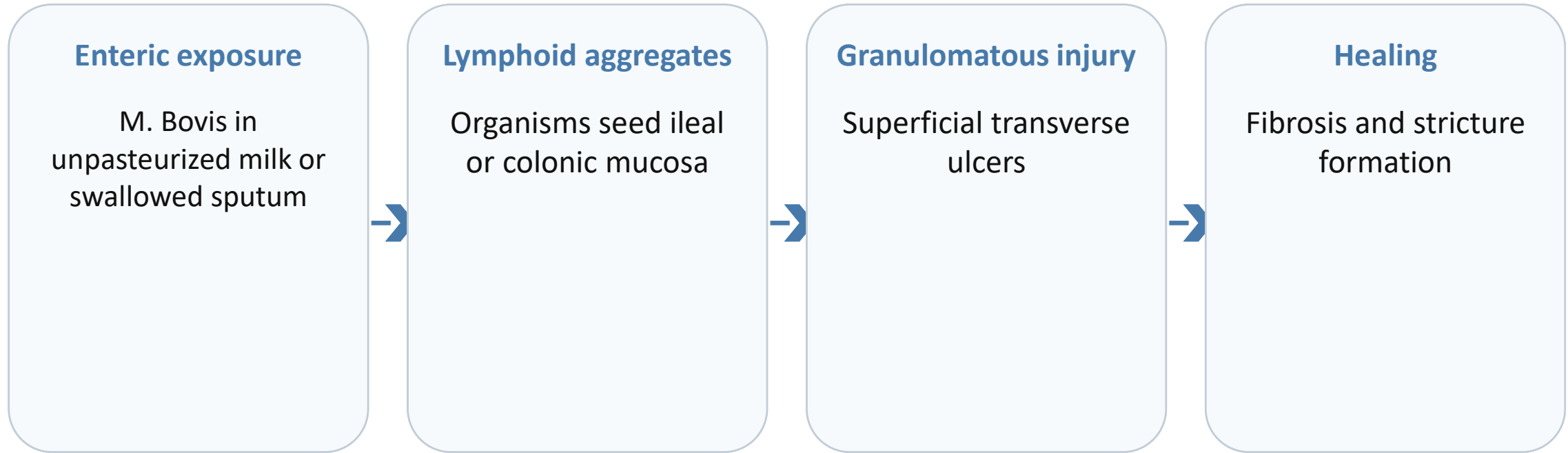
Cervical tuberculous lymphadenitis

- Lymphadenitis is the most frequent extrapulmonary presentation.
- Cervical nodes are a common site: Traditionally called scrofula.
- In HIV-negative hosts, disease is often localized and unifocal.
- In HIV-associated immunodeficiency, multifocal nodal and systemic disease are common.

Vertebral tuberculosis and cold abscesses

- Tuberculosis may seed vertebrae and produce destructive osteomyelitis.
- Vertebral infection is referred to as Pott disease.
- Paraspinal collections may track along fascial planes.
- A cold abscess can present at a site distant from the original spinal lesion.

Intestinal tuberculosis: A route-to-morphology link



Pleural and airway complications

- Parenchymal spread can involve the pleura and produce effusion.
- Progressive cases may lead to empyema or fibrous pleuritis.
- Endobronchial, tracheal or laryngeal lesions may follow drainage or direct seeding.
- Mucosal granulomas may be microscopic rather than grossly obvious.

HIV profoundly alters the phenotype

- All stages of HIV infection confer increased tuberculosis risk.
- Low CD4 T-cell count is a risk for subsequent active disease.
- Pulmonary findings range from focal lesions to multifocal infiltrates or cavitation.
- Severe immune compromise substantially increases extrapulmonary involvement.

Why HIV-associated TB can be smear-negative

- Advanced T-cell deficiency impairs granuloma and cavity formation.
- Less bronchial destruction may reduce expulsion of organisms into sputum.
- Sputum acid-fast smear may therefore be negative despite high tissue bacterial burden.
- Histology may show organisms without organized granulomatous inflammation.

Diagnostic questions must be kept separate

Is there active disease?

- Examine sputum or involved tissue
- Acid-fast microscopy and culture
- Rapid nucleic-acid amplification

Is there immune sensitization?

- Tuberculin skin test (PPD / Mantoux)
- Interferon- γ release assay (IGRA)
- Neither establishes active disease alone

Acid-fast sputum smear: What it can show

- Demonstrates acid-fast bacilli when present above the assay's detection threshold.
- A positive result is not equivalent to M. Tuberculosis species confirmation.
- Sensitivity falls with low sputum bacillary burden.
- Smear must be interpreted alongside molecular tests, culture and the clinical context.

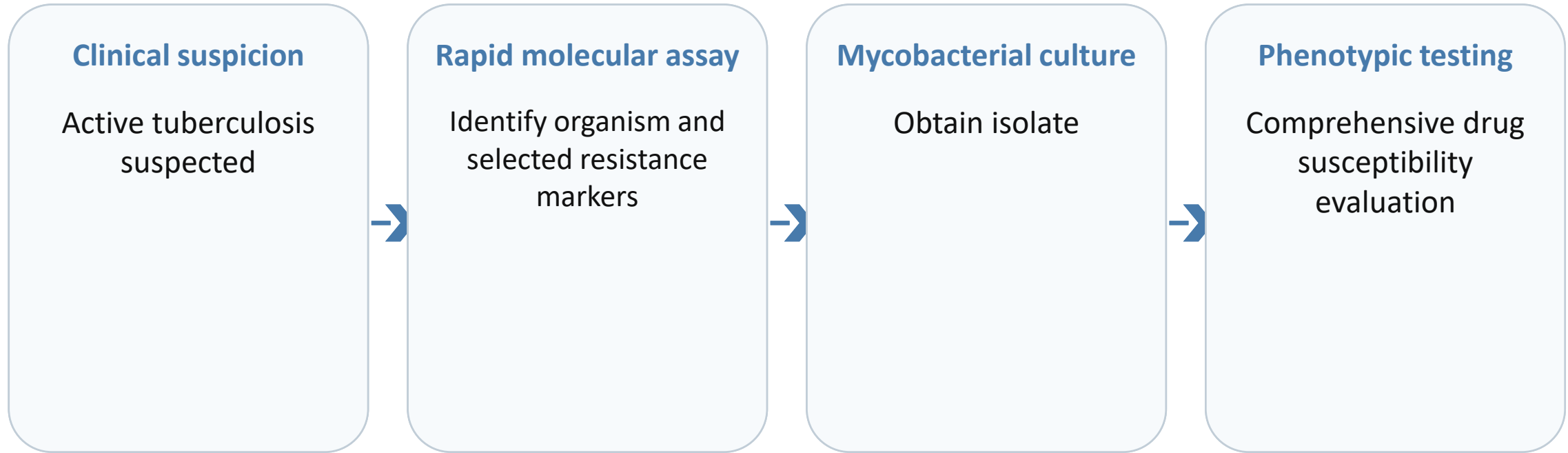
Culture: Identification and susceptibility

- Mycobacterial cultures can detect viable organisms.
- The source reports solid-medium growth over approximately 3–6 weeks.
- Liquid culture media can provide results sooner, sometimes within 2 weeks.
- Culture permits comprehensive phenotypic drug susceptibility testing.

Molecular testing accelerates active-TB evaluation

- PCR detects M. Tuberculosis DNA much faster than culture.
- Some assays also identify mutations associated with drug resistance.
- Sensitivity is lower in smear-negative disease and especially in children.
- Molecular results complement rather than wholly replace culture.

Drug-resistance determination



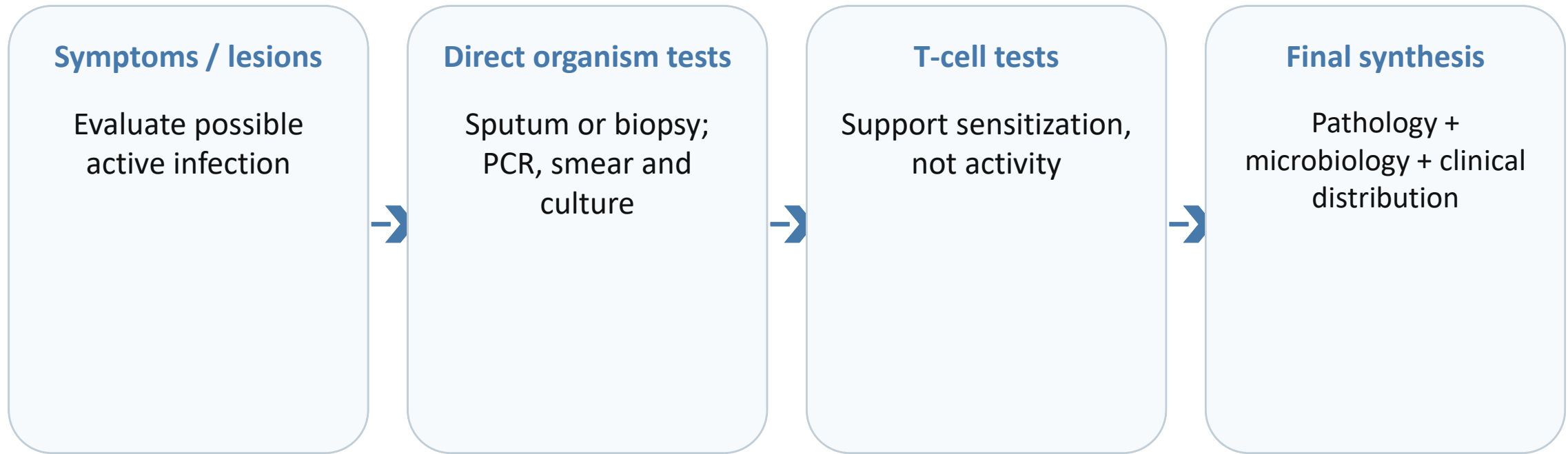
TST and IGRA detect an immune response

Characteristic	Tuberculin skin test	IGRA
Biologic basis	Delayed-type skin induration	Ex vivo T-cell IFN- γ release
Readout	Induration at 48–72 h	Antigen-triggered IFN- γ assay
BCG effect	May produce false positive	False positives uncommon
Active vs latent	Cannot distinguish	Cannot distinguish

Negative immunologic tests can be misleading

- A negative TST or IGRA is not definitive evidence against tuberculosis.
- Immunosuppression or severe disease can weaken detectable T-cell responses.
- Other associated false-negative contexts include malnutrition and Hodgkin lymphoma.
- Active disease demands direct organism testing and clinicopathologic correlation.

Integrated diagnostic interpretation



Nontuberculous mycobacteria: Different ecology

- NTM excludes the M. Tuberculosis complex and very fastidious M. Leprae.
- Many species are environmental inhabitants of soil and water.
- Routine person-to-person transmission is uncommon.
- Species identification matters because pathogenicity and treatment differ.

Important NTM pathogens

M. Avium complex

Includes M. Avium, M. Intracellulare and M. Chimaera



M. Abscessus complex

Often clinically relevant in structural lung disease



M. Kansasii

Another important human NTM pathogen

NTM requires a susceptible host environment

- Structural lung damage predisposes to chronic pulmonary NTM disease.
- Examples include bronchiectasis, cystic fibrosis and pneumoconiosis.
- Immune defects and immunosuppressive drugs increase disseminated disease risk.
- IL-12 / IFN- γ pathway defects and anti-IFN- γ autoantibodies are relevant susceptibility mechanisms.

NTM has several clinical presentations

Presentation	Characteristic context
Pulmonary disease	Bronchiectasis or preexisting structural lung disease
Lymphadenitis	Localized mycobacterial involvement
Skin / soft tissue	Trauma, surgery or medical-device infection
Disseminated infection	Marked T-cell deficiency, particularly advanced HIV

NTM lung injury involves innate cells

- MAC can stimulate neutrophil extracellular trap formation.
- Infected airways show IL-8 signaling and neutrophil recruitment.
- Neutrophil proteases and matrix metalloproteinases can increase inflammation.
- The result may exacerbate existing structural lung damage.

Disseminated MAC: Organisms without granulomas

- In severe T-cell deficiency, MAC can multiply widely in macrophages.
- Infected macrophages may fill lymph nodes, liver, spleen and other organs.
- Abundant acid-fast bacilli are a characteristic tissue finding.
- Well-formed granulomas and major tissue destruction may be uncommon.

Tuberculosis versus pulmonary NTM disease

Dimension	Tuberculosis	NTM disease
Typical reservoir	Human pulmonary cases	Soil / water environments
Transmission	Airborne person-to-person	Usually environmental acquisition
Host pattern	May affect immunocompetent hosts	Structural damage / immunodeficiency often important
Clinical issue	Containment, reactivation, transmission	Species-specific pathogenicity and management

Leprosy: Skin and peripheral nerve infection

- Slowly progressive infection caused primarily by *M. Leprae*.
- *M. Lepromatosis* is a less frequent cause.
- Organisms favor cooler tissues, especially skin and distal extremities.
- The host T-cell response determines the clinical spectrum.

Leprosy: Distinctive biologic constraints

- M. Leprae is obligately intracellular and cannot be cultured in vitro.
- Growth is favored by temperatures near those of human skin.
- Bacillary cell-wall lipid PGL-1 facilitates host-cell invasion.
- Peripheral nerves are vulnerable because bacilli invade Schwann cells and associated macrophages.

Immune polarity determines leprosy phenotype

Tuberculoid pole

- Strong Th1 response; IFN- γ -mediated macrophage activation
- Few demonstrable bacilli (paucibacillary)
- Localized skin / nerve granulomatous injury

Lepromatous pole

- Weak cell-mediated immunity
- Numerous acid-fast bacilli (multibacillary)
- Widespread lesions and symmetric nerve invasion

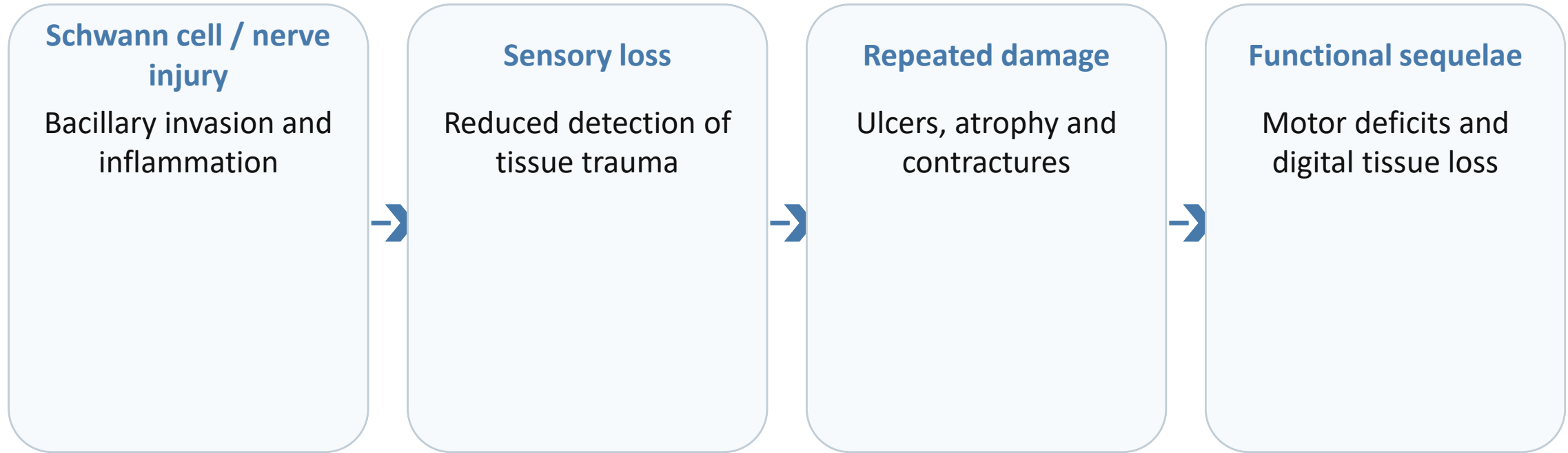
Tuberculoid leprosy: Destructive nerve granulomas

- Localized, dry and often anesthetic skin plaques are characteristic.
- Granulomatous inflammation involves and can destroy peripheral nerve twigs.
- Sensory loss exposes skin to repeated unrecognized trauma.
- Marked cellular immunity makes bacilli difficult to identify in tissue.

Lepromatous leprosy: Heavy bacillary burden

- Diffuse skin thickening, papules and nodules may develop.
- Lipid-laden lepra macrophages may contain aggregates of acid-fast bacilli (globi).
- Ulnar and peroneal nerves can be symmetrically infiltrated.
- Extensive skin and peripheral nerve involvement may cause deformity.

Leprosy: Nerve dysfunction creates downstream injury



Leprosy spectrum: Morphologic distinctions

Feature	Tuberculoid pole	Lepromatous pole
Immunity	Strong Th1	Weak Th1
Skin	Discrete anesthetic plaques	Numerous / diffuse lesions
Nerves	Focal granulomatous destruction	Often symmetric invasion
Bacilli	Scant or undetectable	Abundant within foamy macrophages
Tissue pattern	Well-formed granulomas	Bacilli-filled lepra cells

Clinicopathologic exercise: Apical cavitary lesion

CLINICAL STEM

A patient with weeks of night sweats, weight loss and productive cough has an apical lung cavity.

Question

Which disease pattern is most likely, and why is the patient potentially infectious?

Interpretation

Postprimary pulmonary tuberculosis; Erosion into an airway allows bacilli to enter sputum.

Apical location, caseous tissue breakdown and airway communication support postprimary disease.

Clinicopathologic exercise: Weak granulomas

CLINICAL STEM

A markedly immunosuppressed patient has numerous acid-fast bacilli in tissue macrophages but poorly formed granulomas.

Question

Why can bacterial load be high while classical granulomas are absent?

Interpretation

Severe T-cell dysfunction impairs IFN- γ -dependent macrophage activation and granuloma formation.

The host response that contains organisms also produces much of the characteristic granulomatous injury.

Clinicopathologic exercise: Numb skin plaque

CLINICAL STEM

A patient has an anesthetic plaque and a thickened peripheral nerve; Biopsy shows granulomatous neuritis with scant detectable organisms.

Question

Which end of the leprosy spectrum fits best?

Interpretation

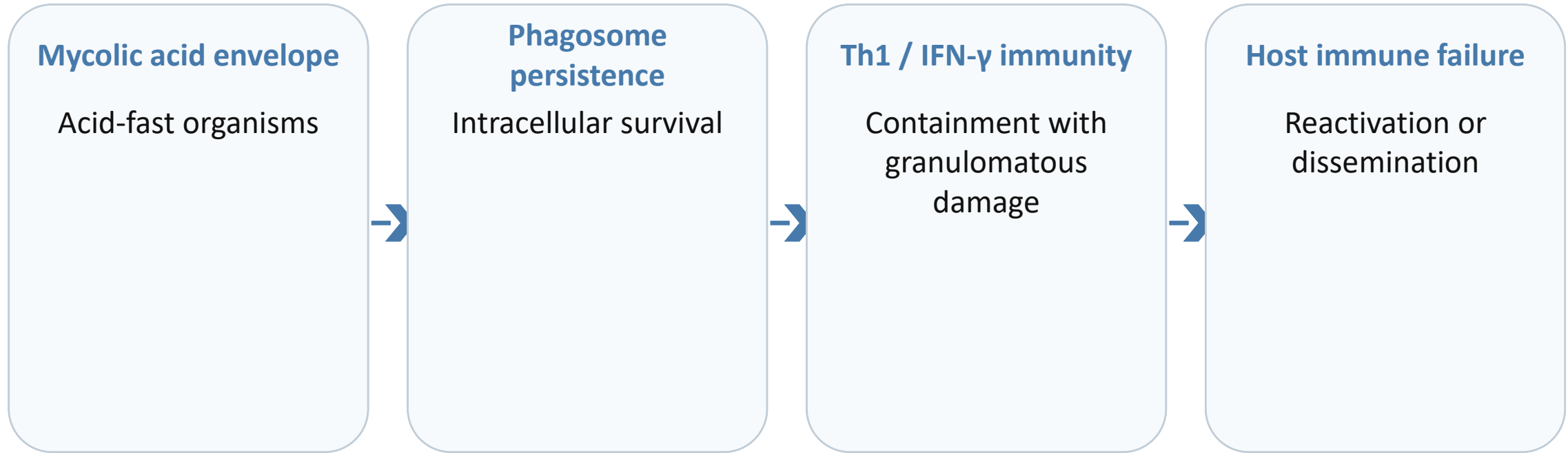
Tuberculoid (paucibacillary) leprosy.

Strong cell-mediated immunity restrains bacilli but causes localized granulomatous nerve injury.

How to discriminate the major entities

Feature	Tuberculosis	NTM disease	Leprosy
Reservoir / acquisition	Airborne infectious case	Environmental exposure	Likely respiratory; uncommon zoonosis
Main target	Lung ± systemic	Lung; skin; disseminated	Skin and peripheral nerves
Signature mechanism	Th1 granuloma ± caseation	Opportunistic growth in susceptible host	Immune-spectrum nerve injury
Important pitfall	Latent ≠ active	AFB ≠ M. tuberculosis	Scant bacilli in tuberculoid disease

Major mechanisms to retain



Morphologic rules of interpretation

- Caseating granulomas support but do not independently establish tuberculosis.
- A noncaseating granuloma does not exclude mycobacterial infection.
- Loss of T-cell immunity may increase bacilli while diminishing granuloma formation.
- Direct microbial identification remains essential when clinical management depends on species.

Primary source

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Infectious Diseases: Mycobacterial Infections, Tuberculosis, Nontuberculous Mycobacterial Infections and Leprosy.
- Original conceptual diagrams and tables were authored specifically for this lecture.