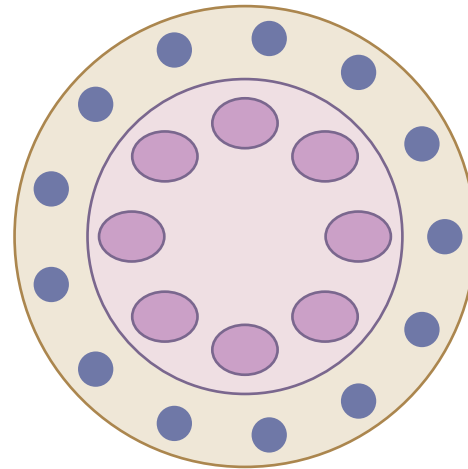


GRANULOMATOUS INFLAMMATION

Organized macrophage response to persistent stimuli



Dr Abu Suraih Sakhri

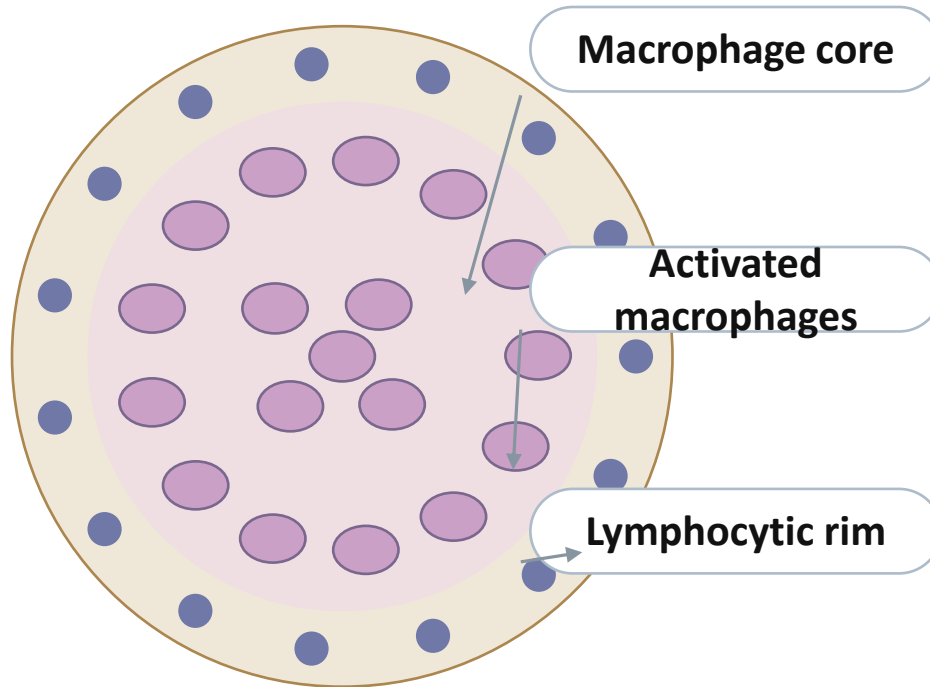
MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain why a persistent or indigestible stimulus generates a granuloma.
- Distinguish foreign-body and T-cell–dependent immune granulomas.
- Identify the principal cellular and morphologic components.
- Interpret key disease-associated patterns without equating pattern with cause.
- Construct an etiology-directed workup for tissue granulomas.

A granuloma is an organized macrophage collection



Schematic — not a tissue image

- Activated macrophages form the principal cellular component.
- T lymphocytes often participate; Necrosis may or may not be present.
- Organization reflects attempted containment of a difficult-to-clear stimulus.

Granulomatous inflammation is a chronic pattern

Chronic inflammation

Prolonged response to persistent stimuli

Macrophages and lymphocytes predominate

Tissue injury and repair coexist

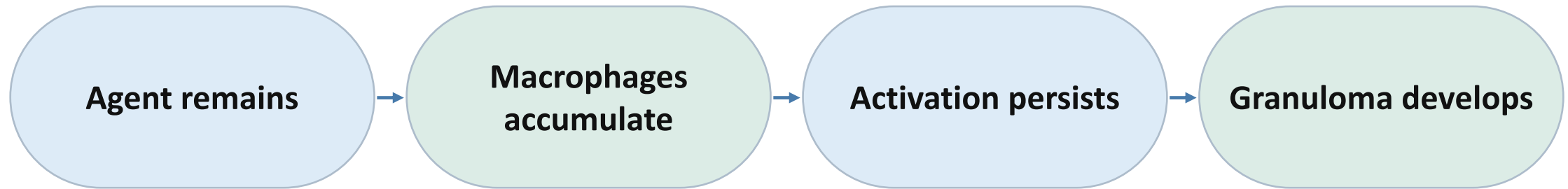
Granulomatous subset

Organized macrophage aggregates

Often a T-cell–macrophage circuit

Necrosis present in some lesions

Persistent stimuli drive granuloma formation



- The response is sustained because the stimulus is not readily eliminated.
- Organization may sequester the agent but does not guarantee eradication.

Containment and collateral injury coexist

Potential benefit

Limits dispersion of resistant material

Concentrates phagocytes around the stimulus

Supports sustained local host defense

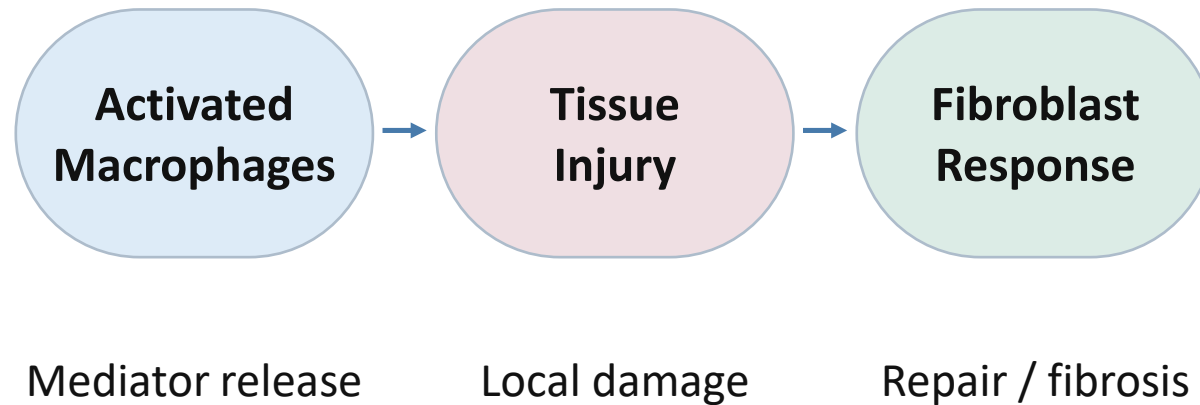
Potential cost

Activated cells injure adjacent tissue

Necrosis may accompany the reaction

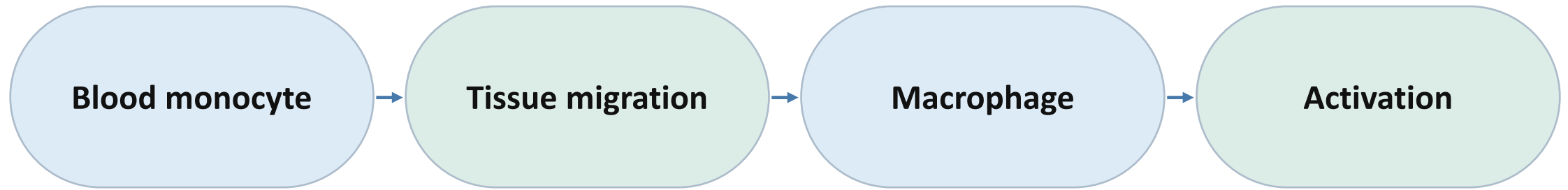
Repair may culminate in scarring

Chronic inflammation contains injury and repair



- Inflammatory mediators sustain leukocyte recruitment.
- Activated macrophages can damage parenchymal tissue.
- The same cells contribute to fibroblast activation and repair.

Macrophages arise from several sources



- Many macrophages in inflamed tissue arise from marrow-derived monocytes.
- Some organs also contain long-lived tissue-resident macrophages.

Resident and recruited macrophages

Recruited population

Monocytes enter inflamed tissues

Continued influx maintains chronic infiltrates

May become dominant within ~48 hours

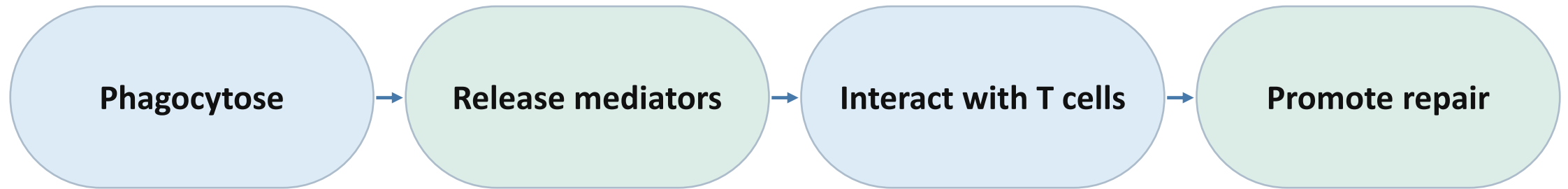
Tissue-resident population

Established early in some organs

Examples: Microglia, Kupffer cells

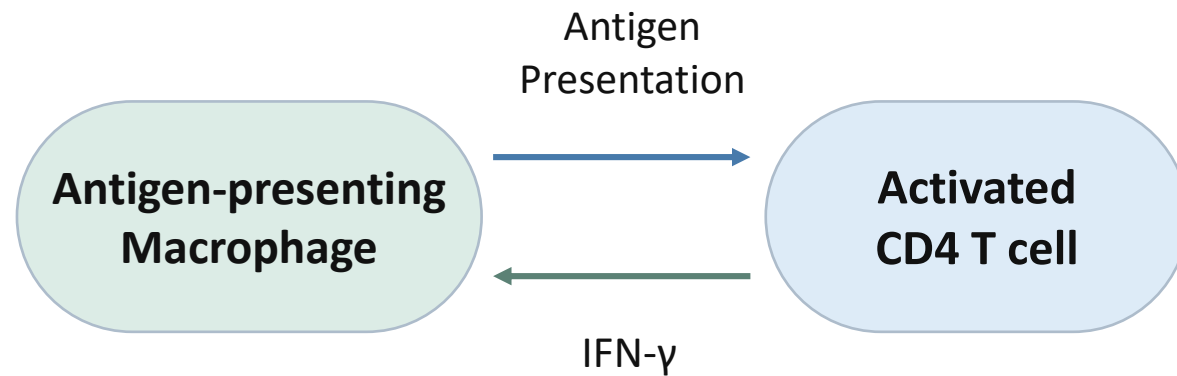
Contribute to local immune responses

Macrophages link defense, signaling and repair



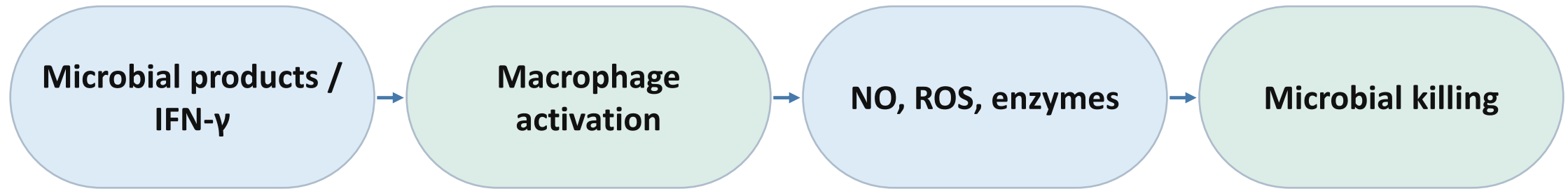
- The same functional repertoire can both protect and injure tissue.
- Their persistence is central to chronic inflammation.

Macrophage–T-cell communication is reciprocal



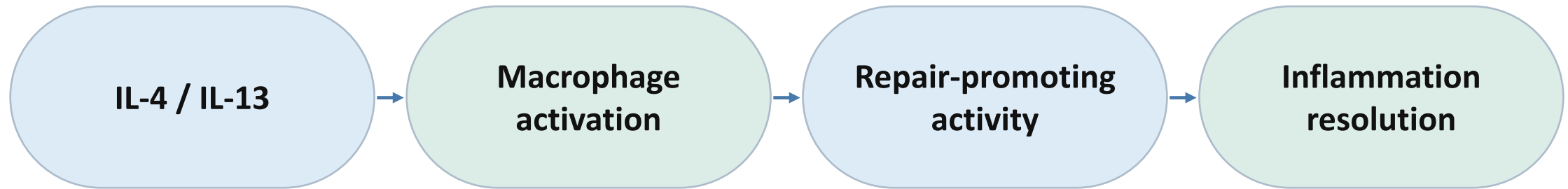
- Macrophages present antigens and influence T-cell responses.
- Activated T cells release cytokines that modify macrophage function.
- The feedback loop can maintain an inflammatory lesion.

Classical activation favors inflammatory defense



- Classical or M1-like activation can intensify inflammation and tissue injury.

Alternative activation supports tissue repair



- This is a functional polarization concept—not proof of a homogeneous cell subset.

M1-like and M2-like labels have limitations

Useful model

Different signals elicit different functions

Classical: Killing and inflammation

Alternative: Resolution and repair

Biologic reality

Phenotypes overlap and change

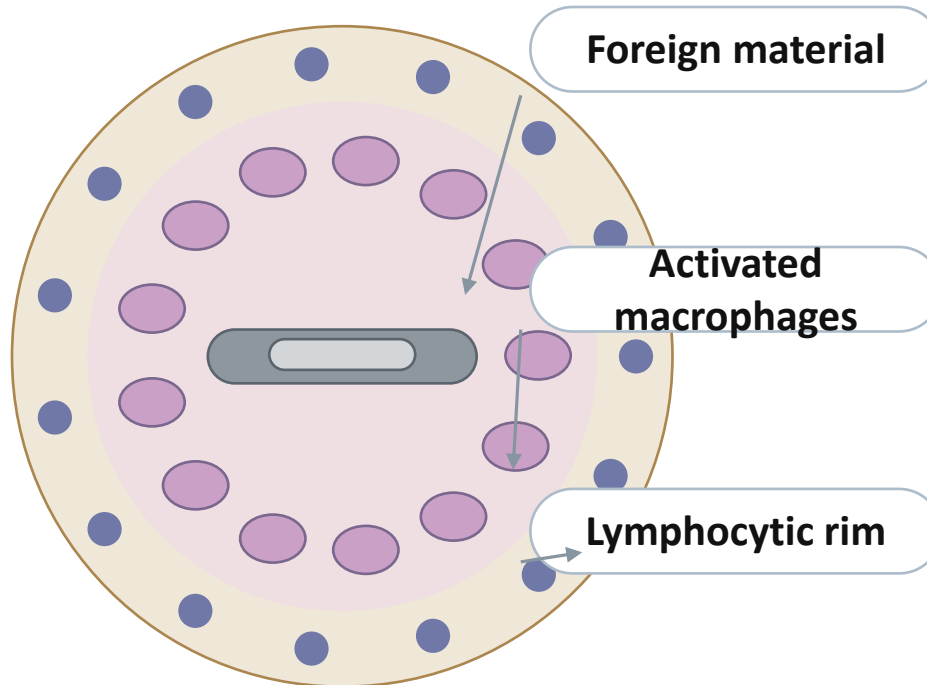
Mixed states occur in lesions

Strict M1 → M2 temporal sequence is unproven

Two mechanistic categories of granuloma

Dimension	Foreign-body	Immune
Trigger	Inert, indigestible material	Persistent antigen or microbe
T-cell dependence	No specific T-cell response required	T-cell–mediated response central
Major components	Macrophages and giant cells	Activated macrophages and T cells
Primary clue	Material in/near center	Persistent immunologic stimulus

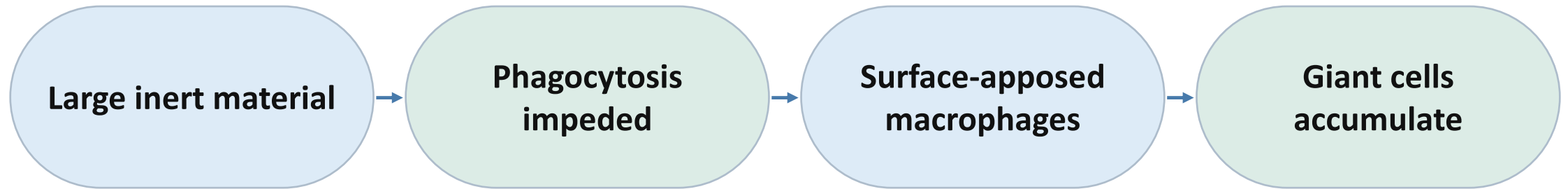
Foreign-body granulomas form without specific immunity



Schematic — not a tissue image

- Inert foreign substances are large or otherwise difficult to ingest.
- Macrophages and giant cells gather along the foreign surface.
- A specific T-cell-mediated immune response is not required.

Failure of phagocytosis localizes the reaction

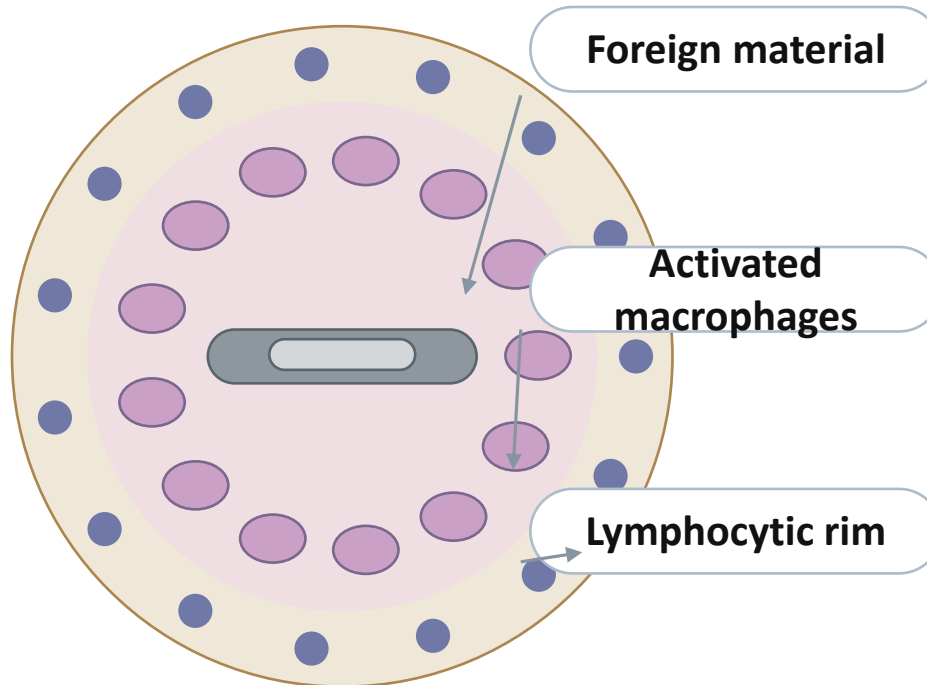


- The physical properties of the foreign material help determine the lesion's architecture.

Recognized foreign-body triggers

- Suture material left in tissue after a procedure.
- Talc particles; Exposure can occur with intravenous drug use.
- Other fibers or inert materials too large for ordinary phagocytosis.
- These examples are nonimmunogenic description.

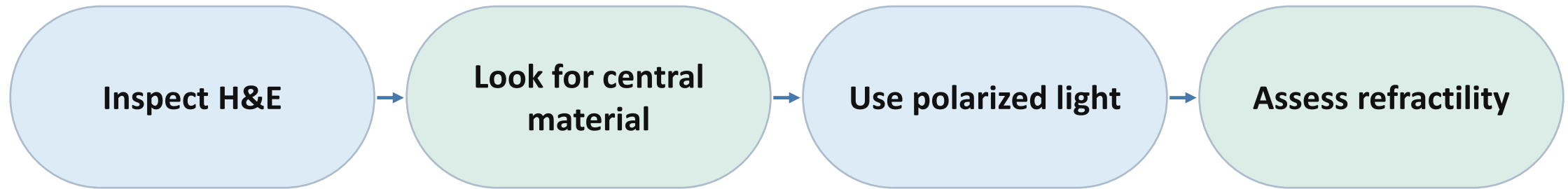
Foreign-body reaction: Cellular disposition



Schematic — not a tissue image

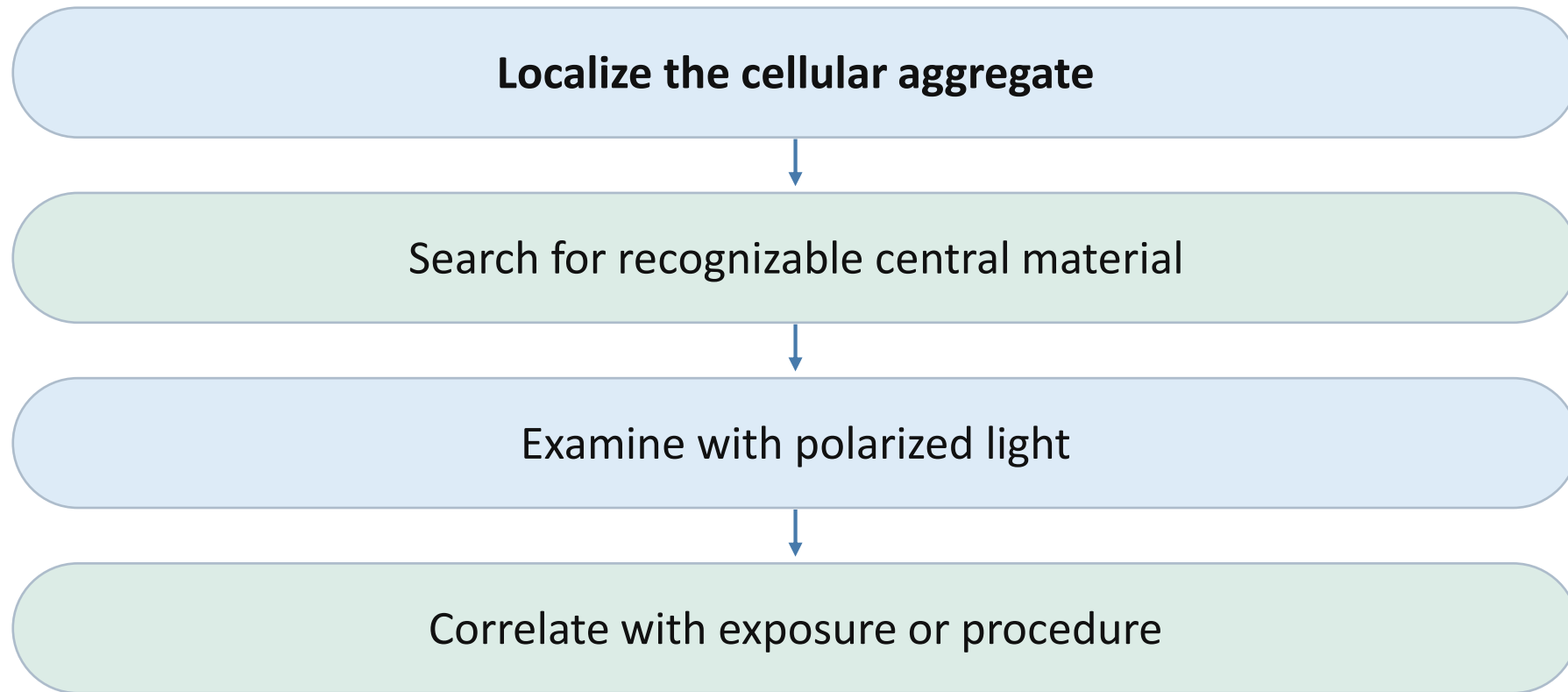
- Cells gather along the foreign-material interface.
- Multinucleated giant cells may directly abut or contain material.
- Identifying the foreign object changes the etiologic interpretation.

Polarized microscopy can reveal foreign material



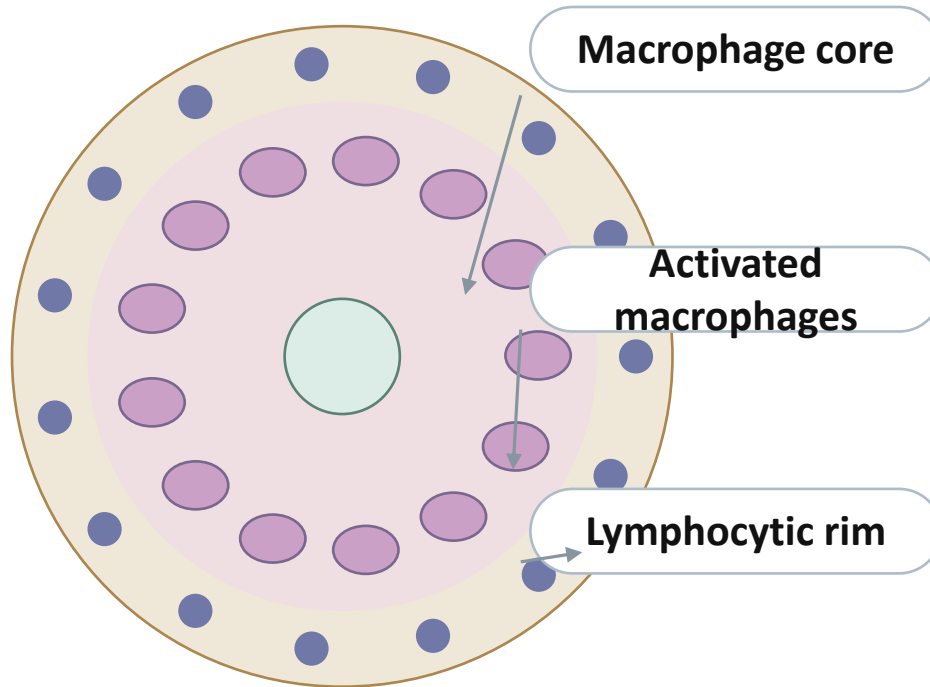
- Not all foreign substances are equally refractile.
- Polarization is an adjunct to, not a replacement for, routine morphology.

Reasoning from a possible foreign-body granuloma



The morphologic pattern suggests, but does not independently prove, the source.

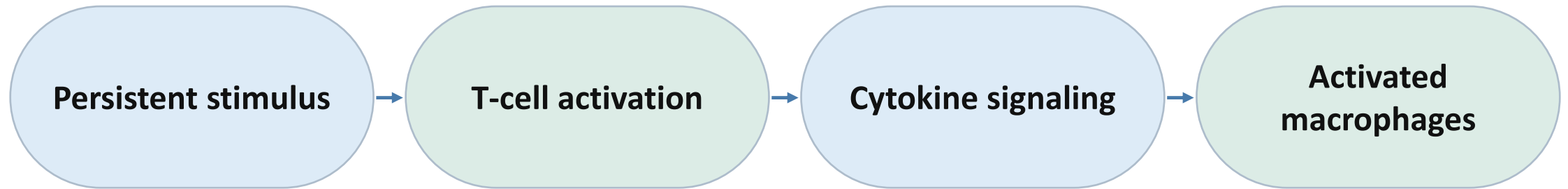
Immune granulomas depend on sustained T-cell responses



Schematic — not a tissue image

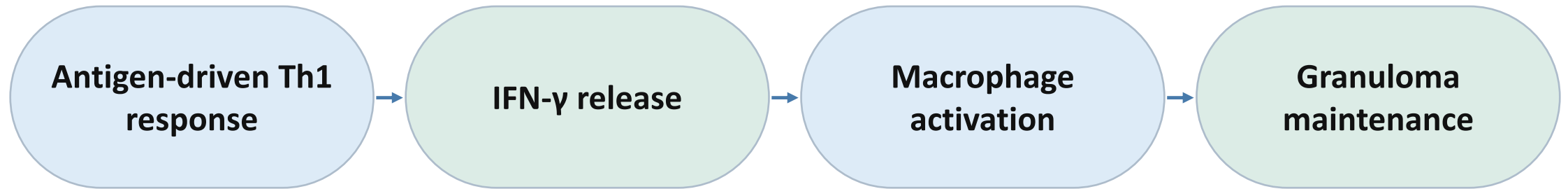
- Persistent microbes and other stimuli activate T cells.
- T-cell cytokines sustain macrophage activation.
- The resulting focus may damage local tissue despite its containment function.

Adaptive immunity maintains an immune granuloma



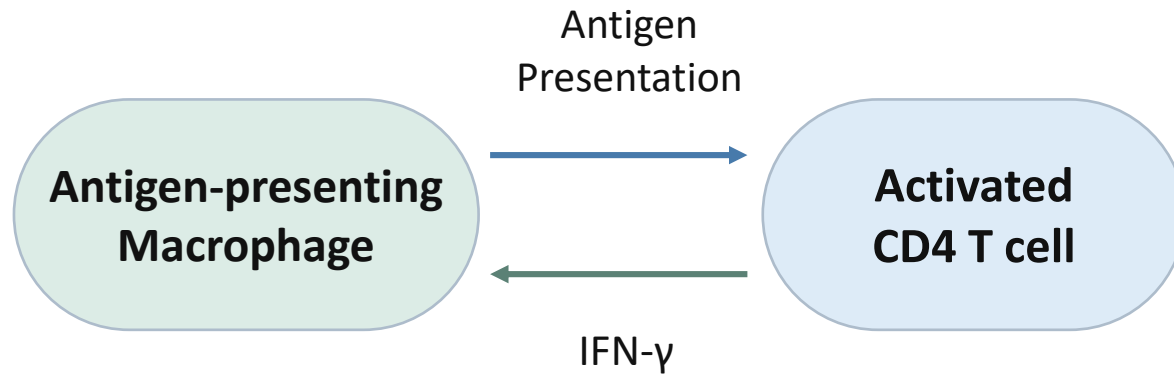
- The stimulus must remain sufficiently persistent to sustain the cellular response.

Th1 cells activate macrophages through IFN- γ



- IFN- γ is a central mechanistic link emphasized.

Th1–macrophage signaling forms a reinforcing loop

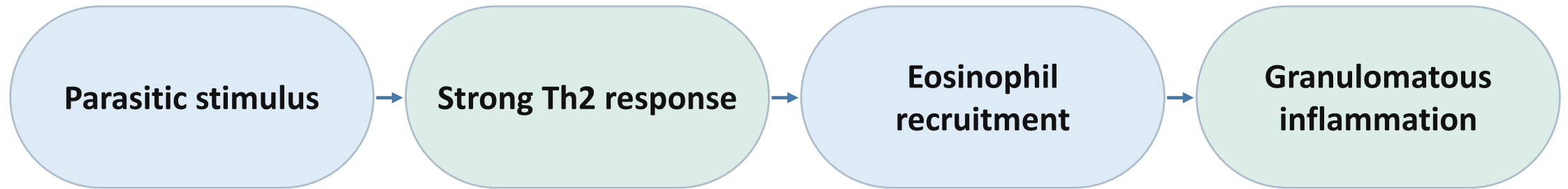


- T cells release IFN- γ that increases macrophage activation.
- Macrophages present antigen and sustain T-cell interactions.
- Amplification is helpful against microbes but can damage host tissue.

T-cell subsets shape the inflammatory milieu

Subset	Textbook mediators	Principal effect
Th1	IFN- γ	Classical macrophage activation
Th2	IL-4, IL-5, IL-13	Eosinophils; Alternative activation
Th17	IL-17	Chemokines; Neutrophil / monocyte recruitment

Schistosomiasis illustrates a Th2-associated pattern

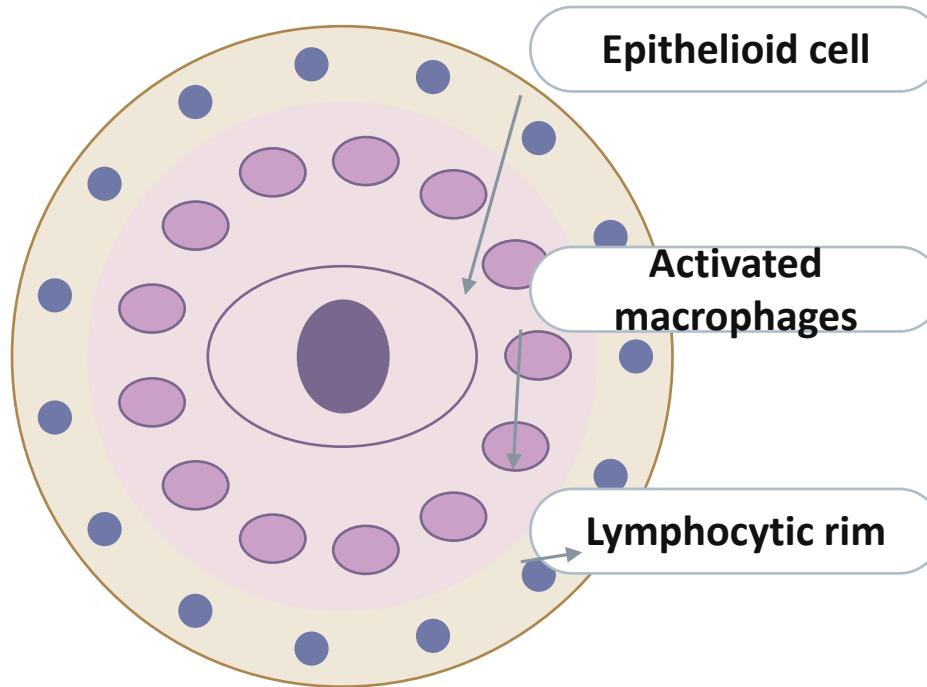


- Schistosomiasis as a granulomatous setting with a prominent Th2/eosinophilic response.

Foreign-body versus immune granuloma: Practical clues

Question	Foreign-body pattern	Immune pattern
What is in the lesion?	Visible/refractile material possible	Specific stimulus may be microscopic
What sustains the cells?	Persistent inert surface	Persistent T-cell activation
Which pathway dominates?	Macrophage/giant-cell response	T-cell–macrophage interaction
What confirms the cause?	Material and exposure correlation	Organism / disease-specific studies

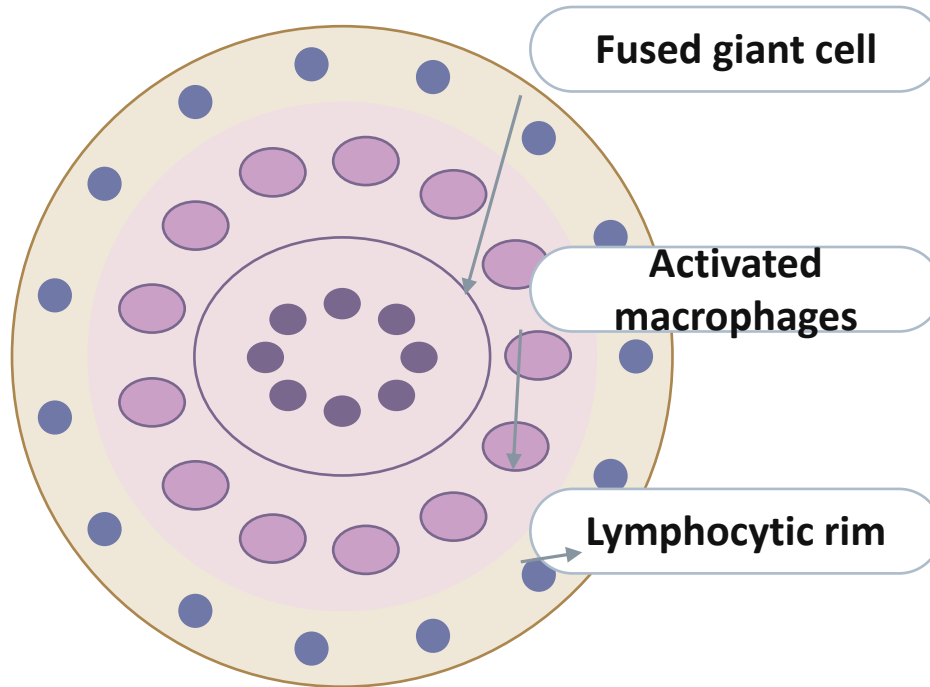
Epithelioid cells are activated macrophages



Schematic — not a tissue image

- Macrophages enlarge and develop abundant cytoplasm.
- Their epithelial-like appearance explains the name “epithelioid.”
- They are not derived from epithelial cells.

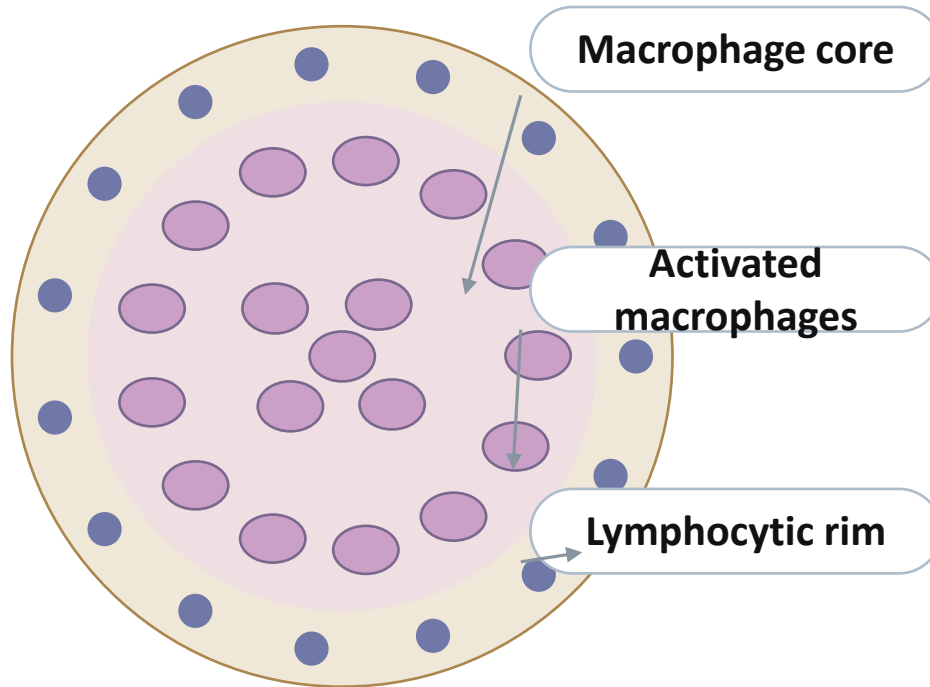
Multinucleated giant cells arise by fusion



Schematic — not a tissue image

- Some activated macrophages fuse to form giant cells.
- A giant cell contains multiple nuclei within one cytoplasm.
- Giant cells can occur in both granuloma types.

Granulomas have recognizable spatial organization



Schematic — not a tissue image

- An activated macrophage aggregate forms the principal focus.
- T lymphocytes often surround or intermingle with it.
- Some lesions have peripheral fibroblasts and connective tissue.

Necrosis may be absent or present

Nonnecrotizing pattern

Organized epithelioid cell aggregate

No central necrotic zone identified

Described in sarcoidosis and Crohn disease

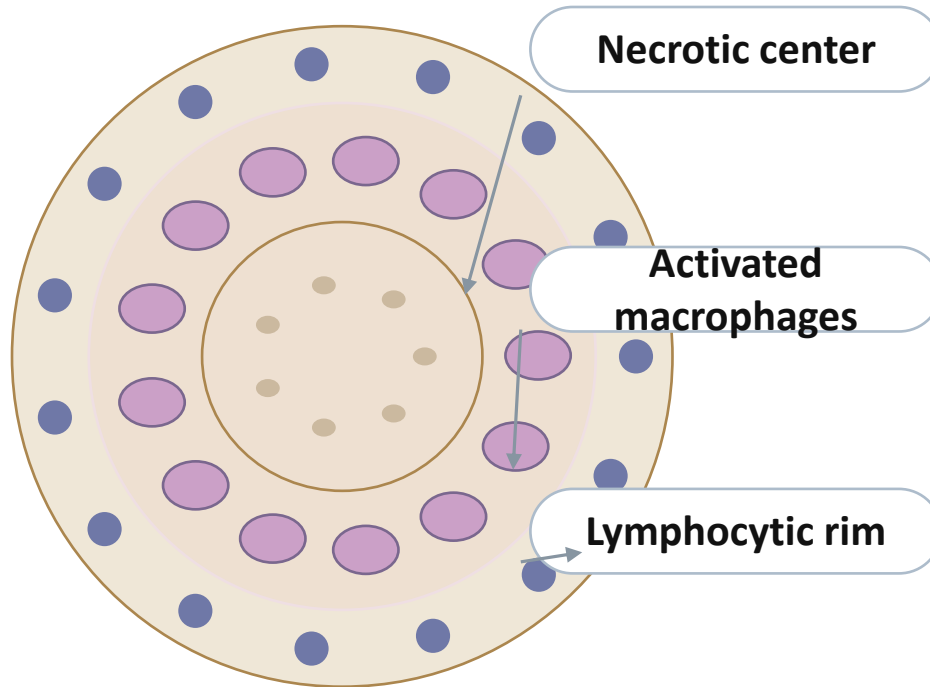
Necrotizing pattern

Central necrotic material present

Common prototype: Tuberculosis

Necrosis alone does not identify an organism

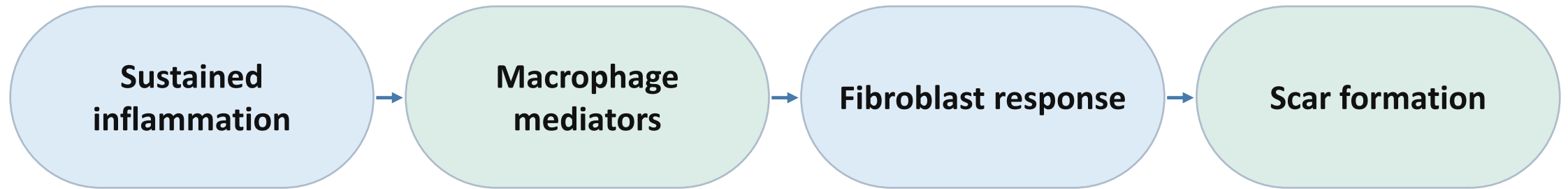
Caseating granulomas include central necrosis



Schematic — not a tissue image

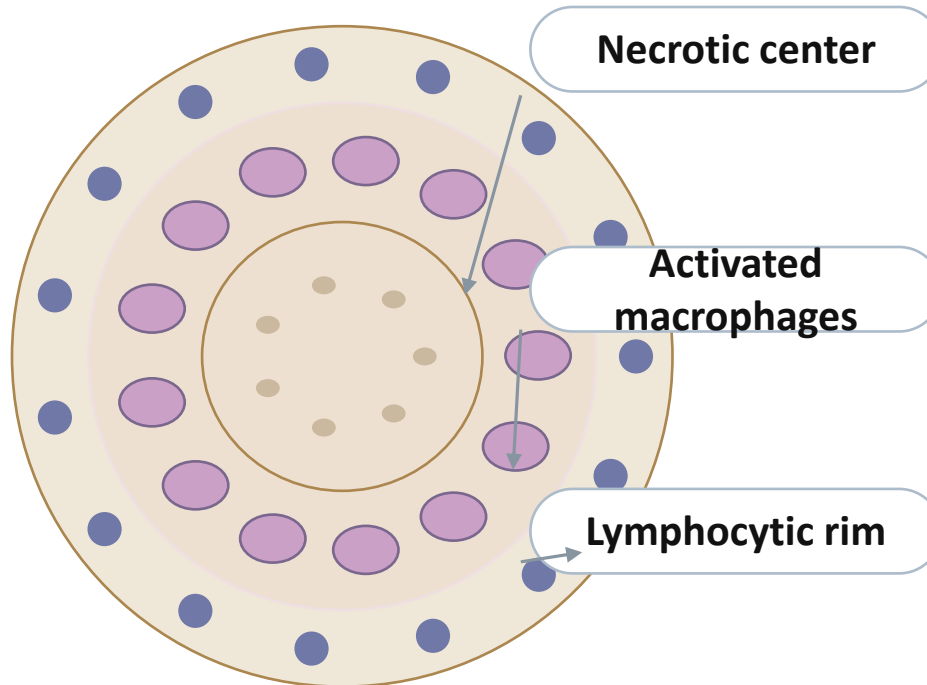
- A necrotic center contains amorphous granular debris.
- The center is surrounded by activated macrophages.
- Lymphocytes and fibroblasts may form a more peripheral rim.

Chronic granulomas may acquire fibrous rims



- Repair can coexist with persistent inflammation and tissue injury.

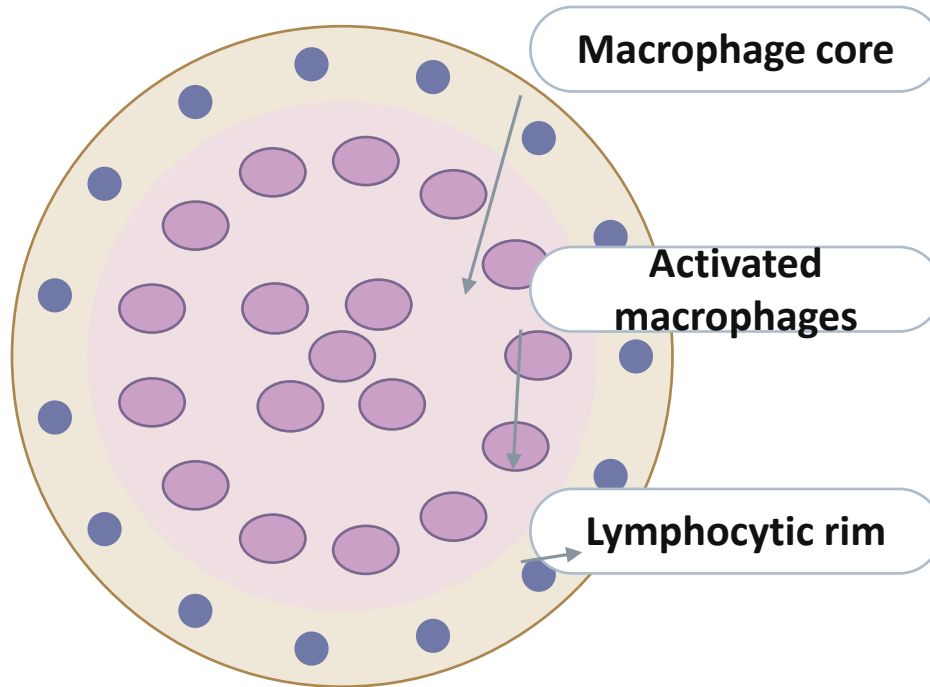
Necrotizing granuloma: Schematic cross-section



Schematic — not a tissue image

- Central necrosis is a distinct compartment.
- Epithelioid cells and giant cells occupy the cellular zone.
- A surrounding lymphocytic/fibroblast-rich region may be present.

Nonnecrotizing granuloma: Schematic cross-section



Schematic — not a tissue image

- Activated macrophages occupy the core.
- T lymphocytes can surround and intermingle with macrophages.
- Absence of necrosis does not identify a unique etiology.

Reading granulomatous histology systematically

Recognize macrophage aggregate



Assess epithelioid and giant cells



Record necrosis or suppuration



Search for foreign material / organisms

Describe what is actually present before inferring a cause.

Morphology suggests an etiology, not a final answer

What morphology can do

Define the reaction pattern

Prioritize plausible causes

Guide targeted ancillary tests

What morphology cannot do alone

Identify every organism

Exclude infection reliably

Replace clinical and microbiologic data

Tuberculosis: Prototype infectious granuloma

Tuberculosis

ETIOLOGY

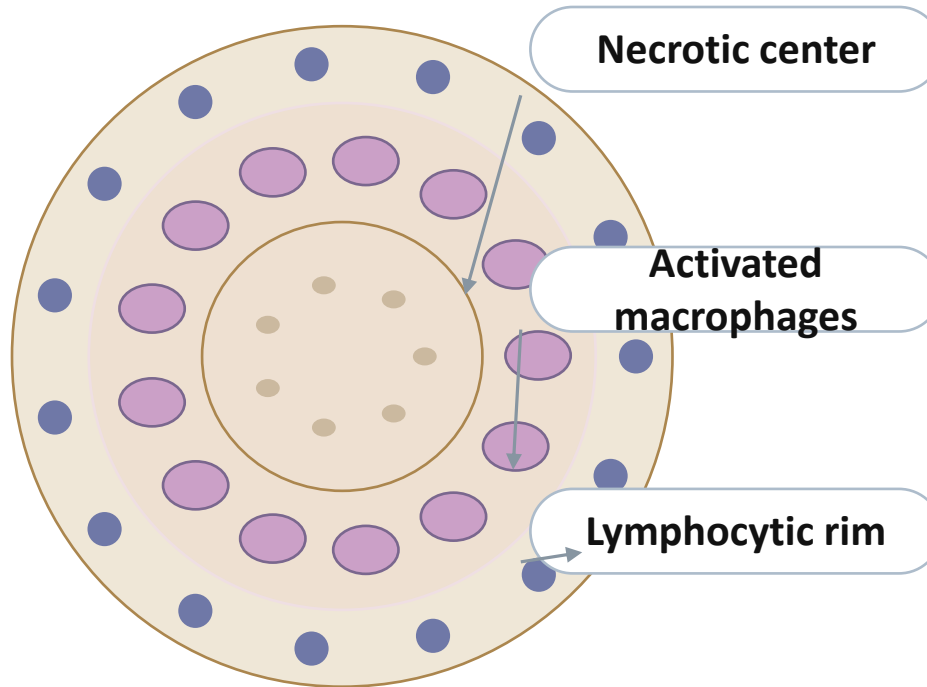
**Mycobacterium
tuberculosis**

PATTERN / TISSUE REACTION

Often caseating “tubercles”; Epithelioid histiocytes, giant cells, lymphocytes and a necrotic center

Always evaluate for tuberculosis when granulomas are discovered.

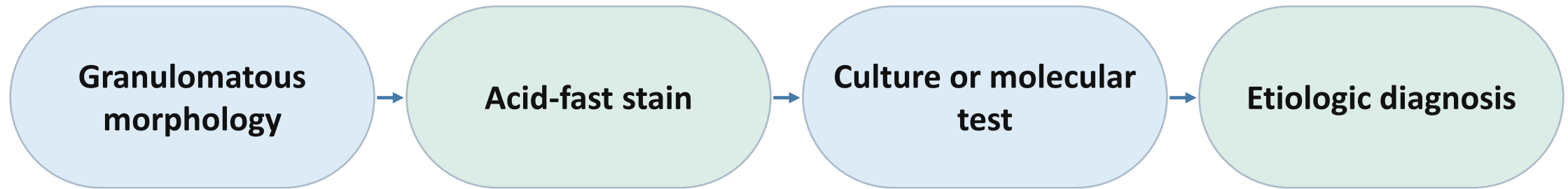
The classic tubercle has layered components



Schematic — not a tissue image

- Amorphous granular necrosis occupies the center.
- Epithelioid macrophages and occasional Langhans giant cells are present.
- Lymphocytes and fibroblasts surround the focus.

Tuberculosis requires microbiologic confirmation



- A characteristic granuloma is a clue; Organism identification is the objective.

Tuberculosis can overlap with other patterns

Supports tuberculosis

Caseating epithelioid granulomas

Compatible host and clinical setting

Demonstration of acid-fast bacilli

Does not prove tuberculosis

Necrosis without microbial evidence

A giant cell by itself

A nonnecrotizing pattern alone

Leprosy: Macrophages can harbor acid-fast bacilli

Leprosy

ETIOLOGY

Mycobacterium leprae

PATTERN / TISSUE REACTION

Acid-fast bacilli within macrophages; Noncaseating granulomas comparison

Interpret with the complete tissue findings and organism-directed study.

Syphilis: The granulomatous gumma

Syphilis

ETIOLOGY

Treponema pallidum

PATTERN / TISSUE REACTION

Gumma surrounded by histiocytes; Plasma-cell infiltrate; Central necrotic cells may retain their outlines

Serologic studies are an important component of etiologic evaluation.

Cat-scratch disease: Granulomas with neutrophils

Cat-scratch disease

ETIOLOGY

Bartonella henselae

PATTERN / TISSUE REACTION

Rounded or stellate granuloma; Granular central debris and recognizable neutrophils

Giant cells are uncommon in this pattern.

Sarcoidosis: A noncaseating example

Sarcoidosis

ETIOLOGY

Unknown etiology

PATTERN / TISSUE REACTION

Noncaseating granulomas with abundant activated macrophages

Noncaseating architecture does not eliminate infectious possibilities.

Crohn disease: Granulomas in the intestinal wall

Crohn disease

ETIOLOGY

**Immune response to
intestinal bacteria;
Possible self-antigens**

PATTERN / TISSUE REACTION

Occasional noncaseating granulomas with dense chronic inflammation in the intestinal wall

A granuloma must be interpreted with bowel distribution and other pathology.

Etiologic classification: Examples

Category	Examples	Common reaction feature
Infectious	Tuberculosis; Leprosy	Mycobacterial / acid-fast association
Infectious	Syphilis; Cat-scratch disease	Gumma or suppurative granuloma
Immune-mediated / unknown	Crohn disease; Sarcoidosis	Often noncaseating pattern
Foreign material	Suture; Talc; Fibers	Particle-centered giant-cell response

Compare textbook granulomatous disease patterns

Disease	Distinctive clue	Caution
Tuberculosis	Caseating tubercle	Confirm M. Tuberculosis
Syphilis	Gumma; Plasma cells	Use etiology-specific testing
Cat-scratch	Stellate / neutrophilic center	Suppuration is a clue
Sarcoidosis	Noncaseating focus	Exclude mimics
Crohn disease	Occasional intestinal granulomas	Requires tissue/context integration

Location and clinical context refine the differential

- Intestinal wall with chronic mucosal disease: Crohn disease may enter the differential.
- Granulomatous lymphadenitis with neutrophils: Consider a suppurative cause.
- Implant or suture site: Search directly for embedded material.
- Any granulomatous lesion demands evaluation for infectious causes, particularly tuberculosis.

Necrosis does not uniquely diagnose tuberculosis

What necrosis tells you

Tissue destruction occurred

A necrotizing granuloma is present

Tuberculosis becomes important to test

What it cannot tell you

Which organism is responsible

Whether organisms remain viable

Whether all infection has been excluded

Nonnecrotizing does not uniquely diagnose sarcoidosis

Examples with nonnecrotizing lesions

Sarcoidosis

Crohn disease

Leprosy in textbook table

What to do next

Review organ site and systemic history

Assess organism-specific evidence

Correlate with other tissue features

Initial questions after identifying a granuloma

Does it contain identifiable foreign material?



Is there necrosis or suppuration?

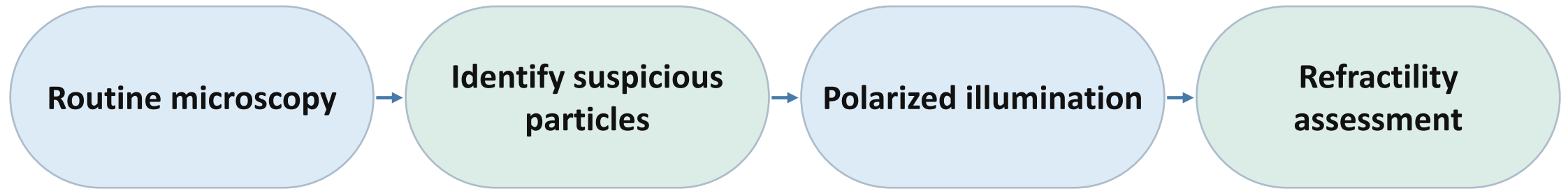


Where is the lesion and what is the clinical setting?



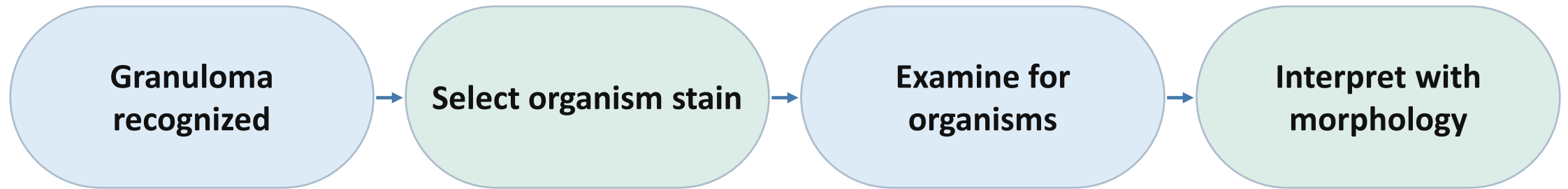
Which organisms or diseases need specific tests?

Polarized light is an adjunct for foreign material



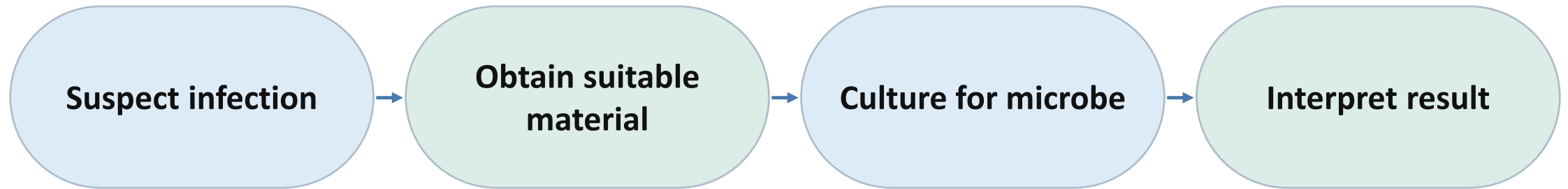
- Some foreign material can be found within giant cells.
- A negative polarized-light finding does not by itself resolve etiology.

Special stains target suspected organisms



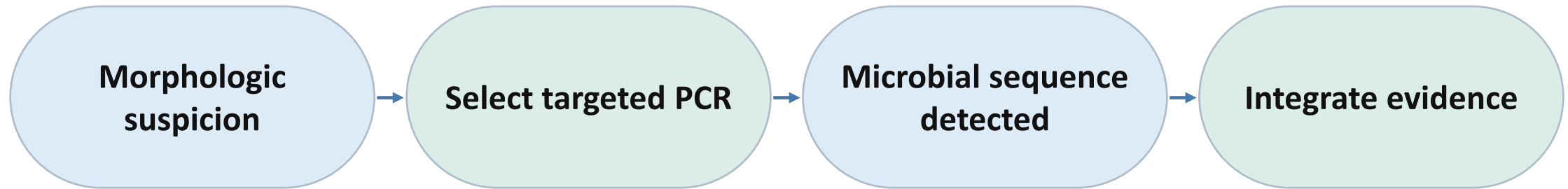
- The textbook specifically cites acid-fast staining for tubercle bacilli.

Culture provides organism-directed confirmation



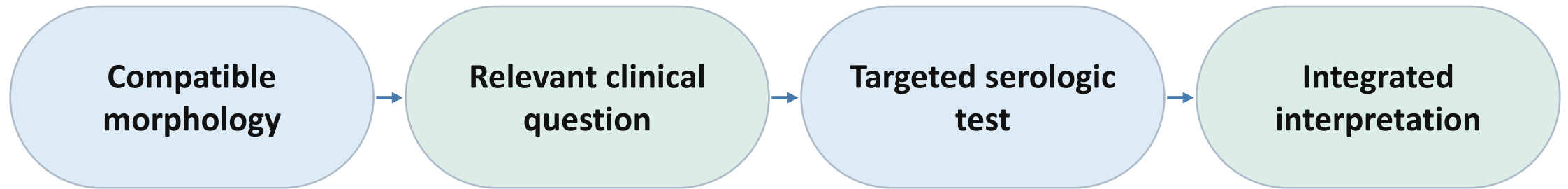
- Culture methods for tuberculosis and fungal diseases.
- Culture requires appropriately collected clinical material.

Molecular testing may establish an infectious cause



- The chapter specifically mentions polymerase chain reaction in tuberculosis.

Serology can answer selected etiologic questions



- The chapter highlights serologic studies for syphilis.

Integrated diagnostic workflow

Describe the granulomatous pattern



Evaluate foreign material and tissue context



Exclude key infections using appropriate studies



Integrate ancillary findings with clinical evidence

No single morphologic pattern can substitute for identifying the cause.

Case: Nodule at a previous operative site

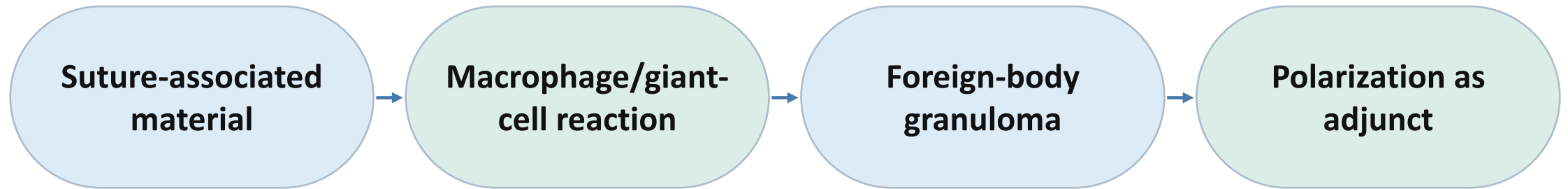
Clinical–pathologic observation

A localized nodule develops at the site of an earlier surgical repair. Biopsy contains histiocytes and multinucleated giant cells surrounding a small linear structure.

Which etiologic class is favored, and which microscope technique could help?

Look for material at the center.

Case resolution: Foreign-body granuloma



- Local exposure and material identify the likely trigger.
- This mechanism does not require an antigen-specific T-cell response.

Case: Necrotizing granulomatous lymphadenitis

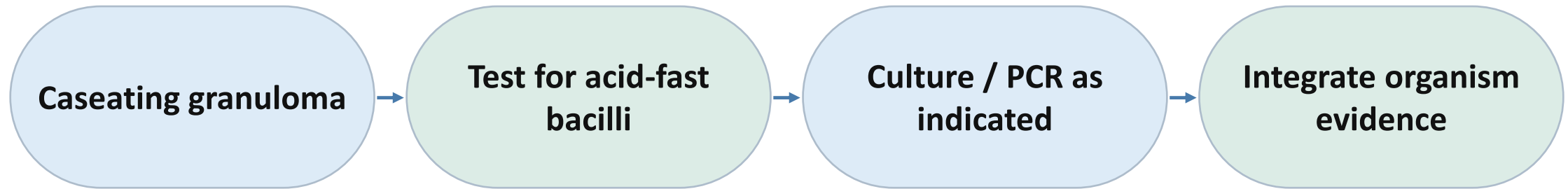
Clinical–pathologic observation

A lymph node contains an epithelioid granuloma with central amorphous necrotic debris and a peripheral lymphocytic rim. No organism is identified on routine H&E.

Which infectious disease must be excluded, and which confirmatory tests are named?

Morphology alone is insufficient.

Case resolution: Exclude tuberculosis



- Necrosis increases concern but does not establish mycobacterial etiology.

Case: A nonnecrotizing intestinal granuloma

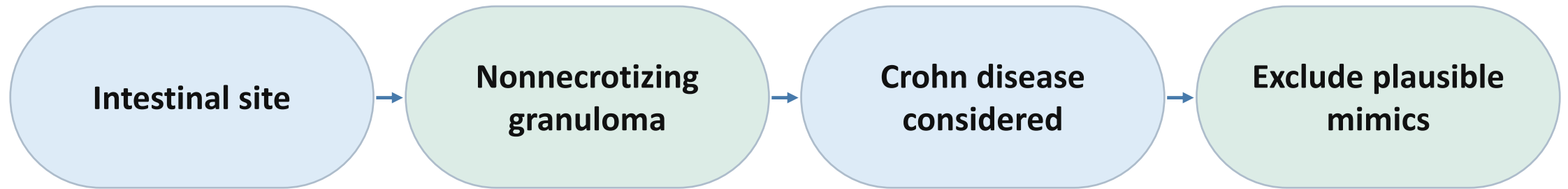
Clinical–pathologic observation

An intestinal wall biopsy shows a small nonnecrotizing epithelioid granuloma together with a chronic inflammatory infiltrate.

Which immune-mediated disease fits, and what diagnostic shortcut is unsafe?

Granuloma pattern is not disease-specific.

Case resolution: Clinicopathologic correlation



- The histologic pattern fits but cannot alone establish the full diagnosis.

Common reasoning errors and the corrective step

Error	Why misleading	Corrective action
"Caseation proves TB"	Pattern overlaps other causes	Pursue organism-specific studies
"No necrosis proves sarcoidosis"	Several diseases are nonnecrotizing	Correlate site and etiologies
"Giant cells prove infection"	Foreign-body reactions also form them	Look for particles / exposure
"H&E identifies every cause"	Organisms/material may be subtle	Use ancillary tests

Integrated mechanism–morphology comparison

Origin	Dominant driver	Clue to investigate
Foreign material	Inert, hard-to-ingest particle	Embedded/refractile material
Mycobacterial infection	Persistent microbial antigen	Tubercle; Targeted microbiology
Th2-related parasite	Parasite-driven response	Eosinophil-rich granuloma
Crohn / sarcoidosis	Immune context / uncertain cause	Organ site and exclusion of infection

Synthesis: Four rules for tissue granulomas

- Granuloma = organized collection of activated macrophages, often with T cells.
- Foreign-body and immune granulomas differ primarily in their initiating mechanism.
- Epithelioid cells, giant cells, necrosis and fibrosis are components—not etiologic proof.
- Confirm the cause by combining morphology, exposure, clinical context and targeted tests.

Primary reference and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Chapter 3, “Inflammation and Repair,” granulomatous inflammation (pp. 90–91).
- Parent sections: chronic inflammation, macrophages and lymphocytes (pp. 87–90).
- Disease examples and microscopic descriptions follow Table 3.9.
- All diagrams in this lecture are original, editable teaching schematics—not photomicrographs.