

Chronic Inflammation

Persistent stimuli, tissue injury, and attempted repair

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Learning outcomes

- Explain chronic inflammation as simultaneous inflammation, damage, and repair.
- Distinguish its main causes and histologic pattern from acute inflammation.
- Describe macrophage–lymphocyte interactions and activation programs.
- Recognize granulomatous inflammation and its diagnostic implications.

A prolonged response—not merely prolonged time

- Chronic inflammation persists for weeks or months because the stimulus is sustained or poorly eliminated.
- Inflammation and parenchymal injury occur alongside attempts at tissue healing.
- It may follow an acute episode or begin without a clinically apparent acute phase.

Three processes coexist in the same lesion

**Inflammatory cell
recruitment and
activation**

**Injury to the original
tissue**

**Angiogenesis and
fibrosis during repair**

Concurrent or complementary components of the host response

Chronic inflammation can begin by two routes

After acute inflammation

Persistence of the injurious stimulus prevents complete resolution.

Example: Acute bacterial pneumonia progressing to a chronic lung abscess.

Insidious onset

A sustained immune or toxic stimulus produces a prolonged response from the outset.

Example: An evolving autoimmune or particle-related lesion.

Acute versus chronic: Predominant cellular pattern

Acute response

Vascular changes and edema are prominent.

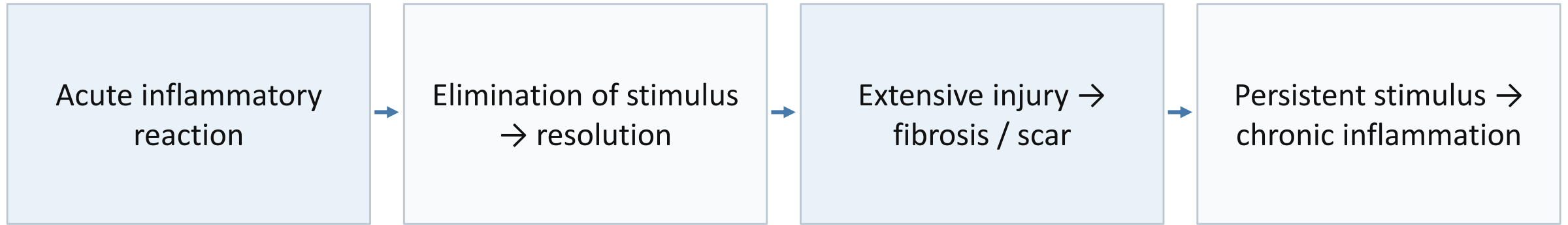
Neutrophils usually dominate the early infiltrate.

Chronic response

Macrophages, lymphocytes and plasma cells accumulate.

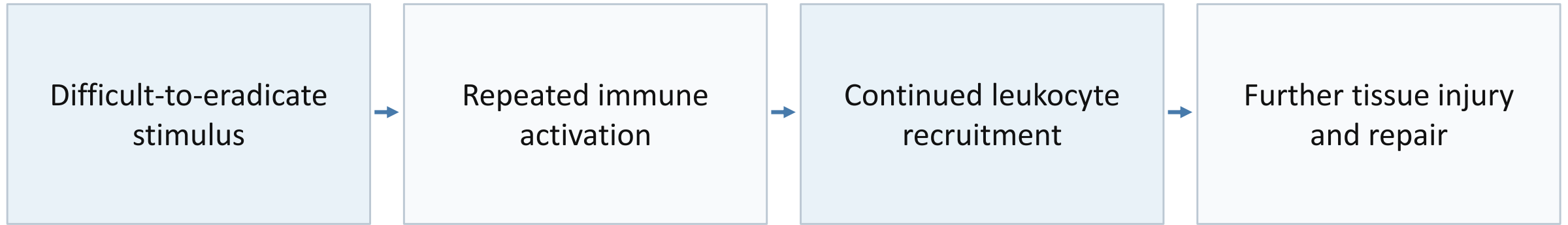
Tissue loss and fibrosis often coexist with ongoing recruitment.

Possible outcomes of an acute inflammatory focus



Mechanistic sequence — schematic

Why chronic inflammation persists



Mechanistic sequence — schematic

Three major classes of persistent stimuli

**Infections that resist
clearance**

**Hypersensitivity or
dysregulated immune
reactions**

**Prolonged exposure to
toxic materials**

Concurrent or complementary components of the host response

Persistent infection sustains cellular immunity

- Mycobacteria and some viruses, fungi, and parasites are difficult to eliminate.
- Persistent microbial antigens may elicit T-lymphocyte responses of the delayed-type hypersensitivity pattern.
- Some infections evoke granulomatous inflammation to contain the stimulus.

Not all chronic infections form granulomas

Granulomatous pattern

Aggregates of activated macrophages, frequently with T lymphocytes.

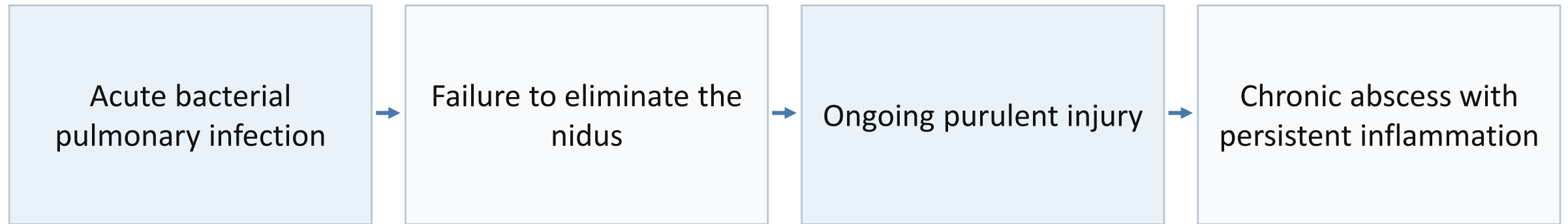
Characteristic but not universal for persistent infections.

Nongranulomatous pattern

Diffuse or mixed inflammation may persist in tissues.

The morphologic pattern depends on the agent and host response.

Unresolved bacterial infection: A lung-abscess example

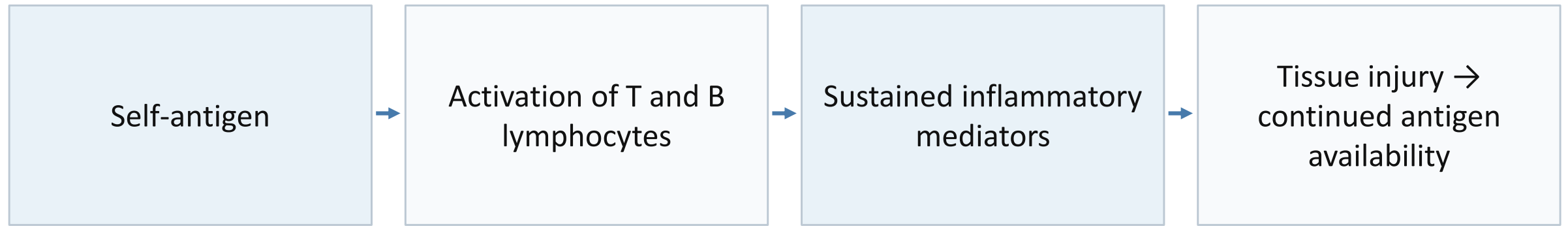


Mechanistic sequence — schematic

Hypersensitivity causes injury without useful clearance

- Excessive or inappropriate activation of the immune system can maintain chronic inflammation.
- The trigger may be a self-antigen, microbial component, or ordinary environmental substance.
- Persistent immune activation can damage otherwise viable host tissues.

Autoimmune inflammation is self-perpetuating



Mechanistic sequence — schematic

Examples of autoimmune chronic inflammation

- Rheumatoid arthritis: An immune response in joint tissues is associated with chronic inflammation.
- Multiple sclerosis: Immune responses against the nervous system produce tissue injury.
- Autoantigen-driven lymphocyte activation can create a continuing disease process.

Dysregulated responses to microbes

- Not every inflammatory injury reflects ongoing invasive infection.
- Inflammatory bowel disease exemplifies an inappropriate immune response to microbial antigens.
- The resulting reaction can persist because the immune stimulus is continually present.

Allergic inflammation: Ordinarily harmless antigens

- Environmental substances may provoke disproportionate immune responses.
- Bronchial asthma is an example in which immune activation drives tissue inflammation.
- Repeated exacerbations can produce mixed acute and chronic patterns.

Repeated flares may obscure an acute–chronic boundary

During exacerbation

Freshly recruited acute inflammatory cells may accompany an established chronic infiltrate.

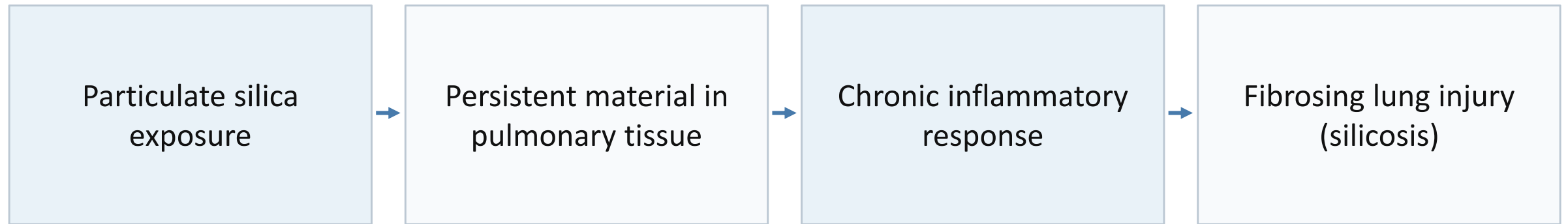
One biopsy can show an active mixed-cell pattern.

Late-stage evolution

Connective tissue deposition may become prominent.

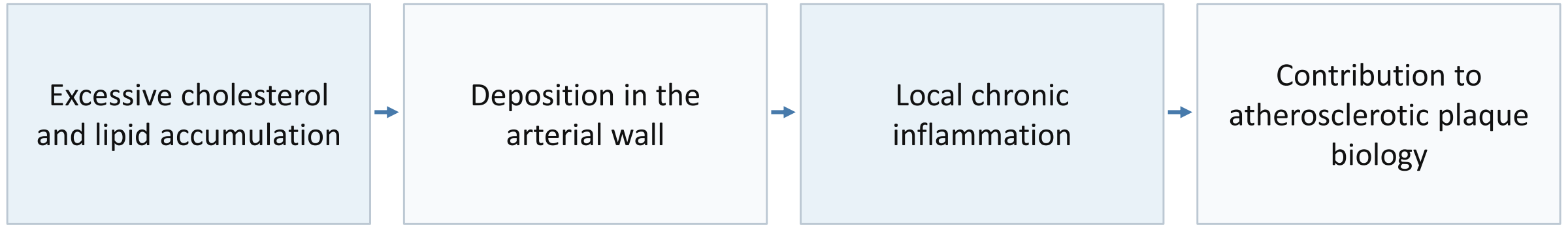
Fibrosis is evidence of sustained injury and repair, not necessarily inactivity.

Inhaled silica: A nondegradable foreign stimulus



Mechanistic sequence — schematic

Endogenous lipids can maintain inflammation



Mechanistic sequence — schematic

The inciting agent predicts the immune pattern

Setting	Main driver	Tissue response
Persistent microbe	T lymphocytes / macrophages	Sometimes granulomas
Self or environmental antigen	Activated lymphocytes $\pm$ eosinophils	Chronic or recurrent inflammation
Toxic particle or lipid	Macrophage-rich tissue response	Damage with fibrotic repair

Three histologic hallmarks of chronic inflammation

**Mononuclear cell
infiltration**

**Destruction of tissue
architecture**

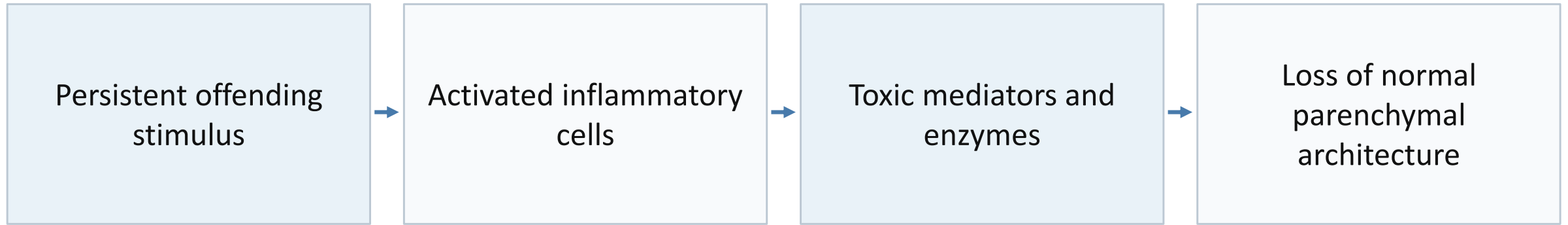
**Repair: Small vessels
and collagen
deposition**

Concurrent or complementary components of the host response

Mononuclear infiltrate: Identify the cells

- Macrophages are major phagocytic and secretory effectors.
- Lymphocytes amplify antigen-specific immune responses.
- Plasma cells reflect antibody-secreting B-cell differentiation.
- The mixture varies according to the etiology and tissue.

Tissue destruction identifies ongoing injury



Mechanistic sequence — schematic

Angiogenesis is part of attempted repair

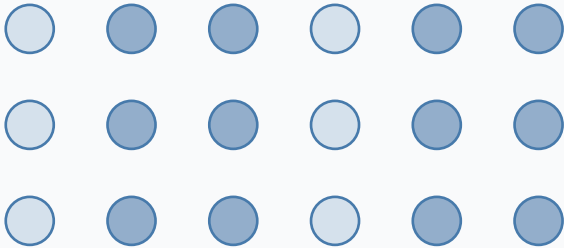
- Small new vessels proliferate as the damaged tissue attempts to heal.
- Angiogenesis can coexist with dense inflammatory infiltrates.
- Repair features should be assessed together with the extent of parenchymal loss.

Fibrosis replaces tissue that cannot regenerate fully

- Collagen deposition can substitute for irreversibly destroyed parenchyma.
- The resulting scar may impair specialized organ function.
- Marked fibrosis may dominate older or recurrent lesions.

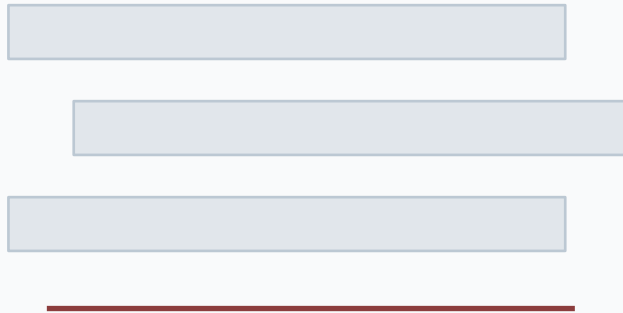
How to read a chronic inflammatory biopsy

Cell-rich focus



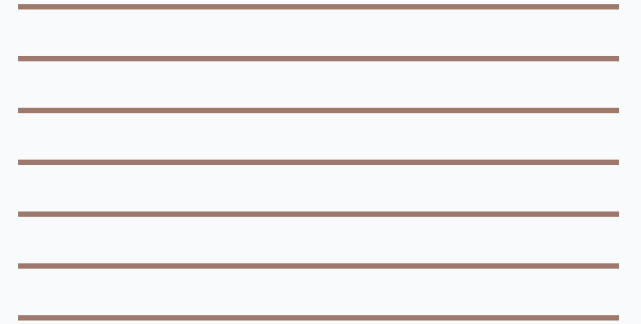
Locate mononuclear-cell-rich areas.

Lost architecture



Look for loss of normal tissue units.

Fibrous repair



Identify fibroblasts, vessels and collagen-rich replacement.

Schematic only — not a histologic specimen

A mixed infiltrate does not exclude chronicity

- Neutrophils may remain when microorganisms or irritating stimuli persist.
- Repeated injury can recruit fresh acute inflammatory cells into chronic lesions.
- Classify the full tissue response rather than treating one cell type as decisive.

Macrophages coordinate injury and repair

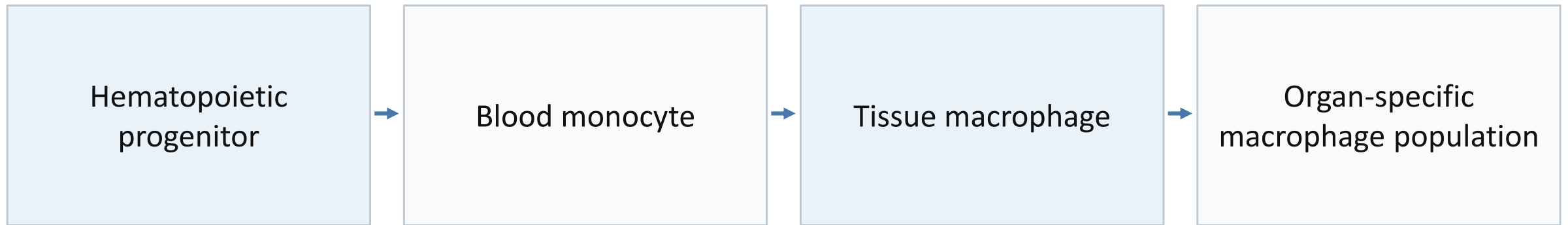
**Destroy microbes and
dead cells**

**Communicate through
cytokines and antigen
display**

**Recruit repair
programs and
connective-tissue
deposition**

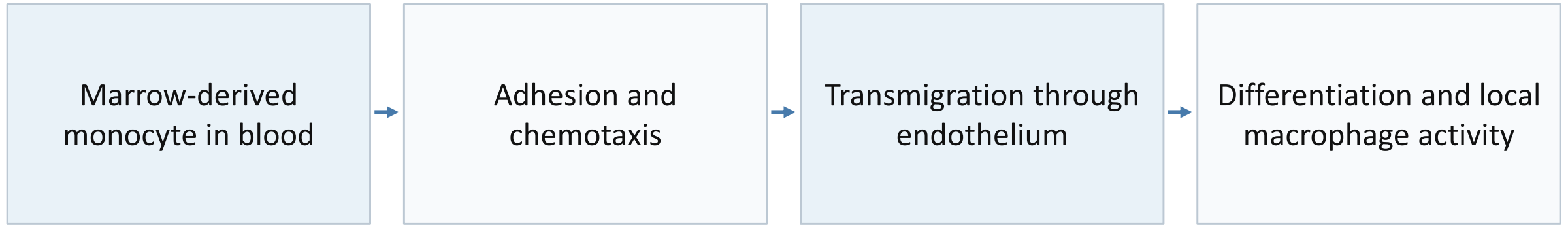
Concurrent or complementary components of the host response

The mononuclear phagocyte system



Mechanistic sequence — schematic

Circulating monocytes enter inflamed tissues



Mechanistic sequence — schematic

Not all tissue macrophages derive from adult monocytes

Monocyte-derived

Adult marrow progenitors generate blood monocytes.

Important in inflammatory foci and some renewing tissue sites.

Embryonically seeded

Yolk-sac or fetal-liver progenitors seed selected organs.

Long-lived resident cells can persist in the tissue.

Organ-specific macrophage populations

Tissue	Cell name	Function
Liver	Kupffer cells	Resident parenchymal surveillance
Brain	Microglia	Resident immune surveillance
Lung	Alveolar macrophages	Airspace defense and debris clearance

Recruitment and lifespan differ by compartment

- Blood monocytes are short-lived relative to many tissue macrophages.
- In an inflammatory lesion, monocytes can become the dominant population within about 48 hours.
- Resident macrophages may be maintained for extended periods in their organ.

Macrophages execute three connected functions

**Phagocytosis and
microbial killing**

**Cytokine and lipid-
mediator secretion**

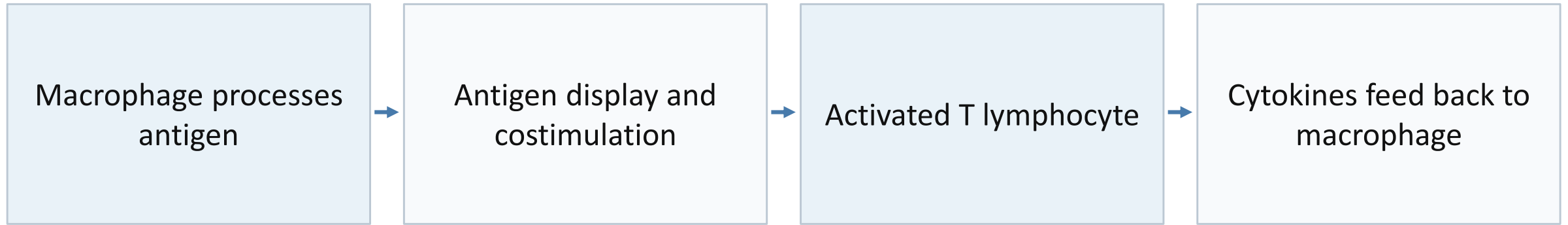
**Regulation of healing
and scar formation**

Concurrent or complementary components of the host response

Proinflammatory macrophage secretions

- Tumor necrosis factor (TNF) and interleukin-1 (IL-1) amplify inflammation.
- Chemokines guide additional leukocytes into the tissue.
- Eicosanoids also participate in inflammatory mediator networks.

Antigen display activates adaptive immunity

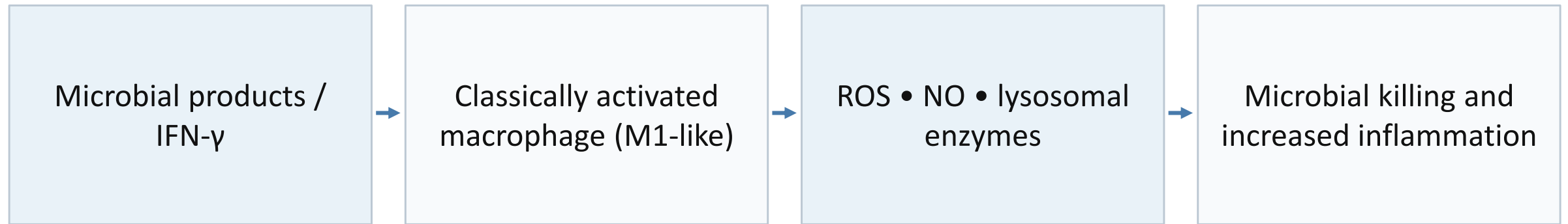


Mechanistic sequence — schematic

Classical activation: Initiating signals

- Microbial products activate innate sensors such as toll-like receptors (TLRs).
- T-cell-derived interferon- γ (IFN- γ) is a major activating cytokine.
- Crystals and other particulates can also drive classical activation.

Classical activation favors host defense

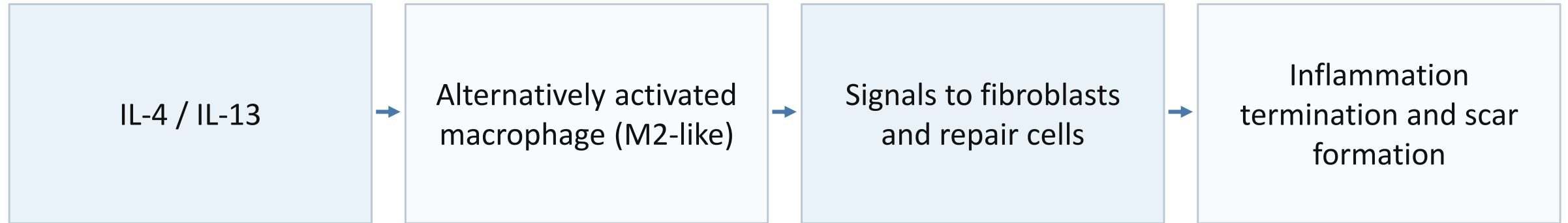


Mechanistic sequence — schematic

Alternative activation: Initiating signals

- Interleukin-4 (IL-4) and IL-13 can induce an alternative macrophage program.
- These mediators are often produced by Th2 cells and other immune cells.
- Alternative activation is linked more strongly to resolution and tissue repair than to direct microbial killing.

Alternative activation favors tissue reconstruction



Mechanistic sequence — schematic

M1-like and M2-like responses: Functional poles

M1-like

Driven by microbial products or IFN- γ .

Microbicidal substances and inflammatory cytokines.

M2-like

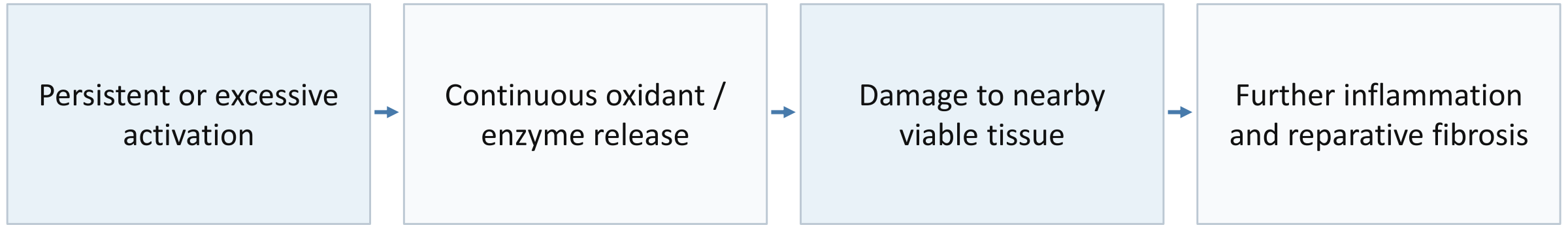
Driven by cytokines including IL-4 and IL-13.

Resolution-associated activity and tissue repair.

M1/M2 are models, not rigid cell diagnoses

- Actual inflammatory tissues often contain mixed activation states.
- Many intermediate macrophage phenotypes cannot be reliably assigned to a binary subset.
- A universal sequence of M1 followed by M2 has not been documented across most lesions.

Macrophage defense can become collateral injury



Mechanistic sequence — schematic

Why macrophages remain in chronic lesions

- Persistent recruitment of circulating monocytes replenishes the infiltrate.
- Local macrophage proliferation can sustain the population.
- After stimulus removal, macrophages may die or exit via lymphatic drainage.

T and B lymphocytes amplify chronic inflammation

- Microbial and environmental antigens stimulate lymphocyte responses.
- Activated T cells generate cytokines that recruit and alter macrophage behavior.
- Long-lived memory lymphocytes can help sustain the reaction.

CD4 T-cell subsets generate distinct inflammation

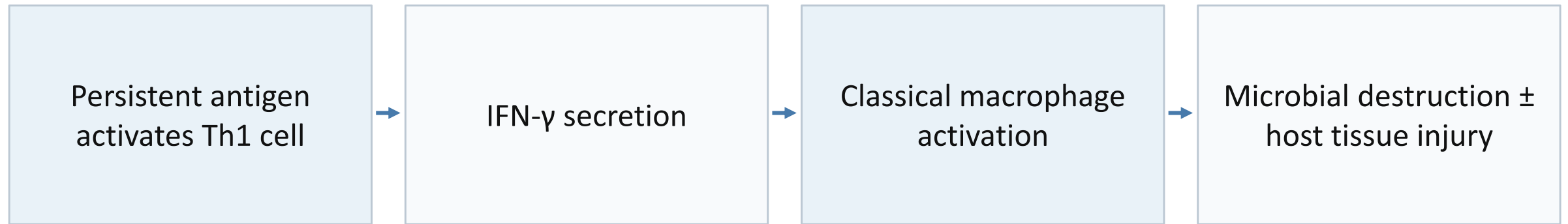
**Th1 → IFN- γ →
macrophage activation**

**Th2 → IL-4, IL-13, IL-5
→ allergy / eosinophils**

**Th17 → IL-17 →
chemokines /
neutrophils**

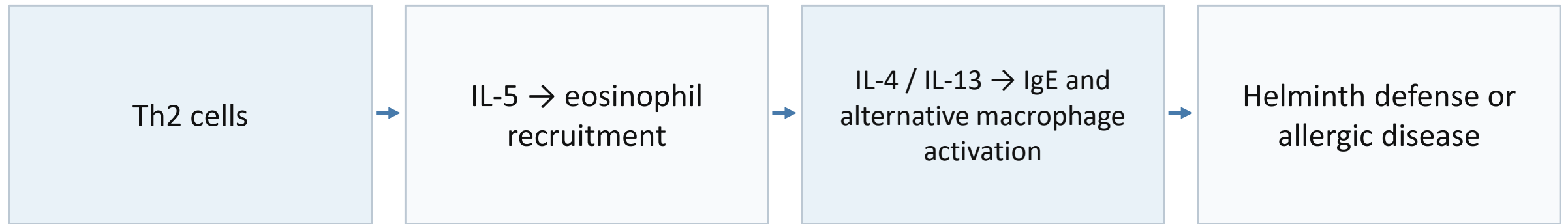
Concurrent or complementary components of the host response

Th1 cells connect cellular immunity to macrophages



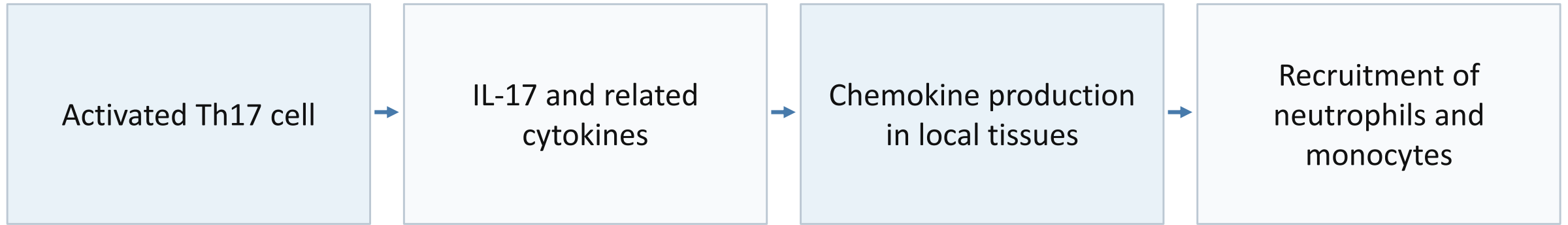
Mechanistic sequence — schematic

Th2 mediators recruit distinct effectors



Mechanistic sequence — schematic

Th17 cells recruit neutrophilic inflammation

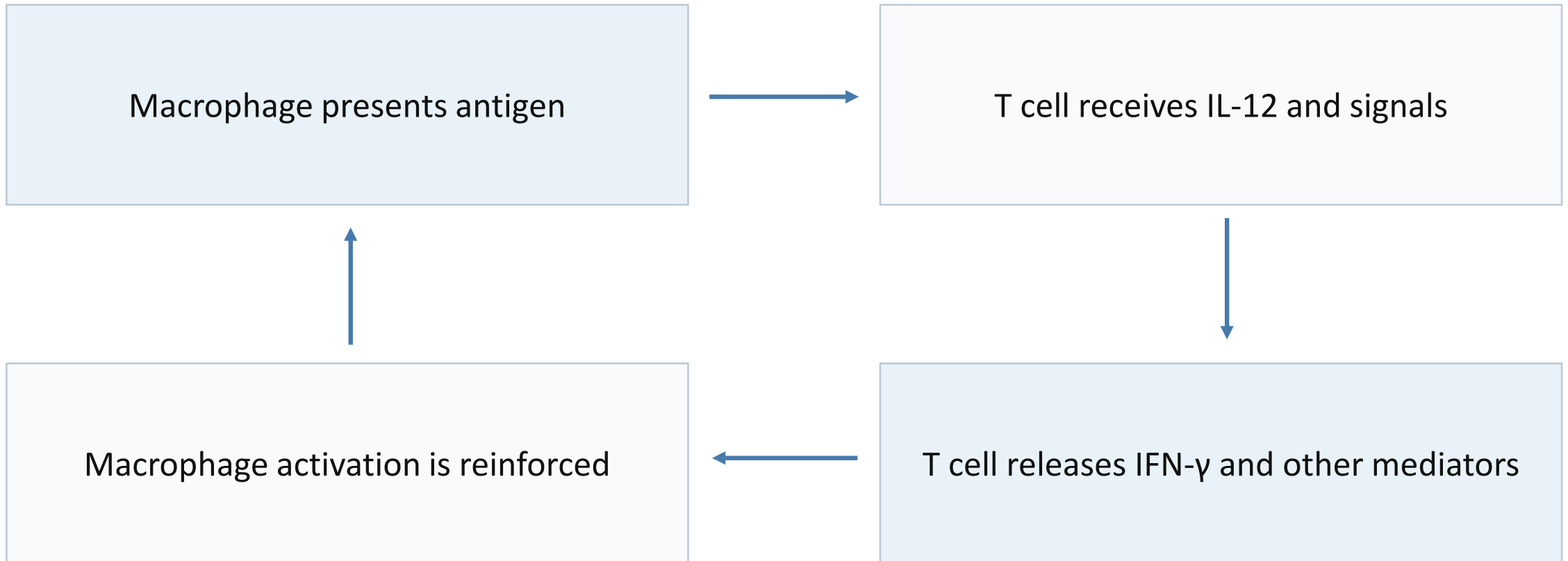


Mechanistic sequence — schematic

T-helper pathways: Mediator to tissue phenotype

T-cell pathway	Downstream response	Pattern
Th1 / IFN- γ	Macrophage activation	Cell-mediated inflammation
Th2 / IL-4, IL-5, IL-13	IgE, eosinophils, M2-like signals	Allergic / helminth response
Th17 / IL-17	Chemokine-driven recruitment	Neutrophil-rich component

The macrophage–T-cell feedback loop



Why adaptive immunity prolongs inflammation

- Antigen presentation, costimulation and macrophage cytokines drive T-cell responses.
- Activated T lymphocytes release cytokines that recruit and activate macrophages.
- Persistent antigen closes the feedback loop and can support granuloma formation.

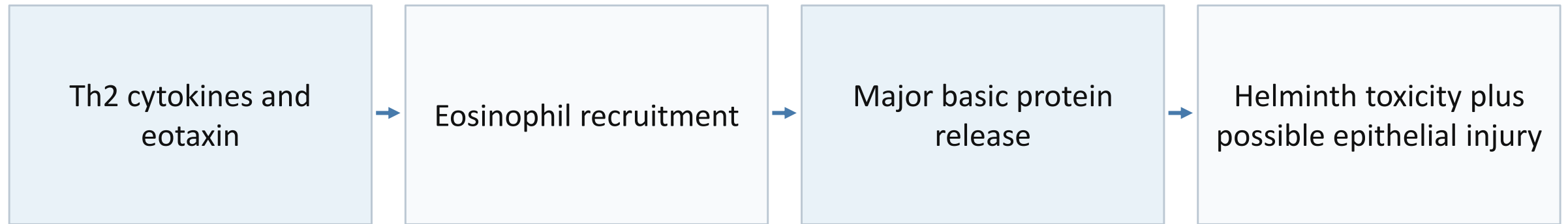
Plasma cells reveal a humoral response

- B lymphocytes may differentiate into antibody-secreting plasma cells at an inflamed site.
- The antibodies can recognize persistent foreign antigens, self-antigens or altered tissue components.
- The overall pathogenic contribution of local antibodies is uncertain in many conditions.

Tertiary lymphoid structures can form in tissues

- Lymphocytes, antigen-presenting cells and plasma cells may assemble into follicle-like structures.
- Examples include rheumatoid synovium, Hashimoto thyroiditis and inflammation around some tumors.
- Their role in perpetuating local immune responses remains incompletely established.

Eosinophils contribute to chronic allergic injury



Mechanistic sequence — schematic

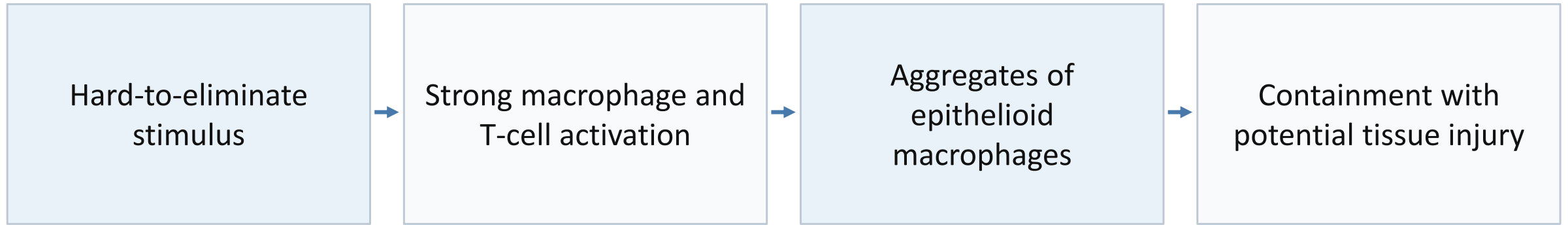
Mast cells can sustain inflammatory signaling

- Tissue mast cells express the high-affinity IgE receptor FcεRI.
- Antigen engagement of surface-bound IgE can release histamine and prostaglandins.
- Mast-cell-derived cytokines may also contribute to chronic inflammatory lesions.

Neutrophils may persist for months

- Neutrophils are not restricted to purely acute lesions.
- Chronic osteomyelitis may show prolonged purulent inflammation.
- Smoking-related pulmonary injury may also involve continuing neutrophilic damage.

Granulomas attempt to contain resistant agents



Mechanistic sequence — schematic

Two major pathogenetic classes of granulomas

Foreign-body granuloma

Inert, large, poorly phagocytosed material.

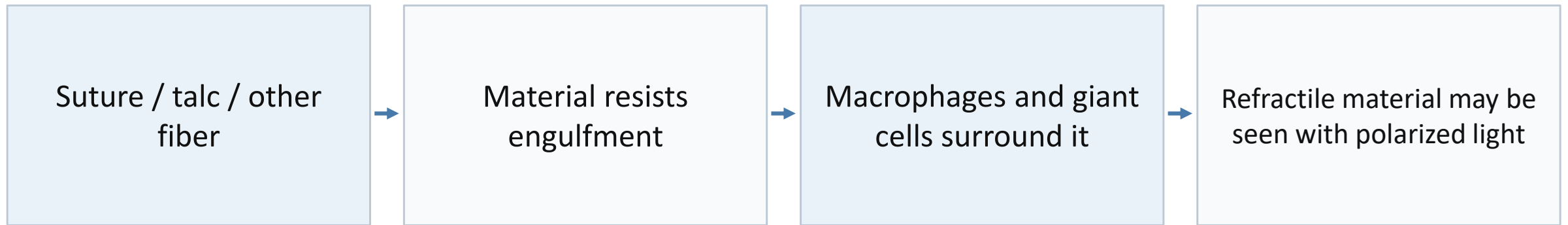
May develop without a specific T-cell immune response.

Immune granuloma

Persistent microbe or antigen activates T cells.

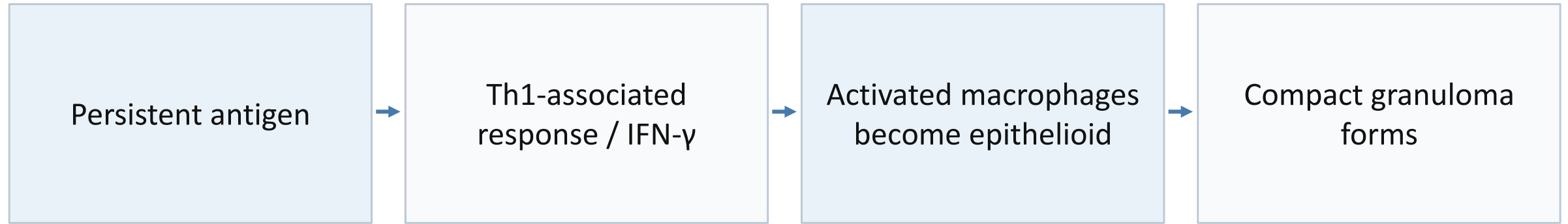
Cytokine-driven macrophage activation is central.

Foreign-body granuloma: Material at the center



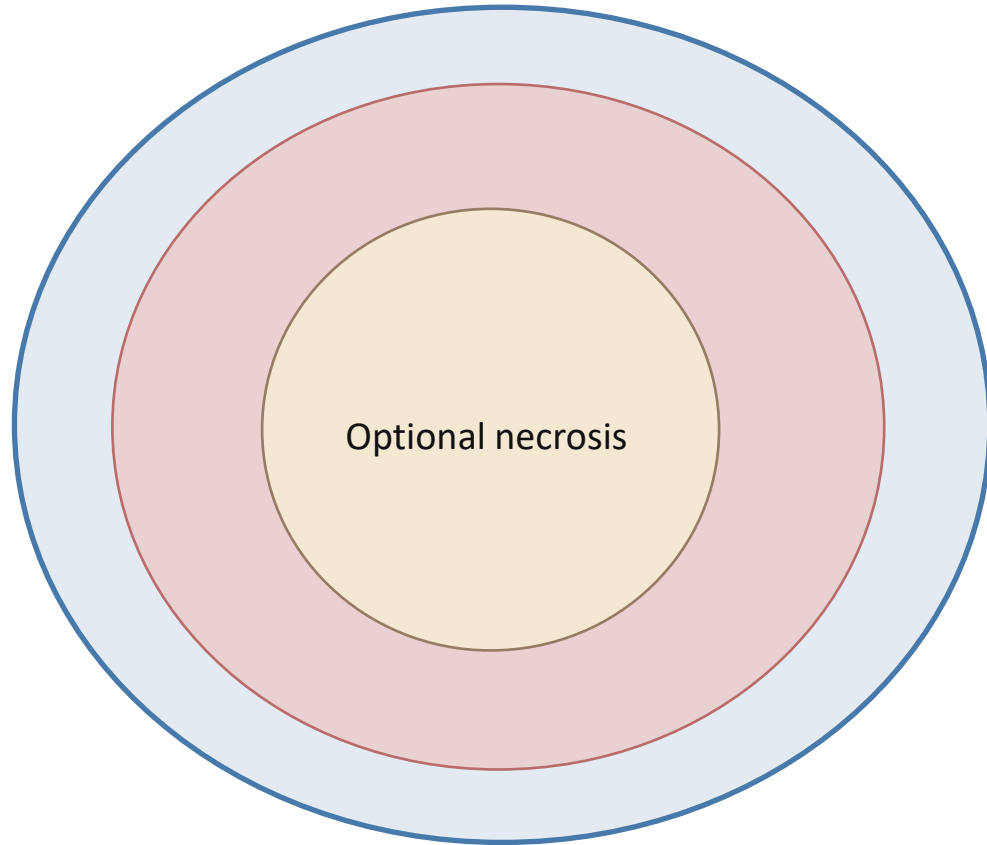
Mechanistic sequence — schematic

Immune granuloma: A T-cell-driven arrangement



Mechanistic sequence — schematic

Basic granuloma architecture



Schematic only — central necrosis is not obligatory

Organized inflammatory focus

Epithelioid macrophage center

Peripheral lymphocyte collar

Sometimes giant cells, necrosis and fibrosis

Epithelioid cells are activated macrophages

- Activated macrophages acquire abundant granular, pink cytoplasm on H&E sections.
- Cellular outlines may become indistinct in tightly packed epithelioid clusters.
- The name reflects their epithelial-like appearance, not epithelial lineage.

Multinucleated giant cells arise by fusion

- Some activated macrophages fuse to form large multinucleated cells.
- Langhans-type giant cells contain many nuclei, often arranged near the periphery.
- Giant cells support a granulomatous pattern but are not invariably present.

Central necrosis is an important descriptor

- Caseous necrosis shows granular, acellular eosinophilic debris and loss of cell outlines.
- *Mycobacterium tuberculosis* is a prototypical cause of necrotizing granulomas.
- The presence or absence of necrosis alone does not identify the etiology.

Necrotizing and nonnecrotizing patterns

Necrotizing

A central zone of amorphous, structureless necrotic debris.

Can be found in tuberculosis and other infections.

Nonnecrotizing

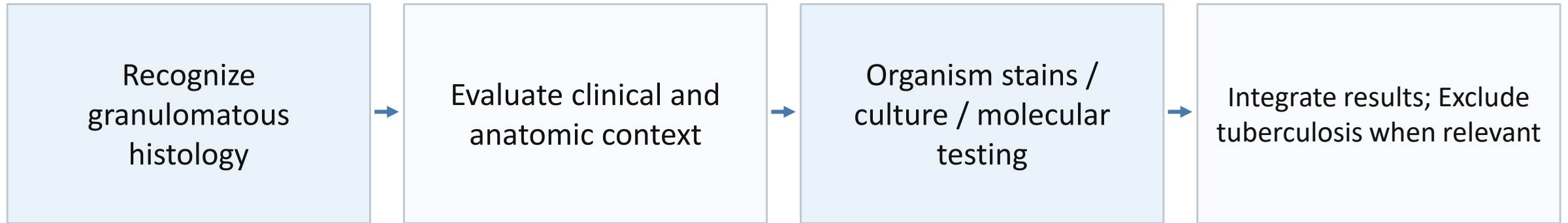
Epithelioid aggregates without a central necrotic focus.

May occur in sarcoidosis, Crohn disease or foreign-body reactions.

Granulomatous diseases: Targeted examples

Condition	Known cause	Typical pattern
Tuberculosis	Mycobacterium tuberculosis	Often necrotizing granulomas
Sarcoidosis	Etiology unknown	Often nonnecrotizing granulomas
Crohn disease	Dysregulated intestinal immune response	Occasional nonnecrotizing granulomas

Granulomas require an etiologic work-up



Mechanistic sequence — schematic

Granuloma $\neq$ granulation tissue

Granuloma

Organized cluster of epithelioid macrophages.

Immune or foreign-body response to a persistent stimulus.

Granulation tissue

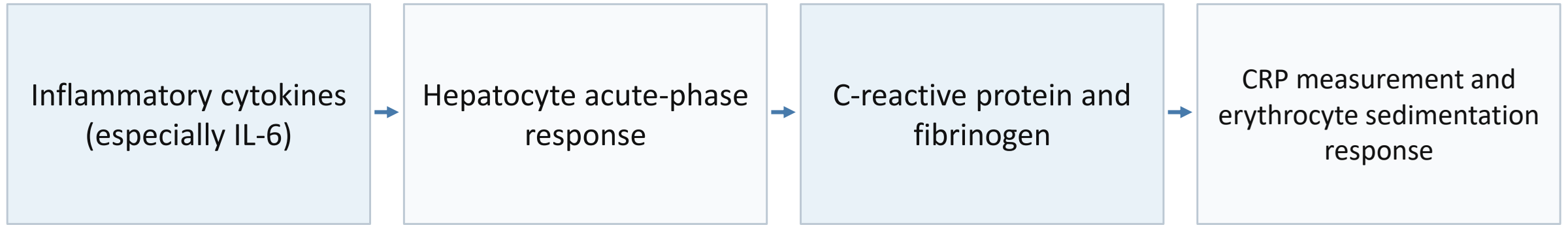
New capillaries, fibroblasts and loose extracellular matrix.

A reparative tissue that forms during wound healing.

Systemic inflammation can accompany local lesions

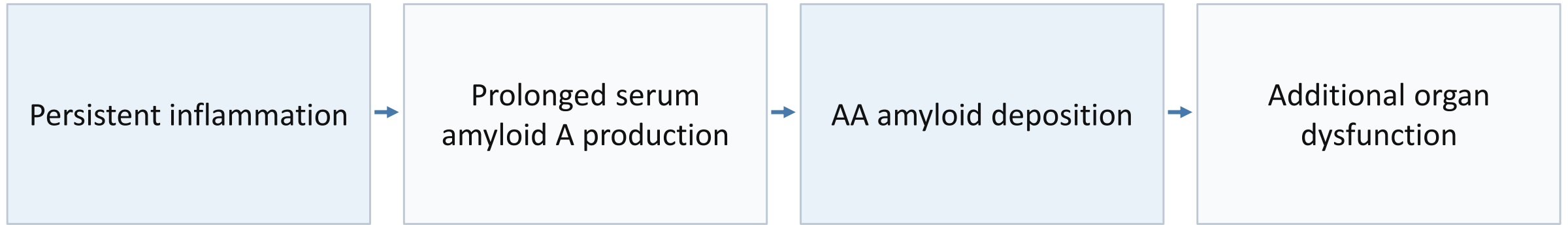
- Cytokines released during inflammation have effects beyond the affected organ.
- TNF, IL-1 and IL-6 contribute to systemic inflammatory reactions.
- Acute-phase protein concentrations may rise during chronic as well as acute inflammation.

CRP and fibrinogen reflect acute-phase signaling



Mechanistic sequence — schematic

Sustained SAA production can cause amyloid deposition



Mechanistic sequence — schematic

Clinicopathologic example: Pulmonary granuloma

Observation

Biopsy: Clusters of epithelioid histiocytes with necrotic centers.

Interpretation

Interpretation: Necrotizing granulomatous inflammation; Infection is a major consideration.

Next diagnostic principle

Next step: Evaluate for organisms with appropriate stains and microbiologic tests.

Clinicopathologic example: Persistent synovitis

Observation

Joint tissue contains lymphocytes, plasma cells and macrophages with fibrosis.

Interpretation

Interpretation: Chronic immune-mediated injury and repair can coexist.

Next diagnostic principle

The infiltrate alone does not establish a specific diagnosis without clinical correlation.

Clinicopathologic example: Foreign material

Observation

A lesion contains multinucleated giant cells adjacent to identifiable suture material.

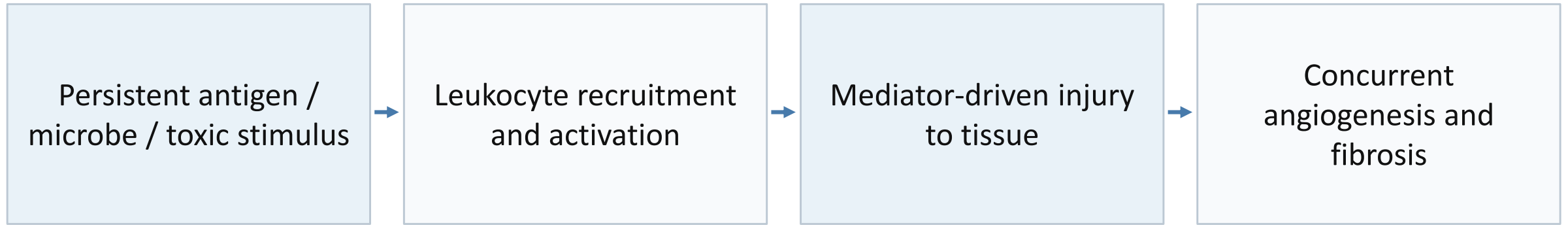
Interpretation

Interpretation: A foreign-body granulomatous response is favored.

Next diagnostic principle

Use polarization and the clinical history to evaluate retained material.

Integrated mechanism of chronic injury



Mechanistic sequence — schematic

Five distinctions to retain

- Chronic inflammation is defined by an ongoing response, not by a fixed number of days.
- Mononuclear cells, tissue destruction and repair form its characteristic histologic triad.
- Macrophages can eliminate agents and simultaneously damage host parenchyma.
- T-cell–macrophage feedback explains persistence in many immune-driven lesions.
- A granuloma is a specific reaction pattern, not a final etiologic diagnosis.

Reference

Primary textbook and material

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Inflammation and Repair: chronic inflammation, granulomatous inflammation, and systemic consequences.
- All diagrams are explanatory schematics, not histopathology specimens.