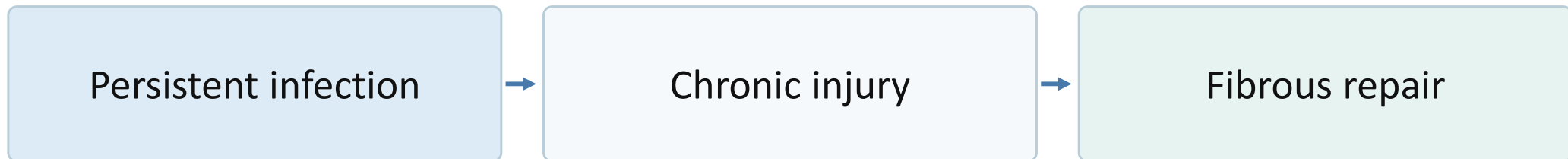


Chronic Inflammation and Scarring

The host response, the scar, and the organ consequence



Dr Abu Suraih Sakhri

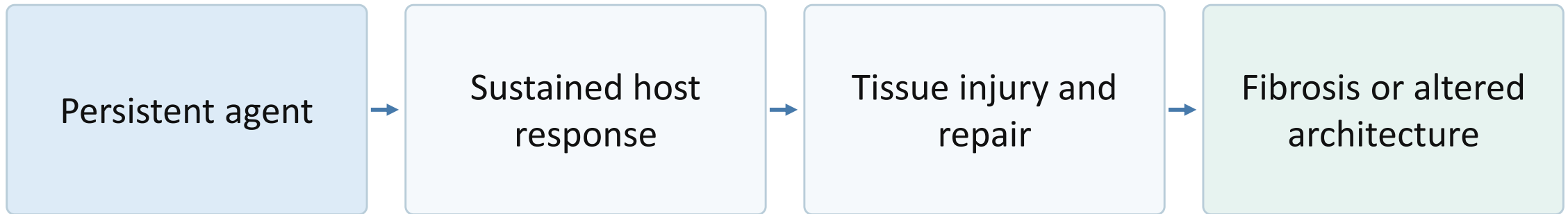
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Learning outcomes

- Identify the morphologic triad of chronic inflammation.
- Explain how persistent infection drives fibrotic repair.
- Relate HBV, schistosome infection, and tuberculosis to organ-specific scarring.
- Distinguish fibrosis, granulomatous inflammation, and regenerative nodularity.

A chronic infection can outlast its initial inflammatory response



Causal sequence (schematic)

Two distinct endpoints of long-standing inflammation

Healing with preserved function	Excessive scarring with dysfunction
Offending stimulus controlled	Inflammation persists or injury is extensive
Parenchyma and matrix substantially restored	Collagen replaces or distorts functional tissue
Architecture remains usable	Vessels, ducts, or chambers may be compromised

Chronic inflammation is defined by simultaneous processes

- Inflammation, tissue destruction, and attempted repair occur together.
- The process may follow acute inflammation or begin insidiously.
- Its defining feature is persistence, not simply the age of a lesion.

The microscopic triad of chronic inflammation

Mononuclear
inflammatory infiltrate

Ongoing tissue
destruction

Repair by angiogenesis
and fibrosis

These three processes can be active in the same tissue section.

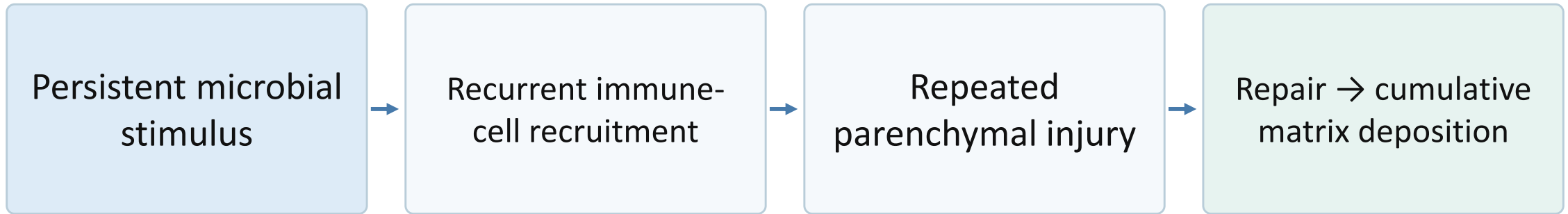
Acute and chronic inflammation have different signatures

Acute inflammation	Chronic inflammation
Vascular change and edema prominent	Mononuclear cell infiltration prominent
Neutrophils often dominate	Macrophages, lymphocytes, plasma cells
May resolve completely	Tissue injury and repair coexist
Fibrosis not a defining feature	Fibrosis may be marked

Persistent microbes are one major initiating category

- Mycobacteria, certain viruses, fungi, and parasites can resist eradication.
- Ongoing antigen exposure sustains lymphocyte–macrophage responses.
- Some persistent infections produce granulomas; Others cause diffuse inflammation.

Why repeated episodes amplify tissue damage



Causal sequence (schematic)

A chronic lesion is not simply “full of lymphocytes”

- Macrophages, lymphocytes, and plasma cells form the characteristic infiltrate.
- Destruction may be caused by microbes and by host inflammatory cells.
- Fibroblasts, new vessels, and collagen indicate concurrent repair.

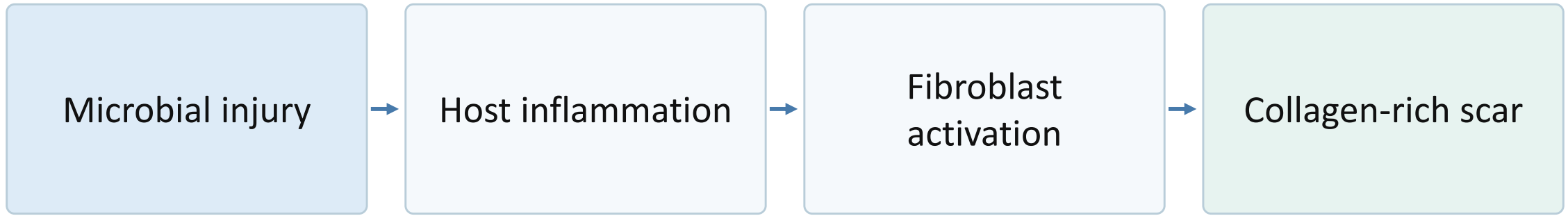
The cellular infiltrate offers clues—not an organism ID

Pattern	Interpretation in infectious pathology
Lymphocyte rich	Cell-mediated responses, including chronic HBV
Plasma-cell rich	May be conspicuous in syphilis
Macrophage rich	Persistent intracellular microbes or granulomatous reaction
Eosinophils with granulomas	Consider helminth-associated responses such as schistosomiasis

Tissue destruction may persist despite a robust response

- Leukocytes release mediators that can injure adjacent normal cells.
- Persistent microorganisms maintain inflammatory-cell activation.
- Functional parenchymal loss reduces the capacity for complete restoration.

Infection is one cause of a general fibrotic response

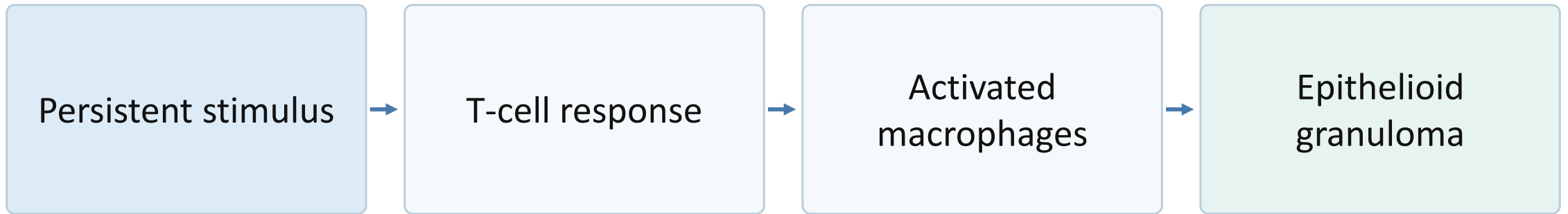


Causal sequence (schematic)

The outcome depends on both the organism and the organ

- Microbial persistence determines duration of stimulation.
- Host immunity influences whether inflammation becomes diffuse or granulomatous.
- Preexisting tissue architecture determines what scarring obstructs or distorts.

Granulomatous inflammation localizes persistent stimuli



Mechanistic schematic

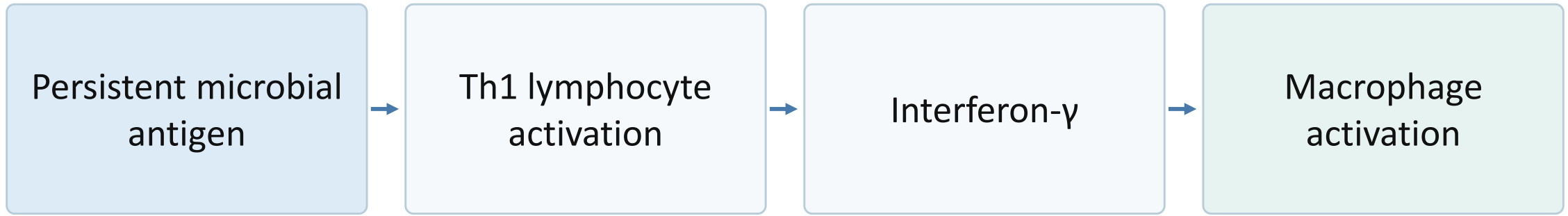
An epithelioid granuloma is an organized cell collection

- Activated macrophages gain abundant cytoplasm and epithelioid morphology.
- Some macrophages fuse into multinucleated giant cells.
- Lymphocytes and fibroblasts may form a peripheral cuff.

Granulation tissue and granuloma are not synonyms

Granulation tissue	Granuloma
New capillaries + proliferating fibroblasts	Aggregated activated macrophages
Loose ECM with inflammatory cells	Often epithelioid cells and giant cells
A component of tissue repair	A pattern of chronic inflammation
Can mature into scar	May coexist with surrounding fibrosis

The Th1–macrophage circuit sustains some granulomas



Causal sequence (schematic)

The same granuloma can protect and damage tissue

- Containment helps localize agents resistant to elimination.
- Activated macrophages may damage tissue during host defense.
- Chronic granulomatous inflammation can be accompanied by fibrous repair.

Granulomas are etiologic clues, not diagnoses

- Tuberculosis is an important infection to exclude when granulomas are identified.
- Noninfectious inflammatory diseases may also produce granulomas.
- Special stains, microbiologic tests, or molecular assays can be needed to identify the cause.

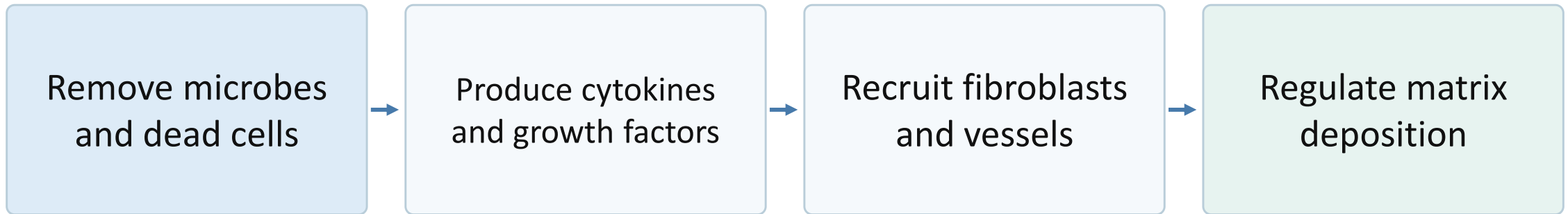
Different microbial reactions produce different patterns

Reactive pattern	Selected example
Suppurative inflammation	Pyogenic bacterial infections
Mononuclear / granulomatous	Tuberculosis, schistosome eggs
Cytopathic / cytoproliferative	Some viral infections
Necrosis-dominant	Toxin-associated infections
Chronic inflammation and scarring	HBV cirrhosis, schistosomal fibrosis

Mixed tissue reactions are common in actual specimens

- Several host-reaction patterns may coexist in a single infected organ.
- The Robbins examples include simultaneous CMV and Pneumocystis pulmonary disease in AIDS.
- Do not assign a specific organism using scar morphology alone.

Macrophages connect antimicrobial defense to tissue repair



Causal sequence (schematic)

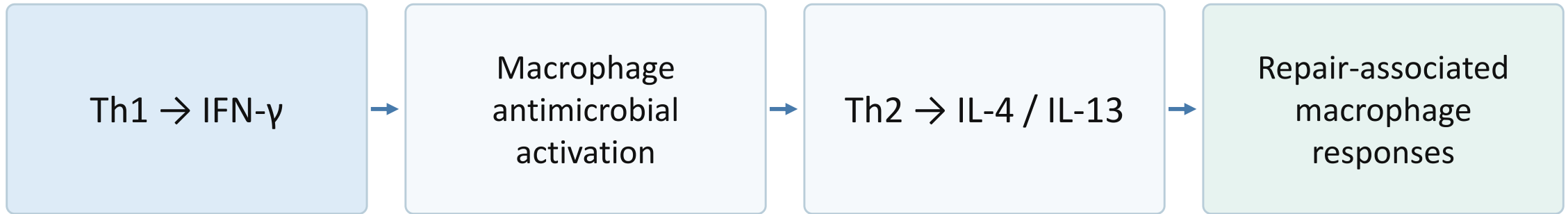
Macrophage activation: Useful functional extremes

Classical / M1-like	Alternative / M2-like
Induced by microbial signals and IFN- γ	Associated with IL-4 and IL-13
ROS, NO, lysosomal enzymes	Inflammation resolution and tissue repair
Microbial killing and inflammation	Fibroblast activation and ECM deposition

M1/M2 should not be treated as fixed tissue identities

- These labels as extreme conceptual phenotypes.
- Many intermediate macrophage states occur in inflammatory lesions.
- A strict temporal switch from M1 to M2 is not established for most reactions.

T-cell signals modulate the repair environment



Mechanistic schematic

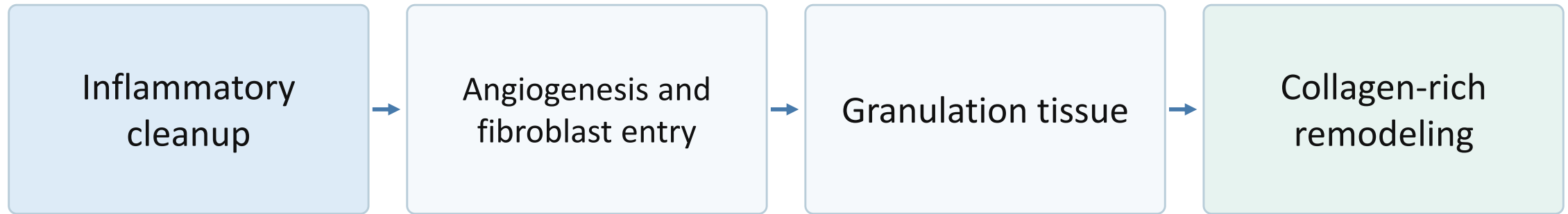
Regeneration and scarring solve different problems

- Regeneration replaces cells with the tissue's own cell types.
- Scar formation replaces damaged structures with connective tissue.
- A scar repairs continuity but cannot necessarily restore specialized function.

Preserved versus destroyed connective-tissue framework

Framework relatively intact	Framework severely disrupted
Surviving cells can proliferate on a usable scaffold	Replacement requires more connective tissue
Regeneration may predominate	Scar formation becomes more important
Normal relationships more likely to recover	Architectural distortion may persist

The sequence of connective-tissue repair

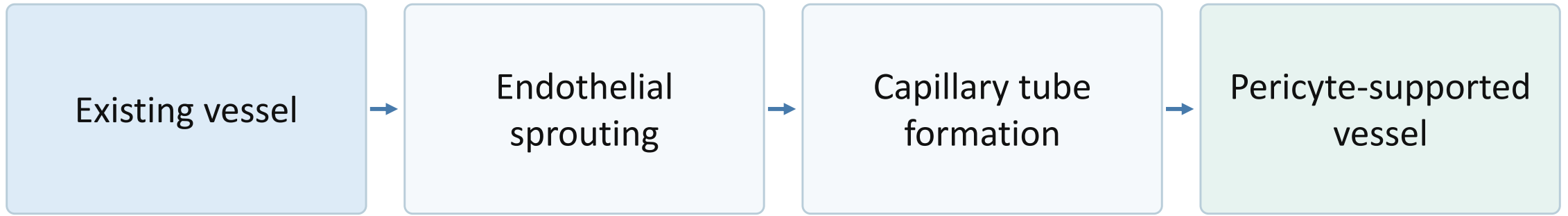


Causal sequence (schematic)

Granulation tissue is a transient repair compartment

- Proliferating fibroblasts deposit a loose extracellular matrix.
- Delicate new capillaries are conspicuous.
- Macrophages and other inflammatory cells may be present.

Angiogenesis supplies the developing repair tissue

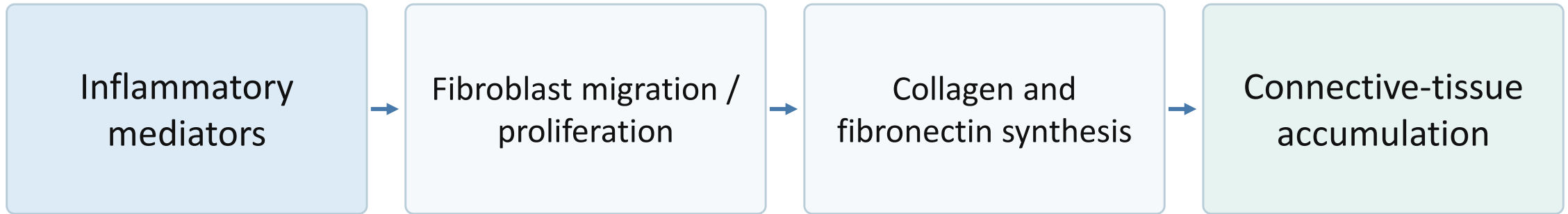


Mechanistic schematic

VEGF, FGF-2, and PDGF have complementary roles

- VEGF promotes endothelial migration, proliferation, and vascular permeability.
- FGF-2 promotes endothelial proliferation and also fibroblast migration.
- PDGF helps recruit periendothelial cells and supports vessel maturation.

Fibroblasts convert inflammation into extracellular matrix

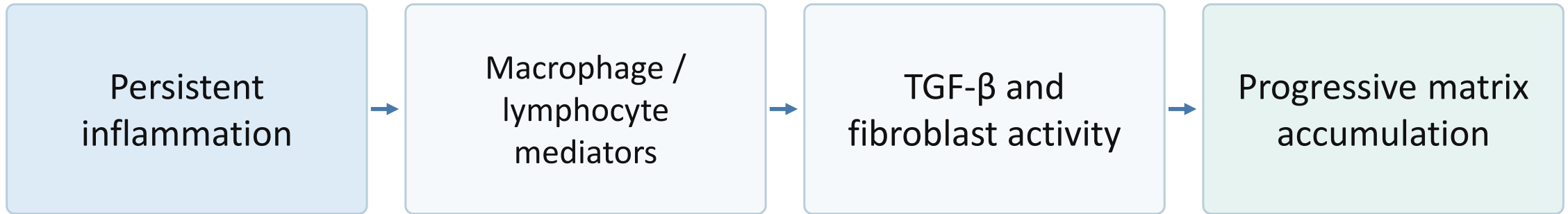


Causal sequence (schematic)

TGF- β is a central driver of fibrotic repair

- Promotes fibroblast migration and proliferation.
- Increases collagen and fibronectin synthesis.
- Decreases matrix degradation, including by inhibiting metalloproteinases.

Sustained signaling shifts repair toward fibrosis



Mechanistic schematic

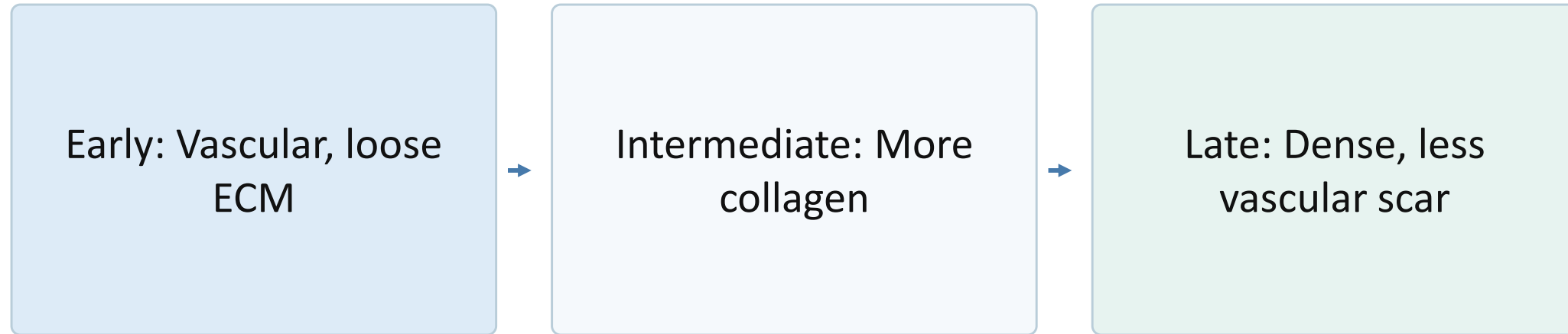
ECM synthesis and degradation set net scar burden

Matrix synthesis	Matrix degradation
Activated fibroblasts deposit collagen / fibronectin	MMPs cleave ECM components
TGF- β supports deposition	Tissue inhibitors of MMPs restrain proteolysis
Excess synthesis favors fibrosis	Effective remodeling can reduce accumulated ECM

Myofibroblasts contribute to scar contraction

- Some fibroblasts develop actin-containing smooth-muscle-like features.
- Contractile activity contributes to progressive shrinkage of scar tissue.
- The outcome may be mechanical distortion as well as tissue replacement.

Granulation tissue matures into a fibrous scar

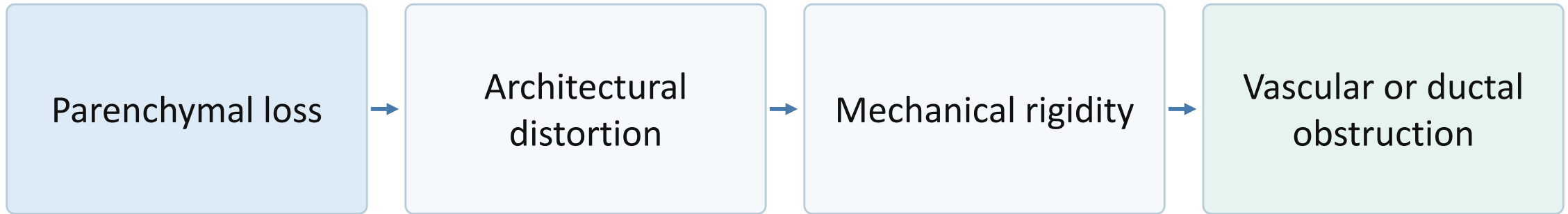


A maturation sequence, not three separate disease entities

The histologic appearance evolves with scar maturity

- Immature repair shows capillaries and active fibroblasts.
- Collagen accumulation increases as granulation tissue matures.
- Late scars have fewer visible vessels and more densely packed matrix.

A scar causes dysfunction through several routes

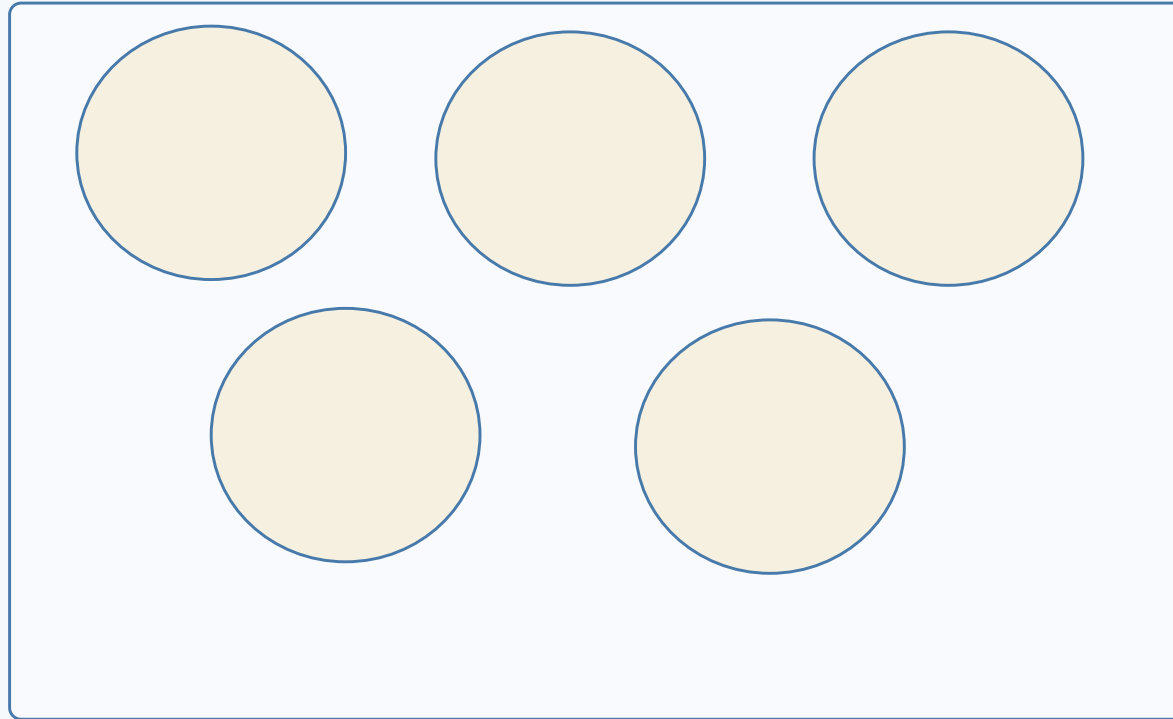


Causal sequence (schematic)

Not all scar burden is proportionate to lost cells

- Fibrosis may obstruct circulation even when parenchyma persists.
- A stiff fibrous envelope can impair normal organ motion.
- The anatomic location of the scar can be as important as its volume.

Chronic HBV: Fibrosis and hepatocyte regeneration coexist



Fibrous septa around nodules (schematic)

STRUCTURE → FUNCTION

Viral hepatitis

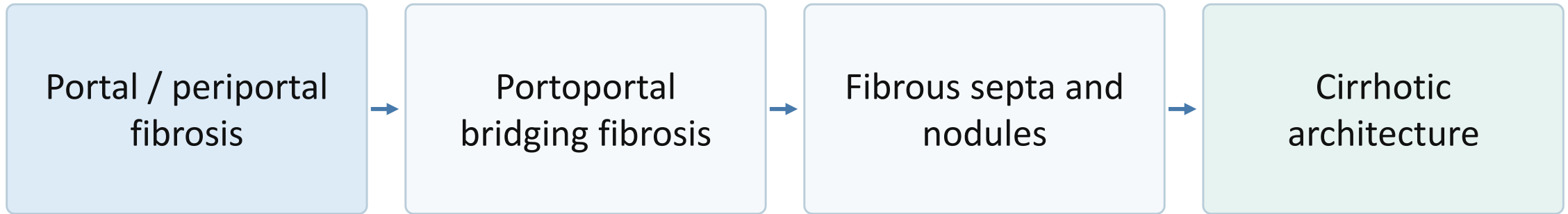
Fibrous septa

Hepatocyte nodules

Chronic viral hepatitis is portal-centered inflammation with fibrosis

- Portal lymphocytic or lymphoplasmacytic infiltrates are characteristic.
- Inflammatory cells may extend across the limiting plate.
- Lobular inflammation varies in intensity.

The morphological progression of hepatic fibrosis

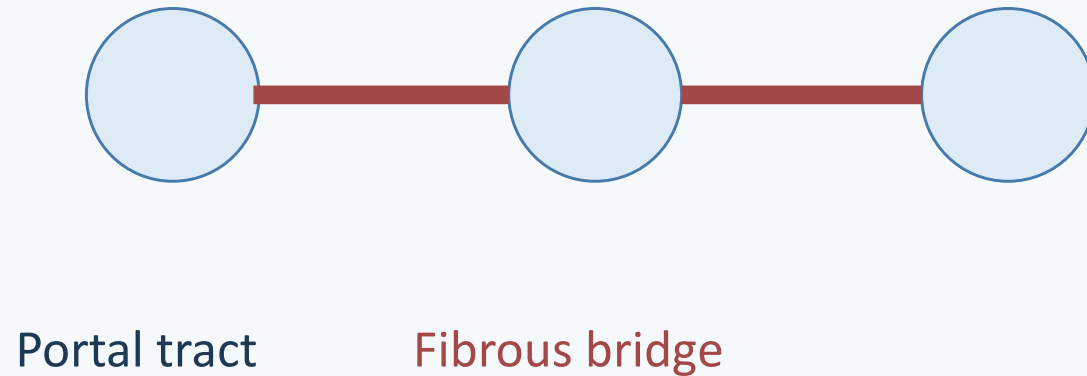


Causal sequence (schematic)

Interface activity marks injury at the limiting plate

- Inflammatory lymphocytes extend from portal tracts into periportal hepatocytes.
- This represents active hepatocyte injury in chronic hepatitis.
- Activity and accumulated fibrosis describe different dimensions of disease.

Bridging fibrosis links portal structures



STRUCTURE → FUNCTION

Portal inflammation

Connecting fibrous bridges

Lobular architectural disruption

Cirrhosis reorganizes the hepatic vascular map

- Dense septa enclose regenerating hepatocyte nodules.
- The usual liver architecture is lost.
- Distortion of the hepatic circulation changes intrahepatic blood flow.

Chronic hepatitis activity is not the same as fibrosis stage

Inflammatory activity (grade)	Fibrosis stage
Current necroinflammatory injury	Accumulated connective-tissue distortion
Assessed from hepatocyte injury and inflammation	Assessed from portal, bridging, and cirrhotic fibrosis
May change over time	Records structural disease progression

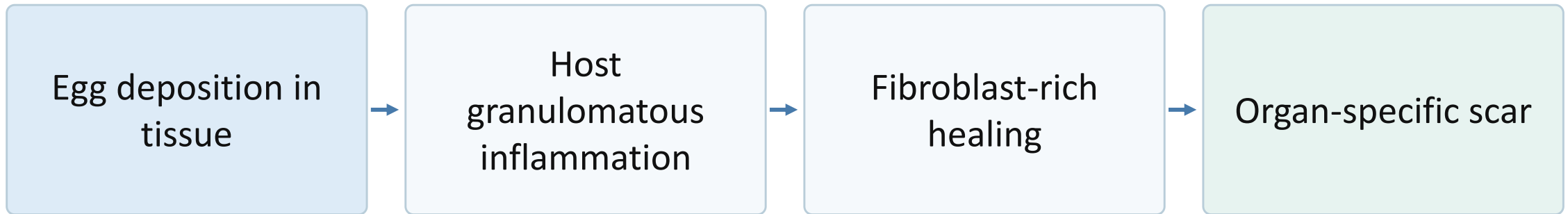
HBV may produce distinctive ground-glass hepatocytes

- Hepatocyte endoplasmic reticulum accumulates hepatitis B surface antigen.
- Cells may acquire a ground-glass cytoplasmic appearance.
- HBsAg and core antigen immunostains can support HBV-specific identification.

Infectious fibrosis is not synonymous with cirrhosis

Cirrhotic architecture	Noncirrhotic periportal fibrosis
Regenerative hepatocyte nodules enclosed by fibrous septa	Fibrous expansion may occur without intervening regenerative nodules
Exemplified by chronic HBV	Exemplified by schistosomal “pipestem” change

Schistosome eggs provoke the most important host injury



Causal sequence (schematic)

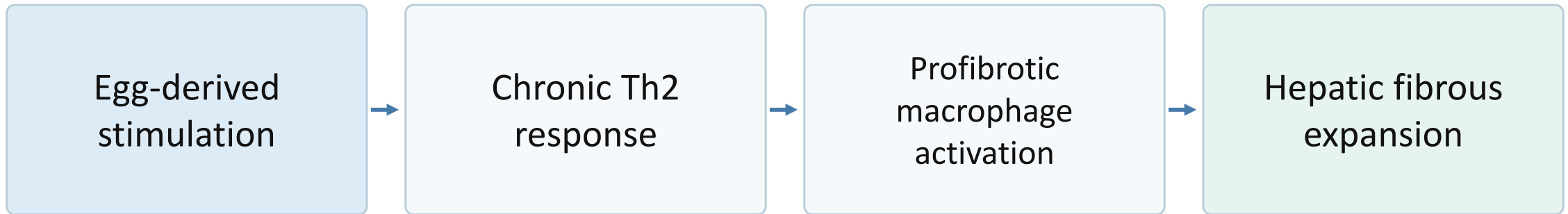
The parasite's location determines the diseased organ

- *S. Mansoni* and *S. Japonicum* predominantly affect intestinal and hepatic territories.
- *S. Haematobium* prominently involves the urinary bladder and ureters.
- The injury is driven substantially by host responses to deposited eggs.

Schistosome egg granulomas have recognizable components

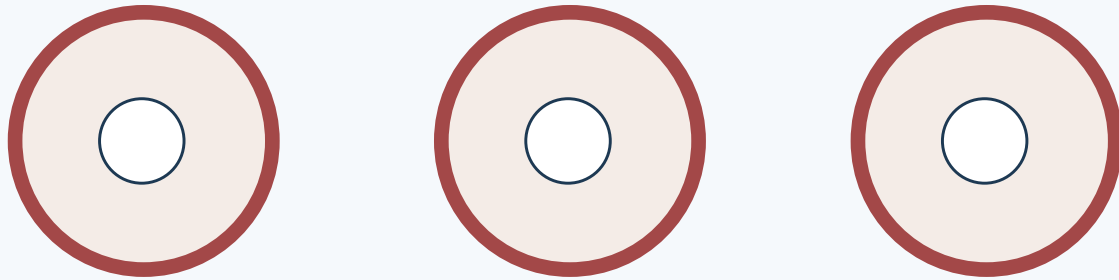
- An egg can occupy the granuloma center.
- Histiocytes, lymphocytes, neutrophils, and eosinophils surround it.
- Older eggs may degenerate and calcify.

Schistosomiasis can shift toward Th2-associated fibrosis



Mechanistic schematic

Hepatic pipestem fibrosis is periportal—not nodular cirrhosis



Expanded portal tracts

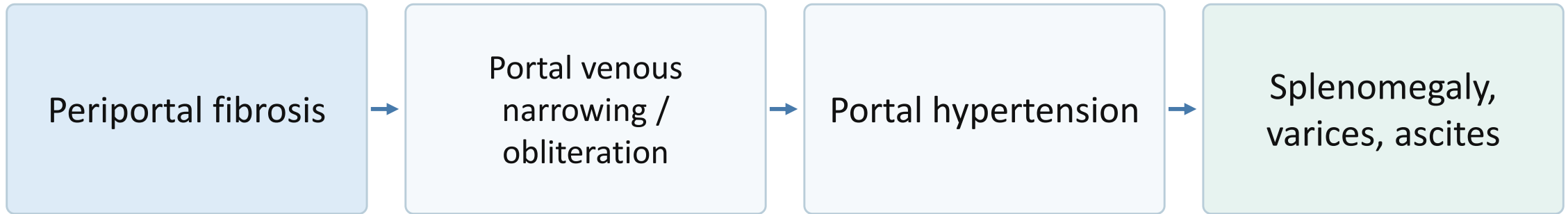
STRUCTURE → FUNCTION

Enlarged fibrotic portal tracts

Intervening parenchyma lacks regenerative nodules

Portal vein compromise

Portal vascular obstruction explains hepatosplenic disease

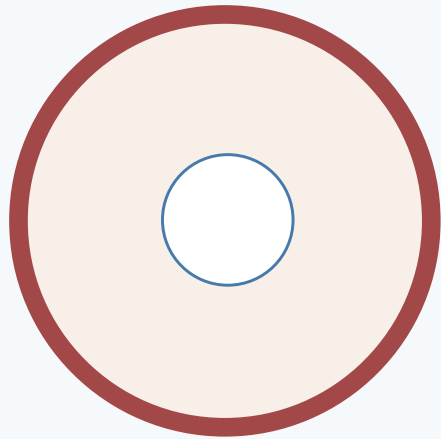


Causal sequence (schematic)

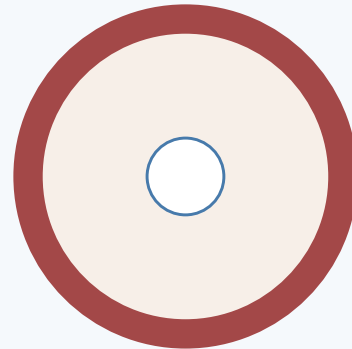
Urinary schistosomiasis begins with egg-associated cystitis

- *S. Haematobium* eggs provoke inflammation and granulomas in the bladder wall.
- Early mucosal injury may produce erosions and hematuria.
- Fibrosis and calcification accumulate in long-standing disease.

Fibrotic urinary tract injury becomes obstructive



Patent lumen



Narrowed lumen

STRUCTURE → FUNCTION

Egg-associated inflammation

Ureteral-wall fibrosis

Urinary outflow obstruction

Long-standing urinary schistosomiasis has additional sequelae

- Ureteral obstruction can cause hydronephrosis and chronic pyelonephritis.
- Calcified egg granulomas can produce a “sandy” or calcified bladder wall.
- Urinary schistosomiasis is associated with squamous cell carcinoma of the bladder.

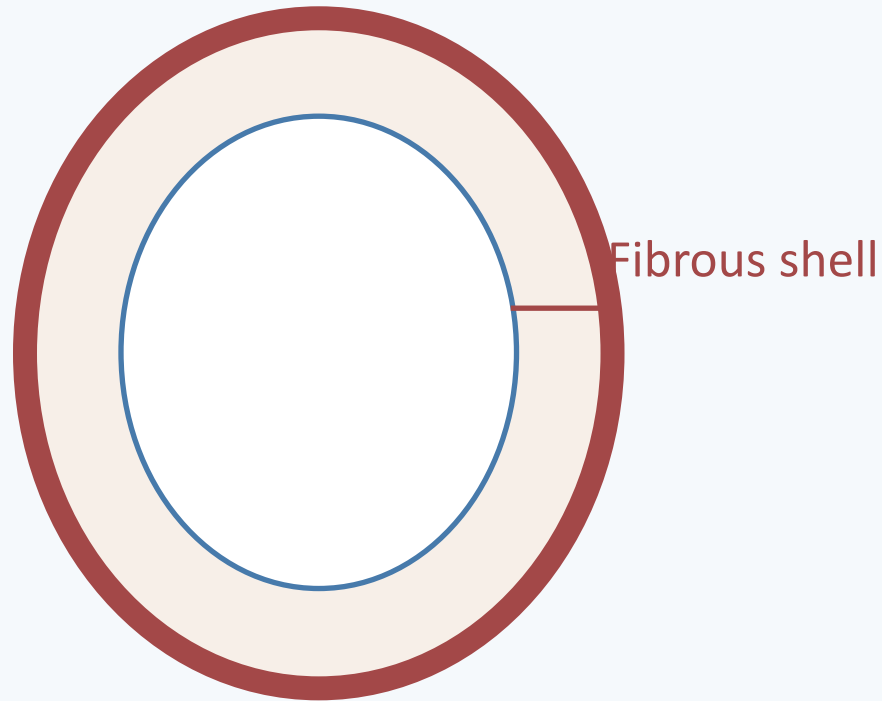
HBV versus schistosomiasis: Different liver architecture

Chronic HBV liver disease	Hepatic schistosomiasis
Portal inflammation and hepatocyte injury	Egg granulomas and portal-predominant fibrosis
Bridging fibrosis; cirrhotic nodules may form	“Pipestem” fibrosis without intervening nodules
Architectural distortion with altered blood flow	Portal vein loss / obstruction and portal hypertension

Tuberculosis can produce a fibrosing pericardial lesion

- Constrictive fibrous pericarditis as a scarring sequel.
- Tuberculous pericarditis can exhibit caseation.
- Chronic organization may leave a thickened fibrous or fibrocalcific envelope.

Constrictive pericarditis: A mechanical consequence of scar



Schematic pericardial encasement

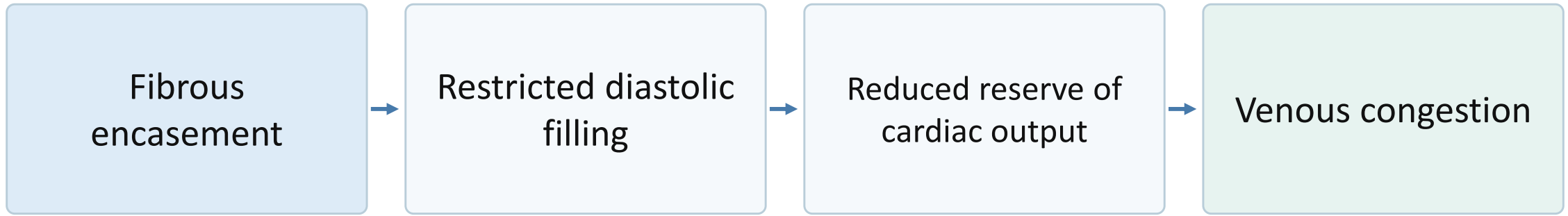
STRUCTURE → FUNCTION

Inflamed pericardium

Dense encasing scar

Limited diastolic expansion

A rigid pericardium impairs cardiac performance



Causal sequence (schematic)

Constrictive pericarditis has a distinctive clinical logic

- Elevated jugular venous pressure and peripheral edema reflect venous congestion.
- Cardiac output may be limited, particularly during increased demand.
- Pericardiectomy removes the restraining fibrous envelope in suitable cases.

How pathologists frame suspected infection-associated scarring

Observed tissue feature	Pathologic question
Mononuclear infiltrate	Is inflammation ongoing?
Granuloma and giant cells	Is a persistent antigen/organism driving it?
Collagen-rich septa	What architecture is lost or separated?
Obliterated vessel / duct	How does fibrosis explain organ dysfunction?

Etiologic confirmation requires more than fibrosis

- Tissue reaction patterns are useful but not organism-specific.
- Use clinical context and microbiologic / pathologic testing where appropriate.
- Granulomas warrant assessment for mycobacterial and fungal causes, among others.

Case 1 — fibrotic liver with regenerative nodules

A patient with chronic HBV has portal inflammation, bridging fibrosis, and hepatocyte nodules surrounded by dense septa.

INTERPRETIVE QUESTION

Question: What architectural diagnosis follows, and why may hepatic blood flow change?

Case 2 — portal fibrosis without regenerative nodules

A patient from a schistosomiasis-endemic setting has portal hypertension and markedly expanded fibrotic portal tracts.

INTERPRETIVE QUESTION

Question: What morphologic feature distinguishes this pattern from cirrhosis?

Case 3 — a scarred, poorly compliant pericardium

A patient with a prior tuberculous pericardial process has venous congestion and a rigid, fibrous pericardial envelope.

INTERPRETIVE QUESTION

Question: What is the mechanical basis of impaired cardiac output?

Case 4 — bladder scarring with calcified eggs

A patient has hematuria and a thickened bladder wall containing granulomas and calcified helminth eggs.

INTERPRETIVE QUESTION

Question: Which infection fits, and what obstructive complication may develop?

Four mechanisms link infection to chronic dysfunction

Mechanism	Illustrative outcome
Repeated parenchymal injury	Hepatocyte loss during chronic hepatitis
Septal fibrosis and regeneration	Cirrhotic hepatic architecture
Perivascular / periductal scarring	Portal hypertension or urinary obstruction
Fibrous encasement	Restricted cardiac diastolic filling

Consolidated pathologic principles

- Chronic infection may produce inflammation, injury, and repair simultaneously.
- Profibrotic mediators and fibroblasts translate persistent injury into ECM deposition.
- The functional result depends on which normal architecture the scar replaces, encloses, or obstructs.

Primary Robbins sections used in this lecture

- Chapter 8, Infectious Diseases: “Chronic Inflammation and Scarring,” pp. 312–313.
- Chapter 3, Inflammation and Repair: “Chronic Inflammation” and “Tissue Repair,” pp. 86–97.
- Chapter 8, Schistosomiasis, pp. 363–365; Chapter 18, Viral Hepatitis, pp. 760–762.
- Chapter 12, The Heart: pericardial inflammation and constriction, pp. 526–527.