

Hepatocyte and Parenchymal Responses

Mechanisms of liver injury, cell death, regeneration, and fibrosis

Cell injury · tissue loss · regeneration · fibrosis

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Learning objectives

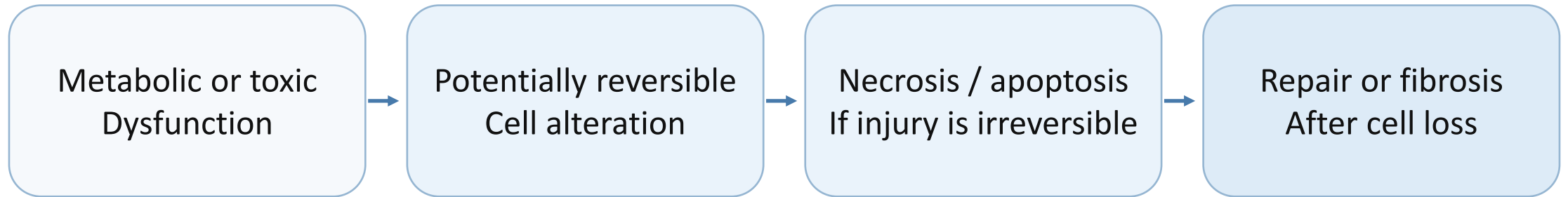
By the end of this lecture, distinguish:

- Potentially reversible changes from irreversible cell death
- Necrosis from apoptosis in hepatocellular injury
- Focal, confluent, bridging, and pan-acinar parenchymal loss
- Regeneration, ductular reactions, fibrogenesis, and scar regression

One organ, multiple pathologic responses

The pattern depends on severity, duration, and site of injury

Schematic



- These responses can coexist within one diseased liver.

Why liver architecture matters

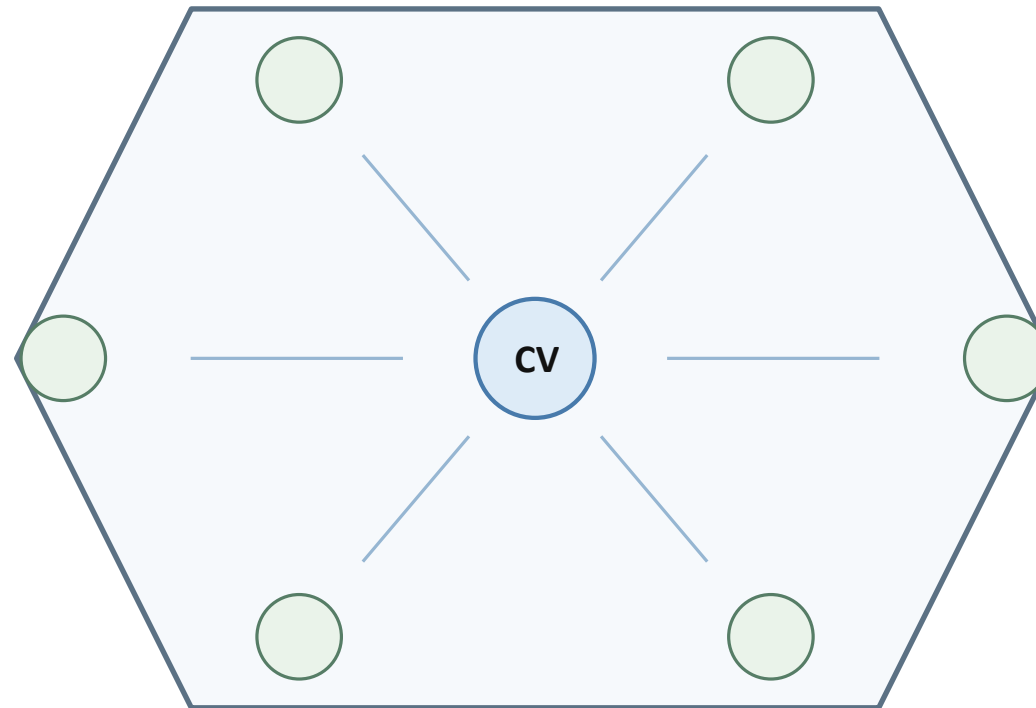
Spatial organization predicts injury distribution

- Portal tracts carry portal venous, arterial, and bile duct branches.
- Hepatocyte plates abut sinusoids and drain into central veins.
- Hepatocytes near the portal supply and those near central veins face different metabolic environments.

The classic hepatic lobule

Central vein in the middle; Portal tracts at the periphery

Portal tracts

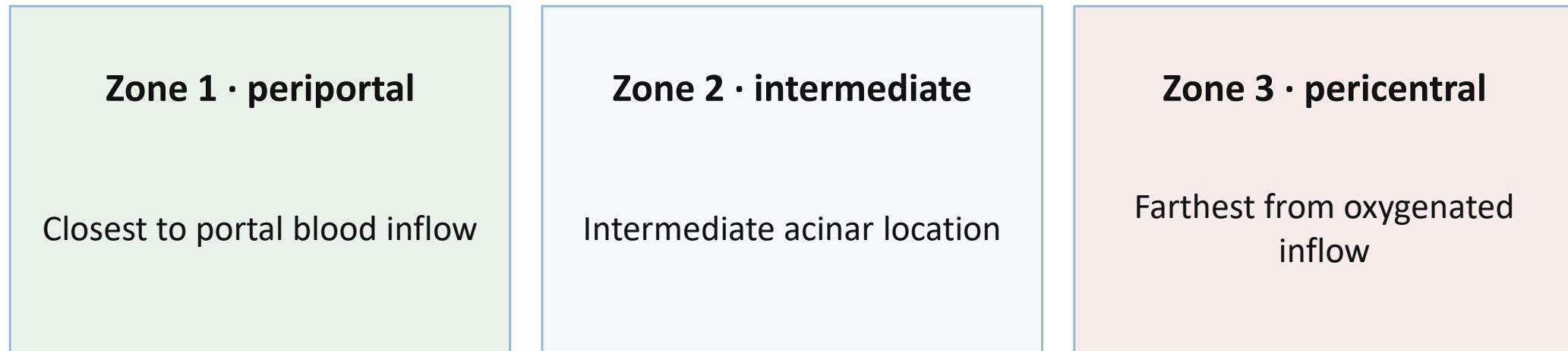


Central vein

Blood approaches via portal tracts, then drains toward the central vein.

The acinar oxygenation gradient

Zone 1 receives the most oxygen; Zone 3 the least

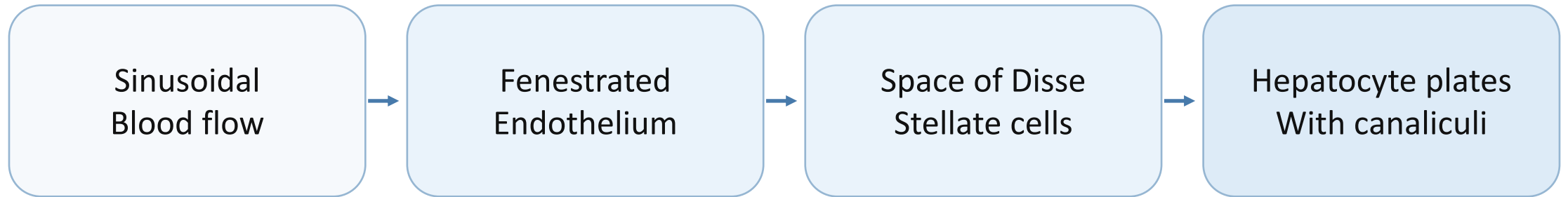


Direction of sinusoidal blood flow (schematic)

Sinusoidal compartments and injury

Vascular, immune, and matrix compartments communicate

Schematic



- Kupffer cells occupy the sinusoidal interface and participate in injury responses.

Cell injury is not equivalent to cell death

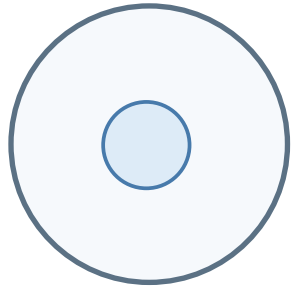
Terminology should describe the observed response

Potentially reversible	Irreversible
Steatosis	Necrosis
Cholestasis	Apoptosis
Ballooning	Confluent parenchymal loss

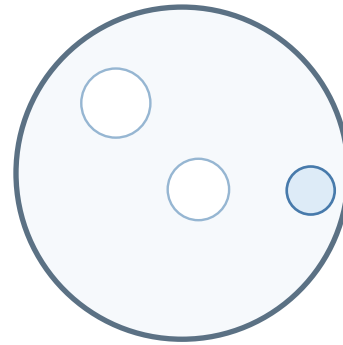
Steatosis is intracellular lipid accumulation

Steatosis is a potentially reversible hepatocellular change

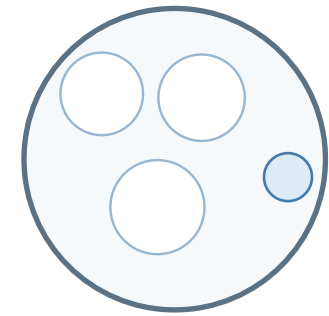
Schematic: Not an H&E micrograph



Baseline hepatocyte



Lipid vacuoles



Fat-laden cell

Fat accumulation is a morphologic response, not a diagnosis of its cause.

Reading a steatotic pattern

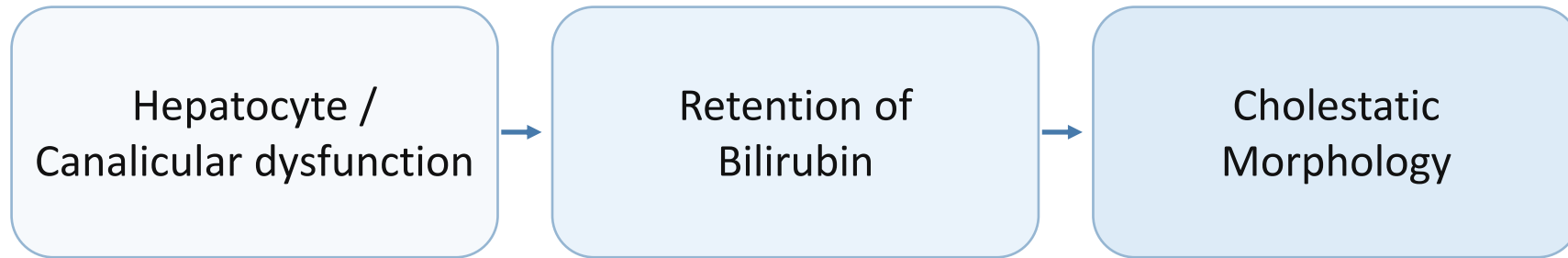
The microscopic descriptor alone is insufficient for etiology

- Steatosis among potentially reversible responses.
- Steatosis may coexist with ballooning in steatohepatitis.
- Attribution to alcohol or metabolic dysfunction requires broader disease context.

Cholestasis is retention of biliary constituents

Impaired biliary handling permits bilirubin accumulation

Schematic



- Bile canaliculi connect hepatocytes to the biliary drainage system.

Steatosis and cholestasis are different

The material retained determines the response

Steatosis

Lipid in hepatocytes

Parenchymal fat accumulation

Potential reversibility

Cholestasis

Bilirubin and bile constituents

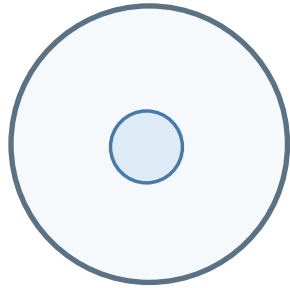
Impaired biliary handling

Potential reversibility

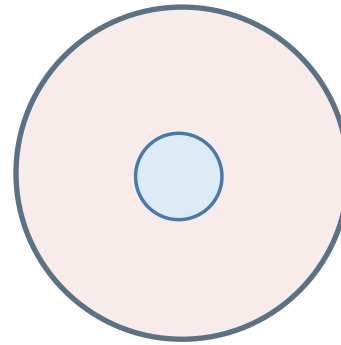
Ballooning reflects hepatocellular injury

Swelling + pale cytoplasm + cytoskeletal alteration

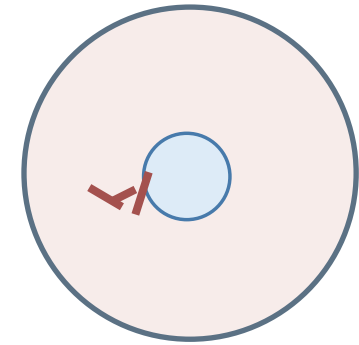
Schematic: Not an H&E micrograph



Baseline cell



Ballooned cell



Prominent injury

The key features are enlargement, cytoplasmic clearing, and clumped intermediate filaments.

Mallory hyaline arises from filament clumping

A cytoskeletal abnormality becomes visible as an inclusion

Schematic



- Do not equate the presence of Mallory hyaline with a unique etiology.

Ballooning: Common disease contexts

Ballooning is not restricted to steatotic liver disease

Steatohepatitis

Alcohol-associated disease

Metabolic dysfunction–associated

Other injury

Ischemic injury

Toxic injury

Biliary context

Cholestasis

May coexist with swelling

The reversible-response triad

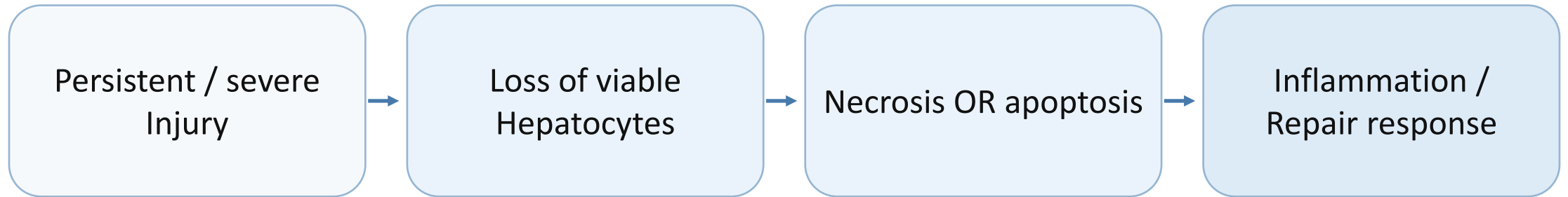
Different injuries may converge on three descriptors

Fat	Bile	Cytoskeleton
Steatosis	Cholestasis	Ballooning
Intracellular lipid	Bilirubin retention	Swelling; Clearing; Filament clumps

When repair is insufficient

Irreversible hepatocyte injury culminates in cell death

Schematic

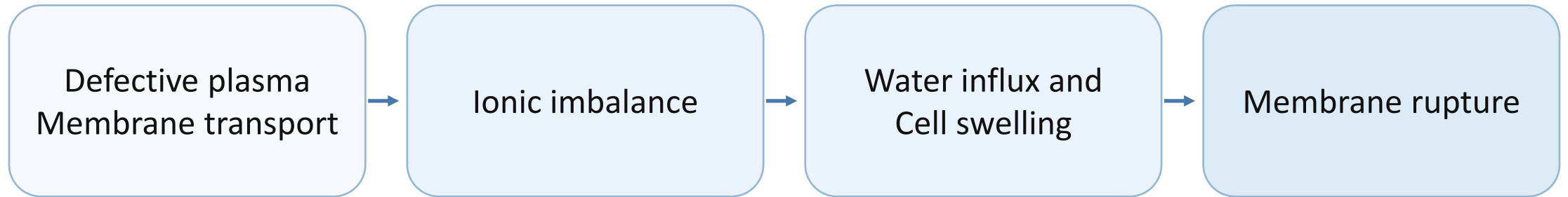


- The two death programs differ in morphology and tissue reaction.

Necrosis begins with membrane dysfunction

Ion-transport failure leads to hepatocyte swelling

Schematic

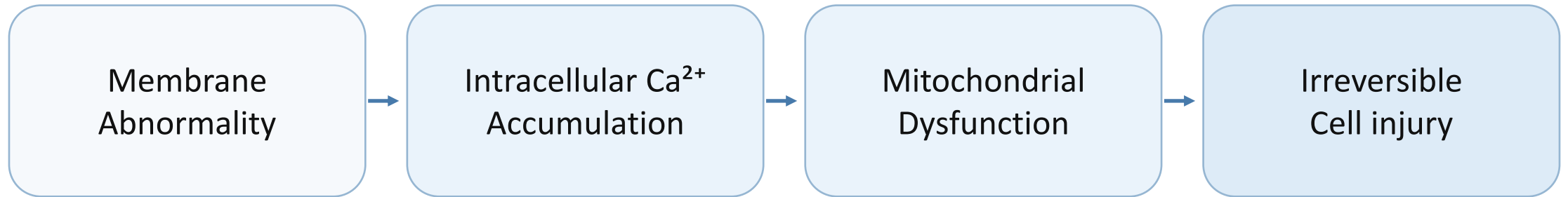


- Necrosis is a disruptive form of cellular death.

Calcium and mitochondrial injury amplify necrosis

Abnormal membrane permeability triggers intracellular injury

Schematic

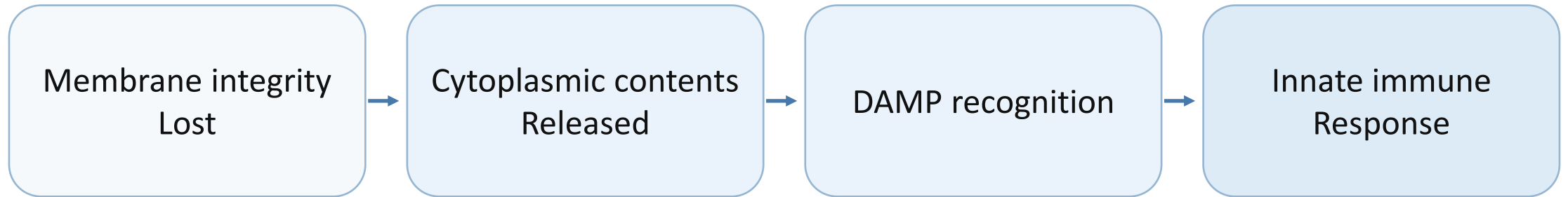


- Cellular injury can progress before the membrane visibly ruptures.

Necrotic hepatocytes release danger signals

Damage-associated molecular patterns (DAMPs) alert immunity

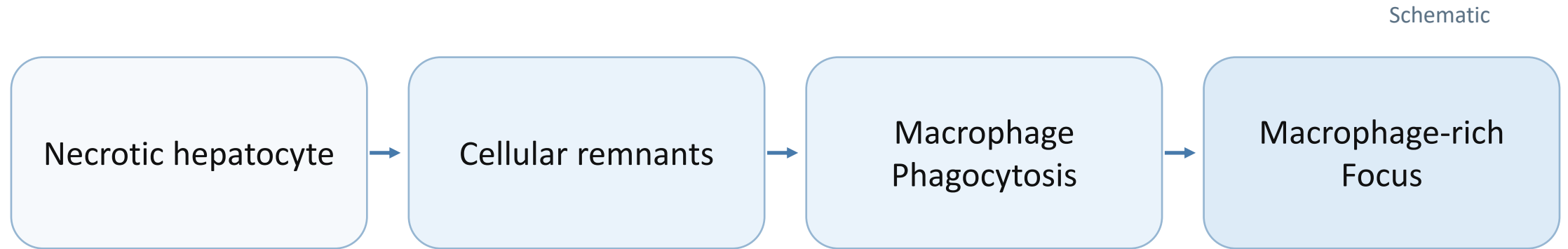
Schematic



- This explains why necrosis is coupled to an inflammatory response.

Macrophages map sites of necrosis

Hepatocyte debris is cleared by phagocytes



- Clusters of macrophages marking prior hepatocyte death.

Necrosis in the clinical setting

Context shifts the expected dominant mode of cell death

Ischemic / hypoxic

Necrosis predominates

Zone-related susceptibility

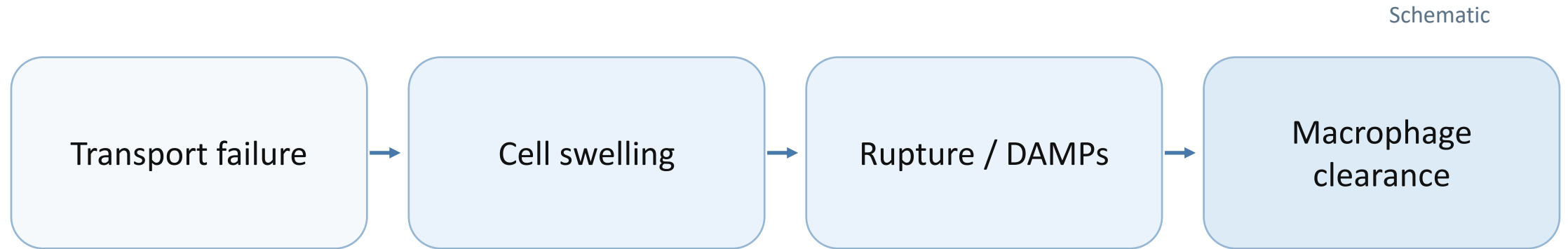
Oxidative stress

Necrosis contributes

Membrane and mitochondrial injury

The temporal sequence of necrotic change

Membrane damage precedes tissue clearance

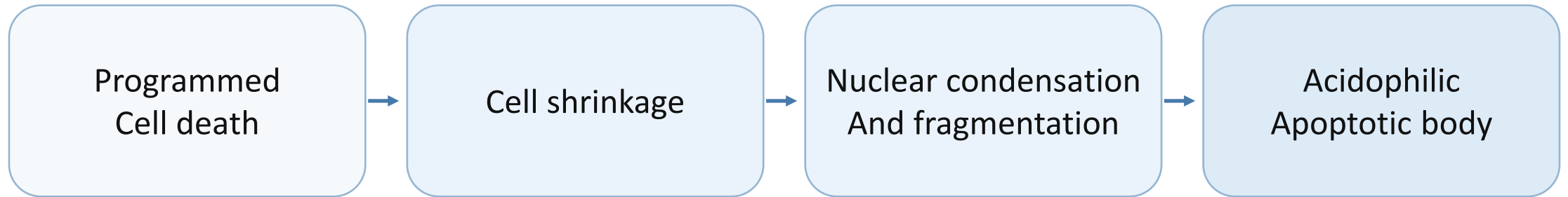


- Different stages may be represented within a single biopsy.

Apoptosis is a different death program

Apoptosis produces a condensed, fragmented hepatocyte

Schematic



- Apoptosis is described in numerous inflammatory hepatic disorders.

Pyknosis and karyorrhexis

Recognize the nuclear sequence during apoptosis

Pyknosis

Condensation of nuclear chromatin

Dark compact nucleus

Karyorrhexis

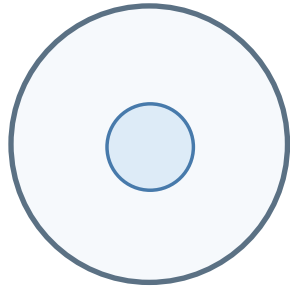
Breakup of nuclear material

Nuclear fragments

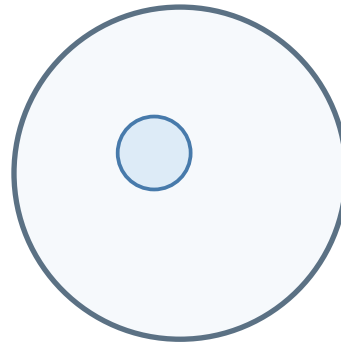
Acidophil bodies reflect apoptotic hepatocytes

Compact eosinophilic fragments are the characteristic result

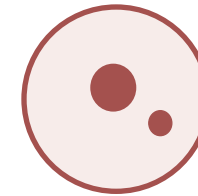
Schematic: Not an H&E micrograph



Viable cell



Shrinking cell



Acidophil body

Cytoplasmic condensation contributes to strong eosinophilic staining.

Councilman bodies: Precise nomenclature

The eponym is conventionally reserved for yellow fever

- Councilman first described apoptotic hepatocytes in yellow fever.
- In other hepatitides, use the descriptive term “acidophil body.”
- An acidophil body does not establish a particular cause of hepatitis.

Hepatitis can contain apoptotic hepatocytes

Lobular injury may show scattered acidophil bodies

- Apoptosis in inflammatory liver disease.
- Acute and chronic hepatitis are named examples.
- Interpret an acidophil body with the lobular inflammatory pattern and clinical context.

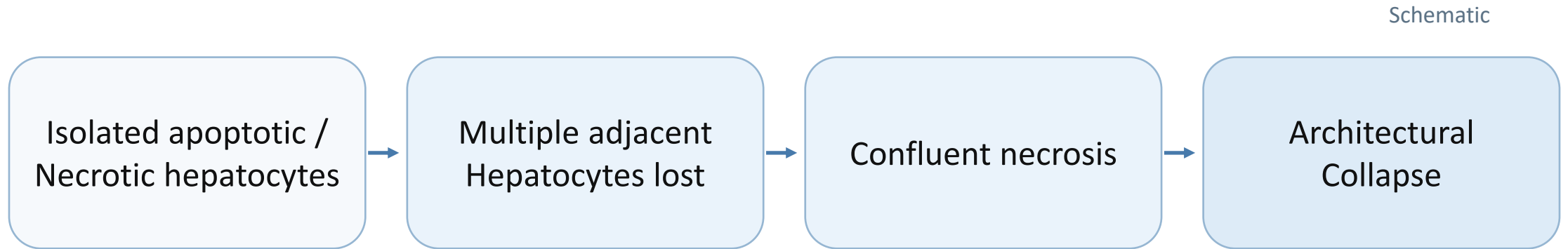
Necrosis versus apoptosis

The dominant morphologic contrasts

Necrosis	Apoptosis
Cell swelling	Cell shrinkage
Membrane rupture	Chromatin condensation
DAMP release	Nuclear fragmentation
Macrophage-rich cleanup	Acidophil bodies

Why scattered deaths differ from confluent loss

Extent of injury creates an additional pattern



- “Confluent” describes topographic continuity, not a separate molecular pathway.

Confluent necrosis is contiguous hepatocyte loss

A zonal area of parenchyma has disappeared

- Acute toxic or ischemic injury can produce confluent damage.
- Severe viral and autoimmune hepatitis are additional contexts.
- The empty region contains macrophages, debris, and remnants of reticulin.

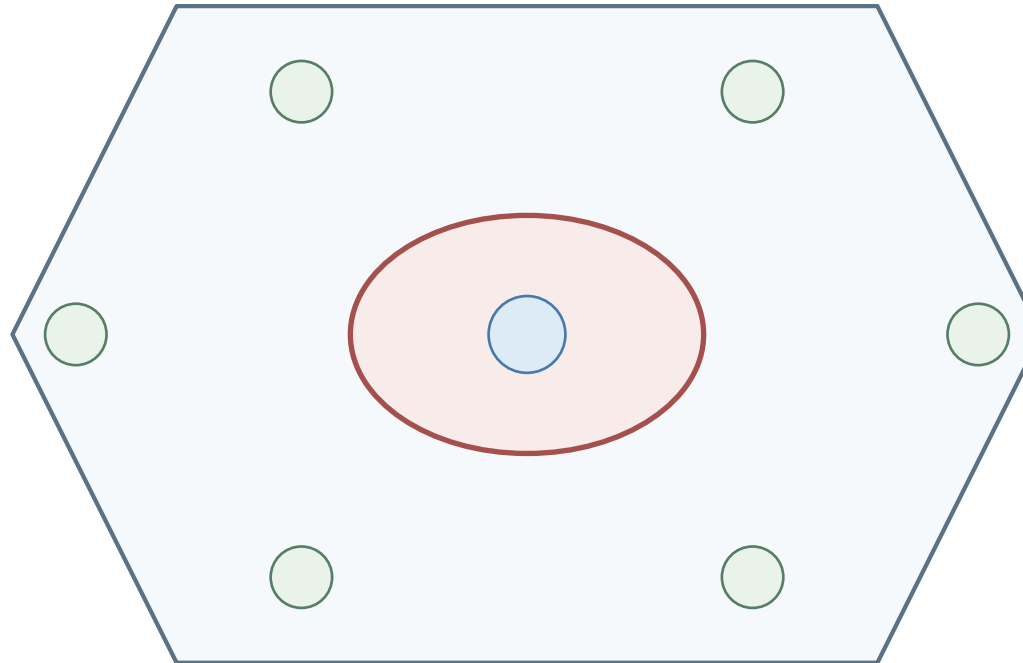
Pericentral dropout in zone 3

Confluent loss may begin adjacent to central veins

Schematic: Not a histologic specimen

Green = portal tracts

Blue = central vein

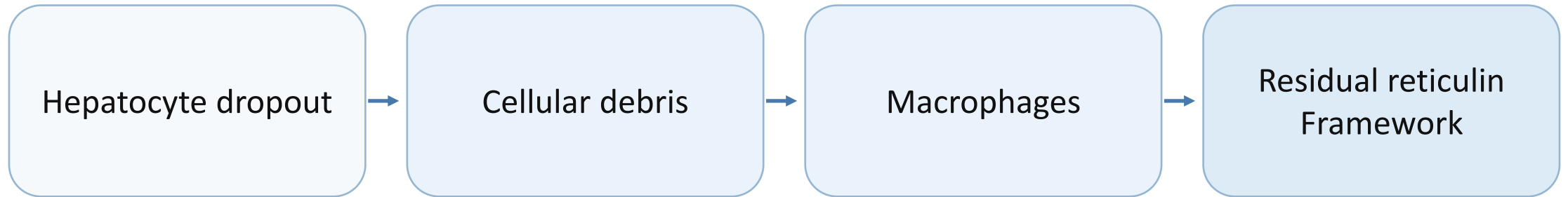


Zone 3 injury forms a pericentral area of contiguous hepatocyte loss.

What fills the area after dropout?

The injured zone contains more than a vacant space

Schematic



- The reticulin framework may subsequently collapse after extensive cell loss.

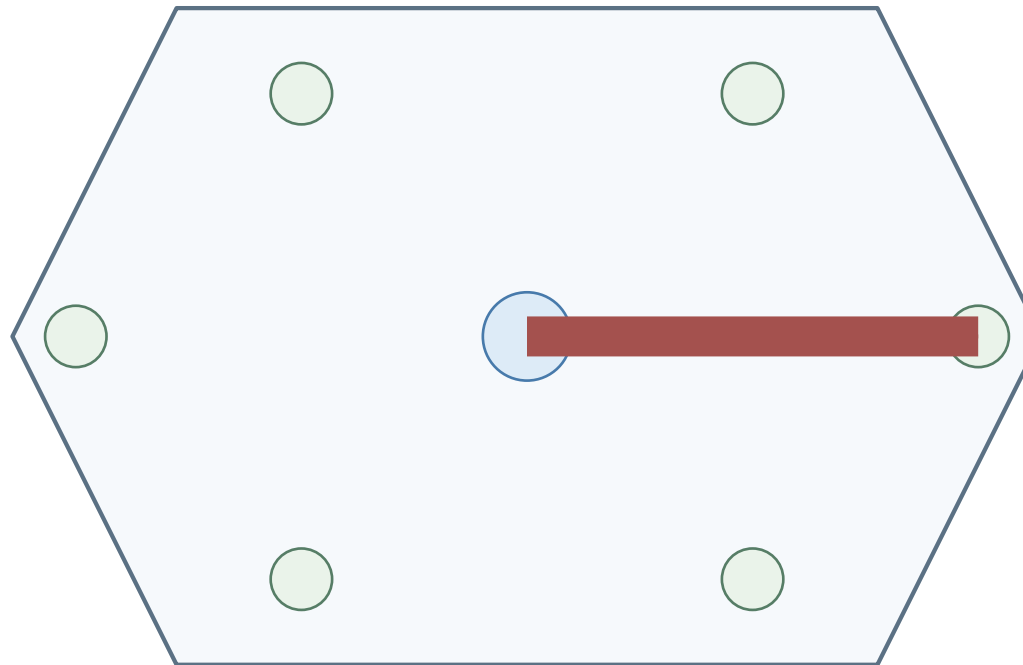
Central-to-portal bridging necrosis

A necrotic bridge links the central and portal compartments

Schematic: Not a histologic specimen

Green = portal tracts

Blue = central vein



A continuum of parenchymal loss extends from a central vein to a portal tract.

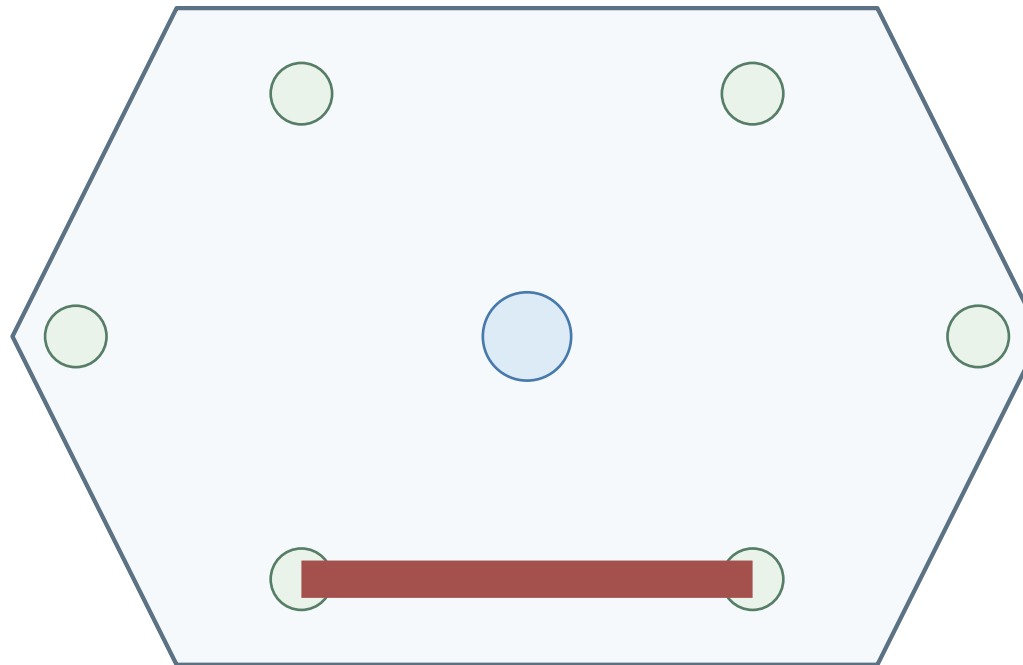
Portal-to-portal bridging necrosis

Contiguous injury may link two neighboring portal tracts

Schematic: Not a histologic specimen

Green = portal tracts

Blue = central vein



The central vein may be difficult to recognize within the affected field.

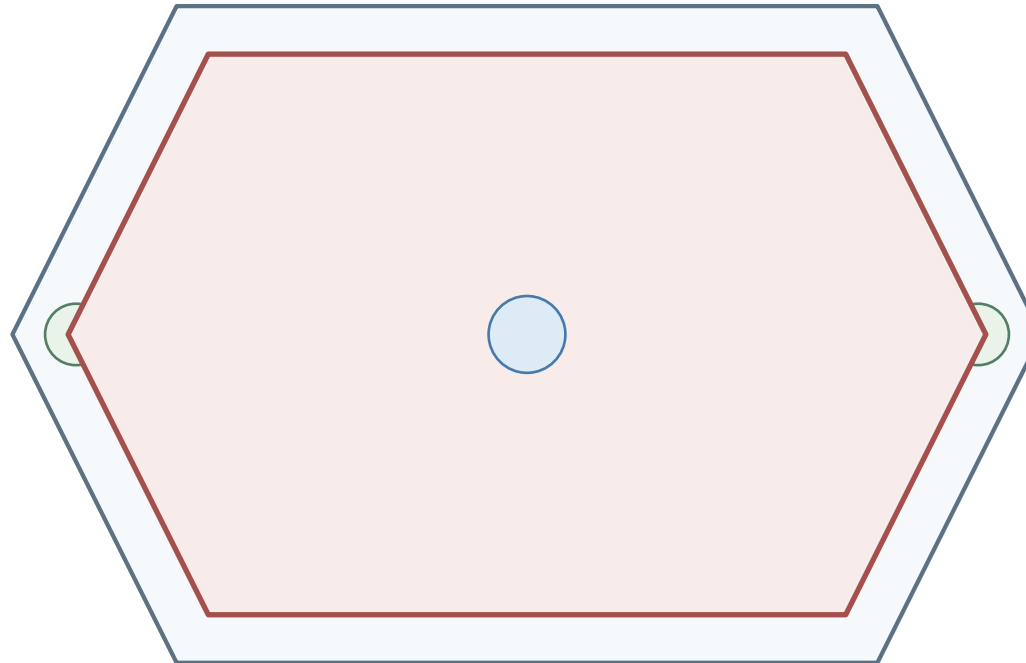
Pan-acinar necrosis

Parenchymal necrosis may involve the entire lobule

Schematic: Not a histologic specimen

Green = portal tracts

Blue = central vein



Pan-acinar necrosis denotes obliteration of a whole lobular unit.

Topography of severe parenchymal injury

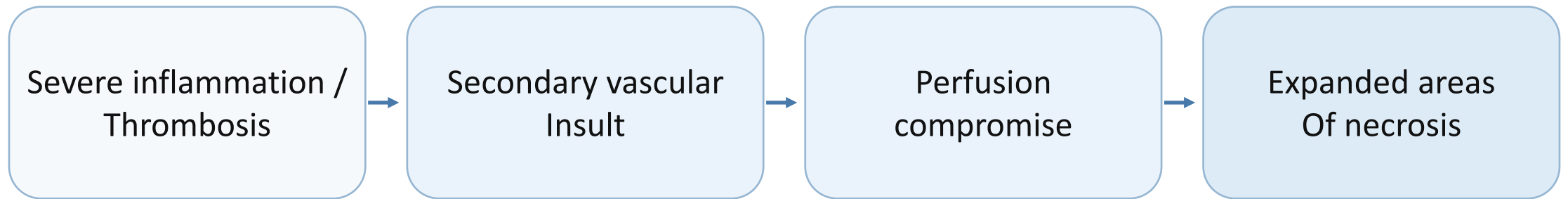
Specify extent and landmarks rather than using “severe” alone

Zonal / confluent	Bridging	Pan-acinar
Contiguous area	Vascular landmarks linked	Entire lobule
May begin in zone 3	Central–portal or portal–portal	Loss of complete lobular unit

Severe hepatitis can include vascular injury

Parenchymal necrosis need not be entirely cell-targeted

Schematic

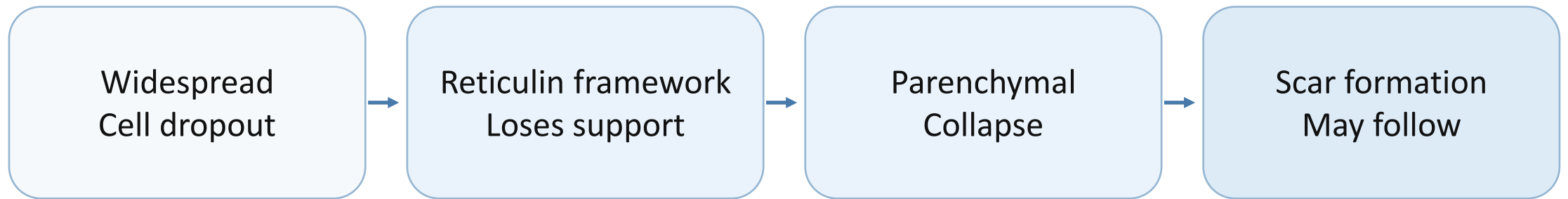


- Even when hepatocytes are the primary immune target, vascular injury can enlarge the damaged zone.

Reticulin collapse after hepatocyte loss

Loss of supporting parenchyma changes tissue architecture

Schematic

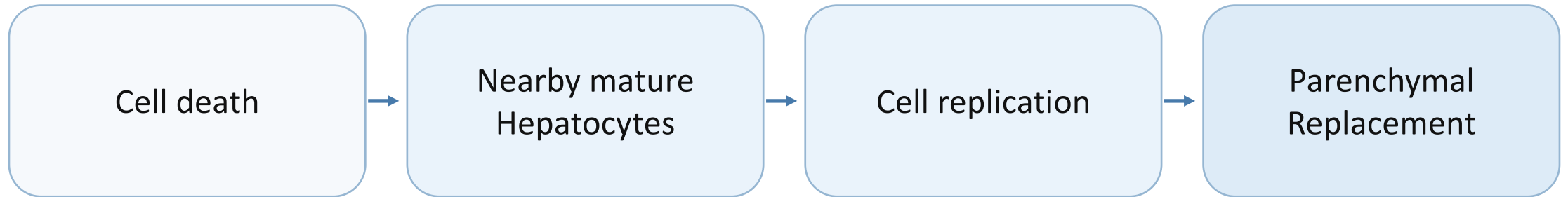


- Collapse and new collagen deposition both contribute to the injured architecture.

Hepatocytes are a powerful regenerative pool

Mature hepatocytes usually replace lost hepatocytes

Schematic



- The liver may regenerate even after substantial confluent necrosis.

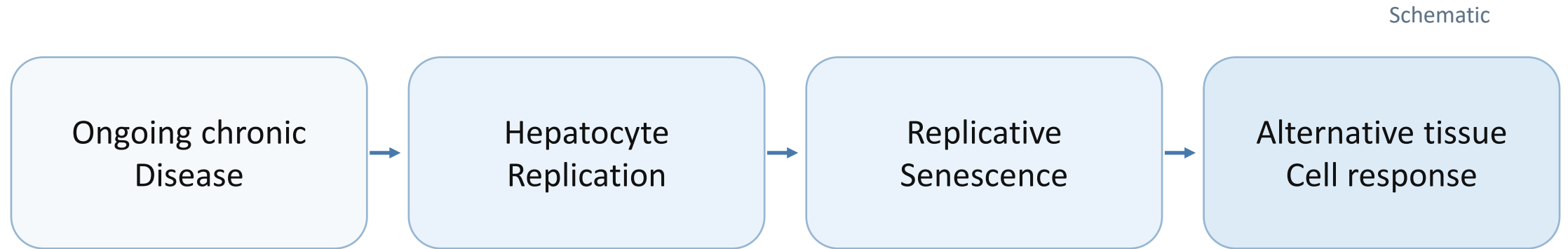
Regeneration after confluent necrosis

Large injury does not automatically imply failed regeneration

- Replacement derives mainly from adjacent mature hepatocytes.
- This regenerative ability is unusually high for differentiated cells.
- Final tissue architecture depends on the balance of loss, repair, and scarring.

Chronic injury can exhaust replication

Replicative senescence changes the repair strategy

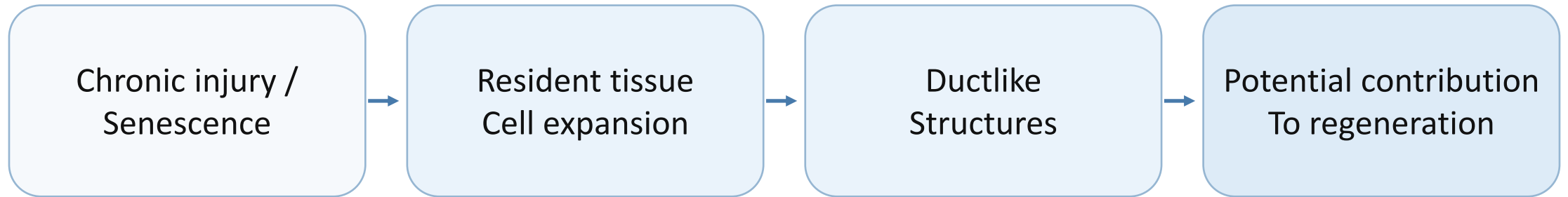


- This transition is most relevant in prolonged liver injury.

Ductular reactions emerge in chronic injury

Resident multipotent cells may participate in repair

Schematic



- Ductular reaction is a tissue response, not by itself proof of a particular disease.

Mature hepatocytes versus ductular response

Both responses participate in the regenerative compartment

Dominant repair route

Adjacent mature hepatocytes

Replication even after confluent loss

Chronic-disease response

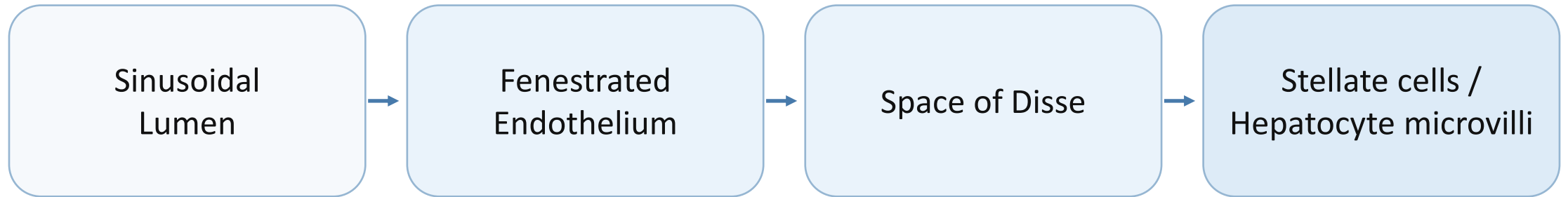
Ductular reaction

Expansion of multipotent populations

The space of Disse contains stellate cells

Cells beside the sinusoidal endothelium can deposit matrix

Schematic



- The location provides a link between inflammation, injury, and matrix remodeling.

Quiescent hepatic stellate cells

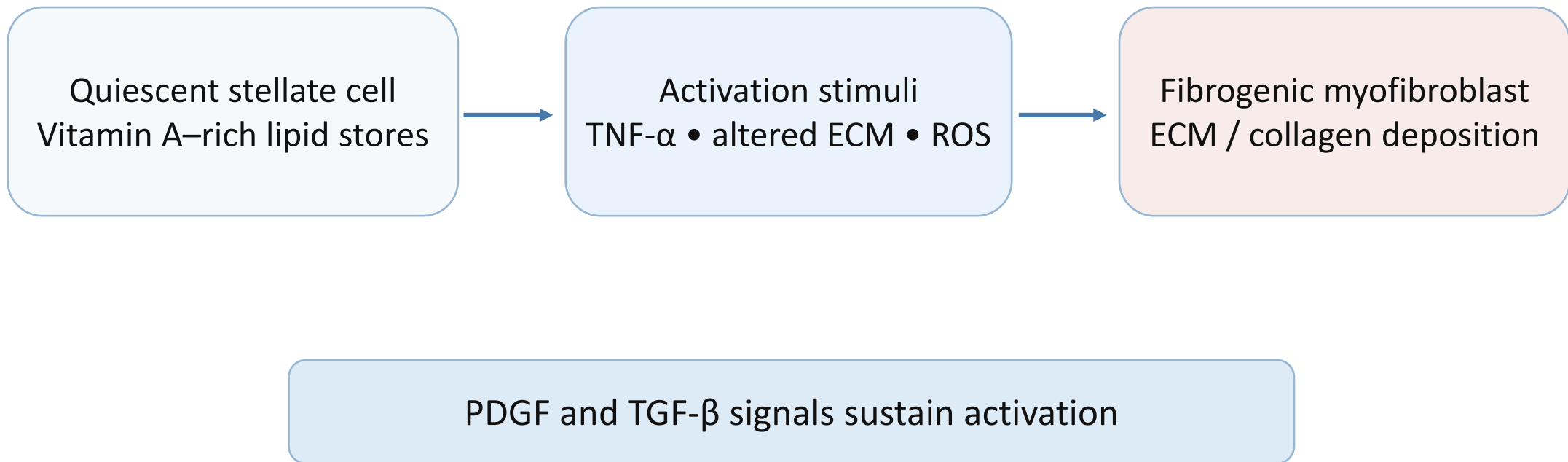
Stellate cells normally serve as lipid-storage cells

- They reside in the space of Disse.
- A characteristic quiescent function is storing lipid, including vitamin A.
- Injury can convert them into strongly fibrogenic cells.

Stellate-cell activation

Inflammatory, chemical, and matrix signals converge on fibrosis

Schematic



Three sources of stellate activation

Activation does not require one unique trigger

Cytokines

TNF- α

Macrophages / other cells

Matrix changes

Altered ECM interactions

Changed extracellular milieu

Direct injury

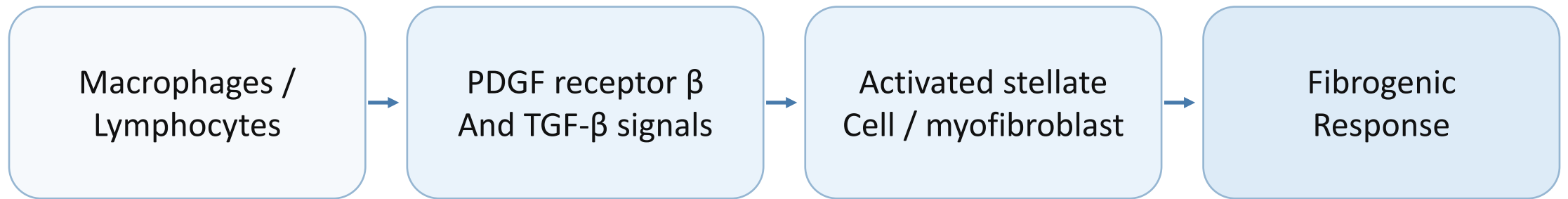
Toxins

Reactive oxygen species

PDGF and TGF- β amplify fibrogenesis

Growth factor and cytokine signals sustain activation

Schematic



- Robbins also describes chemokine inputs from these inflammatory populations.

Stellate cells become myofibroblasts

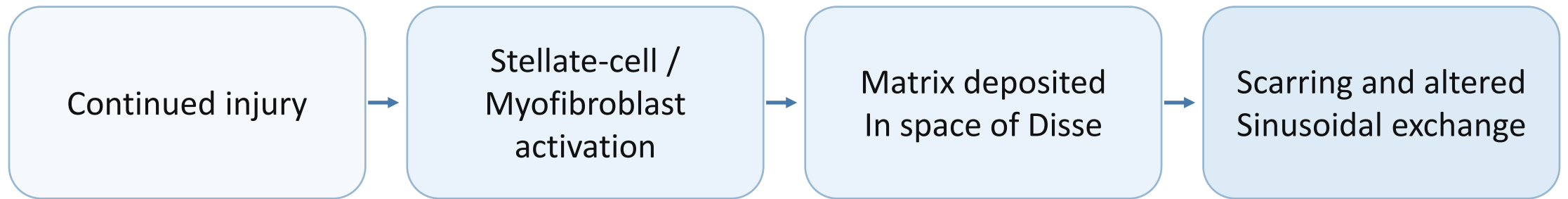
Cellular activation is a phenotypic transition

- Quiescent lipid-storing stellate cells acquire a fibrogenic phenotype.
- Activated myofibroblasts deposit extracellular matrix.
- Activated stellate cells also release growth, chemotactic, and vasoactive factors.

The first matrix changes may affect Disse

Persistent activation promotes perisinusoidal ECM deposition

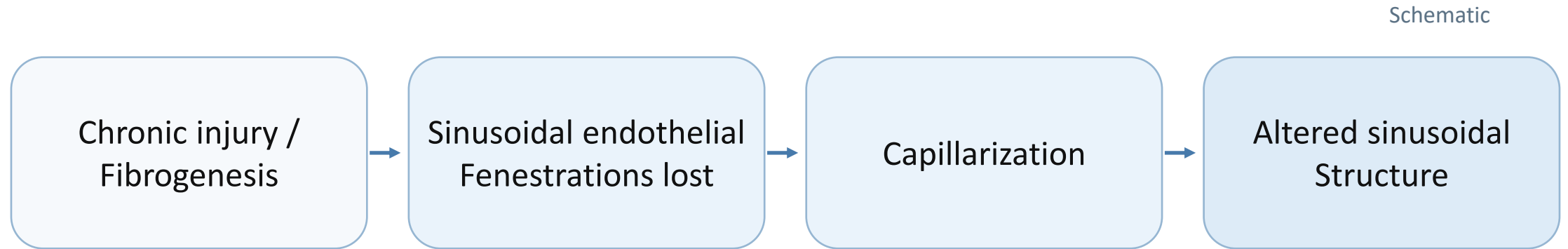
Schematic



- The space of Disse is a key early anatomic compartment.

Sinusoidal capillarization

Fenestration loss changes the endothelial interface



- Described in metabolic dysfunction–associated steatohepatitis and hepatocellular carcinoma.

Fibrosis combines deposition and collapse

An existing framework can collapse while collagen accumulates

Parenchymal collapse

Loss of hepatocytes

Reticulin framework contracts

Fibrotic deposition

Activated myofibroblasts

Extracellular matrix / collagen laid down

Portal fibroblasts are additional contributors

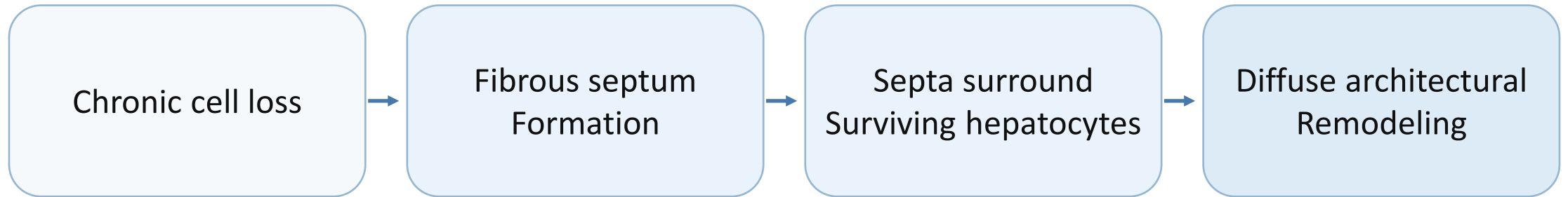
Fibrogenesis is not exclusively a stellate-cell process

- Stellate cells as the principal scar-forming population.
- Portal fibroblasts may also contribute to chronic scarring.
- The specific cellular contribution is influenced by injury distribution.

Fibrous septa reorganize chronic liver

Repeated injury progressively disrupts the native architecture

Schematic

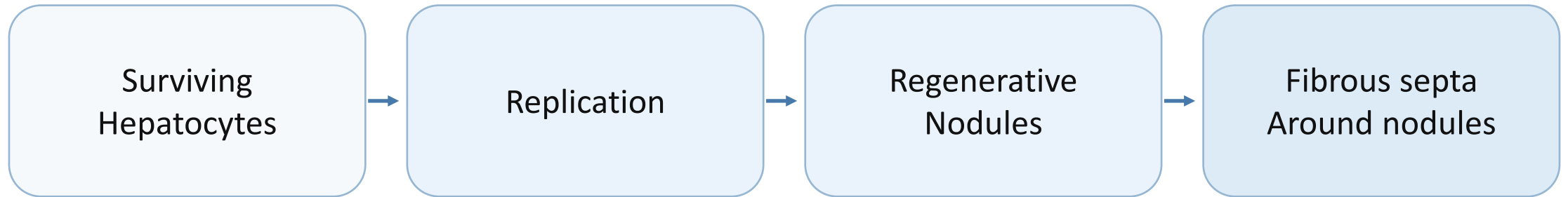


- This sequence supports the development of a cirrhotic pattern.

Regenerative nodules in chronic injury

Hepatocyte proliferation can coexist with scarring

Schematic



- Nodule formation does not mean the original vascular architecture is restored.

Cirrhosis is an architectural end point

Its hallmark is a combined fibrotic and regenerative pattern

Fibrous response

Septa surrounding surviving parenchyma

Distorted architecture

Regenerative response

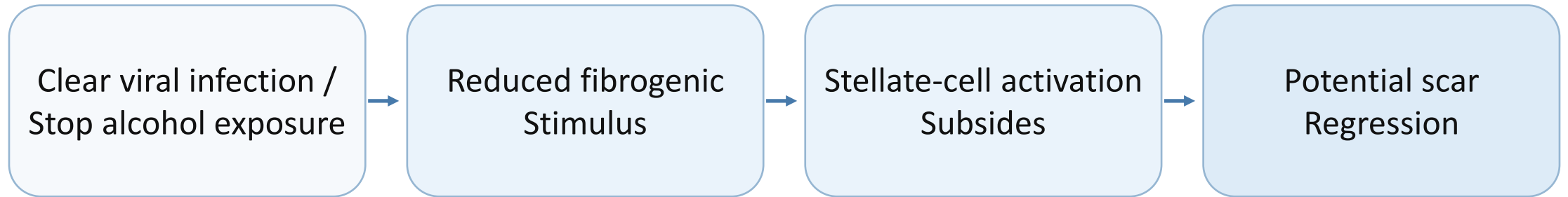
Hepatocellular nodules

Persistent repair amid injury

Removing the injurious stimulus matters

Interruption of chronic injury may halt active scarring

Schematic

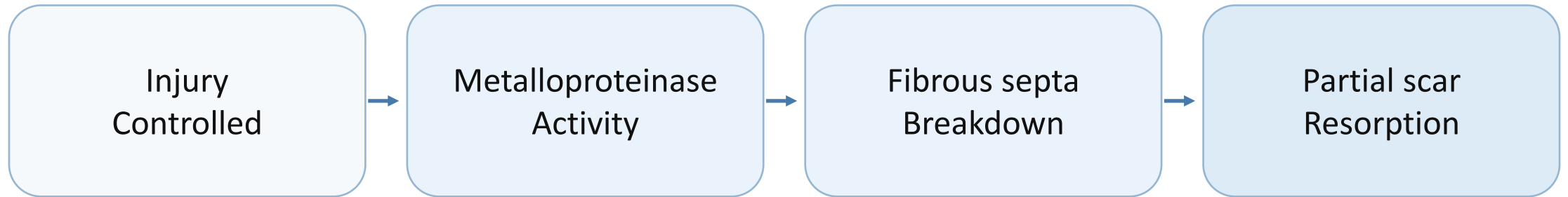


- Regression is conditional and can be incomplete.

Metalloproteinases can remodel scars

Hepatocyte-associated enzymes contribute to septal breakdown

Schematic



- The outcome may resemble incomplete septal cirrhosis.

Incomplete septal cirrhosis after regression

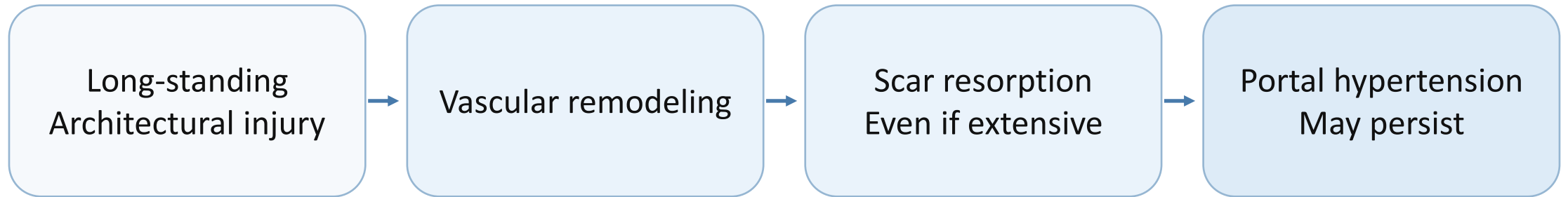
Morphologic scar resorption does not imply normal liver

- Previously deposited septa can become attenuated or partially removed.
- “incomplete septal cirrhosis” for a regression-associated appearance.
- Residual architectural and vascular changes may persist.

Why portal hypertension may persist

Vascular remodeling may be less reversible than matrix burden

Schematic

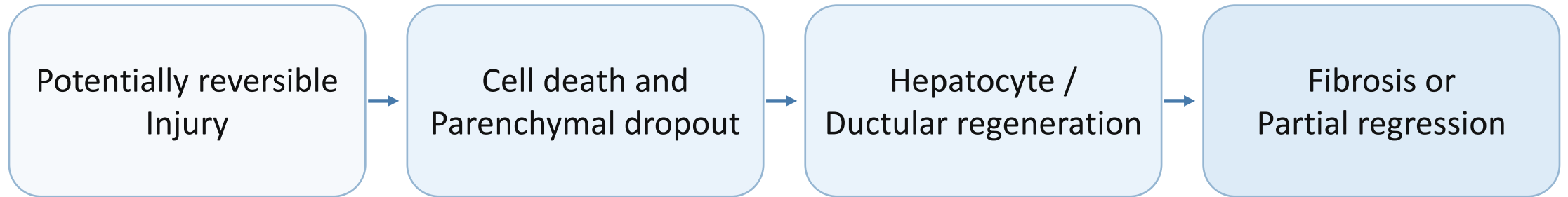


- Fibrosis burden and portal pressure need not improve in parallel.

A unified response model

The outcome reflects injury, death, repair, and scarring

Schematic



- These processes overlap; The sequence is conceptual, not obligatory.

Which morphologic terms describe what?

Do not confuse a cell change with a zonal distribution

Cell change	Injury distribution	Repair response
Steatosis / cholestasis	Zone 3 dropout	Hepatocyte replication
Ballooning	Bridging necrosis	Ductular reaction
Necrosis / apoptosis	Pan-acinar necrosis	Fibrotic septa / regression

Laboratory interpretation after liver injury

Biochemical tests interrogate different functions

Integrity	Biliary excretion	Synthetic function
AST, ALT, LDH	Bilirubin, ALP, GGT	Albumin, coagulation factors
Often increased with cell injury	Increased when biliary handling impaired	Impairment reflects declining synthesis

Clinical reasoning: Zonal toxic injury

Clinicopathologic exercise

Following a severe systemic hypoxic episode, a liver specimen shows contiguous hepatocyte loss surrounding central veins, with debris and macrophages.

What injury distribution is most likely?

Answer in speaker notes: Zone 3 / pericentral confluent necrosis; Interpret within the hemodynamic context.

Clinical reasoning: Apoptotic hepatocyte

Clinicopathologic exercise

A biopsy from a patient with hepatitis contains scattered shrunken cells with intensely eosinophilic cytoplasm and fragmented nuclear material.

What is the correct descriptive term, and what does it not establish?

Answer in notes: Acidophil body; It is not disease-specific.

Clinical reasoning: Chronic liver remodeling

Clinicopathologic exercise

A liver with longstanding injury shows fibrous septa that surround islands of replicating hepatocytes, and abnormal sinusoidal microarchitecture.

Which two tissue responses are occurring simultaneously?

Answer in notes: Fibrogenesis and nodular hepatocyte regeneration.

Clinical reasoning: Scarring improves, pressure persists

Clinicopathologic exercise

After a chronic liver insult is removed, serial specimens suggest resorption of fibrous septa, but clinically important portal hypertension remains.

Why can vascular manifestations outlast histologic scar regression?

Answer in notes: Remodeling of vascular and tissue architecture may be incompletely reversible.

Integrated learning summary

Five linked ideas organize the pathology

- Steatosis, cholestasis, and ballooning may be reversible.
- Necrosis releases danger signals; Apoptosis produces acidophil bodies.
- Extent of hepatocyte loss defines confluent, bridging, or pan-acinar injury.
- Mature hepatocytes regenerate; Chronic disease also recruits ductular reactions.
- Stellate-cell fibrogenesis may regress, while vascular distortion persists.

Primary reference and visual provenance

Textbook and internal provenance

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Chapter 18, pp. 749–751.
- Textbook content paraphrased from the supplied source; page mapping and slide-specific locators are retained in presenter notes.
- All explanatory figures in this deck are editable native PowerPoint schematics, not diagnostic micrographs.