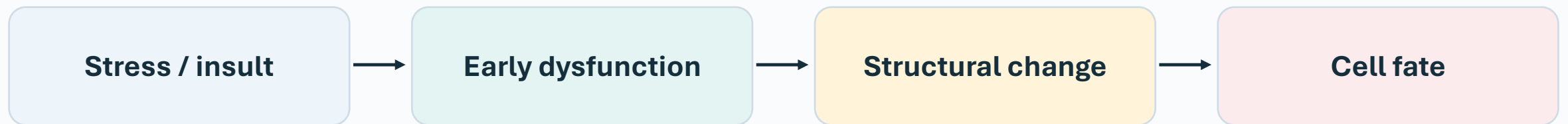


Progression of cell injury and death

From biochemical disturbance to reversible injury, irreversibility, and cell death



Dr Abu Suraih Sakhri

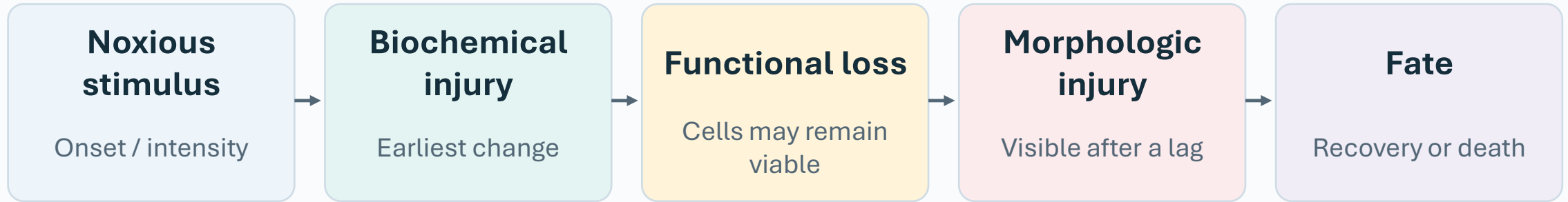
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Learning outcomes

- Sequence biochemical dysfunction, functional impairment, and structural injury.
- Explain why different tests detect injury at different stages.
- Distinguish reversible injury from the transition to irreversible injury.
- Relate necrosis and apoptosis to structural and inflammatory outcomes.
- Interpret myocardial ischemia as a timing-dependent clinicopathologic example.

The central progression



- Morphology is a delayed readout of preceding molecular injury.
- The pathway is not identical in every tissue or with every insult.

Cellular dysfunction is not synonymous with cell death

A cell may be markedly dysfunctional and still recover.

- Viability, functional competence, and morphologic appearance are distinct dimensions.
- Loss of function can precede irreversible injury.
- Recovery depends on the severity and duration of the insult.

Four different clocks are running

Insult clock

When does oxygen loss, toxin exposure, or another stressor begin?

Biochemical clock

When are energy metabolism, protein function, or membrane processes disturbed?

Morphology clock

When are structural alterations visible using a particular method?

Clinical clock

When does organ dysfunction or a biomarker become detectable?

Why intensity and duration matter



- Persistent or excessive injury instead raises the probability of irreversible damage.
- The transition is mechanistically complex, not governed by a universal stopwatch.

Severity and time are not interchangeable

Severe, brief insult

- Can rapidly disrupt essential cellular systems.
- Recovery may be impossible even if exposure ends.
- Threshold depends on insult and cell type.

Milder, prolonged insult

- May initially produce correctable changes.
- Repair capacity can eventually be exhausted.
- Persistent exposure can culminate in death.

A normal light micrograph cannot exclude early injury

Microscopy-negative does not mean biochemically normal.

- Sensitive biochemical or ultrastructural methods can reveal injury first.
- Routine H&E findings may lag the onset of severe dysfunction.
- The tissue sampling time must be considered in every interpretation.

Earliest effects occur at the molecular level

Energy metabolism

Reduced oxidative phosphorylation and ATP-dependent work.

Membrane homeostasis

Ion gradients and water distribution begin to change.

Protein systems

Protein synthesis, folding, or degradation can be perturbed.

Organelle function

Mitochondria, ER, and plasma membrane respond to injury.

Cellular function may fail before morphology

Biochemical

ATP formation and other intracellular processes are compromised.

Physiologic

Contractile, transport, secretory, or electrical work may decline.

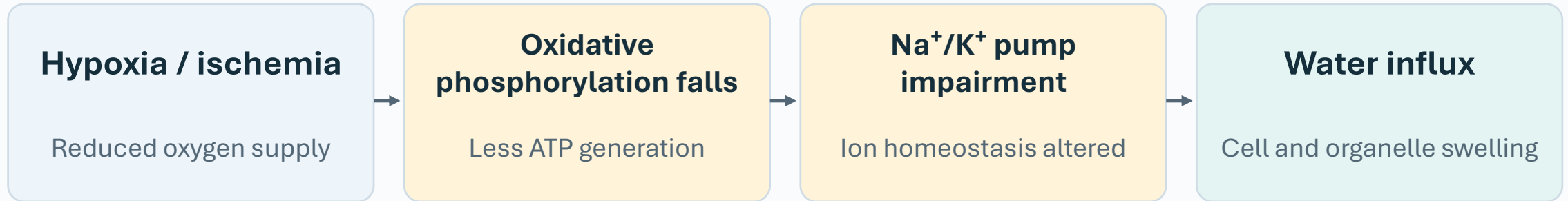
Structural

Swelling, blebs, and organelle alterations subsequently emerge.

Pathologic

Irreversible structural damage and cell death may occur later.

ATP depletion connects metabolism to swelling



Different cellular targets create different injury phenotypes

Mitochondria

ATP deficit; Severe damage may become unrecoverable.

Plasma membrane

Transport defects early; Leakage when structural damage is profound.

Endoplasmic reticulum

Ribosome detachment and disturbed protein handling.

Nucleus

Reversible chromatin clumping versus destructive nuclear changes.

Analytic methods reveal injury at different times

4. Grossly recognizable morphologic alterations

3. Light-microscopic morphological alterations

2. Ultrastructural alterations (electron microscopy)

1. Biochemical / histochemical alterations

The levels indicate detection order, not universally fixed intervals.

Method sensitivity determines apparent onset

High-resolution / molecular

- Reports subcellular events.
- May detect minutes-to-hours changes.
- Does not alone establish cell death.

Routine morphology

- Requires visible structural alteration.
- Often appears hours-to-days later.
- Negative early findings require caution.

Biochemical evidence: A lead indicator

Early biochemical injury is often invisible on H&E.

- Changes in ATP production can precede cell swelling.
- Sensitive tests can demonstrate altered cellular constituents.
- Interpret the assay in relation to tissue specificity and timing.
- A biochemical abnormality is not always a marker of irreversible death.

Ultrastructural change precedes routine morphology

Plasma membrane

Blebs; Blunted or lost microvilli.

Mitochondria

Swelling; Small amorphous densities in reversible injury.

Endoplasmic reticulum

Dilation and reduced attached ribosomes.

Cytoplasm

Membrane-derived myelin figures can appear.

Light microscopy detects accumulated structural injury

- Swollen cells and fine cytoplasmic vacuoles support reversible injury.
- Cytoplasmic eosinophilia increases as RNA is lost and proteins denature.
- Nuclear loss or fragmentation provides evidence of necrosis.
- Diagnostic certainty depends on sampled tissue and interval.

Gross changes are comparatively late

Pallor

In some tissues, widespread swelling or injury changes appearance.

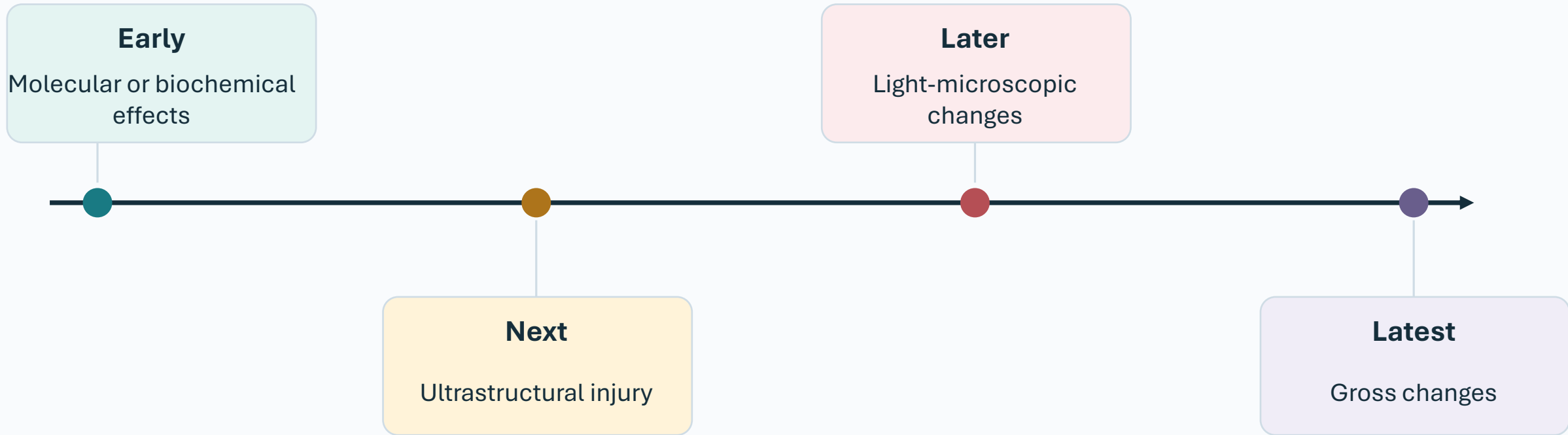
Increased turgor

Cellular water accumulation may increase firmness.

Increased organ weight

An aggregate effect of swelling in many cells.

The detection sequence is a hierarchy—not a clock



Relative sequence shown schematically; The absolute intervals depend on the tissue, insult, and method.

Clinical example: Ischemic myocardium



Myocardial ischemia: The first minutes

Reversible cell swelling may appear within minutes.

- This finding indicates ongoing cellular injury, not necessarily cell death.
- Biochemical dysfunction has already begun before light-microscopic necrosis.
- Short-duration injury may be recoverable if perfusion is restored.

Myocardial ischemia: Progression to irreversibility

example, injury may become irreversible within 1–2 hours.

- This is a specific illustrative interval, not a universal biologic threshold.
- Persistent ischemia progressively overwhelms repair mechanisms.
- The irreversible state may precede visible necrosis by routine microscopy.

Myocardial ischemia: Late light-microscopic confirmation

Unequivocal microscopic death may not appear until 4–12 hours.

- Injury can be lethal before histology displays unmistakable necrosis.
- Timing affects the sensitivity of morphologic diagnosis.
- Clinical interpretation must integrate history and other evidence.

The myocardial timeline must be interpreted correctly



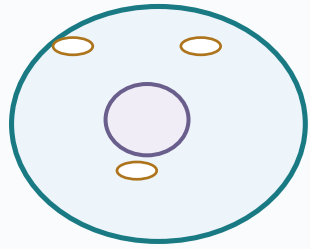
These ranges are the textbook's illustrative myocardial ischemia sequence; They are not fixed diagnostic cutoffs.

Reversible injury: The defining condition

If the stress abates within repair limits, cellular homeostasis can return.

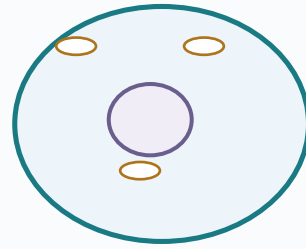
- Structural change need not equal irreversible loss of viability.
- Cell swelling and organelle alterations are initially correctable.
- Recovery may require restoration of energy-dependent transport and organelle function.

Normal cell: A reference schematic



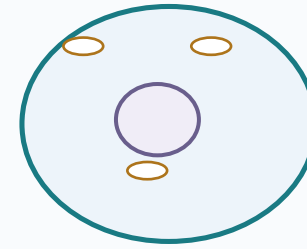
Intact membrane

Selective barrier and polarized transport.



Functional organelles

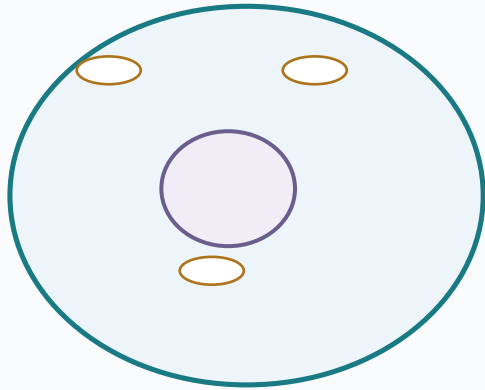
ATP generation and protein synthesis.



Nucleus preserved

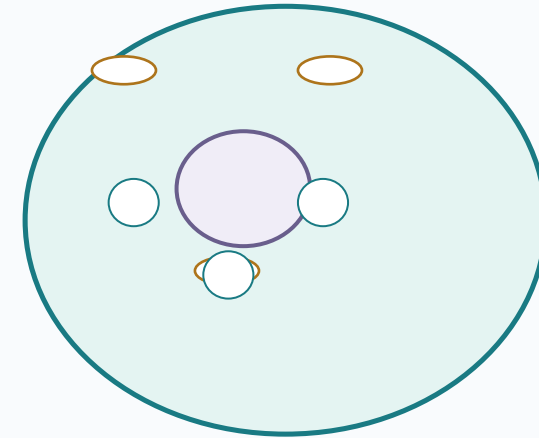
Organized chromatin and intact DNA compartment.

Cellular swelling: Early reversible morphology



Uninjured

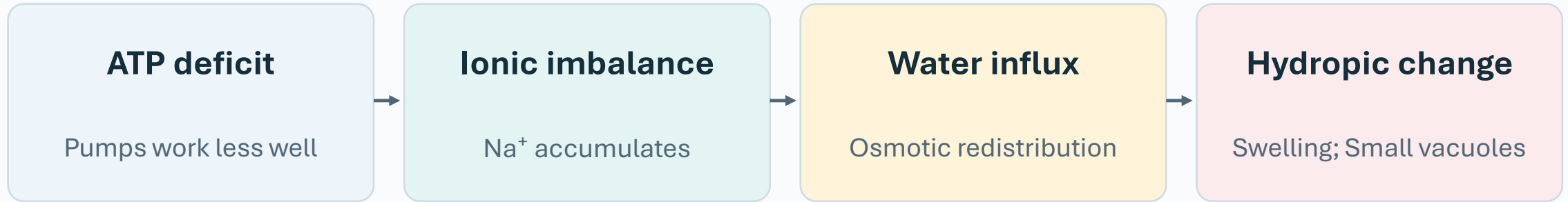
Effective ion pumps; Stable volume.



Reversibly injured

Water influx causes enlarged cell and organelles.

Why cytoplasmic vacuoles appear



Membrane blebs are not equivalent to rupture

Early blebbing

- Surface protrusions may appear.
- Plasma membrane continuity persists.
- Can accompany reversible injury.

Membrane disruption

- Severe loss of barrier integrity.
- Cell contents may escape.
- A defining feature of necrosis.

Ultrastructural signs of reversible injury

Surface microvilli

May be blunted or lost.

Mitochondria

Swelling with small amorphous densities.

ER / ribosomes

Dilation and ribosomal detachment.

Membrane phospholipids

Myelin figures may form from injured membranes.

Nuclear clumping differs from nuclear dissolution

Reversible nuclear change

- Chromatin may clump.
- Nuclear envelope can remain intact.
- Changes can resolve with recovery.

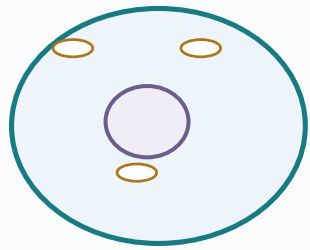
Necrotic nuclear changes

- Pyknosis: Nuclear shrinkage.
- Karyorrhexis: Fragmentation.
- Karyolysis: Fading / loss.

Fatty change: A different reversible phenotype

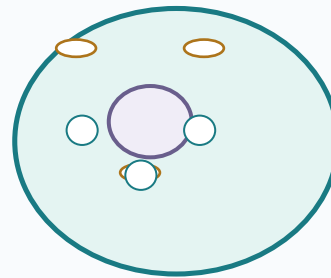
- Accumulation of triglyceride-filled vacuoles can result from metabolic disruption.
- Classically prominent in cells active in lipid metabolism, such as hepatocytes.
- Not every stress causes fatty change; It is not a generic stage before necrosis.
- Interpret as a context-dependent response, not a universal sequence.

Reversible injury: Integrated visual summary



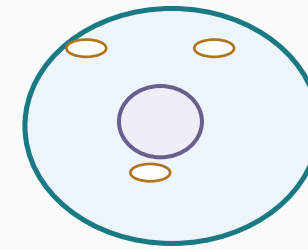
Homeostasis

Normal transport and volume.



Early injury

Blebs, swollen organelles.



Insult removed

Repair / restored gradients.

Recovery is a possible branch—not a mandatory endpoint after any injury.

Recovery requires termination of the insult



The “point of no return” is not a single visible line

Irreversibility is biologically complex and incompletely defined.

- An injured cell may cross into lethality before morphology confirms it.
- Multiple interacting failures contribute rather than one universal marker.
- The term conveys loss of recoverability despite removal of the insult.

Two hallmarks of irreversible injury

Persistent mitochondrial dysfunction

Oxidative phosphorylation and ATP generation fail to recover even after the original insult ends.

Profound membrane defects

Major plasma and organelle membrane derangements compromise compartment integrity.

Mitochondria: Reversible swelling versus permanent failure

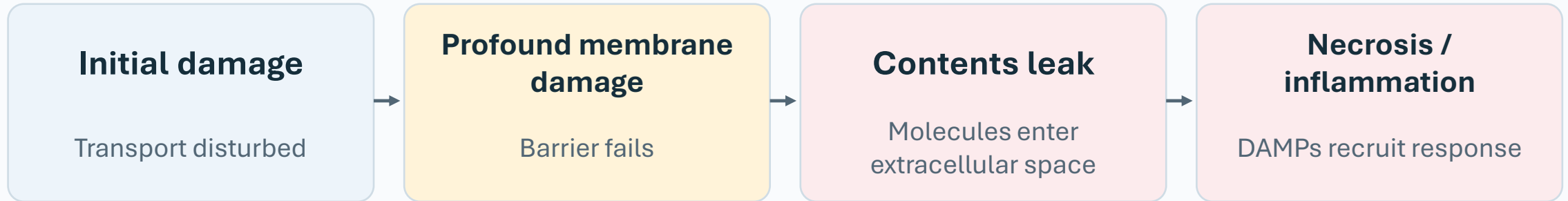
Potentially recoverable

- Transient swelling.
- Oxidative phosphorylation may recover.
- Cell retains a route back to homeostasis.

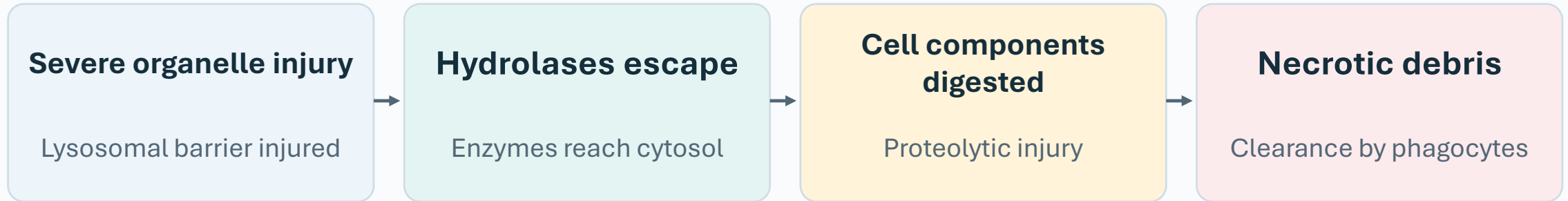
Irreversible

- Persistent failure of ATP production.
- Severe mitochondrial structural damage.
- Energy-dependent repair cannot be sustained.

Membrane integrity is a key fate determinant



Lysosomal membrane disruption accelerates self-digestion



Cell injury need not follow a linear, uniform trajectory

Reversible injury → recovery

Insult ends while repair remains possible.

Reversible injury → necrosis

Persistent severe injury destabilizes membranes.

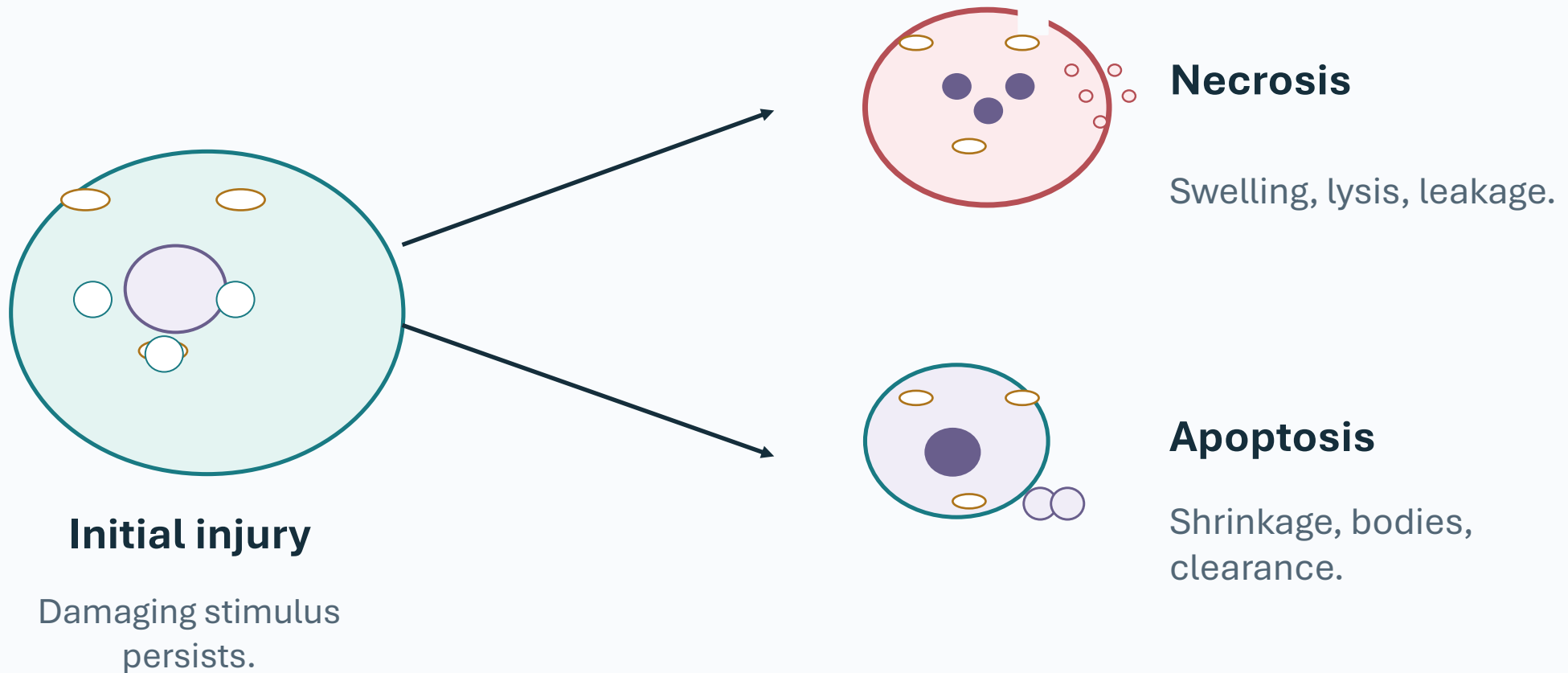
Stress → apoptosis

Molecular signaling activates regulated cell removal.

Mixed / overlapping patterns

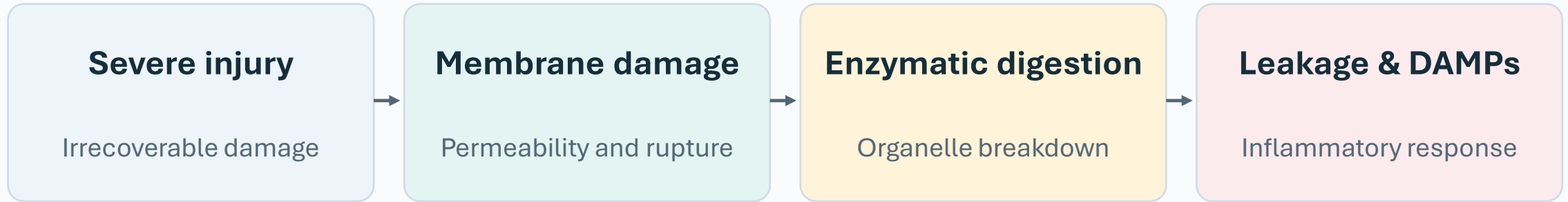
Some lesions show features that do not fit one pure category.

Severe injury can culminate in different death modes



Necrosis and apoptosis are alternative patterns, not a compulsory three-stage sequence.

Necrosis: Structural sequence



Nuclear evidence of necrosis

Pyknosis

Nuclear shrinkage with intensified basophilia.

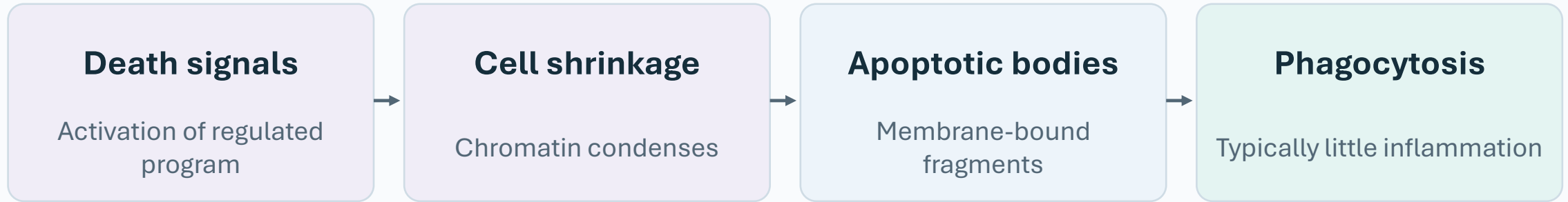
Karyorrhexis

Fragmentation of condensed nuclear material.

Karyolysis

Progressive fading from DNA degradation.

Apoptosis: An alternative controlled elimination pathway



Necrosis versus apoptosis: Structural signatures

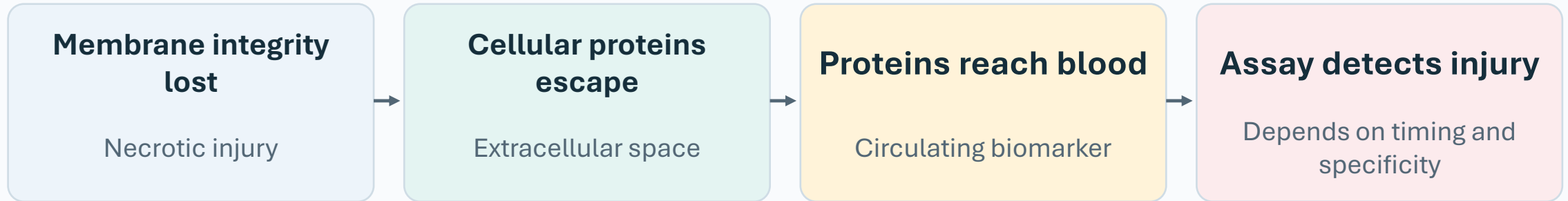
Feature	Necrosis	Apoptosis
Cell size	Swelling / enlargement	Shrinkage
Plasma membrane	Disrupted	Intact; Altered lipids
Cell content	Digested; May leak	Contained in apoptotic bodies
Nucleus	Pyknosis / fragmentation / lysis	Fragmentation into small pieces
Inflammation	Common	Usually absent

A single insult does not prescribe a universal death mode

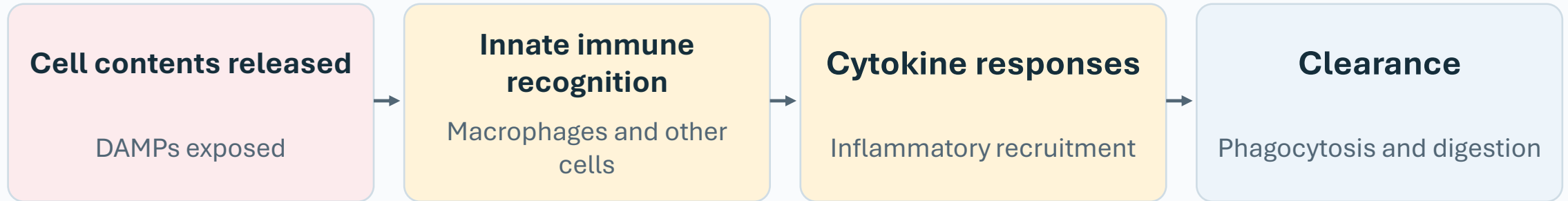
The cell type, insult, duration, and signaling context shape the outcome.

- Necrosis and apoptosis as major death patterns.
- Different injuries may activate one or more death pathways.
- Morphologic and mechanistic boundaries may overlap.

Cell contents become clinical biomarkers after leakage



Necrotic debris provokes an inflammatory response



Biomarkers and histology answer different questions

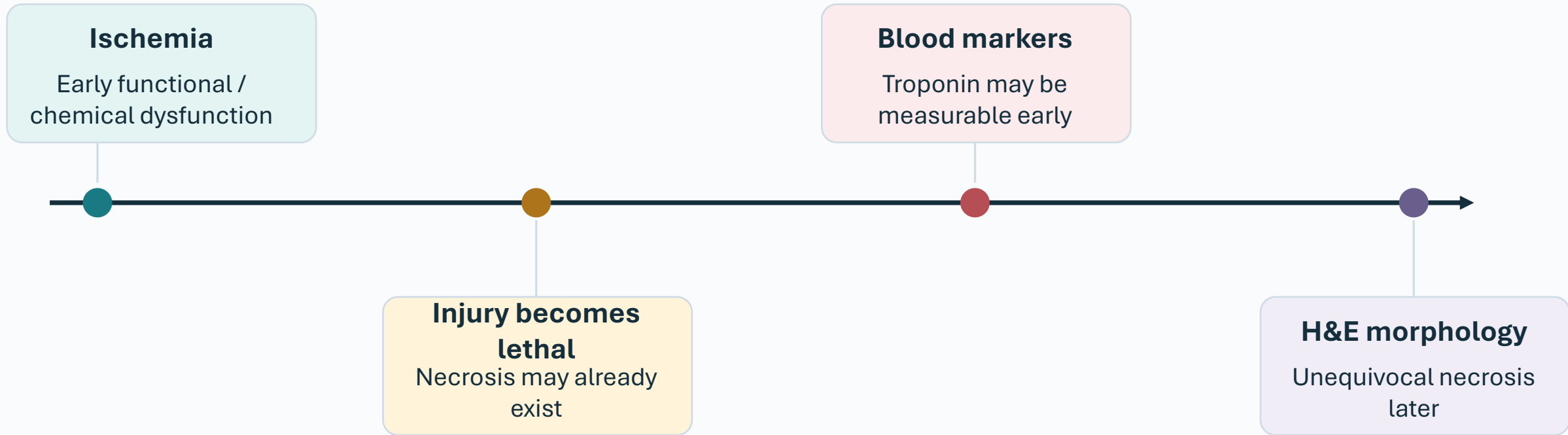
Circulating marker

- Evidence of cellular leakage or injury.
- Potentially detectable before clear H&E change.
- Needs clinical and assay context.

Tissue morphology

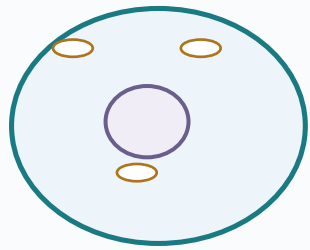
- Shows structural pattern and distribution.
- Can support irreversible injury.
- May remain equivocal early.

Cardiac troponin illustrates temporal dissociation



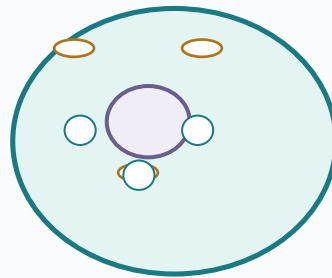
Troponins can be detected in blood as early as ~2 h after myocardial cell necrosis; Timing varies clinically.

Renal tubular injury: Tissue-level illustration



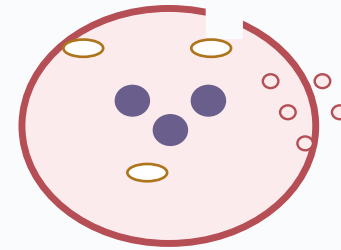
Intact tubule cell

Brush border / epithelial
polarity retained.



**Early reversible
injury**

Cell swelling and surface
blebbing.



Necrotic injury

Membrane breakdown
and nuclear loss.

Original schematic of epithelial cell stages; Not a histologic specimen.

Injured tubules: What H&E can and cannot show

Observation	Interpretive value
Swollen epithelial cells	Supports injury; Does not independently prove death
Cytoplasmic vacuolization	Often associated with hydropic / reversible change
Epithelial nuclear loss	Stronger evidence of irreversible necrotic damage
Disrupted epithelium and debris	More advanced injury with cell fragmentation
Minimal early abnormality	Does not exclude significant biochemical injury

The functional–morphologic mismatch has two directions

Severe dysfunction, subtle histology

Early ischemia may profoundly impair work before H&E becomes diagnostic.

Visible swelling, preserved viability

A cell can show substantial structural change yet retain recovery potential.

Elevated marker, limited localization

A blood assay signals an injury-related process but does not map each dying cell.

Established necrosis, delayed clearance

Histologic dead-cell remnants can persist during inflammatory removal.

Clinical application 1: Chest pain at an early time point

A patient develops acute ischemic chest discomfort. Tissue sampled very early shows no unmistakable light-microscopic necrosis. Cellular function is markedly disturbed.

What is the most defensible interpretation?

- Early severe injury may precede routine microscopic evidence of death.
- Absence of necrosis on H&E proves normal myocardium.

Clinical application 1: Interpretation

Early H&E cannot reliably exclude ongoing or irreversible injury.

- Molecular and biochemical alterations precede visible morphology.
- Cell swelling may be reversible, but continued ischemia threatens viability.
- Time course and clinical evidence must accompany tissue interpretation.

Clinical application 2: Renal epithelial injury

Following a toxic or ischemic insult, a renal tubule shows swollen epithelial cells and scattered apical blebs. Most nuclei remain intact.

Which observation would most strengthen evidence of necrosis?

- An increase in cellular volume alone.
- Loss of nuclei with cell fragmentation and membrane disruption.

Clinical application 2: Interpretation

Nuclear loss and membrane breakdown favor necrotic cell death.

- Swelling and blebbing can occur in reversible injury.
- Necrosis is associated with cell-content leakage and enzymatic digestion.
- Morphology must be interpreted with the insult, extent, and sampling time.

Sampling stage determines what we can confidently conclude

Very early

Biochemical findings may be informative; H&E can remain non-diagnostic.

Early reversible

Swelling and organelle alterations; Death is not established.

Irreversible

Recovery is no longer feasible, although morphology may lag.

Established death

Nuclear changes, membrane destruction, necrotic debris and reaction.

Three frequent interpretation errors

Error 1

“No necrosis visible, therefore no serious injury.”

Error 2

“Cell swelling proves the cell is dead.”

Error 3

“The 1–2 h example is a fixed threshold for all tissues.”

Knowledge check: Early light microscopy

Which statement best reflects the textbook's temporal sequence?

(A) H&E abnormalities always precede biochemical dysfunction.

(B) Gross morphologic changes are the first indicator of injury.

(C) Biochemical injury can be present without clear routine-microscopy changes.

(D) Swelling always means irreversible necrosis.

Knowledge check: Irreversible transition

Which combination best characterizes irreversible injury?

(A) Transient blebbing and preserved metabolic recovery.

(B) Persistent mitochondrial failure and profound membrane defects.

(C) Purely reversible chromatin clumping and water influx.

(D) Normal organelles and membrane integrity.

Knowledge check: Why necrosis causes inflammation

Why does necrosis commonly trigger a tissue inflammatory reaction?

(A) Apoptotic bodies are always phagocytosed too slowly.

(B) Cellular contents leak and act as danger signals.

(C) Membrane integrity is fully preserved.

(D) Cells synthesize more proteins during death.

Integrated summary: Five rules for interpretation

- Noxious stimuli first produce biochemical and molecular perturbations.
- Functional decline and structural damage are temporally separated.
- Cell swelling is an early, potentially reversible sign.
- Persistent mitochondrial failure plus major membrane injury favor irreversibility.
- Necrosis and apoptosis differ in morphology, leakage, and inflammatory response.

Selected source and figure provenance

- Primary source: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Chapter 2.
- Principal source section: “Progression of Cell Injury and Death,” p. 35.
- Adjacent source context: “Reversible Cell Injury” and “Necrosis,” pp. 35–38; “Apoptosis,” pp. 38–39.
- Conceptual references: Fig. 2.6 and Fig. 2.7; morphology: Figs. 2.8–2.9; Table 2.2.
- All illustrations in this deck are newly constructed native PowerPoint schematics; no textbook figures are reproduced.