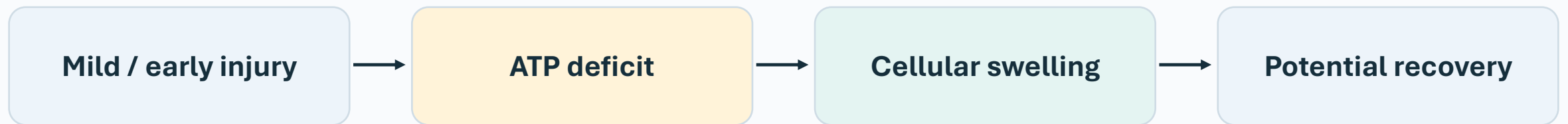


Reversible cell injury

Mechanisms, hydropic change, organelle alterations, and fatty change



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Learning outcomes

- Define reversible injury in terms of cellular viability and repair.
- Trace ATP depletion to ionic imbalance and cellular swelling.
- Recognize plasma-membrane, mitochondrial, ER and nuclear alterations.
- Explain hydropic change and fatty change in the appropriate tissue context.
- Discriminate reversible injury from morphological evidence of necrosis.

Reversible injury: Definition

Early or mild functional and structural alterations that can be corrected when the harmful stimulus is removed.

- Viability is preserved during the potentially reversible phase.
- Injury is not synonymous with cell death.
- Recovery requires restoration of cellular homeostasis.

Three conditions frame reversibility

Insult burden

Magnitude, duration, and biological target of the injury.

Repair competence

Residual organelle function and the capacity to restore homeostasis.

Timely removal

Cessation of the stressor before irreparable damage develops.

Two dominant patterns

Cellular swelling

Intracellular water accumulation caused by disturbed ATP-dependent ion transport.

Fatty change

Cytoplasmic accumulation of triglycerides after disturbance of lipid metabolism, especially in the liver.

Reversibility and normal appearance are different

Morphologically abnormal

- Swelling and organelle distortion may be conspicuous.
- Cells may still retain viability.
- Routine H&E cannot directly measure future recovery.

Functionally recoverable

- Damaging stimulus must cease.
- Energy-dependent systems must recover.
- Return toward a stable cell volume is possible.

Etiologic routes into reversible injury

Oxygen deficiency

Hypoxia reduces ATP generation by mitochondrial oxidative phosphorylation.

Ischemia

Reduced perfusion can impose both oxygen and metabolic substrate deficits.

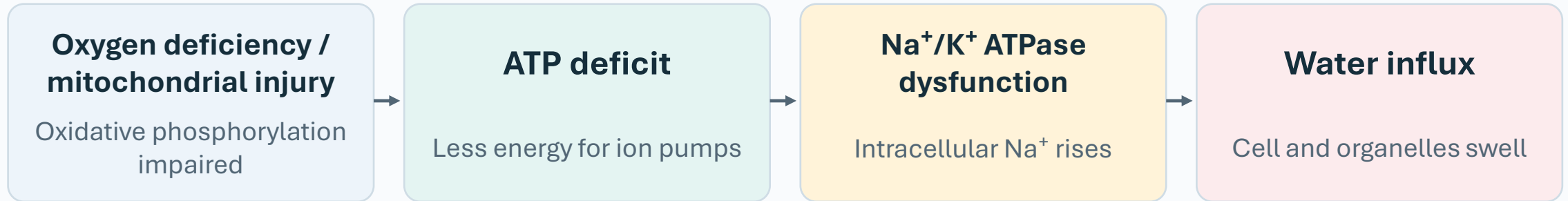
Radiation / toxins

Mitochondrial injury can disturb ATP availability.

Toxic metabolic effects

Perturbations in hepatic lipid handling can create fatty change.

The core swelling mechanism



- Swelling initially reflects transport failure, not necessarily membrane rupture.

ATP supply couples organelles to membranes

Mitochondria

Oxidative phosphorylation normally supplies ATP.

Membrane pumps

Energy-dependent ion gradients maintain volume and polarity.

Osmotic balance

Impaired ion transport favors intracellular water accumulation.

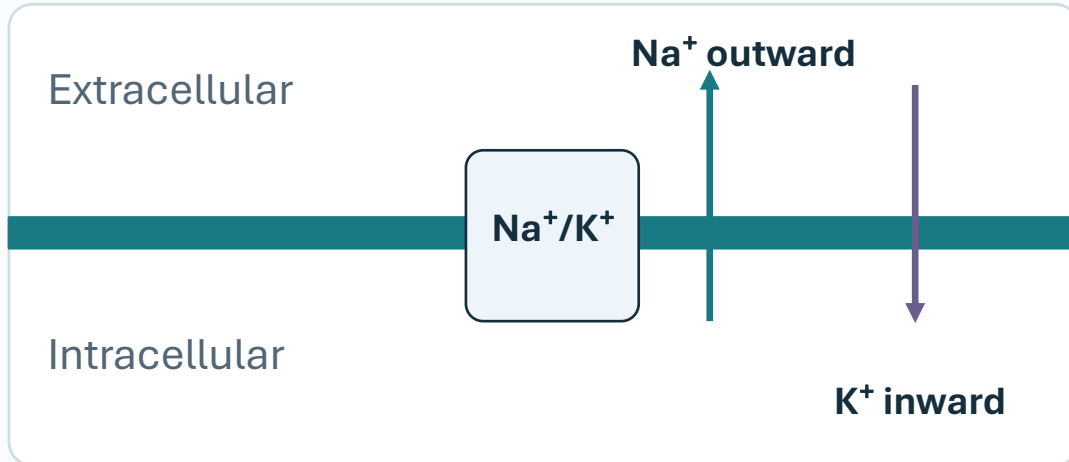
Morphology

Cell size and multiple organelles become enlarged.

Normal versus impaired ion regulation

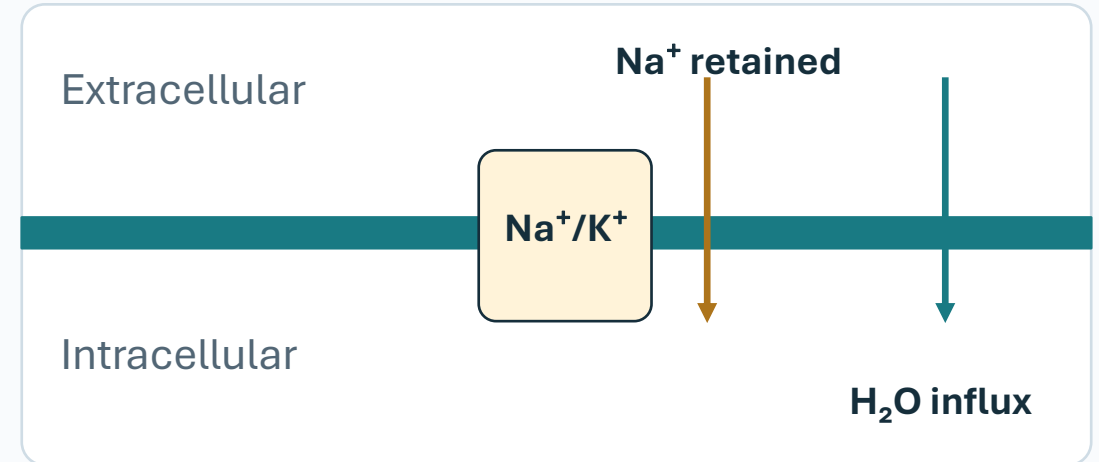
ATP-dependent ion transport

Water follows the net solute disturbance



Uninjured cell

ATP available



Reversibly injured cell

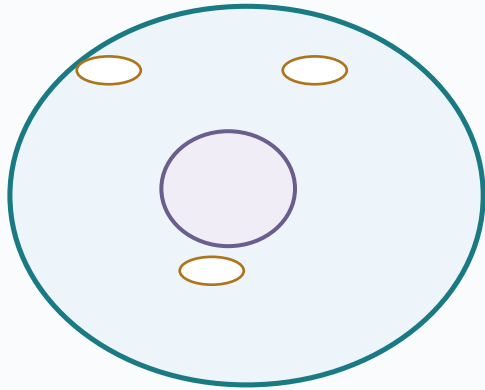
ATP depleted

Why ATP depletion produces swelling

Reduced ATP does not directly create water; It disrupts ionic homeostasis.

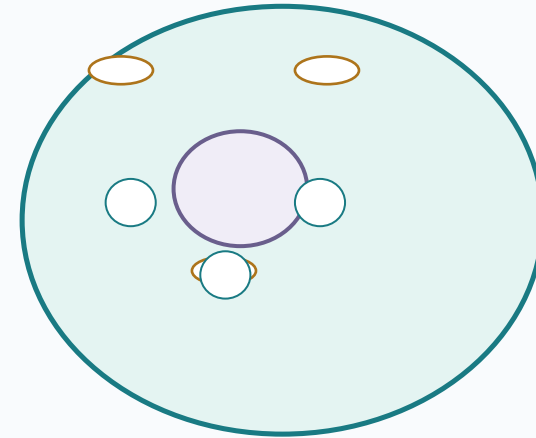
- Less ATP compromises the Na^+/K^+ pump.
- Intracellular sodium accumulation alters osmotic driving forces.
- Water redistributes into the cell and membrane-bound compartments.
- Cytoplasmic volume and organelle volume increase.

Swelling can involve several compartments



Baseline

Normal cell volume and organelle dimensions.

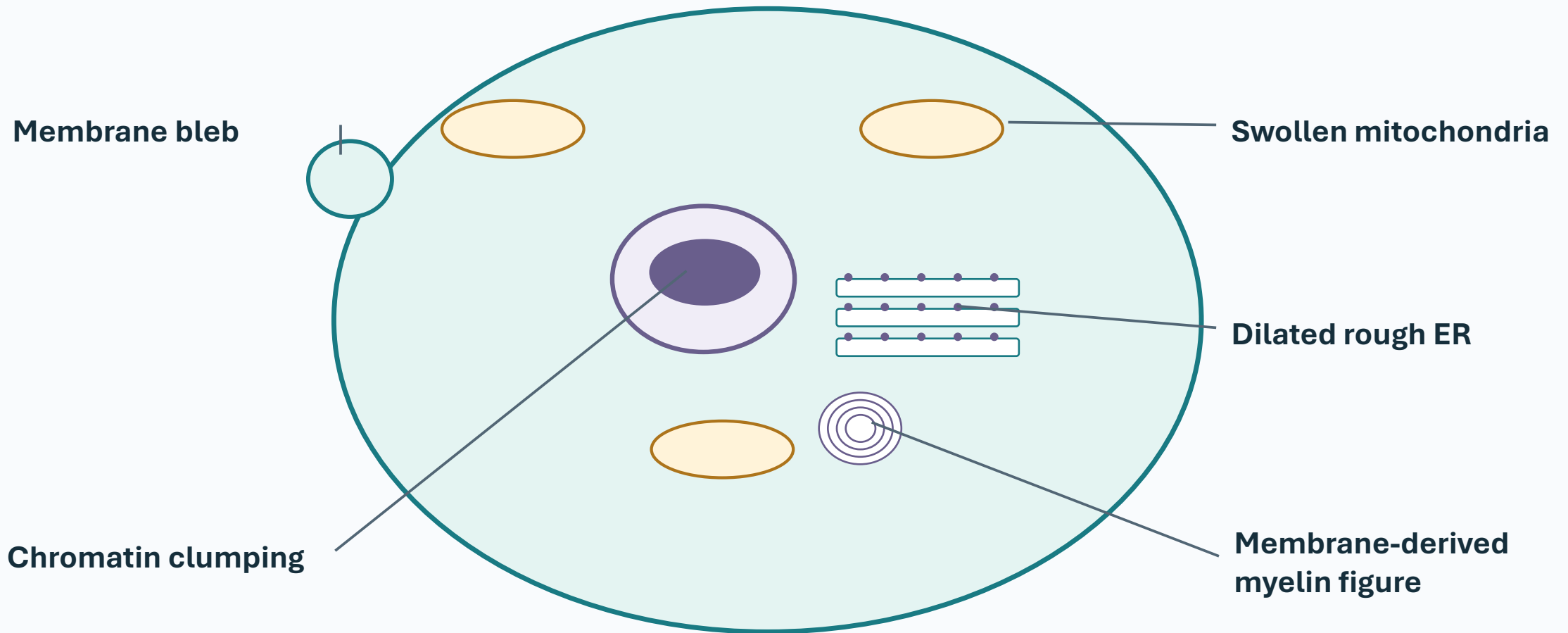


Reversible swelling

Cell volume increases; Membranes remain potentially repairable.

A cell-wide view of early injury

Original cellular schematic — not an electron micrograph



Plasma membrane: Early blebbing

What is a bleb?

Localized protrusion of the cell surface caused by altered membrane–cytoskeletal relationships.

Why it matters

Indicates cellular injury but does not, by itself, establish membrane rupture or irreversible death.

Blebs are not equivalent to lysis

Early reversible alteration

- Plasma membrane remains largely continuous.
- Small surface blebs can form.
- Normal membrane architecture may be restored.

Necrotic membrane damage

- Profound permeability defects or disruption.
- Contents may leak from the cell.
- Associated with loss of cellular viability.

Microvilli: Loss of specialized surface

- Blunting or disappearance of microvilli is an ultrastructural feature of reversible injury.
- Brush borders support epithelial functional surface area.
- In kidney proximal tubules, apical membrane changes may precede unequivocal necrosis.
- The observed structural severity depends on injury and sampling stage.

Mitochondria respond to mild injury

Swelling

Mitochondria may enlarge with altered ionic and water balance.

Amorphous densities

Small amorphous densities are included among reversible ultrastructural changes.

Functional consequence

Lower ATP availability may amplify membrane-pump failure.

Important boundary

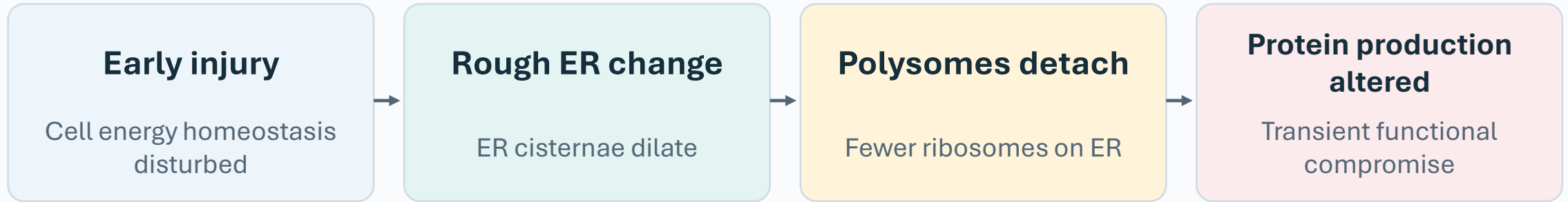
Marked, sustained damage with dense deposits occurs in more advanced injury.

Endoplasmic reticulum: Dilation

ER dilation is part of the reversible subcellular response.

- Swelling of ER cisternae may appear as clear cytoplasmic vacuoles on H&E.
- Some vacuoles represent distended, pinched-off ER segments.
- Dilation can coexist with detachment of ribosomes.

Ribosome detachment and protein synthesis



Chromatin alterations can be reversible

Reversible nuclear response

- Clumping of nuclear chromatin.
- Disaggregation of granular and fibrillar nuclear elements.
- Not sufficient to establish necrosis.

Destructive nuclear changes

- Pyknosis: Dense shrunken nucleus.
- Karyorrhexis: Nuclear fragmentation.
- Karyolysis: Progressive nuclear dissolution.

Myelin figures reflect membrane phospholipids

Material

Concentric phospholipid-rich membrane-derived structures.

Origin

Derived from membranes injured during cellular stress.

Interpretation

An ultrastructural injury feature; Isolated presence does not prove death.

Five ultrastructural alterations at a glance

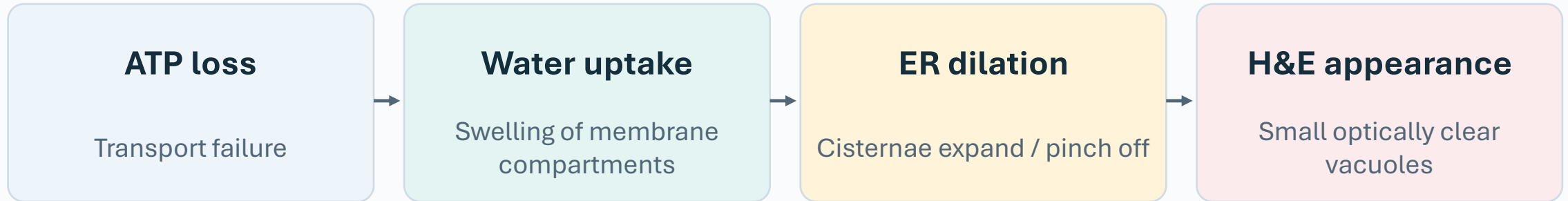
Compartment	Reversible ultrastructural finding
Plasma membrane	Blebs; Blunted or absent microvilli
Mitochondria	Swelling; Small amorphous densities
Cytosol	Phospholipid-rich myelin figures
Endoplasmic reticulum	Dilation with detached polysomes
Nucleus	Changes in chromatin and nuclear ultrastructure

Light microscopy: Hydropic change

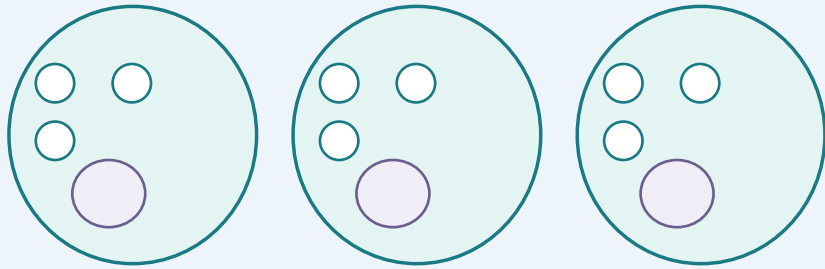
Cellular swelling is the earliest morphologic expression of many injuries.

- Enlarged cells may develop small clear intracytoplasmic vacuoles.
- The terms hydropic change and vacuolar degeneration describe this nonlethal pattern.
- Affected cells can remain viable despite obvious cytoplasmic changes.

Clear vacuoles: What they represent

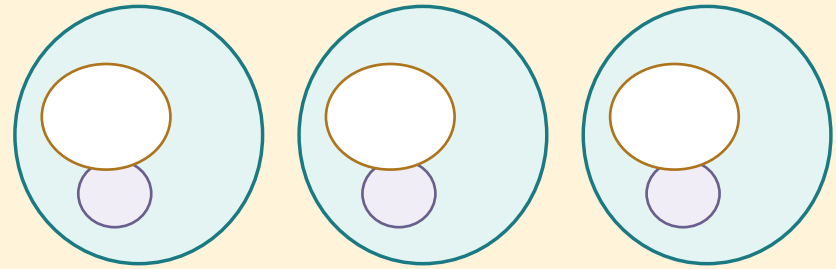


Hydropic change versus fatty change



Hydropic vacuoles

Water-related dilated ER segments



Lipid vacuoles

Triglyceride accumulation; H&E clear spaces

Cell swelling and fatty change are not synonyms

Feature	Cellular swelling	Fatty change
Stored substance	Water	Triglycerides
Immediate context	ATP-dependent ion pump failure	Lipid metabolic pathway disruption
H&E feature	Fine clear cytoplasmic vacuoles	Often clear lipid vacuoles
Typical setting	Many injured cell types	Lipid-handling organs, notably liver
Teaching pitfall	Not automatically necrosis	Not necessarily identical to edema

Why swollen cytoplasm can appear eosinophilic

- RNA normally contributes to cytoplasmic basophilia on H&E.
- Loss of cytoplasmic RNA reduces hematoxylin binding.
- Injured-cell cytoplasm may therefore look relatively more pink/red.
- Greater eosinophilia during progression toward necrosis is not a stand-alone indicator of irreversibility.

H&E eosinophilia requires context

Hematoxylin

Highlights nucleic-acid-rich structures, particularly chromatin and ribosomal RNA.

Eosin

Highlights many proteins in cytoplasm and extracellular matrix.

Relative staining shift

Loss of RNA and altered proteins shift injured cytoplasm toward pink.

Key diagnostic consideration:

Eosinophilia alone is not an assay of membrane integrity or cell viability.

Nuclear preservation is informative—but limited

An intact nucleus supports the possibility of reversible injury; It does not prove recovery.

- Early injury may exhibit chromatin changes without frank nuclear loss.
- Nuclear fragmentation and disappearance favor necrosis in the appropriate context.
- A static biopsy cannot establish the subsequent fate of every cell.

Macroscopic changes from widespread swelling

Pallor

Affected tissue may become paler.

Increased turgor

The organ may feel more tense or firm.

Increased organ weight

Aggregate water accumulation enlarges tissue mass.

Microscopic versus gross examination

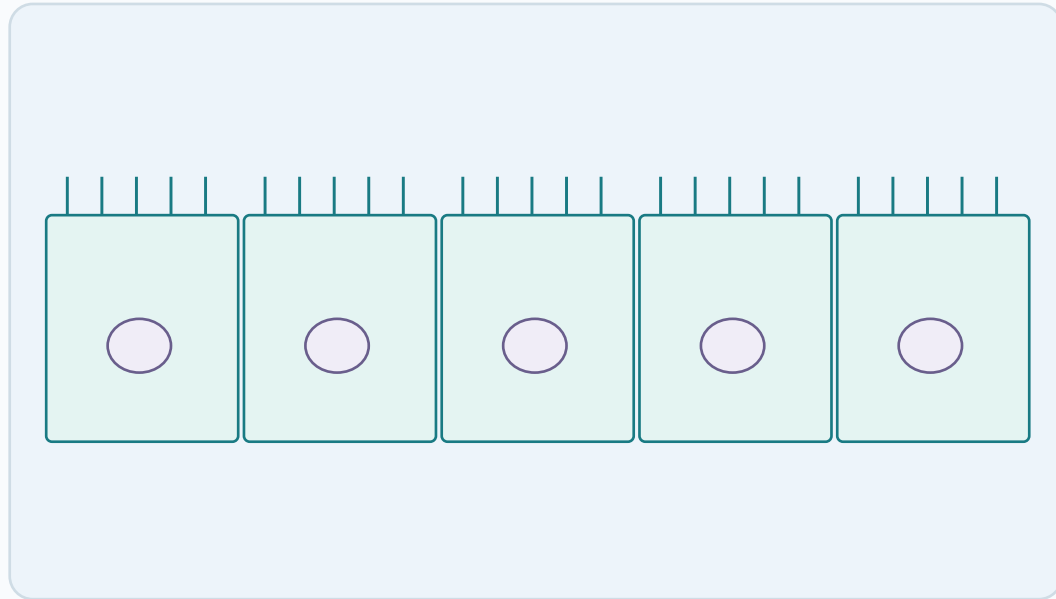
Light-microscopic scale

- Swollen epithelial or parenchymal cells.
- Small clear vacuoles in cytoplasm.
- Variable eosinophilic change.

Organ scale

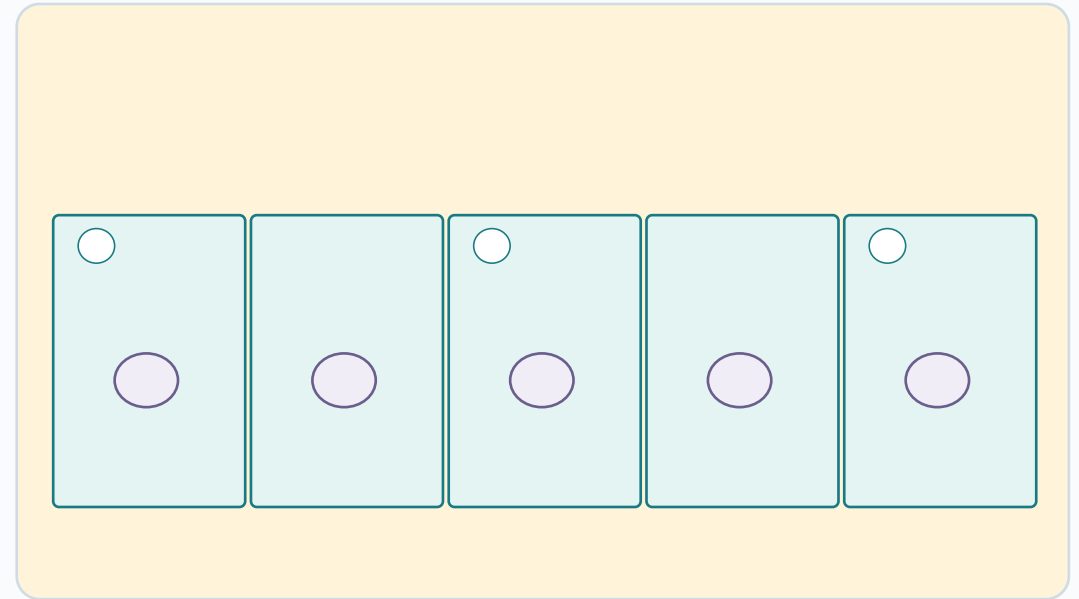
- Gross appearance requires a sufficient extent of injury.
- Pallor and turgor may change.
- Organ weight may increase.

Renal tubule: Architectural example



Intact tubular epithelium

Luminal microvilli and intact epithelial nuclei



Swollen tubular epithelium

Less regular brush border; Cytoplasmic vacuoles

Schematic of epithelial organization; Real sections vary by tubule segment

Kidney injury: What can be reversible?

Surface blebs

Early surface distortion of viable tubular epithelial cells.

Brush-border loss

Altered microvilli may precede irreversible injury.

Cellular swelling

Water influx enlarges the cytoplasm and organelles.

Intact nuclei

More consistent with non-necrotic injury than total nuclear loss.

Reading a hypothetical renal H&E field

A renal biopsy after a short ischemic episode shows enlarged tubule epithelial cells with fine cytoplasmic vacuoles; Many nuclei remain identifiable and the tissue is not extensively fragmented.

Which description best fits the morphology?

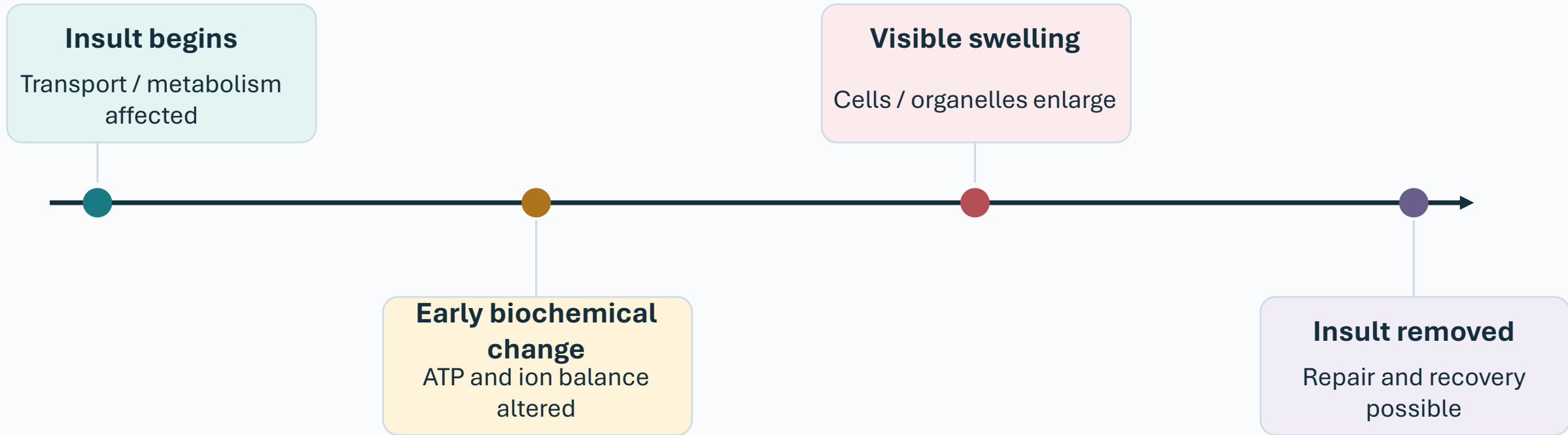
- Hydropic / vacuolar cell injury.
- Established confluent tubular necrosis.

Renal H&E case: Interpretation

Cell swelling with vacuoles supports hydropic change.

- Water-related ER dilation is a plausible basis for the clear vacuoles.
- Preserved nuclei are compatible with reversible injury.
- A biopsy cannot by itself prove future recovery; Evaluate extent, context, and time.

The reversible injury phenotype is dynamic



A conceptual sequence only; No universal duration or fixed recovery interval is implied.

Why morphology may lag function

Biochemistry

ATP generation and membrane transport may decline first.

Function

Active secretion, absorption, or contractility may be compromised.

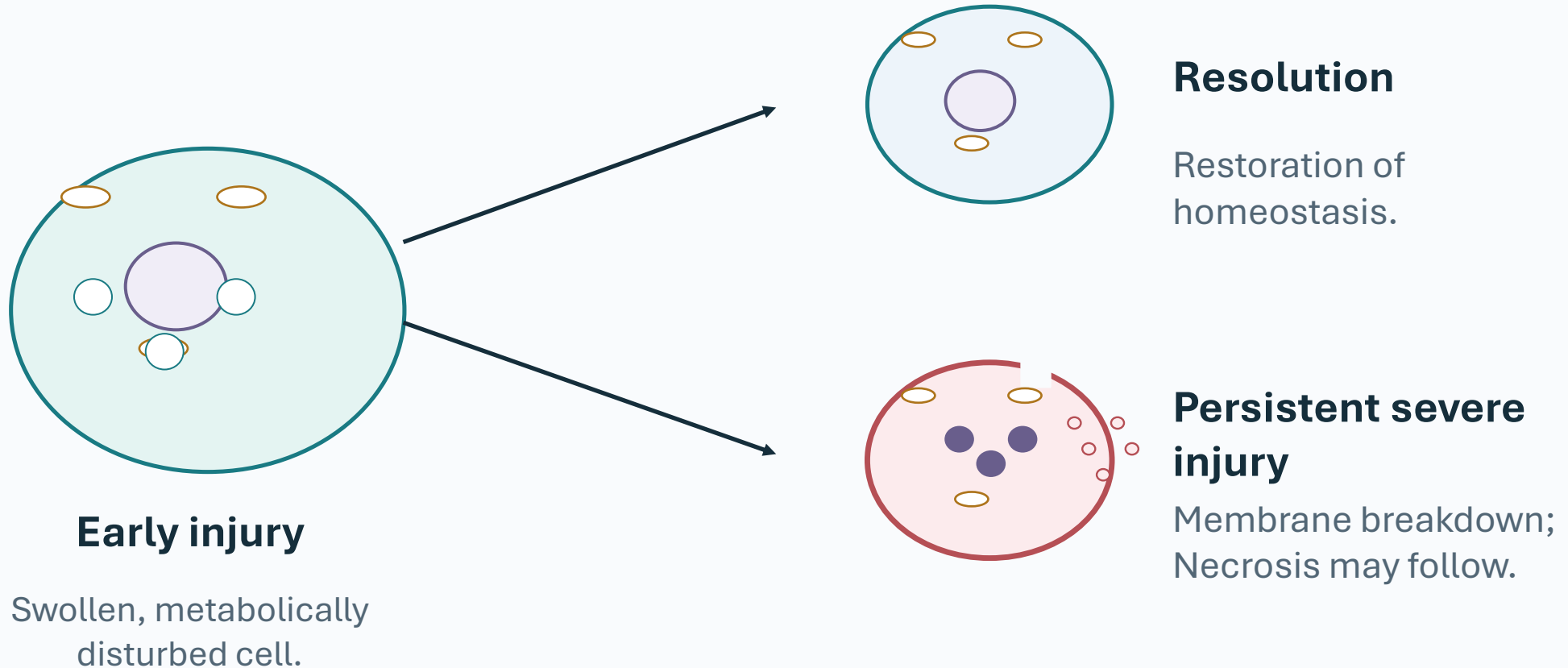
Ultrastructure

Blebs, swollen mitochondria and dilated ER become detectable.

Routine microscopy

Cell swelling and vacuolation become recognizable.

The threshold to irreversibility



Potential recovery and progression are distinct outcomes; Exact thresholds vary.

Reversible swelling versus necrosis

Attribute	Reversible injury	Necrosis
Cell size	Often enlarged	Often enlarged; Cellular disruption
Plasma membrane	Blebbing; Substantial integrity retained	Disrupted with leakage
Nucleus	Chromatin alterations, generally retained	Pyknosis, karyorrhexis, karyolysis
Cytoplasm	Hydropic vacuoles possible	Digestive breakdown and cell debris
Recovery	Possible if insult removed	Not possible for dead cells

Fatty change: Definition

Accumulation of intracellular triglyceride droplets in cells with disrupted lipid metabolism.

- Organs involved in lipid processing—especially the liver.
- Toxic injury is one described route to the altered metabolic pathways.
- Fatty change is a morphologic response, not a specific etiologic diagnosis.

Why hepatocytes show fatty change

Metabolic role

Hepatocytes ordinarily handle large lipid fluxes.

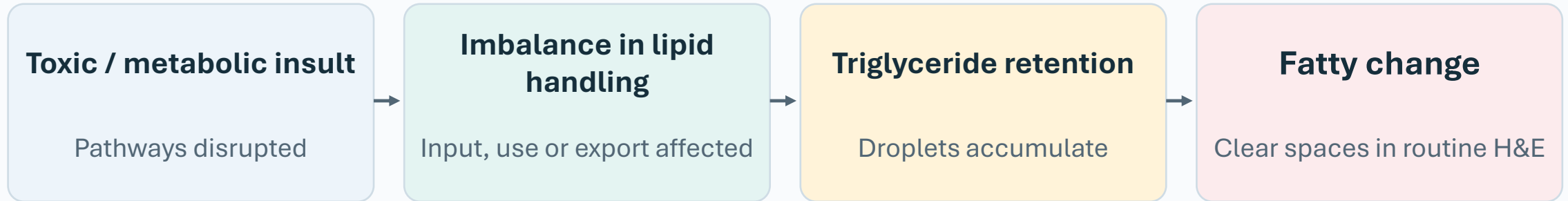
Toxic disturbance

Disrupted metabolic pathways alter triglyceride handling.

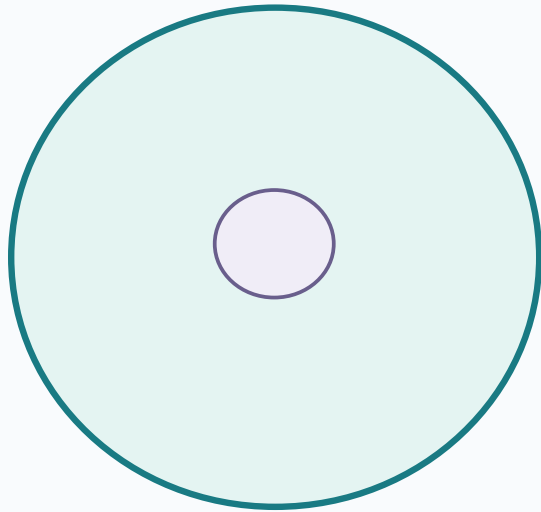
Cell phenotype

Lipid accumulates in cytoplasmic droplets.

Fat accumulation: A qualitative pathway

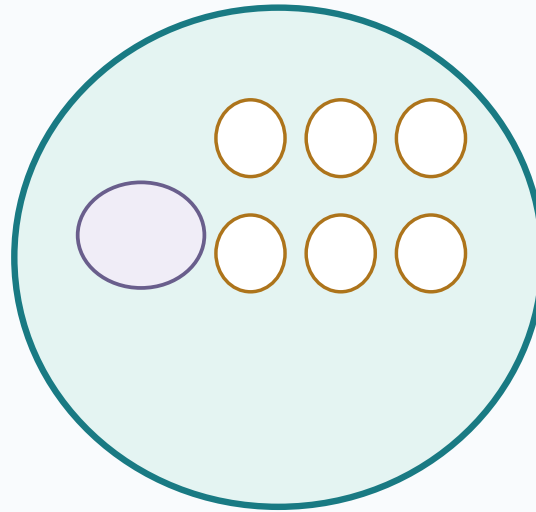


Fatty change: An original cell schematic



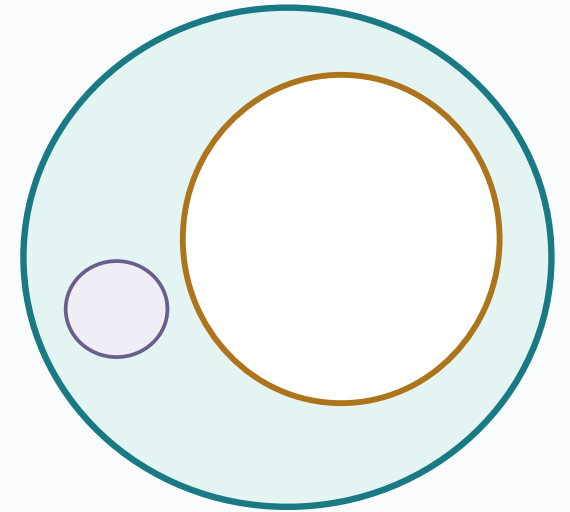
Normal hepatocyte

No conspicuous fat



Multiple lipid droplets

Small clear spaces



Large lipid vacuole

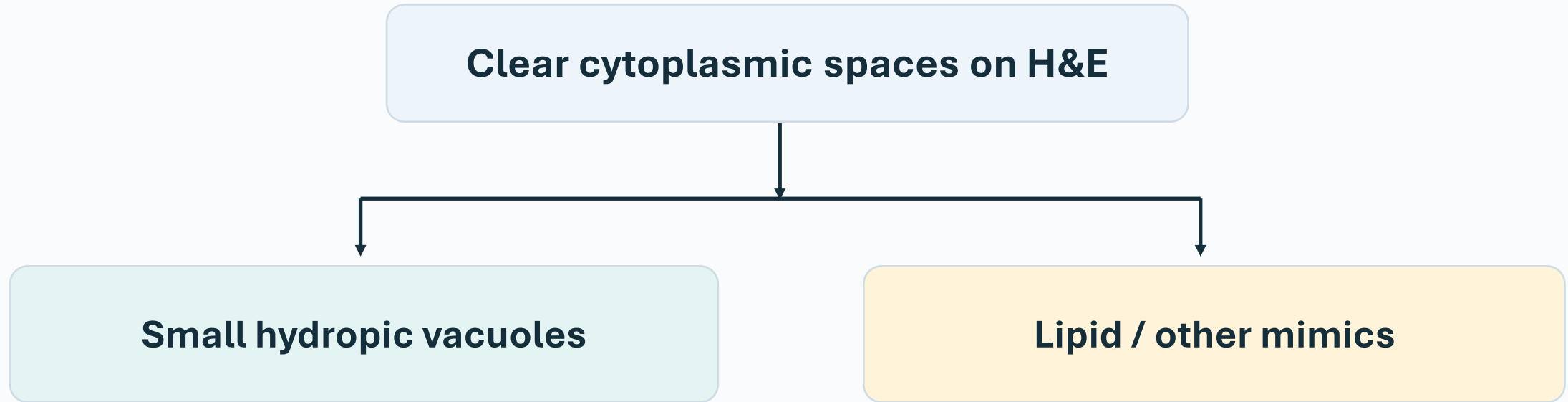
Nuclear displacement may occur

Schematic only; Not a histologic classification of clinical steatosis

What a lipid droplet looks like in H&E

- Routine tissue processing can dissolve neutral lipid, leaving optically empty spaces.
- Droplet size and number may vary between affected hepatocytes.
- Large vacuoles may shift the nucleus toward the cell periphery.
- Histologic appearance does not uniquely identify the cause of steatosis.

Do not confuse water, lipid, and clearing artifacts



- Correlate cell type, architecture, and insult history.
- Use additional stains or preparations only when indicated.
- Do not assign reversibility from a single image alone.

When vacuoles have different origins

Potential explanation	Interpretive clue / limitation
Water-related swelling	Small clear vacuoles may reflect distended ER
Triglyceride accumulation	Lipid droplets are conspicuous in metabolically stressed hepatocytes
Glycogen accumulation	Clear cytoplasm may require periodic acid–Schiff correlation
Processing / fixation artifact	Distribution and technical context help interpretation

Fatty change is not synonymous with necrosis

Fatty change

- Triglycerides accumulate in cytoplasm.
- Many affected cells may remain viable.
- Morphology by itself does not prove death.

Necrosis

- Irreversible loss of cellular viability.
- Nuclear and membrane destruction develops.
- Often produces tissue inflammation.

Cell swelling and steatosis can coexist

Distinct substances

Water accumulation and triglyceride deposition reflect different immediate processes.

Shared context

A severe systemic or toxic insult can perturb several pathways at once.

Morphologic heterogeneity

A single tissue may contain cells at different degrees or types of injury.

Reporting discipline

Describe what is observed without assuming one mechanism explains all vacuoles.

Cellular phenotype depends on tissue role

Renal tubular epithelium

- ATP-dependent transport is crucial.
- Cell swelling may affect apical microvilli.
- Hydropic and ultrastructural changes are demonstrable.

Hepatocytes

- Extensive intermediary lipid metabolism.
- Triglyceride imbalance manifests as fatty change.
- Clear lipid vacuoles can be prominent.

What a routine H&E section cannot prove

- Whether the cell will eventually recover after the insult ends.
- The precise ATP concentration in a particular cell.
- The number or composition of small ultrastructural membrane lesions.
- Whether all pale vacuoles contain the same substance.

How electron microscopy adds information

Routine H&E	Ultrastructure (electron microscopy)
Swollen epithelial cells	Plasma-membrane blebbing and altered microvilli
Pale vacuolated cytoplasm	ER dilation / altered cisternae
Subtle early injury	Mitochondrial swelling and small densities
Limited organelle localization	Detached polysomes and myelin figures

Five cautionary statements

Swelling ≠ death

Enlarged volume is compatible with reversible injury.

Blebbing ≠ lysis

Early membrane distortions can occur before rupture.

Steatosis ≠ necrosis

Intracellular fat alone does not establish cell loss.

Eosinophilia ≠ irreversible injury

Relative pink staining needs morphologic context.

Normal H&E ≠ normal function

Biochemical disturbance can precede routine visible changes.

Application: Hypoxia and renal cells

In an experiment, renal epithelial cells briefly experience low oxygen tension. Electron microscopy shows moderate mitochondrial swelling and membrane blebs, but severe membrane rupture is not seen.

What is the most accurate classification?

- Compatible with early potentially reversible injury.
- Proof that all cells are necrotic.

Hypoxia case: Interpretation

This constellation is compatible with reversible injury.

- The insult can lower mitochondrial ATP production.
- Blebbing and moderate mitochondrial swelling are among reversible changes.
- Cell survival still depends on injury severity, duration, and recovery.

Application: Liver with vacuolated hepatocytes

A liver biopsy shows hepatocytes containing optically empty rounded vacuoles; Several large vacuoles displace nuclei. The patient has a relevant toxic or metabolic exposure.

Which reversible pattern should be considered?

- Fatty change from triglyceride accumulation.
- Mandatory liquefactive necrosis.

Hepatic case: Interpretation

Fatty change is a strong morphologic consideration.

- Lipid metabolism disturbance can produce cytoplasmic triglyceride droplets.
- Routine H&E may show empty vacuoles after lipid extraction.
- A specific cause requires clinicopathologic context; Fat alone is not death.

Knowledge check: First visible change

What is the characteristic early morphologic expression of many reversible injuries?

(A) Generalized cellular swelling.

(B) Confluent karyolysis in every cell.

(C) Extensive tissue fibrosis.

(D) Complete cell-membrane rupture.

Knowledge check: Mechanisms

Which sequence most directly accounts for reversible hypoxic cell swelling?

(A) ATP rises → Na⁺ pump accelerates → water enters.

(B) ATP falls → Na⁺/K⁺ pump fails → intracellular water rises.

(C) Triglycerides disappear → mitochondria shrink → water exits.

(D) Ribosomes detach → the plasma membrane must rupture.

Knowledge check: Ultrastructure

Which change belongs to the reversible ultrastructural injury spectrum?

(A) Distended ER with detached polysomes.

(B) Universal absence of all nuclei.

(C) Complete dissolution of cytoplasmic membranes.

(D) Replacement of cells by dense collagen.

Knowledge check: Fatty change

What best defines the fatty-change pattern?

(A) Edema in the interstitium only.

(B) Triglyceride-rich intracellular lipid vacuoles.

(C) Accumulation of extracellular amyloid.

(D) Irreversible rupture of lysosomal membranes.

Integrated summary

- Reversible injury is early or mild injury with potential restoration after removal of the stimulus.
- Cell swelling follows disturbed ATP-dependent ion transport and water redistribution.
- Ultrastructural findings include blebs, microvillus loss, mitochondrial/ER swelling, myelin figures, and nuclear alterations.
- Hydropic change produces fine clear vacuoles; Fatty change reflects triglyceride accumulation, often in liver.
- Morphologic injury alone does not establish irreversibility; Membrane and nuclear destruction favor necrosis.

Primary references and figure provenance

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026), Chapter 2, “Reversible Cell Injury,” pp. 35–36.
- Adjacent interpretive context: “Progression of Cell Injury and Death,” p. 35; “Cell Death / Necrosis,” pp. 36–38.
- Morphology source: Fig. 2.8 caption; reversible ultrastructural description and Fig. 2.9 caption.
- All illustrations are new native, editable PowerPoint schematics, not textbook figures or microscopy.
- No external diagnostic tissue micrograph was embedded; authentic source imagery can be added where redistribution rights permit.