

Intracellular Accumulations

Mechanisms · Lipid storage · Protein inclusions · Glycogen

Cell injury, cell death, and adaptations

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Learning objectives

- Classify the four major mechanisms of abnormal intracellular accumulation.
- Interpret the morphologic patterns of lipid, protein, and glycogen accumulation.
- Relate selected histologic inclusions to metabolic, secretory, and degradative defects.
- Distinguish potentially reversible storage from progressive storage-associated injury.

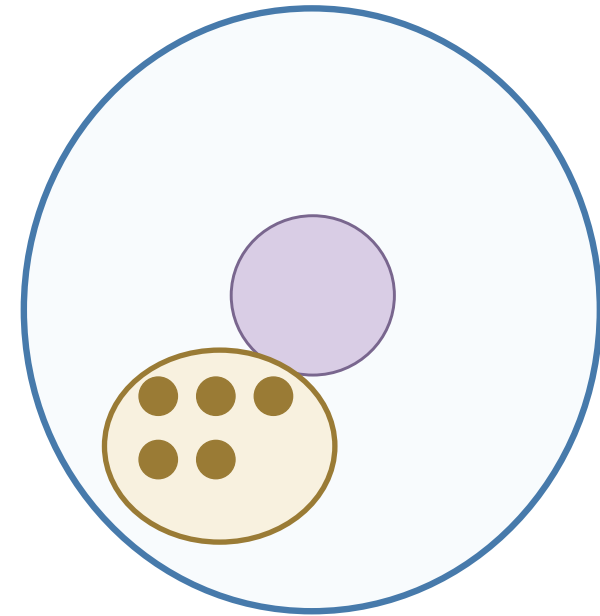
Accumulation is a manifestation of metabolic derangement

- Cells may accumulate substances that are normal or abnormal, endogenous or exogenous.
- Storage may be incidental and harmless, or contribute to cellular dysfunction and injury.
- The accumulated material may originate within the affected cell or elsewhere.

Accumulation is a morphologic pattern, not by itself a diagnosis.

Cellular localization helps explain the mechanism

- Cytoplasmic deposits can reflect disordered metabolism or excess protein synthesis.
- Organelles—especially lysosomes—may retain incompletely degraded substrate.
- The source also recognizes nuclear accumulation in some settings.



Schematic — not histology

Illustrative lysosomal compartment

Origin: Material synthesized in the cell or acquired

Origin	Route to accumulation	Example
Endogenous / synthesized	Formation exceeds processing or secretion	Triglycerides in hepatocytes
Endogenous / undegraded	Defective disposal of a metabolite	Lysosomal storage disorders
Exogenous / taken up	Phagocytosed material cannot be removed	Carbon or silica particles

Four principal pathways to intracellular accumulation

1 Normal substrate

Inadequate metabolic processing, removal, or transport

2 Endogenous abnormal protein

Defective folding, intracellular transport, or secretion

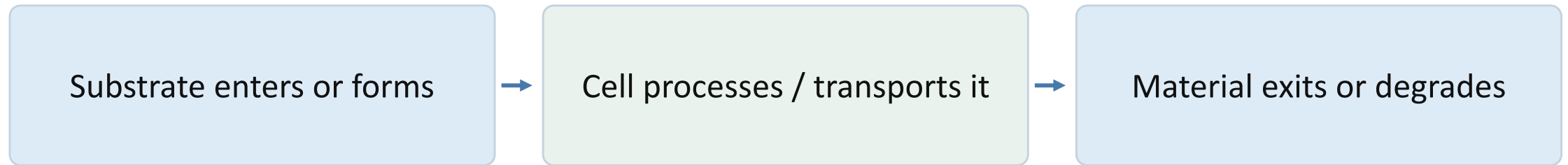
3 Lysosomal degradation

Inherited enzyme deficiency prevents breakdown

4 Exogenous material

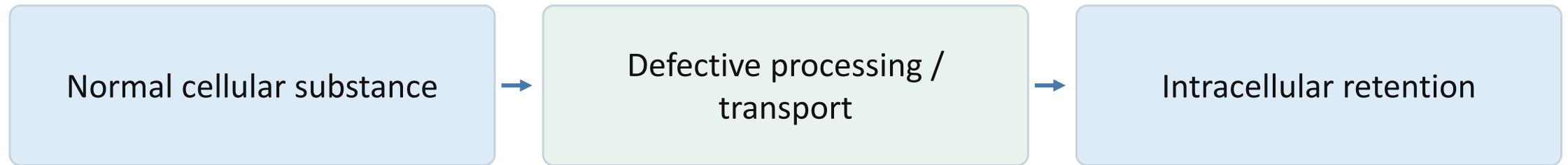
Indigestible particles remain in the receiving cell

The intracellular balance is a flux problem



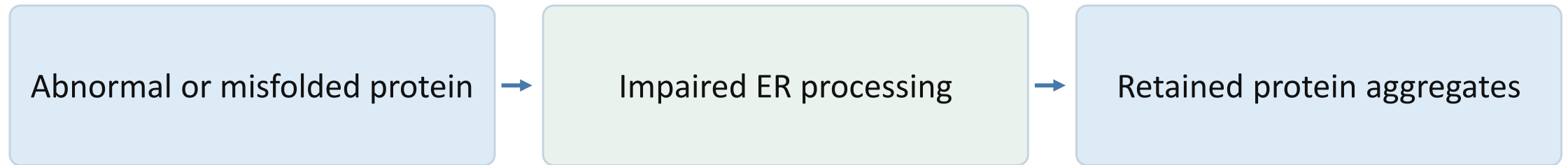
- Accumulation occurs when input and formation exceed effective processing or clearance.
- A visible deposit can therefore indicate a biochemical bottleneck rather than increased synthesis alone.

Mechanism 1: Inadequate removal of a normal substrate



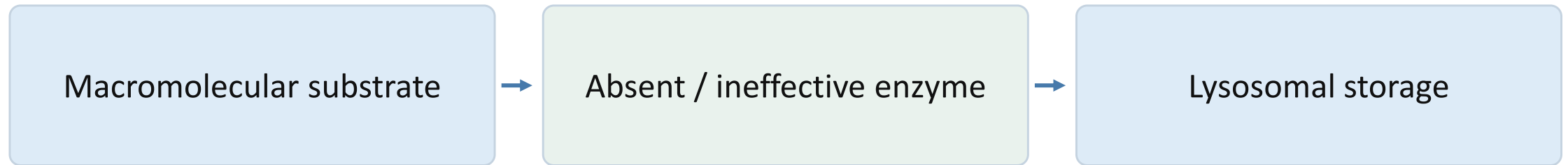
- The substance itself need not be abnormal.
- Hepatic triglyceride accumulation illustrates disturbed handling of a physiological lipid.

Mechanism 2: Folding or secretion is defective



- Mutant α 1-antitrypsin is a representative example.
- Local retention and deficient secretion can produce different organ consequences.

Mechanism 3: Lysosomal breakdown fails



- Inherited deficits in degradative enzymes impair the conversion of complex substrates into products.
- Continued substrate delivery may make the deposits progressive.

Mechanism 4: Indigestible exogenous material persists



- Carbon and silica are examples of inhaled material retained after cellular uptake.
- Accumulation can persist because the receiving cell lacks a relevant removal pathway.

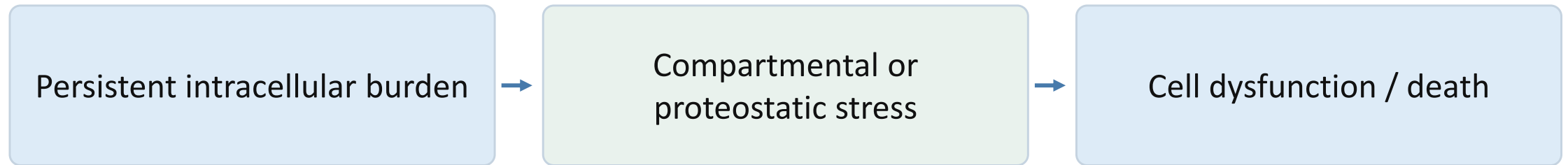
Match accumulation mechanisms with examples

Dominant failure	Illustrative condition	Underlying logic
Normal-substrate processing	Steatosis	Triglyceride handling is inadequate
Folding / trafficking	α 1-antitrypsin-related inclusions	Protein remains in the endoplasmic reticulum
Enzyme-mediated degradation	Lysosomal storage disease	Substrate cannot be degraded
Disposal of exogenous material	Carbon or silica storage	Material cannot be metabolized or exported

Reversibility depends on the source of overload

Setting	Expected course	Reason
Overload can be stopped	Potentially reversible	Intracellular burden can be processed or cleared
Persistent inability to degrade substrate	Often progressive	Substrate continues to accumulate
Advanced tissue injury	May be irreversible	Loss of viable cells or tissue architecture

Storage becomes harmful through cellular dysfunction



- The source explicitly distinguishes innocuous accumulation from injury-producing accumulation.
- Severity depends on substance, cellular context, duration, and ability to restore homeostasis.

The accumulated molecule determines the morphologic pattern

Stored material	Representative finding	Common compartment
Triglyceride	Clear cytoplasmic vacuoles	Parenchymal cell cytoplasm
Protein	Pink eosinophilic droplets or inclusions	Cytoplasm / ER
Glycogen	Pale or clear cytoplasmic spaces	Cytoplasm
Complex undegraded substrates	Lysosomal enlargement / inclusion	Lysosomes

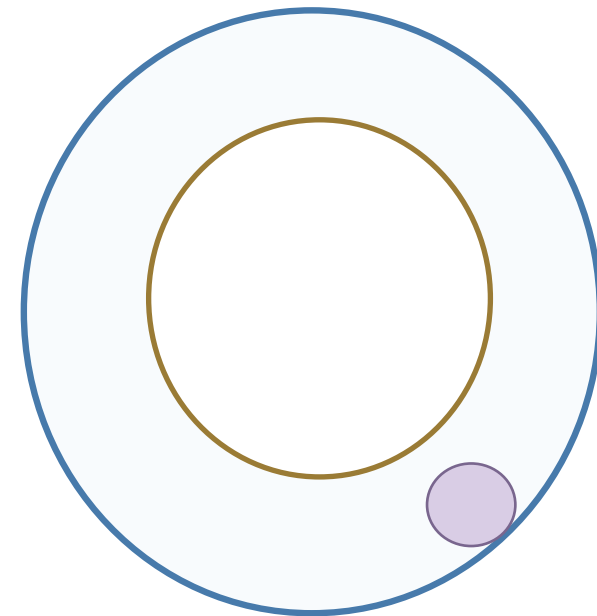
Different lipid classes can accumulate

- Triglycerides, cholesterol and cholesterol esters, and phospholipids can accumulate in cells.
- Phospholipids are constituents of myelin figures associated with necrotic cells.
- Complex lipid–carbohydrate substrates can accumulate in lysosomal storage disorders.

This lecture emphasizes triglyceride steatosis; Cholesterol accumulation is treated separately.

Steatosis is abnormal triglyceride storage

- Steatosis, or fatty change, refers to excess triglycerides within parenchymal cells.
- The liver is the principal organ affected because of its central role in lipid metabolism.
- An intracellular fat vacuole is the morphologic expression of this accumulation.



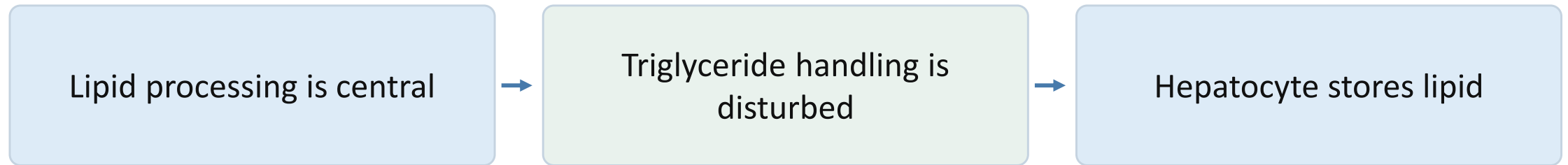
Schematic — not histology

Large triglyceride droplet with
nuclear displacement

Fatty change also occurs outside the liver

Organ	Potential cellular site	Interpretive point
Liver	Hepatocytes	Most common and conspicuous site
Heart	Myocardial cells	Fatty change may accompany injury
Skeletal muscle	Myocytes	Parenchymal lipid storage
Kidney	Renal tubular cells	Lipid can accumulate in tubular epithelium

Why the liver is particularly susceptible



- Normal hepatic lipid metabolism makes the hepatocyte vulnerable to an imbalance of storage and removal.
- The morphologic lesion is storage; The cause must be established from clinical context.

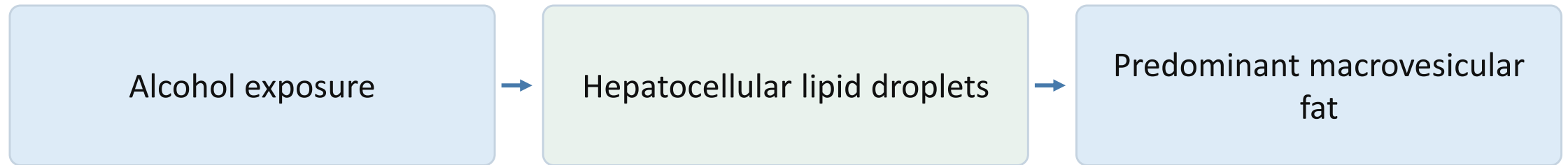
The causes of steatosis are diverse

Category	Source-described examples	Interpretive point
Metabolic	Diabetes mellitus; obesity	Requires systemic metabolic context
Toxic	Excessive alcohol; other toxins	Exposure history is important
Nutritional	Protein malnutrition	Disordered nutrient handling may contribute
Hypoxic	Anoxia	Reduced oxygen availability accompanies injury

Diabetes and obesity are frequent clinical associations

- The source identifies diabetes and obesity among the causes of hepatic fatty change.
- Insulin resistance and broader metabolic abnormalities commonly coexist with steatotic liver disease.
- Steatosis should not be assigned a single etiology on morphology alone.

Alcohol exposure can produce early hepatic steatosis



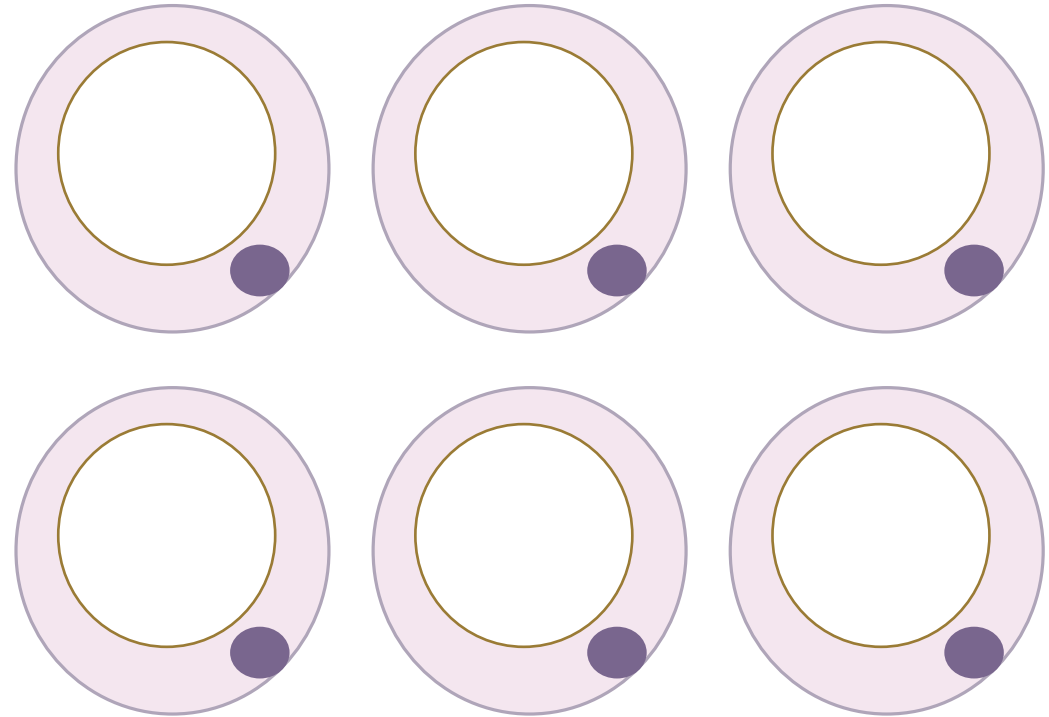
- In the liver chapter, steatosis is described as an early effect of alcohol exposure.
- With ongoing injury, inflammation and fibrosis may develop; Fat alone does not establish steatohepatitis.

The textbook uses evolving fatty-liver nomenclature

Location in textbook	Terminology used	Teaching interpretation
Chapter 2 overview	Nonalcoholic fatty liver disease	Older umbrella terminology retained in this passage
Chapter 18 liver discussion	Metabolic dysfunction–associated steatotic liver disease (MASLD)	Updated metabolic-dysfunction framing

Fat vacuoles appear optically clear in routine sections

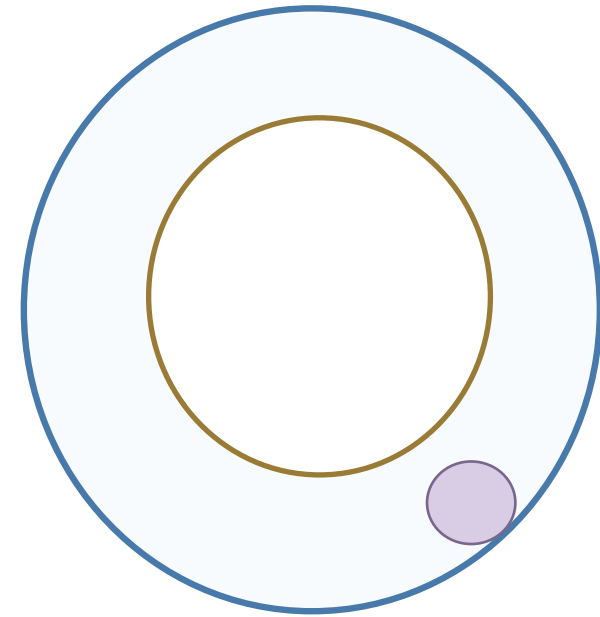
- Triglyceride droplets form rounded clear cytoplasmic spaces after routine processing.
- The vacuoles vary in size and distribution.
- Interpret the pattern in the context of the affected organ.



Schematic of cellular appearances — not a specimen

A large fat droplet displaces the hepatocyte nucleus

- A dominant droplet expands within the cytoplasm.
- The nucleus is compressed toward the cellular periphery.
- The remaining cytoplasm forms a narrow surrounding rim.



Schematic — not histology

Schematic of a fat-loaded hepatocyte

Small lipid droplets may coalesce into large droplets



- The liver chapter describes progression from small droplets to larger vacuoles in alcohol-associated steatosis.
- The diagram represents a conceptual morphologic sequence, not a measured temporal rate.

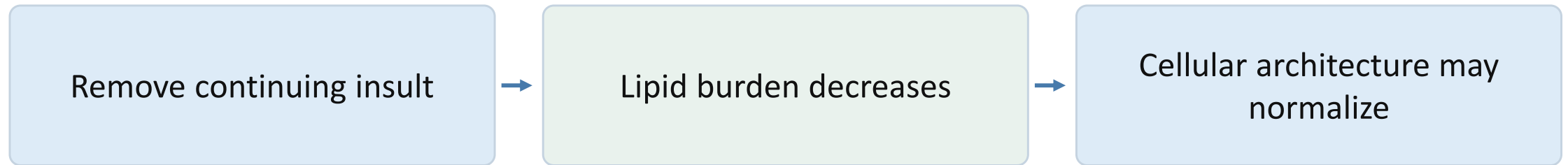
Macrovesicular and microvesicular patterns differ

Pattern	Morphologic principle	Textbook context
Macrovesicular	Large droplets may push nuclei aside	Predominant in alcohol-associated steatosis
Microvesicular	Numerous fine lipid droplets in a cell	Recognized form of fatty change
Mixed	Droplets of different sizes coexist	Described in some settings

Gross fatty liver can be enlarged and yellow

- In chronic alcohol-associated injury, the fatty liver may be enlarged, soft, yellow, and greasy.
- Gross color and texture reflect tissue lipid deposition, but are not etiologic proof.
- Microscopy and clinical history distinguish steatosis from accompanying injury.

Simple steatosis may regress when injury stops



- The source notes that uncomplicated fatty change is often reversible after the cause is removed.
- Established fibrotic remodeling is a different process and is less completely reversible.

Steatosis is not synonymous with steatohepatitis

Simple steatosis	Steatohepatitis
Intracellular triglyceride accumulation	Steatosis with hepatocyte injury and inflammatory change
Fat droplets may be prominent	Ballooning, cell injury, and potentially fibrosis
Potentially reversible storage	Risk of progressive fibrotic disease

Clinical expression of steatosis varies

- Hepatomegaly may result from extensive lipid accumulation.
- The source notes that substantial hepatic dysfunction is unusual in uncomplicated alcohol-associated steatosis.
- Clinical and laboratory abnormalities require assessment for concurrent inflammation, fibrosis, or other disease.

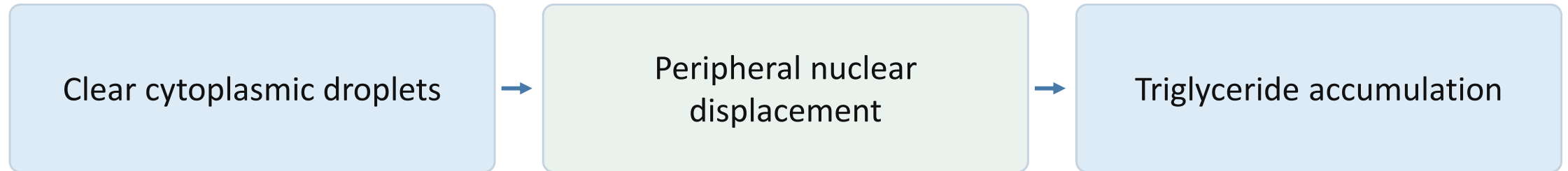
Application 1: Identify hepatic fatty change

A patient with obesity has hepatomegaly. A tissue section contains hepatocytes with rounded clear cytoplasmic vacuoles; Many nuclei lie at the cell margin.

Which stored material best explains this pattern?

- Triglyceride
- Retained immunoglobulin
- Glycogen alone

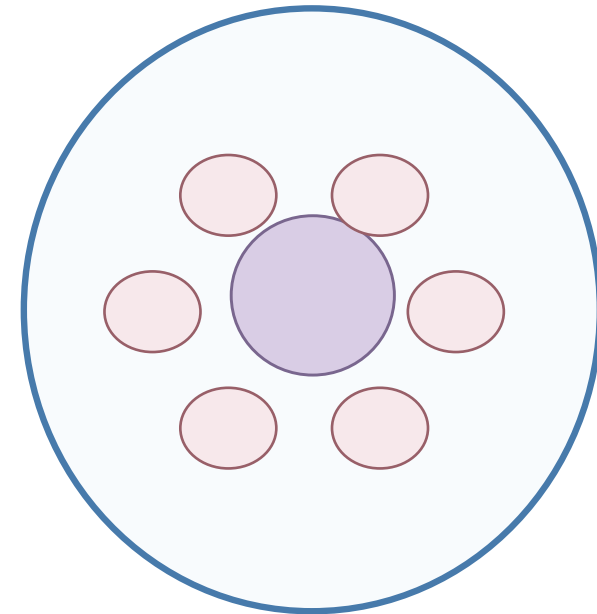
Application 1: The pattern is steatosis



- The lesion is called fatty change or steatosis.
- The morphologic diagnosis does not determine whether alcohol, metabolic dysfunction, or another cause is responsible.

Intracellular protein deposits have varied morphologies

- Light microscopy may show rounded eosinophilic droplets, vacuoles, or aggregates.
- At ultrastructural level, retained material may be amorphous, fibrillar, or crystalline.
- Protein accumulations arise from several different mechanisms.



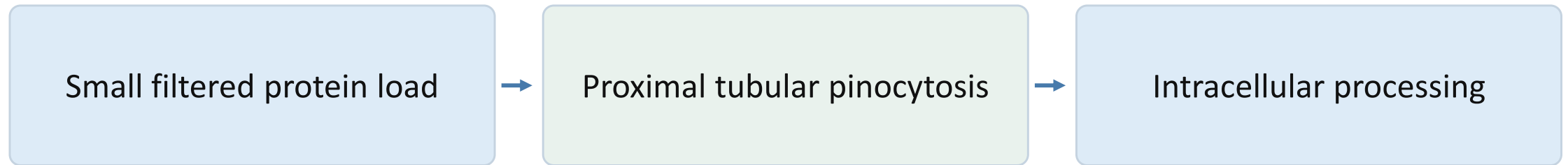
Schematic — not histology

Conceptual protein inclusions

Not all deposited protein is intracellular

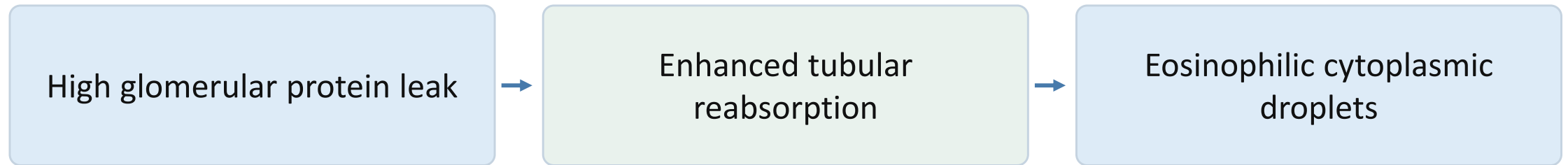
Intracellular accumulation	Extracellular deposition
Protein droplets or inclusions inside a cell	Protein deposited in interstitial/extracellular spaces
Examples: reabsorption droplets, Russell bodies	Certain amyloid deposits are primarily extracellular
Can reflect uptake, synthesis, or retention	Requires distinct molecular and tissue interpretation

Protein uptake is normal in renal proximal tubules



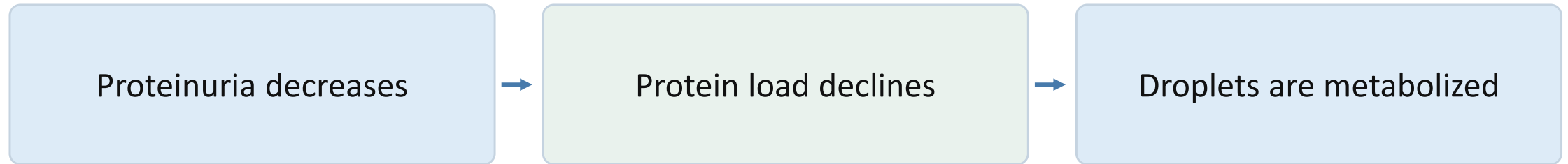
- Normally, small amounts of protein filtered at the glomerulus are reabsorbed by proximal tubules.
- Increased filtered protein can exceed the ordinary processing capacity.

Proteinuria produces proximal tubular reabsorption droplets



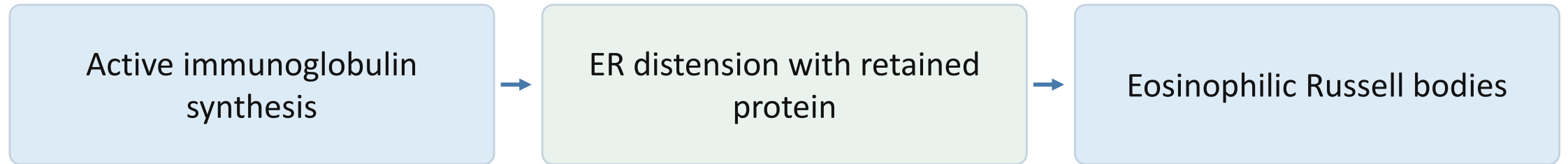
- Abundant reabsorbed protein collects in vesicular structures within tubular epithelial cells.
- The source describes these deposits as pink hyaline droplets in routine sections.

Protein reabsorption droplets can disappear



- The source explicitly identifies this uptake-related accumulation as reversible.
- The example illustrates accumulation from excess supply rather than a primary mutant protein.

Russell bodies result from excess immunoglobulin synthesis

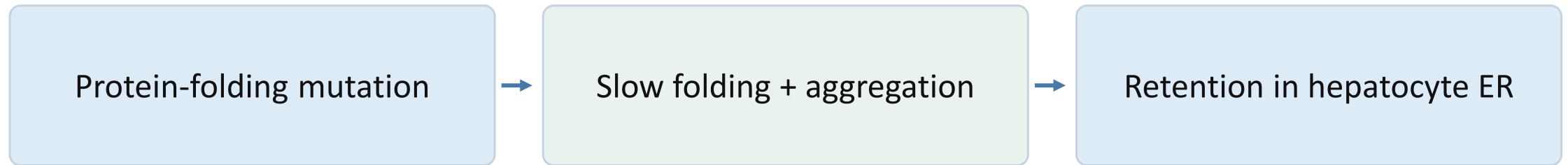


- Certain plasma cells produce more secretory protein than can be processed immediately.
- Their distended endoplasmic reticulum forms large homogeneous inclusions.

Renal droplets and Russell bodies have different origins

Feature	Proximal tubule droplet	Russell body
Origin	Filtered protein taken up from lumen	Immunoglobulin synthesized by plasma cell
Primary mechanism	Excess reabsorption burden	Increased secretory protein production
Characteristic site	Renal tubular epithelium	Plasma cell cytoplasm / ER
Interpretive context	Proteinuric renal disease	Antibody-producing plasma cells

Mutant α 1-antitrypsin is retained in hepatocytes

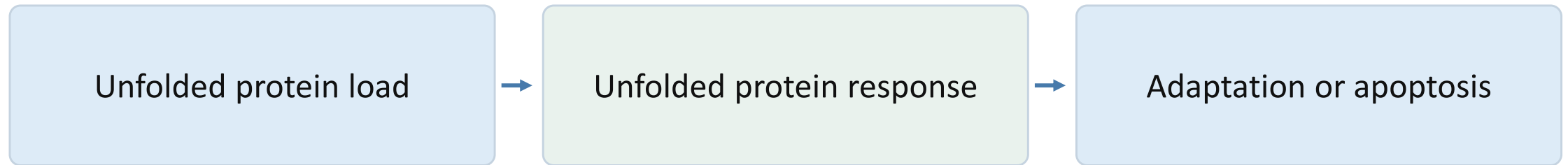


- Partially folded protein intermediates aggregate instead of being efficiently secreted.
- The source identifies α 1-antitrypsin deficiency as a model of defective intracellular processing.

α 1-antitrypsin deficiency links liver and lung injury

Hepatocyte	Pulmonary tissue
Misfolded protein remains in ER	Less circulating antiprotease reaches tissue
Cellular protein retention and stress	Insufficient protection against proteolytic injury
Local aggregate-associated damage	Emphysema can develop

Misfolded proteins trigger ER stress responses



- The source associates accumulated misfolded proteins with ER stress.
- If proteostasis cannot be restored, the cellular response may culminate in apoptotic death.

Protein retention can produce two forms of pathology

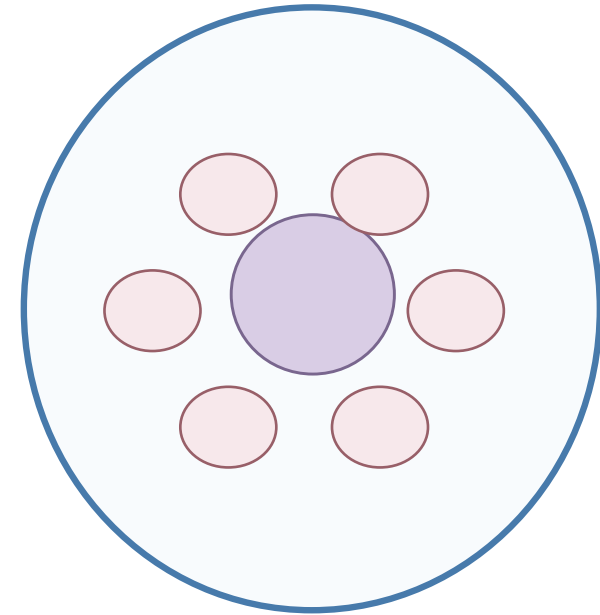
Gain-of-toxic-burden effect	Loss-of-function effect
Protein accumulates in producing cell	Functional protein is absent from its destination
ER stress / proteostasis disturbance	Reduced activity in dependent tissue
Example: hepatocyte α 1-antitrypsin retention	Example: pulmonary antiprotease deficiency

Cytoskeletal accumulations involve structural proteins

- Intermediate filaments form an intracellular scaffold that supports cellular organization and mechanical stability.
- Keratin filaments characterize epithelial cells; Neurofilaments characterize neurons.
- Abnormally concentrated filaments can become visible as pathologic inclusions.

Alcoholic hyaline is a keratin-rich hepatocyte inclusion

- The source describes alcoholic hyaline in liver cells as an eosinophilic cytoplasmic inclusion.
- It consists predominantly of keratin intermediate-filament proteins.
- The liver chapter calls this inclusion Mallory hyaline in the setting of hepatocyte injury.



Schematic — not histology

Conceptual protein inclusion

Neurofibrillary tangles are protein aggregates

- The source cites neurofibrillary tangles in Alzheimer disease as an example of protein accumulation.
- They contain neurofilaments and other proteins.
- An intracellular inclusion is therefore not limited to a metabolic liver or renal disorder.

Abnormal protein aggregation is a broad disease mechanism

Property	Pathologic implication
Misfolded or abnormal protein	May aggregate or deposit
Location varies	Intracellular, extracellular, or both
Biological effect varies	Direct or indirect impairment of cellular function
Example disease class	Proteinopathies / protein-aggregation diseases

Biomolecular condensates: An evolving interpretation

- The source notes that some inclusion bodies may behave as concentrated, dynamic protein assemblies.
- Liquid–liquid phase separation may contribute to the formation of these assemblies.
- Whether these inclusions drive disease progression, protect cells, or do both remains under investigation.

Emerging mechanistic interpretation — avoid treating all inclusions as proven causal condensates.

“Hyaline” is a histologic description, not a substance

- Hyaline describes a homogeneous, glassy, eosinophilic appearance on routine H&E sections.
- The term encompasses different biochemical compositions and pathogenic settings.
- Hyaline change is not inherently specific for cell injury or a single form of accumulation.

Intracellular and extracellular hyaline are distinct

Intracellular hyaline	Extracellular hyaline
Protein reabsorption droplets	Hyalinized collagen in old scars
Russell bodies	Hyaline material in thickened arteriolar walls
Alcoholic / Mallory hyaline	Plasma proteins and basement membrane material may contribute

Do not diagnose a molecular substrate from pink color alone



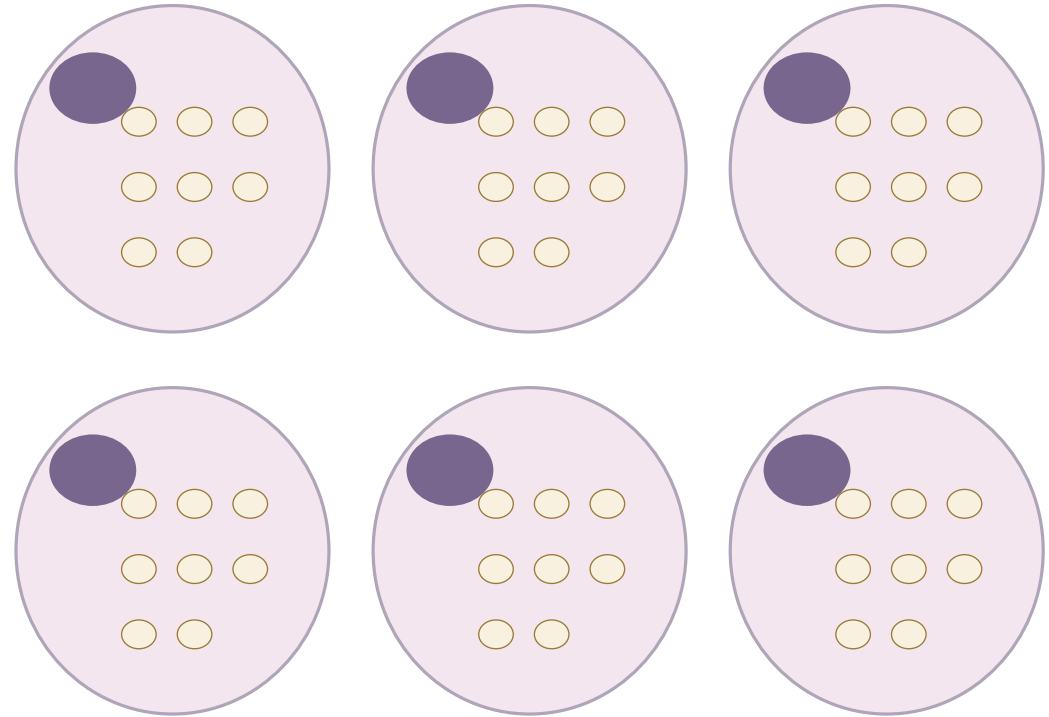
- A pink glassy appearance does not establish the specific stored protein.
- Location, clinical setting, and additional examination are needed to characterize the lesion.

Glycogen is a normal intracellular glucose reserve

- Healthy cells store glycogen in the cytoplasm as an accessible glucose reserve.
- Excess glycogen accumulation occurs with abnormal glucose or glycogen metabolism.
- Both acquired metabolic disorders and inherited glycogenoses may produce deposits.

Glycogen accumulation may resemble clear vacuolation

- With aqueous tissue processing, glycogen can dissolve and leave optically clear cytoplasmic areas.
- The resulting pale or vacuolated appearance is not specific for glycogen.
- Chemical staining is required to support substrate identification.



Schematic of cellular appearances — not a specimen

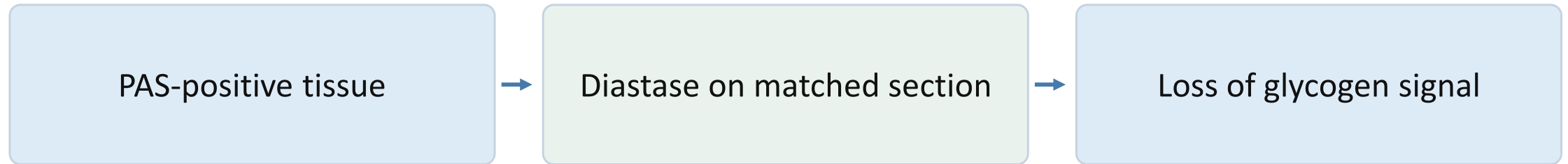
Fixation affects glycogen preservation

Aqueous fixatives	Absolute alcohol
Glycogen may be dissolved or lost	Better preservation of glycogen in tissues
H&E appearance can be clear / vacuolated	Stored polysaccharide more readily retained
Vacuolation remains nonspecific	Substrate still needs appropriate stain confirmation

PAS and Best carmine can detect glycogen

- Periodic acid–Schiff (PAS) staining may impart rose-to-violet color to glycogen.
- Best carmine is another stain used to demonstrate glycogen.
- PAS also stains other carbohydrate-containing compounds, so initial positivity is not proof of glycogen.

Diastase digestion confirms glycogen staining

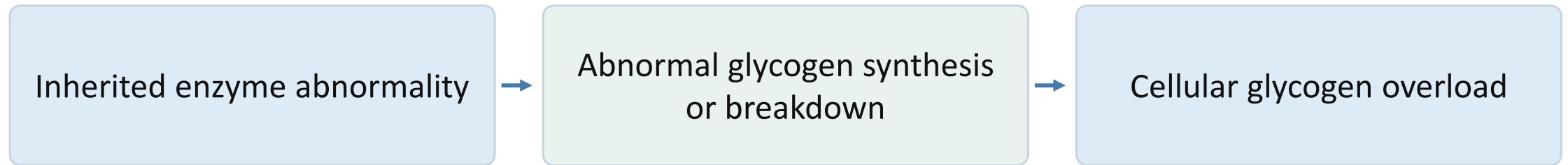


- Diastase hydrolyzes glycogen; Disappearance of PAS staining supports a glycogen substrate.
- Persistently PAS-positive material after diastase treatment can reflect other carbohydrates or glycoproteins.

Diabetes can cause glycogen accumulation in several cells

Anatomical site	Source-described location
Kidney	Renal tubular epithelial cells
Liver	Hepatocytes
Pancreas	Islet β cells
Heart	Cardiac myocytes

Glycogenoses reflect inherited metabolic enzyme defects



- Glycogen storage diseases can cause massive accumulation in selected cells.
- Severe inherited storage can lead to cellular dysfunction and cell death.

Acquired and inherited glycogen deposition differ

Metabolic context	Inherited storage context
Diabetes mellitus	Glycogen storage diseases (glycogenoses)
Altered glucose metabolism	Inherited defect of glycogen metabolic enzymes
Specific organs show deposits	Selected tissues may accumulate massive glycogen
Clinical disease context is essential	Potential progressive cell injury

Clear cytoplasm: Triglyceride or glycogen?

Feature	Triglyceride accumulation	Glycogen accumulation
Routine histology	Clear lipid vacuoles; large droplets can displace nucleus	Pale or vacuolated cytoplasm after glycogen loss
Useful conceptual clue	Large droplet with peripheral nucleus	PAS-positive, diastase-sensitive material
Primary lesion	Steatosis	Glycogen deposition
Interpretation	Requires etiologic context	Requires substrate confirmation

Protein, fat, and glycogen each require a different test

Suspected material	Typical morphology	Interpretive strategy
Triglyceride	Clear cytoplasmic droplets	Cell pattern and metabolic/toxic context
Protein	Eosinophilic droplets / aggregates	Cell identity; location; secretory / uptake context
Glycogen	Pale or clear cytoplasm	PAS with diastase comparison
Undegraded substrate	Lysosomal burden	Inherited enzyme and substrate context

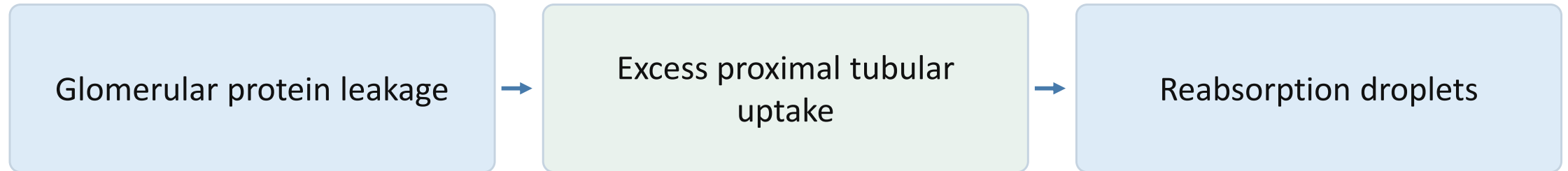
Application 2: Renal protein droplets

A patient with marked urinary protein loss has proximal renal tubular cells packed with rounded eosinophilic droplets. Proteinuria subsequently diminishes.

Which mechanism best explains the inclusions?

- Enhanced uptake of filtered protein
- Mutant α 1-antitrypsin retention
- Abnormal triglyceride clearance

Application 2: Increased reabsorption is the mechanism



- The accumulation is related to protein handling rather than abnormal protein synthesis.
- Droplets can be metabolized after the filtered protein burden decreases.

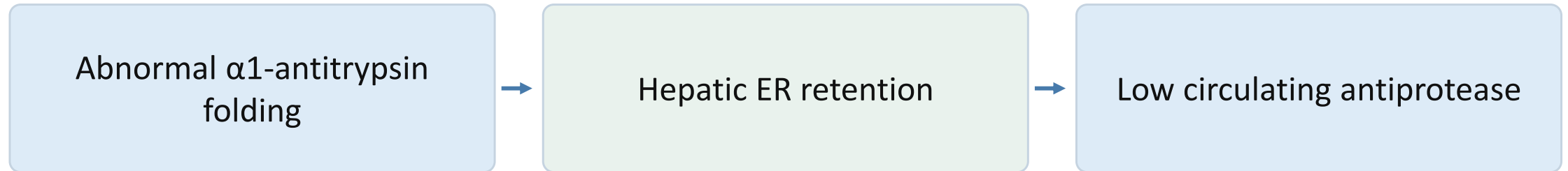
Application 3: Inclusion with deficient secreted protein

A hepatocyte contains retained misfolded secretory protein. The same disorder causes inadequate circulating antiprotease activity and pulmonary emphysema.

Which accumulation mechanism is illustrated?

- Defective folding, transport, or secretion
- Excess filtered protein uptake
- Diastase-sensitive glycogen deposition

Application 3: Intracellular retention plus functional deficit



- Local retention creates protein burden in hepatocytes.
- Deficient circulating protein has consequences in the lung.

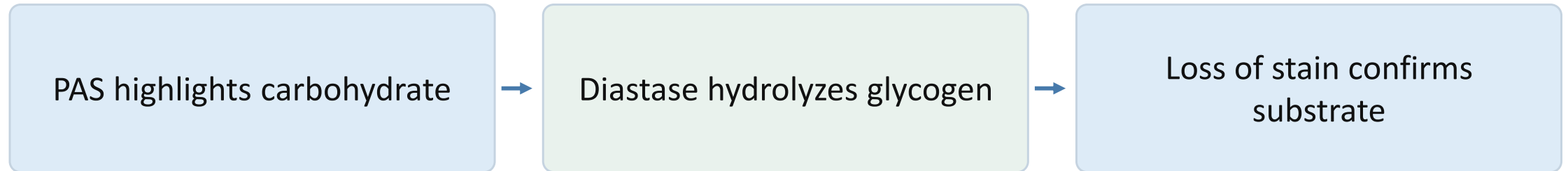
Application 4: PAS-positive hepatic storage

Hepatocytes are pale and show cytoplasmic PAS positivity. The material disappears on staining after diastase digestion.

What accumulated material is supported by this result?

- Glycogen
- Triglyceride
- Keratin intermediate filaments

Application 4: Diastase-sensitive PAS identifies glycogen



- Positive PAS staining alone would not establish glycogen.
- Interpret subsequent diagnosis in the setting of diabetes, an inherited glycogenosis, or other relevant metabolic context.

Synthesis: Substance, mechanism, and clinical context

Pattern	Representative mechanism	Illustrative lesion
Lipid storage	Inadequate normal-substrate handling	Steatotic hepatocyte
Protein droplet	Excess uptake / synthesis	Tubular droplets or Russell bodies
Abnormal protein inclusion	Failed folding and secretion	Retained α 1-antitrypsin
Glycogen storage	Glucose/glycogen metabolic disturbance	PAS-positive, diastase-sensitive deposits

References and visual evidence

Core textbook

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 2: Cell Injury, Cell Death, and Adaptations.
- Supporting intratextbook context: Chapter 18, Liver and Gallbladder, steatosis and alcohol-associated liver disease.

Source illustration limitation

The supplied textbook was available as extracted Markdown, without original diagnostic plates. All drawings in this deck are original editable schematics; none is presented as an authentic micrograph.