

Endogenous pigments

Cellular origin, morphology, and clinicopathologic interpretation

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Learning outcomes

- Distinguish pigments synthesized or generated within the body from exogenous pigment.
- Explain lipofuscin formation, morphology, and its biological significance.
- Describe melanin, ochronotic pigment, and hemoglobin-derived hemosiderin.
- Integrate pigment location with local hemorrhage and systemic iron overload.

Pigments in intracellular accumulations

- Pigments are colored substances found in cells and tissues.
- Some are normal constituents, whereas others accumulate in special circumstances.
- The chemical origin of a pigment shapes its pathologic significance.
- Endogenous pigment is made or generated within the body.

Chemical origin

Cellular localization

Clinical context

Endogenous and exogenous sources

Endogenous	Exogenous
Generated within the body	Introduced from outside the body
Lipofuscin, melanin, hemosiderin	Carbon, tattoo pigment
Metabolism, synthesis, or degradation	Inhalation or direct deposition
Interpret together with cellular history	Interpret with exposure history

Four entities in the core framework

Lipofuscin

Lipid-peroxidation residue

Melanin

Pigment synthesized in melanocytes

Homogentisic acid

Rare ochronotic pigment

Hemosiderin

Hemoglobin-derived iron store

A useful pigment description is multidimensional

- Describe color and granularity in routine tissue sections.
- Identify the involved cell and subcellular location.
- Ask whether the deposition is focal or distributed across organs.
- Connect the finding to synthesis, turnover, hemorrhage, or overload.

Appearance + compartment

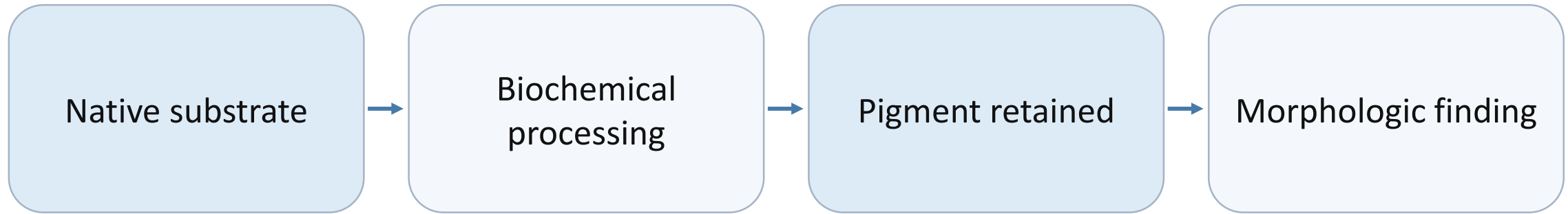
Local versus systemic

Biochemical origin

Do not infer pathogenesis from color alone

Shared appearance	Different origin
Yellow–brown granules	Lipofuscin: Oxidized membrane lipids
Yellow–brown granules	Hemosiderin: Stored iron
Brown-black pigment	Melanin: Synthesis in melanocytes
Dark pigment in connective tissue	Ochronosis: Homogentisic acid

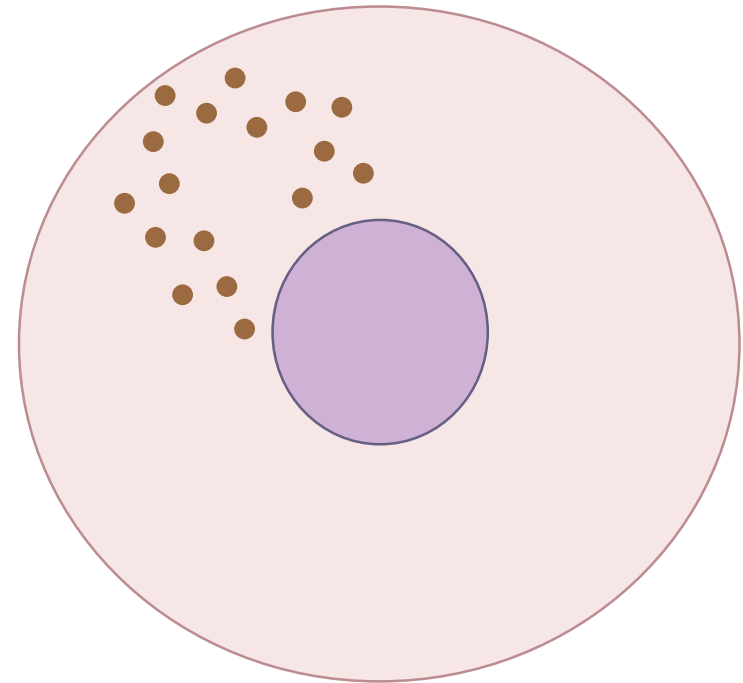
The pigment pathway links substrate to deposit



Interpretation follows the direction of the process

Lipofuscin: Wear-and-tear pigment

- Lipofuscin is an insoluble intracellular pigment.
- It is also called lipochrome or wear-and-tear pigment.
- Its characteristic yellow–brown granules are cytoplasmic.
- Its major significance is evidence of previous oxidative membrane damage.



Schematic — lipofuscin granules (not a photomicrograph)

The composition of lipofuscin is complex

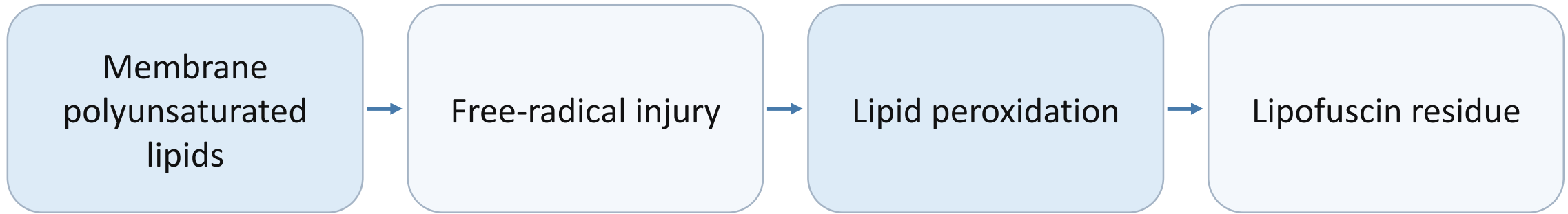
- The pigment contains polymers of lipids and phospholipids.
- These components are complexed with proteins.
- The composition implicates intracellular membrane lipids.
- This is a pigment residue, not a functional storage form of iron.

Lipids

Phospholipids

Protein complexes

Lipid peroxidation produces the precursor material



Interpretation follows the direction of the process

Why membrane composition matters

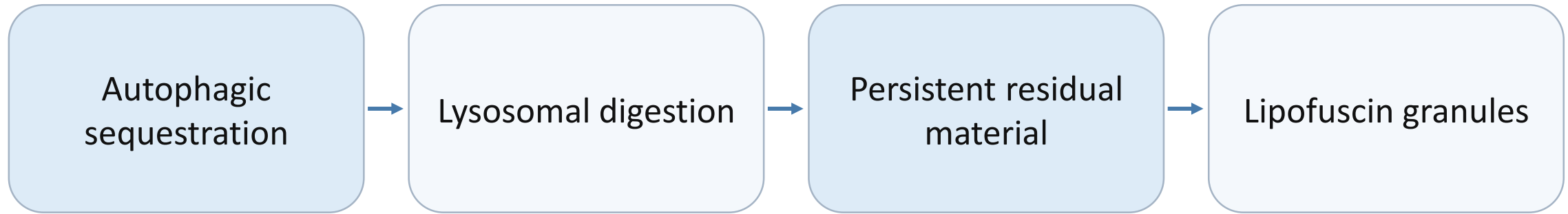
- Polyunsaturated membrane lipids are substrates for peroxidative reactions.
- Oxidative damage alters lipid components of intracellular membranes.
- Lipofuscin composition reflects that damaged material.
- Pigment is therefore a morphologic footprint of injury rather than its primary cause.

Membrane substrate

Peroxidative damage

Residual pigment

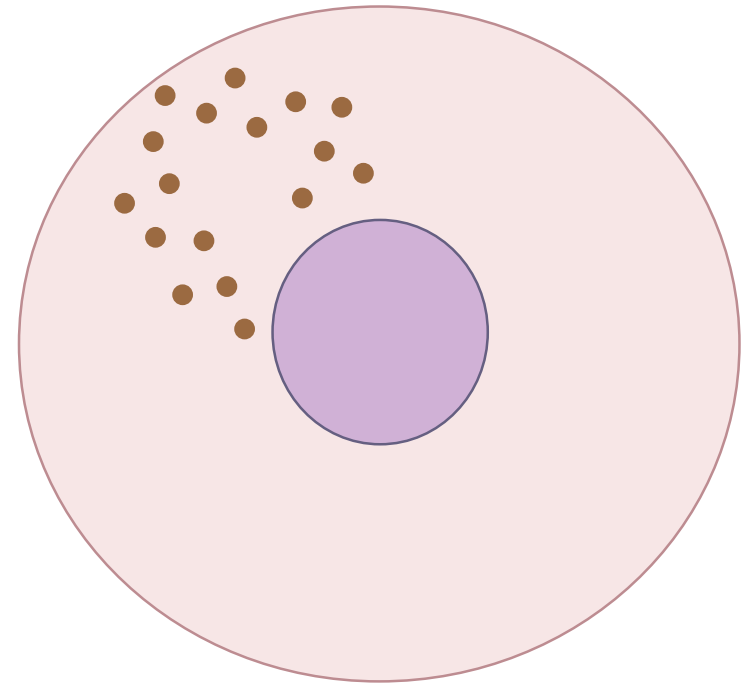
Residual bodies connect autophagy and lipofuscin



Interpretation follows the direction of the process

Lipofuscin localization is often perinuclear

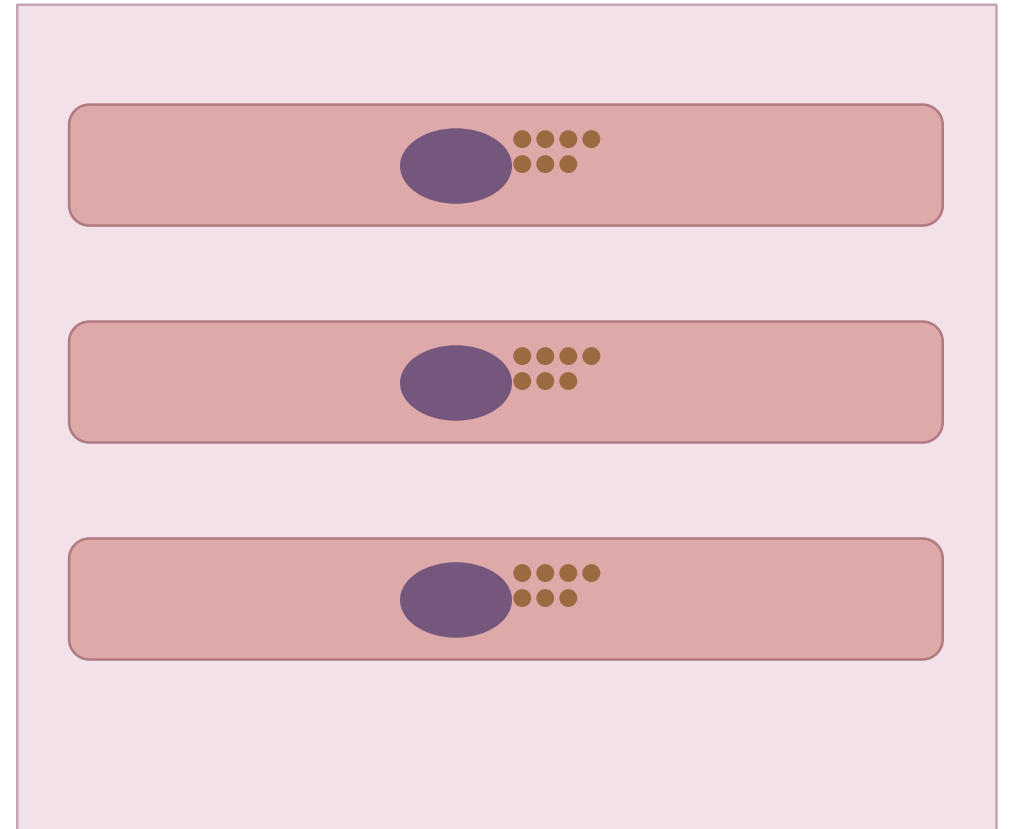
- In routine sections, granules are often near the nucleus.
- Pigment lies in the cytoplasm, not within the nucleus.
- The textbook figure caption notes intralysosomal localization.
- Both color and location are useful descriptive clues.



Schematic — lipofuscin granules (not a photomicrograph)

Histologic pattern in cardiac muscle

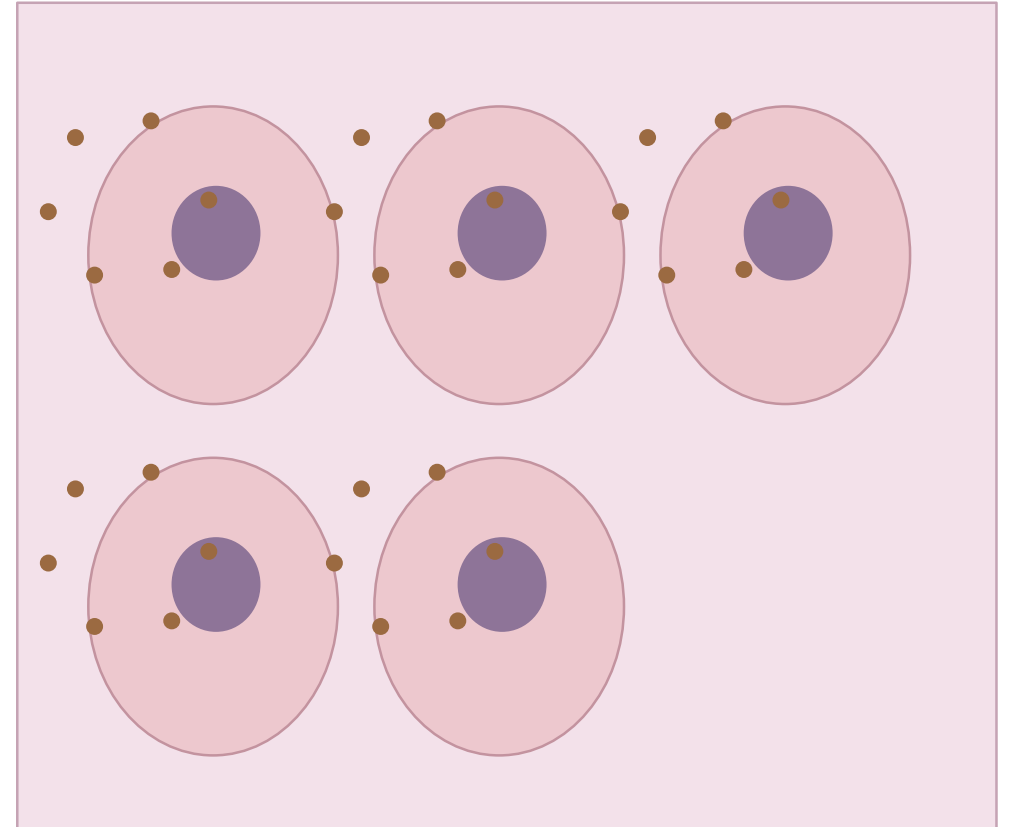
- Fine, yellow–brown cytoplasmic granules are characteristic.
- Granules are commonly concentrated near myocyte nuclei.
- The pattern is particularly prominent in aging hearts.



Schematic — pigment distribution only; Not diagnostic microscopy

The liver is another common site

- Lipofuscin may be found in the cytoplasm of hepatocytes.
- Increasing age is a common clinical context.
- Severe malnutrition and cancer cachexia also favor conspicuous pigment.
- Pigment alone does not establish a specific hepatic disease.



Schematic — pigment distribution only; Not diagnostic microscopy

Lipofuscin and slow regressive change

- Lipofuscin with slowly regressing cells.
- The common examples are cardiac and hepatic cells.
- Accumulation can accompany a chronic imbalance in turnover and clearance.
- Interpret it against age, nutrition, and the broader tissue response.

Aging or chronic stress

Residual pigment persists

Contextual marker

Cancer cachexia provides a clinical setting

- Cancer cachexia is specifically identified as a context for prominent lipofuscin.
- Cachexia can accompany tissue atrophy and catabolic change.
- Lipofuscin marks chronic cellular stress rather than confirming a malignancy.
- Clinical history is indispensable for interpretation.

Systemic catabolic state

Slow regressive changes

Visible lipofuscin

Brown atrophy links pigment with tissue change

- Autophagic residual bodies may persist in atrophic cells.
- When sufficiently abundant, lipofuscin produces brown discoloration.
- The source calls this appearance brown atrophy.
- The pigmentation and the underlying atrophy are distinct observations.

Atrophy

Residual lipofuscin

Brown discoloration

Lipofuscin is not itself injurious

- Lipofuscin does not injure cells or their functions.
- The biologically relevant antecedent is free-radical injury and lipid peroxidation.
- Do not confuse a marker of damage with a damage-causing agent.
- A small pigment burden cannot be used to stage tissue injury.

Prior oxidative stress

Inert pigment deposit

No direct cellular injury

Lipofuscin case: An aging myocardium

An older patient has fine yellow–brown perinuclear granules in cardiac myocytes without a stated iron-overload history.

What is the most source-supported interpretation?

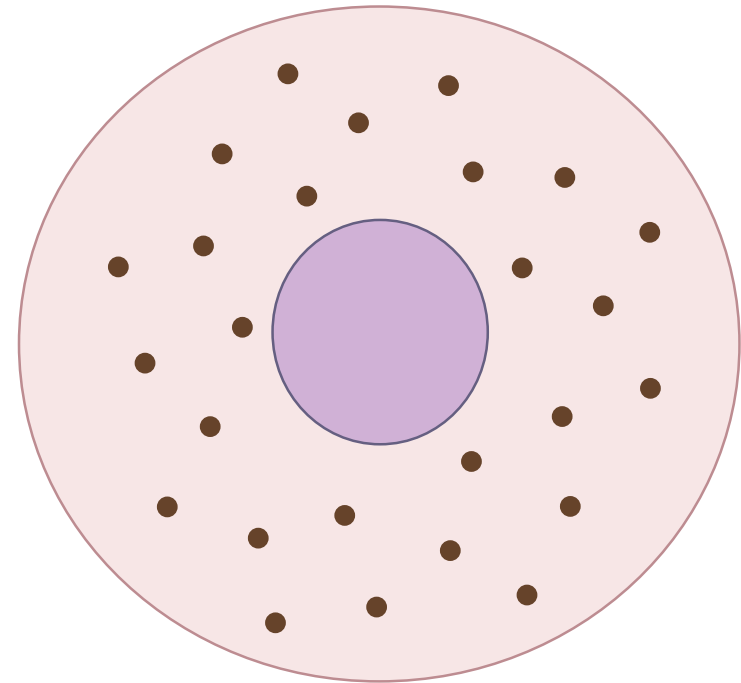
Lipofuscin is favored by the color, fine granularity, perinuclear localization, and aging context. The finding is a marker of prior lipid peroxidation—not proof of pigment-induced myocyte injury.

Lipofuscin: Which observations matter?

Helpful observation	Interpretive consequence
Fine perinuclear granules	Supports lipofuscin morphology
Liver or cardiac muscle	Recognized common sites
Aging, malnutrition, cachexia	Plausible associated contexts
No stated cellular dysfunction	Compatible with a noninjurious pigment

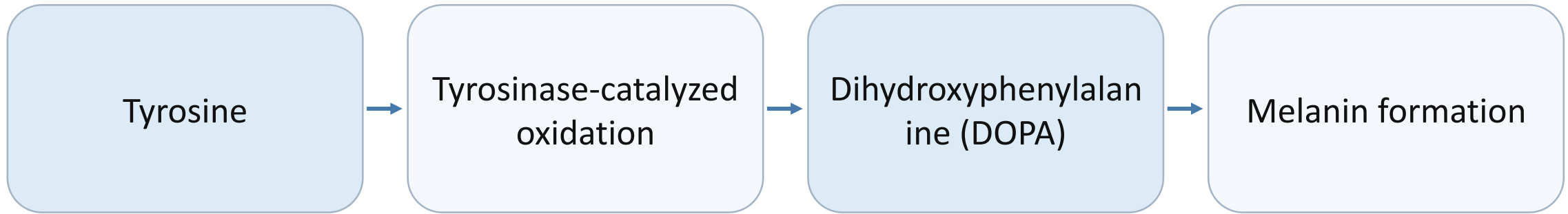
Melanin is synthesized within the body

- Melanin is a brown–black endogenous pigment.
- Its producing cells are melanocytes.
- The relevant biochemical conversion requires tyrosinase.
- Unlike lipofuscin, melanin is the product of a specific pigment-synthesis pathway.



Schematic — melanin granules (not a photomicrograph)

Tyrosinase initiates the described conversion



Interpretation follows the direction of the process

Tyrosine is the pigment precursor

- The source begins the pathway with tyrosine.
- Tyrosinase catalyzes tyrosine oxidation to DOPA.
- This explains why melanin belongs among synthesized endogenous pigments.
- The text does not present a complete downstream reaction sequence.

Substrate: Tyrosine

Enzyme: Tyrosinase

Product pathway: Melanin

Melanin differs from passive cellular residue

Melanin	Lipofuscin
Synthesized by melanocytes	Derived from membrane lipid peroxidation
Tyrosinase is involved	Reflects oxidative lipid damage
Brown–black	Yellow–brown
Physiologic pigment	Wear-and-tear residue

Pigment color alone is insufficient

- Melanin is described as brown–black.
- Hemosiderin can appear yellow–brown to brown.
- Lipofuscin also appears yellow–brown and finely granular.
- Cell type, pigment distribution, and clinical context refine recognition.

Observe the color

Locate the pigment

Determine the origin

Homogentisic acid is the rare exception

- The text identifies homogentisic acid as another endogenous black pigment.
- It is found in patients with alkaptonuria.
- Alkaptonuria is described as a rare metabolic disease.
- Pigment deposition here is not melanocytic synthesis.

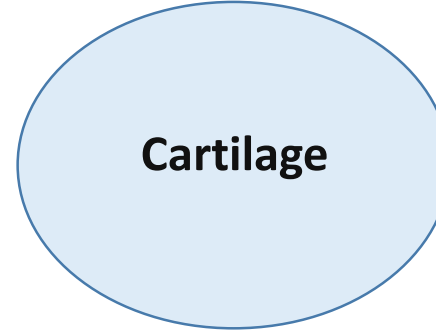
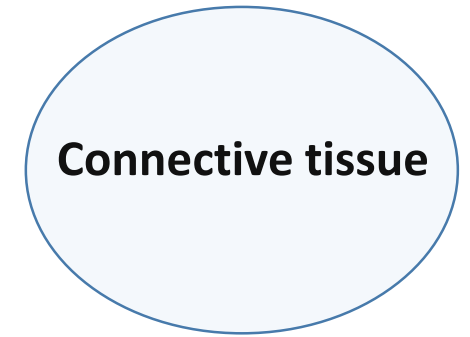
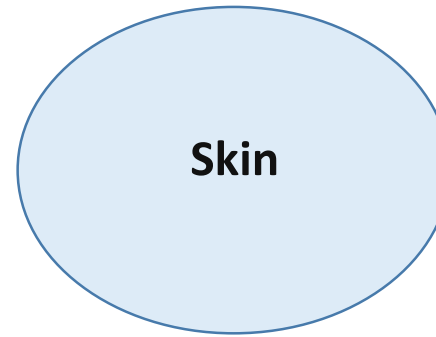
Alkaptonuria

Homogentisic acid

Ochronotic deposition

Ochronosis denotes tissue pigmentation

- Homogentisic acid-derived pigment accumulates in tissues.
- Skin, connective tissue, and cartilage.
- The resulting discoloration is known as ochronosis.
- Its location and metabolic background distinguish it from melanin.



Ochronotic pigment: Recognize the site

Tissue compartment	Core implication
Skin	Visible endogenous pigmentation
Connective tissue	Nonmelanocytic pigment deposition
Cartilage	Characteristic connective-tissue site
Systemic metabolic context	Alkaptonuria

Melanin versus ochronosis

Property	Melanin	Ochronosis
Chemical origin	Tyrosine pathway	Homogentisic acid
Cell/tissue context	Melanocytes	Skin, connective tissue, cartilage
Associated condition	Normal pigment synthesis	Alkaptonuria
Morphologic color	Brown–black	Black

Clinical problem: Dark cartilage

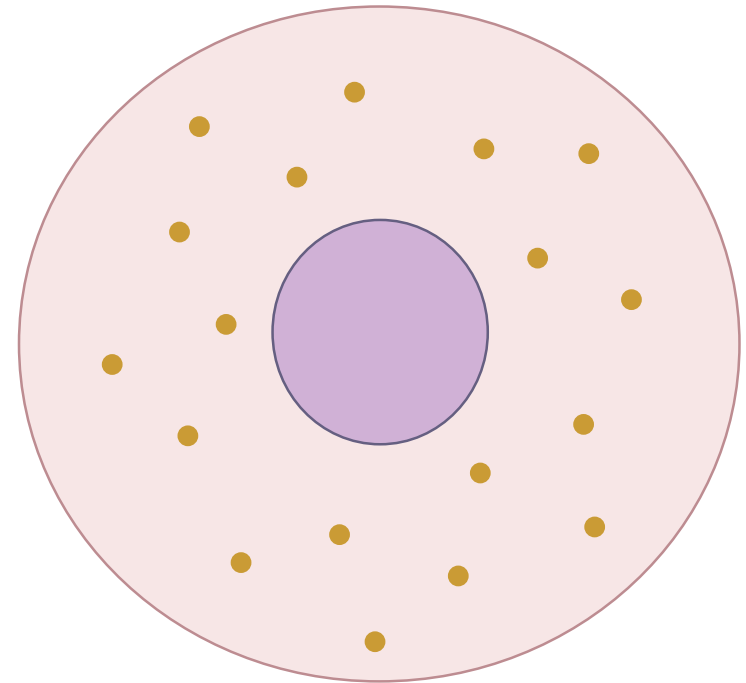
A patient with a rare inherited metabolic disorder develops dark pigment deposition in cartilage and connective tissue.

Which pigment pathway best explains the tissue change?

Homogentisic acid accumulation in alkaptonuria produces ochronosis. The tissue distribution and metabolic context distinguish this process from tyrosinase-dependent melanin synthesis.

Hemosiderin stores iron within cells

- Hemosiderin is a major storage form of iron.
- It is derived from hemoglobin.
- Its appearance ranges from golden-yellow to brown.
- It may form granular or crystalline deposits visible by light microscopy.

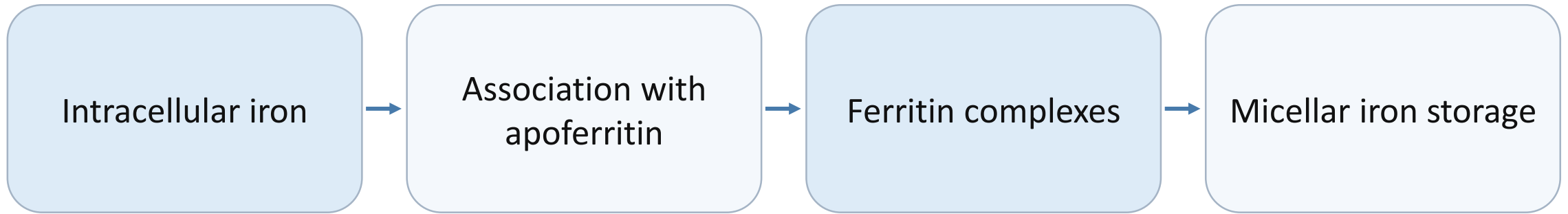


Schematic — hemosiderin granules (not a photomicrograph)

Hemosiderin is not the transport form

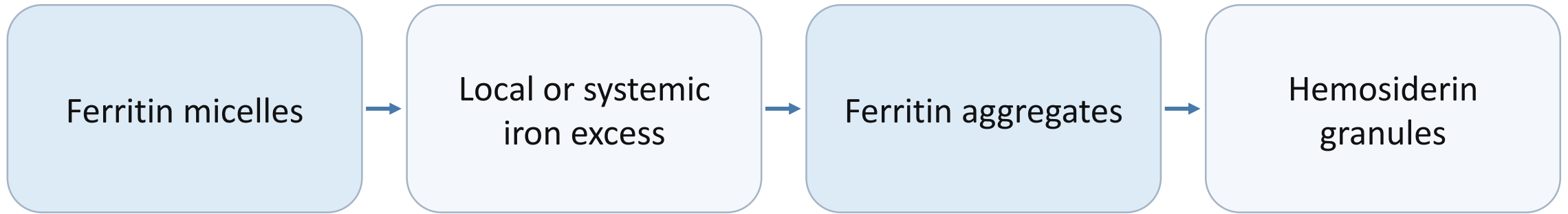
Transport	Intracellular storage
Transferrin carries iron in plasma	Ferritin binds iron inside many cells
Delivers iron to cells	Apoferitin is the protein component
Dynamic iron movement	Hemosiderin appears as aggregated storage material

From apoferritin to ferritin



Interpretation follows the direction of the process

Ferritin can aggregate into hemosiderin



Interpretation follows the direction of the process

The lysosome contributes to iron storage

- Chapter 14 describes hemosiderin granules after ferritin aggregation.
- Partial lysosomal degradation contributes to this process.
- Hemosiderin becomes especially conspicuous in iron-overloaded cells.
- The stored iron remains chemically demonstrable.

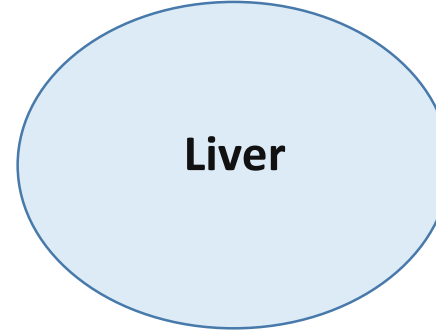
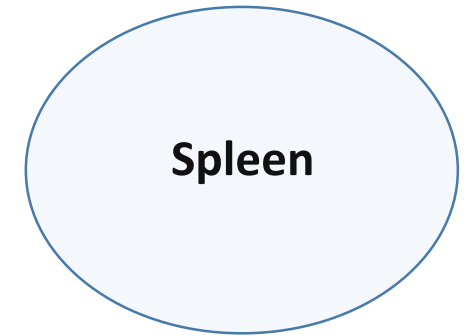
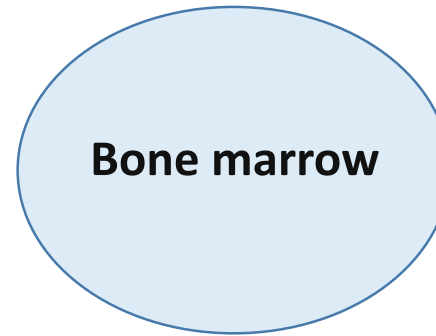
Ferritin aggregates

Lysosomal processing

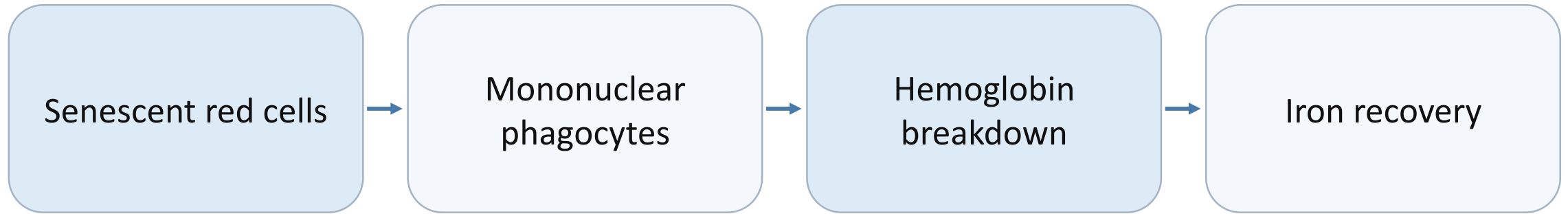
Hemosiderin

Normal hemosiderin is not always abnormal

- Small amounts normally occur in mononuclear phagocytes.
- Common sites are bone marrow, spleen, and liver.
- These cells process senescent circulating erythrocytes.
- Interpret the quantity and distribution before declaring iron overload.



Macrophages recycle erythrocyte iron



Interpretation follows the direction of the process

Iron recycling links blood and tissue

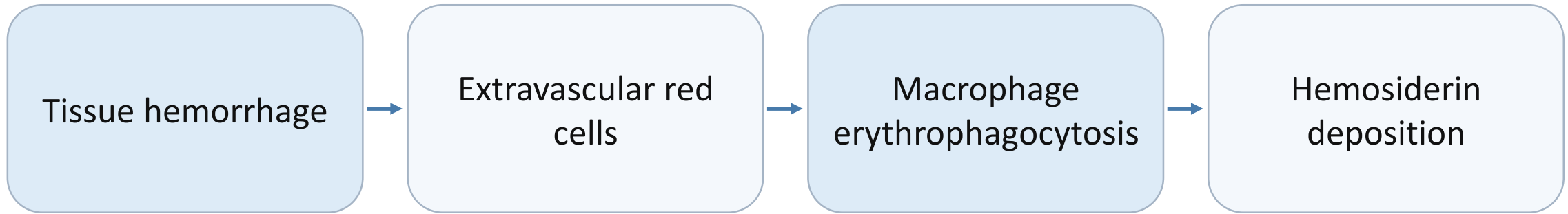
- Phagocytes recover iron from aging red cells.
- Recovered iron can reenter circulating transferrin.
- Iron can be retained intracellularly as ferritin or hemosiderin.
- Normal storage does not imply pathologic tissue hemorrhage.

Red cell turnover

Macrophage processing

Reuse or storage

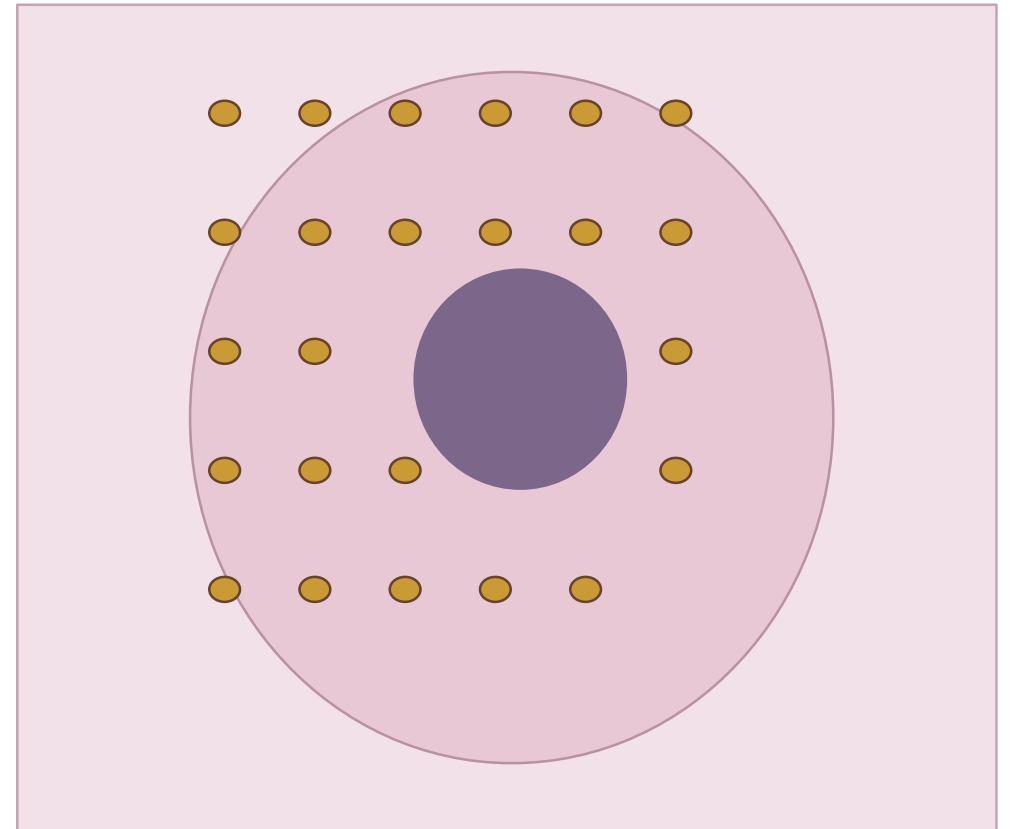
Localized iron accumulation follows hemorrhage



Interpretation follows the direction of the process

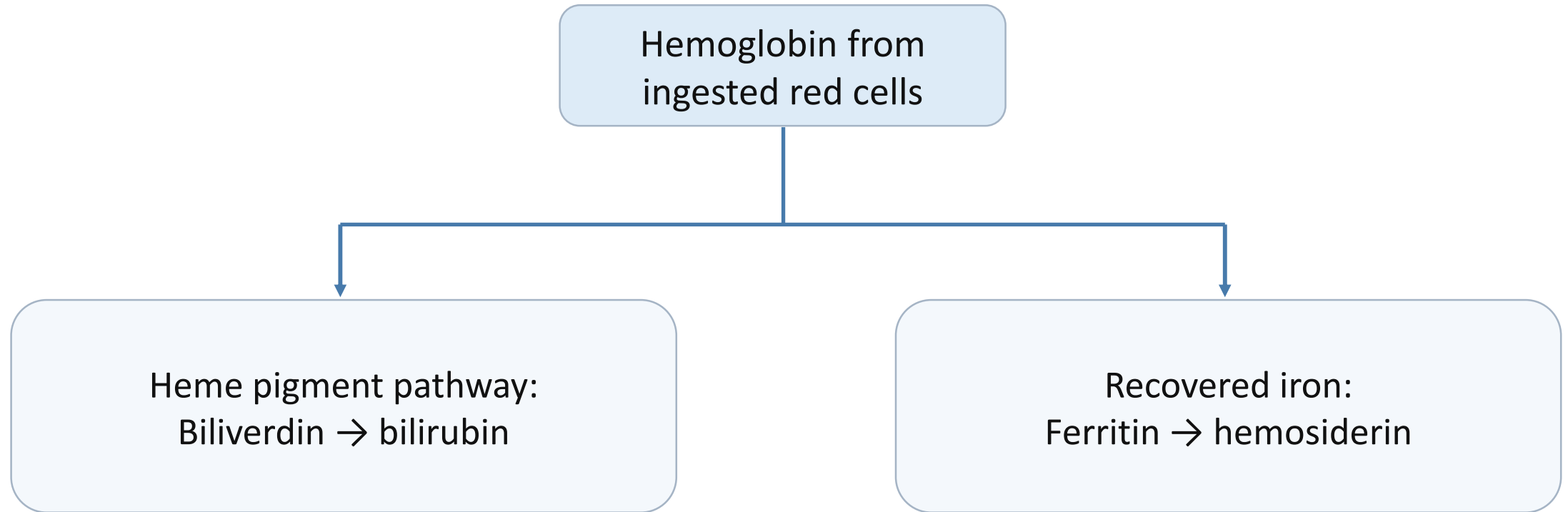
The bruise is localized hemosiderosis

- A bruise is a familiar example of local excess iron.
- Red cells leave the vasculature after tissue injury.
- Macrophages ingest these cells over subsequent days.
- Pigment evolves as hemoglobin components are processed.

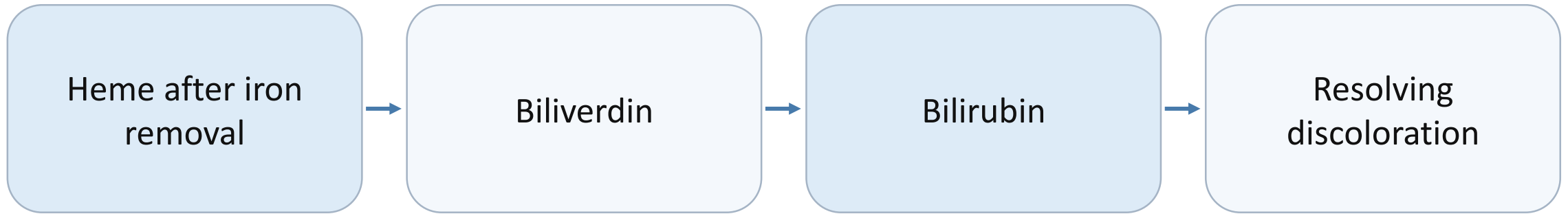


Schematic — pigment distribution only; Not diagnostic microscopy

Hemoglobin breakdown has parallel products

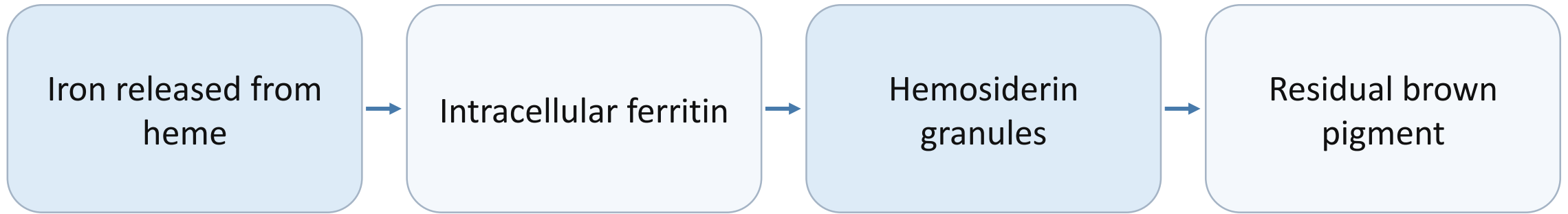


The heme pigment branch changes color



Interpretation follows the direction of the process

The iron branch produces the storage pigment



Interpretation follows the direction of the process

Why a bruise changes appearance

- Color reflects overlapping stages of blood breakdown.
- Biliverdin contributes a green phase in the heme pathway.
- Bilirubin contributes a yellow phase.
- Iron is retained in ferritin and hemosiderin along a parallel branch.

Red–blue

Green–blue

Golden–yellow

Color progression is illustrative; Timing varies

Bruise coloration is a sequence, not a clock

- Red–blue, green–blue, and golden–yellow phases.
- Different stages overlap as tissue products are cleared.
- The color pattern illustrates hemoglobin catabolism.
- The excerpt does not provide a validated method for dating a bruise.

Red–blue

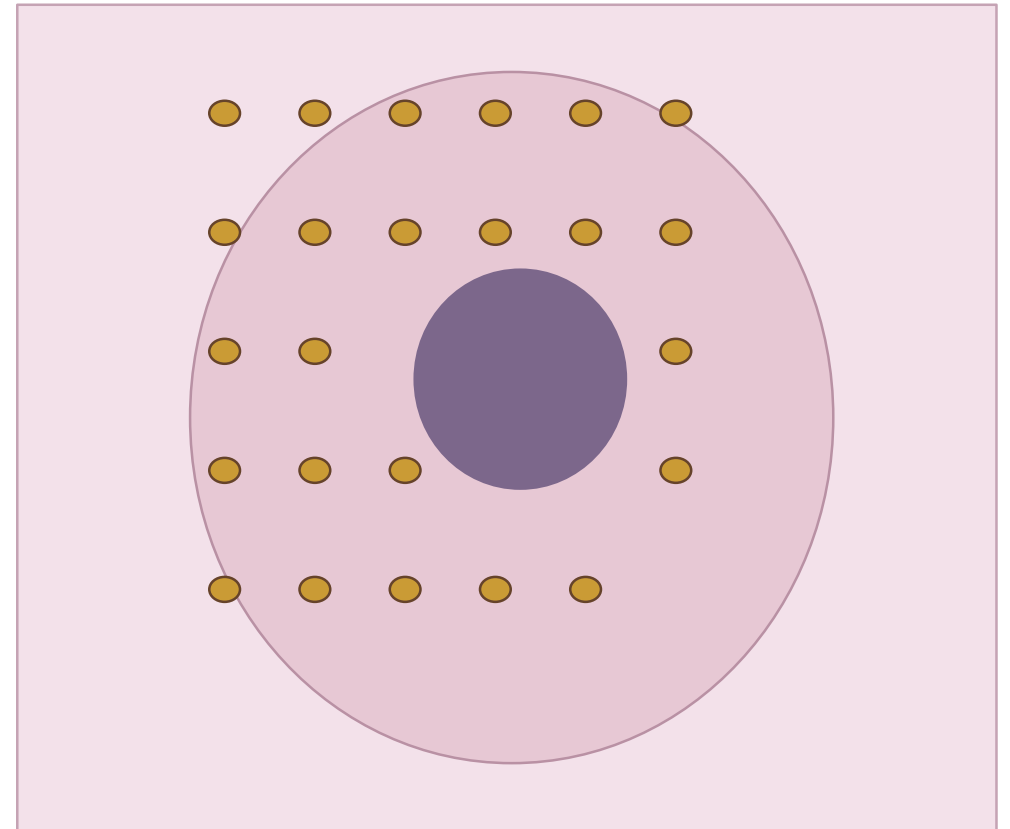
Green–blue

Golden–yellow

Color progression is illustrative; Timing varies

Hemosiderin morphology in phagocytes

- Deposits appear golden-yellow to brown on routine examination.
- Material may be granular or crystalline.
- Macrophage cytoplasm is a plausible site after hemorrhage.
- The schematic depicts pigment location without reproducing a real section.



Schematic — pigment distribution only; Not diagnostic microscopy

Perls Prussian blue identifies stored iron

- Chapter 14 describes a reaction with potassium ferrocyanide.
- Iron in hemosiderin turns blue–black in the Prussian blue reaction.
- This supports identification of iron-containing pigment in tissue.
- The method detects iron; It is not by itself a diagnosis of systemic overload.

Iron-containing granules

Potassium ferrocyanide

Blue–black reaction

Local versus systemic hemosiderosis

Localized	Systemic
Previous tissue hemorrhage	Body-wide iron excess
Bruise as example	Multiple organs can be involved
Macrophage processing of blood	Increased input or iron absorption
Does not alone show systemic loading	Search for the systemic cause

Systemic hemosiderosis reflects excess iron

- Systemic overload allows hemosiderin to accumulate in many organs.
- This pattern differs from iron confined to one prior hemorrhage.
- Three major categories of cause.
- Cause and organ distribution guide interpretation.

Increased absorption

Excess red-cell destruction

Repeated transfusions

Increased absorption: Hemochromatosis

- An inherited error can increase intestinal iron absorption.
- This produces progressive accumulation of total body iron.
- Hemosiderin deposits in tissues when storage capacity is exceeded.
- Further disease-specific discussion appears Chapter 18.

Inborn metabolic error

Increased dietary iron uptake

Tissue iron deposits

Excessive hemolysis increases the iron load

- Hemolytic anemias cause increased destruction of red cells.
- Breakdown of excessive erythrocyte mass liberates more hemoglobin-derived iron.
- Additional iron can be held in the macrophage storage system.
- Such conditions are listed among major causes of systemic hemosiderosis.

Excess RBC destruction

Iron recovery burden

Tissue storage

Repeated transfusion is another iron source

- Transfused red cells carry an additional iron load into the body.
- Repeated transfusions can progressively increase body iron.
- This exposure among the major causes of hemosiderosis.
- The source does not supply a diagnostic transfusion-count threshold.

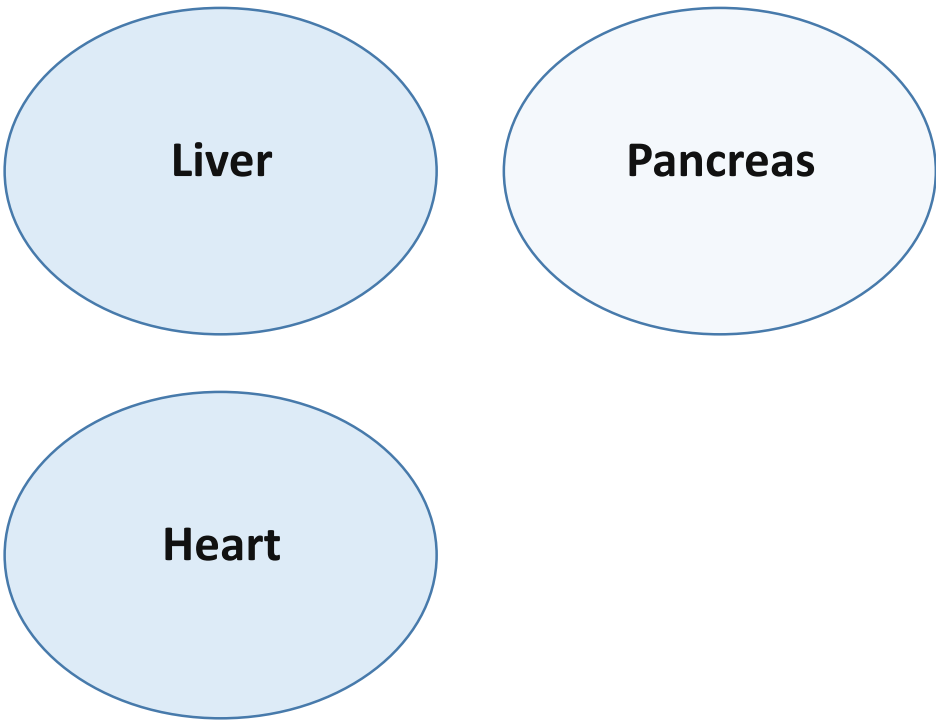
Repeated red-cell transfusion

Accumulated iron input

Systemic iron storage

When iron overload becomes tissue injury

- Hemosiderosis describes excess iron deposition.
- Severe hemochromatosis may also damage parenchymal tissues.
- Chapter 18 describes liver injury, cirrhosis, and pancreatic fibrosis.
- The severity of organ injury is not defined by pigment color alone.



The diagram consists of three light blue ovals with dark blue outlines. Two ovals are positioned at the top, labeled 'Liver' and 'Pancreas', and one oval is positioned below them, labeled 'Heart'. All three ovals are filled with a light blue color and have a thin dark blue border.

Liver

Pancreas

Heart

Iron-loading diseases require contextual diagnosis

Finding	Clinical interpretation
Small phagocyte deposits	Can occur during normal erythrocyte turnover
Focal pigment after bleed	Localized hemosiderosis
Multiorgan iron deposition	Consider systemic overload
Parenchymal damage with overload	Consider hemochromatosis-related injury

Case: Pigment at an old hemorrhage

An organizing soft-tissue hemorrhage contains macrophages with coarse yellow–brown cytoplasmic granules.

Which mechanism is the most direct explanation?

Extravasated erythrocytes were phagocytosed. Their hemoglobin was degraded, and recovered iron was stored first in ferritin and then in hemosiderin. This is localized hemosiderosis.

Case: Multiorgan iron deposition

A patient receiving long-term repeated red-cell transfusions has iron-containing pigment in multiple tissues.

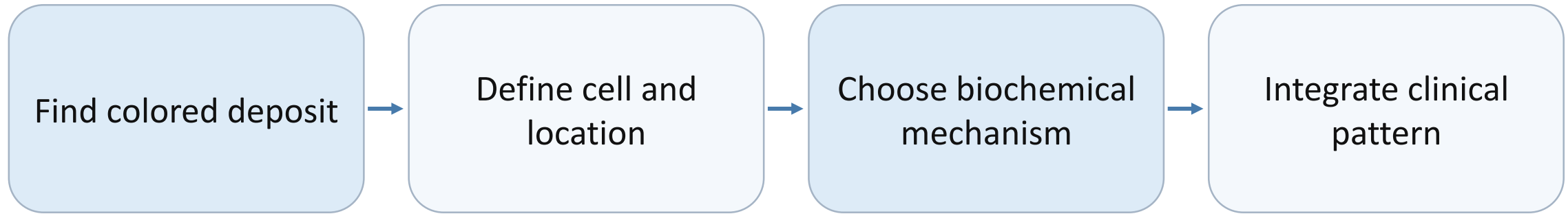
Which upstream exposure explains the deposition?

Repeated transfusions supply iron through the transfused erythrocytes. Their cumulative breakdown can produce systemic hemosiderosis; Organ injury must be assessed separately.

Integrated pigment comparison

Pigment	Origin	Usual clue
Lipofuscin	Oxidized membrane lipid residue	Fine perinuclear yellow–brown
Melanin	Tyrosinase-dependent synthesis	Brown–black in melanocytic setting
Ochronotic pigment	Homogentisic acid in alkaptonuria	Pigmented cartilage/connective tissue
Hemosiderin	Iron derived from hemoglobin	Coarse yellow–brown; Iron reaction

A practical tissue-pigment workflow



Interpretation follows the direction of the process

Integrated interpretation: Three mistakes

- Do not label every brown granule as iron.
- Do not equate lipofuscin with direct pigment toxicity.
- Do not assume a local bruise indicates systemic iron overload.
- Do not classify ochronosis as melanin without considering alkaptonuria.

Describe, then classify

Mechanism matters

Distribution matters

Knowledge check: Identify the mechanism

A pathologist encounters: (A) cardiac perinuclear fine granules, (B) pigmented cartilage in alkaptonuria, and (C) iron-rich phagocytes following hemorrhage.

Match each morphology to the causal process.

A — Lipid peroxidation and residual lipofuscin. B — Homogentisic acid deposition (ochronosis). C — Hemoglobin breakdown and storage of recovered iron as hemosiderin.

Core synthesis

Lipofuscin

Inert trace of prior lipid peroxidation

Melanin

Tyrosinase-related pigment synthesis

Ochronosis

Alkaptonuria-associated homogentisic acid

Hemosiderin

Normal recycling or pathologic iron loading

Reading and verification

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Intracellular Accumulations — Pigments.
- Mechanisms of Atrophy: autophagic residual bodies and brown atrophy.
- Iron Metabolism: ferritin, hemosiderin, and Prussian blue reaction.
- Hemochromatosis: systemic iron loading and organ injury.