

Inherited Liver Disease

Iron overload · Copper accumulation · Protein misfolding

Iron overload

Copper retention

Protein misfolding

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Learning objectives

- Distinguish iron overload, copper transport failure, and α 1-antitrypsin misfolding.
- Connect each molecular defect to liver injury and extrahepatic disease.
- Recognize characteristic histologic patterns and their limitations.
- Select appropriate diagnostic approaches and explain clinical implications.

Three diseases, three mechanisms

Hemochromatosis

Increased intestinal iron
delivery

Hepatic iron deposition →
oxidant injury

Wilson disease

Failed ATP7B-mediated
copper handling

Toxic copper retention → hepatic
/ neural injury

α 1-Antitrypsin deficiency

Misfolded secretory protein
retained in ER

Hepatocyte proteotoxic stress

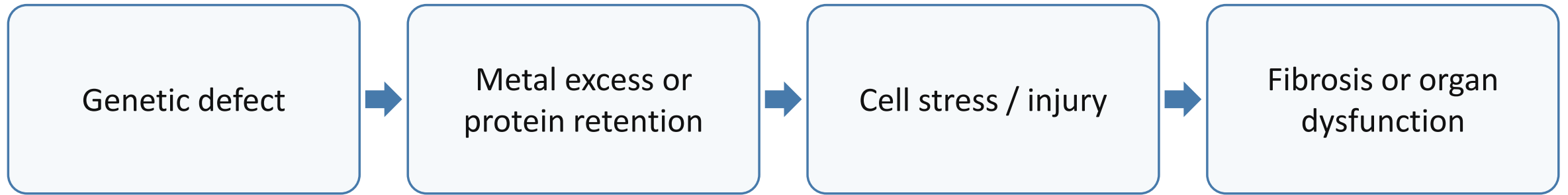
What is inherited—and what is injured?

Disorder	Primary lesion	Hepatic consequence
Hemochromatosis	Iron regulatory genes; hepcidin axis	Hemosiderin deposition, fibrosis, cirrhosis
Wilson disease	ATP7B copper-transport ATPase	Variable hepatocyte injury, hepatitis, cirrhosis
α 1-Antitrypsin deficiency	PiZ misfolding phenotype	ER retention, inclusions, chronic liver injury

Inheritance does not predict phenotype alone

- Gene variant and zygosity influence the biochemical abnormality.
- Clinical penetrance is incomplete in common HFE genotypes.
- Not every PiZZ individual develops clinically overt liver disease.
- The magnitude and duration of tissue accumulation shape organ damage.

Three routes to hepatocyte damage



Different initiating defects converge on progressive tissue injury.

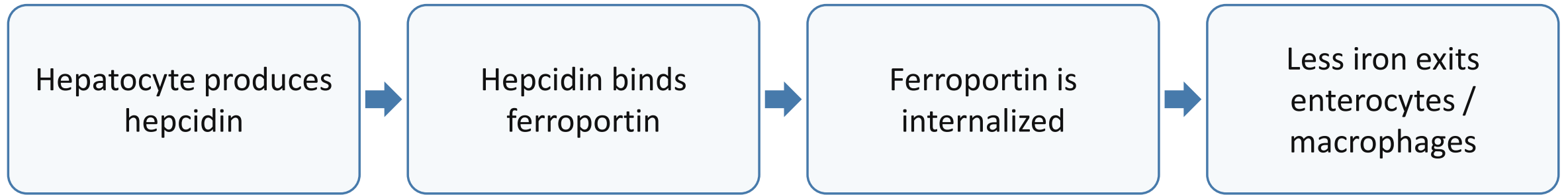
Hemochromatosis: Systemic iron overload

- Excessive intestinal iron absorption drives iron accumulation.
- Liver and pancreas are major sites of deposition; Other organs follow.
- Inherited forms are hereditary hemochromatosis.
- Transfusional and other acquired causes produce secondary iron overload.

Hereditary versus secondary overload

Hereditary hemochromatosis	Secondary hemochromatosis
Usually disrupted iron sensing / hepcidin regulation	Repeated transfusions or increased intestinal iron uptake
Commonly HFE-associated adult phenotype	Ineffective erythropoiesis, severe thalassemias, marrow disease
Iron loads accumulate over years	May occur independently of hereditary hepcidin defects

Hepcidin is the iron-export brake



Normal negative feedback prevents excessive plasma iron delivery.

Ferroportin connects gut and plasma

Intestinal enterocyte

- Absorbs dietary iron
- Ferroportin exports iron to plasma
- Hepcidin restricts export

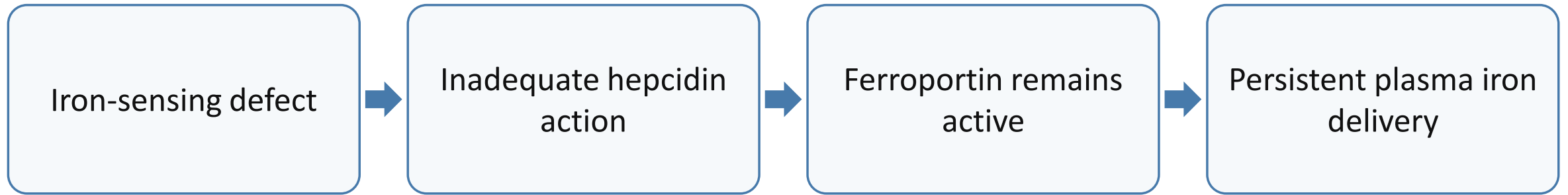
Macrophage

- Recycles iron from erythrocytes
- Ferroportin releases recycled iron
- Hepcidin restricts export

The hereditary hemochromatosis genes

Gene / protein	Normal role	Disease association
HFE	Supports hepatic hepcidin synthesis	Most common adult hereditary form
TFR2 / transferrin receptor 2	Iron sensing / hepcidin regulation	Rare hereditary form
HJV / hemojuvelin	Hepcidin regulation	Juvenile hemochromatosis
HAMP / hepcidin	Hormonal inhibition of ferroportin	Rare juvenile form
SLC40A1 / ferroportin	Cellular iron efflux	Rare ferroportin-related disease

When hepcidin feedback fails

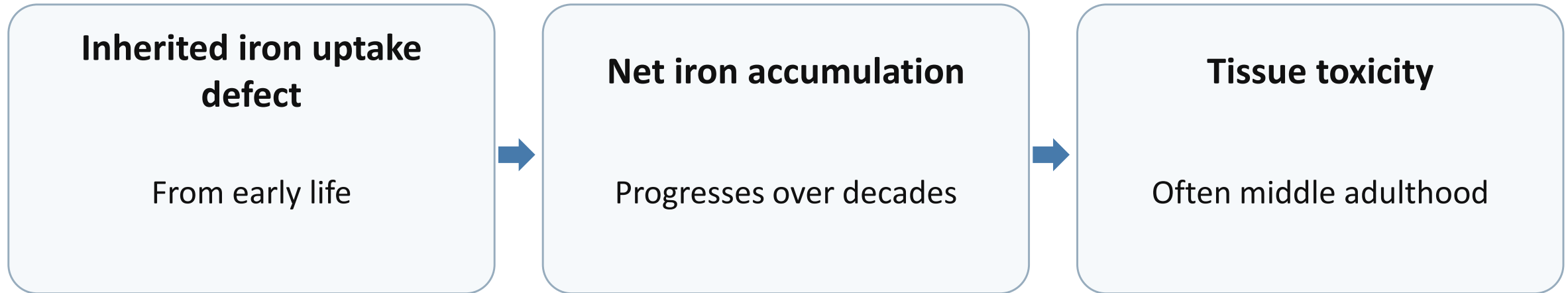


Excess iron eventually deposits in parenchymal organs.

HFE genotype does not equal clinical disease

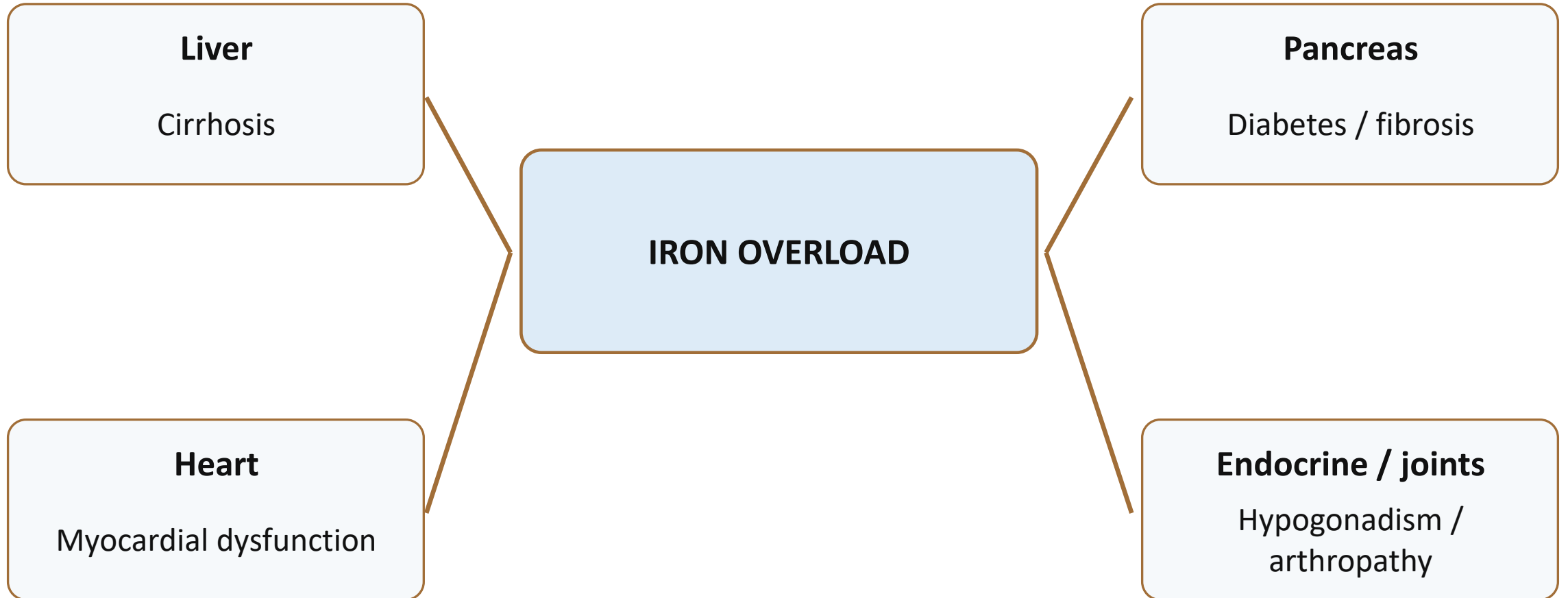
- C282Y is the predominant HFE mutation among diagnosed hereditary cases.
- C282Y homozygosity is commoner than clinically manifest disease.
- The excerpt estimates iron-overload evidence in only about 10% of homozygous males.
- Penetrance is even lower in female C282Y homozygotes and H63D-associated genotypes.

Why manifestations often occur later



Menstrual iron losses can delay clinically important iron accumulation.

Iron accumulation: Organ distribution



Iron toxicity has three principal effects

Free radicals

Iron-catalyzed lipid
peroxidation

Membrane and cellular injury

Stellate cells

Activation of collagen
production

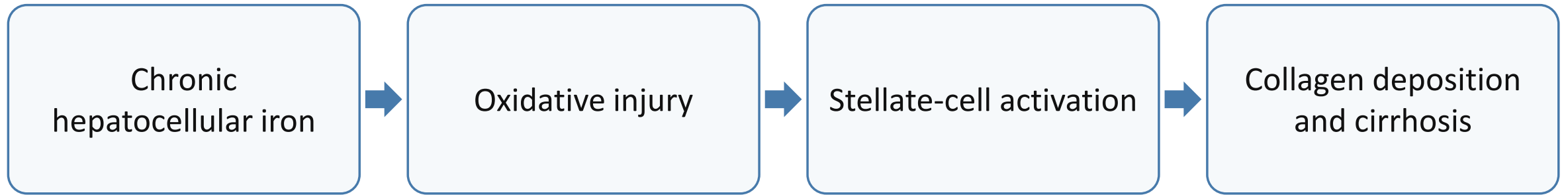
Progressive hepatic fibrosis

DNA injury

ROS and iron-associated
damage

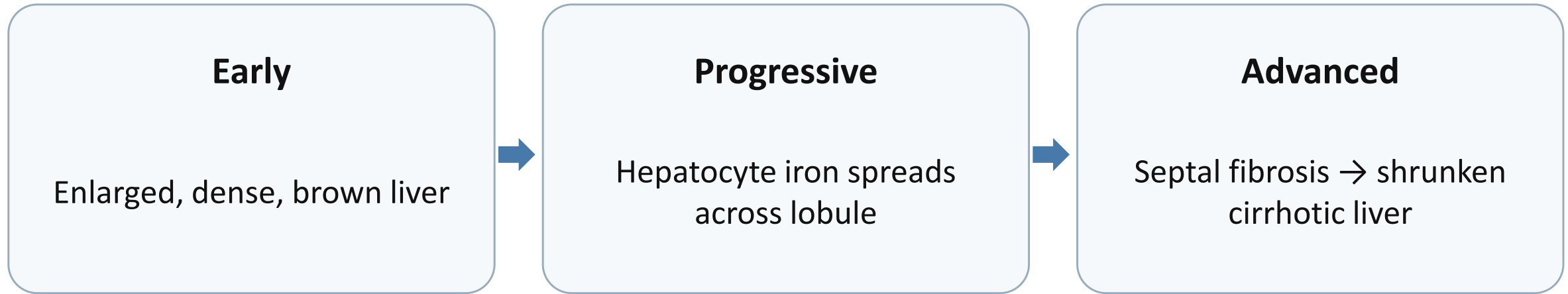
Contribution to carcinogenesis

How iron overload produces fibrosis



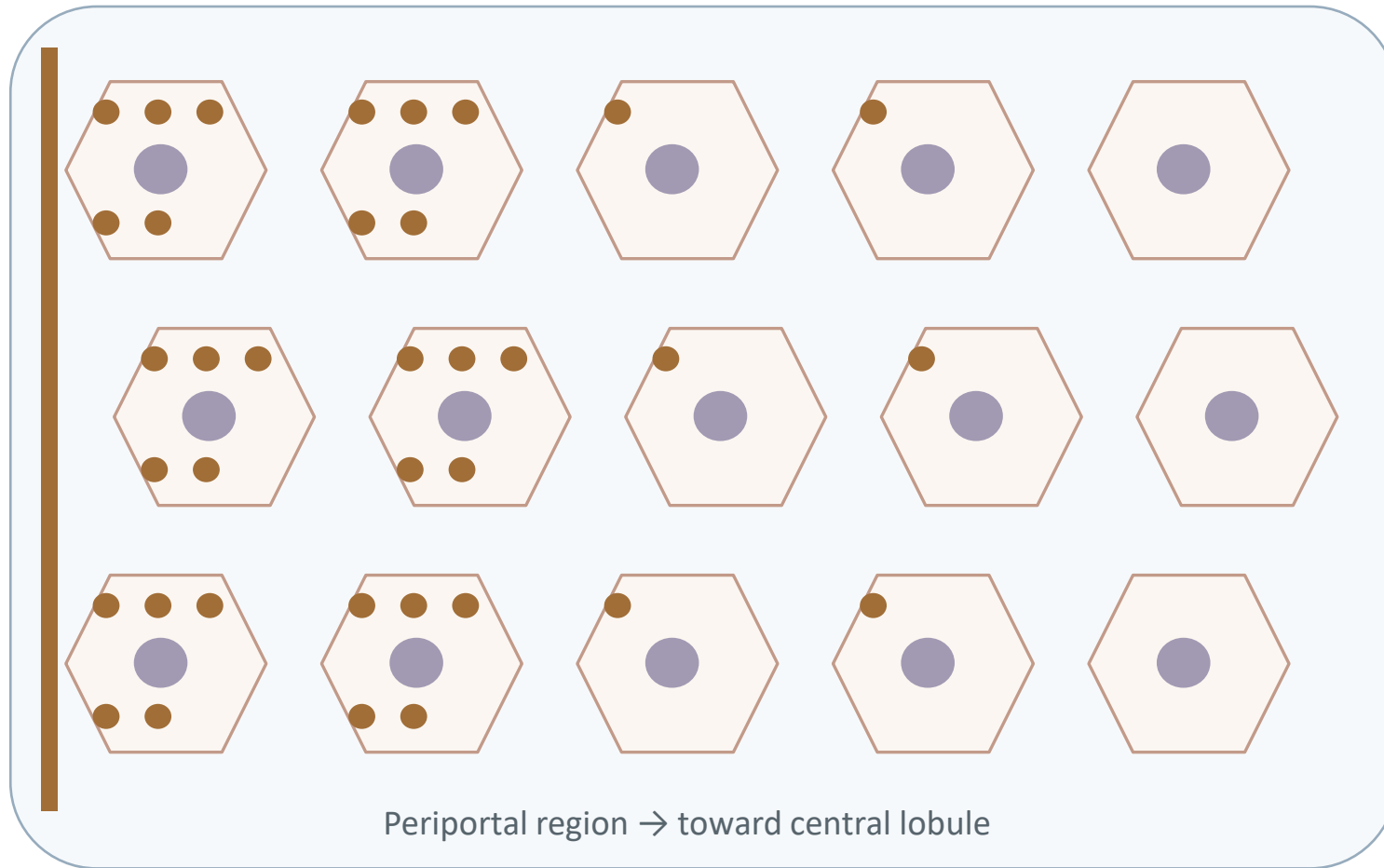
Iron is directly hepatotoxic; Marked inflammation is not a defining early feature.

The liver changes with disease duration



These changes reflect cumulative tissue burden, not a rigid staging criterion.

Hemochromatosis: Periportal iron first



Morphologic principle

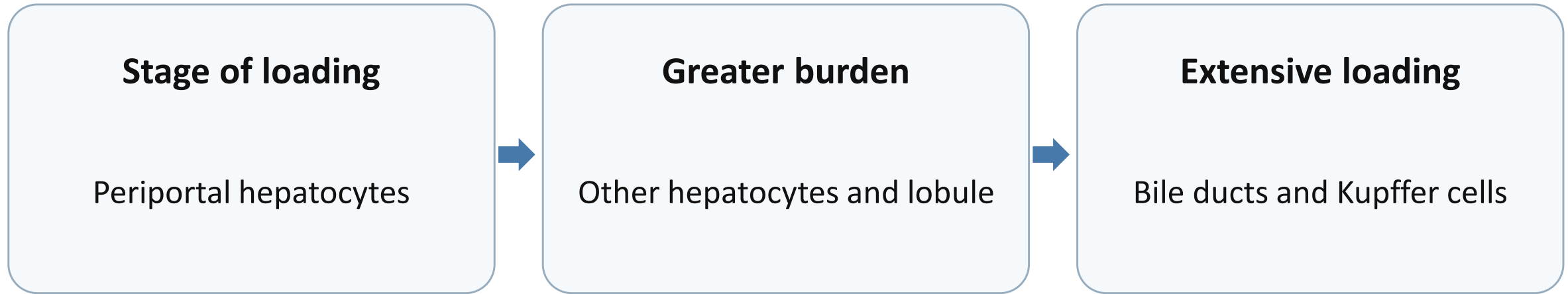
Schematic: Periportal hepatocytes develop cytoplasmic hemosiderin before widespread lobular deposition.

Schematic — not a specimen

Prussian blue reveals iron deposition

- Hemosiderin appears as golden-brown granules with routine microscopy.
- Prussian blue produces a blue reaction in iron-containing deposits.
- Early parenchymal deposition is prominent in periportal hepatocytes.
- Later deposits extend to bile duct epithelium and Kupffer cells.

Distribution changes as iron burden rises



Illustrative progression of deposition distribution, not a validated histologic staging scale.

The pancreatic lesion explains diabetes

Microscopic response

- Iron-related acinar / endocrine damage
- Progressive parenchymal atrophy
- Interstitial fibrosis

Clinical consequence

- Disrupted glucose homeostasis
- Diabetes may emerge late
- Other metabolic disorders may coexist

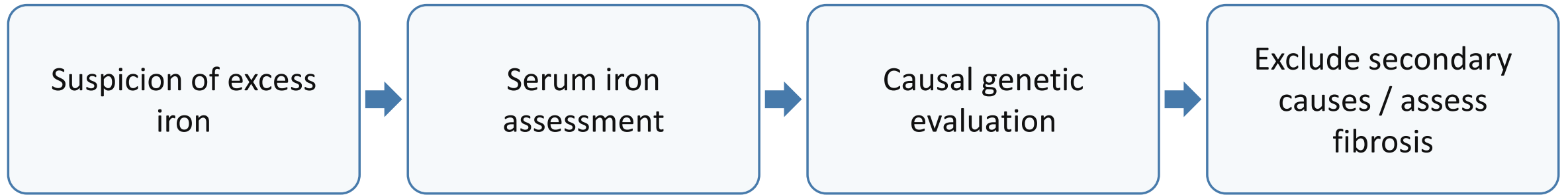
Cardiac, endocrine and joint effects

Organ system	Pathology or physiology	Clinical correlate
Heart	Myocardial hemosiderosis and fibrosis	Arrhythmia / cardiomyopathy
Pituitary–gonadal axis	Pituitary involvement; low gonadotropins	Hypogonadism
Joints	Synovial iron and CPP crystal disease	Arthritis / pseudogout
Skin	Increased melanin, with iron pigmentation	Slate-gray coloration

Recognizing symptomatic hemochromatosis

- Hepatomegaly, abdominal pain and chronic liver disease.
- Skin darkening, particularly in sun-exposed regions.
- Diabetes or abnormal glucose regulation.
- Cardiomyopathy, arrhythmia, arthropathy, or hypogonadism.
- The complete classical combination is a late manifestation.

Diagnosis begins before cirrhosis



Genetic testing and imaging reduce the need for routine quantitative liver biopsy.

Secondary iron overload: The differential

- Repeated red-cell transfusion may cause systemic hemosiderosis.
- Ineffective erythropoiesis can also increase intestinal iron uptake.
- Thalassemia and myelodysplastic syndromes are key examples.
- Other chronic liver diseases can lower hepcidin production.
- Transfusion and marrow-disease history guide the differential.

Phlebotomy alters the natural history

Treatment principle

- Regular phlebotomy removes total-body iron
- Can prevent progressive organ injury
- Best before irreversible damage

Persistent risk

- Advanced cirrhosis may already exist
- HCC risk is not fully eliminated
- Family screening identifies silent disease

Hemochromatosis: Clinical exercise

An adult with diabetes, arthropathy, darkened skin and hepatomegaly has elevated iron indices.

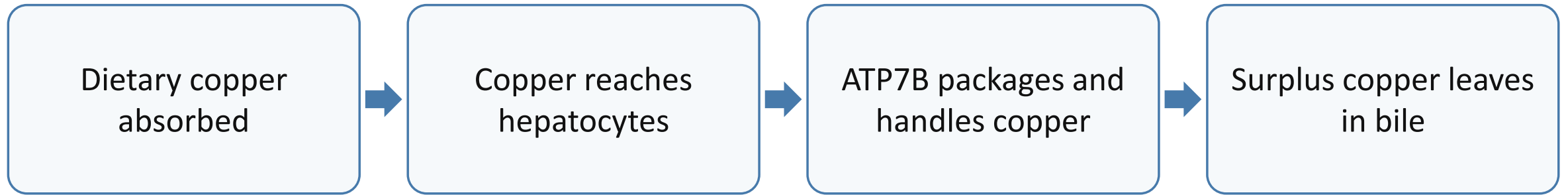
Discussion prompts

- Which common regulatory axis should be considered?
- Why can cirrhosis occur without prominent inflammation?
- What acquired causes should be excluded?

Wilson disease: Inherited copper toxicity

- Autosomal recessive loss of ATP7B transporter function.
- Impaired biliary copper excretion causes hepatic accumulation.
- Copper incorporation into ceruloplasmin is also impaired.
- Liver, brain and eye are prominent injured organs.

Normal copper enters and exits the liver



Ceruloplasmin synthesis and biliary disposal are linked to ATP7B.

ATP7B has two critical functions

Copper handling in Golgi

- Copper incorporation into apoceruloplasmin
- Formation and secretion of ceruloplasmin

Copper elimination

- Movement toward biliary excretion
- Protection from toxic intracellular copper

ATP7B failure creates a double defect

Retained hepatic copper

- Biliary clearance is reduced
- Hepatocellular copper increases
- Cell injury releases copper to blood

Reduced ceruloplasmin

- Less copper is loaded onto apoprotein
- Measured total serum copper may be low
- Unbound copper can still be harmful

Three molecular routes of copper toxicity

Reactive radicals

Copper catalyzes oxidant chemistry

Membrane and protein damage

Protein interactions

Copper binds protein sulfhydryl groups

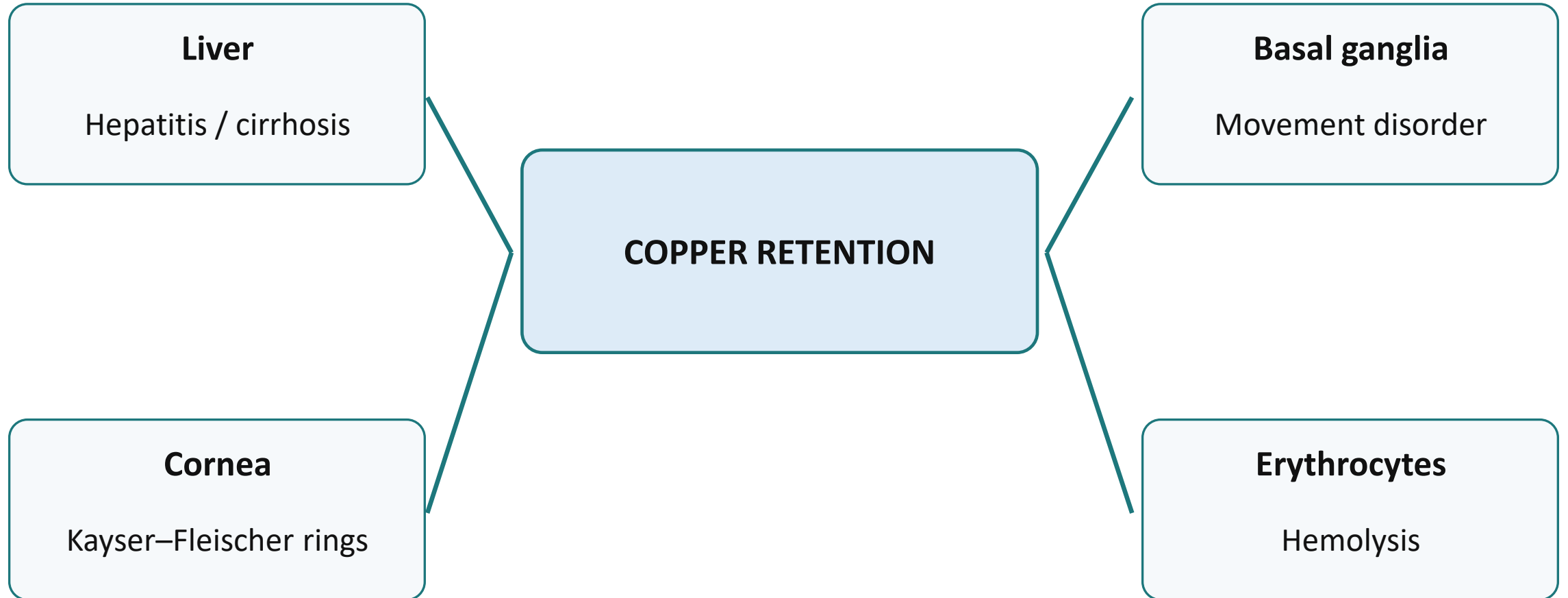
Loss of function / stress

Metalloenzymes

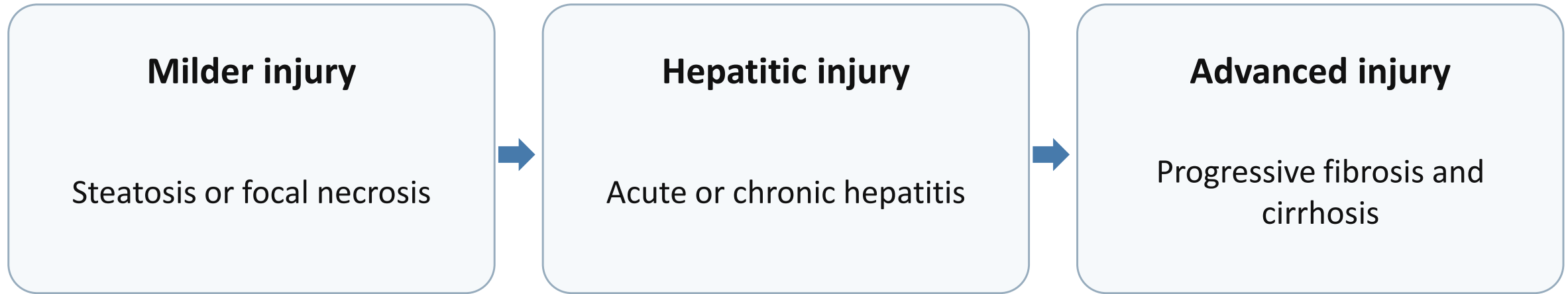
Copper displaces physiologic metals

Enzyme dysfunction

Copper moves beyond the liver



Wilson disease has a broad liver phenotype



Illustrative spectrum—not an obligatory progression for every patient.

Why Wilson disease mimics steatohepatitis

- Hepatocytes may show fatty change and ballooning.
- Mallory hyaline can accompany the injury pattern.
- Perisinusoidal fibrosis may be present.
- Portal inflammation and necrosis can imitate chronic hepatitis.
- Histology alone is not a reliable etiologic label.

Acute Wilson hepatitis can look infectious

Morphologic overlap

- Acute hepatocellular injury
- Focal or severe necrosis
- Inflammatory changes

Diagnostic implication

- Age and family history help
- Copper studies are necessary
- Do not infer a viral cause from biopsy alone

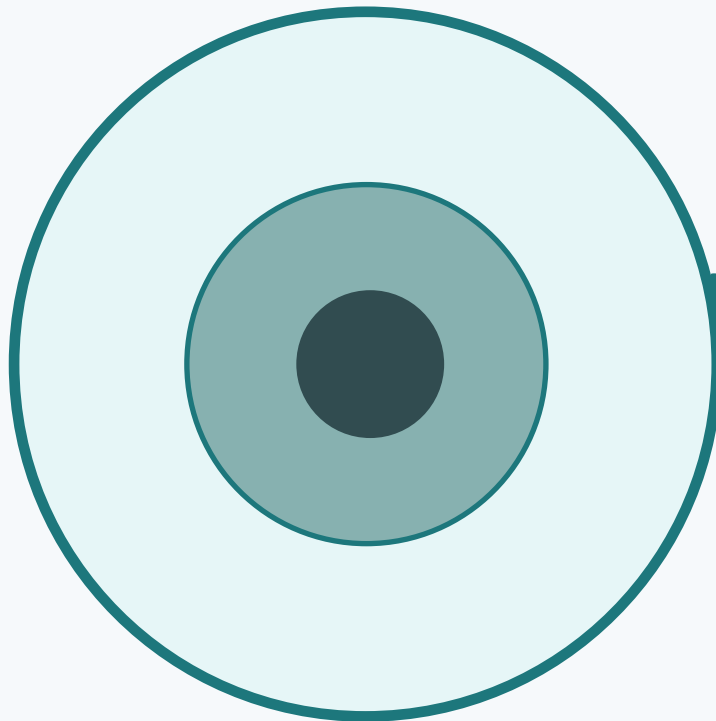
Copper staining cannot confirm Wilson disease

- Hepatic injury may resemble several other liver disorders.
- Histochemical copper staining lacks adequate sensitivity.
- The stain is also not specific for Wilson disease.
- Clinical, biochemical and molecular evidence must be integrated.

Neurologic Wilson disease localizes to basal ganglia

- Tremor, incoordination, chorea or choreoathetosis.
- Rigid or spastic dystonia may develop.
- Masklike facies, gait changes and rigidity are described.
- Psychiatric manifestations may coexist with hepatic disease.

Kayser–Fleischer rings: Tissue localization



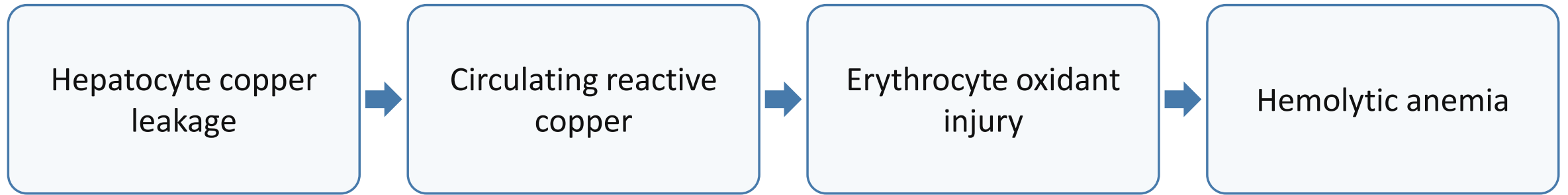
Limbic copper ring

Morphologic principle

Schematic: Copper deposits in Descemet membrane near the corneal limbus.

Schematic — not a specimen

Copper can cause hemolytic anemia



The hemolytic component may accompany otherwise diverse hepatic presentations.

Wilson disease: Diagnostic evidence

Test / finding	Source-described role	Limitation or interpretation
Serum ceruloplasmin	Often reduced	May be normal in liver injury
Hepatic copper	Increased; highly informative	Biopsy and sampling considerations
Urinary copper	Increased excretion	Must be interpreted clinically
ATP7B sequencing	Molecular support	Variants differ in pathogenicity
Slit-lamp assessment	Kayser–Fleischer rings	Not every hepatic case has rings

Interpreting copper tests requires context

- Reduced ceruloplasmin is helpful but not infallible.
- Total serum copper can be low despite tissue overload.
- Hepatic copper and urinary copper reflect different compartments.
- ATP7B sequencing can clarify ambiguous biochemical findings.
- A single nonspecific histologic pattern should not overrule the workup.

Wilson disease is treatable

Reduce circulating / tissue copper

- D-Penicillamine or trientine chelation
- Zinc-based treatment limits intestinal uptake

Advanced liver damage

- Liver transplantation for severe disease
- Transplant can correct hepatic metabolic defect

Wilson disease: Clinical exercise

A teenager has abnormal liver tests, tremor and mood changes; The corneal examination reveals a pigmented peripheral ring.

Discussion prompts

- Which transporter is implicated?
- Why might total serum copper be low?
- Which testing domains support diagnosis?

α 1-Antitrypsin deficiency: Liver and lung

- Inherited deficiency of a circulating serine protease inhibitor.
- Loss of anti-elastase protection promotes pulmonary emphysema.
- Misfolded α 1-antitrypsin accumulates in hepatocyte ER.
- Liver injury reflects a toxic gain of function within secretory cells.

Pi genotype identifies α 1-antitrypsin variants

Genotype / allele	Expected phenotype from source	Clinical interpretation
PiMM	Common wild-type genotype	Normal secreted inhibitor
PiZZ	Markedly diminished serum α 1-antitrypsin	High risk of liver and lung disease
PiMZ	Intermediate α 1-antitrypsin levels	Incomplete / variable manifestations

PiZZ: Low plasma level, retained hepatocyte protein

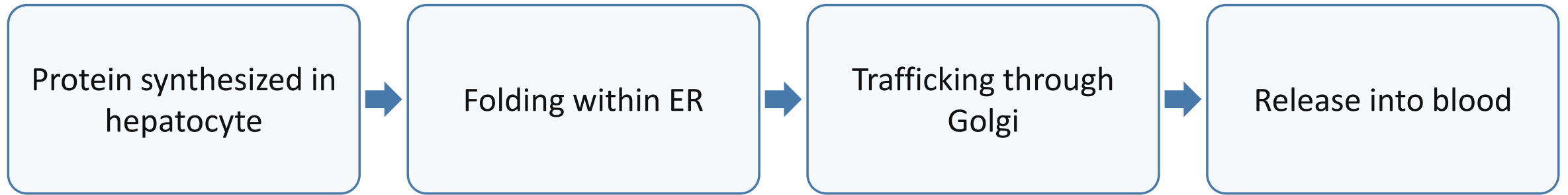
Systemic circulation

- PiZZ levels $\approx$ 10% of normal
- Reduced inhibition of neutrophil proteases

Hepatocyte

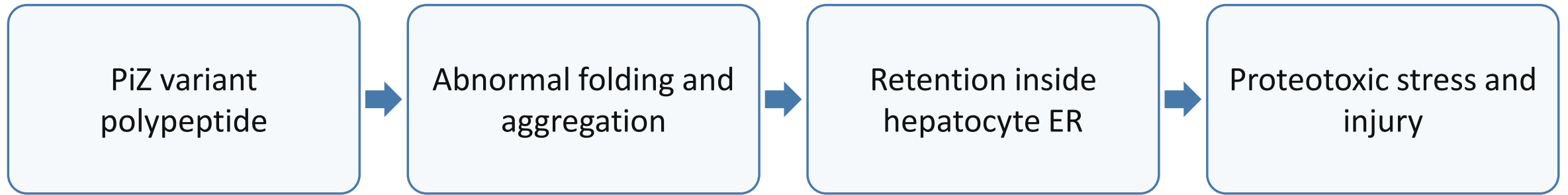
- Mutant protein misfolds and aggregates
- Accumulation occurs in endoplasmic reticulum

Normal α 1-antitrypsin secretion



Normal secretory trafficking supplies antiprotease protection to tissues.

PiZ misfolding blocks secretory trafficking



The retained protein is toxic even though circulating protein is deficient.

Why this is gain-of-function and loss-of-function

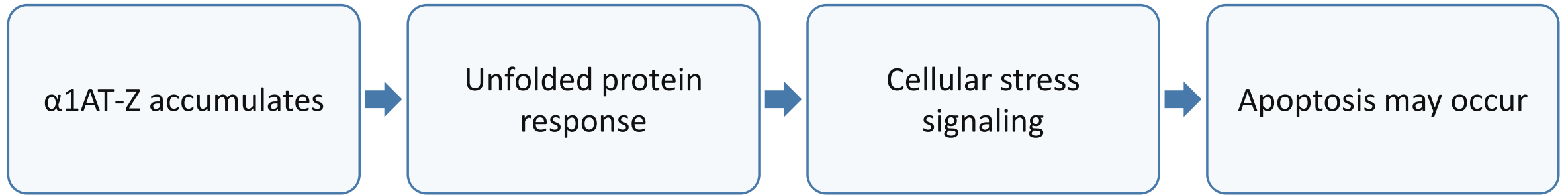
Liver: Toxic gain of function

- Aggregated mutant protein retained
- ER stress and unfolded protein response
- Hepatocellular injury

Lung: Loss of function

- Depleted circulating antiprotease
- Neutrophil elastase remains active
- Parenchymal destruction → emphysema

ER stress links aggregation to injury

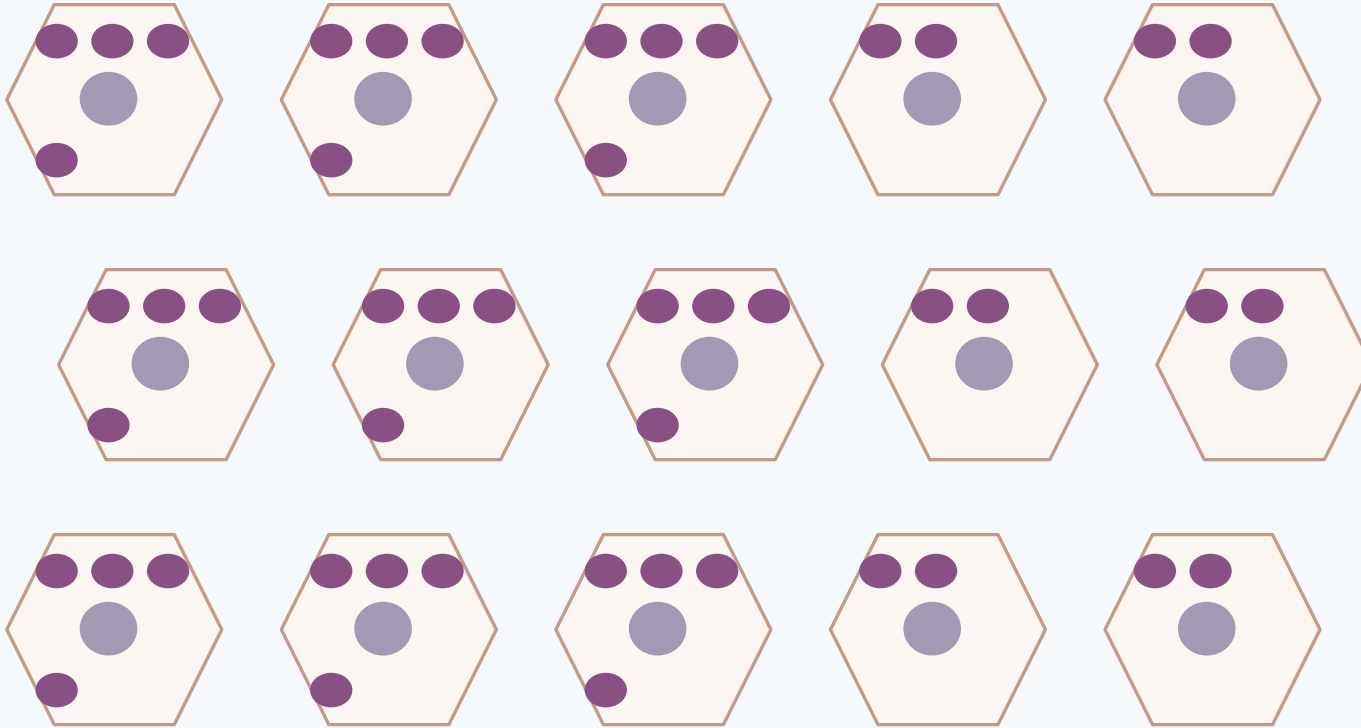


Source describes a pathway that may culminate in hepatocyte apoptosis.

Why PiZZ carriers differ clinically

- Intracellular α 1AT-Z accumulation occurs in PiZZ individuals.
- Only a subset develops overt liver disease.
- Additional genetic and environmental modifiers are suspected.
- The number of cytoplasmic globules does not reliably grade severity.

Characteristic α 1AT hepatocyte inclusions



Stylized retained protein globules, stronger periportally

Morphologic principle

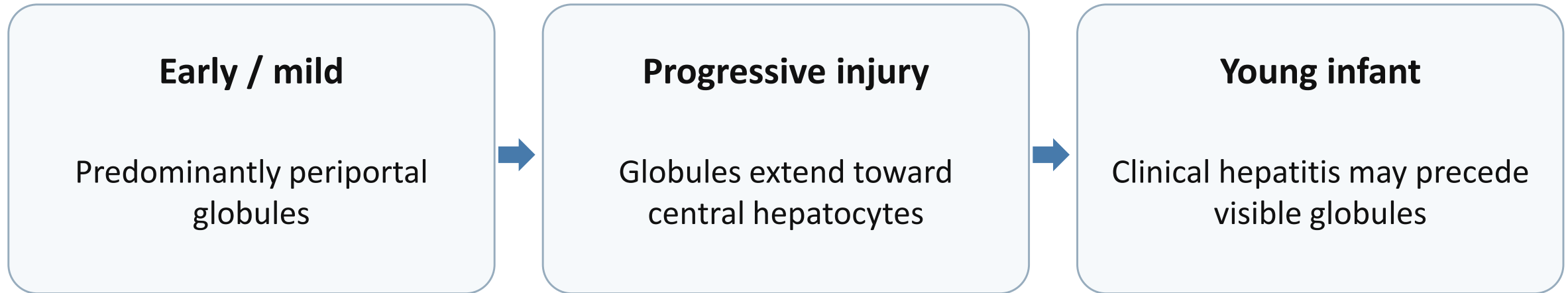
Schematic: Rounded cytoplasmic inclusions in hepatocytes; Not a genuine PAS-D photomicrograph.

Schematic — not a specimen

PAS with diastase highlights the globules

- Affected hepatocytes contain round-to-oval cytoplasmic inclusions.
- Globules are strongly periodic acid–Schiff positive.
- They remain after diastase digestion (PAS-D resistant).
- This pattern reflects retained misfolded α 1-antitrypsin protein.

Zonal distribution and timing matter



Absence of globules early in life does not exclude disease.

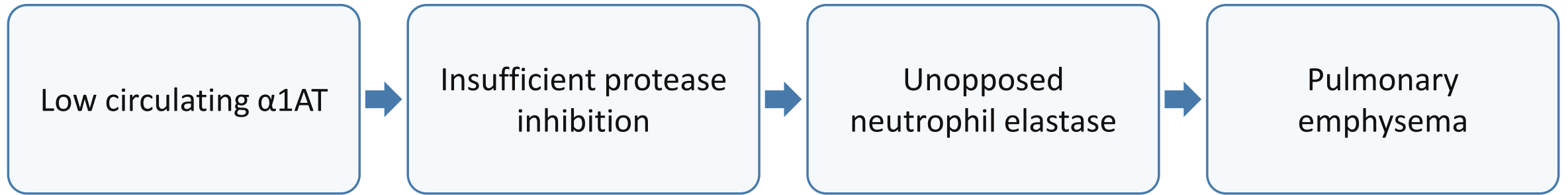
Neonatal α 1AT liver disease

- Can present with hepatitis during infancy.
- Severe neonatal presentations may progress rapidly to cirrhosis.
- Globules may not yet be visible in the earliest biopsies.
- Diagnosis requires integration of phenotype and laboratory findings.

Adult α 1AT liver disease

- May appear as chronic hepatitis or progressive hepatic fibrosis.
- Cirrhosis is a major late complication.
- Hepatocellular carcinoma can occur, often with cirrhosis.
- Some individuals remain without overt liver symptoms.

α 1AT deficiency in the lung



Pulmonary disease is a consequence of deficient inhibitor activity, not hepatic protein accumulation.

The hepatic risk is not only cirrhosis

- Persistent misfolded protein may produce chronic cellular injury.
- Progressive fibrosis can eventually impair hepatic architecture.
- The excerpt describes hepatocellular carcinoma in some PiZZ adults.
- Liver and pulmonary outcomes must be evaluated separately.

Liver transplantation corrects the hepatic defect

After hepatic transplantation

- Donor hepatocytes synthesize functioning protein
- Hepatic protein retention no longer occurs
- Hepatic disease may be cured

What it does not reverse

- Existing pulmonary damage is not cured
- Pulmonary disease requires separate care

α 1AT deficiency: Clinical exercise

A child with chronic liver injury has hepatocytes containing diastase-resistant PAS-positive cytoplasmic globules.

Discussion prompts

- Which inherited secretory-protein defect fits best?
- What is the mechanism of liver injury?
- What extrahepatic disease should be considered?

The defining hepatic lesion differs

Disorder	Principal hepatocyte abnormality	Useful morphological clue
Hemochromatosis	Excess iron deposition	Periportal hemosiderin; Prussian blue positive
Wilson disease	Copper-associated hepatocyte injury	Variable hepatitis, steatosis / steatohepatitis
α 1AT deficiency	ER retention of aberrant protein	PAS-D–resistant globules in hepatocytes

Age and clinical presentation are discriminators

Hemochromatosis	Wilson disease	α 1AT deficiency
Usually adult onset after decades of loading	Often childhood to young-adult presentation	Can present in infancy or adulthood
Diabetes, pigmentation, arthropathy	Hepatitis, neurologic signs, corneal rings	Chronic liver disease with lung emphysema
Iron accumulation and secondary causes	Biochemical / genetic copper evaluation	Protein phenotype / deficiency and PAS-D inclusions

Tests interrogate different disease biology

Iron physiology

Serum iron indices; Causative genotype

Biopsy or imaging for consequences

Copper handling

Ceruloplasmin, urinary / hepatic copper

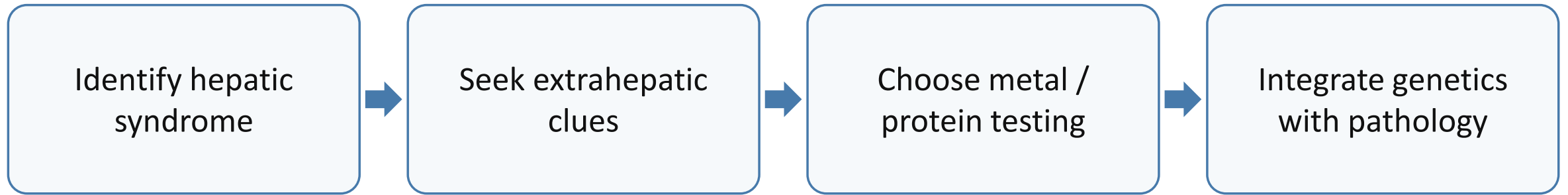
ATP7B and ocular examination

α 1AT secretion

Circulating α 1AT level and Pi phenotype

Biopsy inclusion pattern is supportive

A phenotype-first clinical approach



Morphology is informative but rarely replaces clinical and biochemical context.

Shared outcome; Distinct mechanisms

Iron

Overdelivery + oxidant stress

Cirrhosis; HCC risk

Copper

Transport failure + copper
toxicity

Hepatitis; Neural injury

α 1AT

Proteotoxic ER retention

Chronic liver injury; Emphysema

Integration exercise: Choose the disorder

Three teaching vignettes: (A) adult iron overload with diabetes; (B) adolescent hepatitis with tremor; (C) infant hepatitis with PAS-D hepatocyte inclusions.

Discussion prompts

- Assign one inherited liver disease to each vignette.
- Name the causal molecular pathway for each.
- Identify one potentially informative investigation.

Core distinctions to retain

- Hemochromatosis: Hepcidin–ferroportin dysfunction → excess iron entry.
- Wilson disease: Defective ATP7B → reduced copper clearance and ceruloplasmin loading.
- α 1AT deficiency: Mutant protein is retained in ER while circulating inhibitor falls.
- Diagnostic morphology differs: Iron stain, nonspecific copper injury, PAS-D globules.
- Earlier diagnosis can prevent or limit irreversible organ damage.

Primary reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026)

Inherited Liver Disease: Hemochromatosis, Wilson Disease, α 1-Antitrypsin Deficiency