

Wilson Disease

Inherited disorder of copper metabolism

Molecular pathogenesis • Liver pathology • Clinical diagnosis

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Learning objectives

- Trace normal copper absorption, hepatocyte handling, and biliary elimination.
- Explain how ATP7B dysfunction causes tissue injury and systemic copper deposition.
- Recognize the spectrum of hepatic, neurologic, and ocular manifestations.
- Integrate biochemical, tissue, ophthalmic, and genetic diagnostic evidence.
- Relate copper-directed therapy and transplantation to the underlying defect.

Wilson disease among inherited liver disorders

Inherited metabolic disorders

Wilson disease: Disturbed copper transport

Hemochromatosis: Excess iron handling

α_1 -antitrypsin deficiency: Abnormal protein folding

Distinctive Wilson phenotype

Copper accumulation in hepatocytes

Secondary injury to brain and eye

Mixed hepatic and neurologic presentations

Core definition

Autosomal recessive loss of ATP7B function

Impaired biliary copper excretion and ceruloplasmin loading
produce toxic copper retention.

Three principal tissue targets

Liver

Intracellular copper

→ inflammation, injury,
fibrosis

Brain

Basal ganglia injury

→ movement and other
neurologic symptoms

Eye

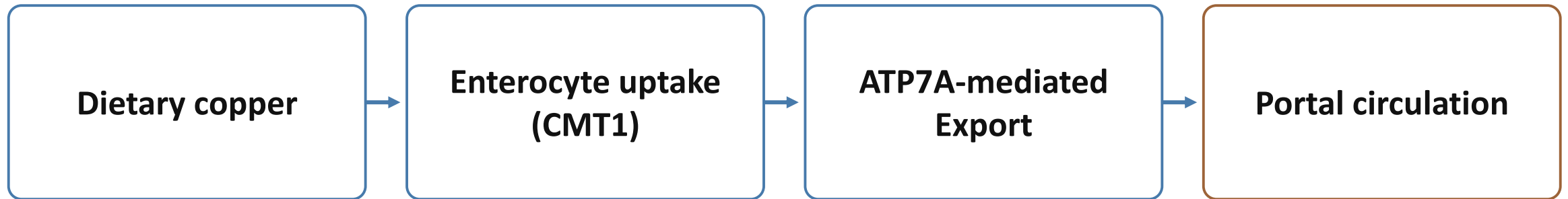
Descemet membrane copper

→ Kayser–Fleischer ring

Copper homeostasis depends on the liver

- Dietary copper is absorbed from the gastrointestinal tract.
- Portal delivery makes hepatocytes central to copper handling.
- Copper is partitioned into circulating ceruloplasmin or a biliary elimination pathway.
- Failure of hepatic transport can simultaneously reduce circulating ceruloplasmin and raise tissue copper.

Intestinal copper entry and transfer



The intestinal step delivers copper to the liver; Wilson disease is primarily a hepatic ATP7B defect.

Portal blood transports newly absorbed copper

From intestine to liver

Copper reaches portal circulation after enterocyte export.

Albumin associates with copper in the blood.

Hepatocytes subsequently take up circulating copper.

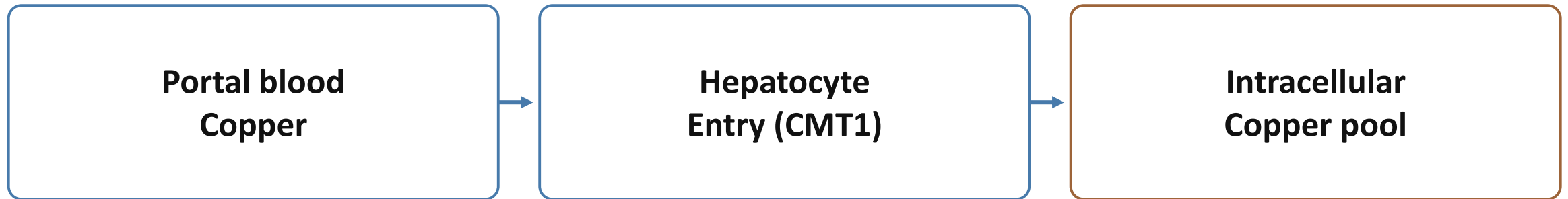
Why this matters

The liver receives copper before its systemic distribution.

Normal handling prevents excessive unbound copper from accumulating.

Excretion and incorporation regulate the circulating pool.

Hepatocyte copper uptake



Copper entering the hepatocyte must be handled by cellular transport and elimination pathways.

Two physiologic destinations of hepatic copper

Secretory destination

Transport toward the trans-Golgi network

Incorporation into apoceruloplasmin

Secretion of ceruloplasmin into blood

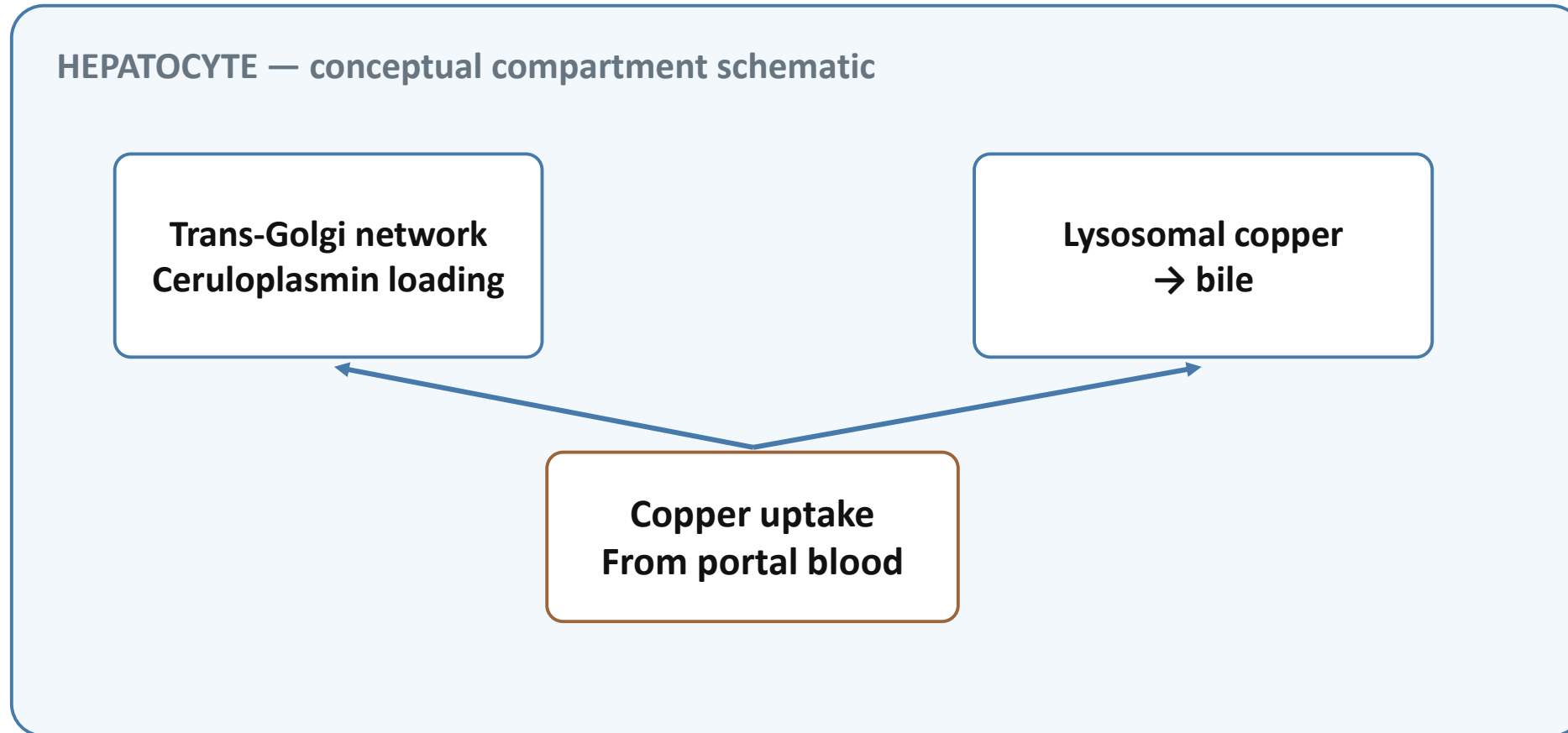
Excretory destination

Intracellular sequestration in lysosomes

Delivery toward canalicular bile

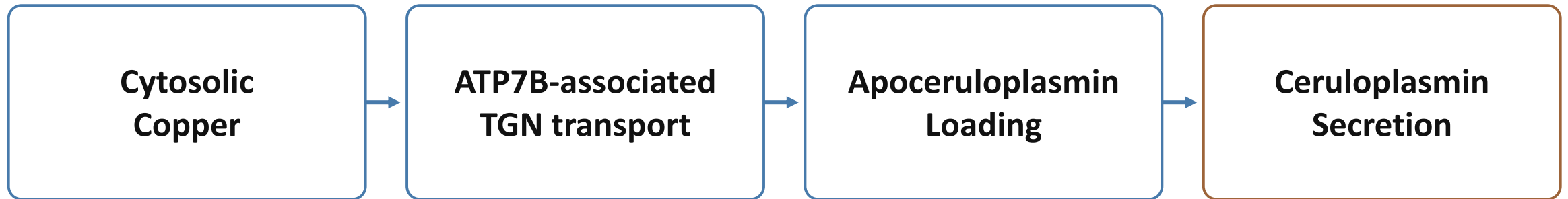
Elimination in feces

ATP7B coordinates hepatocyte copper handling



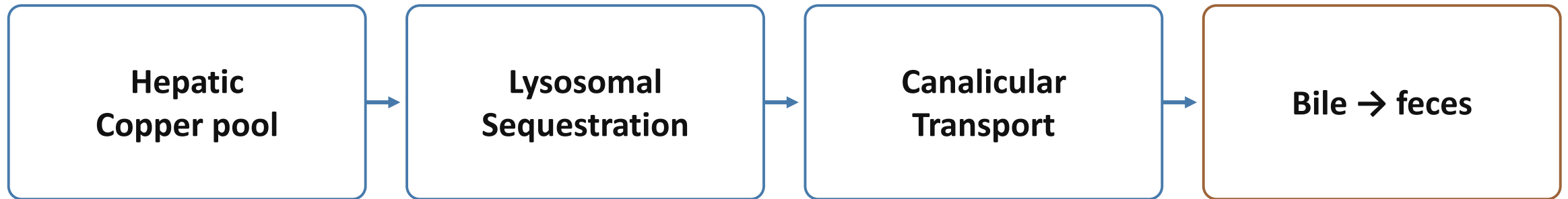
ATP7B enables copper processing and biliary elimination

The trans-Golgi pathway loads ceruloplasmin



Ceruloplasmin forms when copper is incorporated into apoceruloplasmin.

Biliary copper elimination



The biliary pathway is essential for disposing of copper not routed into ceruloplasmin.

Ceruloplasmin carries most plasma copper

- The textbook attributes approximately 90–95% of plasma copper to ceruloplasmin.
- It is produced following copper incorporation into apoceruloplasmin.
- A reduced ceruloplasmin pool can lower total measured serum copper.
- Total circulating copper and toxic free-copper burden are therefore different concepts.

Normal handling versus ATP7B dysfunction

Functional ATP7B

Copper incorporation into ceruloplasmin proceeds.

Copper can be excreted into bile.

Hepatocyte copper retention is limited.

ATP7B loss of function

Ceruloplasmin loading and secretion fall.

Biliary copper transport is impaired.

Copper progressively accumulates in hepatocytes.

Autosomal recessive inheritance

- Disease arises from pathogenic changes affecting both ATP7B alleles.
- ATP7B encodes a transmembrane, copper-transporting ATPase.
- Normal hepatic transport requires sufficient ATP7B function.
- Inherited susceptibility is present before overt clinical injury.

Compound heterozygosity is common

Genotype organization

Patients may carry different ATP7B mutations on the two alleles.

This is termed compound heterozygosity.

Both alleles can contribute to deficient ATP7B function.

Implication for molecular testing

A single detected variant may not establish the biallelic disease genotype.

Variant pathogenicity matters, not merely variant presence.

Clinical and biochemical findings remain relevant.

Not every ATP7B sequence variant is pathogenic

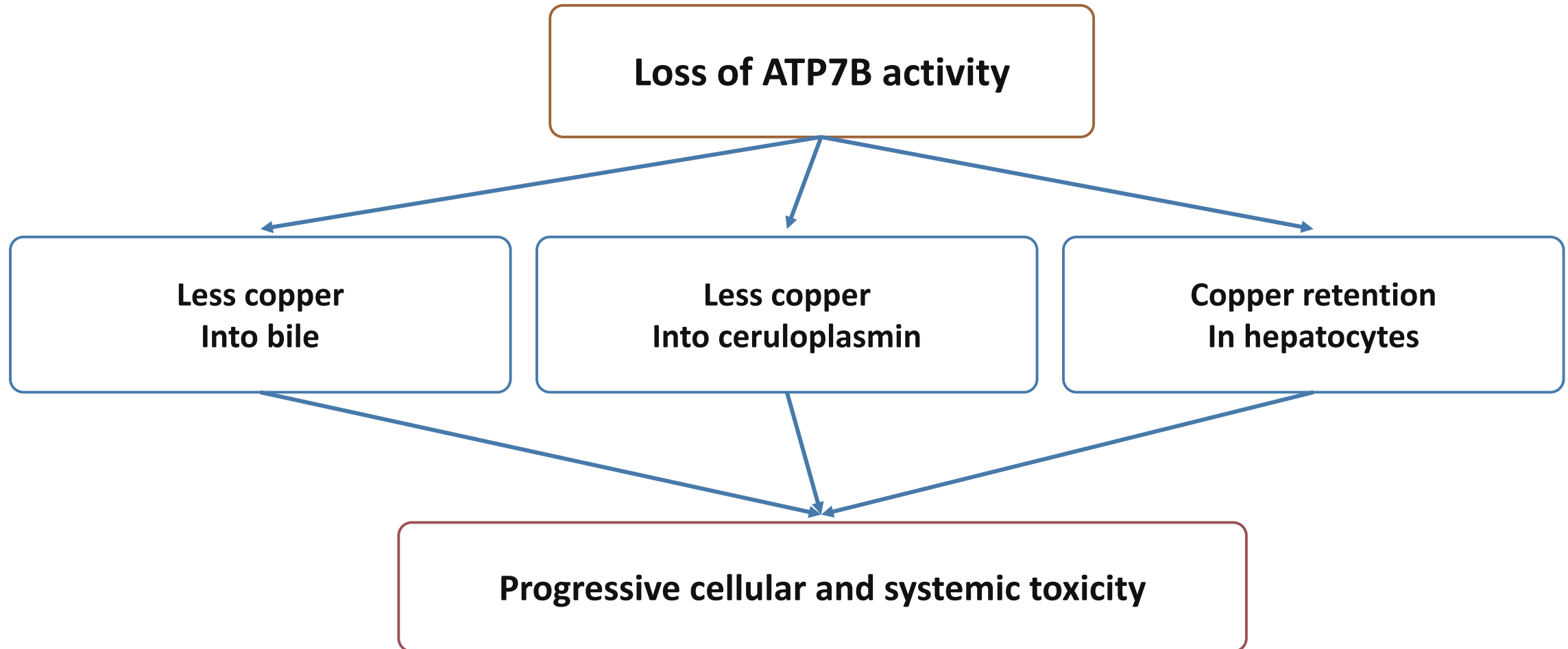
Sequence variation ≠ confirmed disease mechanism

More than 300 identified variants but explicitly notes that not all cause Wilson disease.

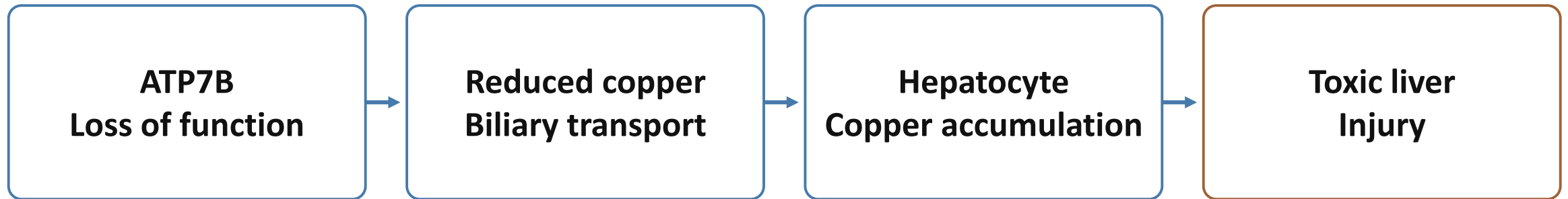
Frequency estimates

Measure	Robbins 11th-edition estimate	Interpretation
Mutated ATP7B allele frequency	Approximately 1:100	Allele frequency, not disease prevalence
Disease prevalence	Approximately 1:30,000–1:50,000	Population-level estimate
Approximate U.S. patient number	About 9,000	Book estimate; not a live registry count

Two primary consequences of ATP7B deficiency

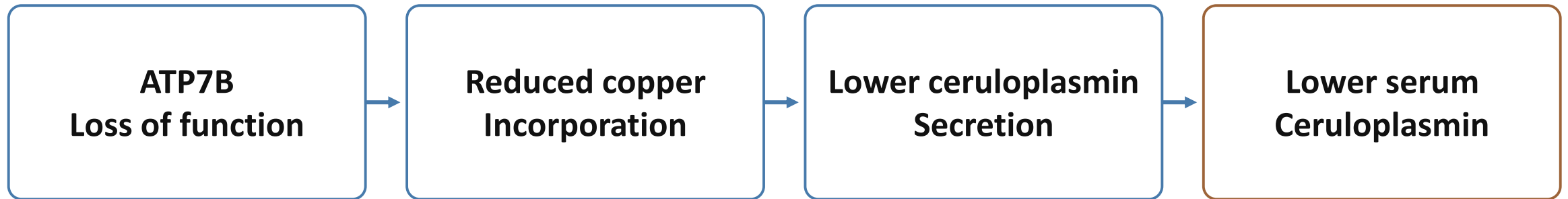


Defective biliary excretion drives retention



Failure of excretion is central: The body cannot eliminate the accumulating hepatic copper efficiently.

Defective ceruloplasmin loading alters blood tests



Serum ceruloplasmin falls for a mechanistic reason; The test indirectly reflects impaired hepatic processing.

Total serum copper may be misleading

Serum total copper

Includes the large ceruloplasmin-bound fraction.

May be reduced when circulating ceruloplasmin is depleted.

A low value does not exclude toxic tissue copper accumulation.

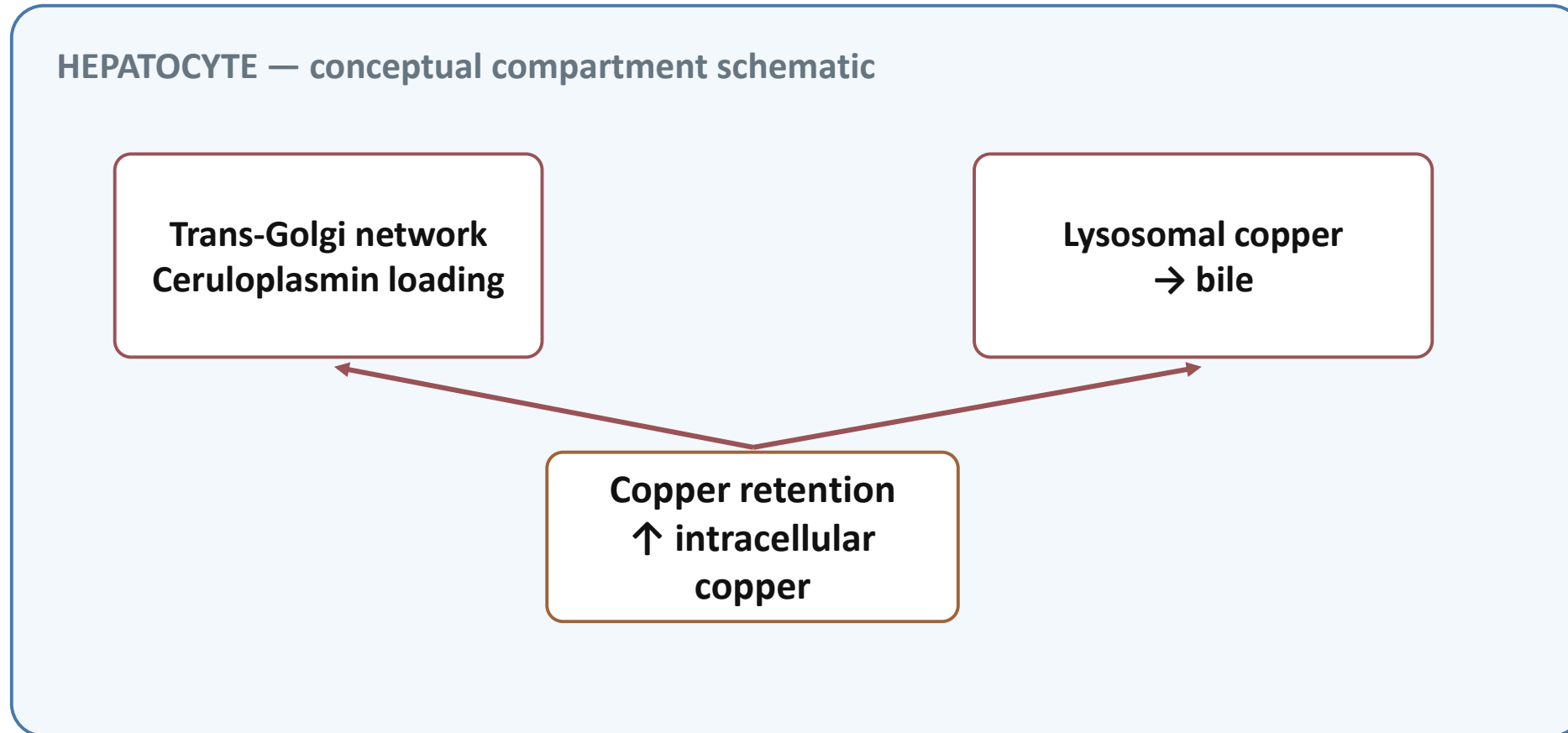
Tissue or nonceruloplasmin copper

Hepatocyte stores rise during impaired elimination.

Copper escapes injured hepatocytes into blood.

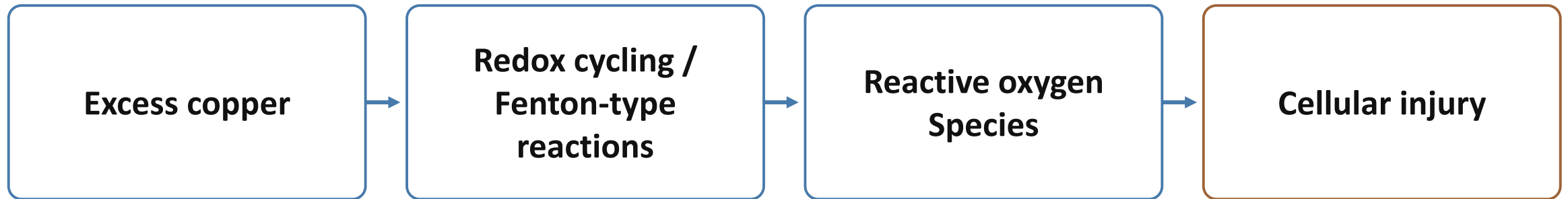
Free copper can exert systemic toxicity.

The hepatic copper paradox



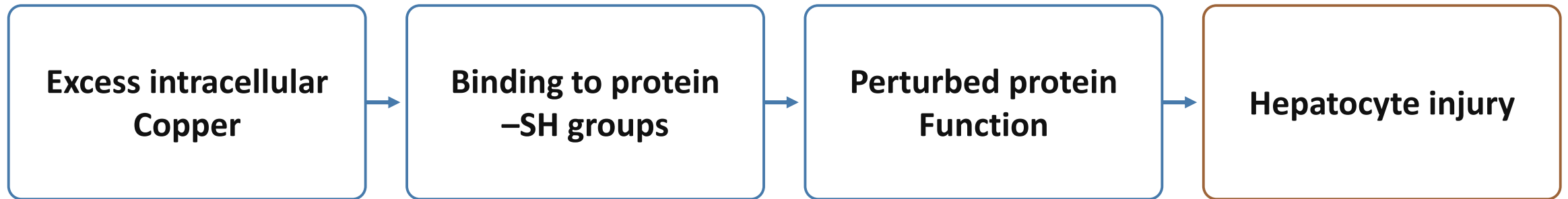
ATP7B loss of function → both exit pathways impaired

Copper promotes free-radical injury



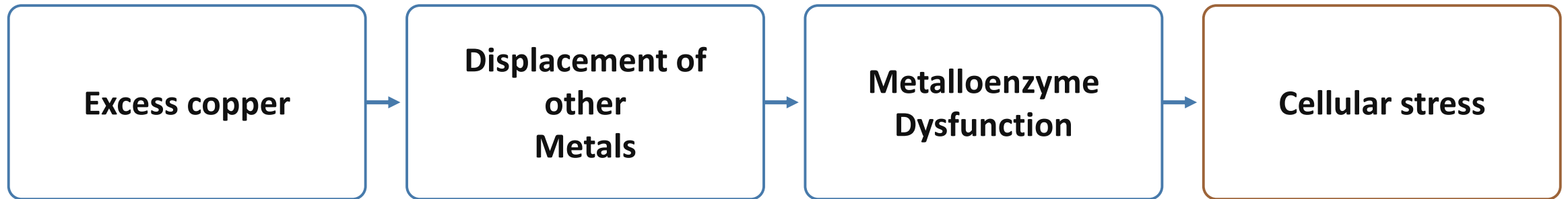
Copper catalyzes oxidative chemistry that can damage hepatocyte macromolecules.

Copper binds sulfhydryl groups



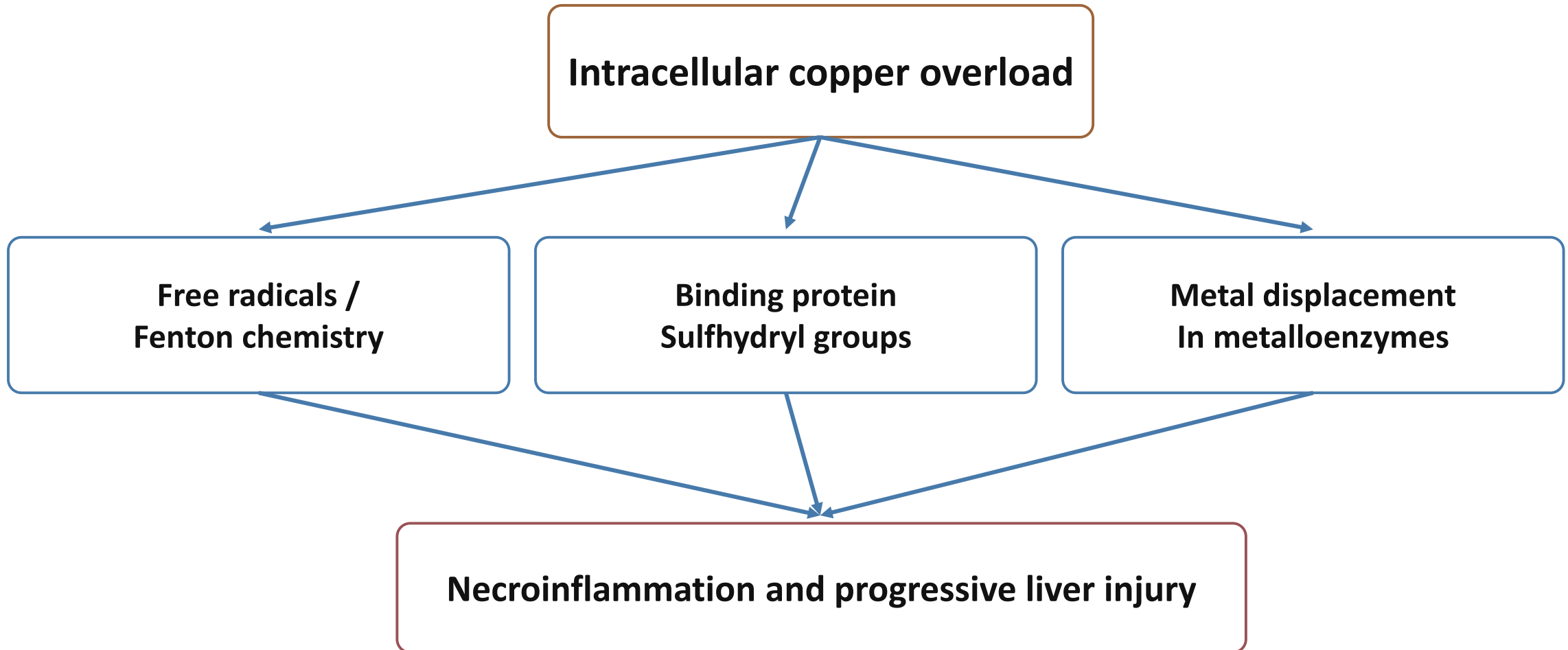
Interaction with sulfhydryl-bearing proteins is a second mechanism of copper toxicity.

Copper disrupts hepatic metalloenzymes

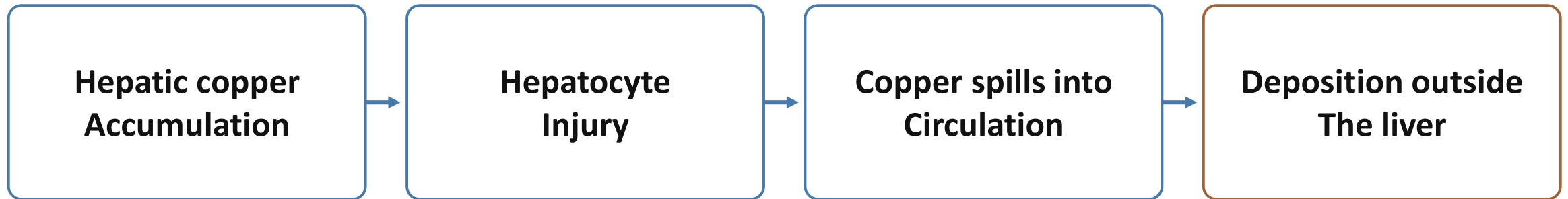


The result is loss of normal enzyme function rather than only copper-induced oxidation.

Three parallel routes to hepatocyte damage



Damaged hepatocytes redistribute copper



Organ-specific injury emerges after the primary defect in hepatocyte copper handling.

Urinary copper increases but does not rescue balance

Renal handling

Excess circulating nonceruloplasmin copper is excreted in urine.

The increase can be marked.

Urinary excretion is diagnostically informative.

Insufficient compensation

The kidney cannot fully prevent tissue deposition.

Hepatic biliary clearance remains impaired.

Copper continues to accumulate in susceptible organs.

Why the brain and cornea are affected

Liver

Intracellular copper

→ inflammation, injury, fibrosis

Brain

Basal ganglia injury

→ movement and other neurologic symptoms

Eye

Descemet membrane copper

→ Kayser–Fleischer ring

A staged model of Wilson disease pathogenesis

1. Inherited ATP7B loss of function



2. Impaired copper secretion and biliary elimination



3. Hepatic copper retention and tissue injury



4. Copper redistribution with multi-organ manifestations

Hepatic morphology spans a broad spectrum

Morphologic pattern

Mild fatty change $\pm$ focal hepatocyte necrosis

Acute massive injury / acute liver failure

Chronic hepatitis with steatohepatitis-like injury

End-stage cirrhosis

Interpretive caution

No single morphology is pathognomonic.

Several patterns mimic other common hepatitides.

Interpret histology together with copper studies.

Steatosis may be an early hepatic manifestation

- Fatty change is part of the described Wilson disease spectrum.
- Steatosis can coexist with focal hepatocyte necrosis.
- Its presence alone cannot establish the diagnosis.
- Copper accumulation provides etiologic context for an otherwise nonspecific morphology.

Focal hepatocyte necrosis marks cell injury

Morphologic finding

Scattered necrotic hepatocytes may accompany steatosis.

Necrosis reflects injury to hepatocytes.

Its extent varies markedly among patients.

Mechanistic linkage

Copper-mediated free-radical generation

Copper-protein and metalloenzyme interactions

These mechanisms provide biological reasons for cell injury.

Acute liver failure can resemble viral hepatitis

Wilson-related acute presentation

Acute severe hepatocellular injury

Potential clinical picture of liver failure

Etiology: Impaired inherited copper handling

Acute viral hepatitis

Potentially similar acute injury pattern

Clinical and morphologic overlap

Etiology requires other evidence

Chronic hepatitis includes portal inflammation

- Chronic Wilson disease can show moderate-to-severe portal inflammation.
- Inflammation occurs in the setting of hepatocellular copper toxicity.
- Associated hepatocyte necrosis can be prominent.
- The pattern is not sufficiently specific without disease-directed workup.

Chronic hepatitis may mix injury patterns

Component	Described Wilson-associated finding	Why it matters
Necroinflammatory	Portal inflammation and hepatocyte necrosis	Can resemble chronic hepatitis
Fatty	Hepatocellular steatosis	Can resemble steatotic liver disease
Steatohepatitic	Ballooning and Mallory hyaline	Can suggest other causes of steatohepatitis
Fibrosing	Perisinusoidal fibrosis → cirrhosis	Supports chronic progressive injury

Ballooned hepatocytes reflect steatohepatitic injury

Reported morphology

Hepatocyte ballooning is described in chronic Wilson disease.

It may coexist with fat and inflammation.

The finding reflects hepatocellular injury.

Diagnostic caution

Ballooning is not specific to Wilson disease.

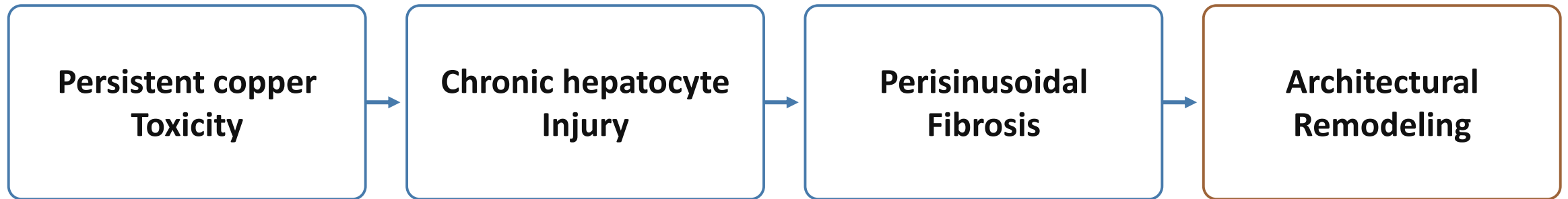
A steatohepatitic pattern must not automatically be assigned a metabolic or alcohol-associated cause.

Consider etiology across clinical and laboratory data.

Mallory hyaline occurs in Wilson disease

- Prominent Mallory hyaline in some chronic cases.
- Its coexistence with ballooning produces a steatohepatitis-like pattern.
- Mallory hyaline is not uniquely associated with alcohol-related injury.
- Pathogenetic interpretation requires the broader copper-metabolism context.

Perisinusoidal fibrosis shows chronic progression



Fibrosis indicates a sustained process rather than isolated acute cytotoxicity.

Cirrhosis is an advanced hepatic outcome

1. Variable early injury: Steatosis and necrosis



2. Chronic portal inflammation and steatohepatic change



3. Progressive fibrosis of hepatic parenchyma



4. Cirrhosis and potentially serious hepatic dysfunction

Copper staining has diagnostic limitations

Histochemical copper stain is neither sensitive nor specific

A positive stain alone does not prove Wilson disease; A negative stain does not exclude it.

Histopathologic diagnosis requires etiologic correlation

What a liver biopsy can show

Steatosis, necrosis, chronic hepatitis

Ballooning, Mallory hyaline, fibrosis

Potential cirrhotic architecture

What routine morphology cannot alone prove

An ATP7B-associated metabolic defect

Specificity of a steatohepatitic pattern

A definitive Wilson diagnosis without biochemical or other correlation

Clinical onset is variable

Feature	Description in Robbins
Reported onset range	6–40 years
Reported mean age	11.4 years
Presentations	Liver disease, movement disorder, psychiatric symptoms, or hemolysis
Clinical expression	Extremely variable across patients

Hepatic and neurologic presentations may diverge

Hepatic-dominant presentation

Acute liver disease

Chronic liver disease

Fatty change, hepatitis, or cirrhosis

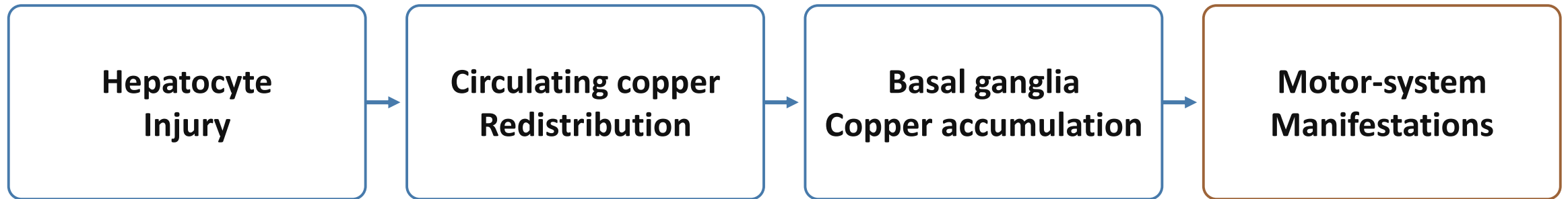
Neurologic-dominant presentation

Movement abnormalities

Rigid dystonia or coordination impairment

Often Kayser–Fleischer rings

Basal ganglia injury explains movement disorders



The primary metabolic defect is hepatic, but clinical disability may be neurological.

Movement-disorder phenotypes are heterogeneous

Phenotype	Clinical manifestations described
Tremor	Involuntary rhythmic movement
Coordination deficit	Poor coordination
Hyperkinetic	Chorea or choreoathetosis
Dystonic / rigid	Spastic dystonia, rigidity and abnormal gait

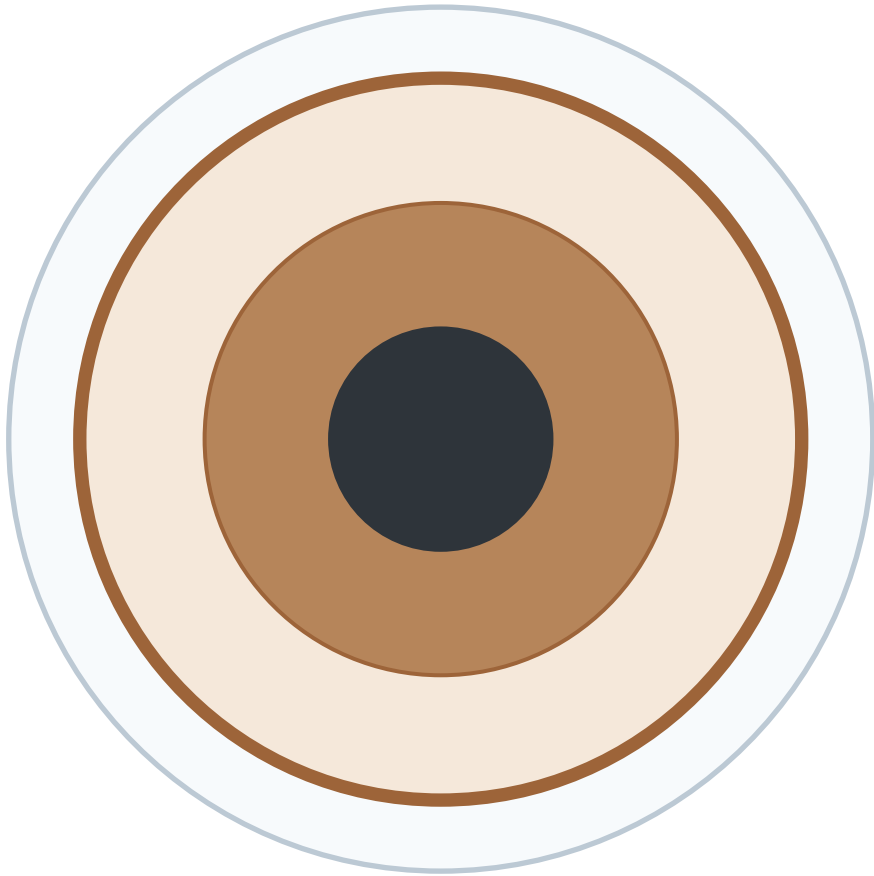
Rigid dystonia can dominate the presentation

- Spastic dystonia can produce persistent abnormal postures and stiffness.
- Masklike facies and generalized rigidity are described.
- Gait disturbance can be a prominent sign.
- Copper toxicity in basal ganglia links these signs with the systemic disorder.

Psychiatric symptoms are part of the phenotype

- The source explicitly includes psychiatric manifestations.
- Neuropsychiatric features may accompany or complicate motor symptoms.
- Recognition requires thinking beyond isolated hepatology.
- A compatible hepatic or ocular finding changes diagnostic suspicion.

Kayser–Fleischer ring: Anatomy and appearance



Schematic—not a clinical slit-lamp photograph

Anatomical localization

Peripheral cornea / limbus

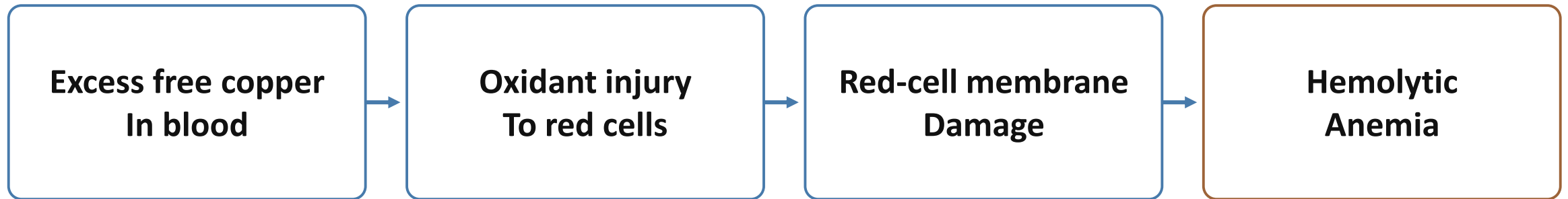
Copper in Descemet membrane

Green-to-brown corneal ring

Kayser–Fleischer ring is especially linked to neurologic disease

- Green-to-brown copper deposits form at the corneal limbus.
- The copper accumulates within Descemet membrane.
- Rings in nearly all patients with neurologic involvement.
- Slit-lamp examination makes the finding diagnostically useful.

Hemolytic anemia results from oxidant injury



Copper-related hemolysis illustrates extrahepatic toxicity without direct hepatic histologic involvement.

Diagnostic assessment integrates several domains

Domain	Evidence sought	Purpose
Serum biochemical	Decreased ceruloplasmin	Indirect marker of defective hepatic loading
Tissue copper	Increased hepatic copper content	Direct tissue-burden assessment
Renal excretion	Increased urinary copper	Evidence of excess mobile copper
Ophthalmic	Kayser–Fleischer ring	Accessible extrahepatic deposition sign
Genetic	ATP7B sequencing	Clarify indeterminate biochemical cases

Serum ceruloplasmin: Useful but not definitive

What a low level supports

ATP7B-dependent copper incorporation is impaired.

Hepatic secretion of ceruloplasmin decreases.

Compatible evidence for Wilson disease.

Why a normal level cannot safely exclude it

Liver injury may raise serum ceruloplasmin.

Clinical context can confound the biochemical result.

Other diagnostic modalities may be needed.

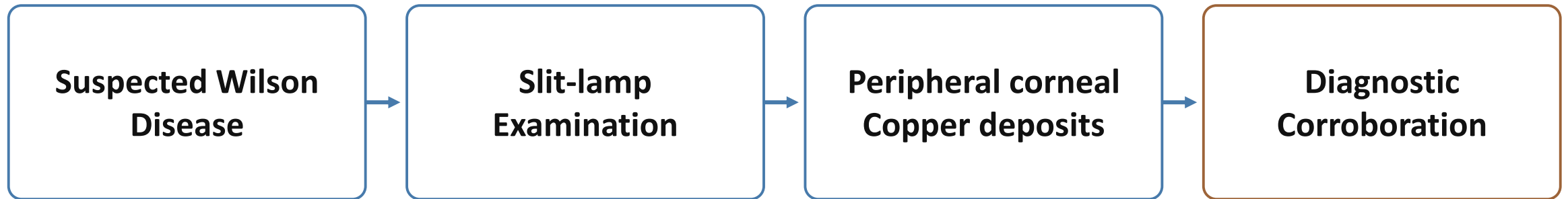
Hepatic copper content measures tissue accumulation

- Liver copper content interrogates the primary site of metal retention.
- Increased hepatic content as its most sensitive and accurate test.
- A tissue value must be interpreted in the diagnostic context.
- No unverified numeric threshold is assumed in this source-based lecture.

Urinary copper reflects excess circulating copper

- Hepatocellular injury increases nonceruloplasmin-bound circulating copper.
- Urinary copper excretion rises substantially.
- The textbook calls increased urinary copper its most specific test.
- Excretion is still insufficient to prevent multi-organ deposition.

Slit-lamp examination provides visual evidence



A ring supports the diagnosis, particularly when neurologic involvement is present.

ATP7B sequencing is a resolving test

When to consider sequencing

Biochemical tests are indeterminate.

Ceruloplasmin may be altered by intercurrent liver injury.

Genetic evidence can help resolve the diagnosis.

How to interpret sequencing

Pathogenicity is not guaranteed by any sequence change.

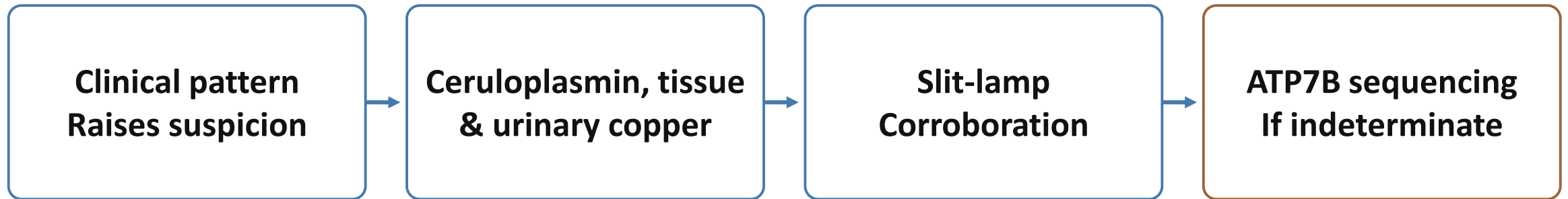
Compound heterozygosity is common.

Genotype should be read with clinical and biochemical phenotype.

Diagnostic pitfalls are predictable

Pitfall	Why it occurs	Safer interpretation
Low total serum copper	Reduced ceruloplasmin-bound fraction	Do not equate with absence of tissue copper
Normal ceruloplasmin	May rise in the setting of liver injury	Avoid single-test exclusion
Nonspecific hepatic histology	Overlaps viral and steatotic disorders	Correlate with copper studies
Copper stain negative	Histochemical stain lacks sensitivity	Do not exclude on stain alone

Source-based diagnostic reasoning sequence



The sequence is a teaching synthesis, not a formal diagnostic scoring system or published guideline.

Treatment targets copper burden or entry

Chelator strategy

D-penicillamine or trientine

Long-term drug-based copper reduction

Targets excessive copper burden

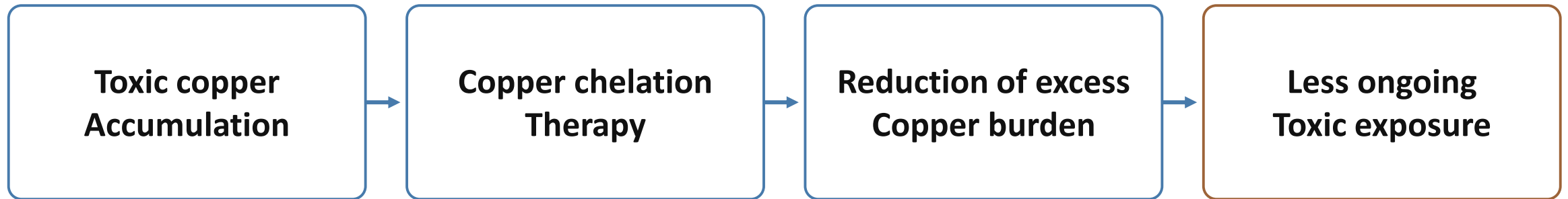
Zinc strategy

Reduces uptake of dietary copper in intestine

Limits addition of newly absorbed copper

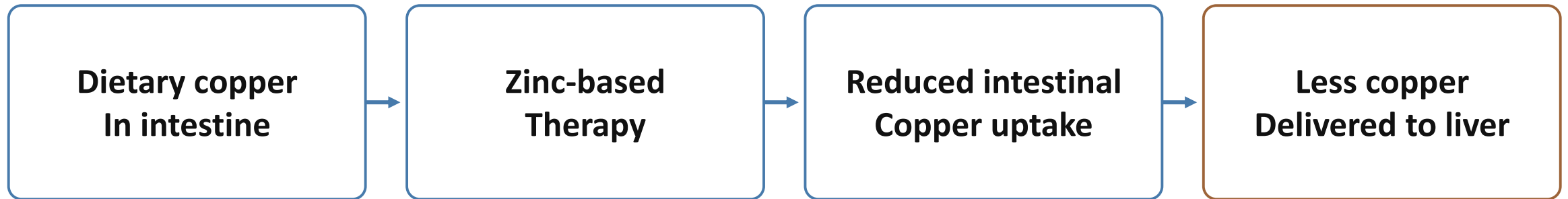
Targets intestinal copper entry

Copper chelation interrupts progressive toxicity



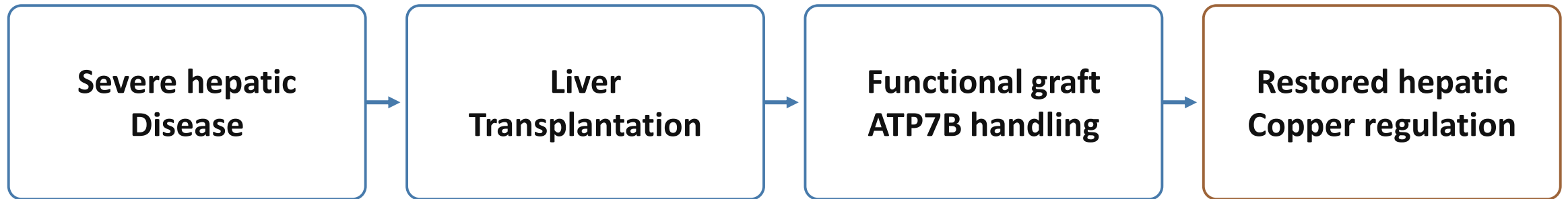
Early recognition and sustained therapy are emphasized.

Zinc decreases intestinal copper uptake



This contrasts with chelation: Zinc addresses incoming copper rather than only existing burden.

Transplantation can correct hepatic transport



Transplantation as potentially curative in severe disease.

Clinical application: Unexplained hepatic injury

HYPOTHETICAL TEACHING SCENARIO

An adolescent develops persistent hepatocellular injury with steatosis and features of chronic hepatitis. The history does not identify a clear acquired cause.

Which inherited transport disorder belongs in the differential, and why can histology alone be insufficient?

Case discussion: Liver pathology

Reasoning from the morphology

Wilson disease should be considered as an inherited copper-transport disorder.

Steatosis, portal inflammation, necrosis, and steatohepatitic change are overlapping patterns.

Biochemical copper studies and additional clinical evidence are needed.

Clinical application: Extrapyrarnidal presentation

HYPOTHETICAL TEACHING SCENARIO

A young patient has tremor, rigidity, gait difficulty, and a peripheral green-brown corneal ring on ophthalmic examination.

Where is copper depositing, and which metabolic defect unifies the neurologic and ocular findings?

Case discussion: Systemic copper deposition

The unifying mechanism

Loss of ATP7B prevents effective hepatic copper processing and biliary elimination.

Injured hepatocytes release copper into the circulation.

Copper accumulates in basal ganglia and Descemet membrane, producing the findings.

Five high-yield conclusions

- ATP7B dysfunction creates two defects: Reduced biliary excretion and reduced ceruloplasmin loading.
- Copper injures hepatocytes through oxidants, thiol interactions, and metalloenzyme disruption.
- Hepatic morphology is broad and can imitate viral or steatohepatitic disease.
- Neurologic movement disorders, corneal rings, and hemolysis reflect extrahepatic toxicity.
- Diagnosis is integrative; Chelation, zinc, and transplantation address different aspects of disease.

Primary reference and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Wilson Disease, within Liver and Gallbladder: disease text, morphology, clinical features.
- Copper metabolism and ATP7B transport mechanism: accompanying textbook figure caption.
- No chapter PDF or licensed histopathology micrographs were supplied; diagrams are editable original teaching schematics.
- Diagnostic numerical cutoffs, drug doses, and current guideline algorithms are intentionally not introduced.