

Hemochromatosis

Iron overload: mechanism, morphology and clinical consequences

Pathology lecture

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Learning objectives

- Explain how hepcidin and ferroportin maintain iron balance.
- Compare hereditary and secondary mechanisms of iron overload.
- Recognize the organ pathology, clinical syndrome and diagnostic approach.
- Explain the rationale and limitations of iron-depleting treatment.

Hemochromatosis: Defining abnormality

- An iron-overload disorder characterized by excessive accumulation of tissue iron.
- Hereditary forms primarily involve inappropriate intestinal absorption.
- Excess iron progressively injures the liver, pancreas and other organs.

Two broad pathways to systemic iron overload

Hereditary hemochromatosis

Inherited disturbance of iron regulation

Iron absorption remains inappropriately high

Long presymptomatic accumulation

Secondary hemochromatosis

Repeated transfusion or other acquired burden

Ineffective erythropoiesis can increase absorption

Tissue deposition may also cause organ injury

Normal and severe total-body iron burdens

2–6 g

Normal adult total-body iron pool

>50 g

Possible iron pool in severe
hemochromatosis

The liver is a major iron reservoir

≈ 0.5 g

Iron ordinarily stored in the adult liver

$> \frac{1}{3}$

Of total body iron may accumulate in
the liver in severe disease

Principal tissue targets of iron overload

Liver

Cirrhosis and cancer risk

Pancreas

Islet injury and fibrosis

Heart

Arrhythmia and
cardiomyopathy

Endocrine glands

Hypogonadism and hormone
loss

Joints

Arthropathy and synovitis

Skin

Characteristic dark
pigmentation

The classic advanced clinical pattern

- Micronodular cirrhosis, diabetes and abnormal skin pigmentation characterize fully developed disease.
- These findings usually emerge after prolonged iron accumulation.
- An individual diagnosed early may have none of the classic manifestations.

Why hereditary disease often presents late

Long latency

Tissue iron accumulates gradually throughout life.



Progressive injury

Oxidant damage and fibrosis develop slowly.



Clinical syndrome

Symptoms typically emerge after years of accumulation.

Age and sex patterns reflect cumulative exposure

- Textbook pattern: Symptoms commonly begin in the fourth to fifth decades in men.
- Menstruation slows net accumulation before menopause in many women.
- Presentation and penetrance vary; Genotype is not equivalent to disease.

Iron excess converts a nutrient into a toxin

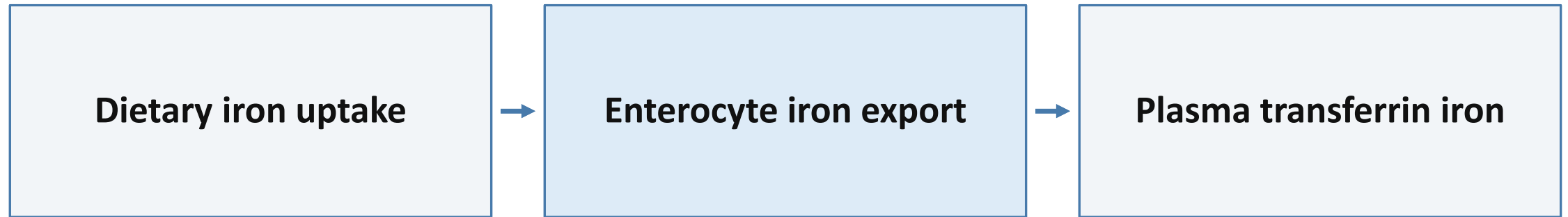


Iron-catalyzed free radical chemistry links iron accumulation to parenchymal injury.

Three major mechanisms of hepatic injury

- Iron-catalyzed lipid peroxidation damages cell membranes.
- Hepatic stellate-cell activation promotes collagen deposition.
- Iron and reactive oxygen species can injure DNA and favor carcinogenesis.

Normal control of dietary iron absorption



The critical regulated gate is ferroportin-mediated iron release to plasma.

Hepcidin is the central systemic regulator

- Hepcidin is a liver-derived peptide encoded by HAMP.
- It regulates iron movement into plasma by acting on ferroportin.
- Its concentration integrates iron availability, inflammation and erythropoietic demand.

Hepcidin restricts iron release



The response limits release from enterocytes and iron-recycling macrophages.

Signals that increase hepcidin synthesis

- Increased iron availability stimulates the liver to raise hepcidin.
- Inflammatory cytokines also upregulate HAMP transcription.
- Reduced ferroportin activity subsequently limits iron entry into plasma.

Signals that decrease hepcidin synthesis

- Iron deficiency lowers HAMP transcription.
- Hypoxia reduces hepcidin production.
- Erythroferrone from erythroblasts suppresses hepcidin during erythropoietic drive.

Ferroportin operates at two important sites

Intestinal enterocyte

Exports recently absorbed dietary iron

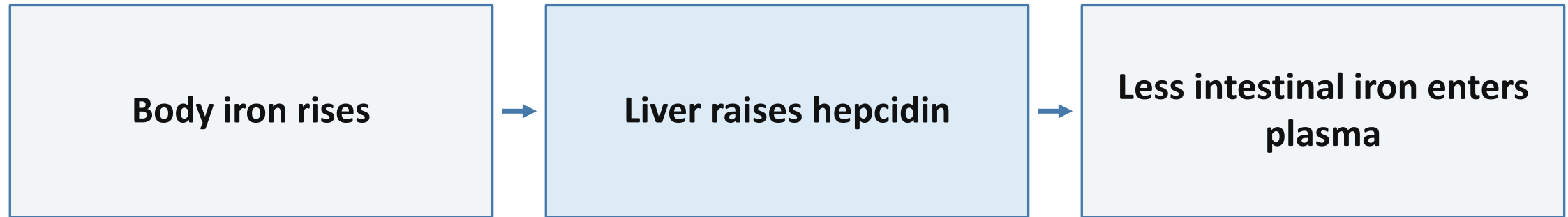
Hepcidin blocks onward transfer to blood

Macrophage

Releases iron recovered from erythrocytes

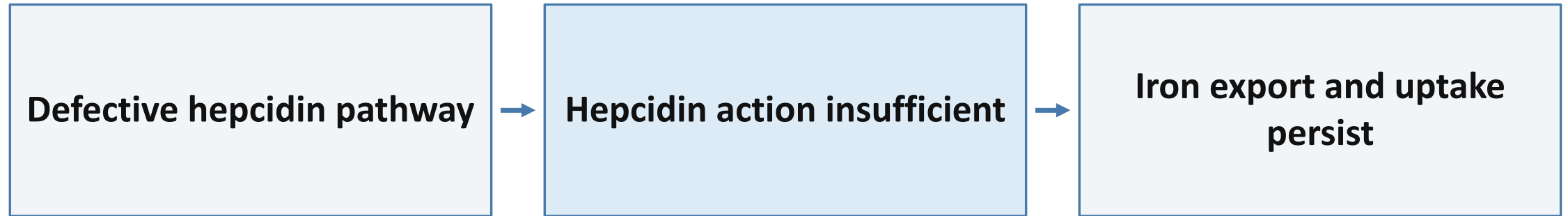
Hepcidin favors intracellular retention

A normal feedback loop protects iron balance



Negative feedback normally restrains further iron acquisition.

Hereditary iron overload breaks this feedback

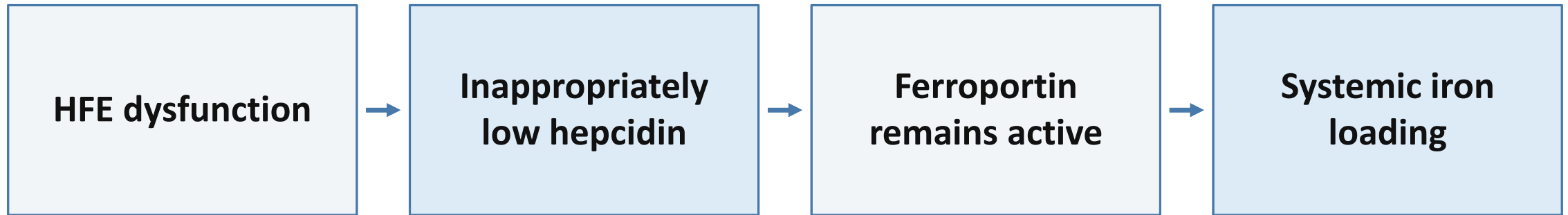


The liver fails to apply the expected brake despite high iron stores.

HFE participates in hepatic iron sensing

- HFE encodes an HLA class I–like protein.
- Normal HFE signaling helps stimulate hepatic hepcidin synthesis.
- Loss of HFE function permits excessive iron absorption.

HFE loss of function: Causal chain



Genes linked to hereditary hemochromatosis

Gene / protein	Textbook-associated phenotype
HFE	Most common adult-onset hereditary form
TFR2 (transferrin receptor 2)	Rare hereditary iron overload
HAMP (hepcidin)	Rare juvenile form
HJV (hemojuvelin)	Rare juvenile form
SLC40A1 (ferroportin)	Rare ferroportin-associated form

Most adult hereditary cases involve HFE

- Adult-onset hereditary hemochromatosis is usually HFE-associated.
- HFE encodes an upstream component of iron-responsive hepcidin regulation.
- Disease develops when iron accumulation ultimately overwhelms tissue tolerance.

Juvenile forms involve HAMP or HJV

- HAMP encodes the circulating inhibitor hepcidin.
- HJV encodes hemojuvelin, an upstream regulator of hepcidin synthesis.
- Loss-of-function variants in either gene can produce juvenile hemochromatosis.

Ferroportin has its own genetic category

- SLC40A1 encodes the iron-export channel ferroportin.
- Rare SLC40A1-associated hereditary hemochromatosis.
- Ferroportin disease should not simply be equated with an HFE defect.

HFE C282Y: The principal textbook variant

C282Y

Cysteine → tyrosine substitution at
amino acid 282

≥70%

Proportion of diagnosed hereditary
cases attributed to C282Y in the text

HFE H63D is a second associated variant

- H63D denotes histidine → aspartate substitution at amino acid 63.
- H63D has a worldwide distribution.
- Its disease penetrance is lower than that of C282Y homozygosity.

The distribution of HFE variants differs

C282Y

Largely confined to populations of European ancestry

Textbook reports about 0.45% homozygosity in European descent

H63D

Worldwide distribution

Homozygosity and C282Y/H63D compound heterozygosity have relatively low penetrance

Genotype is not synonymous with clinical disease

0.45%

C282Y homozygosity in people of European descent; Textbook estimate

≈10%

C282Y-homozygous men with evidence of overload; Textbook estimate

Why a pathogenic genotype may remain silent

- Inheritance establishes susceptibility, not a fixed trajectory of tissue damage.
- Observed penetrance depends on genotype, sex and cumulative iron loading.
- Family evaluation should distinguish a risk genotype from existing organ injury.

A pathologic sequence begins in hepatocytes

Early

Golden-yellow iron granules
in periportal hepatocytes.



Increasing load

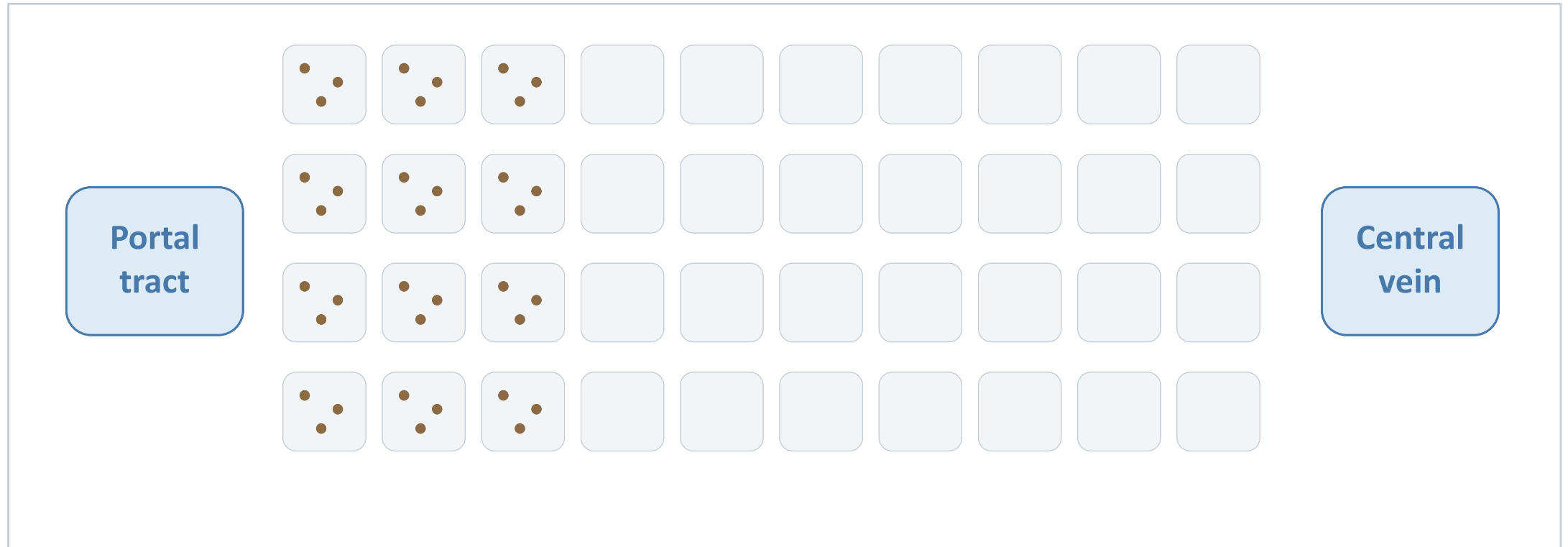
Deposits spread through
more of the hepatic lobule.



Advanced

Additional biliary and Kupffer-
cell deposits accompany
fibrosis.

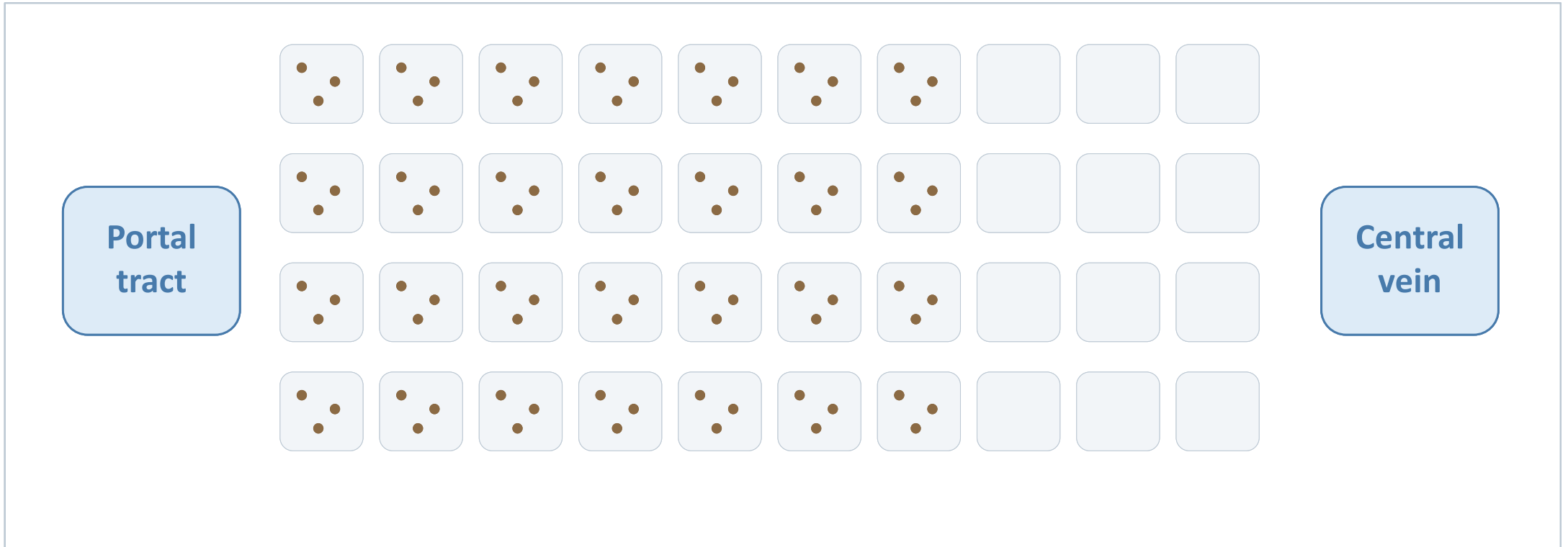
Earliest hepatic iron: Periportal accentuation



Schematic — not a histologic specimen

Iron initially predominates in hepatocytes closest to the portal tract.

Iron deposition extends across the lobule



Schematic — not a histologic specimen

The distribution broadens as total hepatic iron loading increases.

Advanced overload becomes widespread



Schematic — not a histologic specimen

Late-stage iron accumulation includes additional cell compartments.

Prussian blue demonstrates storage iron

- Hemosiderin appears as golden-yellow cytoplasmic granules in routine sections.
- Perls / Prussian blue reaction makes stainable tissue iron blue.
- Staining supports recognition of deposition; Interpretation requires tissue context.

Iron toxicity need not provoke marked inflammation

- Hemochromatosis produces direct hepatocellular toxicity.
- Inflammation is characteristically absent or inconspicuous description.
- Hepatic fibrosis may develop despite limited inflammatory infiltrates.

Gross liver changes evolve with time

Early disease

Slightly enlarged liver

Dense parenchyma

Chocolate-brown discoloration

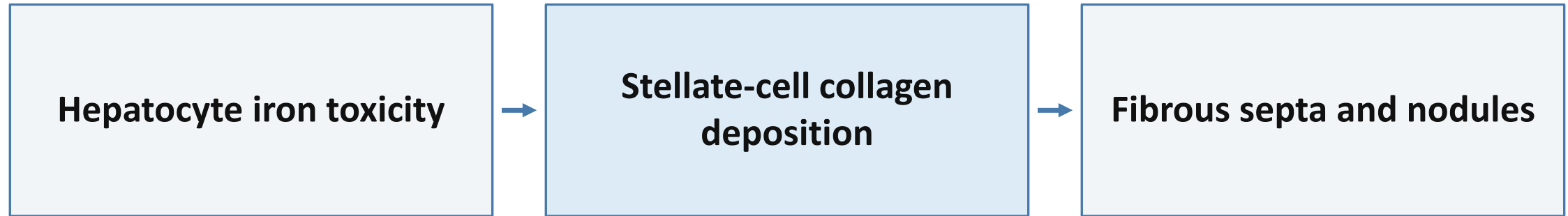
Advanced disease

Fibrous septa and nodular remodeling

Small, shrunken micronodular cirrhotic liver

Dark brown to almost black parenchyma

Iron overload progresses to micronodular cirrhosis



Cirrhosis is a late morphologic consequence

- Progressive iron injury can eventually produce bridging fibrous septa.
- The architectural endpoint is micronodular cirrhosis.
- Early iron deposition and established cirrhosis must not be treated as synonymous.

Pancreatic iron explains glucose dysregulation

- Iron accumulation can produce pancreatic parenchymal atrophy.
- Interstitial fibrosis accompanies advanced pancreatic involvement.
- Injury to islet cells contributes to diabetes mellitus.

Cardiac hemosiderosis damages myocardium

- The heart may be enlarged and strikingly brown from hemosiderin.
- Myocardial iron accumulation can be associated with fibrosis.
- Clinical expressions include cardiomyopathy and arrhythmias.

Endocrine deposition contributes to hypogonadism

- Iron may affect the pituitary and other endocrine glands.
- Reduced gonadotropins and testosterone may lead to testicular atrophy.
- Patients may present with loss of libido, impotence or amenorrhea.

Skin discoloration is not simply stored iron

- Patients can develop a characteristic slate-gray appearance.
- Increased epidermal melanin production is a major contributor.
- The mechanism stimulating melanin is unresolved.

Iron-associated arthropathy



Calcium pyrophosphate crystal deposition contributes to disabling joint disease.

Morphologic findings predict multisystem symptoms

Hepatic fibrosis

Hepatomegaly and cirrhosis

Islet injury

Impaired glycemic control

Myocardial iron

Arrhythmia and failure

Pituitary effects

Sex-hormone deficiency

Synovial disease

Joint pain and pseudogout

Pigment changes

Abnormal skin coloration

Clinical recognition: Presenting complaints

- Patients may report abdominal pain, fatigue or unexplained hepatomegaly.
- Others present with diabetes, arthritis, cardiac abnormalities or gonadal symptoms.
- No single clinical manifestation is sufficiently specific in isolation.

The complete late syndrome is not required

- Cirrhosis, pigmentation, diabetes and cardiac involvement can coexist late.
- Routine biochemical investigations now identify many patients earlier.
- Absence of the classic tetrad does not exclude iron overload.

Liver cancer is a major long-term hazard

- Iron-mediated DNA damage and cirrhosis increase hepatocellular carcinoma risk.
- A marked elevation (200-fold) versus the general population.
- This textbook comparison is not a universal individual risk estimate.

Why risk may persist after iron removal

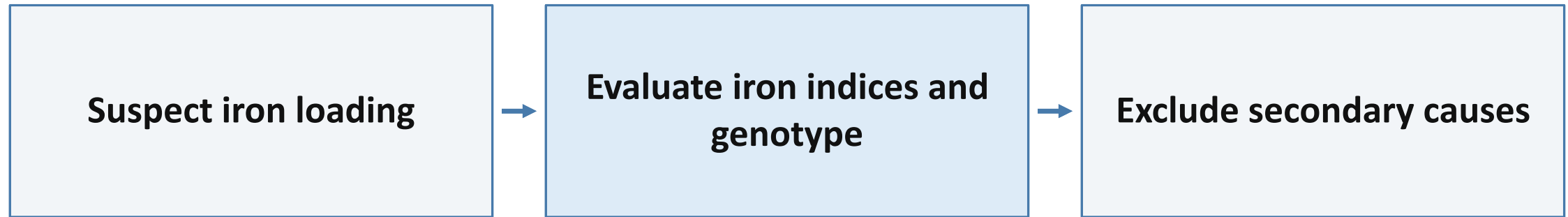


Removing iron cannot necessarily reverse mutations or established cirrhosis.

Early detection can precede irreversible damage

- Many affected individuals are detected before symptomatic cirrhosis.
- Iron-related blood tests trigger further evaluation.
- Molecular testing can establish a causative hereditary variant.

A practical diagnostic reasoning pathway



Assess the extent of organ involvement and fibrosis when indicated; This is a conceptual pathway, not a complete guideline.

Establish the cause, not only iron deposition

- Assess family history and potential inherited susceptibility.
- Investigate transfusion burden and ineffective erythropoiesis.
- Consider concurrent chronic liver disorders and other acquired causes.

Liver biopsy now has a more selective role

- Genetic testing and imaging reduce the need for routine hepatic iron quantification.
- Biopsy may still clarify fibrosis or other hepatic pathology.
- Interpret biopsy findings alongside biochemical and clinical evidence.

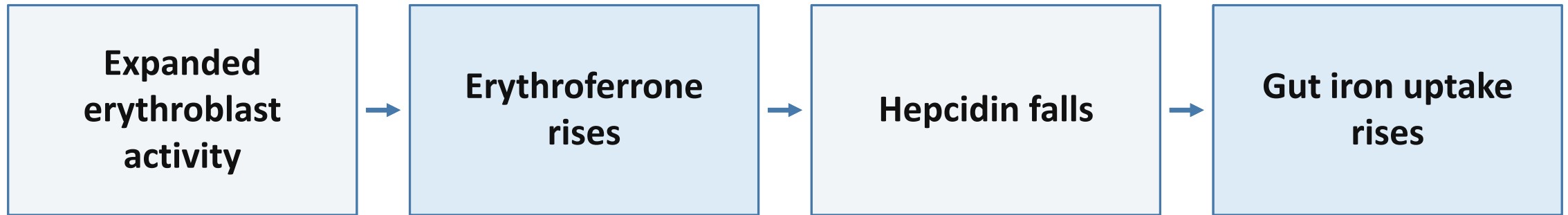
Familial identification supports prevention

- Relatives of an affected proband may carry a susceptibility genotype.
- Family testing identifies at-risk people before symptoms appear.
- Interpret genetic findings together with actual measures of iron loading.

Secondary causes of systemic iron loading

Mechanism / context	Textbook examples
Exogenous iron	Repeated red-cell transfusions; prolonged parenteral loading
Ineffective erythropoiesis	Thalassemia; myelodysplastic syndrome
Other hematologic disorders	Severe chronic hemolytic anemia; marrow failure
Other clinical contexts	Chronic liver disease; alcohol-associated disease; porphyria cutanea tarda

Ineffective erythropoiesis suppresses hepcidin



Repeated transfusions provide iron directly

- Each transfusion brings erythrocyte iron into the recipient.
- Long-term transfusion support can progressively raise tissue iron stores.
- The mechanism can coexist with absorption stimulated by ineffective erythropoiesis.

Cirrhosis itself may worsen iron absorption

- Loss of hepatocyte mass can reduce hepatic hepcidin production.
- This may allow increased intestinal iron uptake.
- Iron deposition in chronic liver disease does not automatically indicate an HFE disorder.

Inherited versus acquired: Pattern recognition

Hereditary pathway

Heritable defect affecting iron sensing or export

Inappropriate iron absorption over many years

Genotype and family assessment central

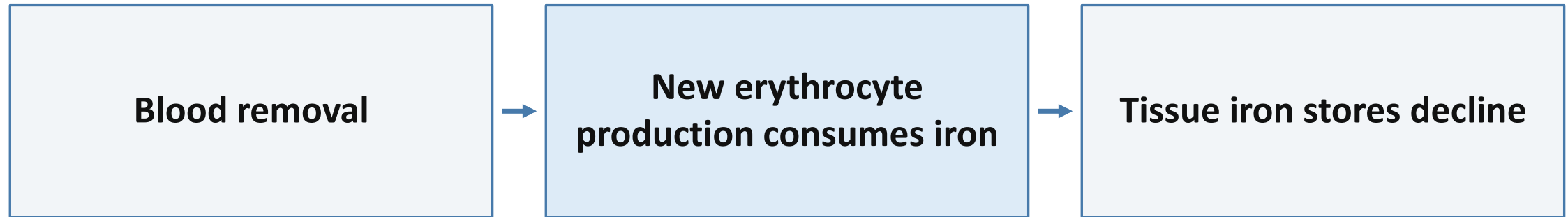
Acquired pathway

Transfusions and/or expanded erythropoietic drive

Absorption may rise through erythroferrone

Underlying hematologic/liver disease central

Phlebotomy reverses the positive iron balance



Regular venesection is the principal preventive treatment described for adult hereditary disease.

Treatment is most effective before organ injury

- Regular phlebotomy progressively depletes excessive stores.
- Timely treatment can prevent development or progression of iron-related disease.
- Already-established cirrhosis and cancer susceptibility may not fully reverse.

Secondary overload requires cause-specific care

- Transfusion-dependent patients may not be candidates for routine phlebotomy.
- Robbins Chapter 14 describes iron chelation in heavily transfused thalassemia.
- Treat the underlying hematologic condition and monitor systemic iron burden.

Case 1: Early hereditary disease

A 43-year-old man has elevated iron measures during an unrelated investigation. He has no cirrhosis, diabetes or skin pigmentation. Genetic evaluation identifies a relevant HFE variant.

What is the central physiologic defect?

Inadequate hepcidin-mediated inhibition of ferroportin permits iron accumulation.

Case 2: Transfusion-associated overload

A patient with a severe chronic anemia has received red-cell transfusions for many years and subsequently develops hepatic and cardiac iron deposition.

How does the iron accumulate?

Exogenous transfused erythrocyte iron can cause overload even without an inherited HFE defect.

Case 3: Joint disease and pigmentation

A middle-aged patient with unexplained diabetes presents with arthropathy and slate-gray skin pigmentation. Hepatic iron deposition is demonstrated.

Which associated tissue changes explain these findings?

Pancreatic islet injury, articular deposition / CPPD disease and increased epidermal melanin.

Case 4: Persistent cancer risk

A patient treated for hereditary hemochromatosis has much lower iron stores but already had established cirrhosis before venesection began.

Why does ongoing liver risk assessment remain relevant?

Prior DNA injury and established hepatic architecture damage may leave residual HCC susceptibility.

Five pathology principles to retain

- Hereditary hemochromatosis is primarily a disorder of iron regulation.
- Low hepcidin activity allows persistent ferroportin-mediated iron export.
- Periportal hepatocellular iron precedes diffuse deposition and cirrhosis.
- Target-organ injury explains diabetes, cardiomyopathy, endocrine disease and arthropathy.
- Early diagnosis and appropriate iron depletion protect organs.

Textbook references

Primary teaching source

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 18, pp. 771–773; complementary iron regulation in Chapter 14.

Supporting foundational section

Robbins, Cotran & Kumar. Chapter 14: iron metabolism, hepcidin–ferroportin regulation, and secondary iron loading in ineffective erythropoiesis.