

Anemia of **Chronic Inflammation**

Iron sequestration · hepcidin · impaired erythroid response

Pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

What the learner should explain

Why circulating iron is low even when iron remains stored

Why erythroid expansion is inadequate for the anemia

How IL-6, hepcidin, and ferroportin determine iron availability

How laboratory patterns distinguish inflammation from iron depletion

Where this anemia fits

Reduced red-cell production

Not primarily accelerated destruction

- The disorder among anemias of diminished erythropoiesis.
- Both iron supply to precursors and marrow proliferative drive are impaired.
- The clinical setting is persistent inflammatory disease.

Two mechanisms produce the same anemia



- Mechanism 1: Iron is retained within storage compartments.
- Mechanism 2: Erythropoietin response is inappropriately low.
- Both converge on reduced production of circulating red cells.

Low circulating iron does not always mean depleted iron

Serum compartment

Low serum iron

Vs

Storage compartment

Iron retained in macrophages

- This compartmental mismatch is the defining interpretive problem.
- The marrow receives insufficient iron despite iron remaining in the body.
- Assess iron availability and iron stores separately.

Three disease families provide the context

Chronic infection

Osteomyelitis · endocarditis · lung abscess

Chronic immune disease

Rheumatoid arthritis · inflammatory bowel disease

Neoplasia

Lung or breast carcinoma · Hodgkin lymphoma

- The shared link is sustained inflammation, not a single organ system.
- Anemia is a consequence of the underlying disease process.

Chronic microbial infection

Clinical setting

Persistent osteomyelitis

Serum iron ↓ · ferritin ↑ · TIBC ↓

What connects the infection to diminished erythropoiesis?

Inflammatory mediators increase hepcidin, restricting iron release and availability.

- Osteomyelitis is a Robbins example of the infectious category.
- The hematologic abnormality may persist with the inflammatory stimulus.

Chronic immune disorders

Clinical setting

Rheumatoid arthritis with anemia

Systemic inflammation · reduced circulating iron

Why can tissue iron stores be maintained?

Hepcidin-mediated restriction prevents macrophage iron mobilization.

- Rheumatoid arthritis and inflammatory bowel disease are textbook examples.
- Inflammatory disease activity provides essential diagnostic context.

Neoplasia-associated inflammation

Clinical setting

Carcinoma of the lung with mild anemia

Ferritin ↑ · serum iron ↓ · TIBC ↓

Which pathological mechanism is plausible?

Inflammation-driven iron sequestration and inadequate EPO stimulation.

- The Robbins examples include lung and breast carcinoma and Hodgkin lymphoma.
- Do not assume the cancer setting identifies the anemia mechanism by itself.

Why the clinical setting matters

Inflammatory disease

Context establishes plausible stimulus

Characteristic iron studies

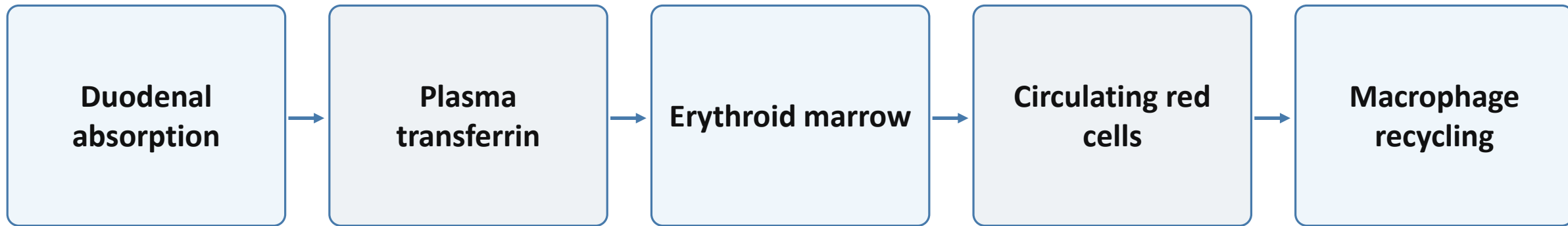
Laboratory pattern supports
sequestration

Reduced RBC production

Production defect explains anemia

- The diagnosis is a clinicopathologic interpretation.
- The same red-cell appearance can arise by other mechanisms.
- Morphology without iron studies is not sufficient.

Follow an atom of iron: Normal cycle



Schematic sequence of iron traffic / diagnostic reasoning

- Transferrin transports iron to developing erythroid cells.
- Senescent red cells return their iron to macrophages.
- Macrophages normally return iron to transferrin for reuse.

Functional iron and storage iron are distinct

Functional compartment

Hemoglobin · myoglobin · enzymes

Storage compartment

Ferritin · hemosiderin

- Iron must move between compartments to sustain erythropoiesis.
- Storage iron can exist without being readily available to marrow.
- Restriction of mobilization is central to inflammatory anemia.

Ferritin: A reservoir, not a delivery vehicle

Tissue ferritin

Binds and sequesters stored iron

Plasma transferrin

Carries iron to erythroid precursors

- Ferritin is especially prominent in hepatocytes and macrophages.
- Plasma ferritin generally relates to storage iron in the Robbins description.
- The two proteins answer different diagnostic questions.

Hemosiderin and stainable iron

Ferritin aggregates

Partially degraded in lysosomes

Hemosiderin granules

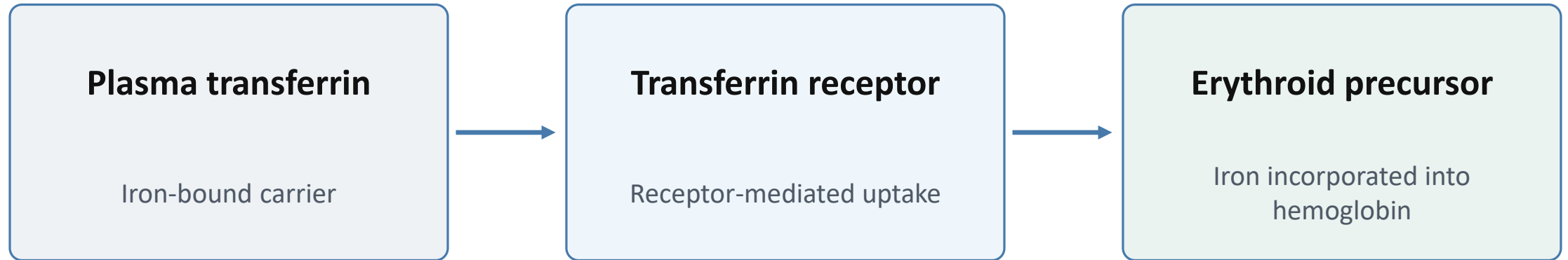
Visible intracellular stored iron

Prussian blue reaction

Granules stain blue-black

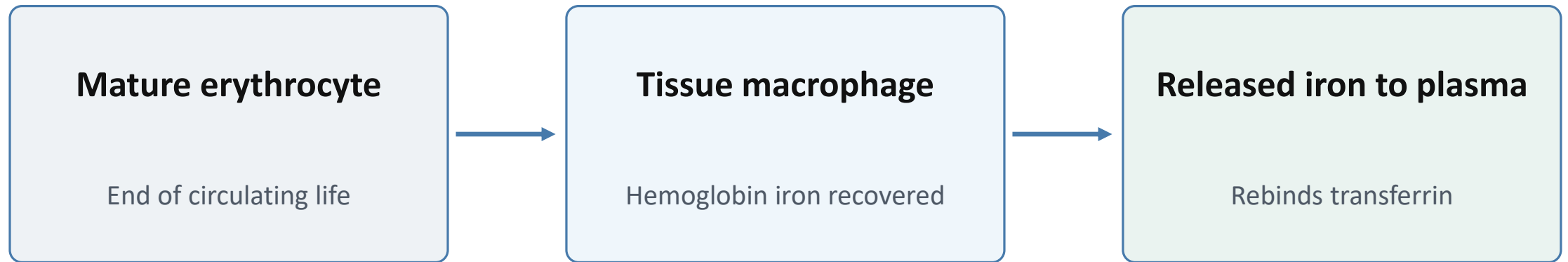
- Prussian blue detects storage iron, not adequate delivery to marrow.
- Iron staining can therefore remain positive in inflammatory anemia.
- This differs from depletion of stainable iron in iron deficiency.

Transferrin delivers iron to precursors



- Transferrin is synthesized in the liver.
- Developing red cells use high-affinity transferrin receptors.
- Low circulating iron compromises this delivery route.

Red-cell recycling is an iron source



- Macrophages in spleen, liver, and marrow recycle red-cell iron.
- In inflammation, this major return pathway is restricted.
- Recycling failure is functional, not necessarily total iron depletion.

The enterocyte is another ferroportin gate

Apical uptake

Dietary iron enters duodenal cell

Basolateral release

Ferroportin transfers iron to blood

- Iron can be held in enterocyte ferritin instead of exported.
- Hepcidin restricts the basolateral export step.
- Iron retained in enterocytes can be lost when they slough.

Hepcidin is the regulatory brake



- Hepcidin controls iron release from enterocytes and macrophages.
- High hepcidin lowers accessible iron in the bloodstream.
- This regulation is amplified during systemic inflammation.

Ferroportin is the exit route

Ferroportin active

Iron exits cells to plasma

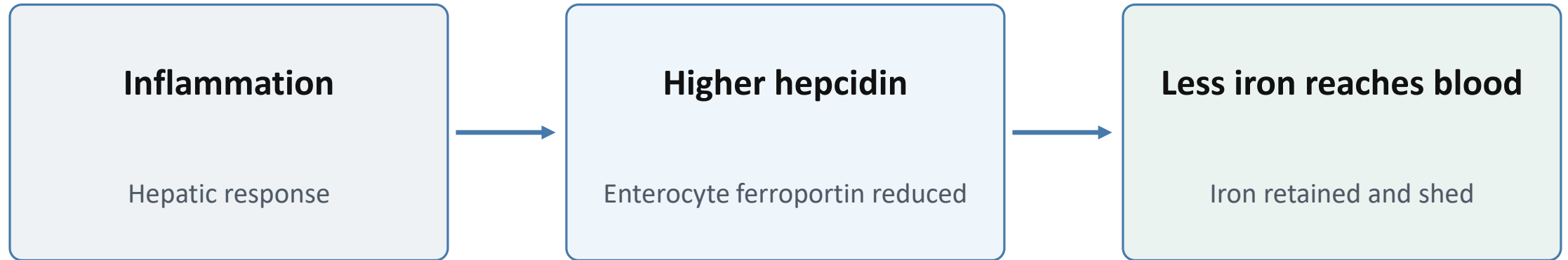
Vs

Ferroportin inhibited

Iron remains intracellular

- Transporter availability determines iron egress.
- Hepcidin promotes ferroportin internalization and degradation.
- In ACI, reduced export produces iron sequestration.

High hepcidin limits intestinal transfer



- Dietary entry into an enterocyte is not equivalent to systemic absorption.
- Heparidin acts at the step exporting iron into plasma.
- The gut thus contributes less iron to circulating transferrin.

High hepcidin traps macrophage iron



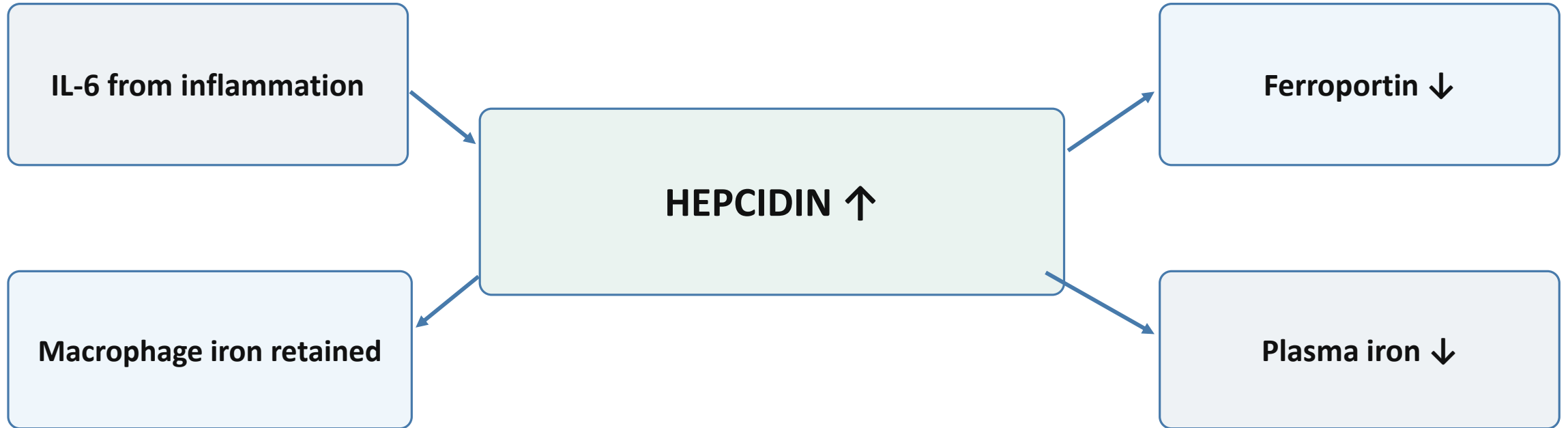
- Macrophage sequestration is emphasized.
- Storage iron accumulates while serum iron declines.
- The marrow cannot readily access this iron reservoir.

Inflammatory cytokines precede hepcidin rise



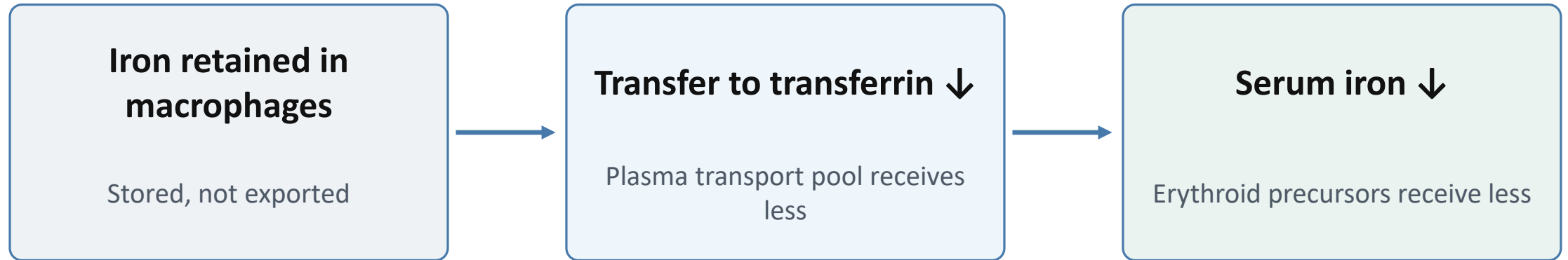
- Interleukin-6 as particularly important.
- Hepcidin is produced in the liver.
- Cytokine-driven regulation links inflammation to iron metabolism.

The central IL-6–hepcidin pathway



- The direction of each relationship matters: IL-6 stimulates hepatic hepcidin.
- Hepcidin inhibits ferroportin, rather than directly destroying iron.
- The resulting iron shortage is one of availability.

Why serum iron falls



- Measured serum iron reflects the circulating compartment.
- It does not directly quantify the total amount of iron in the body.
- An isolated low serum iron cannot identify the cause of anemia.

Iron-rich macrophages, iron-poor precursors

Macrophage compartment

Sustainable iron preserved / ↑

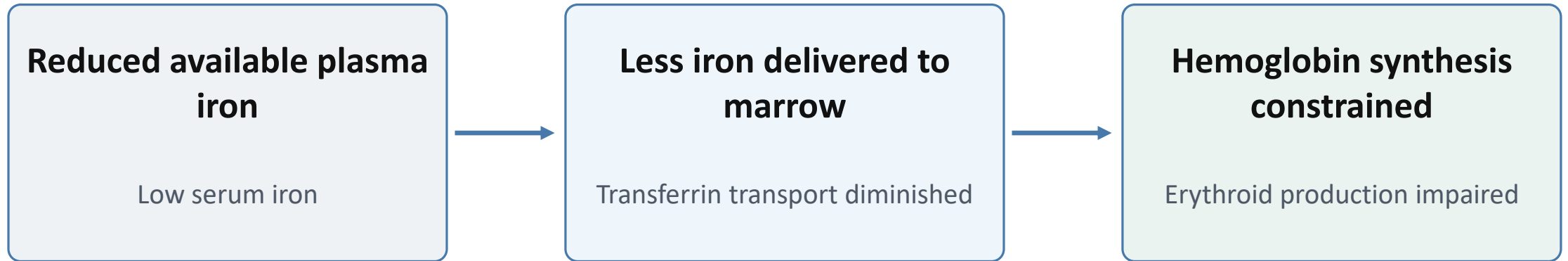
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Marrow precursor compartment

Iron delivery insufficient

- The physiological bottleneck lies between storage and utilization.
- Macrophages can contain abundant iron during anemia.
- Anemia depends on iron accessible for hemoglobin synthesis.

Iron-restricted erythropoiesis



- This mechanism explains hypochromia when present.
- Red cells need iron to synthesize hemoglobin.
- The iron-restricted state can exist with increased tissue reserves.

The “starved amid plenty” paradox

Body iron available in stores

Ferritin and macrophage iron ↑

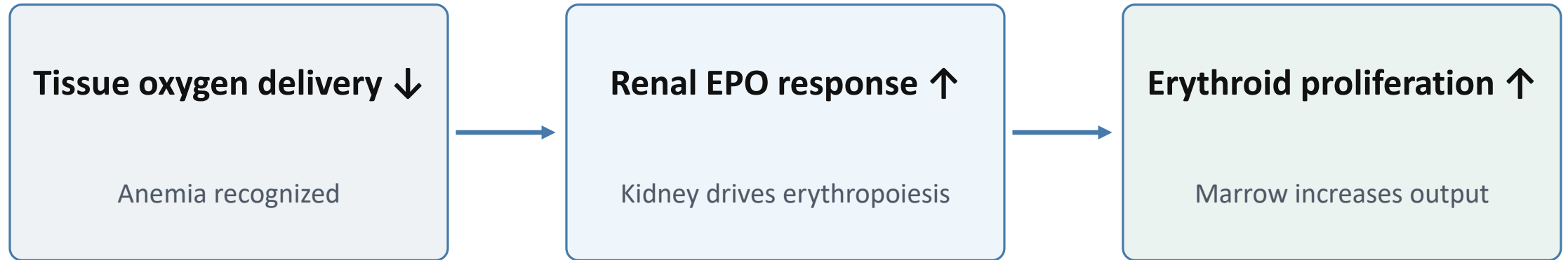
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Iron accessible to erythropoiesis

Transferrin iron ↓

- Iron is redistributed rather than necessarily lost.
- Stored iron is biologically unavailable when ferroportin is inhibited.
- The compartmental distinction resolves the apparent contradiction.

Normal erythropoietin compensation



- Renal EPO release after anemia-associated hypoxia.
- Erythropoietin stimulates committed erythroid progenitors.
- ACI interrupts the expected magnitude of compensation.

Erythropoietin response is inadequate

Expected in anemia

EPO rises sufficiently for stimulus

Vs

In chronic inflammation

EPO inappropriately low for anemia

- The comparison is relative to the severity of anemia.
- The deficit contributes to poor erythroid progenitor proliferation.
- This is independent of the iron-release bottleneck.

What is known—and what is not—about EPO

Textbook-established

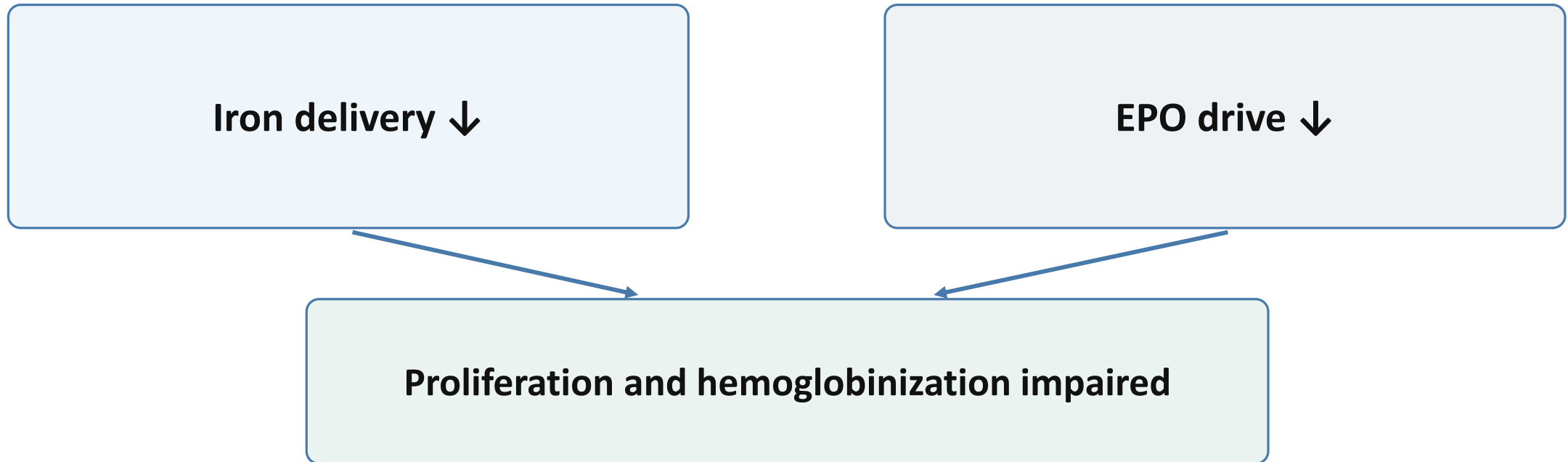
EPO response is inadequate

Proposed explanation

Cytokines may suppress renal EPO

- Robbins explicitly identifies uncertainty in the precise mechanism.
- Direct inhibition of renal EPO production is suspected.
- Do not present the proposed cytokine mechanism as proven.

Two defects converge in the marrow



- Hepcidin and EPO responses affect different parts of erythropoiesis.
- Their simultaneous effects account for reduced red-cell output.
- The disorder is not explained by a single abnormal iron result.

Laboratory pattern: The linked findings

Serum iron

LOW

Total iron-binding capacity

LOW

Plasma ferritin

HIGH

Macrophage storage iron

**INCREASE
D**

- Interpret the pattern as a constellation, not four independent diagnoses.
- Low serum iron coexists with high ferritin and preserved stored iron.
- This is the characteristic Robbins laboratory profile.

Serum iron: The circulating pool is restricted

Measured observation

Serum iron ↓

Vs

Pathophysiologic explanation

Release from stored pool ↓

- Serum iron is not a direct test of total body iron.
- The same low value may occur in iron deficiency.
- Storage markers are needed for interpretation.

Ferritin rises while iron supply falls

Plasma ferritin

Elevated

Vs

Plasma iron

Decreased

- Ferritin and serum iron assess biologically different pools.
- The divergence supports retention of iron in storage tissue.
- High ferritin is part of the textbook ACI profile.

Total iron-binding capacity is reduced

Total iron-binding capacity

Reduced in ACI

Vs

Iron deficiency pattern

Increased in IDA

- Lowered TIBC with chronic inflammation.
- In uncomplicated iron deficiency, transferrin/TIBC rises.
- The direction of TIBC is useful when serum iron is low in both.

Marrow macrophage iron discriminates mechanisms

Inflammatory anemia

Storage iron increased

Vs

Iron deficiency anemia

Stainable storage iron absent

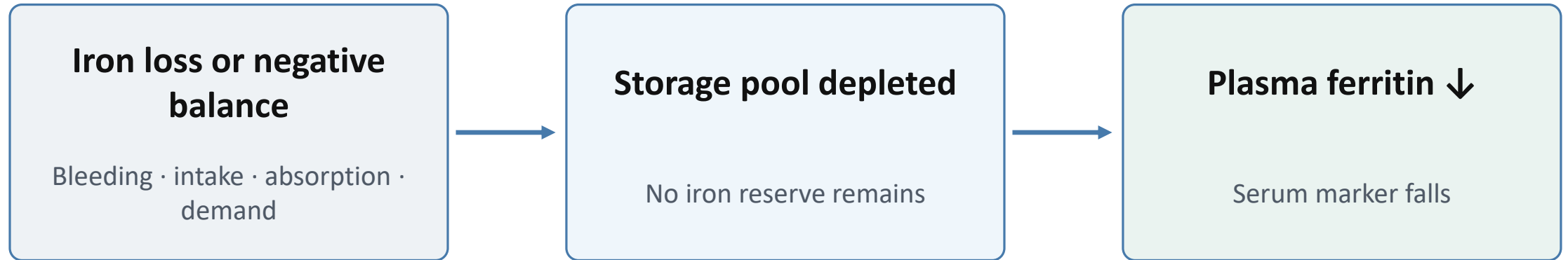
- The comparison concerns macrophage reserves.
- Prussian blue staining reveals marrow storage iron.
- Morphological iron assessment complements serum assays.

Compare the laboratory patterns directly

Measurement	Chronic inflammation	Iron deficiency
Serum iron	Low	Low
Ferritin	Elevated	Low
Total iron-binding capacity	Reduced	Increased
Macrophage iron	Increased	Absent / depleted

- The discriminating value comes mainly from ferritin, TIBC, and stores.
- Serum iron alone does not separate these disorders.

Why iron deficiency gives a different ferritin



- In IDA, insufficient total iron is the primary problem.
- In ACI, sufficient stored iron may remain inaccessible.
- These contrasting mechanisms predict different ferritin patterns.

Why TIBC goes in opposite directions

Chronic inflammation

TIBC ↓

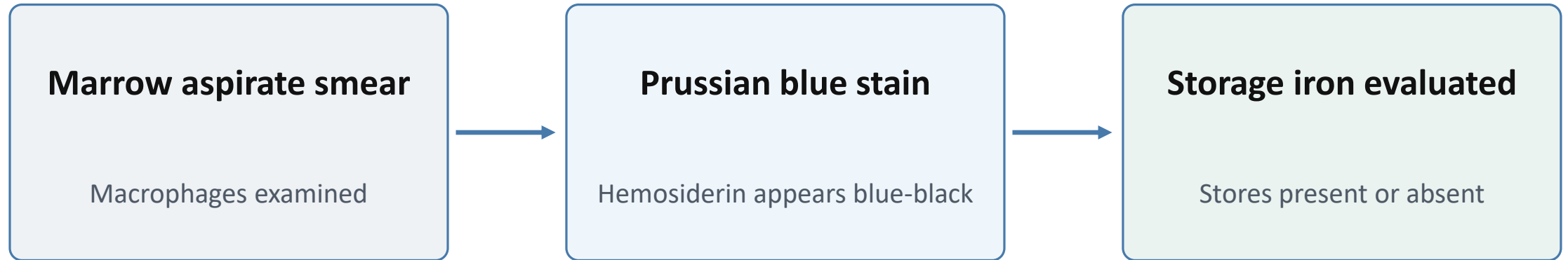
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Uncomplicated iron deficiency

TIBC ↑

- Both disorders can have low serum iron.
- The opposite TIBC directions help interpret the shared finding.
- Use the full clinical and laboratory context.

Prussian blue has a precise question



- The stain documents iron storage in macrophages.
- It does not measure how effectively transferrin delivers iron.
- An image should not substitute for this distinction.

Red-cell appearance is not uniform

Normocytic

Cell size may remain normal

Normochromic

Hemoglobinization may appear normal

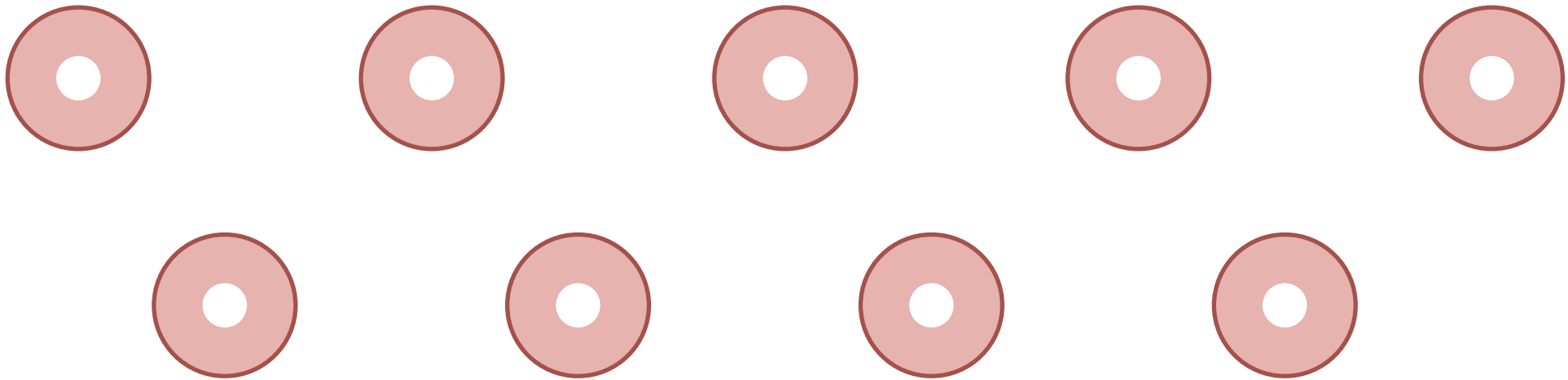
Sometimes mildly microcytic / hypochromic

Iron restriction becomes morphologically
apparent

- Robbins allows both normal-looking and mildly iron-restricted red cells.
- A classic microcytic film is not required to consider ACl.

Normocytic, normochromic presentation

Cells with usual size and central pallor

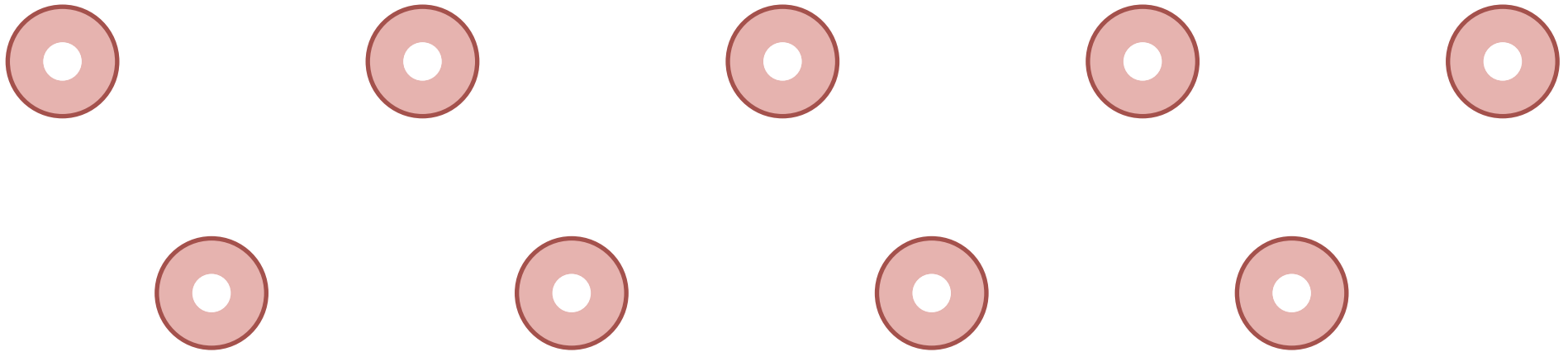


Schematic red-cell forms — not a peripheral-blood photograph

- Cell size and central pallor may remain within the ordinary pattern.
- Low hemoglobin can coexist with relatively unremarkable red-cell morphology.
- Context and iron studies remain diagnostic.

Mild hypochromia and microcytosis

Smaller cells with increased central pallor



Schematic red-cell forms — not a peripheral-blood photograph

- Some red cells are smaller and relatively paler.
- Reduced iron delivery can restrict hemoglobin synthesis.
- This appearance overlaps with iron deficiency anemia.

Morphology cannot prove iron depletion

Small, pale red cells

Microcytic · hypochromic

Vs

Possible interpretations

IDA or chronic inflammation

- The same morphological language applies to more than one mechanism.
- Ferritin, TIBC, and macrophage reserves separate the patterns.
- Always interpret the smear alongside the clinical setting.

Integrated diagnostic reasoning



Schematic sequence of iron traffic / diagnostic reasoning

- Start with anemia and a plausible inflammatory condition.
- Low serum iron is not the end of the diagnostic process.
- The direction of ferritin and TIBC guides differentiation.

Interpretation: Low iron, high ferritin

Clinical setting

Chronic endocarditis; Anemia on laboratory evaluation

Serum iron ↓ · ferritin ↑

Which iron compartment is likely retaining iron?

Tissue macrophages, under increased hepcidin and restricted ferroportin export.

- This pattern favors restricted utilization over complete store exhaustion.
- Reduced TIBC strengthens the source-defined profile.

Interpretation: Low iron, low ferritin

Clinical setting

Anemia with longstanding gastrointestinal blood loss

Serum iron ↓ · ferritin ↓ · TIBC ↑

Which mechanism best explains this constellation?

Depletion of total body iron stores: Iron deficiency anemia.

- This is the comparison condition from the preceding Robbins section.
- The iron study pattern differs despite a shared low serum iron.

Clinical severity is usually modest

Anemia itself

Usually mild

Underlying illness

Often dominant symptoms

- That the underlying disease drives the presentation.
- Anemia-related fatigue may coexist with disease-specific symptoms.
- The severity and trajectory should be interpreted clinically.

The broader symptoms of anemia

Fatigability

Reduced oxygen delivery

Weakness / malaise

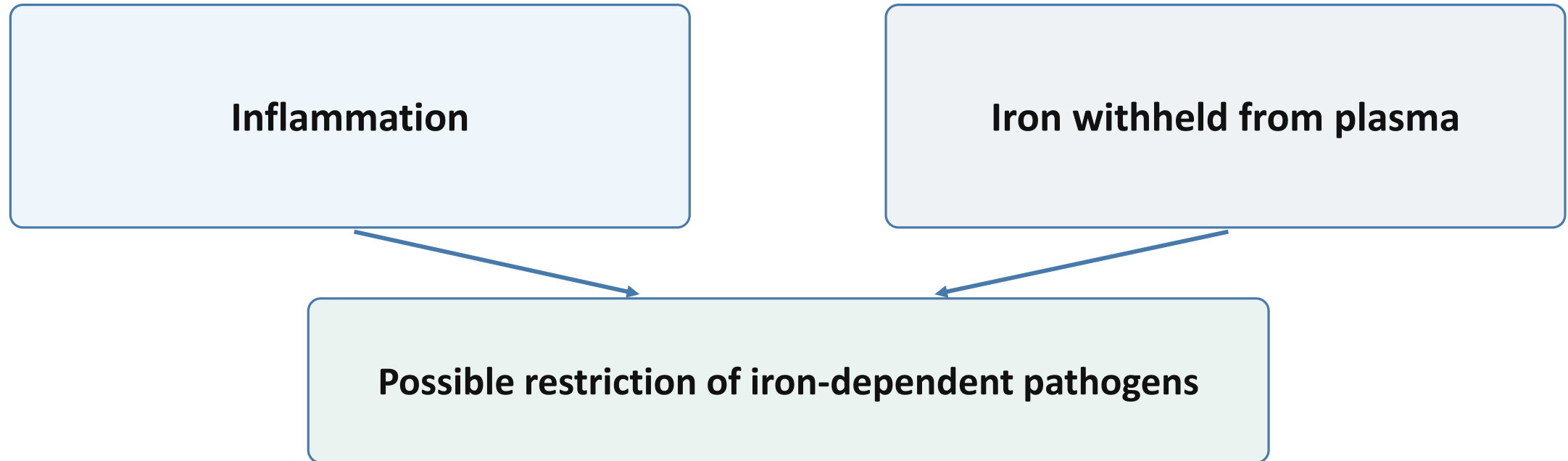
Reduced functional reserve

Exertional dyspnea

Increased demand exposes limited delivery

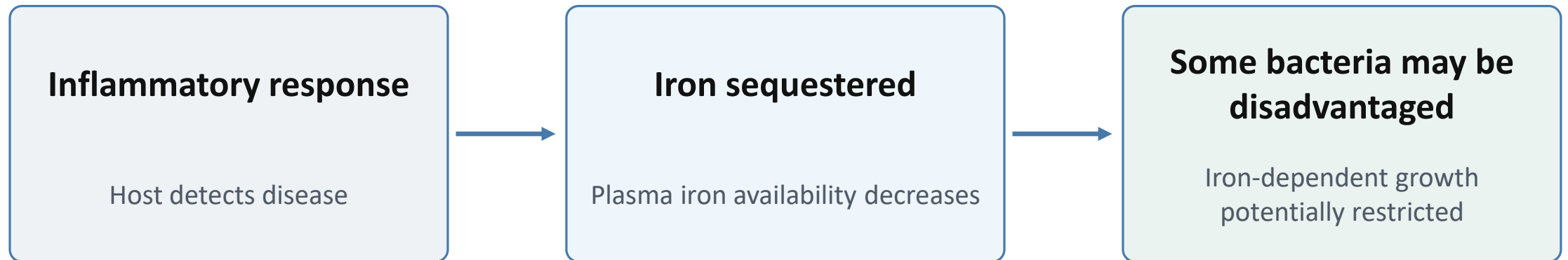
- These are general anemia symptoms in the Chapter 14 introduction.
- They are not specific to the inflammatory mechanism.
- Underlying inflammation may be more clinically prominent.

Why the body might withhold iron



- A protective explanation as a hypothesis.
- Certain bacteria require iron for pathogenicity.
- The host-defense rationale does not eliminate anemia as a consequence.

Bacteria and competition for iron



- H. Influenzae is the specific example given by Robbins.
- The proposal is not a universal claim for all pathogens.
- The source calls this a best guess rather than a proven purpose.

Hepcidin and defensins

Hepcidin

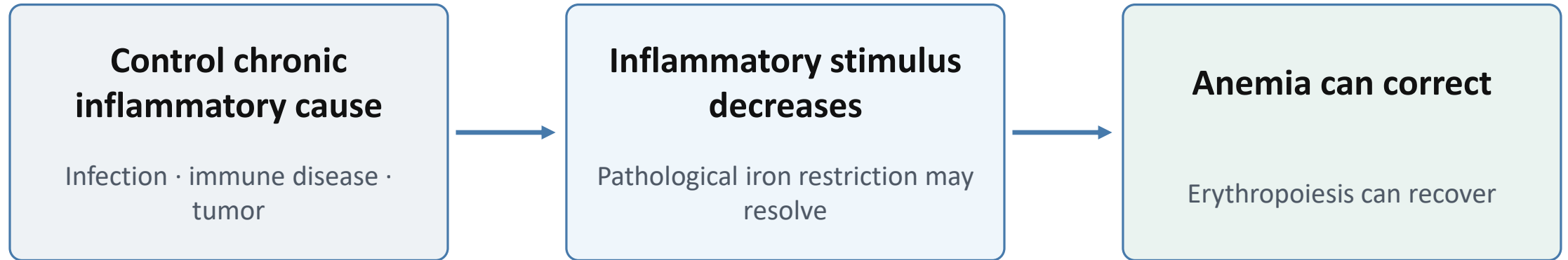
Regulates iron availability

Defensins

Innate antimicrobial peptides

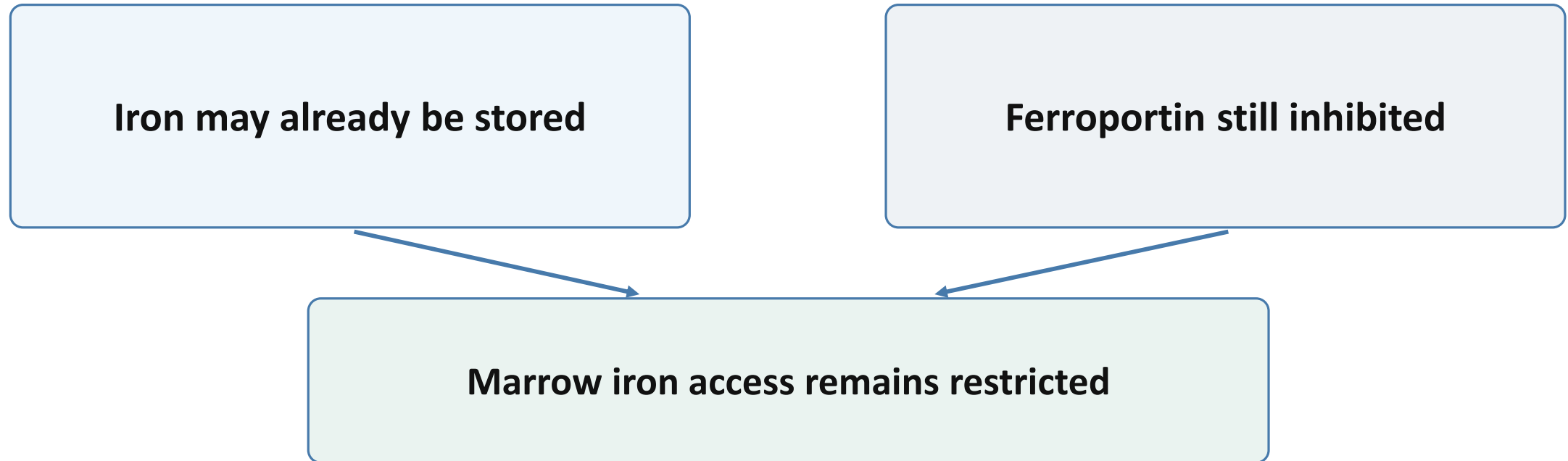
- A structural relationship between hepcidin and defensins.
- This association links iron regulation to innate immunity.
- The precise biological relationship remains incompletely understood.

Therapy addresses the underlying disease



- Successful treatment of the underlying condition is the reliable corrective strategy identified by Robbins.
- The hematologic response is secondary to disease control.
- Management should not stop at a laboratory iron value.

Why iron replacement alone misses the bottleneck



- The textbook mechanism is sequestration, not obligatory iron depletion.
- Increasing iron supply alone does not directly reverse hepcidin regulation.
- Differentiate true iron deficiency before choosing an explanation.

Erythropoietin may help selected patients

Mechanistic rationale

Stimulates erythroid progenitors

Clinical scope

Some patients, especially with cancer, may benefit

- This addresses the marrow-proliferation component of ACI.
- Robbins does not assert that all patients benefit.
- No dosing, eligibility threshold, or safety algorithm is specified.

Case: Infection-associated anemia

Clinical setting

Chronic lung abscess with new anemia

Iron ↓ · ferritin ↑ · TIBC ↓

Which changes are expected in macrophages?

Increased stored iron with restricted release to the plasma pool.

- The primary illness and laboratory pattern point to ACI.
- The key lesion is impaired mobilization of stored iron.

Case: Inflammatory bowel disease

Clinical setting

Inflammatory bowel disease with a low hemoglobin

Red cells near normocytic; Iron ↓ · TIBC ↓

What does normal cell size fail to exclude?

Anemia of chronic inflammation; Red cells can remain normocytic and normochromic.

- Do not require a microcytic smear for this mechanism.
- Ferritin and other iron markers refine the interpretation.

Case: Carcinoma and low EPO drive

Clinical setting

Breast carcinoma associated with persistent inflammation

Low iron; Marrow production remains inadequate

What mechanism complements iron sequestration?

Erythropoietin is inappropriately low for the degree of anemia.

- Cancer-related inflammation is a textbook clinical context.
- Reduced EPO stimulation is distinct from reduced iron delivery.

Case: Iron studies identify depletion

Clinical setting

Chronic blood loss with a microcytic smear

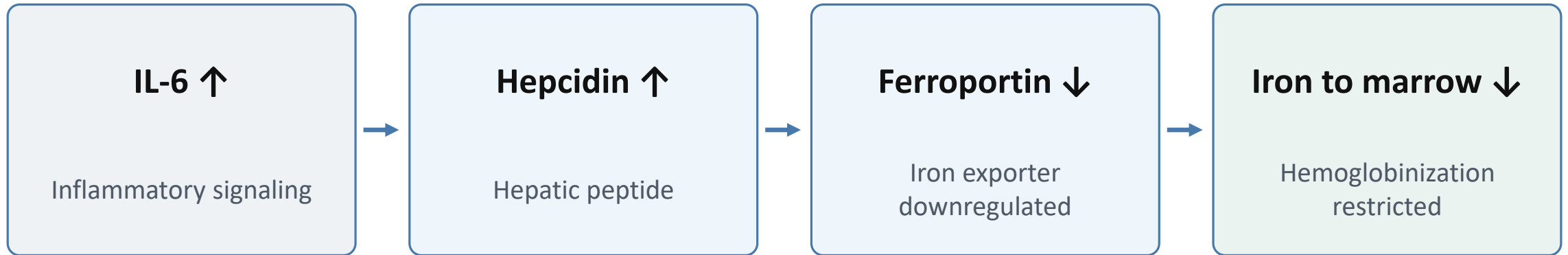
Iron ↓ · ferritin ↓ · TIBC ↑

Why does this not match isolated inflammatory anemia?

Ferritin indicates depleted iron stores and TIBC rises, the reverse of the Robbins ACI profile.

- Morphology alone would not discriminate the disorders.
- The storage and transport markers point toward iron deficiency.

Reason through the full causal sequence



- State the direction of every link, not merely the molecules.
- The reduced EPO response acts in parallel to this chain.
- Ferritin may remain elevated while plasma iron declines.

High-yield comparison: Two iron states

Feature	ACI	Uncomplicated IDA
Core defect	Unavailable stores	Depleted stores
Serum iron	Low	Low
Ferritin	High	Low
TIBC	Low	High
Marrow macrophage iron	Increased	Absent

- The differential hinges on storage versus mobilization.
- Morphologic overlap is expected, particularly with microcytosis.

Explain an apparently paradoxical profile

A patient with rheumatoid arthritis has low serum iron, elevated ferritin, and reduced TIBC. Why is iron delivery to the marrow low?

IL-6 promotes hepatic hepcidin. Hepcidin inhibits ferroportin; Stored macrophage iron cannot reach plasma transferrin efficiently.

- The high ferritin does not contradict low serum iron.
- Each assay represents a different facet of iron homeostasis.

The essential diagnostic and mechanistic synthesis

Context: persistent inflammation

Pathway: IL-6 → hepcidin → ferroportin ↓

Outcome: stored iron, poor marrow supply

Laboratory profile: iron ↓ · TIBC ↓ · ferritin ↑

Second hit: inadequate EPO response

- The anemia is often mild and subordinate to the underlying disease.
- Treating the inflammatory condition is the most reliable corrective approach.