

Iron Deficiency Anemia

Iron homeostasis · Pathogenesis · Morphology · Diagnosis

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Learning objectives

- Explain absorption, transport, storage, recycling, and hepcidin control of iron.
- Distinguish inadequate intake, malabsorption, increased need, and chronic blood loss.
- Predict the morphologic and laboratory changes as stores become exhausted.
- Connect iron deficiency with clinical findings and cause-directed evaluation.

A defect in hemoglobin synthesis

- Iron depletion ultimately restricts hemoglobin production in erythroid precursors.
- Erythrocytes become smaller and contain less hemoglobin.
- The established blood-film phenotype is microcytic and hypochromic.
- Anemia is a late consequence of sustained negative iron balance.

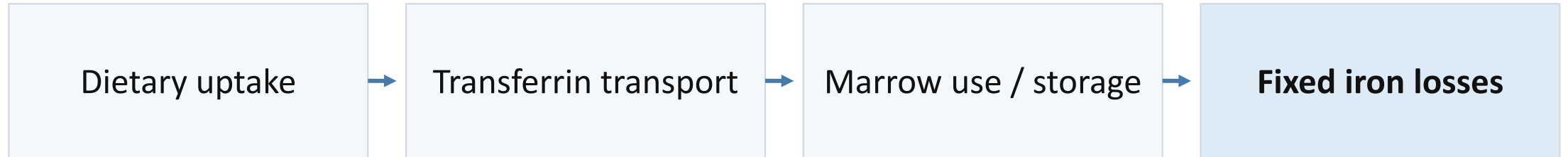
Core pathophysiologic distinction

The primary lesion is inadequate iron availability for erythropoiesis—not defective DNA synthesis.

Who is susceptible?

- Iron deficiency is common worldwide; Burden is greater in low-resource settings.
- Toddlers and adolescents have substantial growth-related requirements.
- Menstruating and pregnant individuals face additional iron demands or losses.
- In adult males and postmenopausal females, occult gastrointestinal loss is especially important.

Iron homeostasis is a balance



- Absorption is regulated at the proximal duodenum.
- Iron excretion lacks a comparable regulated physiological pathway.
- Net deficiency develops when absorbed iron fails to replace losses and demand.

Daily iron turnover and intake

- A typical United States diet as containing 10–20 mg of iron daily.
- Only a fraction of ingested iron enters the circulation.
- Ordinary iron losses arise mainly from shedding of skin and intestinal epithelial cells.
- The textbook estimates baseline loss at about 1–2 mg per day.

Why deficiency accumulates

Small chronic deficits matter because physiological iron excretion is not adjustable to match dietary insufficiency.

Functional iron is used, not stored



- Most body iron is in the functional compartment.
- Hemoglobin contains the largest fraction of functional iron.
- Myoglobin, catalase, and cytochromes account for additional functional needs.

Ferritin sequesters iron safely

- Ferritin is a protein–iron complex found in hepatocytes and tissue macrophages.
- Macrophage stores are prominent in the spleen and bone marrow.
- Intracellular iron sequestration limits free-iron toxicity.
- Circulating ferritin broadly reflects body iron storage under ordinary conditions.

Diagnostic relevance

Ferritin links the storage compartment to a clinically accessible laboratory measurement.

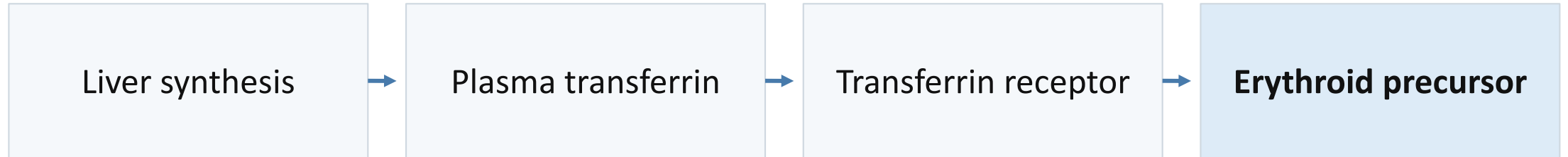
Hemosiderin and stainable iron

- Hemosiderin aggregates form after partial lysosomal degradation of ferritin.
- Iron-containing granules react with potassium ferrocyanide.
- The Prussian blue reaction yields a blue-black pigment.
- Overloaded tissue macrophages preferentially store iron as hemosiderin.

Histochemical implication

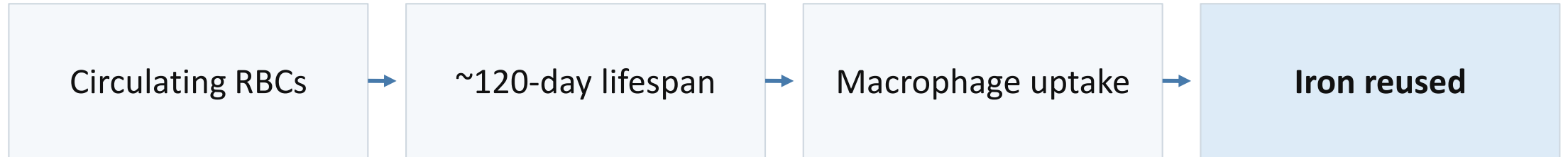
The stain becomes diagnostically useful when demonstrating absent marrow storage iron in iron deficiency.

Transferrin is the plasma shuttle



- Transferrin binds iron in plasma and delivers it to target cells.
- Developing erythroblasts express high-affinity transferrin receptors.
- Receptor-mediated endocytosis brings iron into the erythroid compartment.

Macrophages recycle erythrocyte iron



- Senescent red cells are ingested predominantly in spleen, liver, and marrow.
- Macrophages recover iron from hemoglobin.
- Recovered iron re-enters the transferrin pool for new erythrocytes.

Dietary uptake complements recycling

Absorption primarily replaces unavoidable losses.



Dietary iron occurs in two forms

Property	Heme iron	Nonheme iron
Typical source	Animal products	Vegetable products
Uptake	Relatively bioavailable	Less efficient / variable
Limitation	Distinct luminal handling	Requires Fe ³⁺ reduction

Heme iron follows a distinct entry route

- Heme iron in animal foods is more absorbable than nonheme iron.
- Apical heme uptake uses transporters that are incompletely characterized.
- Intracellular heme metabolism releases Fe^{2+} .
- Liberated Fe^{2+} joins the cellular iron pool.

Mechanistic qualification

Do not draw a fully established single heme transporter: Uptake mechanisms remain incompletely characterized.

Nonheme iron requires reduction



- Dietary nonheme iron is commonly ferric (Fe³⁺).
- Brush-border ferrireductases generate ferrous (Fe²⁺) iron.
- Divalent metal transporter 1 (DMT1) mediates apical uptake.

Two fates of iron in an enterocyte

Decision	Iron storage	Iron export
Molecular site	Cytosolic ferritin	Basolateral ferroportin
Immediate fate	Retained inside enterocyte	Transferred to plasma
Clinical meaning	May be lost at cell shedding	Supplies circulating transferrin

Ferroportin enables iron export



- Ferroportin is a basolateral exporter of cellular iron.
- Hephaestin and ceruloplasmin support oxidation before transferrin binding.
- Ferroportin also mediates release of iron from macrophage stores.

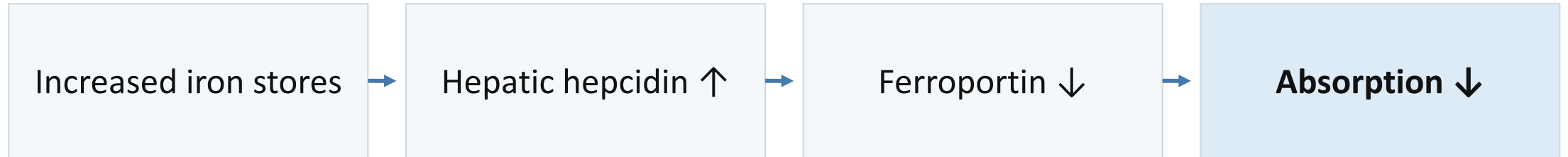
Hepcidin is the systemic iron gate

- Hepcidin is a peptide synthesized in the liver.
- It binds ferroportin and promotes its internalization and degradation.
- This reduces iron export from enterocytes into plasma.
- It also restrains iron release from macrophages.

Functional consequence

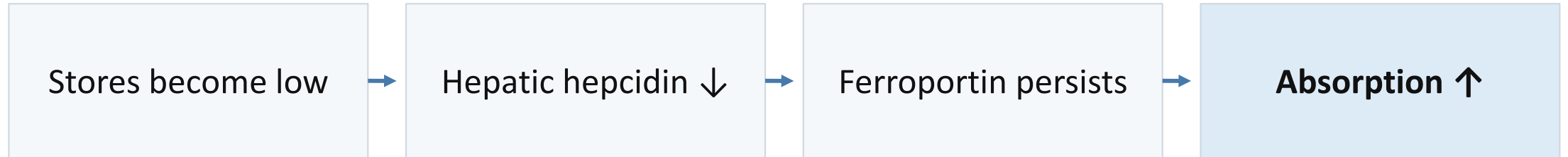
Higher hepcidin → less iron reaches transferrin → reduced availability to erythroid precursors.

Iron repletion increases hepcidin



- High iron availability signals hepatic hepcidin production.
- Enterocyte ferritin retains more of the incoming iron.
- Iron trapped in enterocytes is lost when epithelial cells are shed.

Iron depletion suppresses hepcidin



- Low iron stores physiologically reduce hepcidin synthesis.
- Lower hepcidin facilitates iron movement from enterocytes and macrophages.
- This compensation cannot overcome major ongoing loss or very poor intake.

Inflammation restricts iron availability

- Inflammatory mediators increase hepatic hepcidin production.
- High hepcidin reduces macrophage iron export and intestinal transfer.
- Iron can be sequestered despite sufficient body stores.
- This mechanism helps explain anemia of chronic inflammation.

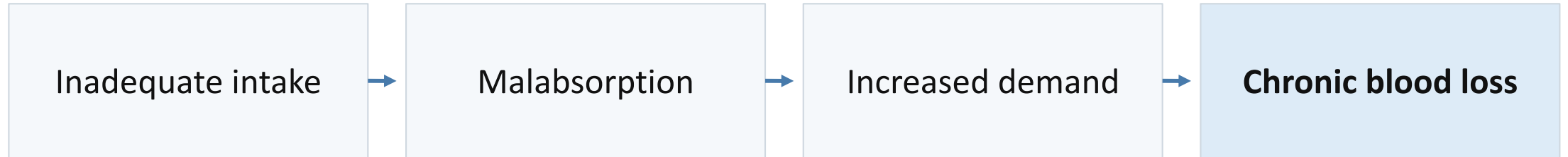
Absolute vs functional restriction

Iron deficiency = lack of total body stores. Inflammatory iron restriction = inadequate access to iron retained in storage.

Three hepcidin states

Setting	Expected hepcidin effect	Physiologic outcome
Low storage iron	Hepcidin decreases	Greater ferroportin activity
Iron-replete state	Hepcidin rises	Intestinal export restrained
Systemic inflammation	Hepcidin rises	Macrophage iron sequestration

Four etiologic routes converge



- All four mechanisms create negative iron balance over time.
- Multiple contributors may coexist in one patient.
- Identification of the primary cause is as important as recognition of the anemia.

Total iron content is not bioavailability

- Animal-source heme iron is more efficiently absorbed.
- Plant-source inorganic iron has variable fractional absorption.
- A diet may contain iron yet deliver too little absorbable iron.
- Food composition and intestinal physiology both affect the final absorbed amount.

Source comparison

Roughly 20% absorption of heme iron versus 1–2% of nonheme iron in the dietary context discussed.

Daily requirement rises with loss and growth

- Approximately 1 mg/day absorbed iron to sustain normal balance.
- Ingested requirements exceed absorbed requirements because uptake is incomplete.
- Adult females may require higher dietary intake because of reproductive iron losses.
- Prolonged mismatch gradually depletes iron reserves.

Clinical inference

The relevant variable is the net absorbed amount, not simply milligrams written on a diet record.

Infants are vulnerable to inadequate intake

- Milk contains very little iron relative to rapid early growth needs.
- The source lists human breast milk iron as approximately 0.3 mg/L.
- Cow's milk has poorly bioavailable iron despite a higher content.
- Limited dietary iron can become consequential as infant requirements rise.

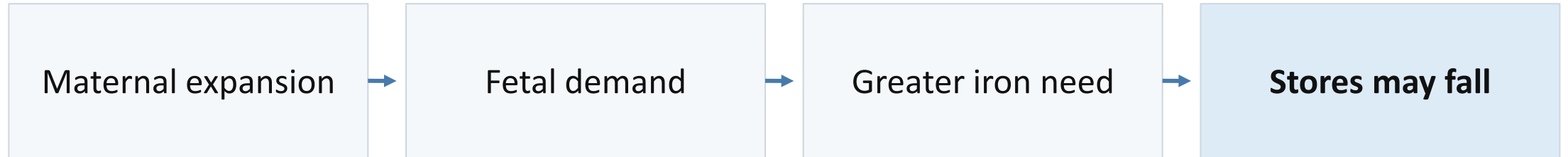
Teaching application

A history of milk-dominant feeding should be evaluated alongside growth and dietary iron sources.

Adolescents combine growth and dietary risk

- Growth expands circulating red-cell mass and iron requirements.
- Adolescent girls may additionally lose iron through menstruation.
- Inadequate iron intake can compound physiological demand.
- The risk therefore reflects several mechanisms rather than age alone.

Pregnancy raises the iron requirement



- Pregnancy is specifically identified as a high-demand state.
- Closely spaced pregnancies can magnify depletion where intake is limited.
- Clinical risk is driven by demand relative to absorption and pre-existing reserves.

Low-resource settings: Compounded deficits

- The diet may rely more heavily on relatively poorly absorbed inorganic iron.
- Overall food availability may be restricted.
- Hookworm and other parasites may contribute chronic blood loss.
- Intake and ongoing loss can act simultaneously.

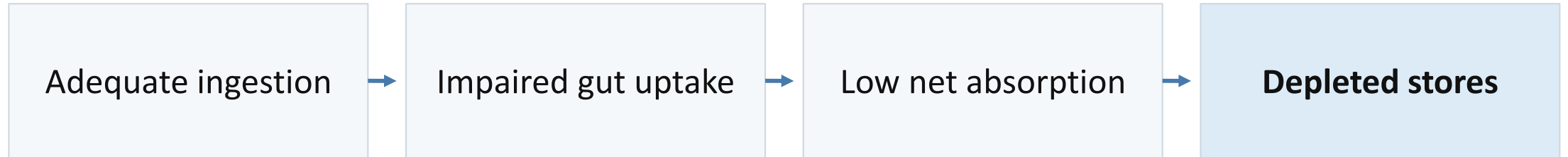
Combined etiology

The higher burden cannot be understood as dietary lack alone; Parasitic blood loss may be important.

Nutritional risk occurs across the lifespan

Population	Context	Mechanistic link
Infants	Milk provides little iron	High growth demand
Socioeconomic deprivation	Restricted food availability	Low intake
Older adults	Limited meat / restricted diet	Low intake
Vegans	No animal-derived heme iron	Lower iron bioavailability

Malabsorption limits iron delivery



- Malabsorptive disorders may cause iron deficiency despite adequate intake.
- Sprue, steatorrhea-associated disorders, and chronic diarrhea.
- Feeding more iron is not synonymous with absorbing more iron.

Gastrectomy can reduce iron absorption

- Gastric surgery alters conditions encountered by luminal iron.
- Reduced proximal duodenal acidity can impair iron uptake.
- Faster passage of contents through the duodenum reduces absorption opportunity.
- A surgical history is therefore mechanistically relevant.

Why surgery matters

Both luminal chemistry and contact time can limit transfer of dietary iron across the duodenum.

Malabsorptive disease deserves a mechanism-based history

- Sprue is a recognized cause of impaired iron absorption.
- Chronic diarrhea and steatorrhea can likewise compromise uptake.
- An affected patient may present with anemia before the intestinal disorder is recognized.
- Iron loss from other sites must still be assessed when clinically relevant.

Dietary modifiers influence nonheme iron uptake

Enhance absorption	Mechanism or context	Inhibit absorption
Ascorbic / citric acid	Favorable dietary milieu	Tannates in tea
Amino acids / sugars	Source-listed enhancers	Carbonates
—	Source-listed inhibitors	Oxalates / phosphates

These are source-listed interactions; Do not interpret the table as treatment guidance.

Chronic blood loss is the major acquired route

- Small recurrent hemorrhages remove hemoglobin-bound iron.
- Iron reserves are mobilized to replace lost erythrocytes.
- If losses outpace absorption, storage pools are gradually exhausted.
- The bleeding source may be clinically occult.

Mechanistic significance

In high-income settings, chronic blood loss is the most common cause of iron deficiency.

Gynecologic blood loss can dominate the history

- Menstrual blood loss reduces available body iron.
- Additional pregnancy-related demand may coexist.
- Gynecologic disease may be the principal clinical manifestation.
- Persistent iron deficiency requires attention to the source as well as replacement.

Adult men: Exclude gastrointestinal bleeding

- Occult gastrointestinal hemorrhage is a priority in adult males with iron deficiency.
- Postmenopausal women require the same level of concern.
- Potential lesions include gastrointestinal cancer.
- Assigning deficiency to diet without investigation may miss significant disease.

Clinical warning

The source strongly emphasizes gastrointestinal blood loss until proven otherwise in these groups.

Potential blood-loss routes

Route	Clinical context	Pathologic consequence
Gastrointestinal	Occult or visible GI hemorrhage	Progressive body-iron loss
Genital	Menstrual or other genital bleeding	Loss plus possible increased demand
Urinary	Bleeding into urinary tract	Chronic iron loss
External	Recurrent external hemorrhage	Net negative iron balance

Different causes, shared final pathway



- The etiology varies by patient, but the biochemical endpoint is similar.
- Iron transport first draws on an existing storage reserve.
- Established anemia signals advanced depletion relative to initial imbalance.

Depletion progresses in recognizable stages



- Early stages may precede measurable reductions in hemoglobin.
- Serum iron and transferrin saturation fall as available iron becomes inadequate.
- Microcytic hypochromic anemia follows severe depletion of stores.

Early depletion may be clinically silent

- Body stores initially buffer a period of negative iron balance.
- Hemoglobin and hematocrit can remain within their usual ranges.
- Serum iron and transferrin saturation may initially remain maintained.
- Absence of anemia therefore does not exclude an emerging storage deficit.

Timing of abnormality

The earliest deficit is in reserve iron, not necessarily in circulating hemoglobin.

Biochemical restriction precedes anemia

- Continued depletion lowers circulating serum iron.
- Transferrin saturation decreases as available plasma iron falls.
- Marrow erythroid activity can increase while anemia has not yet appeared.
- This stage illustrates compensated but increasingly iron-restricted erythropoiesis.

Compensatory response

The marrow attempts to replace red cells but is progressively constrained by iron supply.

Established iron deficiency impairs erythropoiesis



- Anemia emerges after the capacity of storage reserves is exhausted.
- Serum iron, ferritin, and transferrin saturation are reduced.
- Microcytosis and hypochromia become typical blood-film findings.

Why iron deficiency causes microcytosis

- Restricted iron availability reduces hemoglobin production.
- New erythrocytes contain less total hemoglobin.
- The resulting peripheral red-cell population is smaller than normal.
- The morphologic descriptor for these cells is microcytic.

Structure–function link

Cell size reflects the inadequate hemoglobin production that accompanies iron-restricted erythropoiesis.

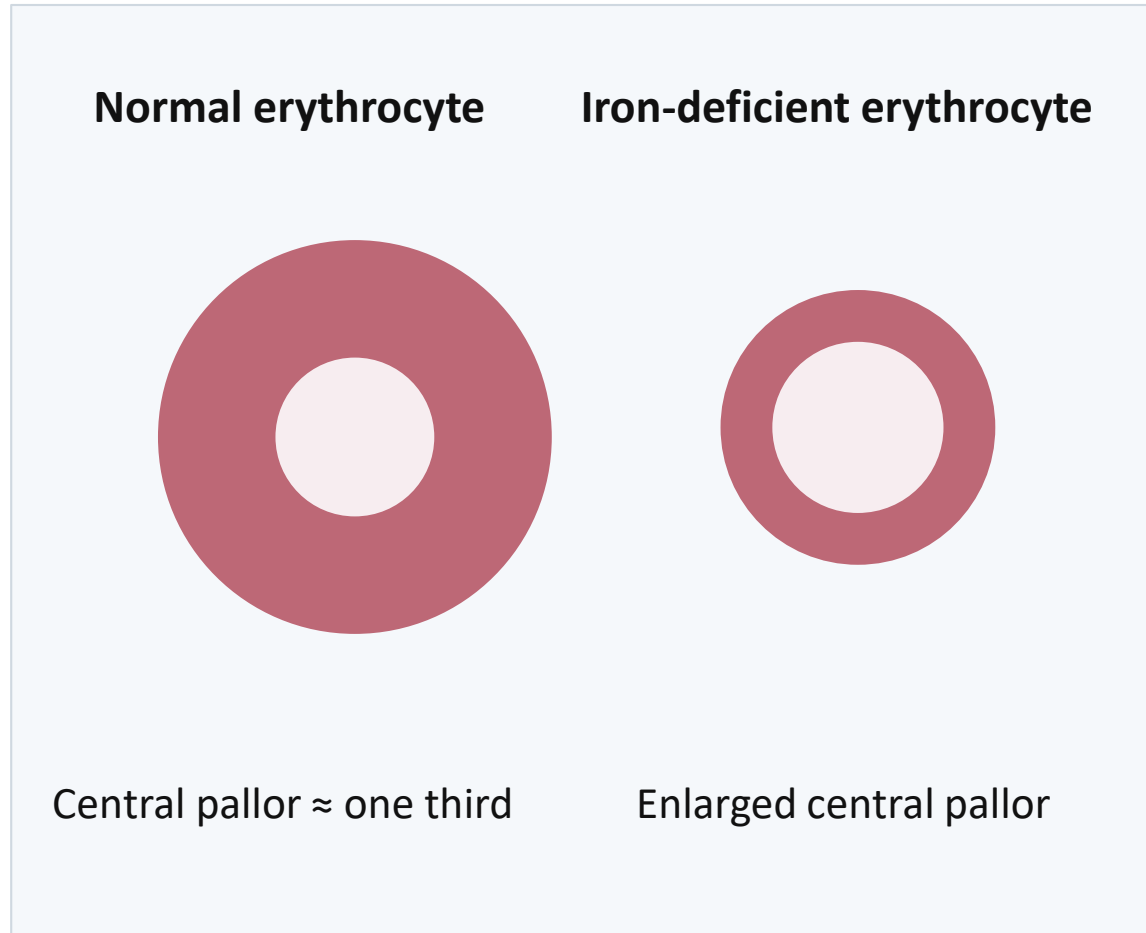
Why cells become hypochromic

- Reduced hemoglobin content makes red cells visibly paler.
- Normal central pallor occupies about one third of cell diameter.
- Established deficiency enlarges the central pale region.
- In marked cases, only a thin peripheral rim remains pink.

Blood-film correlate

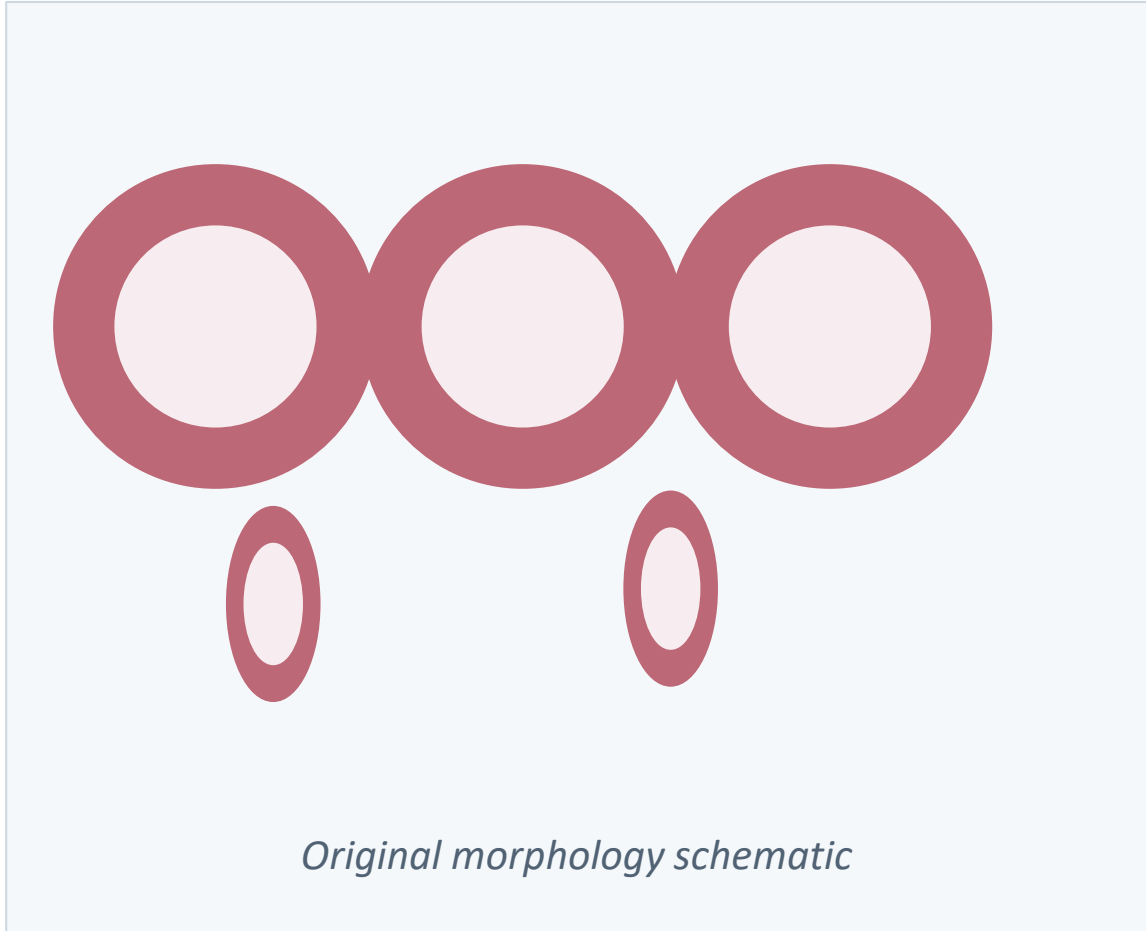
The enlarged pale zone is a morphologic consequence of inadequate hemoglobin synthesis.

Microcytosis and hypochromia: Schematic



- A normal-sized erythrocyte has central pallor around one third of its diameter.
- Iron-deficient red cells are both smaller and paler.
- This is an editable schematic—not an authentic blood smear.

Pencil cells indicate shape variation



- Iron-deficient smears may include elongated, narrow “pencil” cells.
- Poikilocytosis denotes variation in red-cell shape.
- Interpret pencil cells in combination with microcytosis, hypochromia, and iron studies.

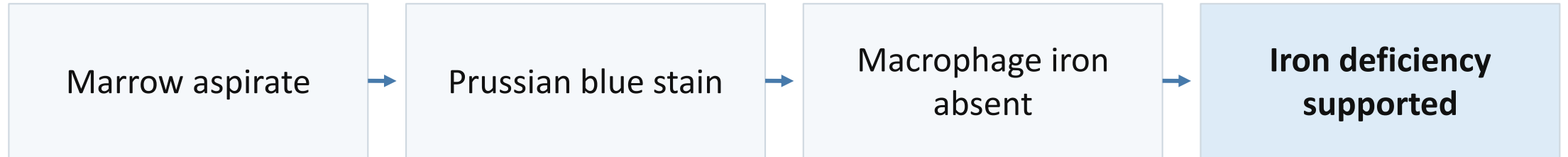
The bone marrow attempts compensation

- Marrow examination may show a mild to moderate increase in erythroid precursors.
- Increased erythroid activity does not guarantee effective hemoglobinization.
- Iron substrate shortage limits erythrocyte production quality.
- Peripheral microcytosis remains an important visible end point.

Cellular response

The marrow responds to anemia, but proliferation alone cannot correct unavailable iron.

Absent storage iron has histochemical value



- Normal marrow macrophages may contain stainable iron.
- Iron deficiency produces absence of demonstrable storage iron.
- The source identifies Prussian blue of aspirate smears as the relevant method.

Complete blood count findings

- Hemoglobin and hematocrit are depressed in established iron deficiency anemia.
- Red-cell size decreases, producing a microcytic pattern.
- Reduced hemoglobinization produces hypochromia.
- Peripheral films may show modest poikilocytosis and pencil cells.

Ferritin reports the status of stores

- Serum ferritin generally correlates with the storage compartment.
- Ferritin values below 12 µg/L in iron deficiency.
- Depleted macrophage stores correspond to reduced tissue storable iron.
- Ferritin interpretation must be integrated with the clinical context and other iron tests.

Storage compartment

A very low ferritin is consistent with exhausted body-iron reserves; It is not just a reflection of serum transport iron.

Serum iron falls as delivery becomes inadequate

- Transferrin carries iron to tissues, especially erythroid precursors.
- Progressive deficiency reduces circulating serum iron.
- Low serum iron reflects limited plasma transport availability.
- Serum iron must be interpreted together with binding capacity and ferritin.

Interpretive limitation

Low serum iron alone is not specific: Inflammatory anemia may also reduce circulating iron.

Total iron-binding capacity increases

- Total plasma iron-binding capacity reflects the transferrin pool.
- In established uncomplicated iron deficiency, transferrin rises.
- Consequently, total iron-binding capacity is increased.
- This behavior contrasts with the source-described inflammatory anemia pattern.

Reason for high TIBC

The plasma expands its iron-binding capacity even though too little iron is available to occupy it.

Transferrin saturation quantifies occupancy



- Transferrin saturation expresses the fraction of iron-binding sites occupied.
- Iron deficiency combines low iron availability with increased binding capacity.
- Transferrin saturation below 15% in established disease.

Integrated laboratory pattern of iron deficiency

Test / feature	Direction	Meaning
Hemoglobin / hematocrit	↓	Established anemia
MCV / cell coloration	↓ / hypochromic	Deficient hemoglobin production
Serum ferritin / iron	↓ / ↓	Depleted stores and transport iron
TIBC / transferrin saturation	↑ / ↓	Unoccupied binding capacity

Iron deficiency vs inflammation-associated anemia

Parameter	Iron deficiency	Chronic inflammation
Serum iron	Low	Low
Iron-binding capacity	High	Reduced
Ferritin / storage iron	Depleted	Increased or sequestered
Hepcidin	Reduced	Increased

Hepcidin is low in uncomplicated deficiency

- Depleted reserves reduce hepatic hepcidin output.
- Lower hepcidin permits persistence of ferroportin.
- This favors intestinal iron absorption and macrophage iron export.
- Inflammation can alter this regulatory response.

Adaptive response

The low-hepcidin response is compensatory: It seeks to restore circulating iron access.

Anemia produces nonspecific manifestations

- Common manifestations relate to reduced hemoglobin-mediated oxygen transport.
- Clinical symptoms may be less revealing than the underlying cause.
- Gastrointestinal or gynecologic features can dominate the presentation.
- Pregnancy, malnutrition, and malabsorptive symptoms may provide etiologic clues.

Severe chronic deficiency affects other tissues

- Iron is needed for enzymes outside erythroid cells.
- Long-standing depletion may disturb epithelial and mucosal tissues.
- Systemic manifestations extend beyond the degree of anemia alone.
- The textbook links these changes to depletion of iron-containing enzymes.

Beyond hemoglobin

Iron deficiency is not exclusively a red-cell disease; It can impair iron-dependent cellular functions.

Skin and mucosal manifestations

Feature	Tissue involved	Association
Koilonychia	Nail plate	Chronic iron deficiency
Alopecia	Hair follicles	Long-standing depletion
Atrophic glossitis	Tongue mucosa	Epithelial atrophy
Gastric / intestinal change	Gastrointestinal mucosa	Atrophy or malabsorption

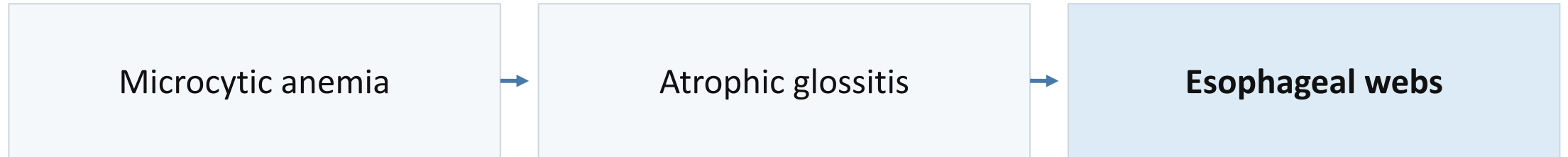
Pica and pagophagia

- Pica involves cravings for nonfood materials or atypical food ingredients.
- Examples in the source include clay, flour, and ice.
- Craving ice specifically is termed pagophagia.
- Pica is not pathognomonic; It can occur in other clinical contexts.

Clinical interpretation

Pica with central-nervous-system iron depletion but also notes other, non-iron-deficiency associations.

Plummer–Vinson syndrome



- This rare syndrome combines three source-described clinical findings.
- The esophageal lesion is a web rather than a generalized mucosal atrophy alone.
- Association is clinically useful but should not be presumed in routine iron deficiency.

Diagnosis has two linked questions

Is anemia iron deficient?



Which process depleted iron?



What lesion needs attention?

- Blood counts and iron tests establish the hematologic syndrome.
- History and examination localize possible blood loss, poor intake, or malabsorption.
- Iron repletion without etiologic assessment may miss serious underlying disease.

Response to iron supports the diagnosis

- In uncomplicated cases, oral iron leads to a reticulocyte rise in about 5–7 days.
- A steady increase in blood counts follows.
- Red-cell indices subsequently normalize as erythropoiesis recovers.
- The result reflects restoration of substrate for hemoglobin production.

Temporal sequence

Reticulocytosis is an early marrow response; It precedes complete correction of circulating indices.

Recovery unfolds in a sequence



- The early reticulocyte response signals resumption of productive erythropoiesis.
- Correction of hemoglobin follows over time rather than immediately.
- Etiologic treatment remains necessary if losses or malabsorption persist.

Case: Adolescent with increased demand

Clinical vignette

An adolescent presents with fatigue and a diet providing limited iron. A blood film is microcytic and hypochromic. Serum ferritin and iron are low, and binding capacity is increased.

Reasoning task

Which mechanisms should be considered? Why do the red cells become small and pale?

Case: Anemia in an older adult

Clinical vignette

A postmenopausal patient develops microcytic anemia and very low ferritin. There is no obvious external hemorrhage. The patient reports fatigue but few additional symptoms.

Reasoning task

What important underlying cause must be investigated?
Why is dietary attribution insufficient?

Case: Low serum iron with inflammation

Clinical vignette

A patient with chronic inflammatory illness has anemia and reduced serum iron. Total iron-binding capacity is not increased, and ferritin is not depleted.

Reasoning task

Is this the typical uncomplicated iron-deficiency pattern? Which pathway explains the difference?

Putting iron studies into context

Observation	Supports depleted stores	Supports inflammatory restriction
Ferritin	Decreased	Often preserved / elevated
TIBC	Increased	Decreased
Macrophage stores	Reduced or absent	Retained
Mechanism	Net iron deficit	Hepcidin-mediated trapping

Clinical synthesis

- Iron balance depends chiefly on regulated intestinal uptake and recycling—not regulated excretion.
- Chronic loss, poor intake, malabsorption, and high demand converge on depleted ferritin stores.
- Inadequate hemoglobin synthesis produces microcytic, hypochromic erythrocytes and pencil cells.
- Low ferritin / iron, high TIBC, and low saturation support established deficiency.
- Always search for the cause; Gastrointestinal bleeding is critical in adult men and postmenopausal women.

Reference and figure provenance

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Chapter 14: Red Blood Cell and Bleeding Disorders; Iron Deficiency Anemia, pp. 595–599.
- Primary reading includes iron physiology, etiology, blood morphology, iron studies, and clinical features.
- All illustrations in this lecture are original editable PowerPoint schematics; no textbook artwork or synthetic clinical specimen is reproduced.