

Anemia of Folate Deficiency

Megaloblastic anemia: metabolism, etiology, morphology and diagnosis

Biochemical mechanism → megaloblastic morphology →
differential diagnosis

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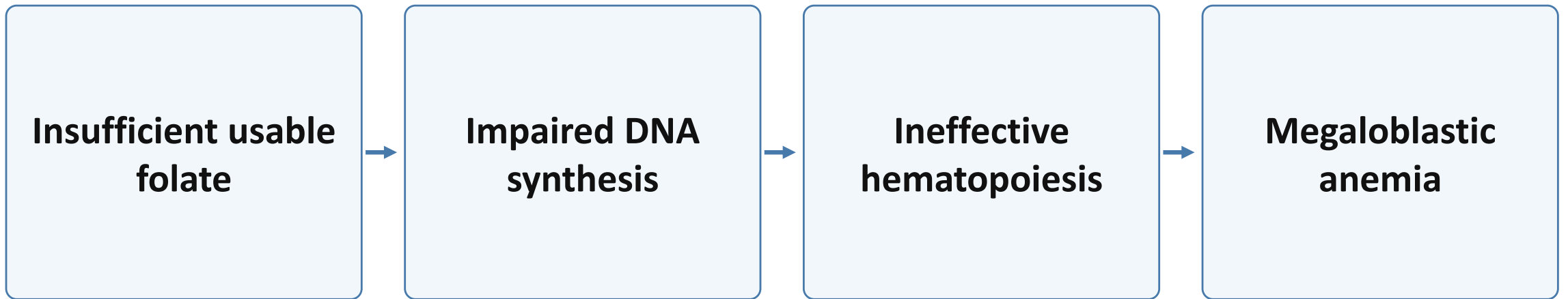
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Learning objectives

- Trace folate-dependent one-carbon transfer into DNA synthesis.
- Classify causes of deficiency by inadequate supply, increased need and impaired utilization.
- Recognize the blood and marrow pattern of megaloblastosis.
- Distinguish folate deficiency from vitamin B₁₂ deficiency safely.

Folate deficiency is a production disorder



Schematic · causal sequence

Where folate deficiency fits among anemias

Red-cell underproduction

Nutritional deficiencies are major causes of diminished erythropoiesis.

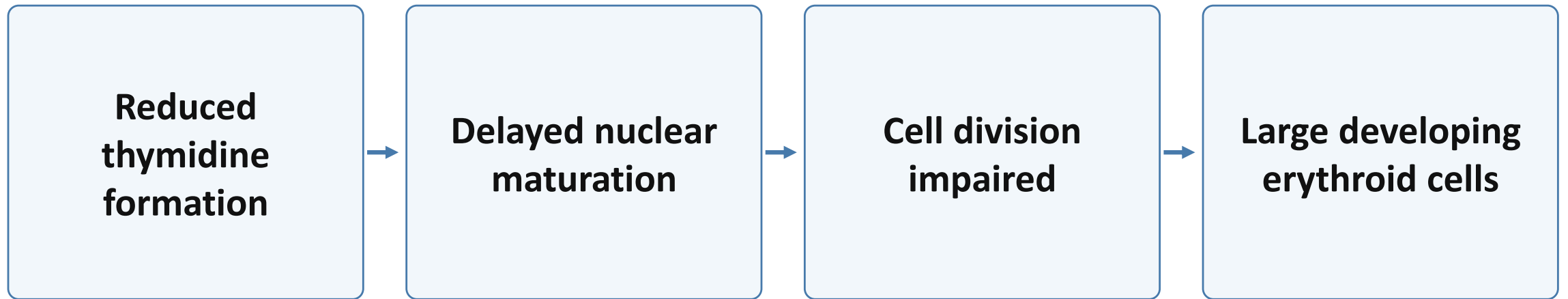
Megaloblastic pattern

DNA synthesis failure produces abnormally large precursors and circulating red cells.

Shared phenotype

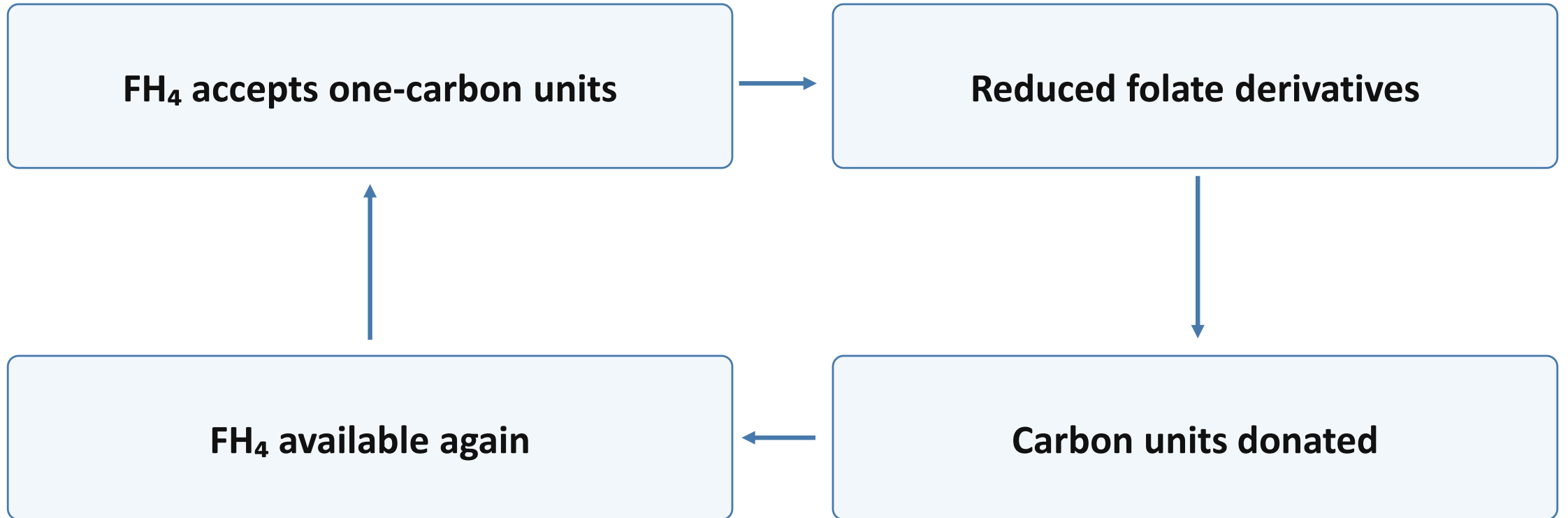
Folate and vitamin B₁₂ deficiencies have indistinguishable hematologic morphology.

Megaloblastosis begins with defective DNA synthesis



Schematic · causal sequence

One-carbon transfer is folate's central role



Original schematic of the folate one-carbon carrier cycle.

Tetrahydrofolate is the metabolic carrier

- FH_4 (tetrahydrofolate) accepts one-carbon fragments.
- Folate derivatives transfer these fragments to biosynthetic reactions.
- The folate pool is recycled through regeneration of FH_4 .

Where the one-carbon fragments originate

Serine

An example donor of one-carbon fragments.

Formiminoglutamic acid

Another donor identified in folate metabolism.

FH₄ pool

Accepts transferred fragments for subsequent biosynthesis.

Three major folate-dependent processes

Purine synthesis

Supplies essential components of nucleic acids.

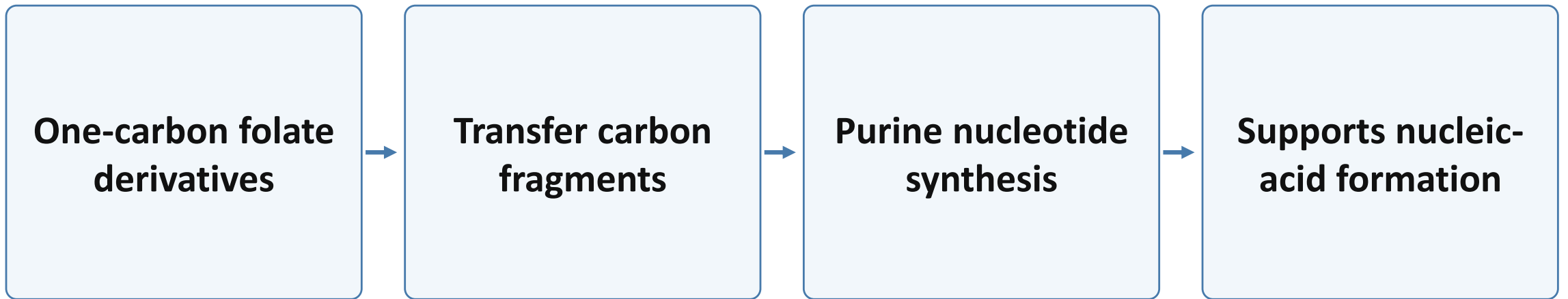
Methionine synthesis

Homocysteine → methionine; Also requires vitamin B₁₂.

DTMP synthesis

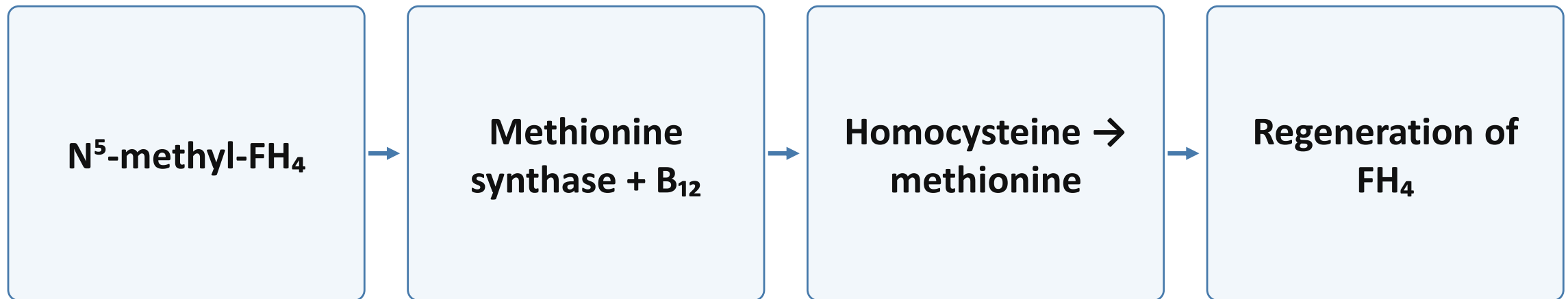
Produces deoxythymidine monophosphate for DNA.

Purine synthesis depends on folate transfer



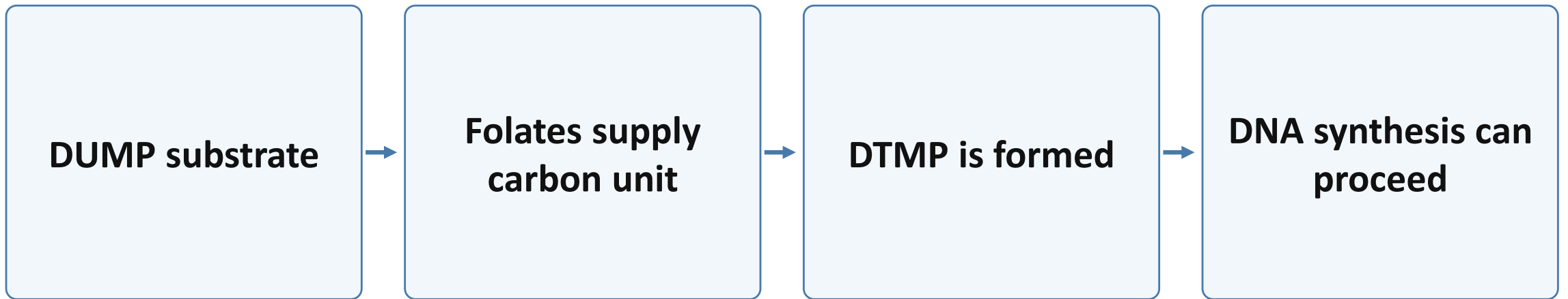
Schematic · causal sequence

Methionine synthesis links folate and vitamin B₁₂



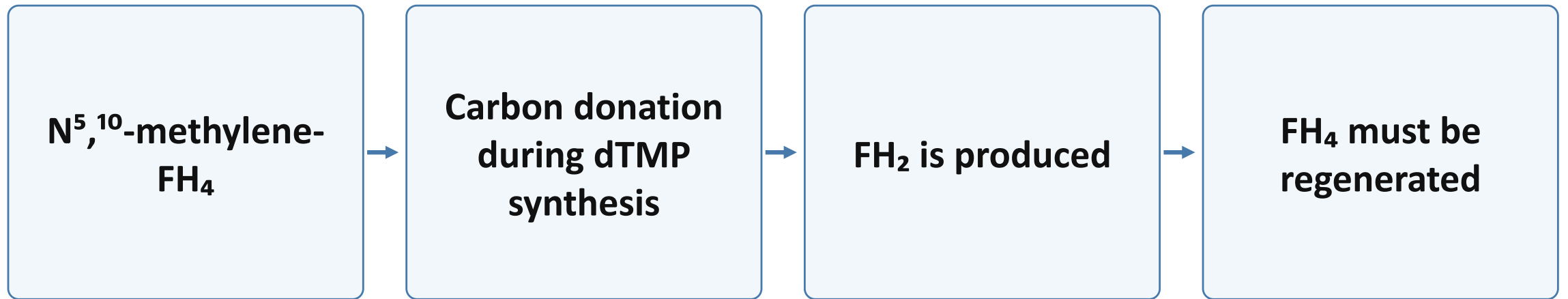
Schematic · causal sequence

DTMP synthesis is critical for DNA replication



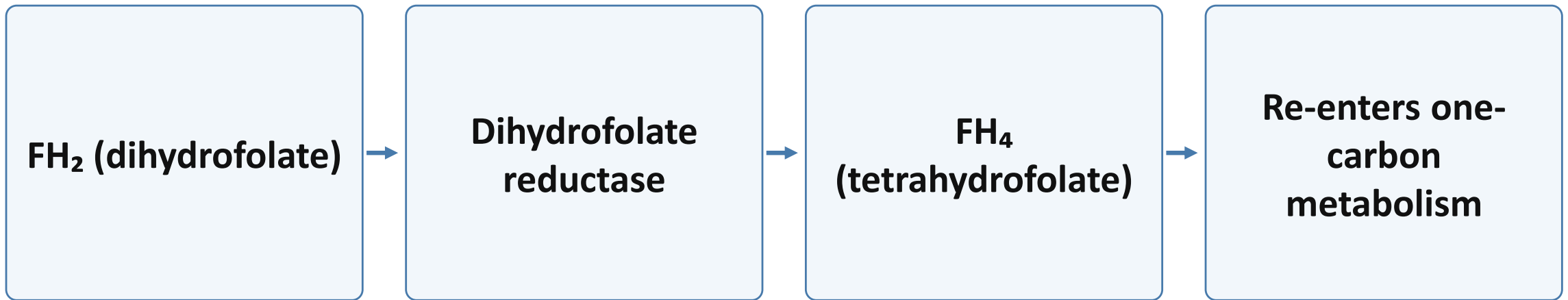
Schematic · causal sequence

Thymidylate production changes the folate pool



Schematic · causal sequence

Dihydrofolate reductase regenerates FH_4

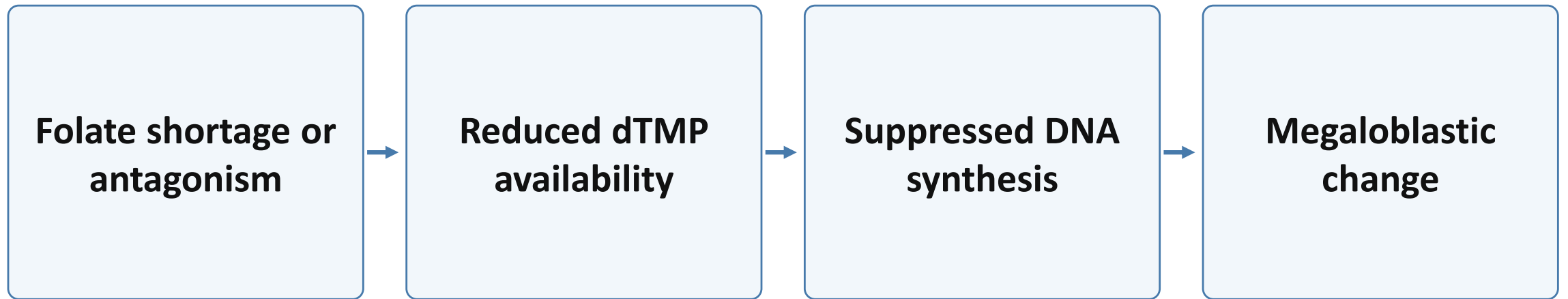


Schematic · causal sequence

Why dihydrofolate reductase matters

Biochemical role	Drug vulnerability	Cellular consequence
Restores reduced folate after dTMP generation.	Dihydrofolate reductase is sensitive to folate antagonists.	Failure of regeneration reduces folate available for DNA synthesis.

Folate deficiency converges on a single lesion



Schematic · causal sequence

Nuclear maturation lags behind cytoplasm

Nucleus

DNA-dependent maturation is delayed.
Chromatin stays abnormally immature.

Cytoplasm

Hemoglobin accumulation continues.
Relative maturation progresses.

The mismatch is nuclear–cytoplasmic asynchrony.

Rapidly dividing tissues are most vulnerable

Bone marrow

Erythroid and granulocytic precursors are affected.

Gastrointestinal epithelium

Rapid turnover increases vulnerability to disrupted synthesis.

Other proliferating cells

Antimetabolite effects are not marrow-restricted.

Three major etiologic pathways

Decreased availability

Inadequate intake or poor intestinal absorption.

Increased requirements

DNA synthesis demand exceeds available supply.

Impaired utilization

Folate-antagonist interference with the FH₄ pool.

Dietary inadequacy reduces folate supply

- Humans depend on dietary sources of folate.
- Most balanced diets contain more than the minimal adult requirement.
- Markedly deficient nutrition places individuals at risk.

Folate-rich food sources

Green vegetables

Lettuce, spinach, asparagus and broccoli are rich sources.

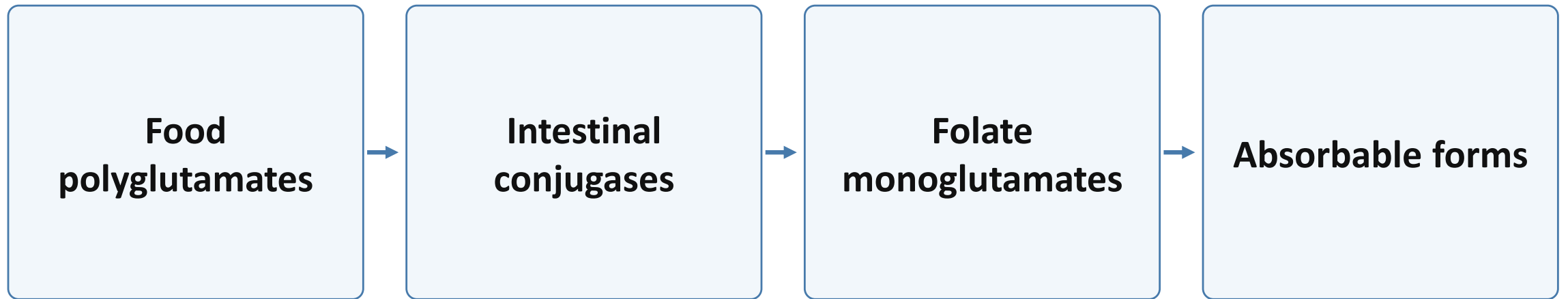
Other plant foods

Examples include lemons, bananas and melons.

Animal sources

Liver contains folate; It as a lesser source.

Food folate occurs largely as polyglutamates

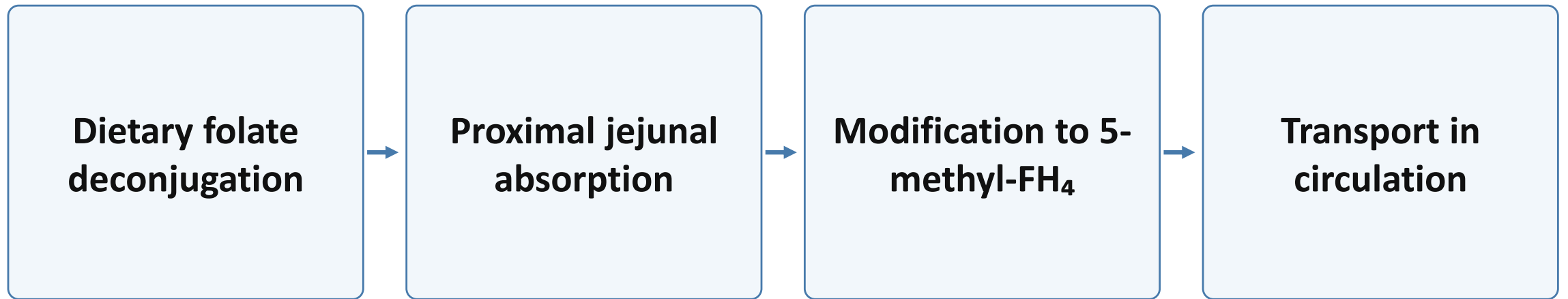


Schematic · causal sequence

Cooking can markedly reduce folate content

- Food folylpolyglutamates are sensitive to heating.
- Substantial losses with brief boiling, steaming or frying.
- Food preparation can alter effective folate intake.

Proximal jejunum is the absorption site



Schematic · causal sequence

5-Methyl-FH₄ is the transport form

Intestinal processing

Absorbed forms undergo metabolic modification.

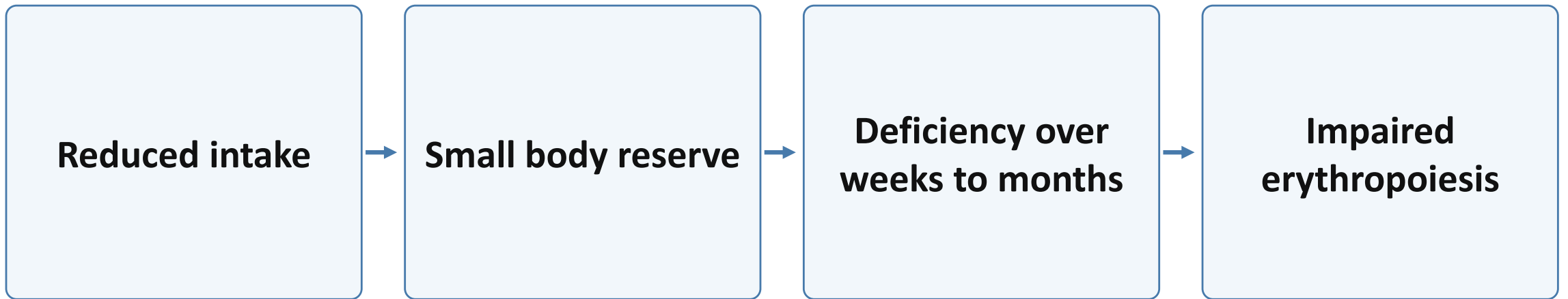
Circulating form

5-methyltetrahydrofolate serves as the transport form.

Cellular use

Folate is supplied to one-carbon metabolism in tissues.

Folate reserves are relatively modest



Schematic · causal sequence

Diet and body stores differ from vitamin B₁₂

Folate

Relatively modest body stores.

Deficiency may develop within weeks to months.

Vitamin B₁₂

Large intrahepatic reserves are typical.

Depletion often takes several years.

Different reserve sizes explain different nutritional time courses.

Who develops inadequate folate intake?

Chronic alcohol use disorder

Deficient nutritional intake is common.

Social deprivation

Markedly inadequate diets may occur.

Advanced age

Poor overall nutrition can contribute.

Alcohol-associated deficiency is multifactorial

Dietary deficit

Intake may be inadequate.

Abnormal folate handling

Hepatic trapping and increased urinary losses are implicated.

Disturbed metabolism

Cirrhosis and alcohol-related metabolic changes can contribute.

Folate deficiency may coexist with malnutrition

- Chronic alcohol-associated folate deficiency may accompany generalized malnutrition.
- Cheilosis, glossitis and dermatitis can reflect other vitamin deficits.
- These manifestations do not specifically identify folate deficiency.

Small-intestinal disease may impair absorption

Sprue	Infiltrative disease	Underlying principle
A malabsorption syndrome associated with reduced folate uptake.	Small-intestinal lymphoma is an example in the source.	Damage to the absorptive intestine reduces availability.

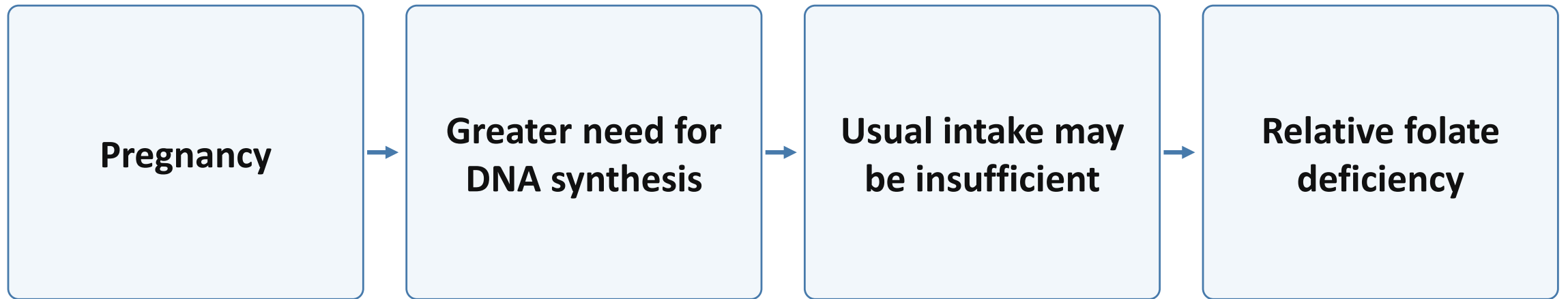
Medications may interfere with folate absorption

- The anticonvulsant phenytoin as interfering with absorption.
- Oral contraceptives are also listed in its account.
- Medication history belongs in the etiologic assessment.

Hemodialysis is listed as an increased-loss cause

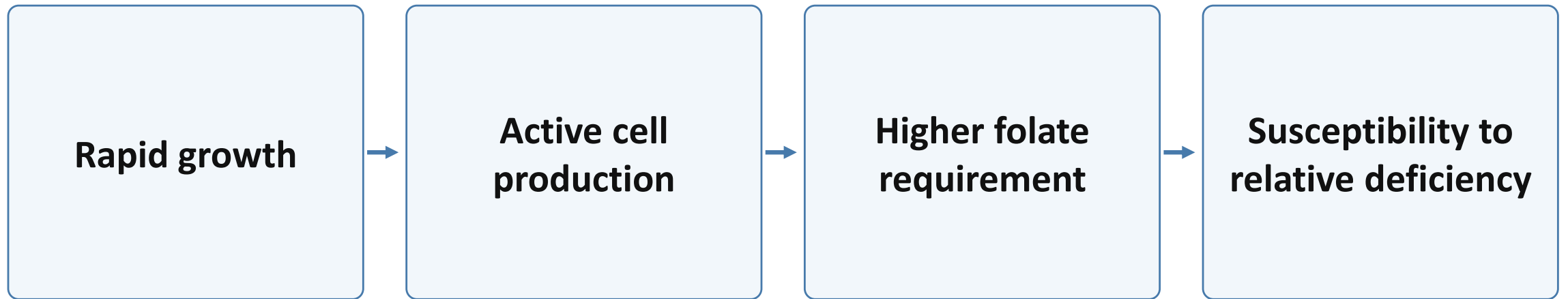
Category	Example	Clinical implication
Increased folate loss.	Hemodialysis appears in the chapter's etiologic table.	Nutritional risk assessment should consider loss as well as intake.

Pregnancy increases folate requirements



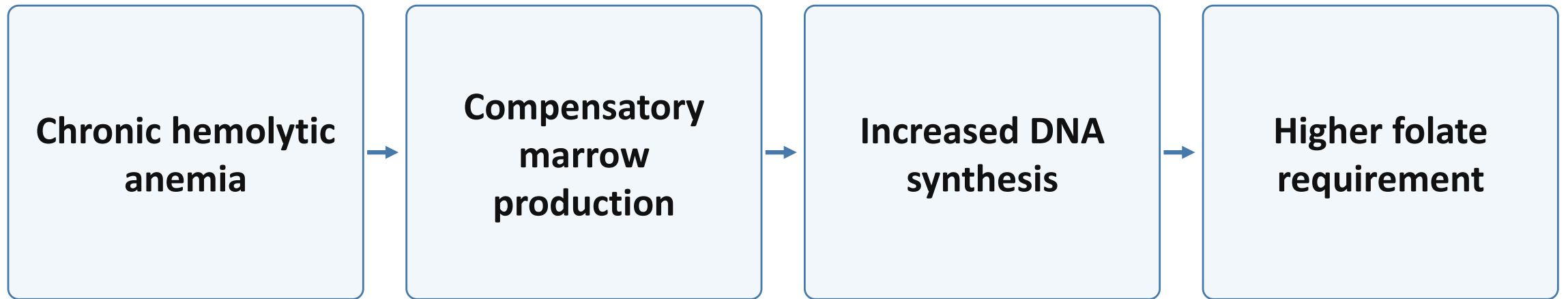
Schematic · causal sequence

Infancy is another high-demand state



Schematic · causal sequence

Hyperactive hematopoiesis increases need



Schematic · causal sequence

Disseminated cancer may increase demand

- Disseminated malignancy is listed among high-requirement states.
- The teaching mechanism is increased cellular proliferation and DNA synthesis.
- Apparent “normal intake” may not satisfy increased metabolic needs.

Normal intake need not exclude deficiency

Adequate dietary supply

Folate is ingested at ordinary levels.

May be sufficient when demands are baseline.

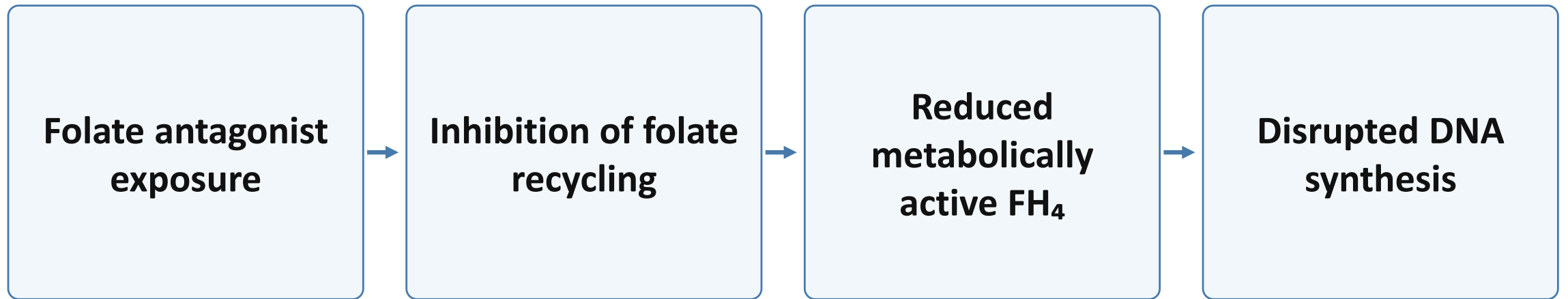
Raised metabolic demand

Pregnancy, infancy or active hematopoiesis.

Usual supply becomes relatively insufficient.

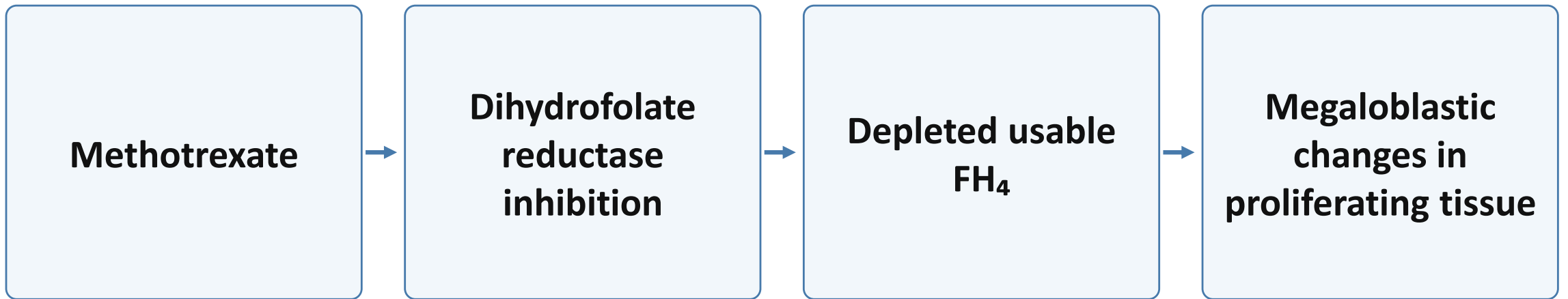
Interpret intake in relation to requirement, not in isolation.

Folate antagonists impair utilization



Schematic · causal sequence

Methotrexate inhibits dihydrofolate reductase



Schematic · causal sequence

Not all drug-related megaloblastosis is folate lack

Direct folate antagonism

Interferes with folate-dependent reactions.

Methotrexate is the source example.

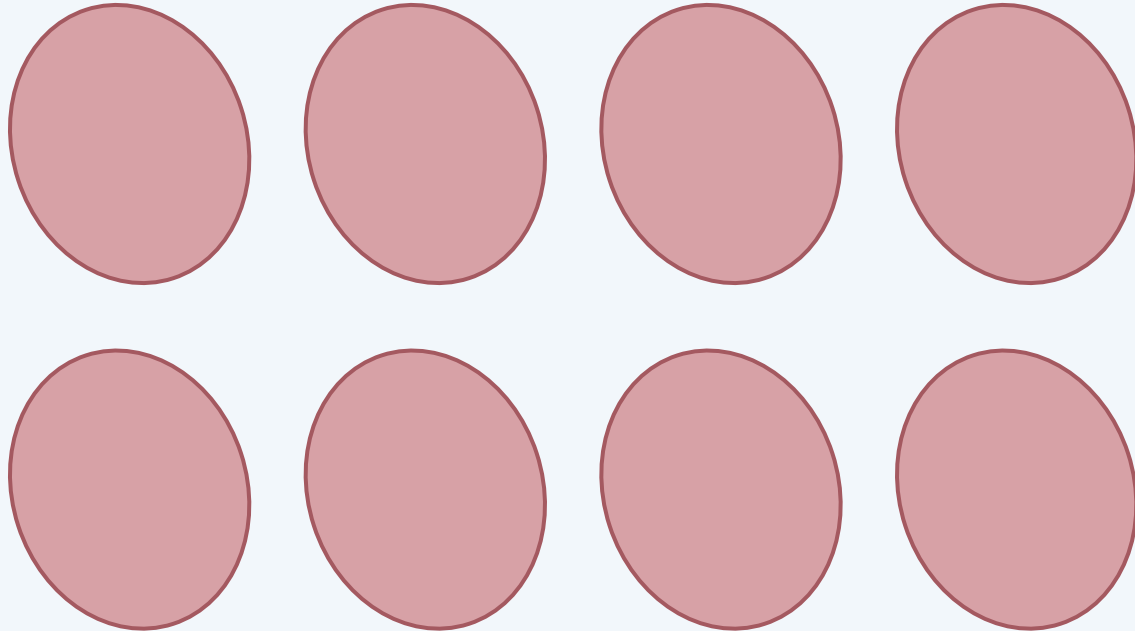
Other DNA-directed drugs

Damage DNA or suppress synthesis by other routes.

Can also create megaloblastic changes.

Morphology reflects disrupted DNA synthesis, not a unique exposure.

The peripheral smear shows macro-ovalocytes



Schematic — original editable drawing; Not a clinical specimen

Diagnostic interpretation

Large oval red cells are characteristic.

Central pallor is often inconspicuous.

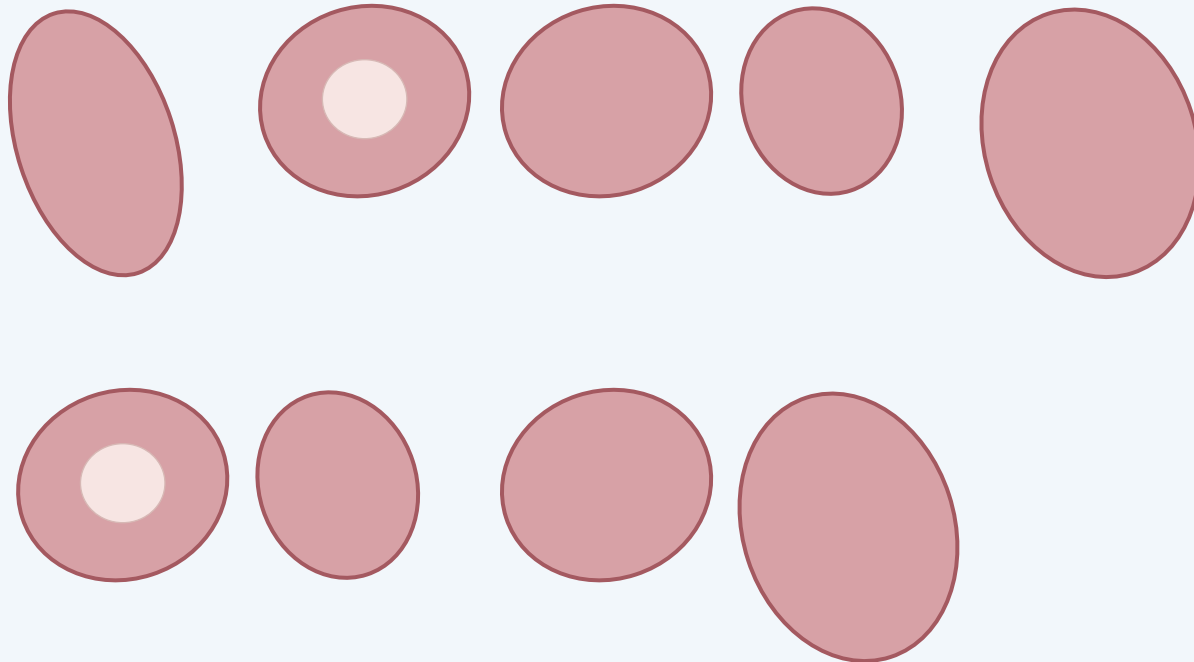
This is a conceptual cell drawing, not a photomicrograph.

Macrocytes can appear “hyperchromic”

Apparent color	MCHC interpretation
Large cells contain ample hemoglobin. Many lack central pallor.	Mean cell hemoglobin concentration is not increased. Appearance should not be confused with true hyperchromia.

Source distinction: Visual appearance is not equivalent to increased MCHC.

Anisocytosis and poikilocytosis are common



Diagnostic interpretation

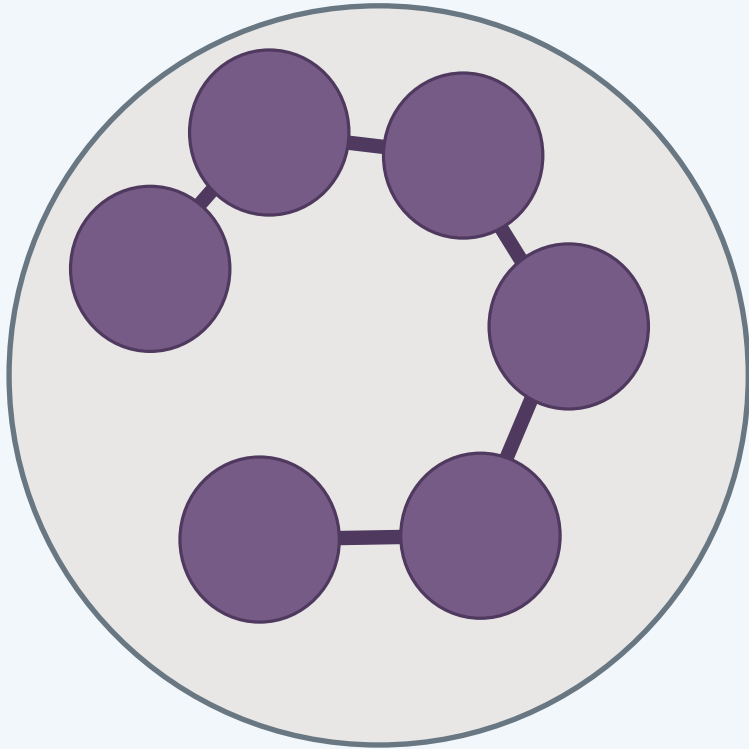
Anisocytosis: Variation in erythrocyte size.

Poikilocytosis: Variation in erythrocyte shape.

Large oval forms supply an important morphologic clue.

Schematic — original editable drawing; Not a clinical specimen

Hypersegmented neutrophils support megaloblastosis



Diagnostic interpretation

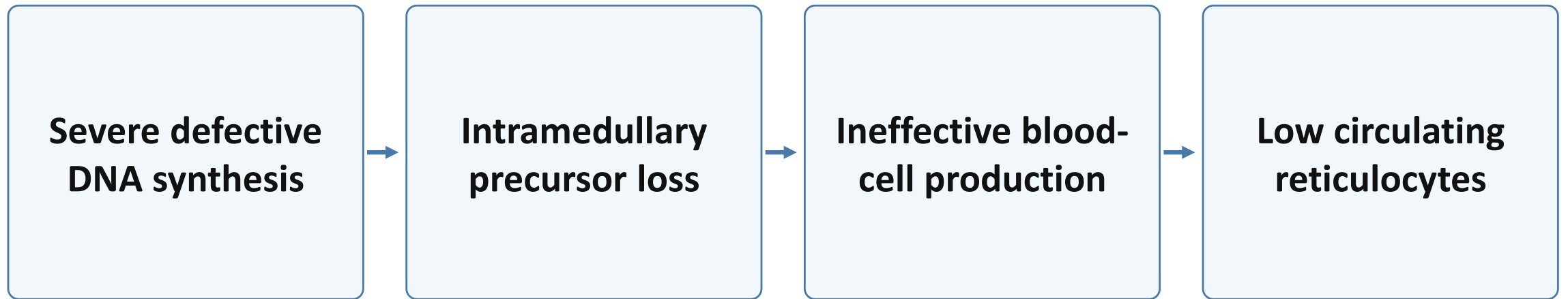
Neutrophil nuclei show excessive segmentation.

Five or more nuclear lobes are described.

This is a schematic, not a patient blood smear.

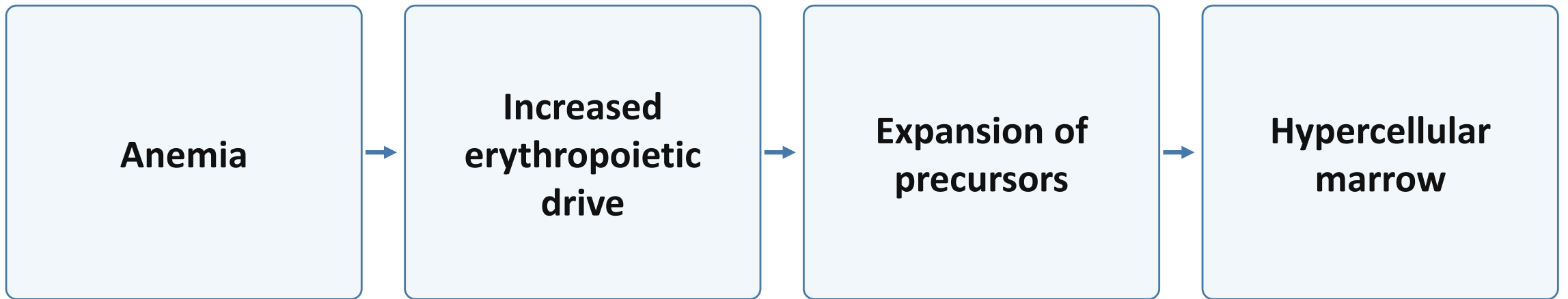
Schematic — original editable drawing; Not a clinical specimen

Reticulocytes are low despite marrow proliferation



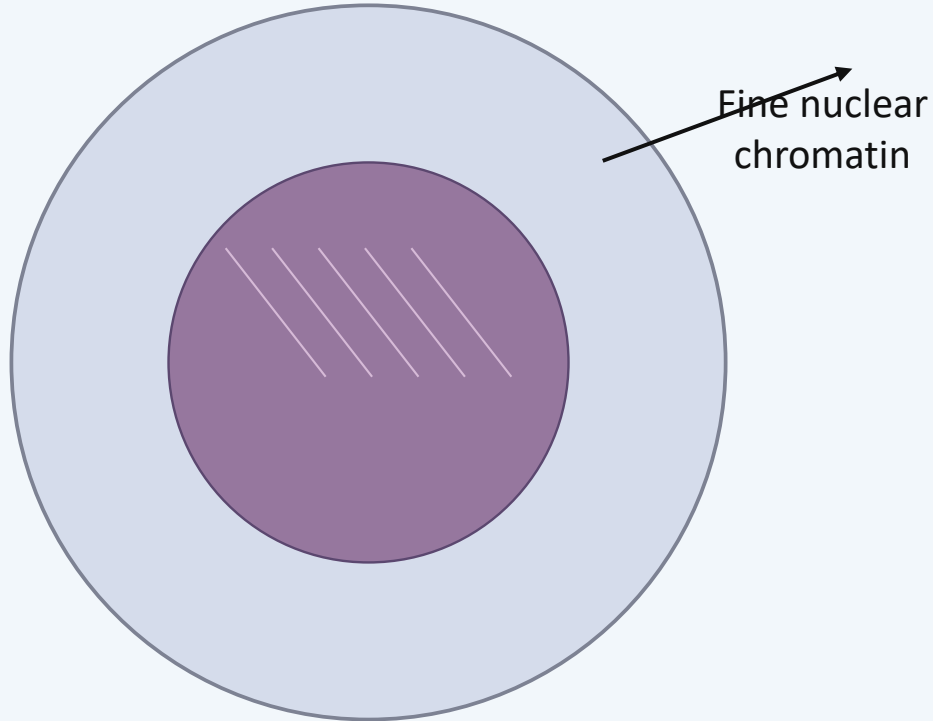
Schematic · causal sequence

The bone marrow is usually hypercellular



Schematic · causal sequence

Megaloblasts retain immature chromatin



Diagnostic interpretation

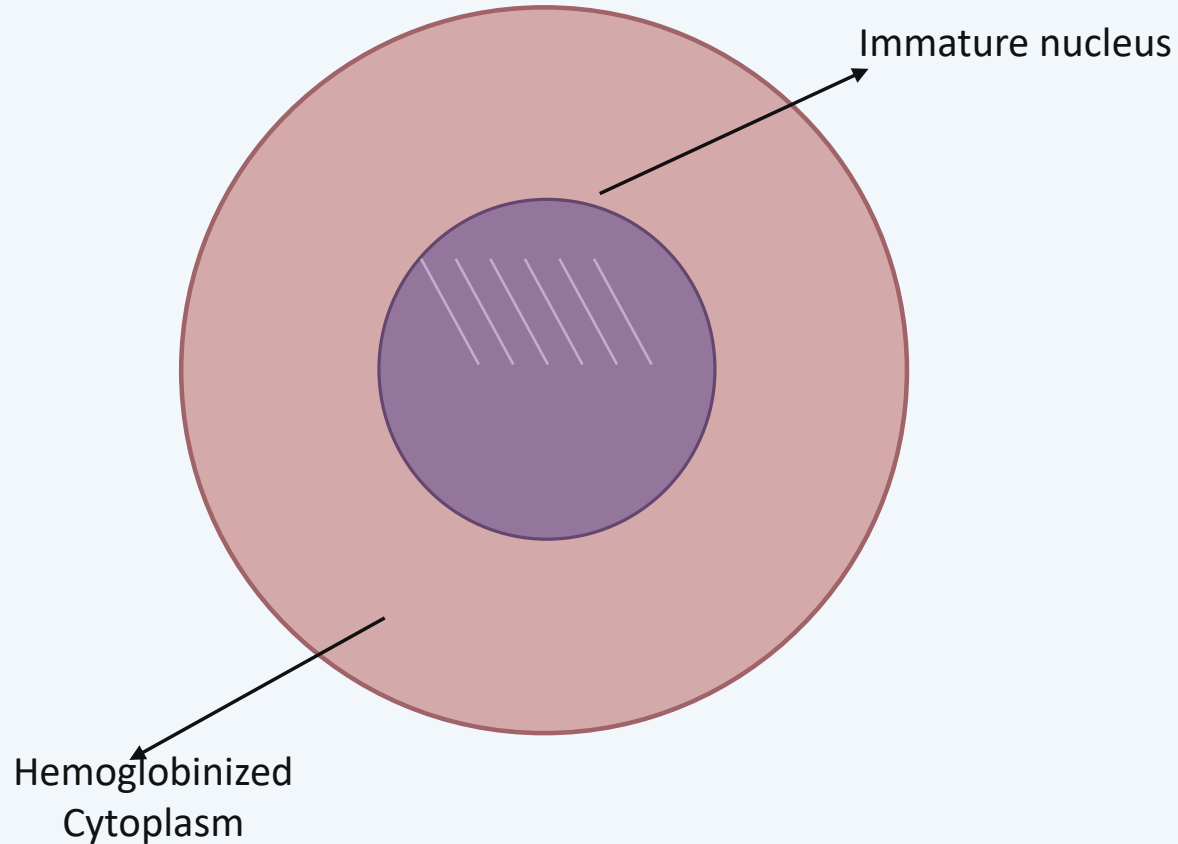
Erythroid precursors become enlarged.

Nuclei retain fine, immature chromatin.

Morphology reflects delayed nuclear maturation.

Schematic — original editable drawing; Not a clinical specimen

Nuclear–cytoplasmic asynchrony



Diagnostic interpretation

Cytoplasmic hemoglobinization advances.

Nuclear condensation lags behind.

Later erythroblasts retain nonpyknotic nuclei.

Schematic — original editable drawing; Not a clinical specimen

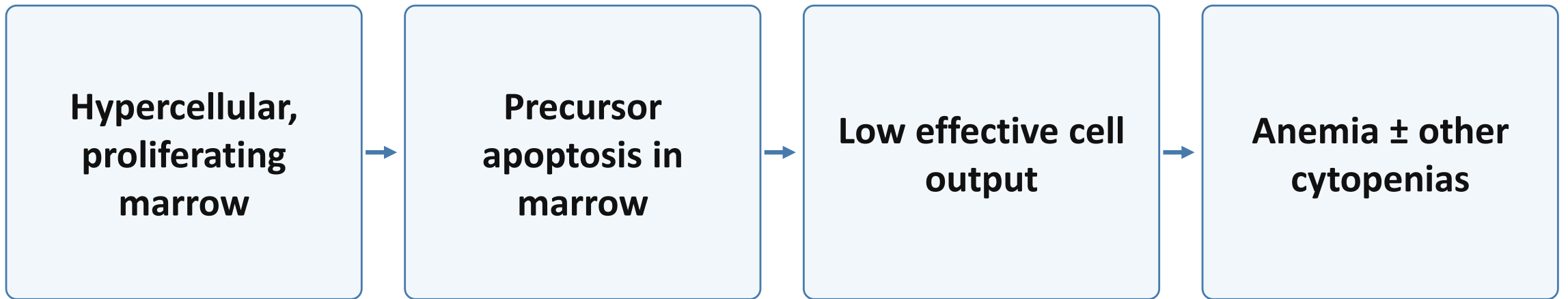
Granulocyte precursors are also dysmature

Giant metamyelocytes	Giant band forms	Shared cause
Enlarged maturing myeloid cells.	Granulocytic nuclear development is abnormal.	DNA synthesis failure affects multiple proliferating lineages.

Megakaryocytes may be abnormal

- Source morphology includes unusually large megakaryocytes.
- Nuclear shapes may be bizarre or multilobate.
- The multilineage pattern supports a broad DNA maturation defect.

Ineffective hematopoiesis drives cytopenias



Schematic · causal sequence

Pancytopenia can occur

Red cells

Megaloblastic anemia is central.

White cells

Leukopenia may coexist.

Platelets

Reduction may accompany ineffective multilineage production.

Folate and B₁₂ deficiency look alike on morphology

Folate deficiency

Macro-ovalocytes and hypersegmented neutrophils.

Megaloblastic marrow changes.

Vitamin B₁₂ deficiency

Same peripheral blood pattern.

Same dysmaturation in marrow.

Morphology establishes megaloblastosis, not the deficient vitamin.

Folate measurement distinguishes the deficiency

- Folate deficiency requires biochemical evidence of reduced folate availability.
- Decreased serum or red-cell folate as diagnostic support.
- Morphology alone cannot separate folate and vitamin B₁₂ deficiency.

Homocysteine rises in both deficiencies

Folate deficiency

Homocysteine is increased.

Folate is needed for the methionine reaction.

Vitamin B₁₂ deficiency

Homocysteine is also increased.

Methionine synthase requires cobalamin.

High homocysteine does not by itself identify the deficient vitamin.

Methylmalonate helps distinguish B₁₂ deficiency

Folate deficiency

Methylmalonate concentration is normal.

No direct block in the B₁₂-dependent mutase reaction.

Vitamin B₁₂ deficiency

Methylmalonate is increased.

Cobalamin-dependent metabolism is impaired.

Interpret markers in context of vitamin assays and the clinical picture.

Neurologic deficits distinguish the classic syndromes

Folate deficiency

Neurologic changes do not occur.

Hematologic features can be severe.

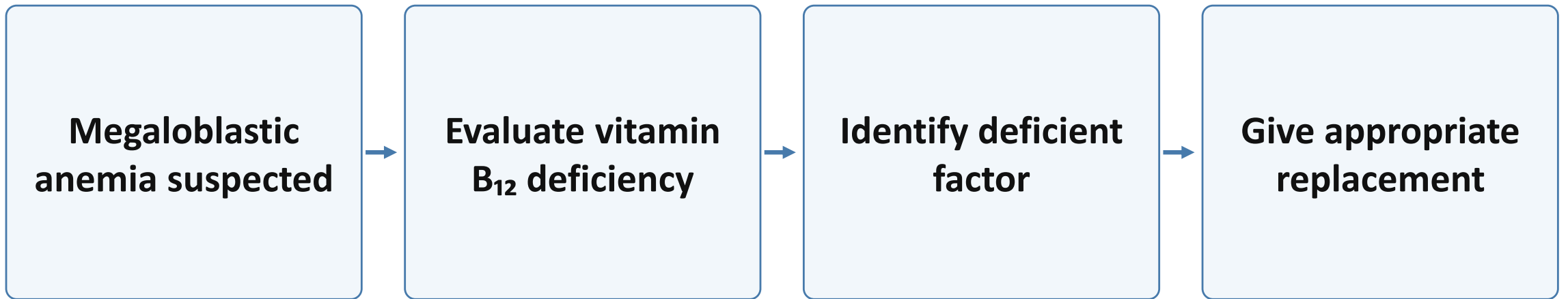
Vitamin B₁₂ deficiency

Neurologic injury may accompany anemia.

Spinal cord and peripheral nerve dysfunction can occur.

Folate replacement does not treat neurologic injury from B₁₂ deficiency.

Do not treat megaloblastosis blindly with folate

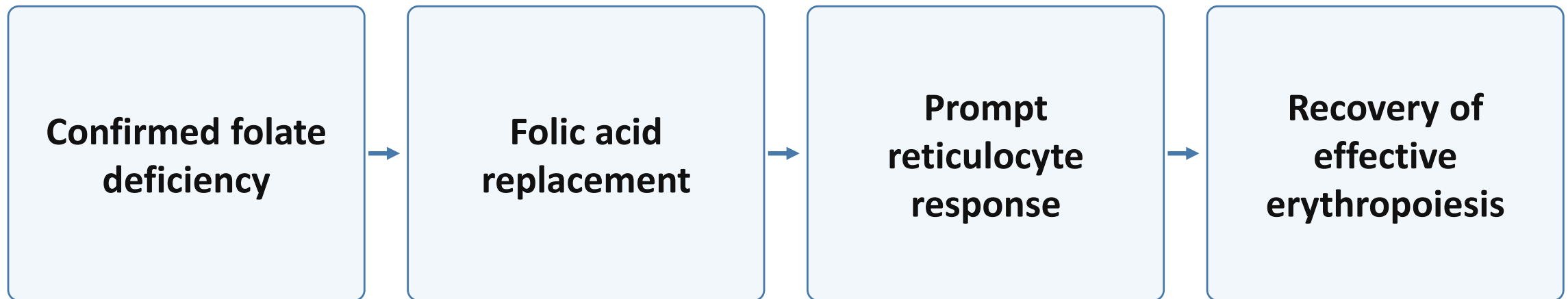


Schematic · causal sequence

Folate can mask vitamin B₁₂ deficiency anemia

- Folate administration can improve the blood counts even when B₁₂ is deficient.
- Hematologic correction does not protect against B₁₂-related neurologic deficits.
- Exclude vitamin B₁₂ deficiency before folate-only treatment.

Reticulocytosis indicates hematologic response



Schematic · causal sequence

Diagnostic reasoning: From pattern to cause

Macrocytic/megaloblastic pattern



Review diet, demand, intestinal disease and drugs



Measure folate and assess B₁₂



Interpret homocysteine + methylmalonate



Correct cause; Avoid overlooking B₁₂ deficiency

Case: Inadequate nutrition and alcohol use

An adult with prolonged poor nutrition and chronic alcohol use develops macro-ovalocytes and hypersegmented neutrophils.

What mechanisms of folate depletion should the clinician investigate?

Inadequate dietary folate.

Altered hepatic handling and urinary loss may contribute.

Assess other deficiencies and B₁₂ before folate alone.

Case: High erythropoietic demand

A patient with chronic hemolytic anemia has increased marrow activity but ordinary dietary folate intake.

Why can folate deficiency still develop?

Sustained erythropoiesis raises DNA synthesis requirements.

The usual intake may be relatively inadequate.

Case: Antimetabolite-associated marrow changes

A patient receiving methotrexate develops megaloblastic marrow changes and cytopenias.

Which biochemical step is directly targeted?

Dihydrofolate reductase is inhibited.

Active FH₄ regeneration is impaired.

Folate-dependent DNA synthesis becomes deficient.

Case: Exclude an occult B₁₂ deficiency

A patient has macro-ovalocytes, high homocysteine and megaloblastic marrow changes. Vitamin B₁₂ status is unknown.

Is isolated folate therapy sufficient at this stage?

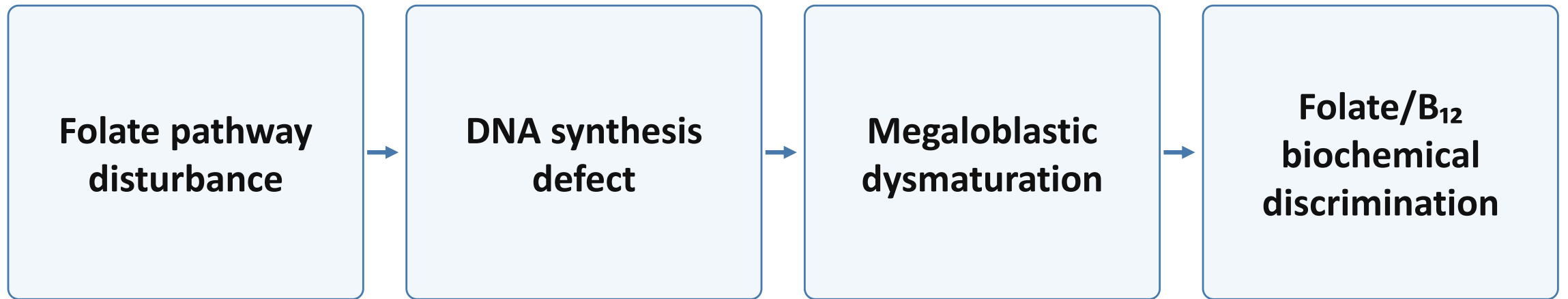
No: Findings may arise from either deficiency.

Evaluate vitamin B₁₂ and methylmalonate before folate-only therapy.

A compact biochemical comparison

Feature	Folate deficiency	Vitamin B ₁₂ deficiency
Megaloblastic morphology	Present	Present
Homocysteine	Increased	Increased
Methylmalonate	Normal	Increased
Classic neurologic effects	Absent	May occur
Response of anemia to folate	Yes	Can improve despite B ₁₂ deficit

Mechanism, morphology and diagnosis connect



Schematic · causal sequence

Five essential conclusions

- The immediate lesion is inadequate DNA synthesis, not defective hemoglobin synthesis.
- Impaired folate availability arises from low supply, greater demand or blocked utilization.
- Blood and marrow morphology are indistinguishable from vitamin B₁₂ deficiency.
- Methylmalonate remains normal in isolated folate deficiency.
- Vitamin B₁₂ deficiency must be excluded before folate-only therapy.

Selected textbook references

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 14, “Anemia of Folate Deficiency,” printed p. 595.
- Companion parent section: “Megaloblastic Anemia,” printed pp. 591–592.
- Related figure discussions: Fig. 14.18 (folate–cobalamin metabolism) and Fig. 14.19 (one-carbon transfer).