

Anemia of vitamin B12 deficiency: Pernicious anemia

Autoimmune gastritis, impaired cobalamin absorption, and
megaloblastic hematopoiesis

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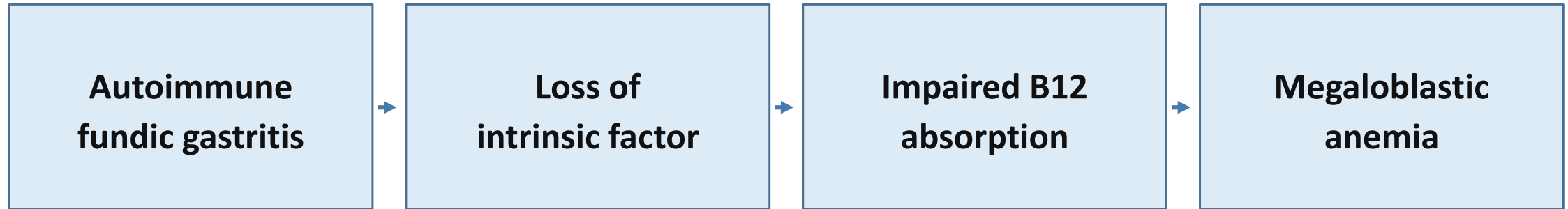
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Learning objectives

- Trace cobalamin from dietary release to ileal uptake and tissue delivery.
- Explain how autoimmune gastric injury causes intrinsic-factor deficiency.
- Connect cobalamin-dependent reactions to hematologic and neurologic injury.
- Recognize morphology, diagnostic patterns, differentials, and response to replacement.

Pernicious anemia: A linked multiorgan disorder



A gastric immune process produces a systemic hematologic deficit.

Neurologic abnormalities may occur in parallel, even without severe anemia.

Pernicious anemia is not synonymous with all B12 deficiency

Pernicious anemia	Other B12-deficiency states
Autoimmune injury to gastric body/fundus	Dietary deficiency or nonautoimmune absorption defect
Loss of parietal-cell intrinsic factor	Multiple possible sites: stomach, pancreas, ileum
Atrophic gastritis persists after replacement	Underlying lesion depends on the cause

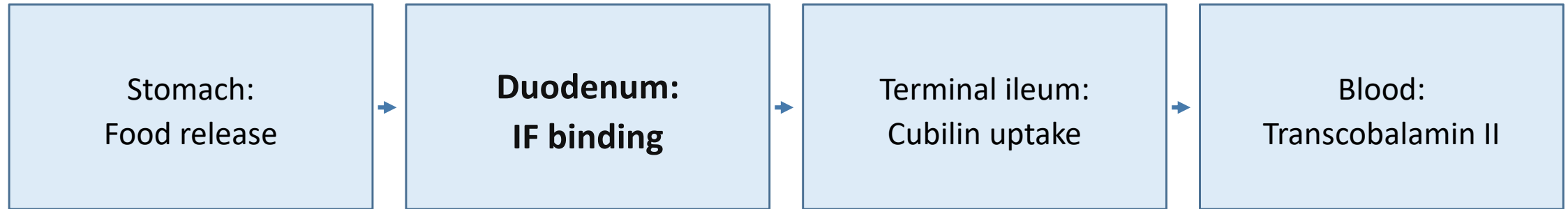
Why cobalamin deficiency develops gradually

- Vitamin B12 (cobalamin) is supplied chiefly by animal-derived foods.
- The daily requirement is approximately 2–3 µg.
- The liver stores sufficient B12 for several years with an adequate diet.
- Clinical deficiency emerges when intake or uptake remains inadequate long enough to deplete stores.

Dietary sources and the need for absorption

- Meat, fish, milk, and eggs are major dietary sources.
- Plants and vegetables contain little cobalamin.
- Normal dietary supply does not prevent pernicious anemia when intrinsic factor is deficient.
- Dietary history alone therefore cannot establish the mechanism of B12 deficiency.

Normal vitamin B12 absorption: The pathway



Pepsin, haptocorrin, pancreatic proteases, and intrinsic factor act sequentially.

Failure at different steps can produce the same deficient state.

Stomach: Release from dietary proteins

Dietary B12 is bound to food proteins.



Pepsin releases B12; It then associates with haptocorrin from saliva.

Loss of gastric acid–pepsin function can compromise food-bound B12 availability.

Haptocorrin protects B12 in the stomach

Salivary haptocorrin binds liberated cobalamin.



The haptocorrin–B12 complex travels to the duodenum.

The next transfer requires pancreatic enzymes; IF does not bind food-derived B12 first.

Duodenum: Transfer from haptocorrin to intrinsic factor

Pancreatic proteases digest
haptocorrin.



Liberated B12 binds intrinsic factor
(IF).

Exocrine pancreatic insufficiency can disrupt this transfer.

Intrinsic factor originates from gastric parietal cells

Fundic parietal cells synthesize intrinsic factor.



IF binds B12 and supports receptor-mediated uptake in the terminal ileum.

Pernicious anemia results when immune-mediated gastric atrophy deprives the gut of IF.

Ileal uptake requires cubilin

The IF–B12 complex reaches the terminal ileum.



Cubilin on ileal epithelial cells mediates complex binding and endocytosis.

Ileal disease or resection bypasses an otherwise intact stomach and pancreas.

Transcobalamin II delivers absorbed vitamin B12

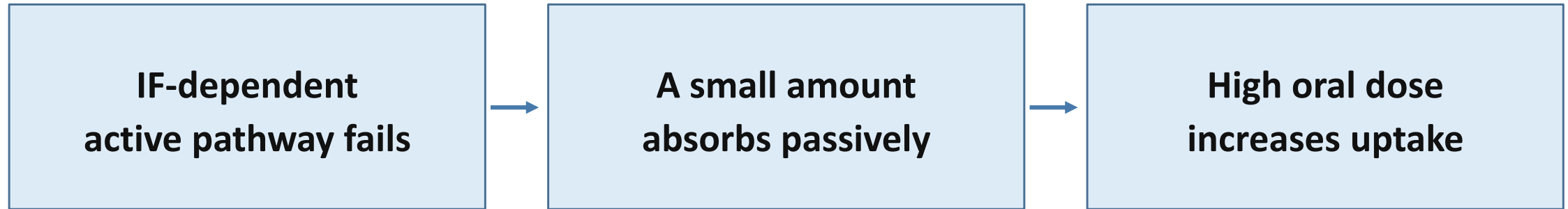
Inside ileal epithelial cells, B12 associates with transcobalamin II.



Bloodborne transcobalamin II carries B12 to the liver, marrow, gut, and other tissues.

Absorption is only the beginning: Highly proliferative tissues require sustained delivery.

Why high-dose oral replacement can work



Passive intestinal absorption is inefficient, but it provides a route independent of the main IF-cubilin pathway.

Both parenteral and high-dose oral B12 can be used for replacement.

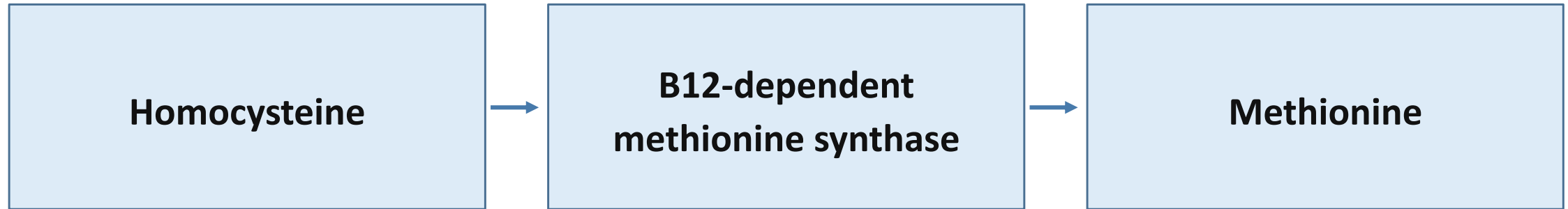
Absorption failure can occur at multiple sites

Site of disruption	Consequence for B12 uptake
Stomach: achlorhydria / pepsin loss	Poor release of B12 from food
Stomach: parietal-cell loss / gastrectomy	Loss of intrinsic factor
Duodenum: pancreatic insufficiency	Failure to release B12 from haptocorrin
Ileum: resection or diffuse disease	Failure of IF–B12 uptake

Only two human enzyme reactions require vitamin B12

- Methionine synthase uses methylcobalamin.
- Methylmalonyl-CoA mutase uses adenosylcobalamin.
- Disruption affects folate recycling, DNA synthesis, and methylmalonate metabolism.
- The mechanism of neurologic injury is less fully resolved than that of anemia.

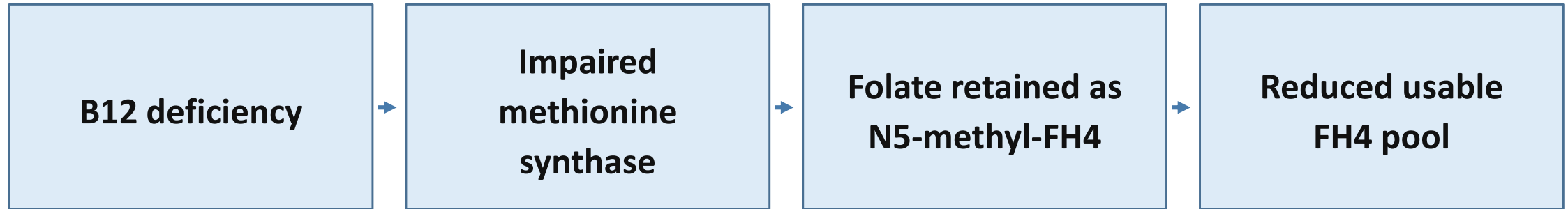
Methionine synthase links B12 to folate



The methyl donor is N5-methyl-tetrahydrofolate (N5-methyl-FH4).

The same reaction regenerates tetrahydrofolate (FH4) for one-carbon transfer reactions.

The methyl-folate trap



This proposed metabolic trap reduces folate available for thymidylate synthesis.

Impaired production of metabolically active folate polyglutamates may also contribute.

Thymidylate synthesis becomes limiting



Thymidylate is required for DNA synthesis in dividing cells.

Cells continue cytoplasmic growth while nuclear maturation lags.

Nuclear–cytoplasmic asynchrony explains megaloblasts

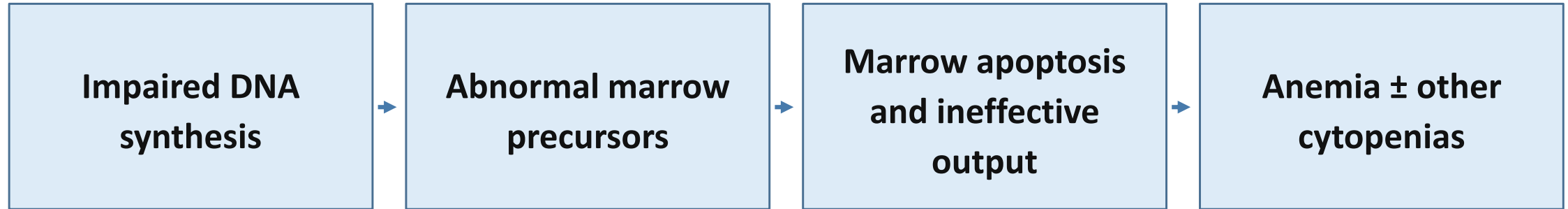
DNA synthesis and nuclear maturation are delayed.



Cytoplasmic protein synthesis and hemoglobin accumulation continue.

Erythroid precursors become large, with immature nuclear chromatin despite mature cytoplasm.

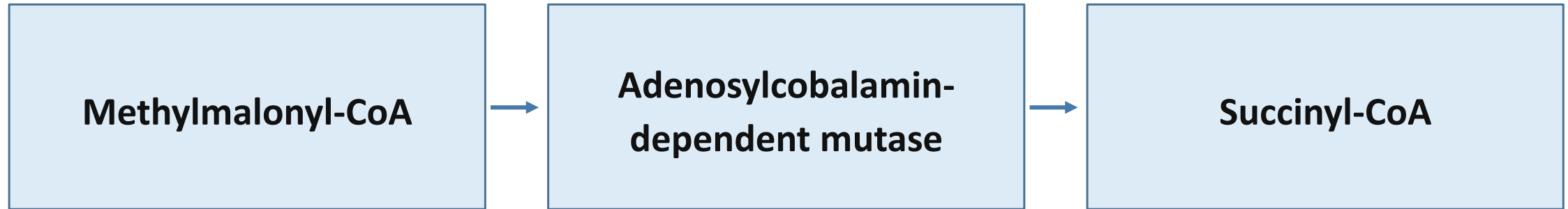
From biochemical deficiency to pancytopenia



The marrow can be hypercellular while peripheral counts are reduced.

High erythropoietic drive does not correct the underlying DNA synthetic block.

The second cobalamin-dependent enzyme



Loss of mutase activity in B12 deficiency causes methylmalonic acid accumulation.

Methylmalonate is a useful biochemical discriminator from folate deficiency.

Methylmalonic acid rises in B12 deficiency

- Adenosylcobalamin is the cofactor for methylmalonyl-CoA mutase.
- Loss of enzyme activity increases methylmalonic acid in plasma and urine.
- Homocysteine also rises through the methionine synthase pathway.
- An elevated methylmalonate supports B12 deficiency, whereas isolated folate deficiency does not raise it.

The neurologic mechanism remains incompletely explained

- Abnormal methylmalonate and propionate metabolism has been proposed to alter neuronal lipids.
- The proposed mechanism would predispose to myelin injury.
- Hereditary mutase deficiencies do not reproduce the same characteristic cord syndrome.
- The association is established; This particular causal explanation remains uncertain.

Folate replacement and B12 replacement are not interchangeable

Hematologic effects

Folate may improve the anemia of B12 deficiency

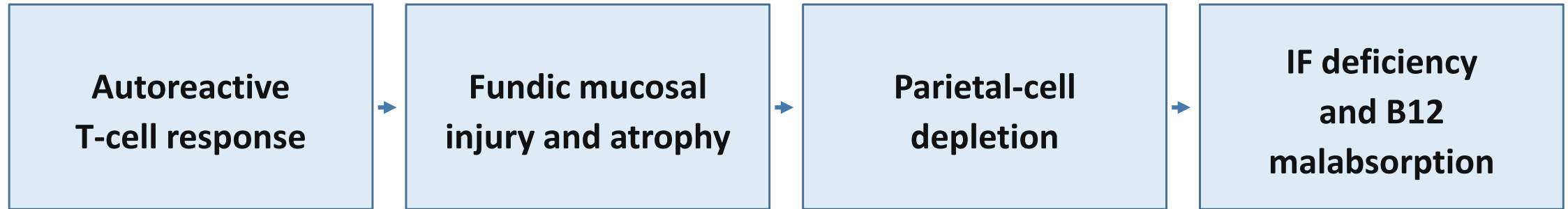
B12 replacement corrects the cobalamin-dependent hematologic deficit

Neurologic effects

Folate does not prevent B12-related neurologic injury

Timely B12 treatment can halt or improve neurologic progression

Autoimmune gastritis drives pernicious anemia



Autoantibodies are useful markers, but are not the primary initiators of mucosal injury.

The immune process precedes depletion of hepatic cobalamin reserves.

The gastric fundus is the principal site of injury

- Chronic atrophic gastritis affects the fundic mucosa.
- Both parietal and chief cells are lost; Parietal cells may be virtually absent.
- Gland atrophy is accompanied by lymphocytes and plasma cells.
- Loss of the intrinsic-factor-producing cell population is central to B12 malabsorption.

T cells initiate the mucosal lesion

An autoreactive T-cell response damages the gastric mucosa.



Loss of gastric glands and parietal cells is followed by autoantibody formation.

Serologic antibodies identify the immune process; They should not be interpreted as its sole pathogenic mechanism.

Type I anti-intrinsic-factor antibodies

Antibody recognizes intrinsic factor.



It blocks B12 binding to IF and prevents normal complex formation.

Type I antibodies are present in about 75% of affected patients.

Type II anti-intrinsic-factor antibodies

The IF–B12 complex may form.



Type II antibody prevents its normal interaction with the ileal cubilin receptor.

Both type I and type II antibodies may occur in plasma and gastric juice.

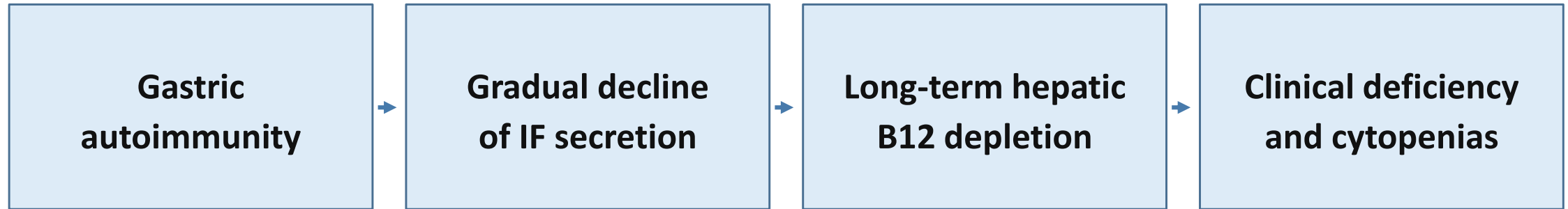
Type III antibodies target the parietal-cell proton pump

- The recognized antigen includes the α and β subunits of the gastric proton pump.
- Type III antibodies are present in 85%–90% of affected patients.
- They are not disease-specific; They may occur in idiopathic chronic gastritis in older adults.
- An anti-parietal-cell result therefore differs from a highly specific anti-IF result.

Autoantibodies: Functional target and interpretation

Autoantibody	Functional target / diagnostic meaning
Type I, anti-IF	Blocks B12 binding to IF; highly specific marker
Type II, anti-IF	Interferes with IF–B12 binding to ileal receptor
Type III, anti-parietal cell	Recognizes proton pump; less specific

Why an immune lesion takes years to cause anemia



The clinical lag reflects substantial pre-existing vitamin stores.

Once stores fall, rapidly dividing hematopoietic cells become vulnerable.

Pernicious anemia usually appears in older adults

- The median age at diagnosis is approximately 60 years.
- Disease before age 30 is uncommon.
- The disorder occurs across ethnic populations, despite some geographic differences in prevalence.
- Genetic susceptibility is suspected; A simple Mendelian pattern is not established.

Autoimmune comorbidity strengthens suspicion

- Autoimmune thyroiditis is an important association.
- Autoimmune adrenalitis is another reported association.
- These associations support an underlying propensity to autoimmunity.
- They do not replace direct evidence of cobalamin deficiency and its mechanism.

B12 deficiency: Autoimmune and nonautoimmune pathways

Pernicious anemia	Other etiologies
Autoimmune fundic gland loss	Low dietary intake
Intrinsic factor deficiency	Gastrectomy or impaired food release
Persistent gastric lesion	Pancreatic or ileal malabsorption
Can coexist with other autoimmunity	Competition by intestinal parasites / overgrowth

Insufficient dietary intake

- Sustained intake without adequate cobalamin eventually exhausts hepatic stores.
- Strictly vegetarian or macrobiotic diets may provide inadequate cobalamin.
- The delay to anemia may be long because endogenous reserves are substantial.
- Dietary deficiency does not itself imply autoimmune gastritis.

Gastrectomy and impaired gastric digestion

- Gastrectomy may remove the intrinsic-factor-producing mucosa.
- Achlorhydria and reduced pepsin can impair release of food-bound B12.
- The latter mechanism may occur in some older adults.
- Both operate proximally but are mechanistically distinct.

Exocrine pancreatic insufficiency

- Normally pancreatic proteases cleave the haptocorrin–B12 complex.
- Failure to release B12 prevents efficient transfer to intrinsic factor.
- Ileal epithelium may be structurally normal despite deficient uptake.
- The location of dysfunction explains the malabsorption.

Ileal disease and ileal resection

- The IF–B12 complex is absorbed in the terminal ileum.
- Resection of the ileal segment can interrupt receptor-mediated uptake.
- Diffuse ileal disease may have the same functional consequence.
- Normal intrinsic factor cannot compensate for absent absorptive surface.

Competition for intestinal cobalamin

- Fish tapeworm infestation can compete for available B12.
- Bacterial overgrowth in blind loops is another cause listed in the megaloblastic-anemia context.
- Dietary adequacy does not exclude intestinal competition.
- Exposure and anatomic history help localize the etiology.

Nitrous oxide can functionally inactivate B12

Recreational nitrous oxide exposure oxidizes and inactivates cobalamin.



Biochemical deficiency and neurologic symptoms may appear despite a different underlying mechanism from pernicious anemia.

Exposure history matters when B12-related neurologic signs are prominent.

Increased demand may produce relative deficiency

- Increased demand is described in pregnancy, hyperthyroidism, disseminated cancer, and chronic infection.
- These circumstances can expose a marginal supply of cobalamin.
- They do not necessarily indicate intrinsic-factor deficiency.
- Evaluate intake, absorption, and demand as separate axes.

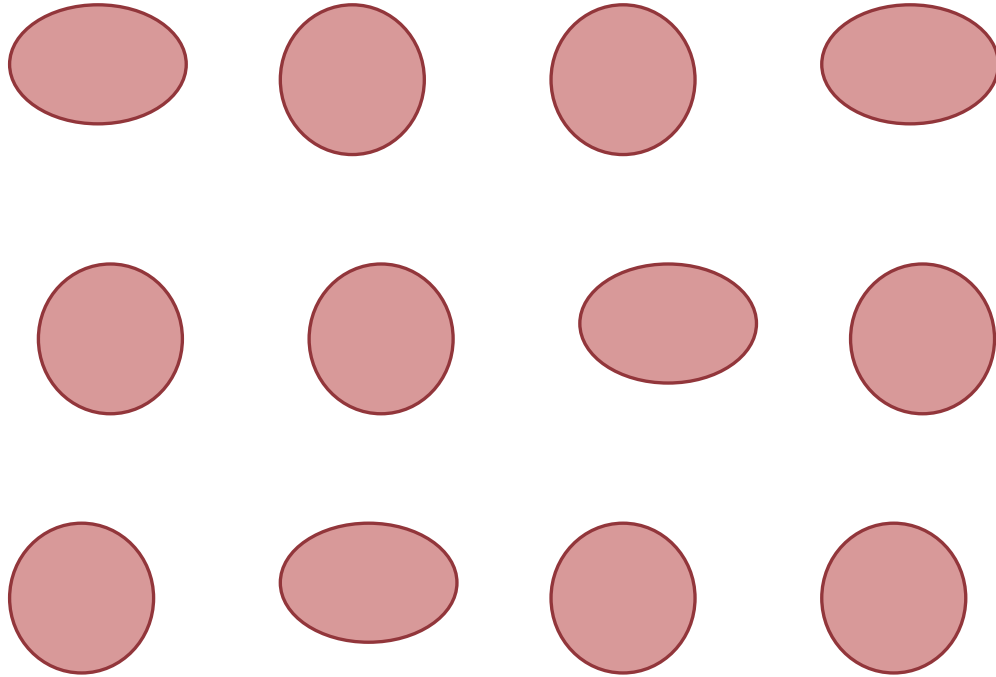
Localize the defect using physiology

Clinical clue	Likely disrupted step
Autoimmune gastric disease	Intrinsic factor production
Pancreatic insufficiency	Haptocorrin proteolysis
Terminal ileal resection	Cubilin-dependent uptake
Dietary restriction	Cobalamin input
Nitrous oxide exposure	Functional cobalamin activity

Peripheral blood: A macrocytic production disorder

- Macro-ovalocytes are highly characteristic of megaloblastic anemia.
- There is variation in red cell size and shape: Anisocytosis and poikilocytosis.
- Anemia can be severe and the reticulocyte response is inappropriately low.
- Nucleated erythroid forms may circulate in marked disease.

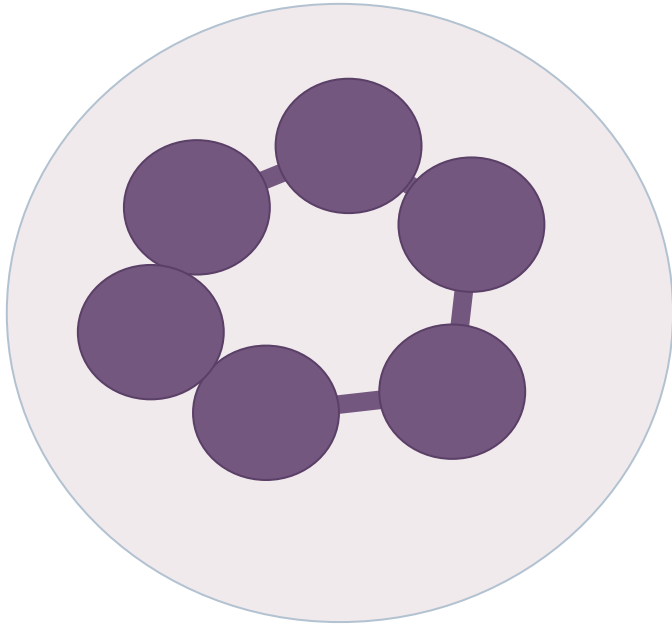
Macro-ovalocytes: A peripheral-smear schematic



Macro-ovalocytes: Exaggerated form (schematic)

- Red cells are enlarged and often oval.
- Apparent deep staining does not mean increased mean corpuscular hemoglobin concentration.
- Actual morphology requires a genuine stained peripheral smear for diagnostic evaluation.

Neutrophil hypersegmentation: A smear clue



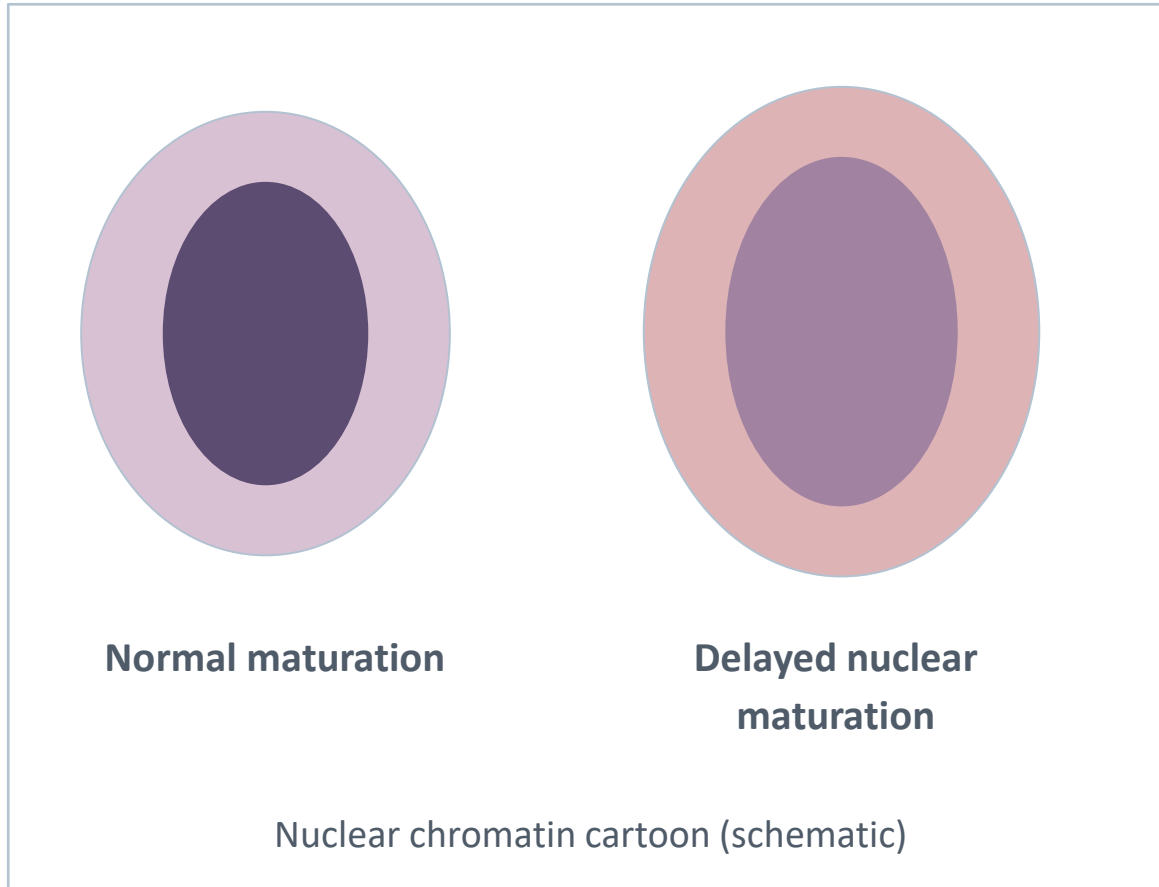
Six-lobed nucleus: Simplified schematic

- Neutrophils show increased nuclear lobation.
- Hypersegmentation involves five or more nuclear lobes.
- It supports a megaloblastic process but does not distinguish B12 from folate deficiency.

Bone marrow: Hypercellularity despite cytopenia

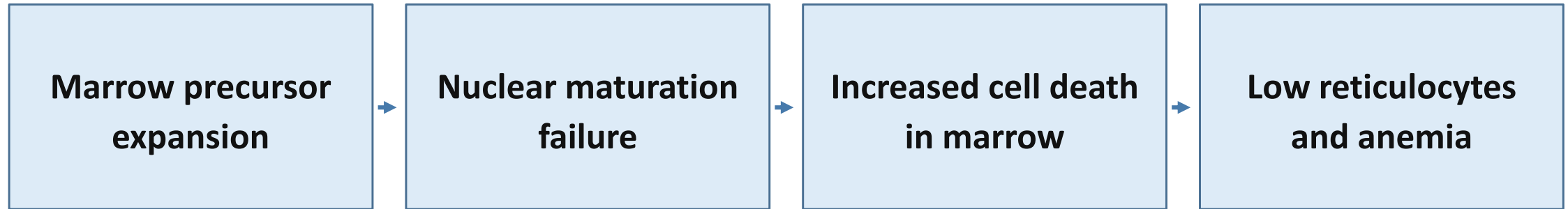
- Increased erythropoietic growth signals expand marrow precursors.
- Defective DNA synthesis prevents effective terminal maturation.
- Many precursors undergo intramedullary apoptosis.
- Marrow hypercellularity therefore coexists with inadequate blood-cell production.

Megaloblasts show nuclear–cytoplasmic asynchrony



- Large erythroid precursors retain finely dispersed nuclear chromatin.
- Hemoglobin accumulation proceeds despite delayed nuclear condensation.
- Granulocytic precursors may be giant metamyelocytes or band forms.

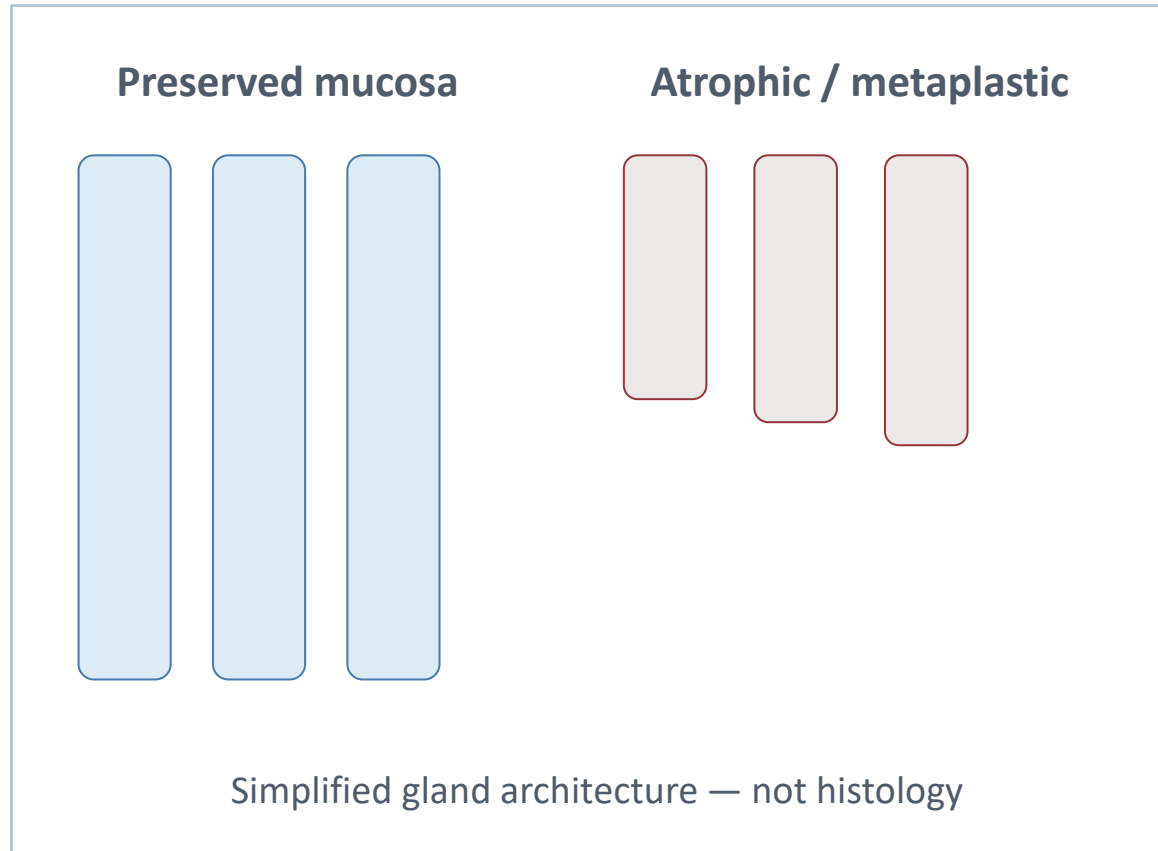
Ineffective erythropoiesis explains laboratory discordance



The marrow response is quantitatively increased but qualitatively ineffective.

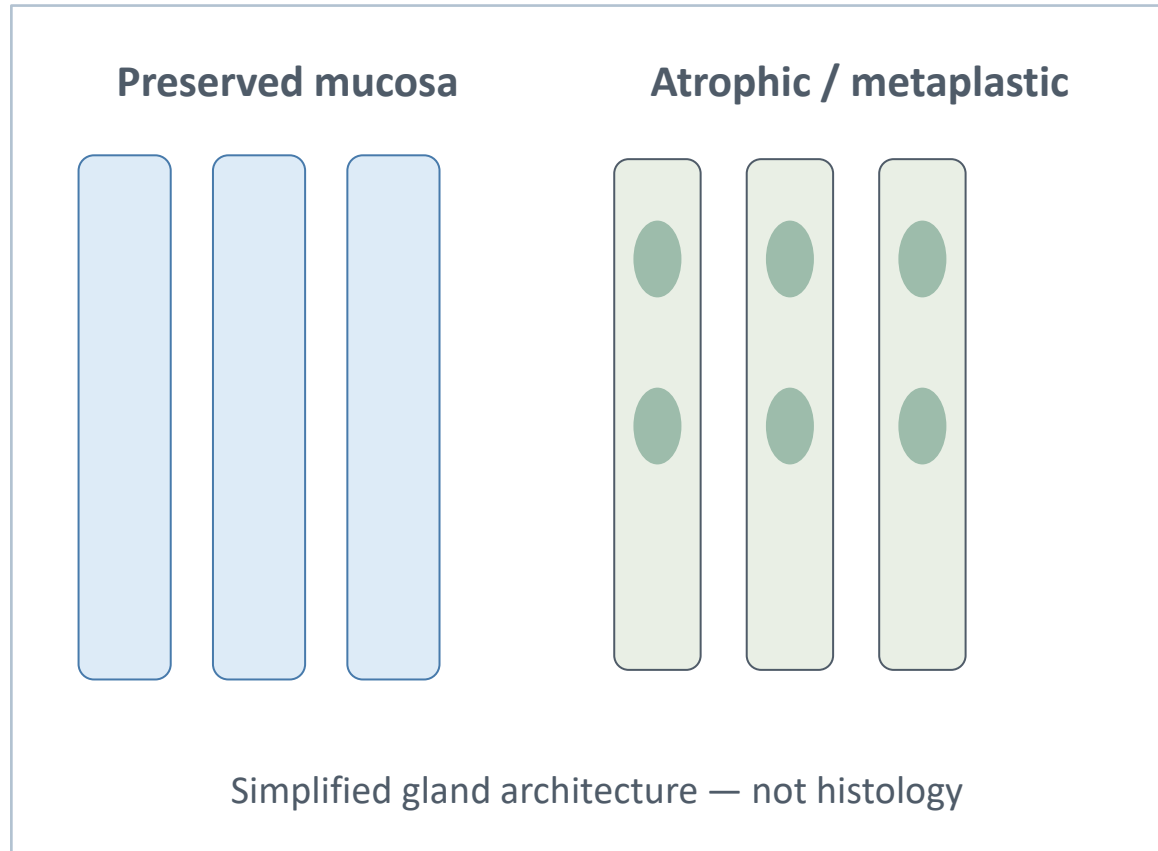
Other blood-cell lineages may also be affected, causing leukopenia and thrombocytopenia.

Fundic atrophy removes the functional gastric glands



- Chronic gastritis produces loss of both parietal and chief cells.
- Parietal cells may become virtually absent in established disease.
- Glandular loss explains loss of intrinsic factor and impaired vitamin uptake.

Intestinal metaplasia replaces fundic epithelium



- Mucus-producing intestinal-type goblet cells may replace gastric glands.
- Some mucosal epithelial cells show megaloblastic enlargement.
- Atrophy and metaplasia persist after B12 replacement.

Atrophic glossitis: A visible mucosal consequence

- The tongue can become smooth, shiny, and “beefy” in appearance.
- This reflects epithelial changes in a rapidly renewing mucosal surface.
- Glossitis is supportive but not specific to pernicious anemia.
- Its presence should prompt correlation with blood morphology and nutritional status.

Hematologic and gastric morphology respond differently

Reversible with B12

Megaloblastic marrow change

Macrocytic anemia and low reticulocyte output

Mucosal megaloblastosis may improve

Persistent despite B12

Autoimmune fundic atrophy

Established intestinal metaplasia

Underlying gastric carcinoma risk

Spinal cord involvement: Major affected tracts

Dorsal columns	Lateral columns
Loss of proprioceptive pathway function	Motor pathway impairment
Sensory ataxia and altered position sense	Spasticity / paraparesis
Part of subacute combined degeneration	Part of subacute combined degeneration

Subacute combined degeneration

- Demyelination affects dorsal and lateral spinal tracts.
- More advanced injury may be accompanied by axonal loss.
- The clinical pattern includes sensory ataxia, spastic paraparesis, and paresthesias.
- Neurologic pathology may appear without conspicuous hematologic disease.

Neurologic symptoms require separate assessment

- Peripheral neuropathic symptoms and severe lower-limb paresthesias may occur.
- Posterior-root ganglia and peripheral nerves can also be affected.
- Severe or longstanding neurologic damage may not fully reverse.
- Hematologic normalization must not be used as the only measure of recovery.

B12 neuropathy can precede anemia recognition

Cord and peripheral-nerve injury may develop independently of the severity of blood abnormalities.



A near-normal blood count cannot safely exclude clinically important cobalamin-related neurologic dysfunction.

Neurologic findings and exposure history warrant direct B12 evaluation.

Clinical presentation is usually insidious

- Anemia develops gradually over years as B12 reserves decline.
- Symptoms may be substantial by the time the disorder is recognized.
- Progression continues if the deficient state is untreated.
- A combination of anemia, glossitis, and neurologic signs is particularly suggestive.

The typical diagnostic laboratory pattern

Finding	Pathophysiologic interpretation
Megaloblastic macrocytic anemia	Impaired DNA synthesis
Leukopenia / hypersegmented neutrophils	Ineffective granulopoiesis
Low serum B12	Cobalamin depletion
High homocysteine + high methylmalonic acid	Impaired B12-dependent reactions

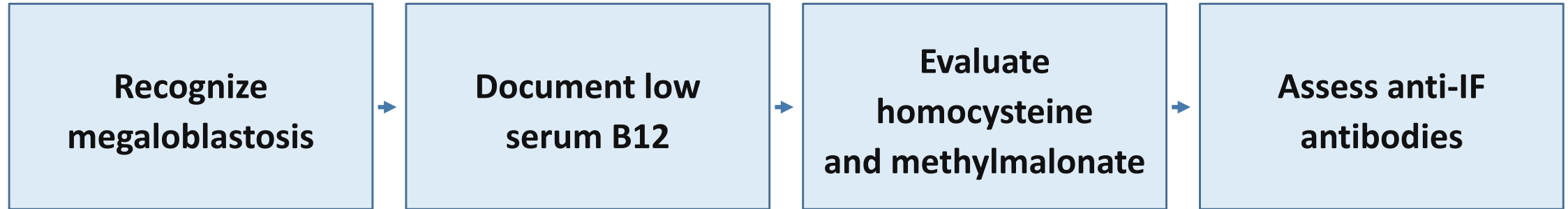
Anti-intrinsic-factor testing identifies the etiology

- Serum anti-intrinsic-factor antibodies are highly specific for pernicious anemia.
- Antibody detection supports autoimmune intrinsic-factor dysfunction.
- Not every patient has detectable antibodies; A negative result cannot rule out disease.
- Anti-parietal-cell antibodies are less specific.

B12 deficiency versus folate deficiency

Vitamin B12 deficiency	Folate deficiency
Megaloblastic blood and marrow changes	Same megaloblastic morphology
Homocysteine increased	Homocysteine increased
Methylmalonic acid increased	Methylmalonic acid normal
Neurologic injury can occur	Characteristic B12 neurologic injury absent

Diagnostic integration: Blood, metabolites, and antibodies



Use the history to assess dietary, gastric, pancreatic, ileal, and nitrous oxide mechanisms.

Interpret the biochemical findings with the clinical history and antibody results.

Reticulocytosis documents early hematologic response

- A marked reticulocyte response follows parenteral B12 therapy.
- A rise in reticulocytes and hematocrit begins at approximately 5 days.
- The response supports the diagnosis and corrects ineffective hematopoiesis.
- Response to replacement should be interpreted alongside the underlying gastric etiology.

Replacement corrects the deficit, not the autoimmunity

- Parenteral B12 or high-dose oral B12 can treat the anemia.
- Neurologic progression may improve or stop; Recovery can be incomplete.
- Gastric atrophy and metaplasia are not reversed by cobalamin therapy.
- Pernicious anemia therefore has implications beyond normalization of blood counts.

Persistent gastric pathology confers cancer risk

- Gastric mucosal atrophy and metaplasia persist despite B12 therapy.
- Pernicious anemia is associated with increased gastric carcinoma risk.
- The cancer risk is not erased by correcting the anemia.
- This reflects the continuing significance of the underlying autoimmune gastric disease.

Application case: Autoimmune deficiency

An older adult has macro-ovalocytes, hypersegmented neutrophils, low serum B12, and high methylmalonic acid. Anti-intrinsic-factor antibodies are detected.

What connects the gastric lesion to the blood findings?

- Autoimmune fundic atrophy reduces parietal cells and intrinsic factor.
- Ileal B12 uptake falls, causing cobalamin deficiency.
- Impaired DNA synthesis produces ineffective, megaloblastic hematopoiesis.

Application case: Neurologic presentation

A person with paresthesias and sensory ataxia has a B12-related biochemical abnormality, but lacks striking anemia.

Why does this not exclude clinically significant B12 deficiency?

- Neurologic injury may occur without overt hematologic changes.
- Spinal dorsal and lateral pathways can be affected.
- Replacing folate alone does not protect against the neurologic deficit.

Final synthesis: Three linked pathologies

Location / system	Defining lesion or consequence
Gastric body and fundus	Autoimmune atrophy → intrinsic factor loss
Bone marrow / peripheral blood	Defective DNA synthesis → megaloblastosis / cytopenias
Spinal cord / nerves	Demyelinating neurologic injury
Gastric mucosa over time	Persistent metaplasia and carcinoma risk

Key conclusions

- Pernicious anemia is the autoimmune-gastritis form of vitamin B12 deficiency.
- Intrinsic-factor loss impairs terminal ileal uptake after a long latency.
- Defective folate-dependent DNA synthesis causes megaloblastic hematopoiesis.
- Neurologic injury and gastric cancer risk must be addressed independently of the anemia.