

Vitamin B₁₂ Deficiency

Subacute combined degeneration of the spinal cord

Neuropathology · Clinicopathologic correlations

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Learning objectives

- Define subacute combined degeneration (SCD) as a B₁₂-related tract disorder.
- Relate bilateral sensory and motor deficits to degeneration of spinal pathways.
- Explain myelin vacuolation, late axonal loss, and the effect of treatment timing.
- Connect absorption, biochemical roles, and systemic features to neurologic disease.

Neurologic consequences distinguish B₁₂ deficiency

- Vitamin deficiency can injure neural tissue as well as hematopoietic tissue.
- Neurologic manifestations need not parallel the severity of megaloblastic anemia.
- Prompt recognition is important because established motor disability may not recover.

Why B-vitamin deficiencies affect the CNS

- Neural tissue has substantial metabolic demands.
- B vitamins participate in reactions essential for cellular metabolism.
- B₁ and B₁₂ deficiency as major neurologic vitamin-deficiency syndromes.

Different principal syndromes

B₁ deficiency: Wernicke–Korsakoff spectrum



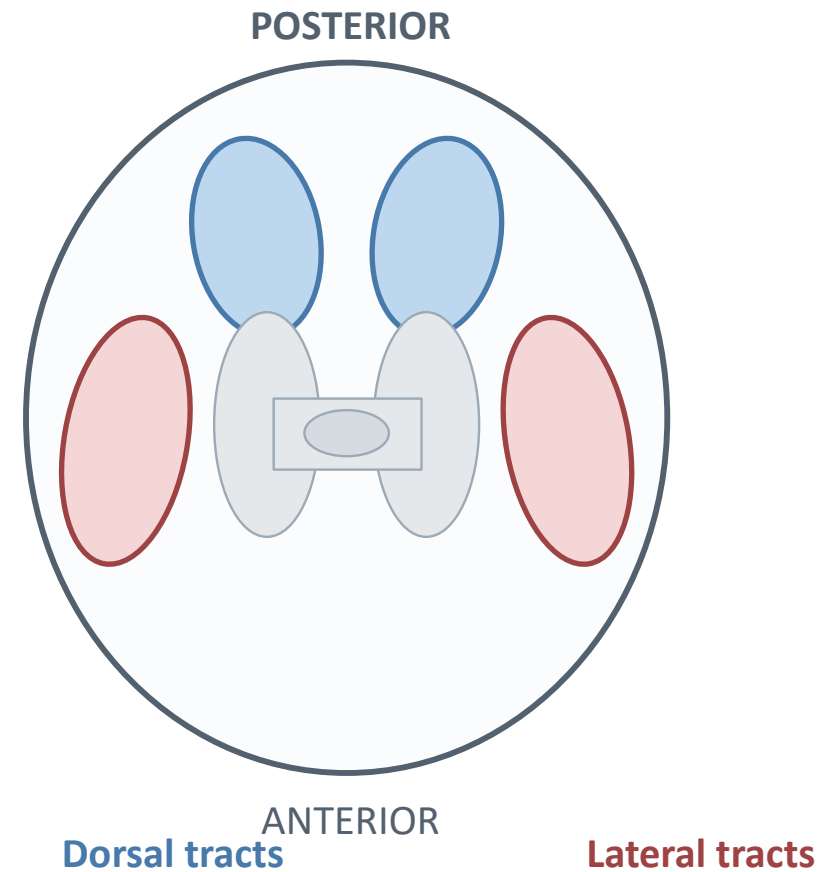
B₁₂ deficiency: Subacute combined degeneration

Subacute combined degeneration: Definition

- A neurologic disorder caused by vitamin B₁₂ deficiency.
- Characterized by degeneration of both ascending and descending spinal tracts.
- White-matter myelin injury is an early pathologic feature; Axonal degeneration may follow.

Spinal cord tract distribution

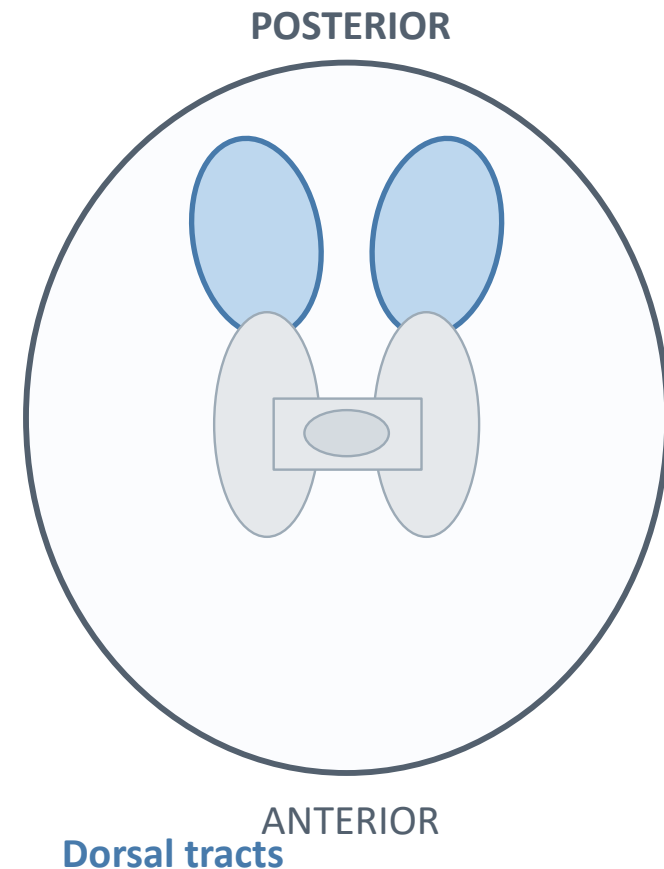
- Involvement of dorsal and lateral spinal tracts.
- The combined pattern accounts for simultaneous sensory ataxia and spastic paraparesis.
- The drawing identifies regions, not precise histologic lesion borders.



Schematic regions · not a histologic section

Dorsal tract injury and sensory ataxia

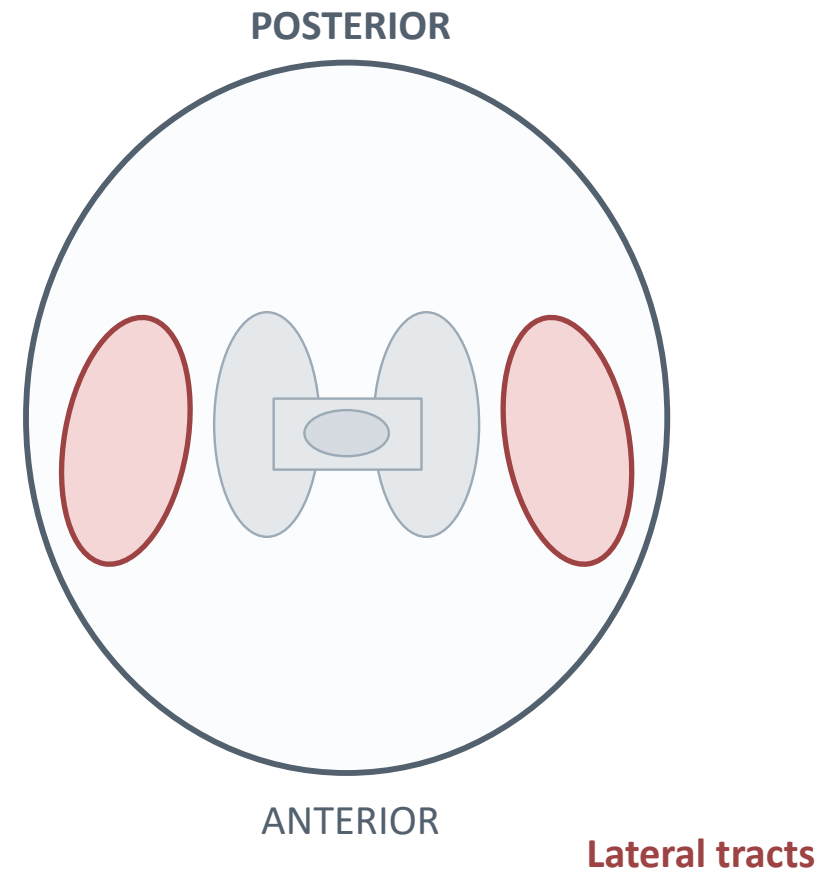
- Ascending tracts convey sensory information from lower body pathways.
- Dorsal-tract involvement corresponds to the sensory ataxia described in the text.
- Sensory abnormalities often appear before severe motor impairment.



Schematic regions · not a histologic section

Lateral tract injury and spastic paraparesis

- Descending motor tracts in lateral cord white matter may degenerate.
- The clinical correlate is progressive spastic weakness of the lower extremities.
- Severe progression can culminate in paraplegia.



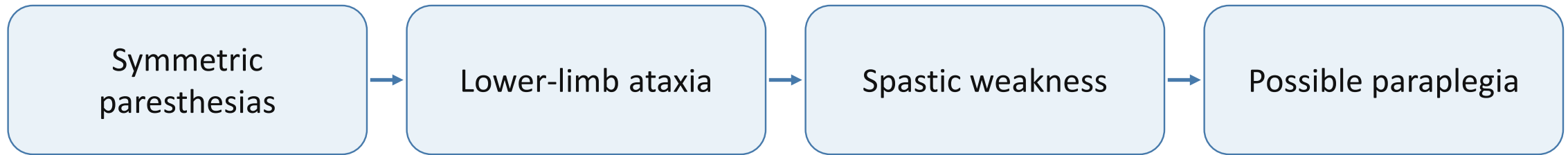
Schematic regions · not a histologic section

Typical neurologic presentation

- Symptoms can evolve over several weeks.
- Early symptoms often comprise symmetric numbness and tingling in both legs.
- Mild gait ataxia may accompany the sensory complaints.
- Spastic weakness generally characterizes more advanced disease.

How symptoms typically evolve

A progressive, rather than abrupt, constellation of deficits.



Later stages can carry substantially poorer neurologic recovery.

Bilateral numbness and tingling

- Paresthesias are an early neurologic complaint.
- The described distribution is symmetric in both lower extremities.
- Initial symptoms may be relatively mild despite evolving tract pathology.

Clinical localization cues

Two-sided sensory symptoms



Lower extremity predominance

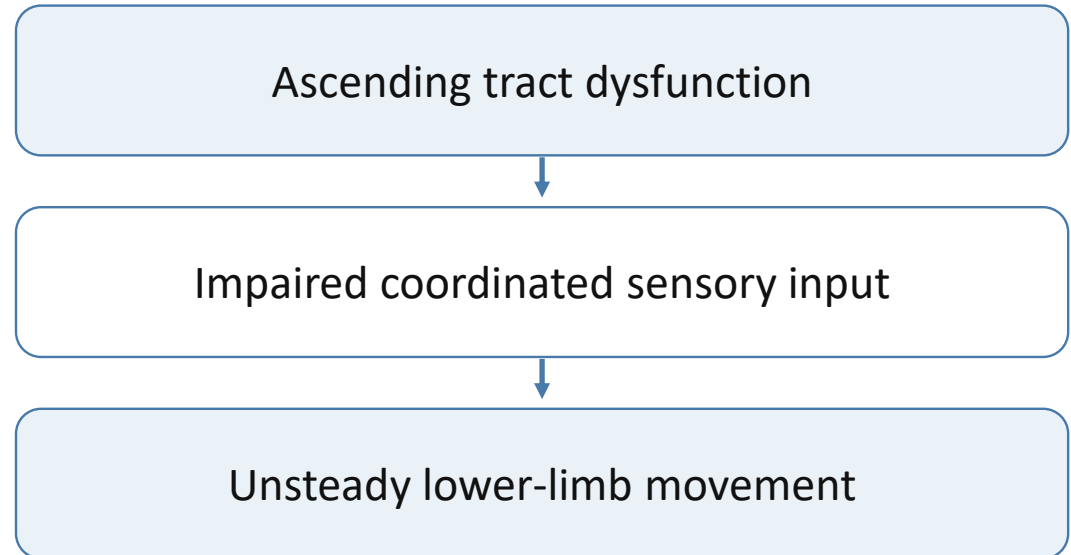


Gradually progressive syndrome

Sensory ataxia

- Lower-limb incoordination may develop early in the syndrome.
- Dorsal spinal tract degeneration provides a clinicopathologic explanation.
- Ataxia occurring with paresthesias should prompt attention to cord pathology.

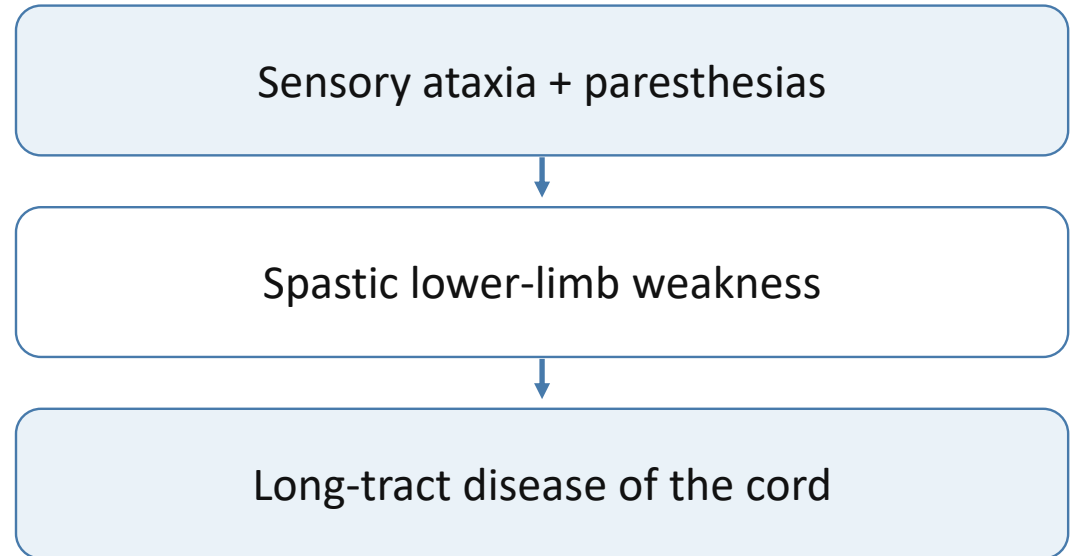
Mechanistic interpretation



Progression to spastic weakness

- Descending tract involvement adds a motor component.
- The lower limbs may develop spastic weakness or paraparesis.
- A combined sensory–motor phenotype reflects injury to more than one tract system.

Combined syndrome



Paraplegia is a late adverse manifestation

- Paraplegia may occur with advanced disease but is usually a later finding.
- Its appearance indicates severe functional compromise.
- Once paraplegia develops, recovery after replacement therapy is poor.

Neurologic progression is clinically time-sensitive

Early

Progressive

Late

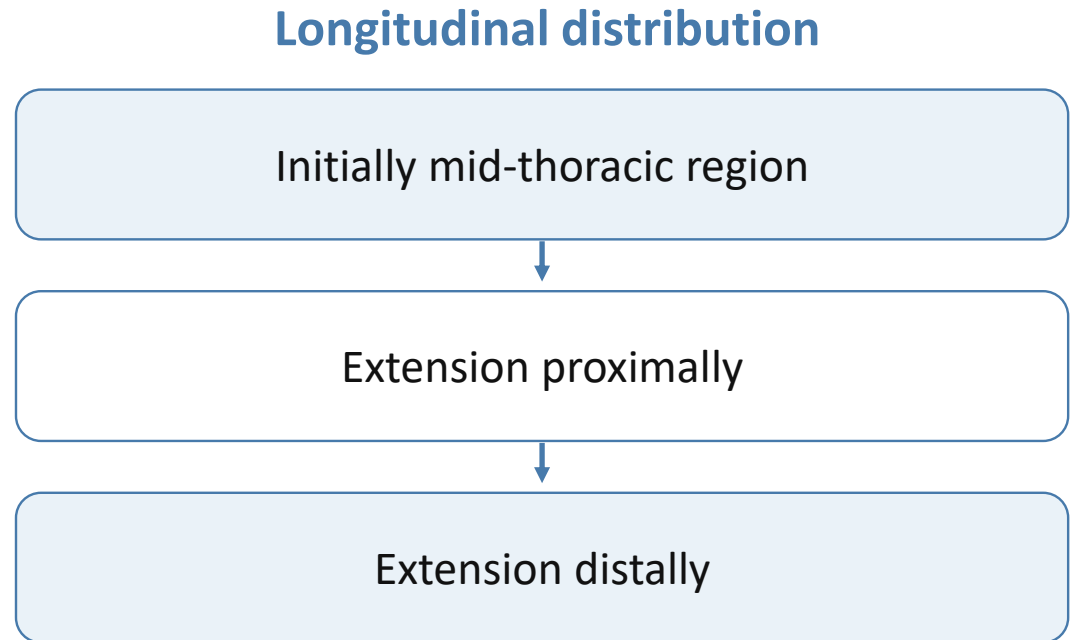
Symmetric sensory symptoms and slight ataxia; An opportunity for recognition.

Spastic weakness joins sensory deficits as descending tracts are affected.

Paraplegia may emerge; Textbook prognosis for recovery is poor.

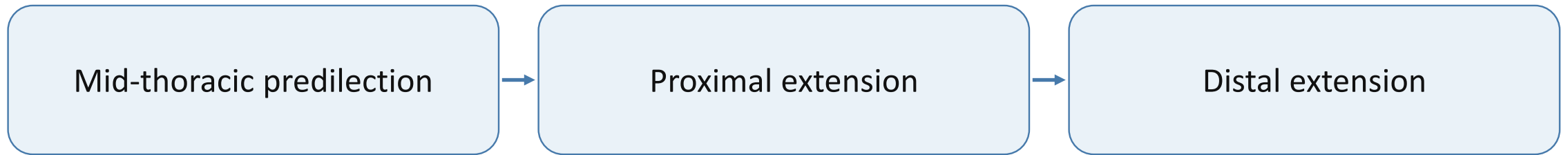
Initial localization favors the mid-thoracic cord

- In early SCD, microscopic injury is preferentially centered at mid-thoracic levels.
- The initial lesion is not described as a focal compressive mass.
- Anatomical spread can extend the distribution beyond this segment.



Longitudinal extension of the lesion

The process may spread along the spinal axis after an initially favored level.



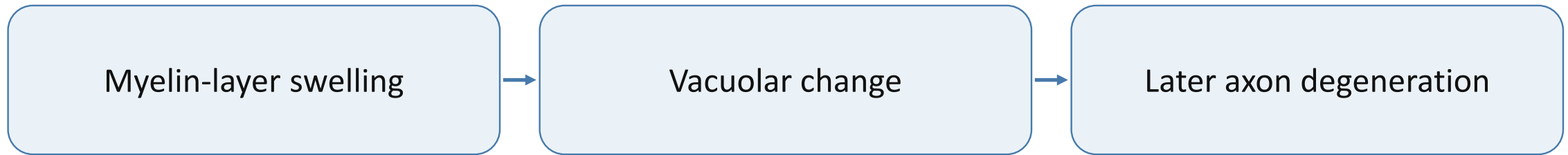
Arrows represent possible spread, not a fixed sequence in every patient.

SCD begins as a disorder of myelin integrity

- The lesions reflect defective formation or maintenance of myelin.
- The exact metabolic steps linking B₁₂ deficiency to myelin injury remain uncertain.
- Pathology includes a myelin abnormality before extensive axonal destruction.

Microscopic sequence: Myelin to axon

The histologic sequence explains why intervention before advanced injury matters.

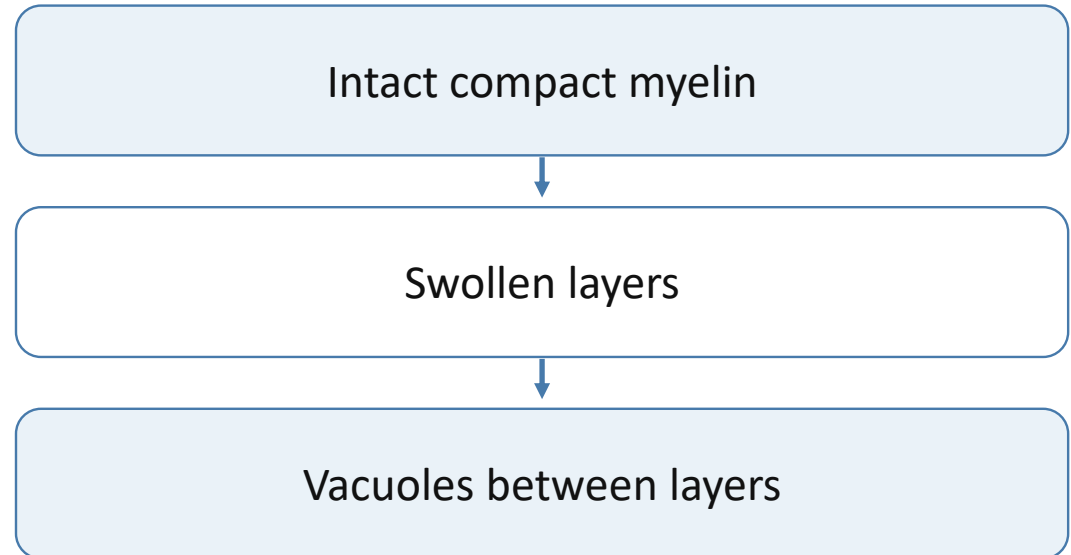


This is an original schematic of the sequence reported by Robbins.

Vacuolation is an early microscopic finding

- Affected myelin layers become swollen.
- Swelling creates vacuoles within the involved white-matter tracts.
- Vacuolar change is a tissue-level correlate of altered myelin integrity.

Native schematic of myelin change



Early versus later pathologic injury

Feature	Earlier injury	More advanced injury
Dominant lesion	Myelin-layer swelling	Associated axonal degeneration
Microscopic appearance	Vacuolar change	Myelin loss with axonal injury
Clinical significance	Potential for earlier improvement	Greater risk of lasting neurologic deficit

Myelin and axons are affected in sequence

- Myelin swelling and vacuolation directly.
- Axon degeneration is a later component of the process.
- The distinction helps explain incomplete reversibility in advanced disease.

Two structural targets

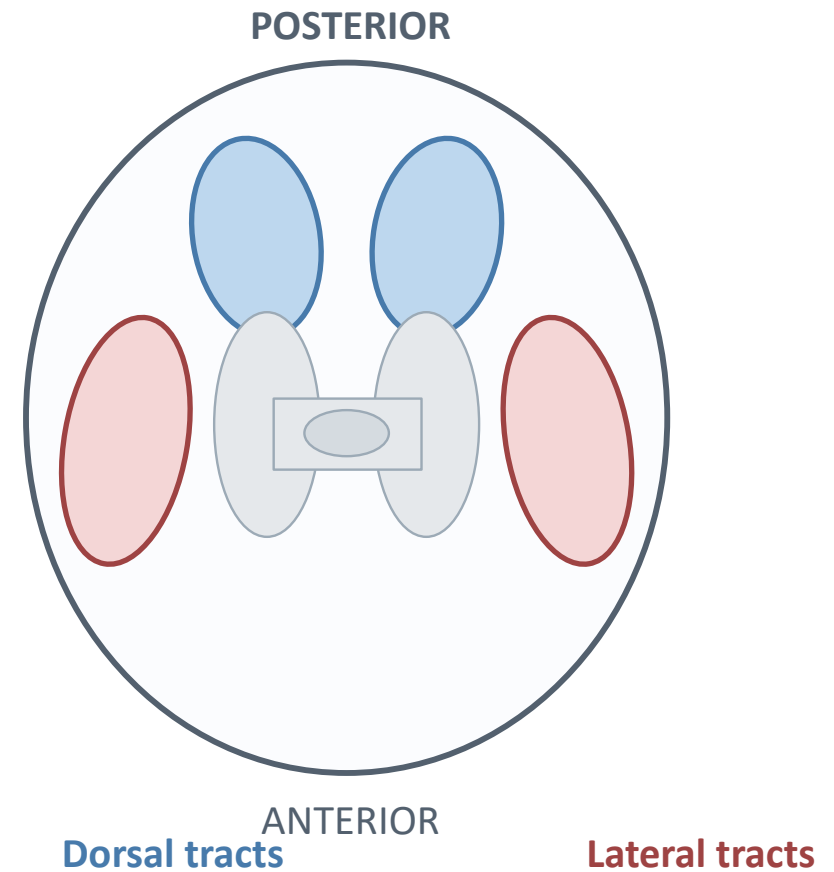
Myelin: Early prominent injury



Axon: Degeneration with time

Morphology tracks the clinical combination

- Dorsal white-matter injury correlates with sensory ataxia.
- Lateral white-matter injury correlates with spastic paraparesis.
- The distribution is combined, rather than a lesion restricted to one pathway.



Schematic regions · not a histologic section

Peripheral neurologic involvement can coexist

- Peripheral nerves can show degenerative changes in vitamin B₁₂ deficiency.
- Mixed axonal degeneration and demyelination in B₁₂-related neuropathy.
- Peripheral nervous system injury may add to the long-tract syndrome.

Sites of involvement

Spinal cord long tracts



Peripheral nerves



Occasionally posterior-root ganglia

Posterior-root ganglia are less frequently involved

- Occasional degenerative changes in posterior-root ganglia.
- This is not presented as the dominant lesion of the neurologic syndrome.
- The characteristic lesion remains combined dorsal and lateral cord tract degeneration.

Central and peripheral manifestations

Compartment	Main structural change	Clinical importance
Spinal cord	Dorsal and lateral tract demyelination ± axon loss	Sensory ataxia; Spastic paraparesis
Peripheral nerve	Axonal degeneration plus demyelination	Additional peripheral neurologic deficits
Posterior-root ganglion	Less frequent degenerative changes	Variable involvement; Not the defining lesion

Neurologic disease may precede overt anemia

- CNS lesions can be present without striking hematologic abnormalities.
- A seemingly modest blood picture does not exclude serious neurologic consequences.
- This dissociation is important in clinical recognition of the deficiency.

Early treatment changes the outlook

- Prompt B₁₂ replacement is associated with clinical neurologic improvement.
- Therapy may halt progression or reverse some peripheral neurologic deficits.
- Outcome depends partly on the extent of established neurologic damage.

Why timing of replacement matters

Clinical state	Source-supported expectation
Early paresthesias / ataxia	Prompt replacement can produce improvement
Progressive lower-limb weakness	Progression may be halted; Recovery varies
Established paraplegia	Neurologic recovery is poor

Vitamin B₁₂ is cobalamin

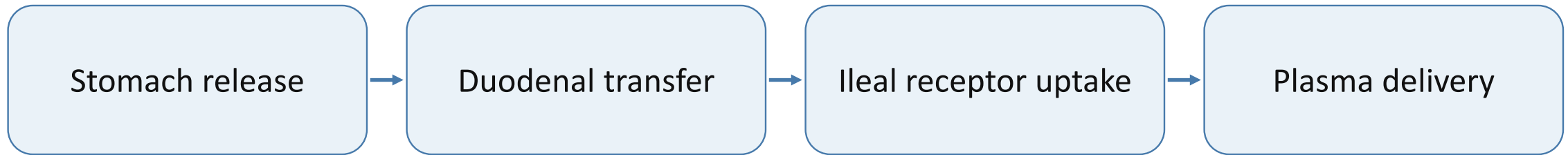
- Cobalamin is an organometallic vitamin required for specific human enzymatic reactions.
- Animal-derived foods—including meat, fish, milk and eggs—are major dietary sources.
- B₁₂ deficiency can affect neurologic pathways and proliferating marrow cells.

Intake, requirement and storage

Component	Robbins description
Daily requirement	Approximately 2–3 µg in the source text
Dietary supply	Adequate animal-product intake generally exceeds this amount
Body stores	Hepatic reserves can cover several years
Low intake	Strictly plant-based diets without reliable B ₁₂ supply can be inadequate

Normal cobalamin uptake crosses multiple organs

Failure at several distinct sites can produce clinically important deficiency.

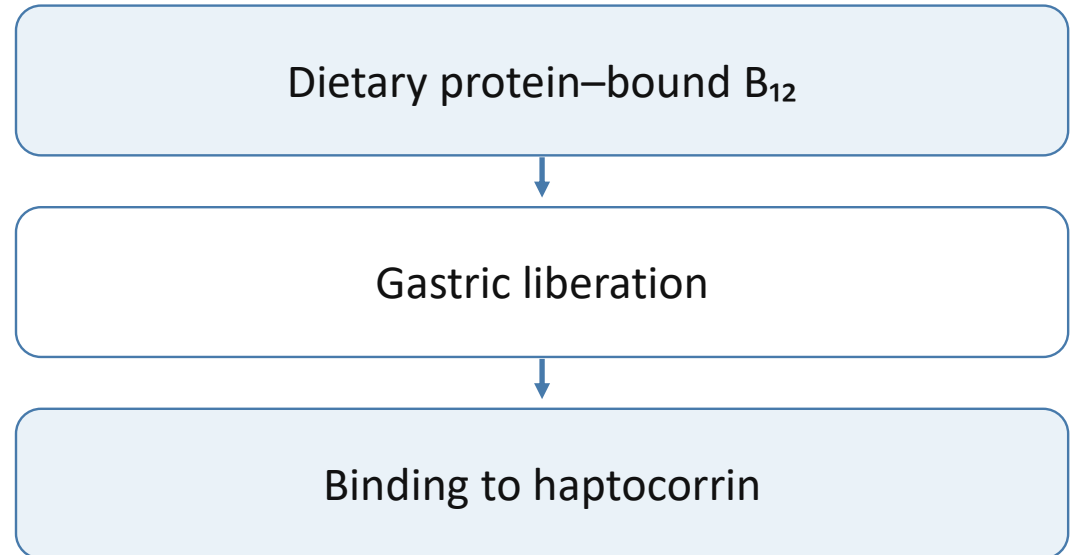


The sequence is a simplified native diagram of Robbins Fig. 14.17.

Stomach: B₁₂ must be released from food

- Food-bound cobalamin is liberated by gastric digestion, including pepsin activity.
- It initially associates with salivary haptocorrin.
- Loss of gastric acid/pepsin secretion can compromise this initial release.

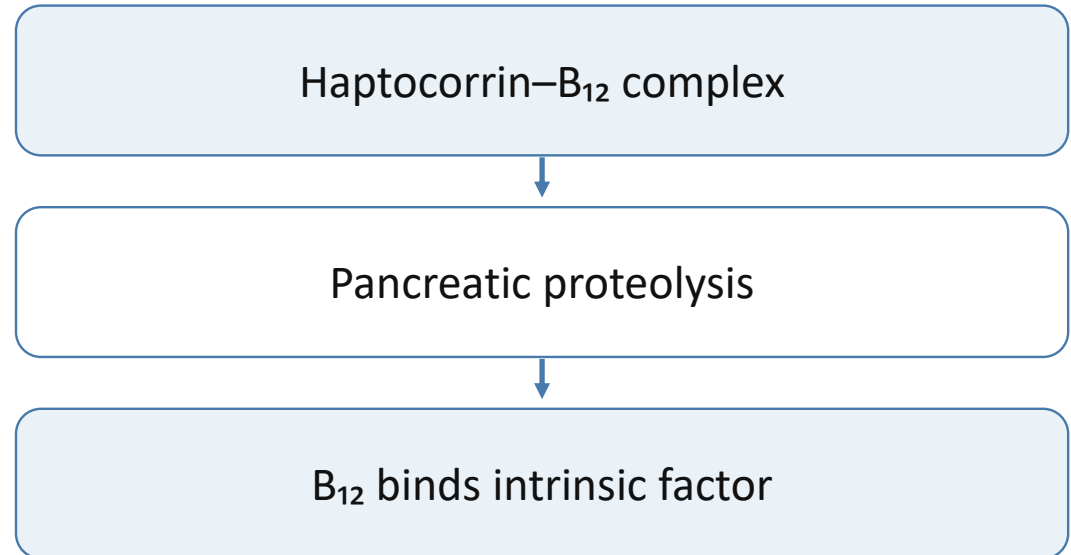
Stomach phase



Duodenum: Pancreatic proteases transfer the carrier

- Pancreatic proteases free cobalamin from haptocorrin.
- Released B₁₂ is then available to bind intrinsic factor.
- Exocrine pancreatic insufficiency may interrupt this step.

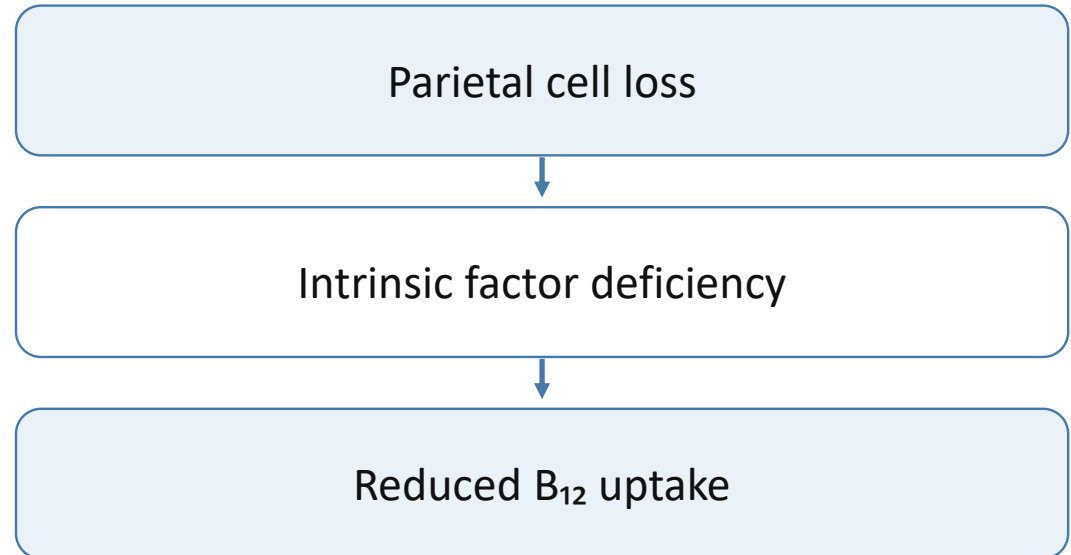
Duodenal phase



Intrinsic factor is indispensable for efficient absorption

- Intrinsic factor is secreted by parietal cells in the fundic gastric mucosa.
- The intrinsic factor–B₁₂ complex moves through the small intestine to the ileum.
- Loss of intrinsic factor is central to pernicious anemia.

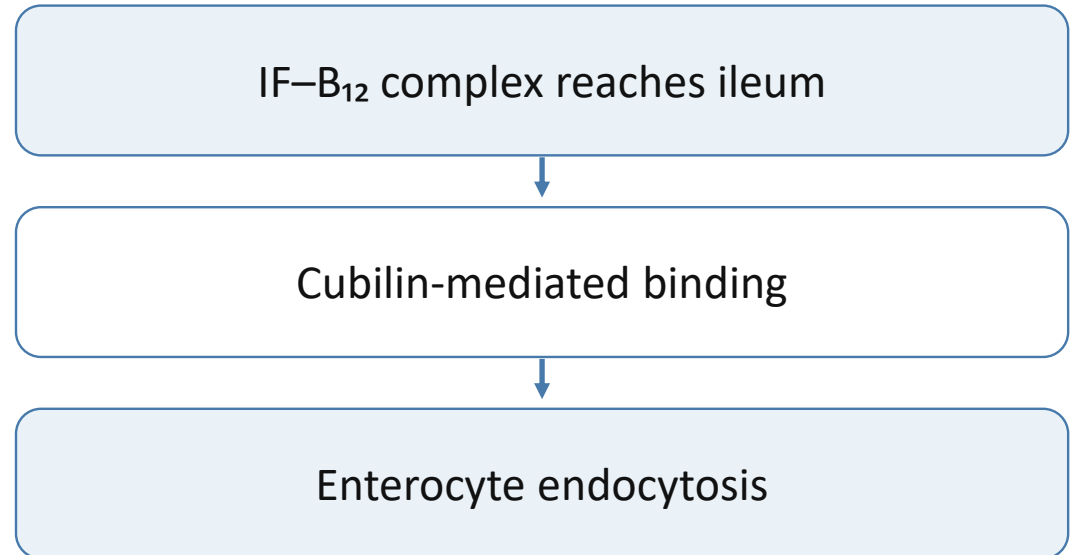
Cause–effect



Terminal ileum: Receptor-mediated uptake

- The intrinsic factor–B₁₂ complex binds an ileal epithelial receptor called cubilin.
- The complex is internalized by endocytosis.
- Ileal resection or ileal disease can prevent adequate absorption.

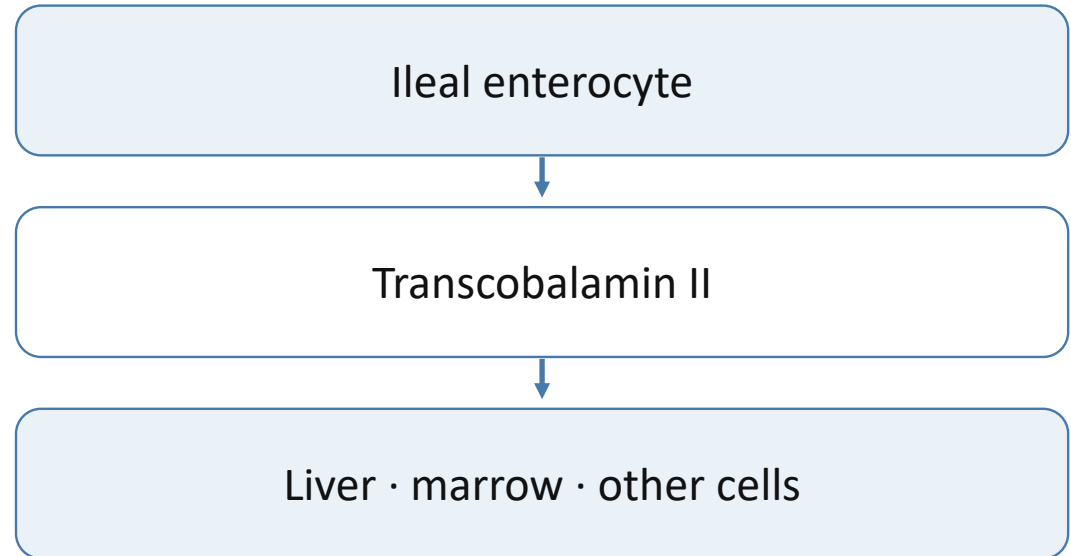
Ileal uptake



Transcobalamin II delivers absorbed B₁₂

- In ileal cells, B₁₂ associates with transcobalamin II.
- The vitamin enters the plasma and is distributed to liver and other tissues.
- Bone marrow and gastrointestinal epithelium are prominent recipient tissues.

Delivery



Absorption defects mapped to their sites

Site / step	Example of interference
Stomach release	Achlorhydria; Loss of pepsin
Intrinsic factor	Autoimmune gastritis; Gastrectomy
Duodenal transfer	Exocrine pancreatic insufficiency
Ileal uptake	Ileal resection; Diffuse ileal disease
Luminal availability	Tapeworm competition; Bacterial overgrowth

Oral absorption has a passive component

- A small amount of cobalamin is absorbed by passive diffusion.
- This uptake is inefficient compared with intrinsic factor–dependent absorption.
- It explains why sufficiently high-dose oral replacement can be effective in some settings, including pernicious anemia.

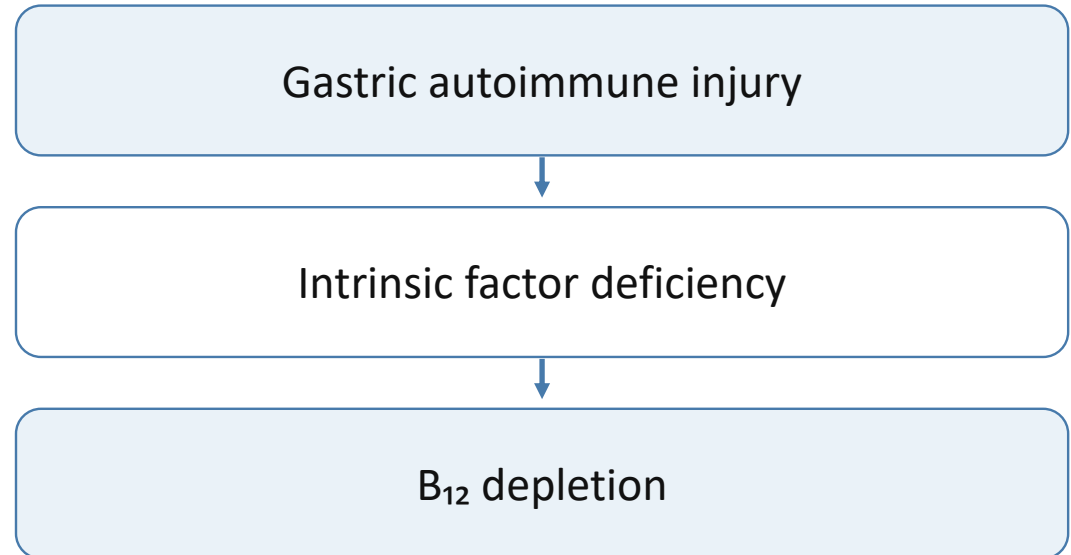
Mechanistic categories of B₁₂ deficiency

Category	Examples
Decreased intake	Inadequate diet; Strict diets lacking dependable B ₁₂ sources
Failure of intrinsic factor	Pernicious anemia; Gastrectomy
Intestinal malabsorption	Diffuse intestinal disorders; Ileitis; Ileal resection
Competition or utilization	Fish tapeworm; Bacterial overgrowth; Increased demand
Vitamin inactivation	Nitrous oxide exposure

Pernicious anemia is autoimmune malabsorption

- A specific megaloblastic anemia associated with autoimmune atrophic gastritis.
- Loss of gastric parietal cells reduces intrinsic factor production.
- Defective ileal B₁₂ absorption eventually depletes stores and causes deficiency.

Core causal chain



Immune injury begins in the gastric mucosa

- Autoreactive T-cell involvement in fundic mucosal injury.
- Lymphocytes and plasma cells are prominent in the chronic gastritis.
- Autoantibodies aid diagnosis but are not established as the sole cause of tissue injury.

Immune pathogenesis

T-cell mediated mucosal injury



Parietal cell atrophy



Intrinsic factor loss

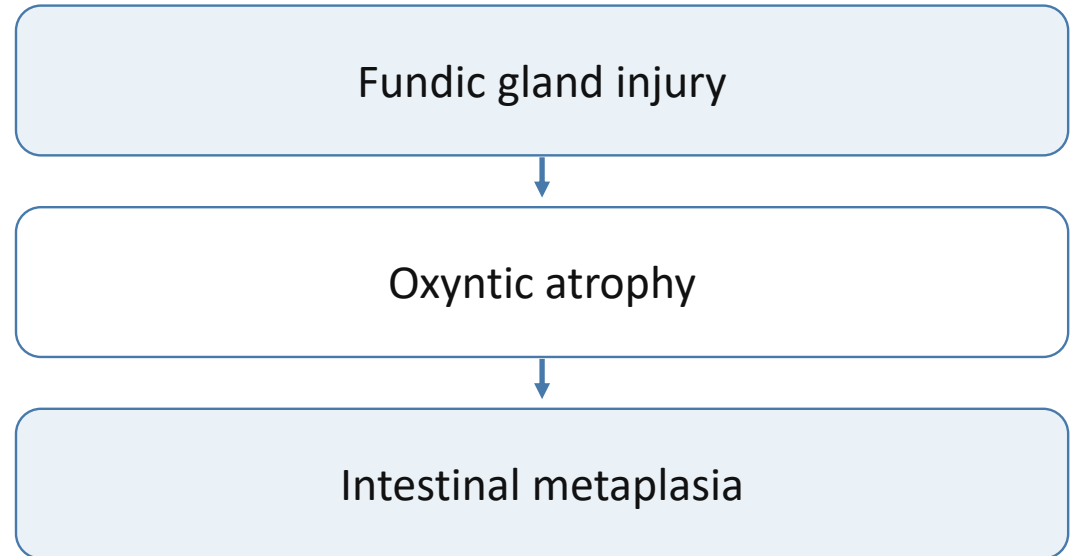
Antibodies in pernicious anemia

Antibody	Mechanism or diagnostic interpretation
Type I anti–intrinsic factor	Interferes with B ₁₂ binding to intrinsic factor
Type II anti–intrinsic factor	Interferes with IF–B ₁₂ complex binding to cubilin
Anti–parietal cell / proton pump	Frequently detectable; Lacks high specificity

Autoimmune gastritis has characteristic morphology

- Parietal and chief cells are lost from oxyntic mucosa of the body and fundus.
- The mucosa becomes atrophic with lymphoplasmacytic inflammation.
- Intestinal metaplasia can replace glandular epithelium with goblet-cell containing glands.

Morphologic sequence



The autoimmune context is clinically relevant

- Pernicious anemia is associated with other autoimmune diseases.
- Autoimmune thyroiditis and adrenalitis among associated conditions.
- Its slow progression reflects depletion of long-standing B₁₂ stores after gastric injury.

Nonautoimmune absorption defects

Etiology	Disrupted step
Gastrectomy	Loss of intrinsic factor–producing gastric mucosa
Achlorhydria / low pepsin	Inefficient release of food-bound B ₁₂
Exocrine pancreatic disease	Inadequate haptocorrin breakdown
Ileal resection / ileitis	Failure of receptor-mediated B ₁₂ uptake

Other routes to functional deficiency

- Intestinal organisms can compete for available vitamin B₁₂.
- Increased physiologic demand may create relative deficiency in selected settings.
- Nitrous oxide can oxidize and inactivate B₁₂, leading to symptomatic deficiency.

Humans have two known B₁₂-dependent reactions

Two major cofactor-dependent enzymatic systems.

Methionine synthase

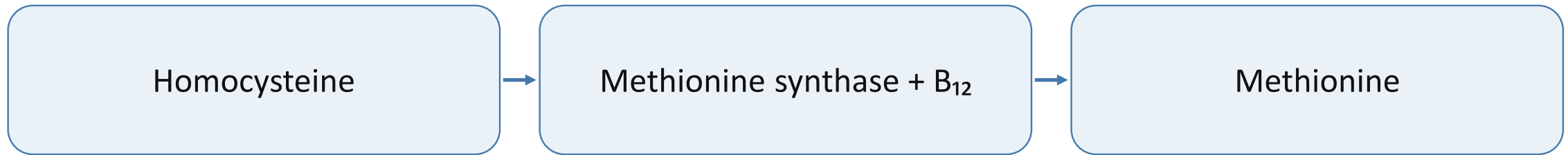


Methylmalonyl-CoA mutase

These reactions connect B₁₂ with one-carbon metabolism and methylmalonate handling.

Methionine synthase: The one-carbon reaction

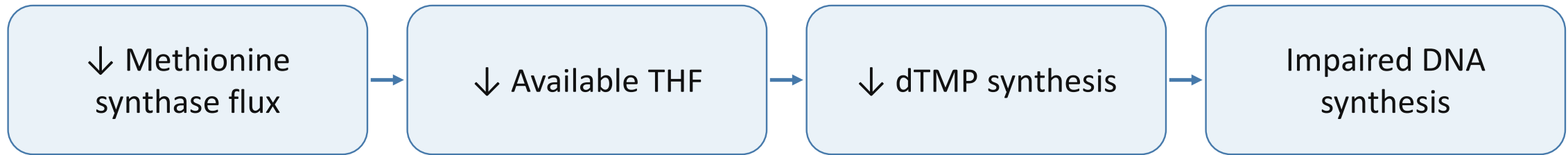
Methylcobalamin supports transfer of a methyl group from N⁵-methyl-THF.



The reaction also regenerates tetrahydrofolate (THF) from N⁵-methyl-THF.

B₁₂ deficiency traps folate in a methylated form

The folate trap contributes to impaired thymidylate availability.

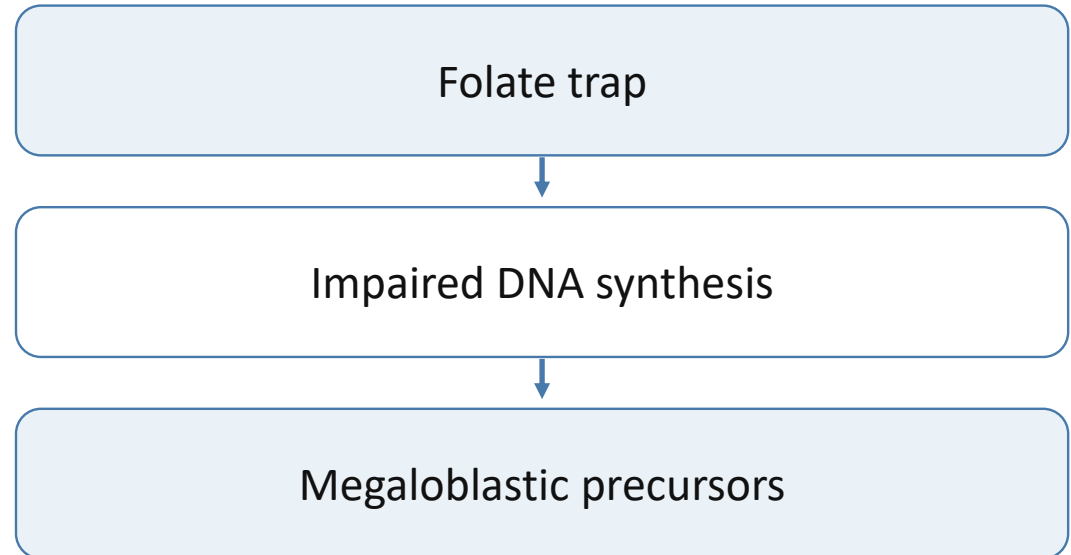


THF = tetrahydrofolate; DTMP = deoxythymidine monophosphate.

Defective DNA synthesis produces megaloblastosis

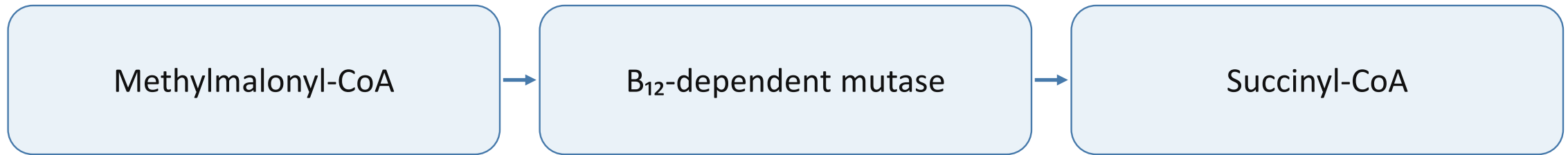
- Nuclear maturation and division are delayed in proliferating marrow cells.
- Cytoplasmic maturation and hemoglobin accumulation continue.
- Nuclear–cytoplasmic asynchrony produces megaloblastic morphology.

Pathology linkage



Methylmalonyl-CoA mutase: The second reaction

Adenosylcobalamin is required in this pathway.



B₁₂ deficiency increases methylmalonic acid in plasma and urine.

A proposed neurologic mechanism remains uncertain

- Methylmalonate and propionate accumulation has been proposed to alter neuronal lipid metabolism.
- Abnormal fatty-acid incorporation could destabilize myelin.
- Hereditary mutase deficiency does not consistently reproduce SCD.

Scientific interpretation

Biochemical association: Established



Causal role in myelin breakdown: Proposed



Complete explanation: Unresolved

Established findings versus mechanistic hypotheses

Established	Proposed / uncertain
B ₁₂ deficiency causes SCD	Exact downstream biochemical lesion
Vacuolar myelin injury and axonal degeneration	Contribution of abnormal neuronal fatty acids
Elevated methylmalonate in deficiency	Methylmalonate as sufficient explanation for SCD

The blood smear in megaloblastic anemia

Feature	Characteristic observation
Erythrocytes	Macro-ovalocytes; Size/shape variation
Neutrophils	Hypersegmented nuclei
Reticulocytes	Reduced count before effective treatment
Broader counts	Leukopenia or pancytopenia can develop

Bone marrow: Megaloblastic dyspoiesis

- Marrow is often hypercellular despite ineffective hematopoiesis.
- Erythroid cells are enlarged, with immature nuclear chromatin.
- Granulocytic precursors may include giant metamyelocytes; Megakaryocytes can be enlarged.

Cause of cytopenias

Disordered DNA synthesis



Intramedullary apoptosis



Ineffective hematopoiesis

Folate deficiency is an important contrast

- Both folate and B₁₂ deficiency can cause morphologically similar megaloblastic anemia.
- Folate deficiency increases homocysteine but not methylmalonate in the source comparison.
- The neurologic syndrome of SCD is associated with B₁₂, not uncomplicated folate deficiency.

Biochemical and neurologic distinction

Feature	B ₁₂ deficiency	Folate deficiency
Megaloblastic anemia	Yes	Yes
Homocysteine	Increased	Increased
Methylmalonate	Increased	Normal in source comparison
SCD neurologic findings	May occur	Not characteristic

Diagnostic pattern

- Serum B₁₂ is reduced in the classic deficiency pattern.
- Homocysteine and methylmalonic acid may be elevated.
- CBC can show macrocytic megaloblastic anemia with hypersegmented granulocytes.
- Anti–intrinsic factor antibodies support a diagnosis of pernicious anemia.

Intrinsic factor antibodies and etiologic diagnosis

- Serum antibodies to intrinsic factor are highly specific for pernicious anemia.
- Parietal cell antibodies are frequent but not individually specific.
- An autoimmune etiology is distinct from other mechanisms of B₁₂ malabsorption.

Diagnostic question

B₁₂ deficiency present?



Autoimmune intrinsic-factor loss?



Other absorption defect?

Atrophic glossitis reflects a systemic epithelial effect

- A shiny, smooth, beefy-red tongue can occur in advanced deficiency.
- Rapidly dividing epithelium shares vulnerability to impaired DNA synthesis.
- Gastrointestinal and marrow manifestations provide context for neurologic disease.

Parallel tissue effects

Marrow: Megaloblastosis



Mucosa: Epithelial changes



Cord: Myelin injury

Autoimmune gastric pathology persists after replacement

- Vitamin B₁₂ replacement reverses the deficiency state but does not repair the autoimmune gastric atrophy.
- Metaplasia and the associated gastric carcinoma risk persist.
- The primary gastric disease remains a separate long-term pathology concern.

Therapeutic response: Blood versus nerves

- The hematologic response can include brisk reticulocytosis after parenteral B₁₂ replacement.
- Megaloblastic marrow and gastrointestinal changes are readily reversible.
- Severe established neurologic injury may not recover despite vitamin replacement.

Differing reversibility

Marrow: Typically responsive



Neurologic: Dependent on disease stage



Gastric autoimmunity: Persists

Folate replacement does not treat SCD

- Folate may improve the hematologic manifestations of B₁₂ deficiency.
- It does not correct the associated neurologic injury and may allow neurologic deterioration to continue.
- The source emphasizes excluding B₁₂ deficiency before treating megaloblastic anemia with folate alone.

Case: Progressive gait difficulty

An adult develops several weeks of bilaterally symmetric lower-limb tingling, followed by sensory ataxia and increasing spastic weakness. Laboratory evaluation demonstrates vitamin B₁₂ deficiency.

Interpretation prompts

- What combined spinal cord syndrome does this suggest?
- Which major tract regions and microscopic lesions are expected?

Case reasoning: Localize the combined syndrome

- The distribution and tempo are compatible with subacute combined degeneration.
- Dorsal and lateral cord tracts are affected together.
- Myelin swelling and vacuolation are characteristic; Axonal degeneration occurs later.
- Replacement before fixed severe deficits offers the best opportunity for improvement.

Case: Megaloblastosis with subtle neurologic signs

A patient with autoimmune fundic atrophy has macro-ovalocytes, hypersegmented neutrophils, and mild bilateral lower-limb paresthesias. Folate is being considered for the anemia.

Interpretation prompts

- Which deficiency must be excluded?
- Why is folate alone insufficient for the neurologic risk?

Case reasoning: Avoid masking neurologic disease

- Autoimmune gastric disease can remove intrinsic factor and cause B₁₂ malabsorption.
- The hematologic phenotype does not measure the full burden of neurologic injury.
- Folate can improve anemia without correcting SCD.
- Biochemical testing and investigation of the etiology are central to interpretation.

Integrated clinicopathologic map

Mechanism	Tissue pathology	Clinical / laboratory result
Poor uptake / vitamin inactivation	Systemic cobalamin depletion	Low vitamin B ₁₂
Folate-cycle disruption	Megaloblastic hematopoiesis	Macro-ovalocytes; Cytopenias
B ₁₂ -dependent metabolite defect	Methylmalonate accumulation	Elevated methylmalonic acid
Unresolved myelin injury pathway	Dorsal/lateral tract vacuolation	Ataxia, paresthesias, spastic weakness

Four principles to retain

- SCD combines dorsal and lateral spinal tract degeneration.
- Microscopy progresses from myelin swelling and vacuolation to axonal loss.
- B₁₂ deficiency may cause neurologic injury without conspicuous anemia.
- Prompt B₁₂ replacement can improve outcomes; Established paraplegia has poor recovery.

Clinical–pathologic reasoning checklist

- Identify a gradually progressive, bilateral lower-limb sensory–motor syndrome.
- Localize sensory ataxia and spastic weakness to combined spinal tract dysfunction.
- Consider B₁₂ deficiency even when megaloblastic anemia is not prominent.
- Investigate dietary intake, gastric intrinsic-factor loss, ileal disease, or vitamin inactivation.
- Interpret MMA, homocysteine and B₁₂ findings in the wider clinicopathologic context.