بسم الله الرحمـٰن الرحيم

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Pharmacology | FINAL 2

V12 deficiency anemia



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Vitamin B_{12} Deficiency Anemia

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- A 50 years old morbidly obese female with diabetes mellitus, underwent a stomach surgery procedure to reduce the capacity of the stomach to be able to reduce weight. 3 years later she developed a macrocytic type of anemia. Her medications included metformin for diabetes. She had a history of dyspepsia. Serum folic acid was normal

Vitamin B_{12}

- Its deficiency leads to anemia, gastrointestinal symptoms and neurological abnormalities.
- It consists of a porphyrin-like ring with a central cobalt atom attached to the nucleotide.

Active forms are:

1. Deoxyadenosylcobalamin
2. Methylcobalamin



❑ Clinical Presentation & Symptoms of Vitamin B12 Deficiency:

- ➢ **Hematological Manifestations:** Vitamin B12 deficiency leads to **Megaloblastic Anemia**.
- ✓ It can also present with **Pernicious Anemia**, which is specifically an autoimmune condition.
- ✓ Pernicious anemia occurs when vitamin B12 deficiency is due to intrinsic factor deficiency.

Note: Folic acid deficiency does **not** cause neurological symptoms, whereas Vitamin B12 deficiency **does** present with distinct **neurological manifestations**.

- ➢ **Gastrointestinal Manifestations:** Includes gastrointestinal symptoms alongside the hematological ones.

❑ Chemical Structure of Vitamin B12:

- ✓ **Structure:** Consists of a **corrin-like ring** with a central cobalt atom attached to a nucleotide (specifically, a cobalt ring, not iron, copper, or zinc).
- ✓ **Status:** Cobalt is considered one of the necessary trace elements in the human body, and it is located within the vitamin B12 structure.
- ✓ **Active Forms:** Vitamin B12 has two active **coenzyme** forms required for two critical biochemical reactions:

1. Deoxyadenosylcobalamin
2. Methylcobalamin

Pharmacokinetics:

1. **Vitamin B_{12}, in physiologic amounts is absorbed after it complexes with the intrinsic factor (a glycoprotein secreted by the parietal cells of the gastric mucosa).**
2. **The intrinsic factor-vitamin B_{12} complex is absorbed in the terminal ileum by a highly specific receptor-mediated endocytosis.** (mediated by cubilin).
3. **Daily absorption ~ 1-5 µg.**
4. **Vitamin B_{12} is stored mainly in the liver with an average normal storage pool of 3-5 mg.**
5. **Daily requirements are ~ 2 µg.**
6. **Only trace amounts are lost in urine and stool.**
7. **Once absorbed it is transported in the body bound to a plasma glycoprotein, transcobalamin II.**

which delivers it to the bone marrow for erythropoiesis and to other tissues for use.

Vitamin B_{12}

How long would it take for the storage pool to be depleted and symptoms of deficiency to appear?

If a patient has a normal B12 level, develops megaloblastic/pernicious anemia, and suddenly has *completely stopped absorption* of vitamin B12 (e.g., total gastrectomy, removing parietal cells, or losing intrinsic factor—unlike dietary deficiency like strict veganism or acid-suppression drugs):

- How long does it take for symptoms to appear? **About 3 to 6 years**.

Mathematical Breakdown (Example):
Normal storage = 4mg (4,000ug).
Daily requirement = 2ug.
4,000ug / 2ug = 2,000 days(which equals approximately **5.5 to 6 years**).

Alternative calculation example given: If storage is 3mg (3,000ug) and daily requirement is 1.5 ug, it equals 2,000 days (~5.5 years).

- **Conclusion on Storage:** Only trace amounts are lost daily through the urine and stool (no specific active mechanism for vitamin B12 elimination). Once absorption stops, it takes years to deplete the body stores entirely.

Vitamin B_{12}

Causes of deficiency: Vitamin B12 deficiency can arise from several key etiologies:

Malabsorption of Vitamin B_{12} due to:

1) Lack of intrinsic factor.

- Pernicious anemia involves autoantibodies against intrinsic factor or gastric parietal cells.
- Acid-lowering agents and proton pump inhibitors (PPIs, e.g., **Omeprazole**) decrease intrinsic factor availability/secretion.

2) Loss or malfunction of the terminal ileum.

- Malfunction or surgical removal (resection) of the terminal ileum (e.g., due to colon cancer near the cecum) leads to severe malabsorption since the terminal ileum is the primary site of Vitamin B12 absorption.

Vitamin B_{12}

3. **Strict vegetarians (long-term):**

- **The vitamin is NOT synthesized by animals or plants.**
- **The ultimate source is microbial synthesis**
- **Mainly present in meat (liver), eggs and dairy products.**
- **It has to be released from these sources before absorption.**

Depletion Over Time: The body stores significant amounts of Vitamin B12 mainly in the **liver** (taking years to deplete), so deficiency typically manifests after years of strict veganism without supplementation

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4. Atrophic gastritis (from *Helicobacter pylori)*

- Often secondary to *Helicobacter pylori* (*H. pylori*) infection.
- Destroys parietal cells responsible for secreting Intrinsic Factor and gastric acid, leading to failure of releasing B12 from food proteins

5. Lack of gastric HCl (cobalamin is NOT released from protein).

6. Drugs: proton pump inhibitors and other gastric acid lowering drugs, and metformin.

- **Proton Pump Inhibitors (PPIs) & Acid-Lowering Agents (e.g., Omeprazole):**

PPIs shut down acid secretion (H+/K+ ATPase pump) completely for around 24 to 36 hours. Without gastric acid, Vitamin B12 cannot be released from ingested proteins.

- **Metformin:**

Long-term use reduces Vitamin B12 absorption in the terminal ileum.

Clinical Pitfall: Doctors often fail to recognize drug-induced B12 deficiency (e.g., patients presenting with peripheral neuropathy/numbness while taking long-term Metformin or Omeprazole). If the underlying drug cause is ignored, symptoms will continue to progress.

Vitamin B_{12}

Pharmacodynamics:

Vitamin B_{12} is involved in 2 essential enzymatic reactions in humans:

1. **Deoxyadenosylcobalamin is responsible for the isomerization of methylmalonyl-CoA to succinyl-CoA by the enzyme methylmalonyl-CoA mutase.** **Clinical Importance:** Crucial for lipid metabolism and **myelin sheath formation/maintenance** in nerve tissue.

- **In Vitamin B_{12} deficiency, methylmalonyl-CoA accumulates.**

Vitamin B_{12}

2. **Methylcobalamine is involved in the transfer of a methyl group from N^5-methyltetrahydrofolate to homocysteine to form methionine and tetrahydrofolate (THF).**

- **THF is the precursor of many folate cofactors.**
- **In Vitamin B_{12} deficiency, folate cofactors become deficient leading to defects in several biochemical reactions involved in the transfer of one-carbon groups.**

❑ Relationship Between Vitamin B12 & Folic Acid (Folate Trap):

- **Co-Factor Interdependence:** In Folic Acid deficiency, Vitamin B12 co-factors remain largely undamaged. However, in **Vitamin** B12 **deficiency**, a **physiological/functional Folic Acid deficiency** is trapped ("Folate Trap").

❑ Neurological vs. Hematological Manifestations:

- Administering High-dose Folic Acid alone can **correct the hematological abnormalities** (macrocytic/megaloblastic anemia).
- ✓ **DANGER:** High-dose Folic Acid **DOES NOT** correct the neurological damage caused by Vitamin B12 deficiency. The neurological manifestations (e.g., subacute combined degeneration of the spinal cord) will continue to progress and become irreversible if B12 is not given.

Question for Next Lecture: Do neurological manifestations occur directly in isolated **Folic Acid deficiency** (e.g., in pregnant women leading to Neural Tube Defects)?

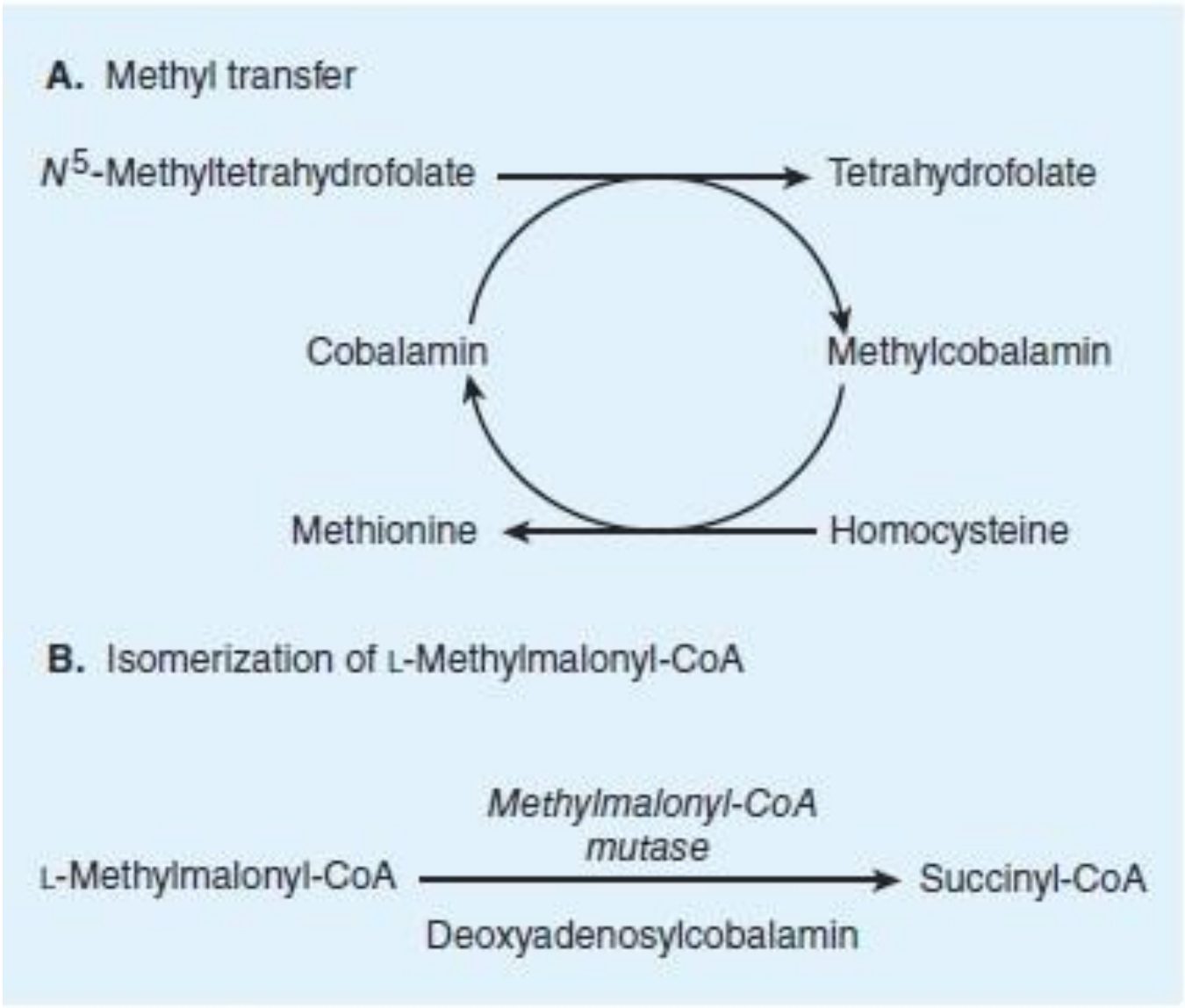
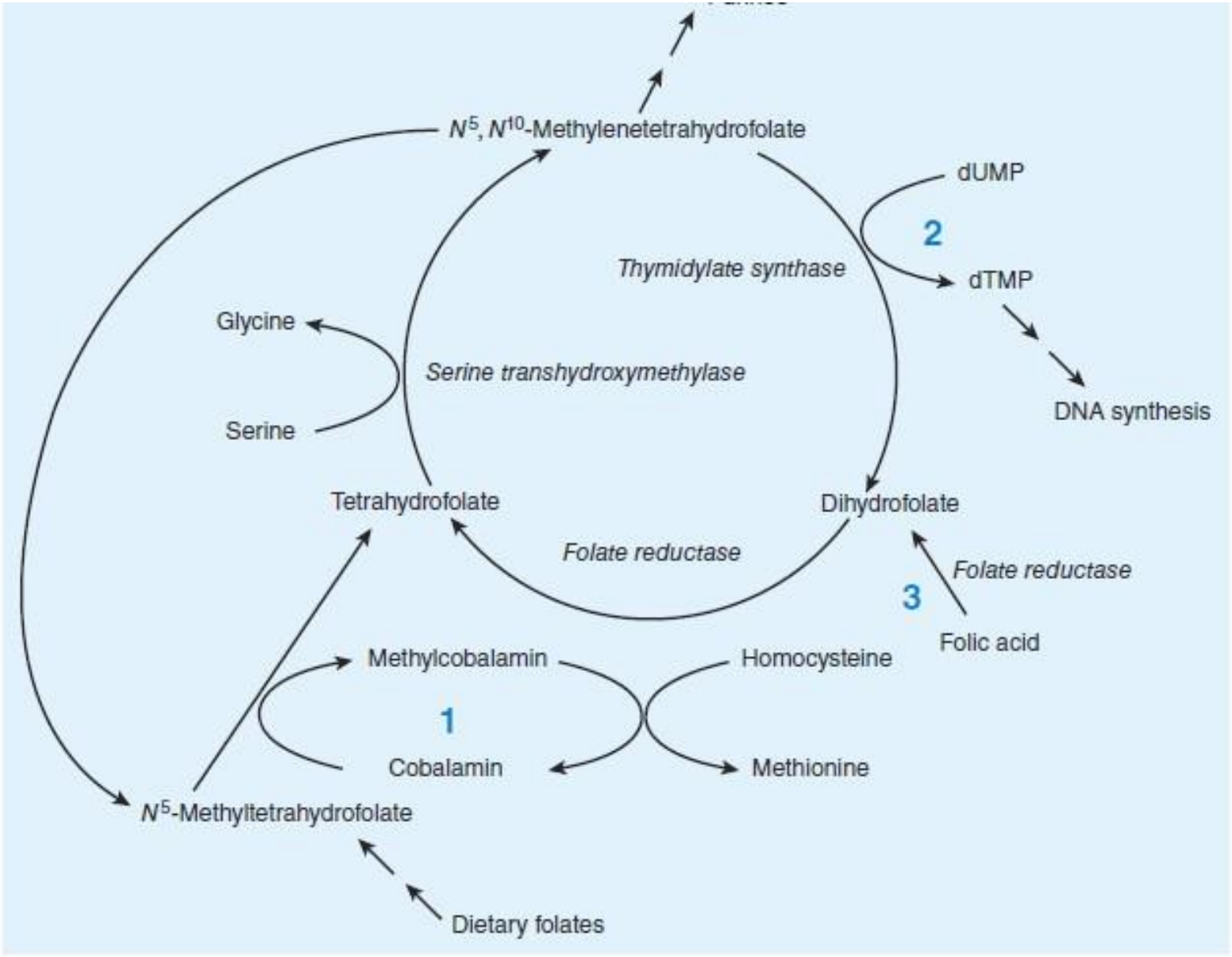


FIGURE 33–2 Enzymatic reactions that use vitamin B_{12}.



URE 33–3 Enzymatic reactions that use folates. **Section 1** shows the vitamin B_{12}–dependent reaction that allows most dietary fol
nter the tetrahydrofolate cofactor pool and becomes the "folate trap" in vitamin B_{12} deficiency. **Section 2** shows the deoxythymidine
ophosphate (dTMP) cycle. **Section 3** shows the pathway by which folic acid enters the tetrahydrofolate cofactor pool. Double arrows

- **Folic Acid Activation:** Folic acid is sequentially reduced to Dihydrofolate (DHF), then to Tetrahydrofolate (THF).
- **Core Function:** THF acts as a vital carrier molecule in one-carbon metabolism.
- **Amino Acid Conversion:** The enzyme *serine hydroxymethyltransferase* converts the amino acid Serine into Glycine.
- **Coenzyme Production:** During this conversion, THF accepts a carbon group to become **N^5,N^{10}-methylenetetrahydrofolate**.
- **DNA Synthesis: N^5,N^{10}-methylenetetrahydrofolate** acts as the carbon donor required to produce **dTMP** (deoxythymidine monophosphate), an essential building block for DNA.

- **The B12-Folate Link:** Vitamin B12 (specifically the methylcobalamin cofactor) is required to convert Homocysteine into Methionine.
- **THF Regeneration:** This enzymatic reaction is crucial because it simultaneously converts **N^5-methyltetrahydrofolate** back into active **Tetrahydrofolate (THF)**.
- **The "Folate Trap" Hypothesis:** If Vitamin B12 is deficient, this reaction halts. Folic acid becomes metabolically "trapped" in the form of N^5-methyltetrahydrofolate.
- **Functional Folate Deficiency:** Because THF cannot be regenerated, all downstream reactions requiring THF (like DNA synthesis) are blocked.
- **Clinical Significance:** This creates a *physiological* folate deficiency caused entirely by a B12 deficiency. If you measure folic acid levels in the blood, the results will be **normal**, but the folate is functionally inactive.

Vitamin B_{12}

- **In particular, depletion of THF prevents the synthesis of dTMP and purines required for DNA synthesis in rapidly dividing cells.**
- That is why megaloblastic anemia occurs, and the mucosa of the GI tract—which consists of rapidly dividing cells—also becomes deficient, developing the gastrointestinal symptoms
- **The accumulation of folate as *N^5*-methyltetrahydrofolate and the associated depletion of THF has been referred to as the "methylfolate trap".**

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- **This is where vitamin B_{12} and folic acid metabolism are linked, and explains why the megaloblastic anemia of Vitamin B_{12} deficiency can be partially corrected by large doses of folic acid, which is converted to dihydrofolate and then to THF by folate reductases.**

- Dietary folic acid is converted into dihydrofolate and then tetrahydrofolate without needing to pass through the B12-dependent step, resulting in partial treatment of megaloblastic anemia when you give folic acid.

Vitamin B_{12}

Causes of neurological manifestations of Vitamin B_{12} deficiency:

There are several theories. One of them was the isomerization reaction and lack of succinyl-CoA needed for myelin synthesis which stated that losing the ability to synthesize myelin damages neurons.

1. **Impaired Methionine Synthase Activity: A deficiency decreases the production of methionine and S-adenosylmethionine (SAM), which is vital for the synthesis and maintenance of the myelin sheath protecting nerve fibers.**

Vitamin B_{12}

2. **Accumulation of Methylmalonic Acid (MMA) and Homocysteine: When B12 is low, MMA and homocysteine levels rise, leading to toxic, abnormal myelination, oxidative stress, and neural overstimulation.**

Vitamin B_{12}

3. Upregulation of Inflammatory Cytokines: The deficiency triggers an increase in neurotoxic tumor necrosis factor-alpha (TNF-alpha) and a decrease in protective neurotrophic factors.

Even in the adult brain, nerve cells require neurotrophic factors or else they undergo degeneration. That is why in conditions like depression, CNS neurotrophic factors are deficient

Vitamin B_{12}

- **Whatever the cause, administration of folic acid for Vitamin B_{12} deficient individuals will NOT correct neurological manifestations, but will largely correct the anemia.**

Vitamin B_{12}

Clinical Pharmacology:

1. **Treatment of pernicious anemia**
2. **Treatment of neurological manifestations of Vitamin B_{12} deficiency.**

- **Used as parenteral injection of cyanocobalamin or hydroxocobolamin, both to replenish stores and maintenance, usually for life.**

- **Parenteral B12 Indication:** Parenteral administration (IV/IM) is strictly required for Pernicious Anemia due to the absolute lack of Intrinsic Factor (IF), making any oral absorption impossible.

- **Metformin-Induced Deficiency:** Patients on Metformin still have Intrinsic Factor. Metformin causes B12 malabsorption via **competitive inhibition** at the terminal ileum.

- **Overcoming the Blockade:** Because the mechanism is competitive inhibition, it can be overcome by significantly increasing the substrate concentration.

- **High-Dose Oral Therapy:** Administering a high oral dose of Methylcobalamin (~1.5 mg or 1,500 µg) provides enough concentration to outcompete Metformin for absorption.

Vitamin B_{12}

- **Hydroxocobalamin is preferred because it is more highly protein-bound and remain longer in the circulation.**

For example, when you give a standard Vitamin B12 injection (cyanocobalamin), approximately 70% of the dose is excreted by the kidneys within 24 to 36 hours.

Because **hydroxocobalamin** is highly protein-bound, it dissociates slowly, reaches the site of action, and remains in circulation—since plasma protein binding acts as a storage reservoir for the drug, releasing it slowly and making it much more effective.

Additional Resources:

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