Doctor.021

no.

HLS

PHARMACOLOGY

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Iron

Adverse effects:

1. (Gastrointestinal side effects) **Nausea, epigastric discomfort, abdominal pain, constipation and diarrhea.** Most people have constipation not diarrhea

- **These effects are dose-related and can be reduced by lowering the dose or giving it with meals or immediately after meals.** (normal duration of treatment takes about 3-6 months , so by lowering the dose the duration prolongs)

2. **Black stools are common** and harmless but **may obscure the diagnosis of continued gastrointestinal blood loss.**

Iron

2. **Parenteral iron therapy:**

- **Should be reserved for patients:**

1) **Unable to tolerate oral iron.** (we often tell patients to take after the meal or right after it, to decrease the chance of these side effects)

2) **Unable to absorb oral iron. Malabsorption syndromes, small bowel resection** (for example resection after colon cancer).Food that can decrease iron absorption: diary products, metals(Ca,Zn..), drugs that reduce the acidity of the stomach (patients who have gastrectomy), antibiotics(tetracyclins: make a reaction that can precipitate metals), whole grains.

3) Severe Anemia **With extensive chronic blood loss.** (like patient has very heavy menstruation and this was not controlled by oral iron)

Iron

- **Iron dextran:**

  - t is a stable complex of ferric hydroxide and low- molecular-weight dextran containing 50 mg elemental iron/mL of solution. Given by deep IM injection or IV infusion.

  - IM injection causes local pain , tissue staining and irritation.

  - IV infusion causes hypersensitivity reactions: headache, fever, arthralgia, N, V (nausea and vomiting), back pain, flushing, bronchospasm and rarely anaphylaxis and death.

- **Iron-sucrose complex.**
- **Iron sodium gluconate.**

  —Given only IV , less likely to cause hypersensitivity.

Iron

Acute Iron Toxicity:

- Usually results from accidental ingestion by children as well as by taking too much of parenteral iron.
- 10 tablets can be lethal in children.
- Causes necrotizing gastroenteritis: vomiting, pain, bloody diarrhea, shock, lethargy and dyspnea.
- Patients may improve but may proceed to metabolic acidosis, coma and death.

Iron

Treatment of Acute Iron Toxicity:

1. **Deferoxamine "Desferal": is a potent iron-chelating compound which binds already absorbed iron and promotes its excretion in urine and feces.** (Not required)
2. **Whole Bowel Irrigation; to flush out unabsorbed pills.**
3. **Activated charcoal is ineffective.** (it's a way that is used to get rid of toxicity by trapping it in the stomach and intestine)
4. **Supportive therapy is also necessary.** (correct other signs and symptoms of toxicity such as acidosis)

Iron

Chronic Iron Toxicity= Hemochromatosis: Excess iron can deposit in the heart, liver, pancreas, and other organs leading to organ failure.

- **Usually occurs in:**

  1. Inherited Hemochromatosis: excessive iron absorption.

  2. Patients with frequent transfusions e.g. in patients with hemolytic anemias.

Iron

Treatment of Chronic Iron Toxicity:

1. **Intermittent phlebotomy.** (donating blood or removing blood from the body with a needle)
2. **Deferoxamine: is much less efficient than phlebotomy.**
3. **Deferasirox" Exjade": oral, more convenient than deferoxamine.**

Case

- **A 35 year old woman is seen for easy fatigue for many months. She is now 24 weeks pregnant with her 3rd child in 3 years. She doesn't see any obstetrician and does not take any vitamins, lately, she has developed a taste for eating ice** (pica) **she has no other complaint. Family and past history are negative. She does not smoke or drink. Physical examination is positive for pale conjunctiva, mild spooning of nails, and a II/VI systolic murmur** (abnormal blood sound that gives an indication of low blood viscosity) **at left lower sternal borders. Stools are negative for occult blood.**
- **Labs: complete blood count (CBC) – Hg 7.1 gm/dl** very low**, HCT 23%** low**, WBC 5,400/mm3** normal**; MCV is 74 fl (normal 85-95 fl); RDW is 17.1% (normal 13-15)**

To confirm the diagnosis further more we can ask for ferritin level test

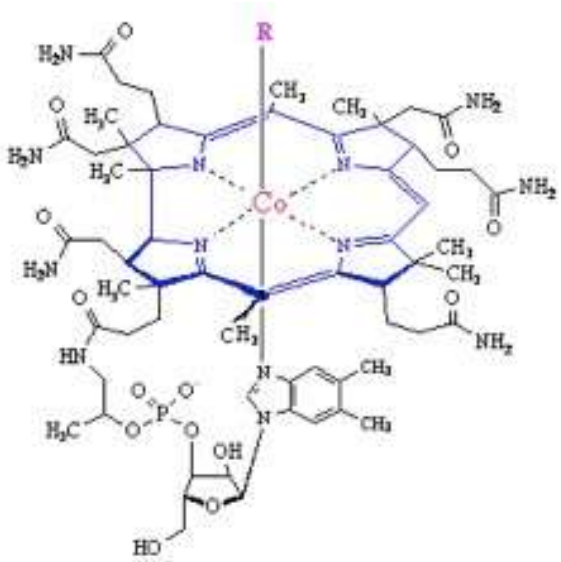
Suggested treatment: iron, (oral not parenteral)

Drugs Used in Blood Disorders

Dr. Alia Shatanawi

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

They differ in the R group

Vitamin B_{12}

Pharmacokinetics:

B12 is absorbed in the terminal ileum but the stomach is important because we need the intrinsic factor

1. **Vitamin B_{12}, in physiologic amounts is absorbed only 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.**

Vitamin B_{12}

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.**

How long would it take for the storage pool to be depleted and symptoms of deficiency to appear If we have 4000 µg (4 mg) stored ?

4000/2 (daily requirement) = 2000day

2000 day/ 365 ~ 6 years

But yet its common mainly because of malabsorption especially in the Mediterranean region

Vitamin B_{12}

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.

Causes of deficiency:

Malabsorption of Vitamin B_{12} due to:

1. Lack of intrinsic factor.
2. Loss or malfunction of the terminal ileum.

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.** (What helps in the release of it from the dairy products is the acidity of the stomach)

Vitamin B_{12}

4. Atrophic gastritis (from *Helicobacter pylori)*

when the acidity levels of the stomach decrease, that will affect the dissociation of vitamin B12 from the protein in the food, and lower levels of acidity in the stomach will affect the production of the intrinsic factor

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

6.Drugs: proton pump inhibitors (they will lower the HCL of the stomach) **and metformin** is used for type 2 diabetes (there is an association between taking metformin for long period of time and vitamin B12 deficiency)

Vitamin B_{12}

Pharmacodynamics:

Vitamin B_{12} is involved in 2 essential enzymatic reactions in humans: don't go deep into this metabolism, you are studying pharma not biochem

1. **Deoxyadenosylcobalamin is responsible for the isomerization of methylmalonyl-CoA to succinyl-CoA by the enzyme methylmalonyl-CoA mutase.**

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

Tetrahydrofolate is the precursor of folate cofactors which are important for nucleotide synthesis

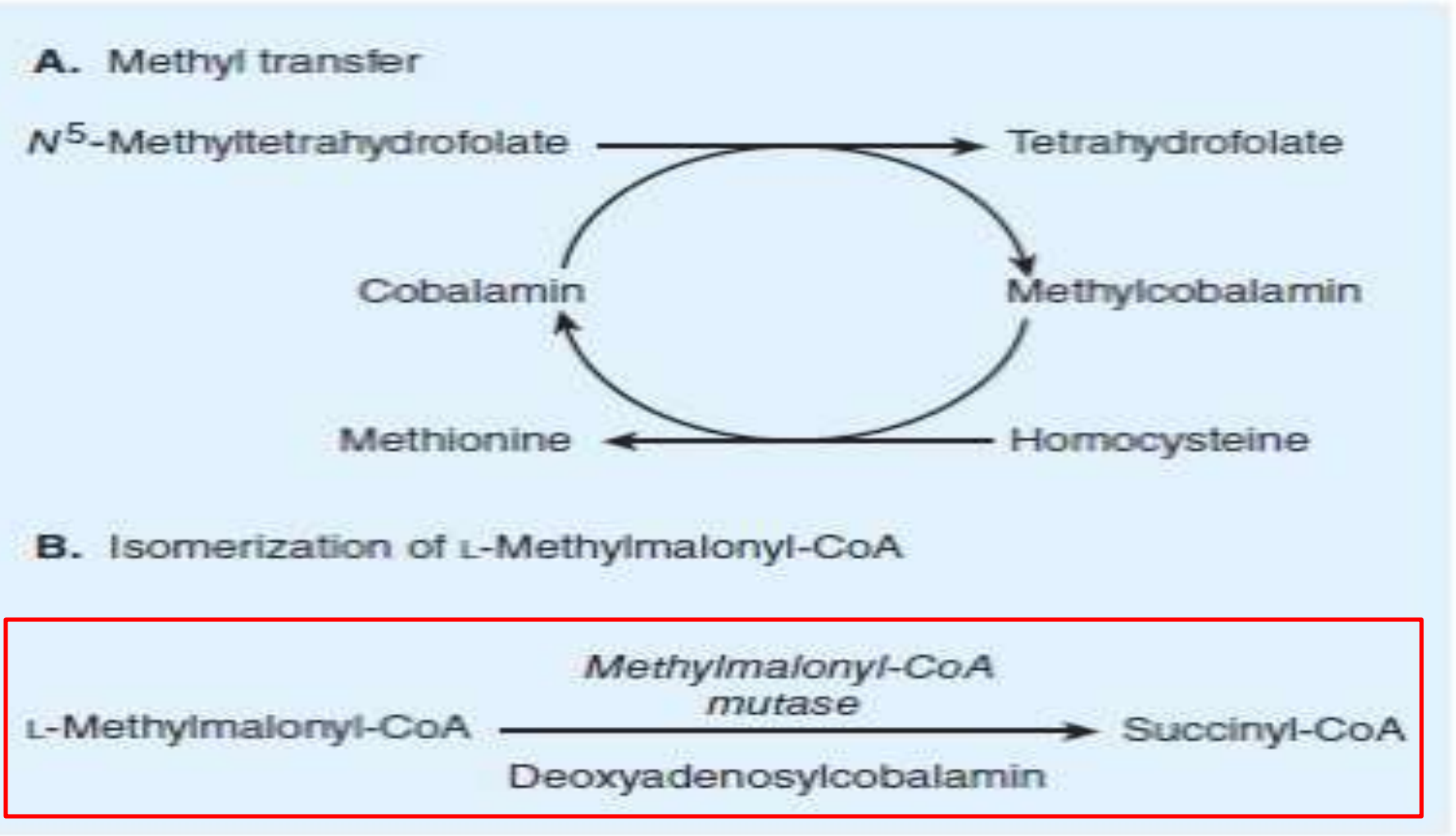
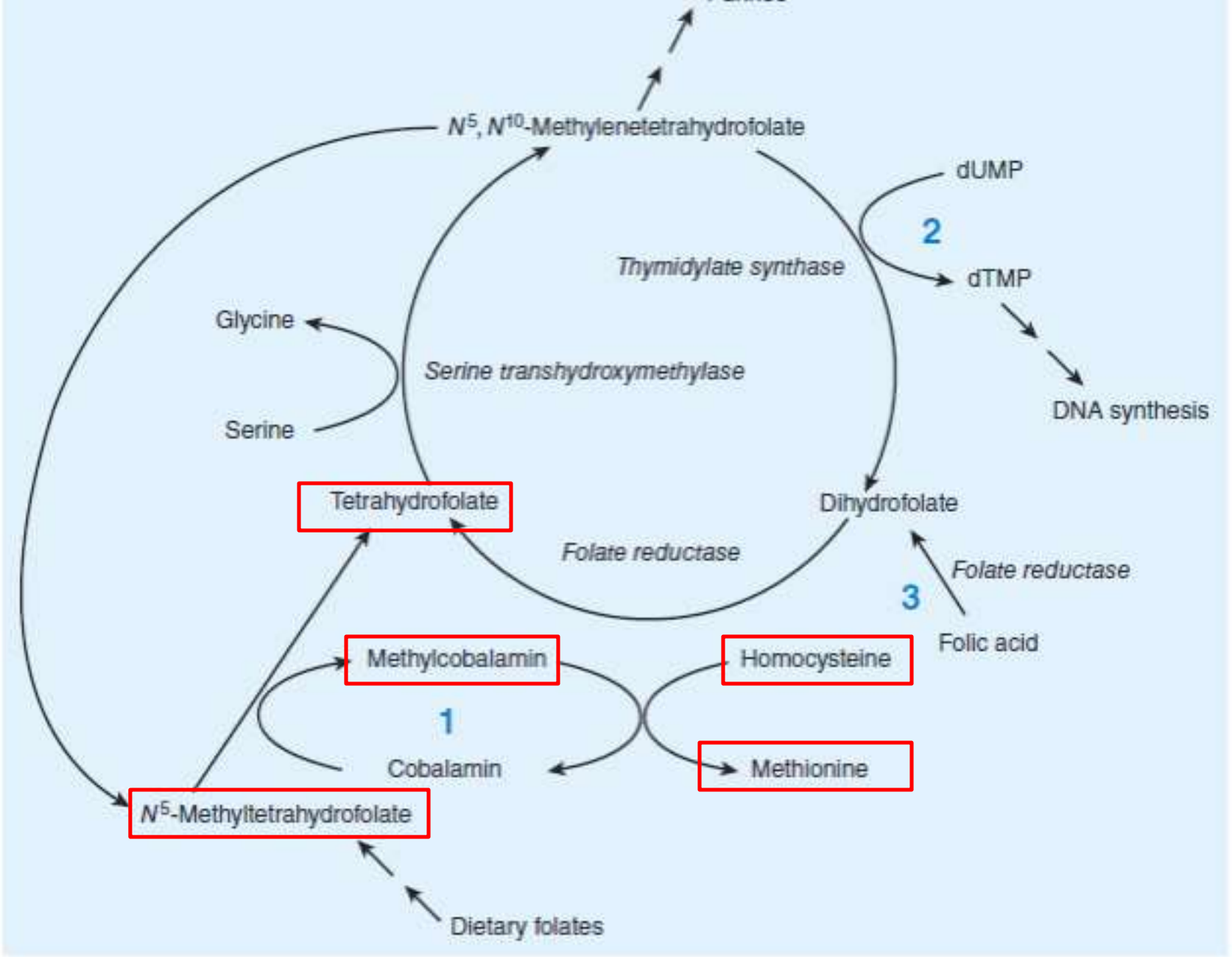


FIGURE 33–2 Enzymatic reactions that use vitamin B_{12}.

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 that is important for synthesis of many nucleotides
- In Vitamin B_{12} deficiency, folate cofactors become deficient leading to defects in several biochemical reactions involved in the transfer of one-carbon groups.



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

Vitamin B_{12}

- In particular, depletion of THF prevents the synthesis of dTMP (deoxythymidine monophosphate) and purines required for DNA synthesis in rapidly dividing cells.
- The accumulation of folate as N^5-methyltetrahydrofolate and the associated depletion of THF has been referred to as the "methylfolate trap".

Vitamin B_{12}

- **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.** The deficiency in THF comes from some nucleotides not get synthesis and this affects DNA replication in rapidly replicating cells specially hematopoietic stem cells (another way to have THF by adding large doses of folic acid to shift this enzyme for producing the THF which is needed)

Vitamin B_{12}

- **Evidence implicates disruption of the methionine synthesis pathway as a cause of neurological manifestations of Vitamin B_{12} deficiency in contrast to accumulation of methylmalonyl-CoA.** Methionine is a fundamental amino acid, cannot synthesized by the body, responsible on many metabolic reactions (ex: methylation of the DNA)
- **Whatever the cause, administration of folic acid for Vitamin B_{12} deficient individuals will NOT correct neurological manifestations, but will largely correct the anemia.** Because it well not recycle the methionine!

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.** Why do we give it parenterally?? Because we have a problem with the absorption
- There are two forms and the preferred one is hydroxocobolamin which is protein-bound which delays its release into the blood so it will correct the anemia over a long period of time

Vitamin B_{12}

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

Folic Acid

- **Reduced forms of folic acid are required for the synthesis of amino acids, purines and DNA.**

The consequences of folate deficiency include:

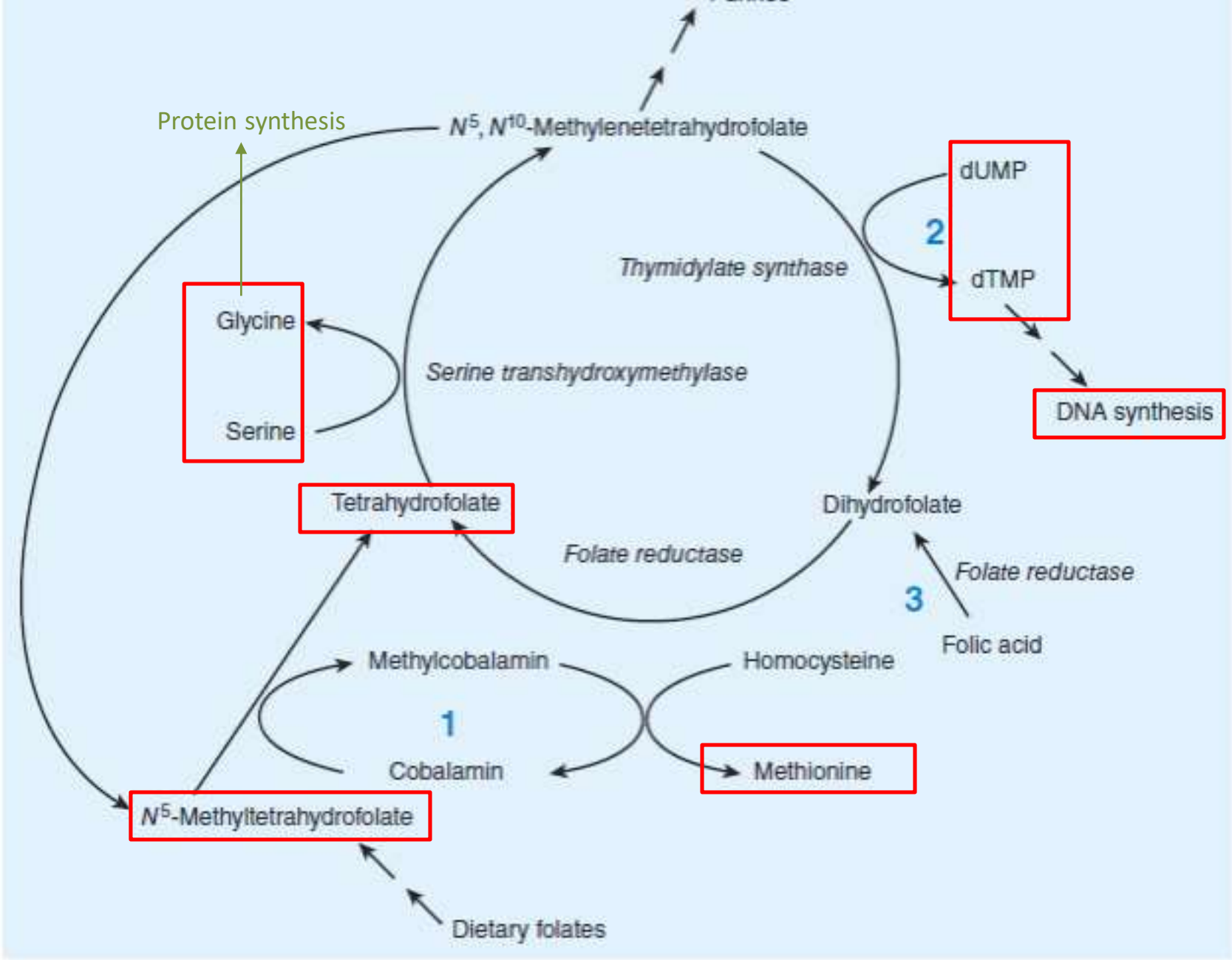
1. **Megaloblastic anemia.** Vitamin b12 deficiency also causes megaloblastic anemia.
2. **Congenital malformations - neural tube defects, such as spina bifida and anencephaly)** the fetal CNS needs high levels of folate for DNA synthesis of the cells especially in the first month, the less folate is available, the more CNS is defected
3. **Occlusive vascular disease due to homocysteine accumulation.**

Folic Acid

- **Folic acid (pteroylglutamic acid) can exist in the form of monoglutamate, triglutamate and polyglutamate.**
- **It undergoes reduction by folate reductase to dihydrofolate and tetrahydrofolate.**

Folic Acid

- **Tetrahydrofolate can be transformed to folate cofactors possessing one-carbon.**
- **The folate cofactors are inter-convertable and serve the donation of one-carbon units at various level of oxidation.**



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Folic Acid

Pharmacokinetics:

- **Food rich in folic acid include yeast, liver, kidney & green vegetables.**

1. **Usual daily absorption from diet ~ 50-100 µg, depending on metabolic requirements.**
2. **Pregnant women may absorb up to 300-400 µg.** More demand for the fetus

Folic Acid

3. **Normal tissue storage in liver and other tissues ~ 5-20 mg.** don't memorize these numbers, just remember that these numbers are put for comparison only like: pregnant woman will absorb more folic acid, in case of iron menstruated woman will absorb more iron and so on.

- **If folic acid absorption stops, megaloblastic anemia develops in 1-6 months.**

4. **Folic acid is absorbed in the proximal jejunum.**

Folic acid

Clinical pharmacology:

1. **Megaloblastic anemia. Vitamin B_{12} deficiency must first be excluded. Why?**

Because I want to know the cause of the anemia is vit B12 or folic acid deficiency

2. **Prevention of folic acid deficiency in high risk groups such as pregnancy, alcohol dependence, hemolytic anemia, …**

- **Usually used orally until the cause is removed and stores are replenished.**

Folic acid

Causes of deficiency:

1. **Inadequate dietary intake.**
2. **Liver disease and alcohol dependence because of diminished stores and poor diet.**
3. **Increased requirements: pregnancy, hemolysis**
4. **Malabsorption syndromes.**
5. **Renal dialysis.**

Folic acid

6. Drugs:

A. Methotrexate, trimethoprim, pyrimethamine inhibit dihdrofolate reductase

B. Long-term phenytoin therapy impair folate absorption