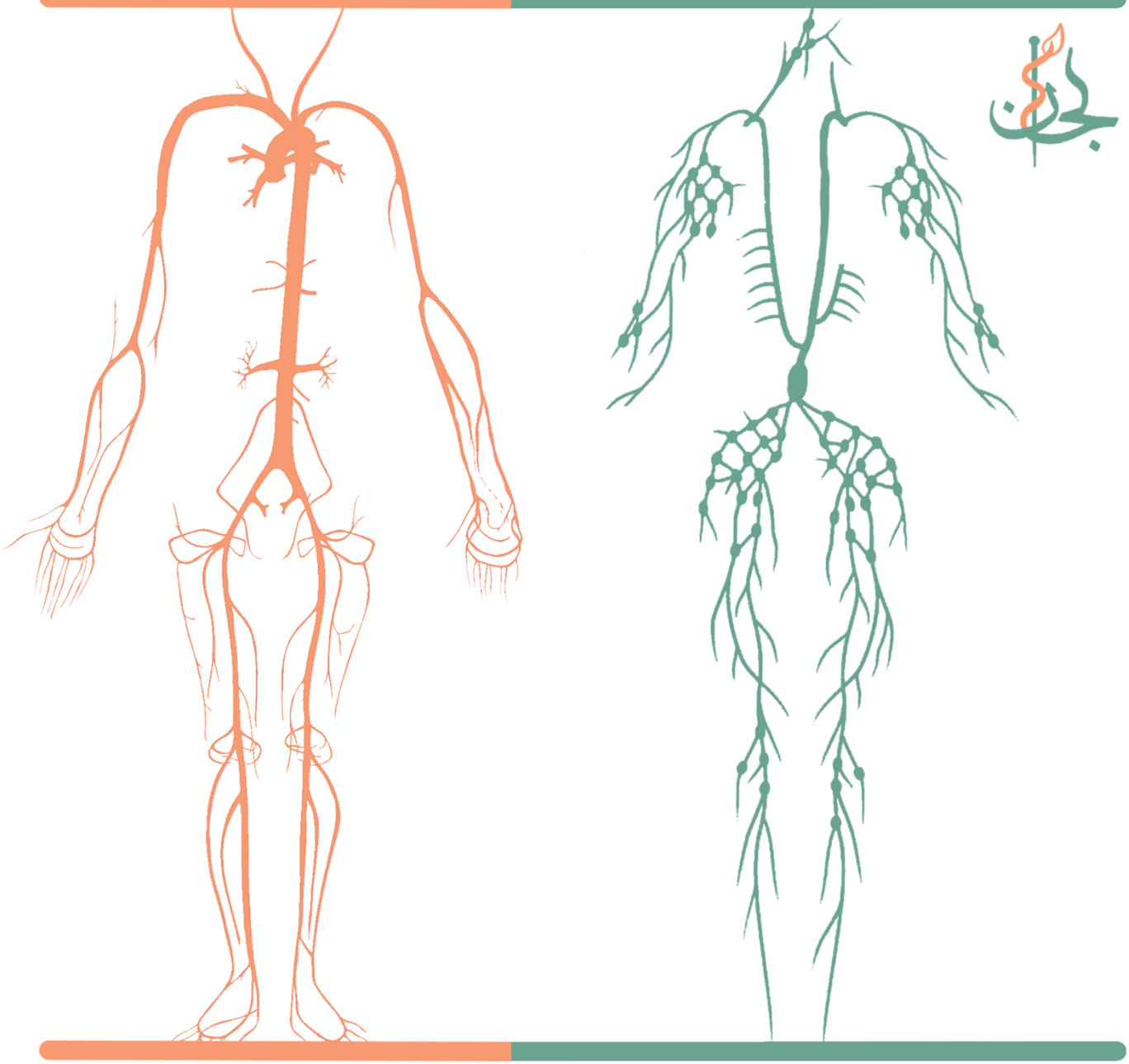
Pharmacology

HematoLymphatic



Title: Sheet 1 – Agents used In anemias

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Agents used in Anemias

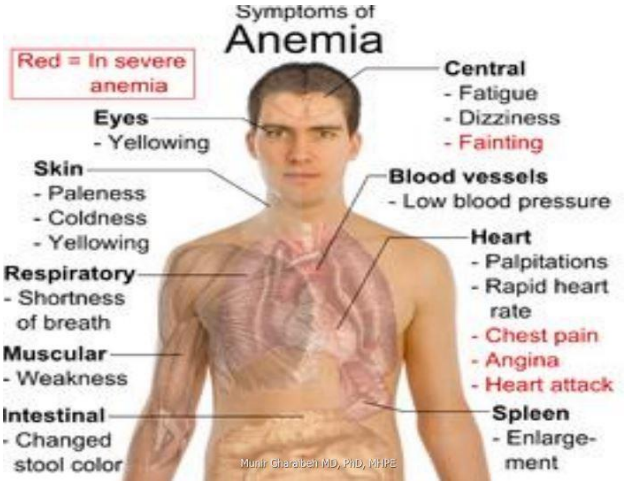
General Information

Hematopoiesis: Requires a constant supply of:

1. **Essential elements**: Iron, vitamin B12 and folic acid. We take them with **food** or sometimes as **medicines**.

2. **Hematopoietic Growth Factors**: a new subject introduced in agents used in anemias.

Anemia is very Important and it is a common symptom of many diseases, It affects the whole body, and as you know, it means **low hemoglobin levels** which means **low oxygen carrying power** of the blood cells into the tissues, so, all the tissues will be affected.



The most important and the most common is **Iron deficiency anemia**, and the involvement of iron in the synthesis of hemoglobin is very important.

Iron deficiency is the most common cause of chronic anemia, it causes **microcytic hypochromic anemia**.

Iron is an important part of many molecules in the body including Hemoglobin, Myoglobin, Enzymes, Transport form (transferrin), storage form (ferritin), and the total iron content in the body is 4248 mg in men and much less in women (2314 mg).

	Iron Content (mg)	
	Men	*Women*
Hemoglobin	3050	1700
Myoglobin	430	300
Enzymes	10	8
Transport (transferrin)	8	6
Storage (ferritin and other forms)	750	300
Total	4248	2314

October 20 Munir Gharaibeh MD, PhD, MHPE 6

If we take Iron as a medicine, we have to know the pharmacokinetics of iron, as you know, **free iron is toxic**, and all iron used to support hematopoiesis is reclaimed (recycled) from catalysis of hemoglobin in senescent or damaged erythrocytes.

- ❖ Only a small amount of iron is lost from the body, but we need to replenish this small amount of iron. So, **if loss was more than the intake of iron**, Iron deficiency anemia will develop.

Possible causes of Iron Deficiency:

- ✓ **Increased iron requirements:** pregnant women need more iron to replenish their iron loss, and to supply their fetuses with it.
- ✓ **Increased iron losses:** bleeding either acute or chronic.

Absorption:

- Daily intake: 10-15mg of elemental iron. This is in normal people taking balanced diet and without any impairment of their **appetite** or their ability to take regular food.
- Heme iron in meat hemoglobin and myoglobin (mainly) is well absorbed (intact), but, Iron from other sources is tightly bound to organic compounds and is less available and should be reduced to **ferrous iron** (by acidifying agents and **vitamin C**) before it can be absorbed. So, iron in plants is **less bioavailable**.
- Daily absorption: 5-10% of the daily intake, usually from **duodenum and proximal jejunum**.
- Absorption can increase in response to low iron or increased requirements (might reach 20-30 % of daily intake, but this might take time).

Mechanism of absorption:

- Divalent Metal Transporter (DMT1) actively transports ferrous iron across the luminal membrane of intestine and it is regulated by mucosal cell iron stores. Intestinal mucosal cells can sense the amount of iron in the body and this transporter can be activated or inhibited.
- Ferroportin1(IREG1), transports iron across the basolateral membrane into the blood.
- Excess iron is stored in the mucosa as ferritin, (a water-soluble complex consisting of a core of ferric hydroxide covered by a shell of specialized protein called apoferritin).

Transport:

Transferrin (Tf) binds two molecules of iron in the plasma, then the complex binds to Transferrin Receptors (TfR) on the **maturing erythroid cells** which internalize the complex through the process of **receptor mediated endocytosis.** Iron is released for hemoglobin synthesis and the **Transferrin- transferrin receptor** complex is recycled to the plasma membrane and transferrin dissociates and returns to the plasma.

Storage:

- Ferritin (apoferritin AF and iron) is the storage form of iron. It is stored in intestinal mucosa and in the macrophages of the liver, spleen, and bone marrow.
- Ferritin in serum is in **equilibrium** with storage ferritin and this is the test **we use to estimate body iron stores.**

Elimination:

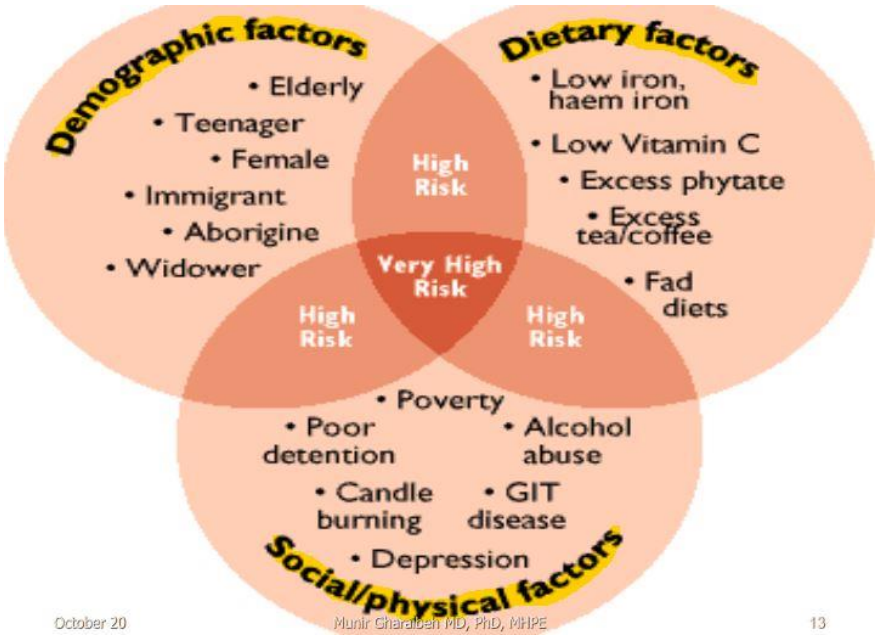
There is no mechanism for excretion. Only Small amounts are lost by **exfoliation** of intestinal mucosal cells, bile, urine, sweat and may be by a minor bleeding.

Iron therapy Indications:

Treatment and prevention of iron deficiency anemia which can result from:

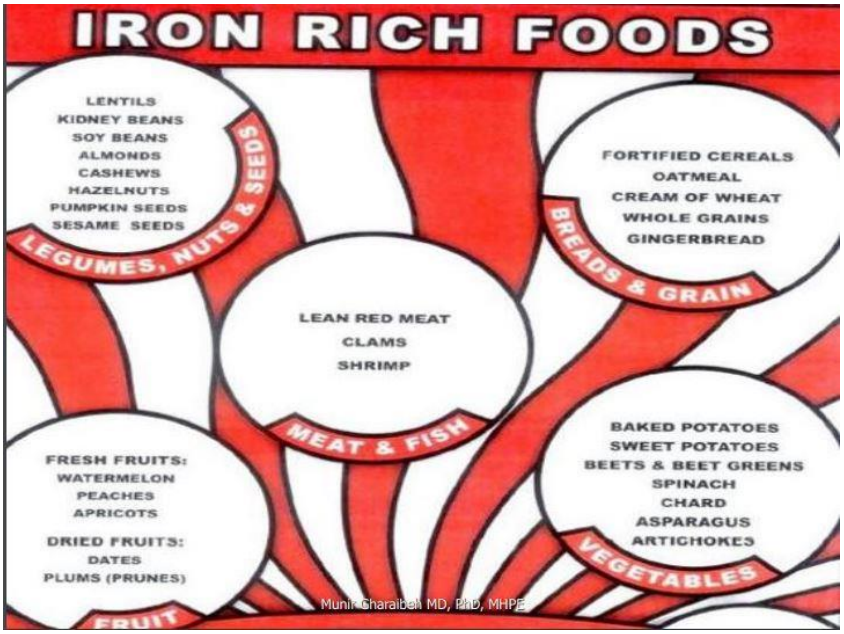
- ✓ **Increased requirements:** infants, children, pregnant and lactating women, patients on hemodialysis, patients on erythropoietin treatment which stimulates erythropoiesis. There is no wisdom in giving erythropoietin to stimulate the bone marrow to produce RBCs without the availability of iron.
- ✓ **Inadequate iron absorption:** after gastrectomy (the acidity of the stomach will be decreased and consequently, ferric iron will not be reduced to the absorbable form), severe small bowel disease.
- ✓ **Blood loss:** is the most common cause of iron deficiency anemia, it is either **Acute** (injury, trauma and cut wounds) OR **Chronic** (peptic ulcer disease, stones or tumor in the GI or the urinary tract).

These are the factors that increase the risk of iron deficiency anemia:



Iron rich foods:

- ✓ **Lean red meat has the highest amount of iron.**



In pharmacology, we can use iron orally or parenterally.

Oral Iron Preparations:

- ❖ Ferrous sulfate.
- ❖ Ferrous gluconate.
- ❖ Ferrous fumarate.

All are effective and inexpensive. Side effects: They can cause nausea, epigastric discomfort, cramps, constipation or diarrhea and black stools.

Ferrous gluconate can cause **diarrhea**, but ferrous sulfate can cause constipation. So, it depends on the patients: Some patients will tell you that Ferrous sulfate is not good for them, and they would like Ferrous gluconate or Ferrous fumarate.

You can find them in simple tablets (**enteric coated tablets**) with sugar covering, they are **red and shining** and this might be an **invitation for children** to take them thinking they are candy.

Parenteral Iron Therapy:

- ❖ Reserved for patients with **documented iron deficiency** who are unable to tolerate or absorb oral iron and for patients with extensive chronic blood loss who cannot be effectively maintained with oral iron alone. They are **rarely needed** because they carry the risk of **iron overload**.
- ❖ In oral iron treatment, if the stores are filled and loaded very well, there will be decreased oral iron absorption, so, there will be **no iron toxicity**. On the other hand, in parenteral iron, you force the iron inside the body, and you need long time or maybe be other procedures to get rid of the excess iron. So, if there is iron deficiency, **oral iron preparations will be quite enough and effective.**

Parenteral iron preparations:

- ✓ Iron dextran: the oldest one, Given by deep **IM** injection or **IV** infusion. IM injection causes **local pain** and tissue staining. IV infusion causes **hypersensitivity**

reactions: headache, fever, arthralgia, Nausea, Vomiting, back pain, flushing, bronchospasm and rarely anaphylaxis and death.

- ✓ Iron-sucrose complex.
- ✓ Iron –sorbitol citrate "Jectofer".
- ✓ Iron sodium gluconate. Modern type and more expensive, it is Given **only IV,** and it is **less likely to cause hypersensitivity.**
- ✓ **Ferumoxytol : the most recent one, IV but can be given quickly**

Acute Iron Toxicity:

- ✓ Usually results from accidental ingestion by **children** as well as **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.**

Treatment of acute iron toxicity:

- **Deferoxamine** "*Desferal*": is a potent iron-chelating compound which binds already absorbed iron and promotes its excretion in urine and feces, given by injection. It is the antidote for the **ABSORBED** iron.
- For the **UNABSORBED** iron, we use laxatives or saline to cause **whole bowel irrigation** to flush out the unabsorbed pills. (غسيل أمعاء)
- Activated charcoal is ineffective for iron toxicity.
- Supportive therapy is necessary.

Chronic iron toxicity (Hemochromatosis):

- ✓ Excess iron build up over a long period of time that results in iron depositing in the heart, liver, pancreas, and other organs leading to organ failure.
- ✓ Chronic iron toxicity doesn't occur after ingestion of iron. Meaning that there must be a cause for the iron overload.

Chronic iron toxicity usually occurs in:

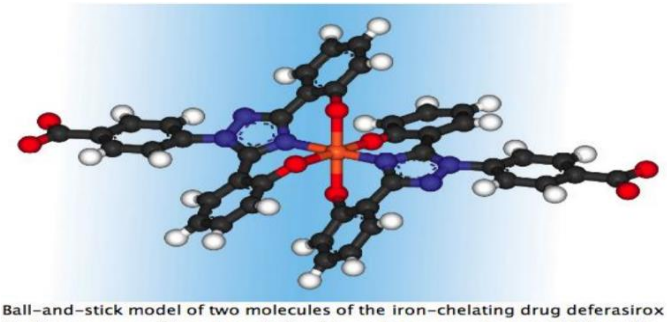
- **Inherited hemochromatosis**, which results in excessive chronic iron absorption.
- **Patients with frequent transfusions**, as in patients with hemolytic anemias (e.g. thalassemia patients).

Treatment of chronic iron toxicity:

- **Intermittent phlebotomy**, which is the process of making a puncture in a vein, usually in the arm, for the purpose of drawing blood.

- **Deferoxamine** can be used to treat chronic iron toxicity. However, it is much less efficient than phlebotomy. Children suffering from thalassemia that require frequent transfusions are given deferoxamine to lose some iron. Given IV or IM.
- **Deferasirox** *"Exjade"*: taken orally, **more convenient than deferoxamine**.

Vitamin B12:



Ball-and-stick model of two molecules of the iron-chelating drug deferasirox binding an atom of iron. Iron chelated in such a manner is unavailable to the fungi that cause mucormycosis.

- ✓ A porphyrin-like ring with a central cobalt atom. It is a water-soluble vitamin and may disappear in high temperatures and washing of food.
- ✓ It has many other different names, such as methyl cobalamin, deoxyadenosyl cobalamin, cyanocobalamin, and hydroxocobalamin.
- ✓ Vitamin B12 is found in meat, liver, eggs, and dairy products. Therefore, nutritional deficiency only occurs in **strict vegetarians.**
- ✓ The daily requirement of vitamin B12 is only **2 mcg.**
- ✓ The body storage pool of B12 ranges from **300-5000 mcg**. That's why the daily requirement for B12 is small.

Because of the large storage pool of B12, it would take 5 years to exhaust all the stored pool and for **megaloblastic anemia** to develop after stopping absorption.

Recall from our pathology lectures that megaloblastic anemia due to vitamin B12 deficiency is macrocytic, hypochromic anemia WITH neurological manifestations.

Pharmacokinetics of Vitamin B12

- ❖ Absorption of B12 requires the complexing with the **intrinsic factor** (*Castle's factor*), which is a glycoprotein secreted by the parietal cells of the stomach.
- ❖ Vitamin B12 is absorbed in the distal ileum.
- ❖ Vitamin B12 is then transported in the body to tissues by **transcobalamine II**.

Schilling's test:

- Measures the absorption and urinary excretion of radioactively labeled vitamin B12. Used to determine if the rate of B12 absorption is normal or not.

Causes of vitamin B12 deficiency:

1) Pernicious anemia
2) Distal ileal disease due to inflammation, resection, or **Diphyllobothrium latum** infestation (a fish worm that can infect and live in the distal ileum).
3) Bacterial overgrowth of the small intestine.
4) Chronic pancreatitis
5) Thyroid disease.
6) Congenital deficiency of the intrinsic factor.
7) Congenital selective vitamin B12 malabsorption (maybe the cause of vitamin B12 deficiency in Jordan).

Vitamin B12 Functions:

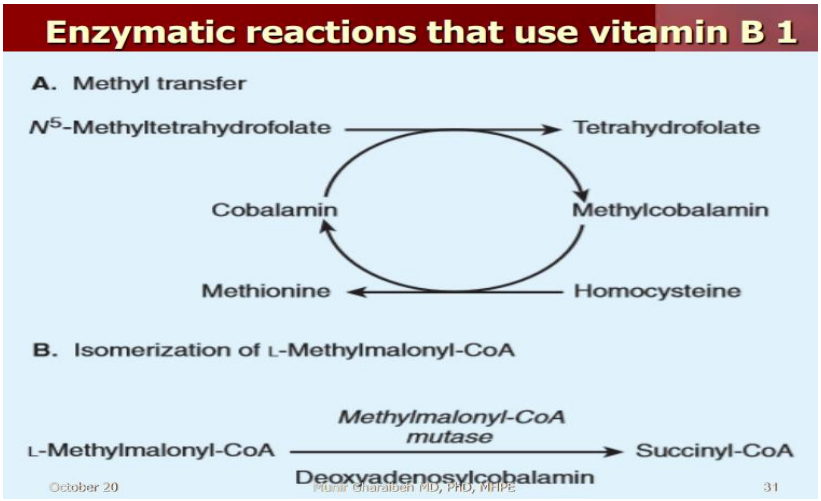
- Vitamin B12 is responsible for the transfer of a methyl group from N5-methyltetrahydrofolate to homocysteine, forming methionine. N5-methyltetrahydrofolate is the major dietary and storage form of folate.

[Extra]: remember that homocysteine is toxic to the heart and the nervous system. And B12 is required in order to complete its metabolism.

- Conversion of N5-methyltetrahydrofolate to tetrahydrofolate. Deficiency of B12 will lead to accumulation of N5-methyltetrahydrofolate cofactors and depletion of Tetrahydrofolate.

Megaloblastic anemia of B12 deficiency can be partially corrected by ingestion of large amounts of folic acid. This is because folic acid can be reduced to dihydrofolate by the enzyme **dihydrofolate reductase**.

- Isomerization of **methylmalonyl-CoA** to succinyl-CoA by the enzyme methylmalonyl-CoA mutase.
  Vitamin B12 depletion leads to the accumulation of **methylmalonyl-CoA.** This is thought to cause the neurological manifestations of vitamin B12 deficiency. (this function is not related to folate).



Therapy with Vitamin B12:

- ✓ Parenteral: (standard treatment)

  Life-long treatment for B12 deficiency is usually needed because they're mainly congenital or cannot be corrected. And is done so by administering parenteral B12.

  (**except in some cases such as Diphyllobothrium latum infestation, where killing the worm will be sufficient and life-long treatment won't be needed**).

  Parenteral injection could be given daily or every other day for 1-2 weeks to replenish the stores.

  Maintenance injections are given every 1-4 weeks
- ✓ Oral:

  Given only to patients who refuse or cannot tolerate injections.

  However, if the patient has a problem in the absorption of B12, oral therapy will be ineffective.

- ✓ Intranasal:

  Given prophylactically for patients in remission.

Everything about folic acid isn't included in the MID-EXAM

Folic acid:

- ✓ Reduced forms of folic acid are required for the synthesis of amino acids, purines, and DNA. It is also important for hematopoiesis.
- ✓ Can be found in yeast, liver, kidney, and green vegetables.
- ✓ Deficiency of folic acid is common, but easily corrected.

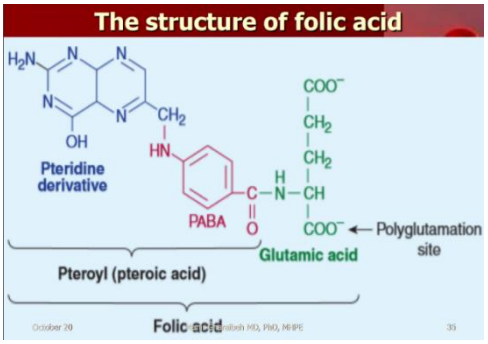
Deficiency can result in:

1) **Megaloblastic anemia** due to folic acid deficiency. (similar to megaloblastic anemia due to B12 deficiency, but megaloblastic anemia due to folic acid deficiency is more common)
2) **Congenital malformations** (can occur in the fetuses of pregnant females with folic acid deficiency).
3) **Occlusive vascular disease** due to elevated homocysteine.

Chemistry of Folic acid:

Folic acid contains pteridine, **para-aminobenzoic acid (PABA),** and glutamic acid.

Folic acid is reduced to dihydrofolate and tetrahydrofolate in the body, and then to folate cofactors, which are interconvertible and can donate one carbon units at various levels of oxidation. (that's why folic acid can be used to **partially correct** megaloblastic anemia due to B12 deficiency)



Folic acid is regenerated in most cases.

Kinetics of folic acid:

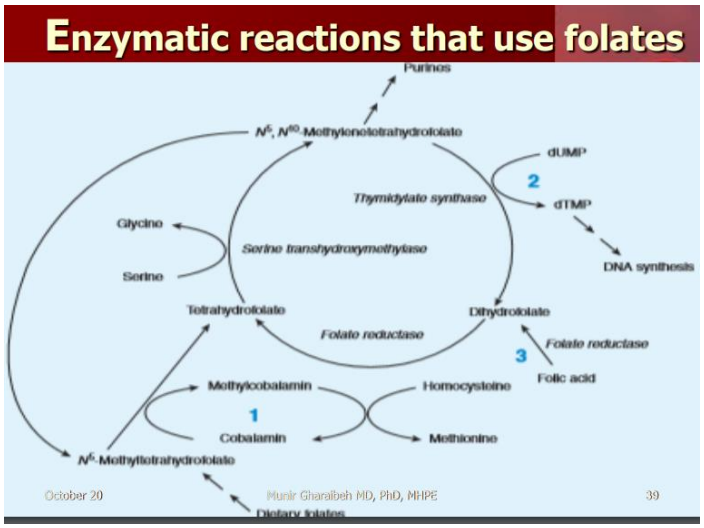
- Folic acid is readily and completely absorbed from the **terminal jejunum**.
- Glutamyl residues are hydrolyzed before absorption by α-1-glutamyltransferase (congugase) within the brush border.
- N5-methyltetrahydrofolate is transported into the bloodstream **by active and passive processes.**
- It is widely distributed in the body.
- **Inside cells**, it is converted to tetrahydrofolate (THF) by demethylation reaction in the presence of vitamin B12.
- There are small amounts of folic acid that are stored in the body (unlike B12).
- Only 5-20 mcg are stored in the liver.
- Folic acid can be excreted in the urine and stool and also can be destroyed by catabolism.
- And due to the small storage pool of folic acid, megaloblastic anemia can develop within 1-6 months after stopping intake.

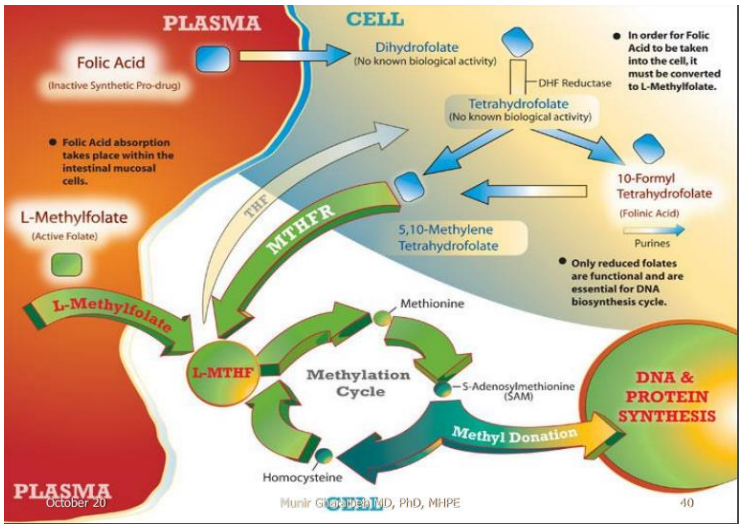
Folic acid functions:

Tetrahydrofolate cofactors are important in one carbon reactions such as:

- Production of **dTMP from dUMP**, which is needed for DNA synthesis.
- Generation of methionine from homocysteine.

- Synthesis of essential purines.





Causes of folic acid deficiency:

- Inadequate dietary intake.
- After alcoholism (due to neglected nutrition)
- Liver disease causing impaired hepatic storage.
- Pregnancy and hemolytic anemia which increase the demand.
- Malabsorption syndrome
- Renal dialysis
- Drugs, such as **methotrexate** (immunomodulatory drug), trimethoprim (antibacterial drug), and **phenytoin** (antiepileptic drug).

Treatment with Folic acid:

- Parenteral administration is rarely necessary because it is well absorbed orally even in malabsorption.
- A dose of **1 mg daily** (until the cause of deficiency is corrected) is enough.
  Or, indefinitely for patients with malabsorption or dietary inadequacy.
- Can be given prophylactically.
- Routinely given in early pregnancy or even before being pregnant.
- Recently, folic acid was added to different foods (such as flour) to make sure that folic acid was enough in the diet.

Good Luck