Pharmacology - MSS

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Agents Used in Anemias

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So first of all, I didn’t like the blood wallpaper, so I removed it and made it pink instead, I hope you're okay with that

Agents Used in Anemias

We will discuss them as the first branch of drugs used in hematopoietic and lymphoreticular system.

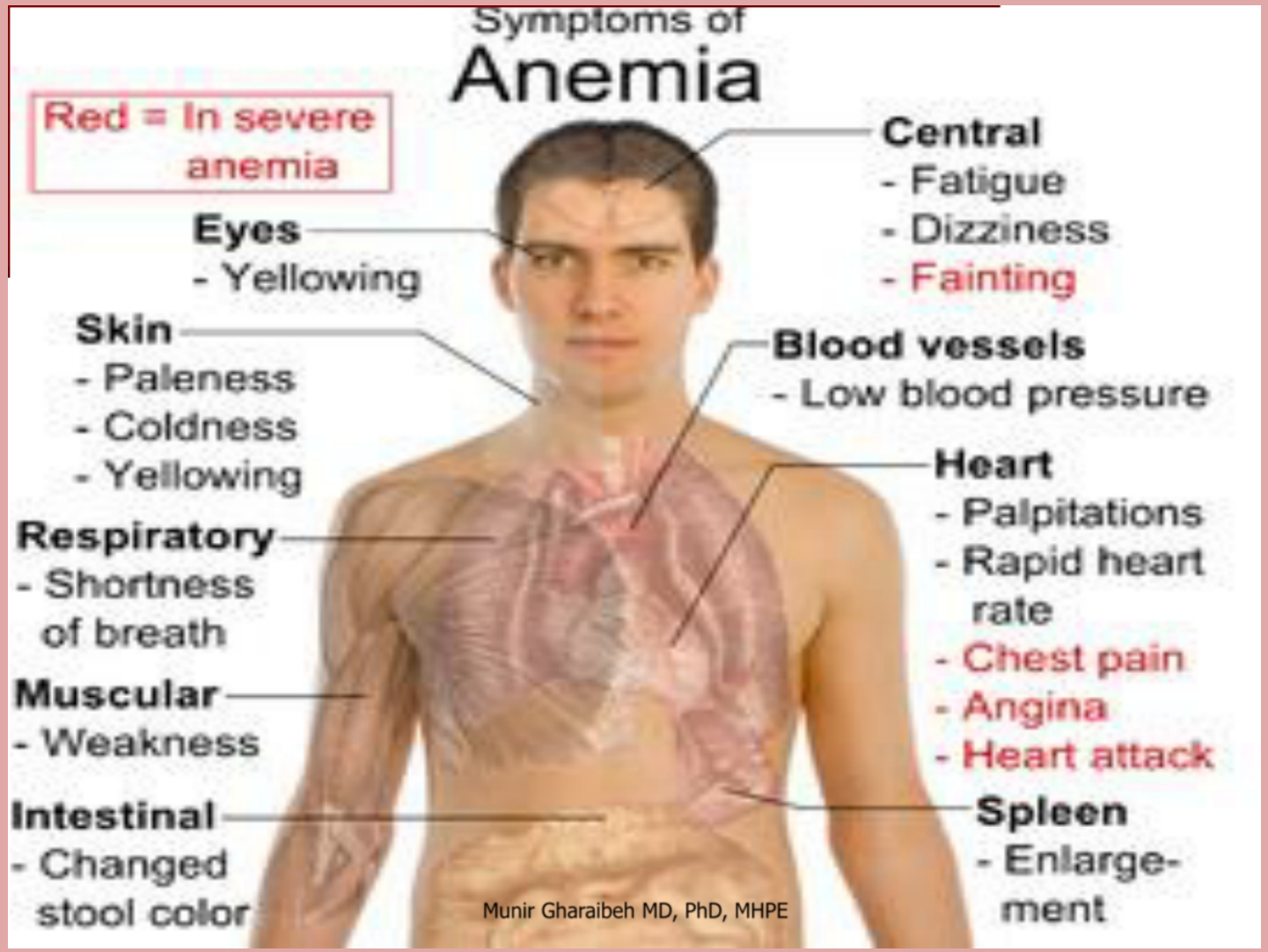
Hematopoiesis:

Requires a constant supply of:

1. Essential elements: Iron, vitamin B12 and folic acid. Our supply of these elements can be taken (absorbed) from food and sometimes medicines and food supplementing pills.

2. Hematopoietic Growth Factors.

It is a new term introduced as an agent or drug used in anemia, and it is given as a part of the treatment of many hematopoietic disorders.



Anemia is a very common symptom of diseases and a very good indicating symptom of them.

Symptoms of anemia affect the whole body; as anemia means low hemoglobin levels, which leads to less oxygen carrying power in the RBCs to the body tissues so all the tissues in the body will be affected.

IRON

- **Iron deficiency is the most common cause of chronic anemia.**

The role of iron in synthesis of hemoglobin is very important; for iron is a major integral part in the structure of hemoglobin.

- **Causes microcytic hypochromic anemia.**

Iron is an important component of many molecules in the body, seen in the table:

The thing we give most attention to is
the iron in hemoglobin.

	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

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Pharmacokinetics of Iron

- **Free iron is toxic.**
- **All iron used to support hematopoiesis is reclaimed from catalysis of hemoglobin in senescent or damaged erythrocytes.**

Most of the iron that results from the destruction of RBC's can be reclaimed (recycled) back into the body.

- **Only a small amount of iron is lost from the body.** So only a small amount of iron is required to compensate that loss (to replenish).

Possible causes of Iron Deficiency:

If the iron loss was greater than the gain or intake this results in iron deficiency anemia

- **Increased iron requirements** As in pregnant women who need iron supply for both themselves and the fetus inside them.
- **Increased iron losses.** Like in the incidences of bleeding, whether acute or chronic bleeding, which result in loss of blood and iron.

Absorption:

- **Usual Daily intake: 10-15mg of elemental iron.**

For normal people with balanced diets without any appetite problems or food intake problems or impairments.

- **Heme iron in meat hemoglobin and myoglobin is absorbed intact.**

Which makes it of more bioavailability; that's why meat is a great source of iron.

- **Iron from other sources is tightly bound to organic compounds and is less available and should be reduced to ferrous iron before it can be absorbed.**

Like in spinach, plants, Etc.. Which makes it less bioavailable because it needs to be reduced by acidifying agents like vitamin C.

- **Daily absorption:** Only **5-10% of the daily intake, usually from duodenum and proximal jejunum.**
- **Absorption can increase in response to low iron or increased requirements.**

So, if the body needs more iron, it will absorb more, absorption will be activated in cases of low body iron or increased body demand, and it can reach 20 to 30% of the intake for the body to compensate but this might take a long time.

Absorption:

- **Divalent Metal Transporter (DMT1)** is a special transporter **actively transports ferrous iron across the luminal membrane of intestine.**
- **Regulated by mucosal cell iron stores.** They can sense the iron levels in the body and activate or inhibit this transporter.
- **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.**
- **The complex binds to Transferrin Receptors (TfR) on the maturing erythroid cells which internalize the complex through the process of receptor- mediated endocytosis.**

Transferrin takes the iron from the intestine after absorption and carries it to the erythrocytes so it can go inside the RBCs through endocytosis, mediated by special receptors.

- **Iron is released for hemoglobin synthesis.** Inside the RBC.
- **Transferrin- transferrin receptor complex is recycled to the plasma membrane and transferrin dissociates and returns to the plasma.** To take other irons and carry them to the RBCs and so on.
- **TfRs are increased with increased erythropoiesis.**
- **Tf concentration increases with iron depletion and with iron deficiency anemia.**

Storage:

- Ferritin (a complex of apoferritin AF and iron) is the storage form of iron.
- Stored in intestinal mucosa and in macrophages in the liver, spleen, and bone.

This is the principle of the test that we use to estimate the iron content of the body stores, it gives us an indirect indication of the total body iron since we can't practically measure total body iron.

- Ferritin in serum is in equilibrium with storage ferritin and can <u>estimate body iron stores</u>.

Hey, look!
That's you counting the slides again,
11 slides through a 44-slide lecture!

Elimination:

- **There is no mechanism for excretion.**

So even if we had excess iron in our bodies, we do not have a general way of excreting it.

- Only **Small amounts are lost by exfoliation of intestinal mucosal cells, bile, urine and sweat.**

- Iron loss can also happen with bleeding obviously, whether it was from a wound, gastrointestinal, or urinary tract bleeding, which give us blood in stool and urine.

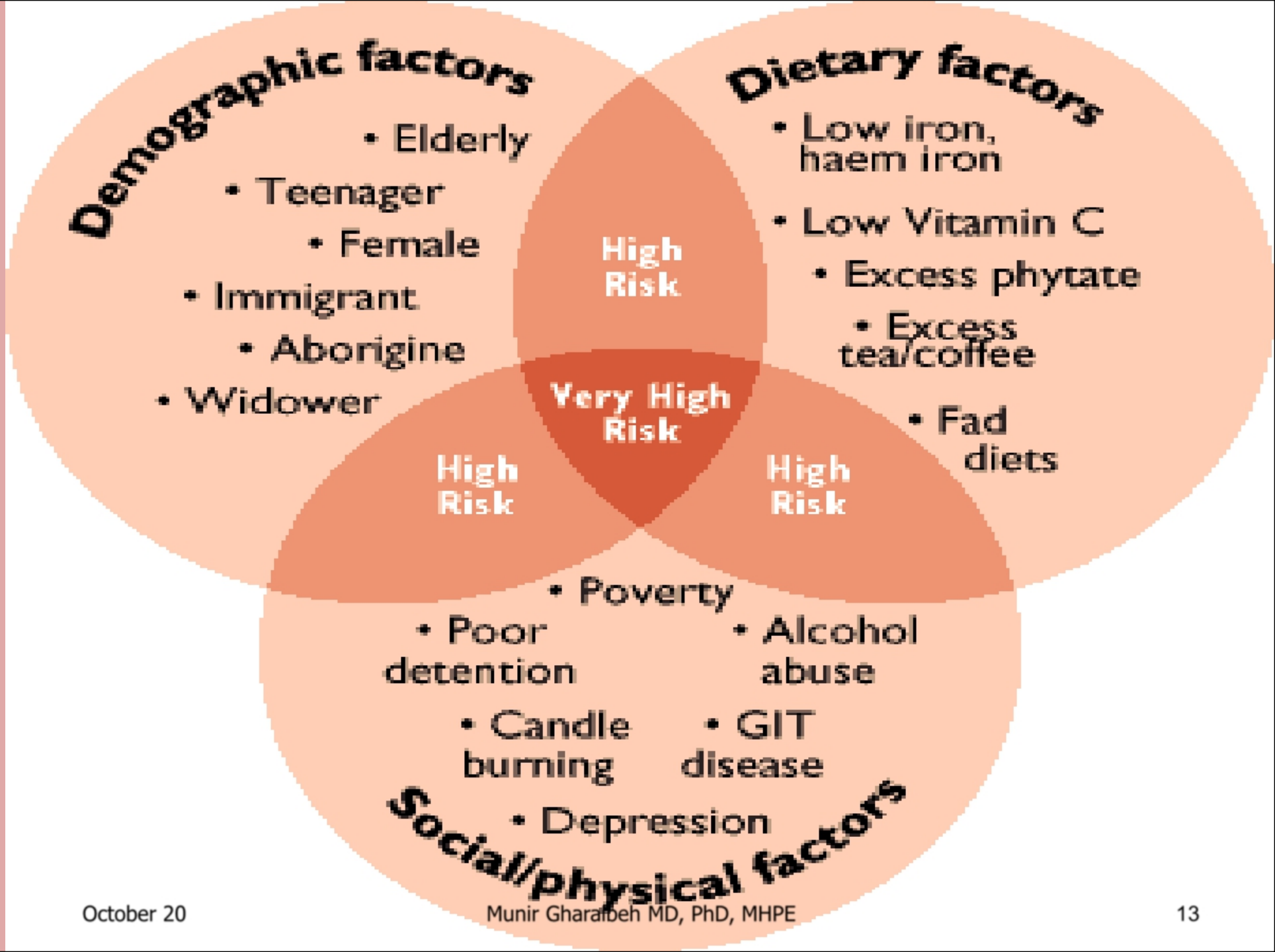
- In routine urine examination, it is acceptable to find one or two RBCs in the urine, it's might be due to a minor injury in the urinary tract, but it is still acceptable since it's a microscopic injury.

IRON THERAPY

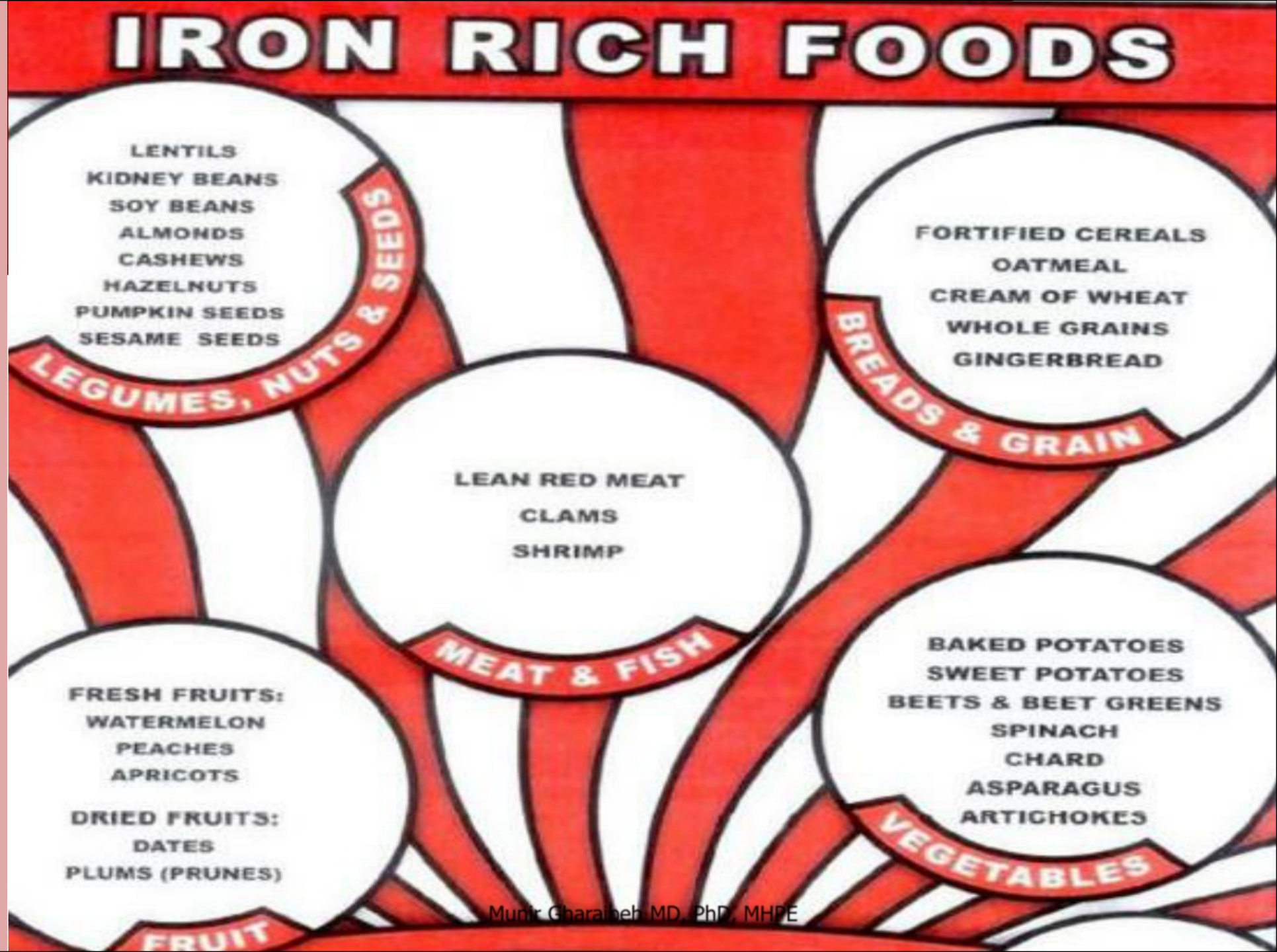
Indications:

- **Treatment and prevention of iron deficiency anemia,** which can result from The Following:
- **Increased requirements: infants, children, pregnant and lactating women, patients on hemodialysis, patients on erythropoietin treatment.**
  Patients here need more iron than what they get from their usual intake erythropoietin is the growth stimulating factor for the erythropoietic system, so they need enough iron in order to fulfill the needs of the body and supply the process of hemoglobin and RBC formation.
- **Inadequate iron absorption: after gastrectomy, severe small bowel disease.**
  Abnormalities in the gastrointestinal tract: like in gastrectomy; cutting a part of the stomach reduces the acidity and so the ferrous iron won't be reduced to the absorbable form of iron.
  Resection of the small intestine is also an example of gastrointestinal abnormalities.
- **Blood loss: acute or chronic, most common cause of iron deficiency anemia.**
  Acute blood loss occurs in injury, or trauma, accidents, and car wounds, Etc..
  While chronic blood loss occurs in gastrointestinal diseases, peptic ulcers, stone or tumor in the gastrointestinal tract, and stones in the urinary tract...

Examples on factors that could cause iron deficiency anemia:



Lean red meat is the food that we concentrate on the most, as it is the most beneficial on the list, and is the richest in iron.



I bet you already counted how many slides will be just pictures in this lecture like 30 minutes ago, eh?

Oral Iron Preparations:

In Pharmacology we use iron either orally or parenterally, orally administered iron exists in the market in many preparations such as:

- **Ferrous sulfate.**
- **Ferrous gluconate.**
- **Ferrous fumarate.**
  - **All are effective and inexpensive.**
  - **Can cause nausea, epigastric discomfort, cramps, constipation or diarrhea and black stools.**

Oral iron preparations are simple compounds as well, they exist in form of sugar-coated tablets, that are red and shiny; which could be dangerous because children could think of them as candies or Smarties, and swallow many of them, putting them in danger of poisoning because of iron toxicity.

An additional side effect that the doctor mentioned was heart pain

Ferrous sulfate has a side effect of constipation while ferrous gluconate has a side effect of diarrhea, so patients prefer some iron pills over others according to their preferences on which drug has side effects that give them more comfort.

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.**

So, it is a rarely needed method of therapy.

- **Carry the risk of iron overload.**

In the case of oral iron administration, if the body didn't need much iron, the absorption will decrease so toxicity will be avoided. But in parenteral iron therapy, we force the iron into our circulation, which requires longer time and other procedures to get rid of the excess iron, and there's a possibility of iron overload (a toxic manifestation of iron therapy).

Examples on Parental iron therapy preparations:

- **Iron dextran:**
  - Given by deep IM injection or IV infusion.
  - IM injection causes local pain and tissue staining.
  - IV infusion is less painful but causes hypersensitivity reactions: headache, fever, arthralgia, N, V, back pain, flushing, bronchospasm and rarely anaphylaxis and death.
- **Iron-sucrose complex.**
- **Iron –sorbitol citrate" Jectofer".**
- **Iron sodium gluconate.**
  - Given only IV, less likely to cause hypersensitivity.

    It is a moderate drug and less extreme than dextran, but it is more expensive.
- **Ferumoxytol:**
  - 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. The appearance of the tablets can be so tempting and inviting for children because they are red and sugar-coated like M&M's like we said before.
- Causes necrotizing gastroenteritis (a Severe gastrointestinal irritation characterized by: vomiting, pain, bloody diarrhea, shock, lethargy (abnormal drowsiness) and dyspnea).
- Patients may improve but may proceed to metabolic acidosis, coma and death.

Are we there yet, Shreck?

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.**

We can think of it as the antidote of absorbed iron

- **Whole Bowel Irrigation; to flush out unabsorbed pills.**

For the unabsorbed iron remaining in the intestines, We can think of this as bowel wash using laxatives, saline, etc..

- **Activated charcoal is ineffective.**

Activated charcoal is used in other toxicities, it binds with toxic compounds, but it doesn't bind with iron, so it cannot be useful here in this kind of toxicity.

- **Supportive therapy is also necessary.**

Like giving the patient fluids in cases of severe diarrhea and fixing cases of acidosis.

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.** Even though patients have regular diets.
  2. **Patients with frequent transfusions e.g.: in patients with hemolytic anemias** Like thalassemia.

     After every hemolytic attack, patients' hemoglobin decreases significantly; so, we must give them either blood transfusion, or packed cell transfusion. Frequent transfusions will increase hemoglobin and lead to hemochromatosis.

Treatment of Chronic Iron Toxicity:

- **Intermittent phlebotomy(الفصد).**

Phlebotomy is blood donation; so, we should advise the patient to donate blood as a sufficient temporary treatment for hemochromatosis.

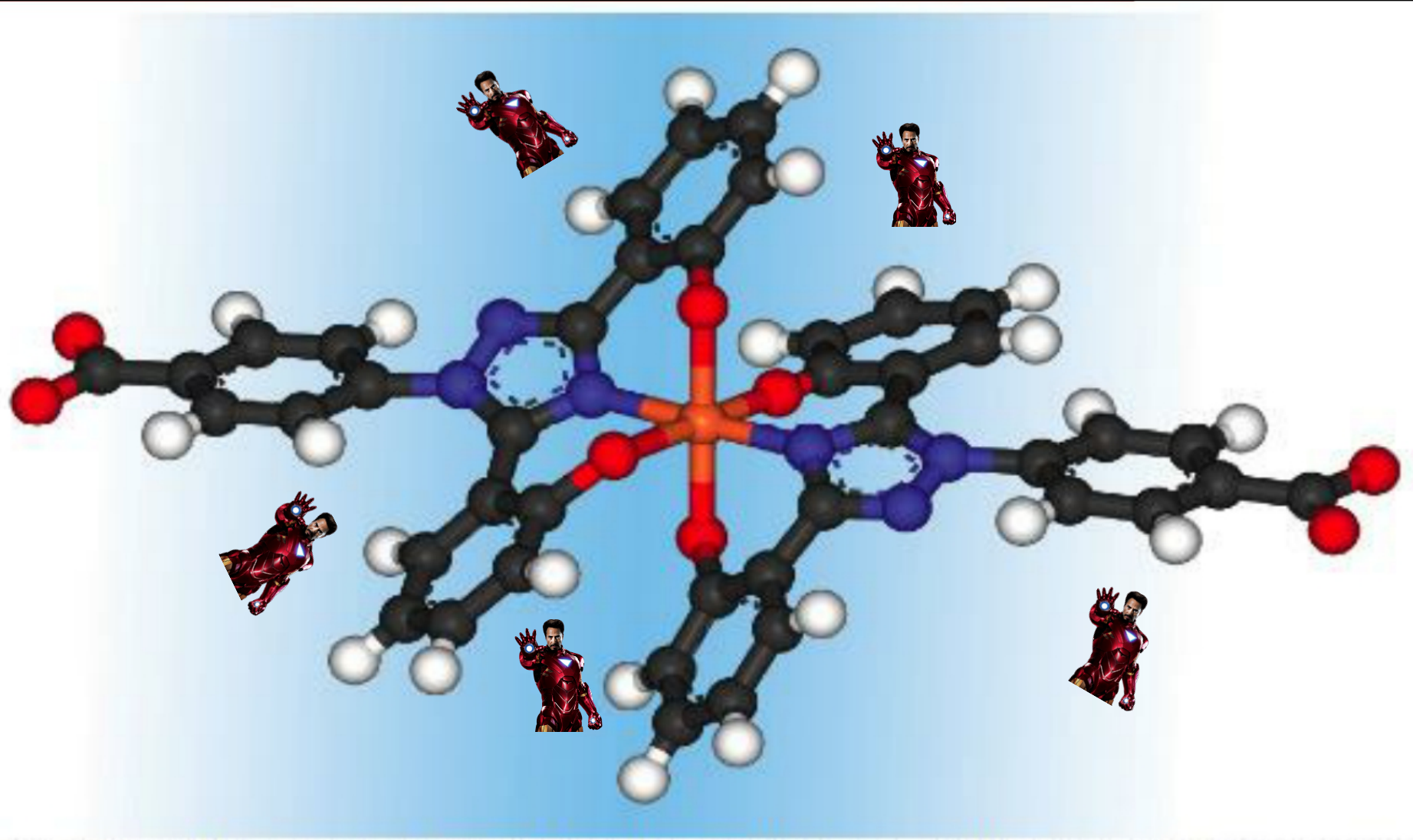
- **Deferoxamine: i.v., is much less efficient than Phlebotomy.**

This drug is an old drug given intravenously and intramuscularly and it's very painful.

- **Deferasirox ”Exjade”: oral, more convenient than deferoxamine.**

This is the structure of deferasirox, which is an iron chelating drug, it can bind two molecules of iron.

Nothing out of the ordinary, just the iron binding drug doing normal iron binding stuff..



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.

Image retrieved from http://en.wikipedia.org/wiki/Image:Deferasirox%E2%80%93iron%28III%29_complex.png (5 April 2008).

Vitamin B12

- **Porphyrin-like ring with a central cobalt atom.**

The family of B vitamins are water soluble vitamins.

The followings are preparation examples of vitamin B12:

- **Methylcobalamine.**
- **Deoxyadenosyl cobalamine.**
- **Cyanocobalamine.**
- **Hydroxocobalamine.**

- **Available in meat, liver, eggs, and dairy products.**
- **Nutritional deficiency only occurs in strict vegetarians.**

  Because it is absent in plant products.

Vitamin B12

- **Daily requirement : 2mcg**
- **Storage pool: 300-5000mcg.** So, we only need very minute amounts to replace our losses of it.
- **It would take about 5 years to exhaust all the stored pool and for megaloblastic anemia to develop after stopping absorption.**

Reminder: deficiency of vitamin B12 causes a kind of megaloblastic anemia, which is macrocytic hypochromic anemia with neurological manifestations.

Pharmacokinetics of Vitamin B_{12}

- **Absorption requires the complexing with the: Intrinsic Factor (Castle's Factor), which is a glycoprotein secreted by the parietal cells of the stomach.**

So, in pernicious anemia, or atrophic gastritis, atrophic peptic ulcer, and gastric ulcers in general, we might expect a deficiency in Castle's factor, and consequently, the development of vitamin B12 deficiency due to malabsorption.

- **Transported in the body by transcobalamine II.**

Schilling's Test:

Measures absorption and urinary excretion of radioactively labeled Vitamin B_{12}. (we give the patient radioactive B12, and then we trace the radioactivity in the stool to know if there is a normal absorption of it or not).

Vitamin B12 Deficiency

Pernicious anemia. It is a form of megaloblastic anemia which is special for vitamin B12 deficiency.
It results from many conditions like:

- **Distal ileal disease,** -Because B12 is absorbed in the ileum- **e.g.: Inflammation or resection or Diphyllobothrium latum infestation** (a worm living in the ieleum and it inhabits the fish that live in Scandinavian countries).
- **Bacterial overgrowth of the small intestine.**
- **Chronic pancreatitis.**
- **Thyroid disease.**
- **Congenital deficiency of the intrinsic factor.**
- **Congenital selective Vitamin B12 malabsorption !!! (may be in Jordan)**

Many people in Jordan are diagnosed with vitamin B12 deficiency, this could be overdiagnosis, but also could be because of congenital selective vitamin B12 malabsorption.

Actions of Vitamin B12

1. Transfer of a methyl group from N_5-methyltetrahydrofolate to homocysteine, forming methionine.

- N_5-methyltetrahydrofolate is the major dietary and storage folate.

2. Conversion of N5-methyltetrahydrofolate to tetrahydrofolate.

Deficiency leads to accumulation of N_5- methyltetrahydrofolate cofactors and depletion of tetrahydrofolate .

Vitamin B_{12}

Megaloblastic anemia of Vitamin B_{12} 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.

Here's a meme about vitamin B12 that's literally 3 slides ago to make you feel like a smart cookie!❤️

Actions of Vitamin B_{12}

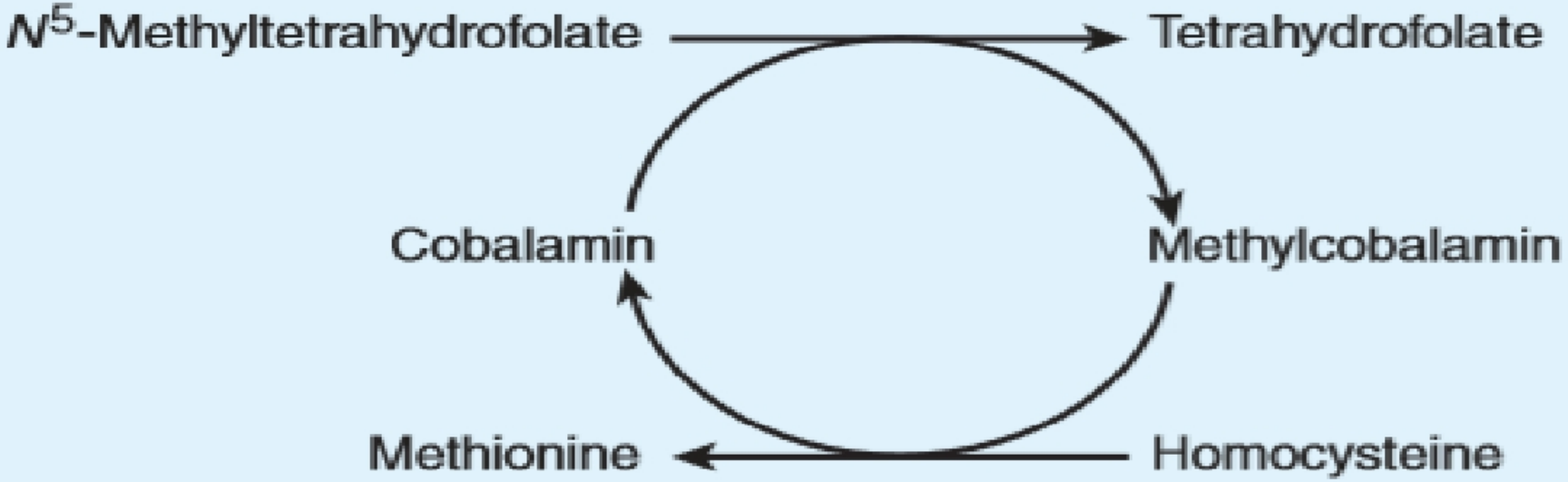
3. Isomerization of methyl malonyl- CoA to succinyl-CoA by the enzyme methyl malonyl-CoA mutase.

Vitamin B_{12} depletion leads to the accumulation of methyl malonyl-CoA , thought to cause the neurological manifestations of Vitamin B_{12} deficiency.

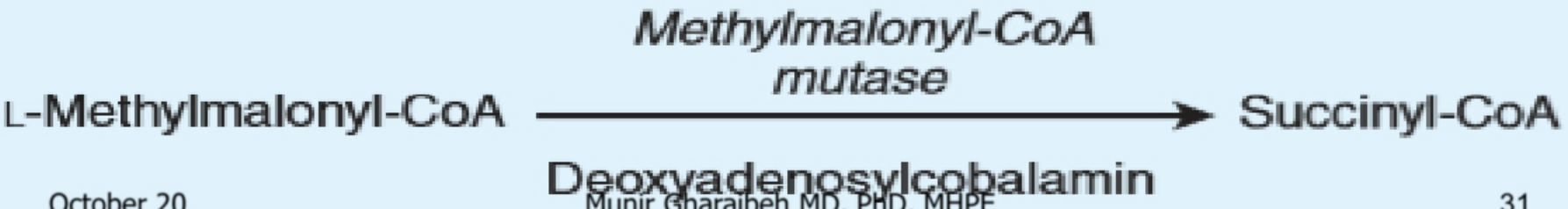
If we give folic acid treatment to these patients, it will correct or (fix) the hematological effects of the Megaloblastic anemia, but it won't fix the neurological deficits or manifestations of it; because folic acid isn't involved in the isomerization of methyl malonyl-CoA.

Enzymatic reactions that use vitamin B 1

A. Methyl transfer



B. Isomerization of L-Methylmalonyl-CoA



Therapy with Vitamin B12

Parenteral: Parenteral therapy is the standard form of therapy; because most of the cases require **Life-long treatment**. And it is applied on two phases:

- **Daily or every other day for 1-2 weeks to replenish the stores.**
- **Maintenance: injections every 1-4 weeks.**

Oral: **Only for patients who refuse or cannot tolerate injections.** not so efficient because the problem is in vitamin B12 malabsorption, so oral vitamin B12 won't be our favorite helping technique.

Intranasal: **For patients in remission** (after replenishing of vitamin B12 stores).

Folic Acid

It plays a major role in hematopoiesis.

- **Reduced forms of folic acid are required for the synthesis of amino acids, purines and DNA.**
  Present in yeast, liver, kidney and green vegetables.

- **Deficiency is common but easily corrected.**
- **Deficiency can result in:**

- **Megaloblastic anemia.** It is very similar to that result thing of B12 deficiency; that's why many confusions happened between them; however, it is more common than vitamin B12 pernicious anemia.
- **Congenital malformations.** Pregnant women with folic acid deficiency might develop megaloblastic anemia and their babies might develop congenital malformations.
- **Occlusive Vascular disease due to elevated homocysteine.** In adults: males or nonpregnant women.

Chemistry of Folic Acid

- **Folic acid=Pteridine+ PABA+ Glutamic acid.**

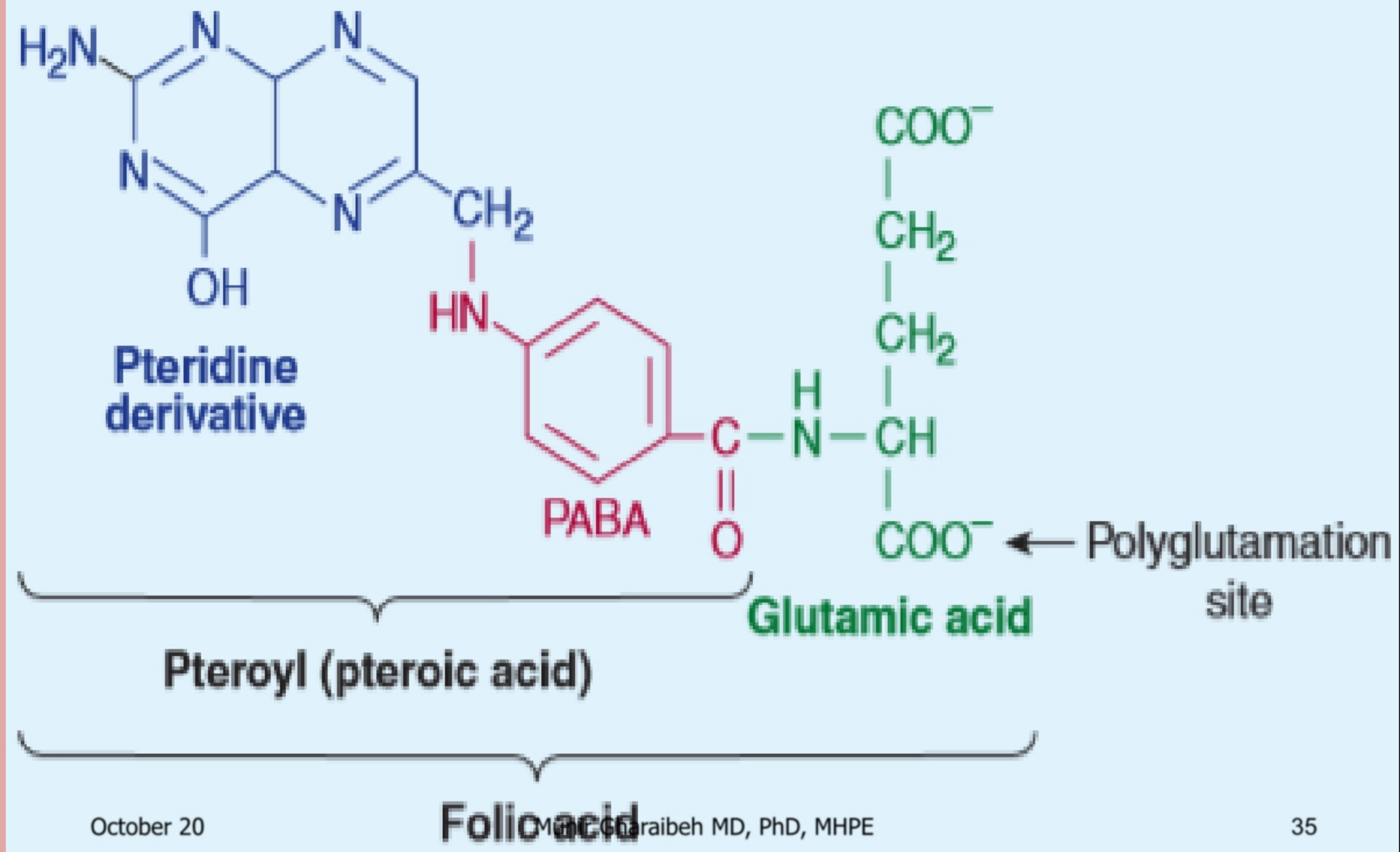
(PABA: para aminobenzoic acid)

- **Folic acid is reduced to Di and Tetrahydrofolate and then to folate cofactors, which are interconvertible and can donate one-carbon units at various levels of oxidation.**

  That is why we mentioned that it can substitute vitamin B12 in one carbon donations earlier.

- **In most cases folic acid is regenerated.** So, we only need small amounts of it.

The structure of folic acid



Kinetics of Folic Acid

- Readily and completely absorbed from the terminal jejunum
- Glutamyl residues are hydrolyzed before absorption by α-1-glutamyltransferase (Congugase), within the brush border of the mucosa.
- N_5-methyltetrahydrofolate is transported into the blood stream by active and passive processes.
- Widely distributed in the body.
- Inside cells, it is converted into THF by demethylation reaction in the presence of Vitamin B_{12}.

Kinetics of Folic Acid

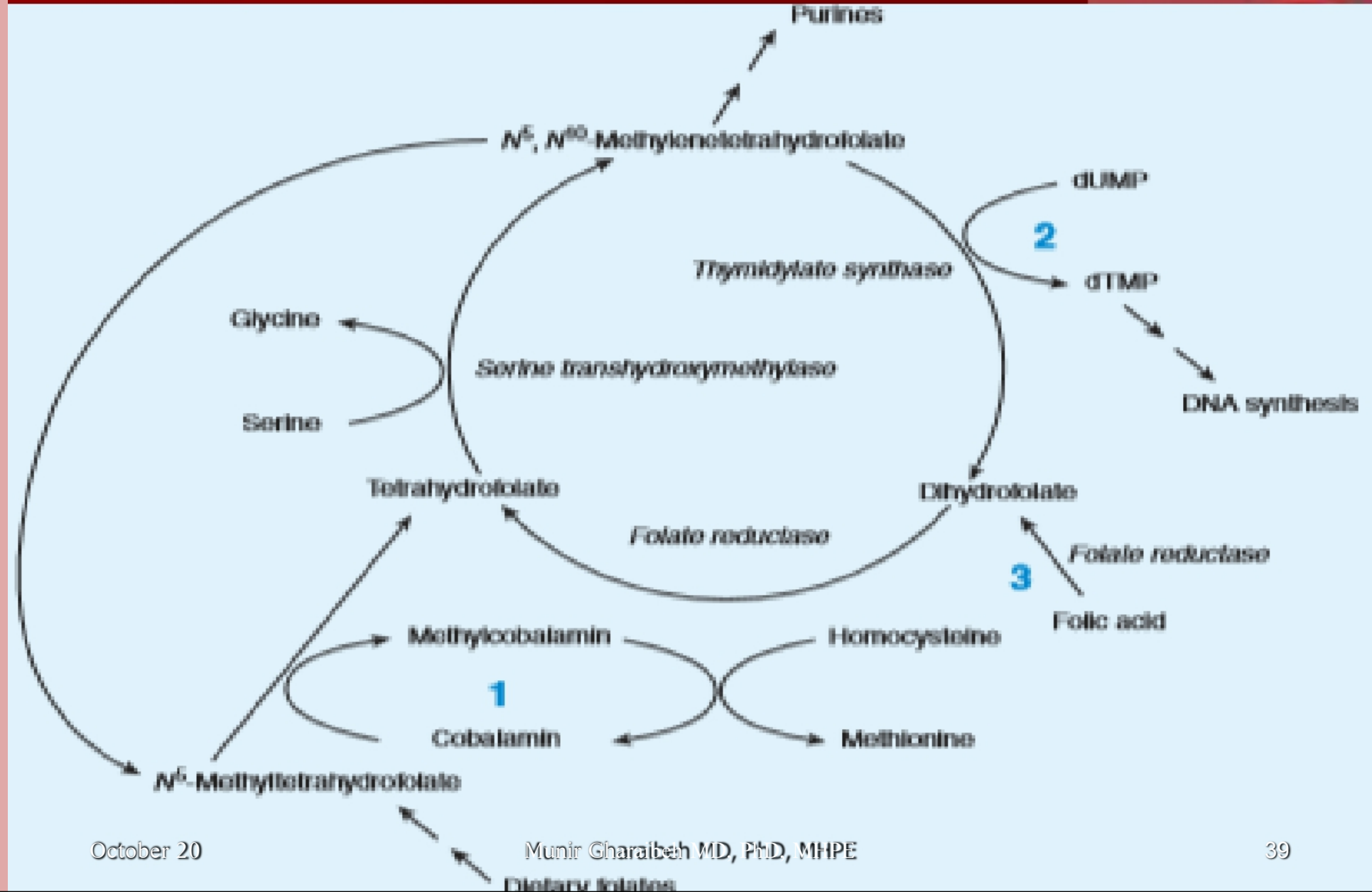
- Only 5-20 mcg are stored in the liver.
- Excreted in urine and stool and destroyed by catabolism.
- Megaloblastic anemia can develop within 1-6 months after stopping intake.

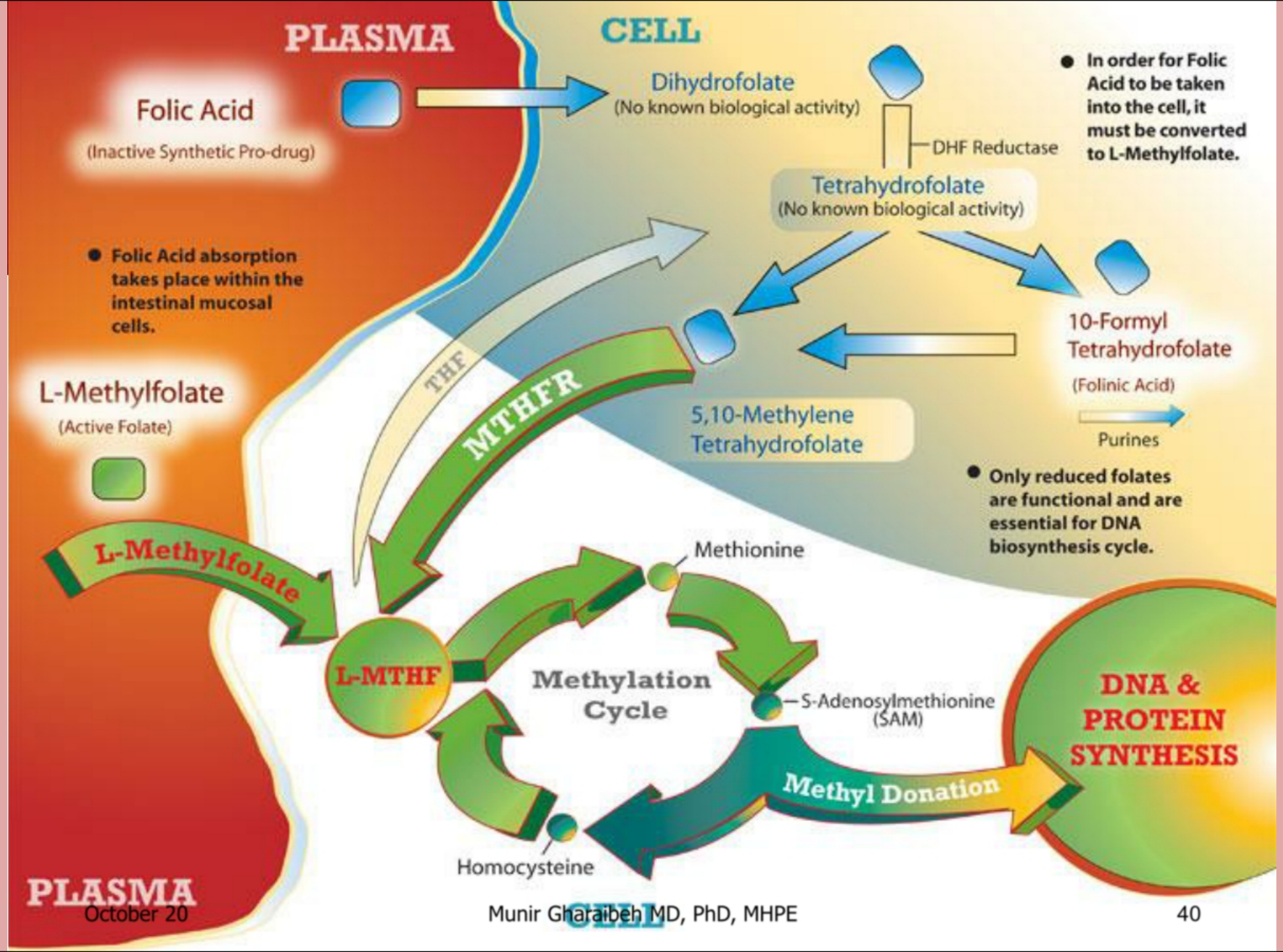
PERRY THE PLATYPUS??

Actions of Folic Acid

- **THF cofactors are important in one-carbon reactions:**
  - **Production of dTMP** (deoxythymidine monophosphate) **from dUMP** (deoxyuridine monophosphate)**, which is needed in DNA synthesis.** Hint: check next picture.
  - **Generation of methionine from homocysteine.**
  - **Synthesis of essential purines.**

Enzymatic reactions that use folates




PLASMA
CELL
Folic Acid
(Inactive Synthetic Pro-drug)
Dihydrofolate
(No known biological activity)
DHF Reductase
Tetrahydrofolate
(No known biological activity)
In order for Folic Acid to be taken into the cell, it must be converted to L-Methylfolate.
Folic Acid absorption takes place within the intestinal mucosal cells.
L-Methylfolate
(Active Folate)
THF
MTHFR
5,10-Methylene Tetrahydrofolate
10-Formyl Tetrahydrofolate
(Folinic Acid)
Purines
Only reduced folates are functional and are essential for DNA biosynthesis cycle.
L-Methylfolate
Methionine
L-MTHF
Methylation Cycle
S-Adenosylmethionine (SAM)
DNA & PROTEIN SYNTHESIS
Methyl Donation
Homocysteine
PLASMA
CELL

Causes of Megaloblastic Anemia of Folic Acid Deficiency

- Inadequate dietary intake.
- Alcoholism, due to neglected nutrition.
- Liver disease causing impaired hepatic storage.
- Pregnancy and hemolytic anemia which increase the demand.
- Malabsorption syndrome.
- Renal dialysis.
- Drugs: Methotrexate, Trimethoprim and Phenytoin.

  (Methotrexate is an anti-cancer & immunomodulator drug, Trimethoprim is an antibacterial drug and Phenytoin is an anti-epileptic drug).

Treatment with Folic Acid

- Parenteral administration is rarely necessary because it is well absorbed orally even in malabsorption.
- 1 mg daily until cause is corrected.
- Or, indefinitely for patients with malabsorption or dietary inadequacy.
- Can be given prophylactically.
- Routinely given in early pregnancy or even before being pregnant (for women planning to get pregnant).
- Recently supplemented to foods. (In flour to make sure there is enough of it in their diets).

Congratulations, buddy! You survived!
That's it for today, you've been great, have a wonderful day and make great choices ❤️