Agents Used in Anemias

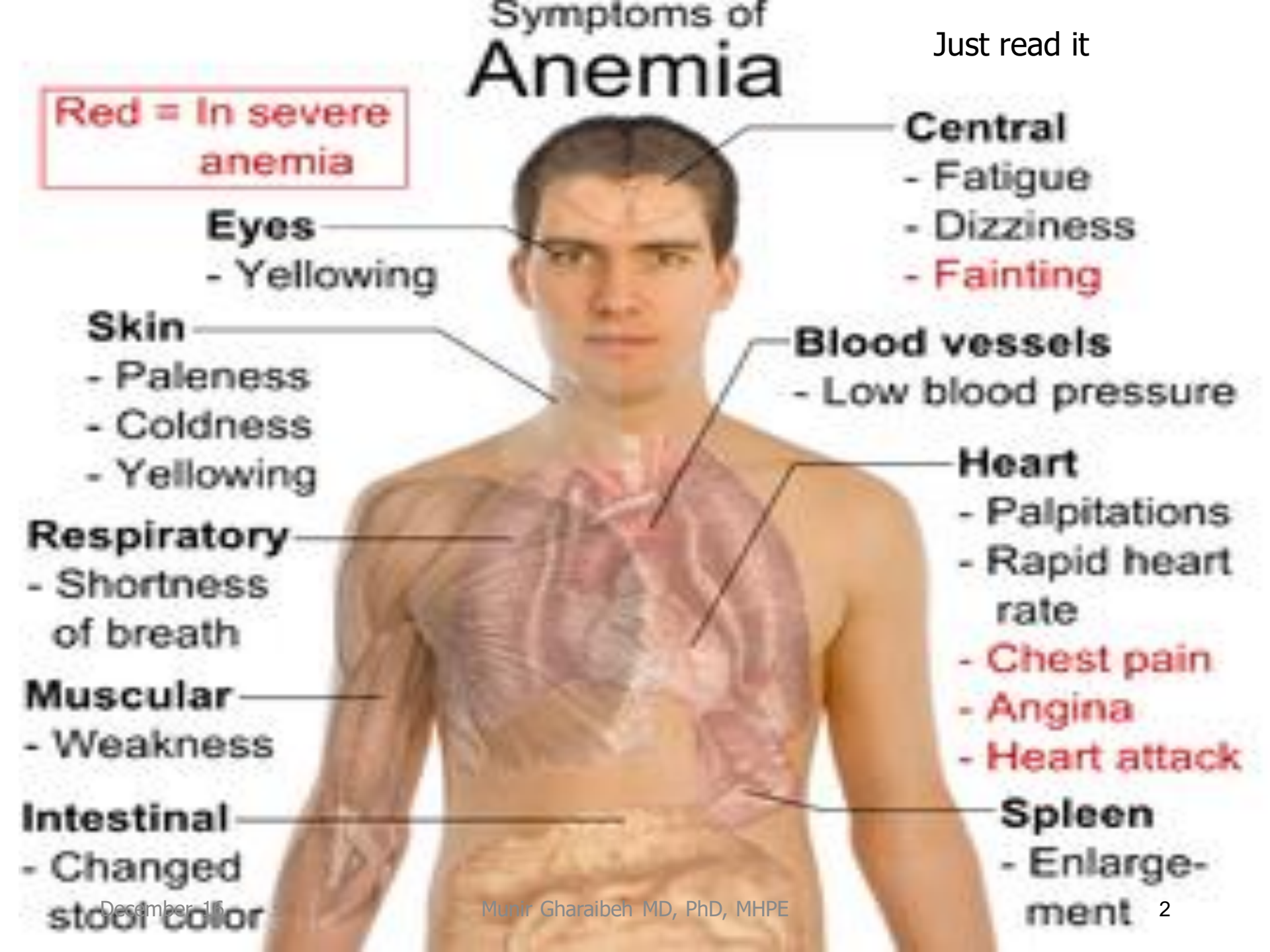
Hematopoiesis:

Requires a constant supply of:

1. Essential elements: Iron, vitamin B12and folic acid.

2. Hematopoietic Growth Factors

Just read it


Symptoms of
Anemia
Red = In severe anemia
Central
- Fatigue
- Dizziness
- Fainting
Eyes
- Yellowing
Skin
- Paleness
- Coldness
- Yellowing
Blood vessels
- Low blood pressure
Heart
- Palpitations
- Rapid heart rate
- Chest pain
- Angina
- Heart attack
Respiratory
- Shortness of breath
Muscular
- Weakness
Intestinal
- Changed stool color
Spleen
- Enlarge-ment

IRON

- **Iron deficiency is the <u>most common cause of chronic anemia.</u>**
- **Causes microcytic hypochromic anemia which is very easily diagnosed using blood films.**

IRON

Pharmacokinetics:

- **Free iron is toxic that's why the body converts it to other formulations (*bound*).**
- **All iron used to support hematopoiesis is reclaimed from catalysis of hemoglobin in senescent or damaged erythrocytes.**
- **Only a small amount of iron is lost from the body and we need to replace this lost amount .**

Possibilities/causes of Iron Deficiency:

- **Increased iron requirements** ***in pregnancy for ex***
- **Increased iron losses** ***extraordinary causes***

Although we need a small amount to replace the lost iron , we give a large dose to the patient because only a small amount is absorbed.

IRON

Absorption:

- **Daily intake: 10-15mg of elemental iron.**
- **The bioavailability of iron from meats is more than that of plants.**
- **Heme iron in *meat hemoglobin and myoglobin* is absorbed intact *(because meat contain RBCs remenants)*.**
- **Iron from other sources is tightly bound to organic compounds (*phytates)* and is less available and should be reduced to ferrous iron before it can be absorbed.**
- **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.**

***in the stomach, the iron is converted from ferrous state to ferric.***

IRON

The doctor read only the underlined in this slide and skipped the next one.

Absorption:

- ***Divalent Metal Transporter (DMT1)*** **actively transports ferrous iron across the luminal membrane of intestine.**
- **Regulated by mucosal cell iron stores.**
- ***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*****).**

IRON

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.**
- **Iron is released for hemoglobin synthesis.**
- **Transferrin- transferrin receptor complex is recycled to the plasma membrane and transferrin dissociates and returns to the plasma.**
- **TfRs are increased with increased erythropoiesis.**
- **Tf concentration increases with iron depletion and with iron deficiency anemia.**

IRON

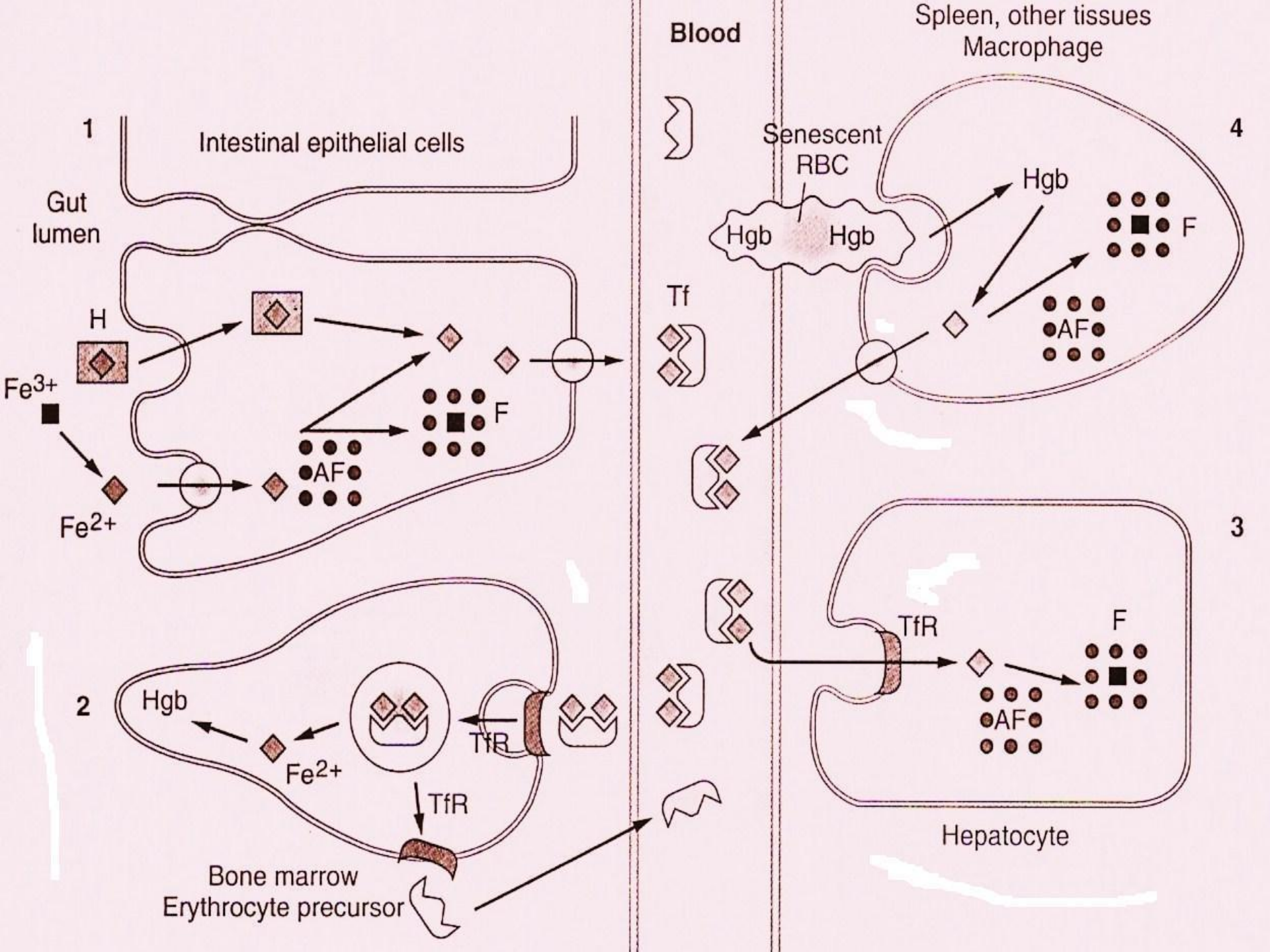
Storage:

- **Ferritin(apoferritin AF and iron) is the storage form of iron.**
- **Stored in intestinal mucosa and in macrophages in the liver, spleen, and bone.**
- ***Ferritin in serum is in equilibrium with storage ferritin and can estimate body iron stores.***

So serum ferritin is a good indicator of storage ferritin and that's why serum ferritin is used in the diagnosis of iron deficiency (not serum iron-I think the doctor means serum transferritin- because it doesn't reflect the storage iron states)

IRON
Elimination:

- **There is no mechanism for excretion.**
- ***Small amounts are lost by exfoliation of intestinal mucosal cells, bile, urine and sweat.***

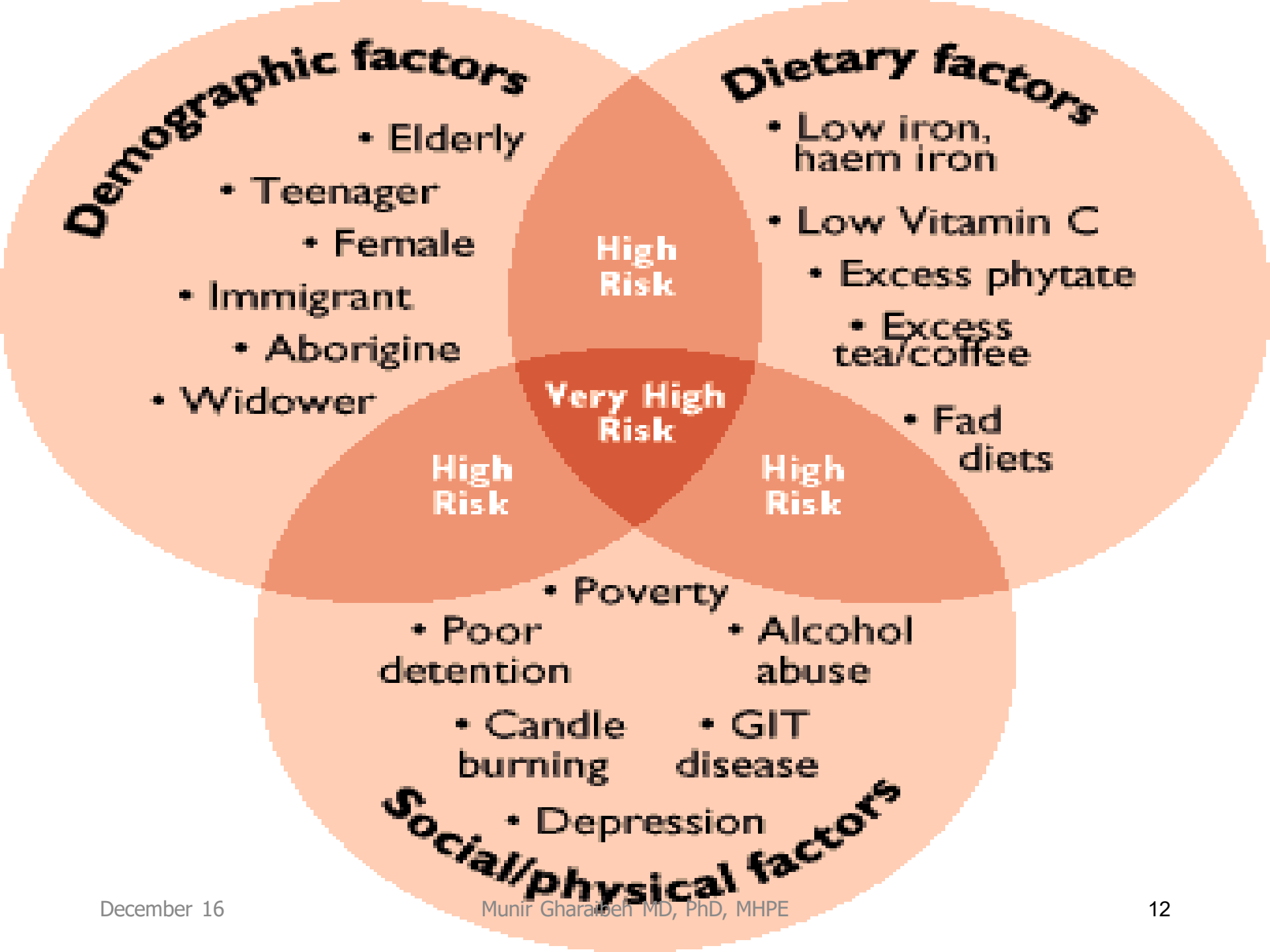

Blood
Spleen, other tissues
Macrophage
1
Intestinal epithelial cells
Gut
lumen
H
Fe3+
Fe2+
F
AF
Tf
Senescent
RBC
Hgb
Hgb
Hgb
F
AF
4
3
TfR
F
AF
Hepatocyte
2
Hgb
Fe2+
TfR
TfR
Bone marrow
Erythrocyte precursor

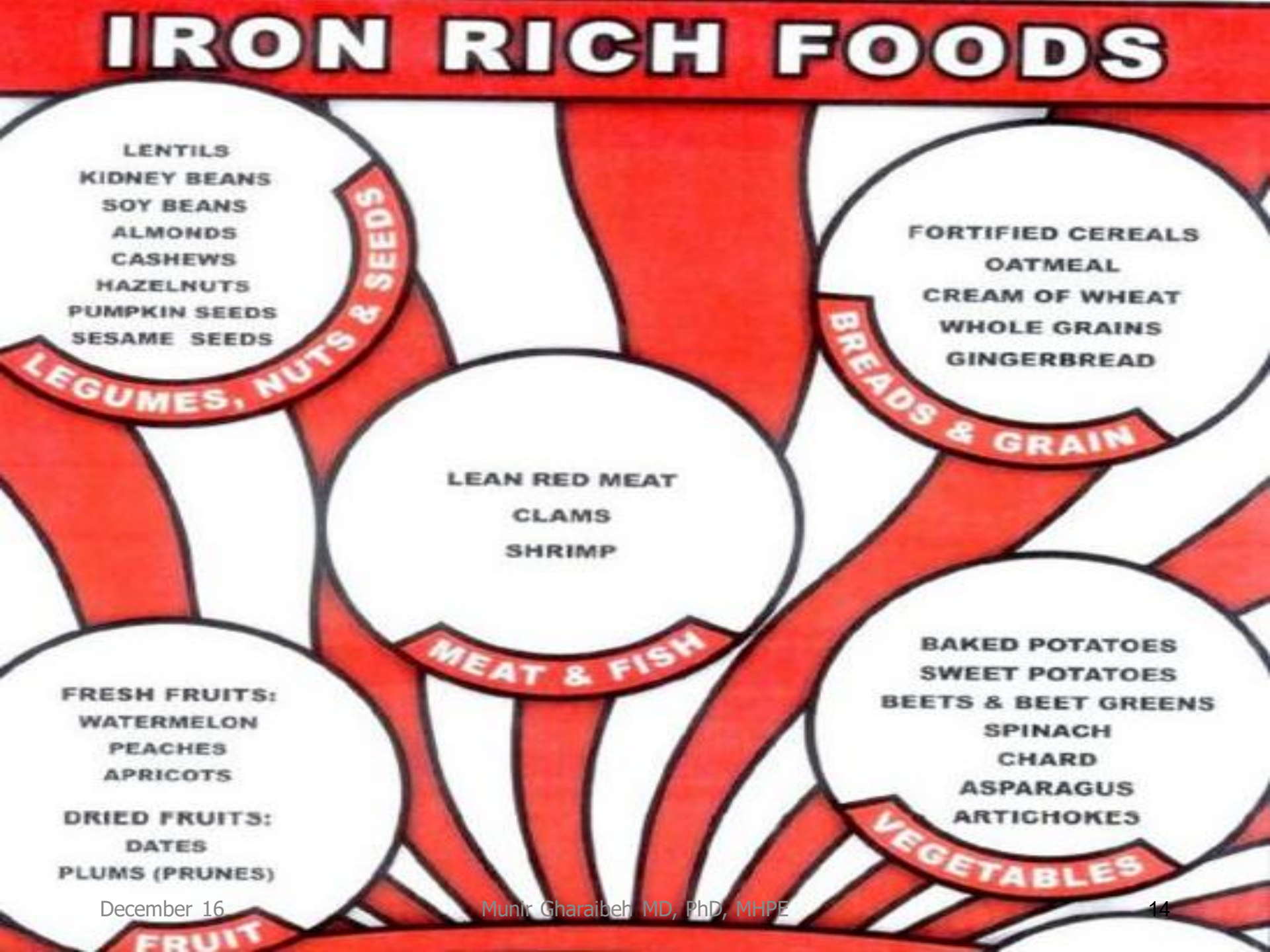
IRON THERAPY

Indications:

Babies after the age of 6 months should receive iron supplements because at that age human milk is no longer sufficient to overcome the requirements.

- **Treatment and prevention of iron deficiency anemia:**
- **Increased requirements: *infants, children, pregnant and lactating women, patients on hemodialysis (غسيل الكلى), patients on erythropoietin treatment.***
- **Inadequate iron absorption: *after gastrectomy, severe small bowel disease (celiac disease)***
- **Blood loss: *acute or chronic, most common cause of iron deficiency anemia*.**


Demographic factors
• Elderly
• Teenager
• Female
• Immigrant
• Aborigine
• Widower
Dietary factors
• Low iron, haem iron
• Low Vitamin C
• Excess phytate
• Excess tea/coffee
• Fad diets
High Risk
Very High Risk
High Risk
High Risk
• Poverty
• Poor detention
• Alcohol abuse
• Candle burning
• GIT disease
• Depression
Social/physical factors


IRON RICH FOODS
LENTILS
KIDNEY BEANS
SOY BEANS
ALMONDS
CASHEWS
HAZELNUTS
PUMPKIN SEEDS
SESAME SEEDS
LEGUMES, NUTS & SEEDS
FORTIFIED CEREALS
OATMEAL
CREAM OF WHEAT
WHOLE GRAINS
GINGERBREAD
BREADS & GRAIN
LEAN RED MEAT
CLAMS
SHRIMP
MEAT & FISH
FRESH FRUITS:
WATERMELON
PEACHES
APRICOTS
DRIED FRUITS:
DATES
PLUMS (PRUNES)
FRUIT
BAKED POTATOES
SWEET POTATOES
BEETS & BEET GREENS
SPINACH
CHARD
ASPARAGUS
ARTICHOKES
VEGETABLES

IRON

Oral Iron Preparations (more commonly used than parenteral):

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

Especially *ferrous sulfate*.
**sulfate and magnesium causes diarrhea.

IRON

Parenteral Iron Therapy:

- **Reserved for patients with documented iron deficiency** ***(not prophylactic)*** **who are** ***unable to tolerate or absorb oral iron(in celiac disease for ex.) and for patients with extensive chronic blood loss who can not be effectively maintained with oral iron alone.***
- ***Carry the risk of iron overload*** ***(because there is no regulation mechanism here as parenteral injections have 100% bioavailability)*****.**

IRON

- **Parenteral preparation :**
- **Iron dextran *(the oldest preparation)*:**
  - **Given by deep IM injection or IV infusion.**
  - **IM injection causes local pain and tissue staining.**
  - **IV infusion causes hypersensitivity reactions: headache, fever, arthralgia, N, V, back pain, flushing, bronchospasm and rarely anaphylaxis and death.**
- **Iron-sucrose complex --> given in IV injections .**
- **Iron sodium gluconate.**
  - **Given only IV , less likely to cause hypersensitivity.**

IRON

Acute Iron Toxicity:

Accidental ingestion rarely affects adults , because a high dose is needed to cause toxicity for them

- **Usually results from accidental ingestion by children as well as parenteral iron.**
- **10 tablets can be lethal in children.**
- ***Oral* administration might Cause necrotizing gastroenteritis: vomiting, pain, bloody diarrhea, shock, lethargy(كسل) and dyspnea.**
- **Patients may improve but may proceed to metabolic acidosis, coma and death.**

IRON

Treatment of Acute Iron Toxicity:

- **Deferoxamine" Desferal": is a potent iron-chelating compound which binds already absorbed iron *(serum iron)* and promotes its excretion in urine and feces.**
- **Whole Bowel Irrigation; to flush out unabsorbed pills.**
- **Activated charcoal is ineffective.**
- **Supportive therapy is also necessary.**

Whole bowel irrigation (WBI) is a medical process involving the rapid administration of large volumes of an osmotically balanced solution via a nasogastric tube, to flush out the entire gastrointestinal tract

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

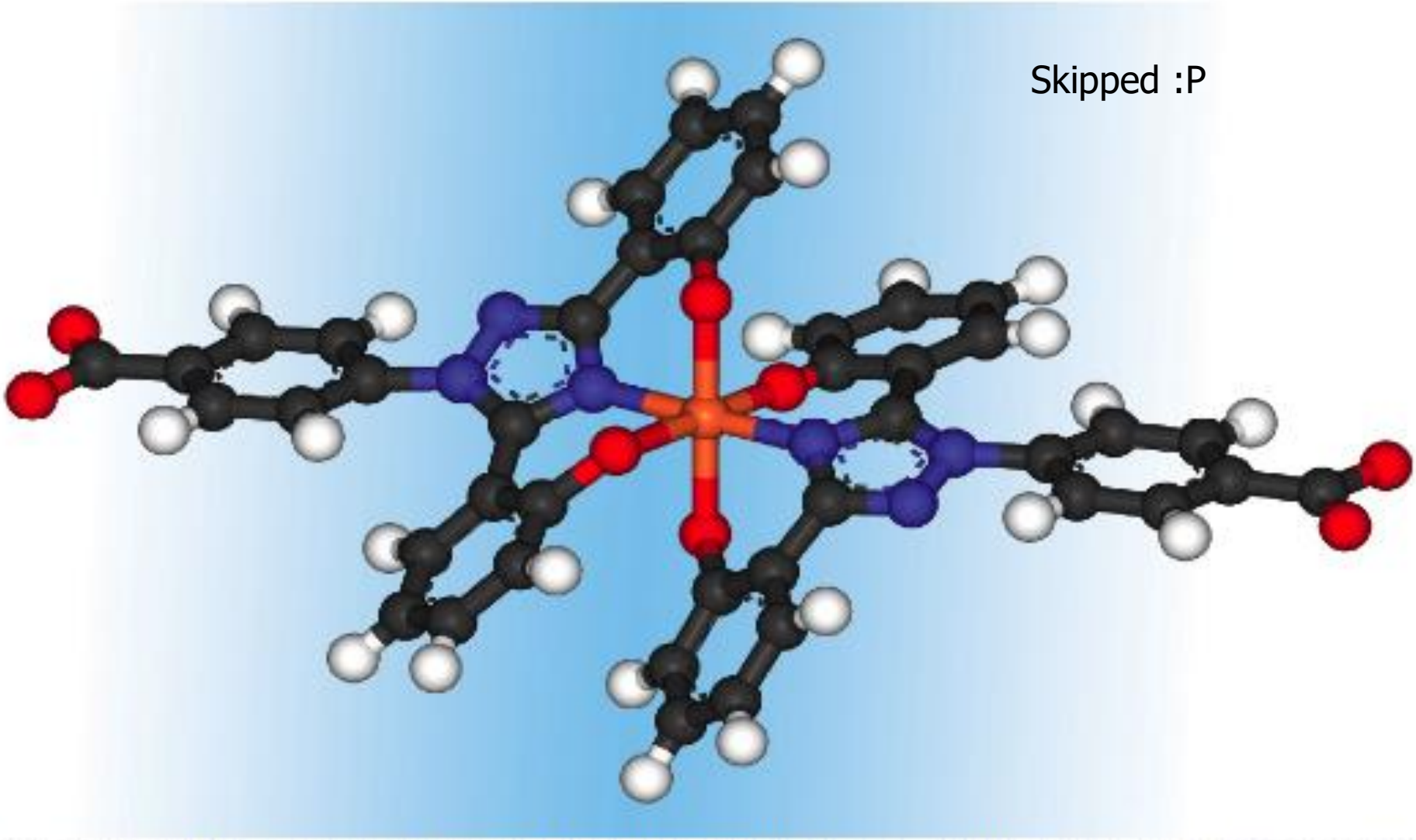
Treatment of Chronic Iron Toxicity:

Intermittent phlebotomy(الفصد) in the cases of inherited hemochromatosis.

Deferoxamine: is much less efficient than phlebotomy.

Deferasirox" Exjade": oral, more convenient than deferoxamine. ***for acquired cases***

Skipped :P



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 B_{12}

- **Porphyrin-like ring with a central cobalt atom.**
- **Methylcobalamine ……. Active form.**
- **Deoxyadenosyl cobalamine. …….. Active.**
- **Cyanocobalamine.**
- **Hydroxocobalamine.**

- **Source is microbial.**
- **Meat, liver, eggs, and dairy products.**
- **Nutritional deficiency only occurs in strict vegetarians.**

Vitamin B_{12}

- **Daily requirement : 2mcg**
- **Storage pool: 300-5000mcg.**
- **It would take 5 years to exhaust all the stored pool and for megaloblastic anemia to develop after stopping absorption** ***(because of malabsorption, intestinal resection ..etc)*****.**

Pharmacokinetics of Vitamin B_{12}

- **Absorption requires the complexing with the: <u>Intrinsic Factor(Castle's Factor),</u> which is a glycoprotein secreted by the parietal cells of the stomach.**
- **Transported in the body by <u>Transcobalamine II</u>.**

The intrinsic factor production is interrupted in gastric carcinoma, and it's the first clinical symptom of the carcinoma.

***Schildling's Test** (ancient test :P, how we measure the serum vit.b12 :*

- **Measures absorption and urinary excretion of radioactively labeled Vitamin B_{12} by administering the labeled vit.b12 and measuring the excreted, if the excreted is more than the absorbed then there is malabsorption**

Vitamin B_{12} Deficiency

Pernicious(hypochromhic megaloblastic) anemia.

Remember :
-Pernicious anemia is only related to vit.b12 deficiency
But Megaloblastic anemia can occur due to folic acid or vit.b12 deficiency
- vit.b12 deficiency results in blood and neurological abnormalities.

Distal ileal disease e.g. Inflammation or resection or *Diphyllobothrium latum* infestation.

Bacterial overgrowth of the small intestine.

Chronic pancreatitis.

Thyroid disease.

Congenital deficiency of the intrinsic factor.

Congenital selective Vitamin B_{12} malabsorption !!! (may be in Jordan)

Actions of Vitamin B_{12}

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 N^5-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.*

Its important to diagnose and treat megaloblastic anemia correctly, because if its caused by vit.b12 and we treated it as its folic acid deficiency, we will correct the blood abnormalities but not the neurological ones.

Actions of Vitamin B_{12}

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

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

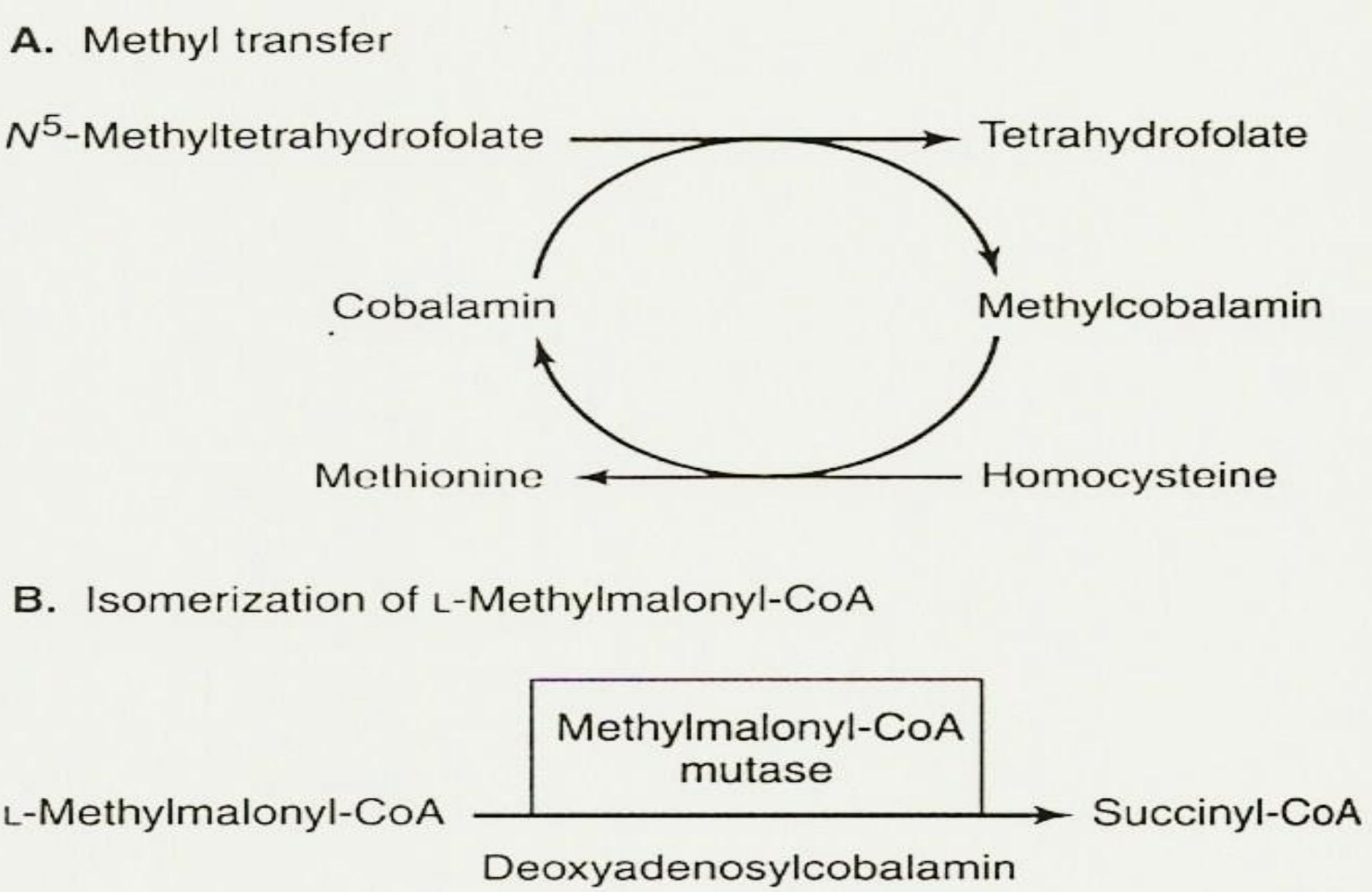


Figure 33–2. Enzymatic reactions that use vitamin B_{12}. See text for details.

Therapy with Vitamin B_{12}

Parenteral *(in contrast to iron therapy, parenteral is more common here)*:

Life-long treatment because the malabsorption usually lasts life-long.

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 can not tolerate injections.

Intranasal:

For patients in remission.

Folic Acid

- **Reduced forms of folic acid are required for the synthesis of amino acids, purines and DNA.**
- **Deficiency is common but easily corrected(similar to iron deficiency).**
- **Deficiency can result in:**

  ***Megaloblastic anemia*.**

  Congenital malformations because of deficiency in the mother .

  Occlusive *Vascular disease* *(e.g. atherosclerosis, cerebrovascularand coronary disease)* *due to elevated homocysteine*.

Chemistry of Folic Acid

- **Folic acid=Pteridine+ PABA+ Glutamic acid.**
- **Folic acid is reduced to Di and Tetra hydrofolate (active forms)and then to folate cofactors, which are interconvertible and can donate one-carbon units at various levels of oxidation.**
- **In most cases folic acid is regenerated.**

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}.**

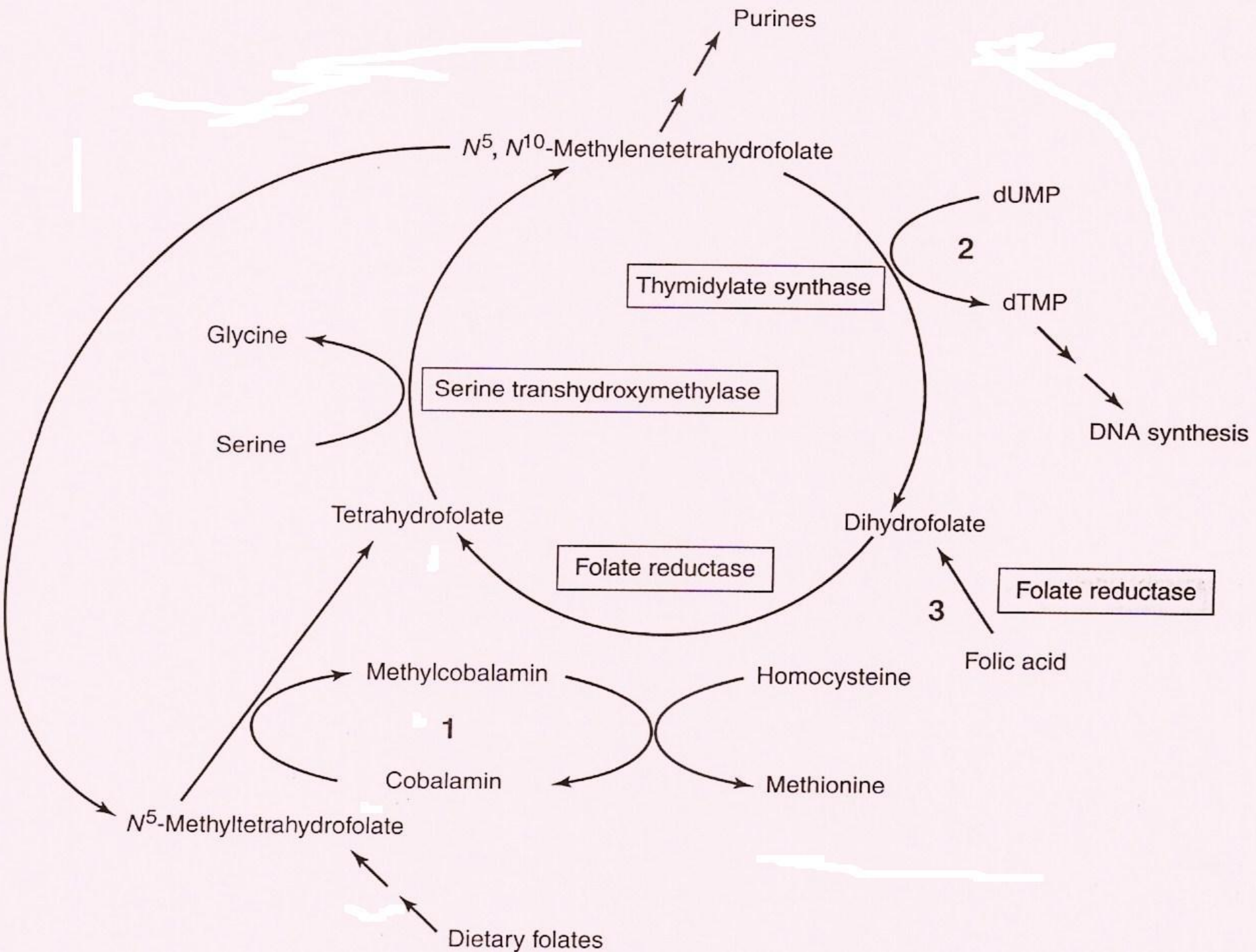
Vit.b12 is not essential as there are other mechanisms to do this conversion

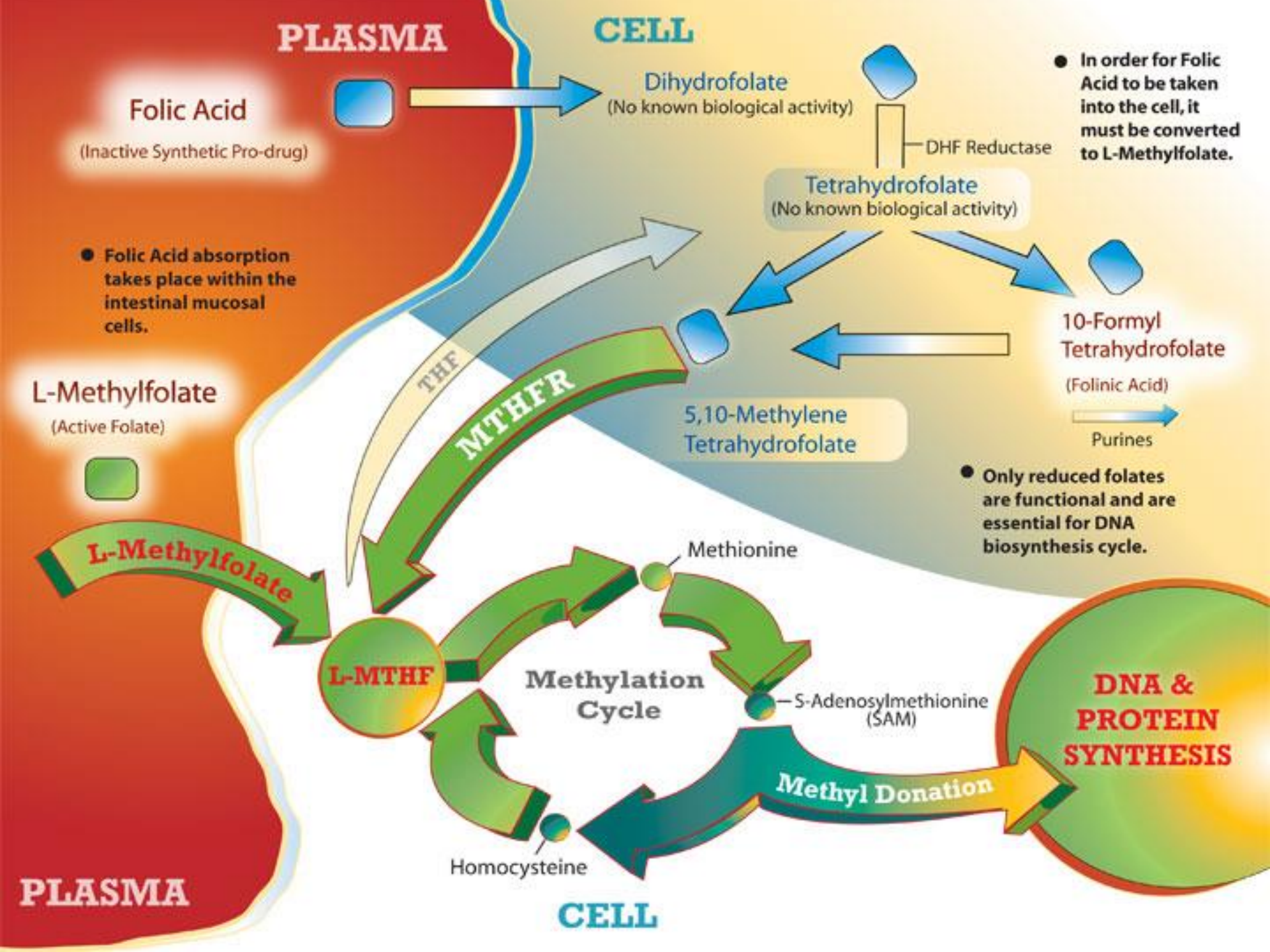
Kinetics of Folic Acid

- **Only 5-20 mcg are stored in the liver.**
- **Excreted in urine and stool and also destroyed by catabolism.**
- **Megaloblastic anemia can develop within 1-6 months after stopping intake.(so unlike vit.b12 we have limited folate stores)**
- **Present in yeast, liver, kidney and green vegetables.**

Actions of Folic Acid

- **THF cofactors are important in one-carbon reactions:**
  - **Production of dTMP from dUMP, which is needed in DNA synthesis.**
  - **Generation of methionine from homocysteine.**
  - **Synthesis of essential purines.**


Purines
N^5, N^{10}-Methylenetetrahydrofolate
dUMP
2
Thymidylate synthase
dTMP
DNA synthesis
Glycine
Serine transhydroxymethylase
Serine
Tetrahydrofolate
Dihydrofolate
Folate reductase
Folate reductase
3
Folic acid
Methylcobalamin
Homocysteine
1
Cobalamin
Methionine
N^5-Methyltetrahydrofolate
Dietary 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.
10-Formyl Tetrahydrofolate
(Folinic Acid)
Purines
L-Methylfolate
(Active Folate)
THF
MTHFR
5,10-Methylene Tetrahydrofolate
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.**
- ***(Important)*Drugs: Methotrxate*(used in cancer by inhibiting folic acid synthesis)*, Trimethoprim*(antibacterial used in combination with sulfamethoxazole)*and Phenytoin*(antiepileptic 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 *(in pregnancy)*.**
- **Routinely given in early pregnancy or even before being pregnant to prevent congenital malformations .**
- **Recently supplemented to foods.**