

Agents Used in Anemias

Hematopoiesis:

Requires a constant supply of:

- 1. Essential elements: Iron, vitamin B12 and folic acid.**
- 2. Hematopoietic Growth Factors**

Symptoms of Anemia

Red = In severe anemia

Eyes
- Yellowing

Skin
- Paleness
- Coldness
- Yellowing

Respiratory
- Shortness of breath

Muscular
- Weakness

Intestinal
- Changed stool color

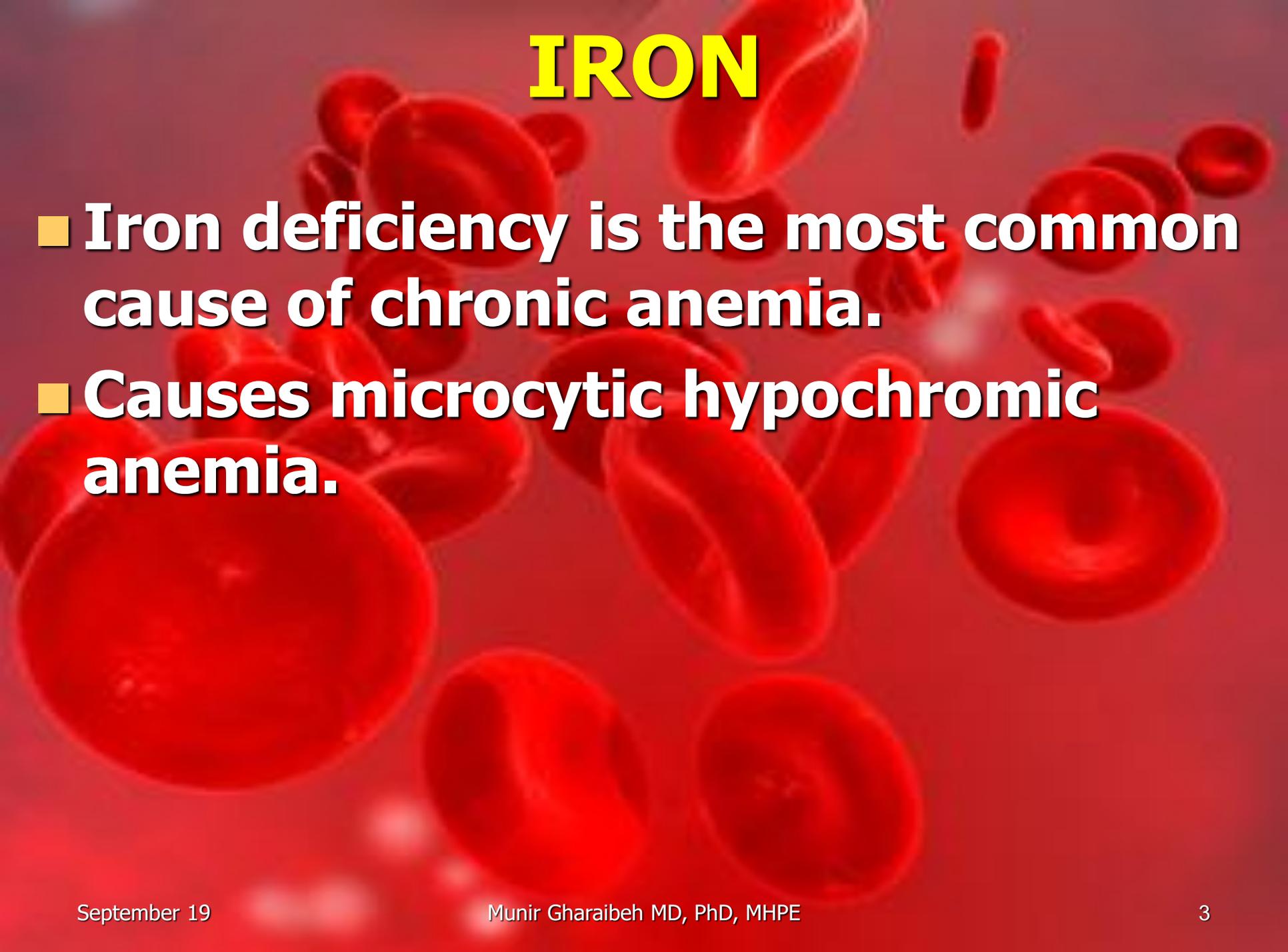
Central
- Fatigue
- Dizziness
- **Fainting**

Blood vessels
- Low blood pressure

Heart
- Palpitations
- Rapid heart rate
- **Chest pain**
- **Angina**
- **Heart attack**

Spleen
- Enlargement

IRON

The background of the slide is a dense field of red blood cells, depicted in various sizes and orientations, creating a sense of depth and movement. The cells are a vibrant red color, and the overall background is a lighter, slightly blurred red.

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

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

Pharmacokinetics of Iron

- Free iron is toxic.
- 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.

Possible causes of Iron Deficiency:

- Increased iron requirements
- Increased iron losses.

Absorption:

- **Daily intake: 10-15mg of elemental iron.**
- **Heme iron in meat hemoglobin and myoglobin is absorbed intact.**
- **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.**
- **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.**

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***).

Transport:

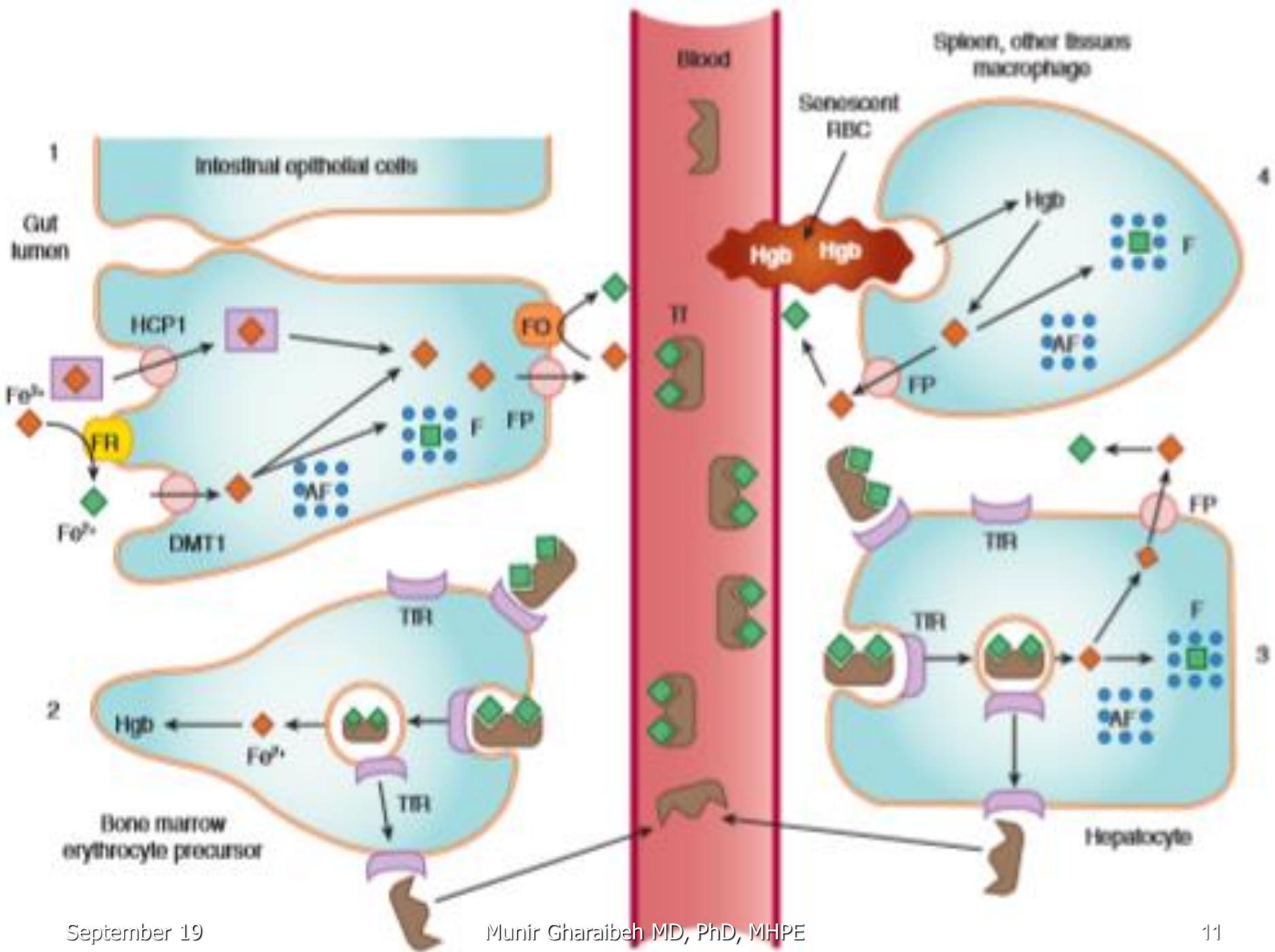
- *Transferrin (Tf)* binds two molecules of iron in the plasma.
- The complex binds to *Transferrin Receptors (TfR)* on the maturing erythroid cells which internalize the complex through the process of receptor-mediated endocytosis.
- Iron is released for hemoglobin synthesis.
- Transferrin- transferrin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

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.

Elimination:

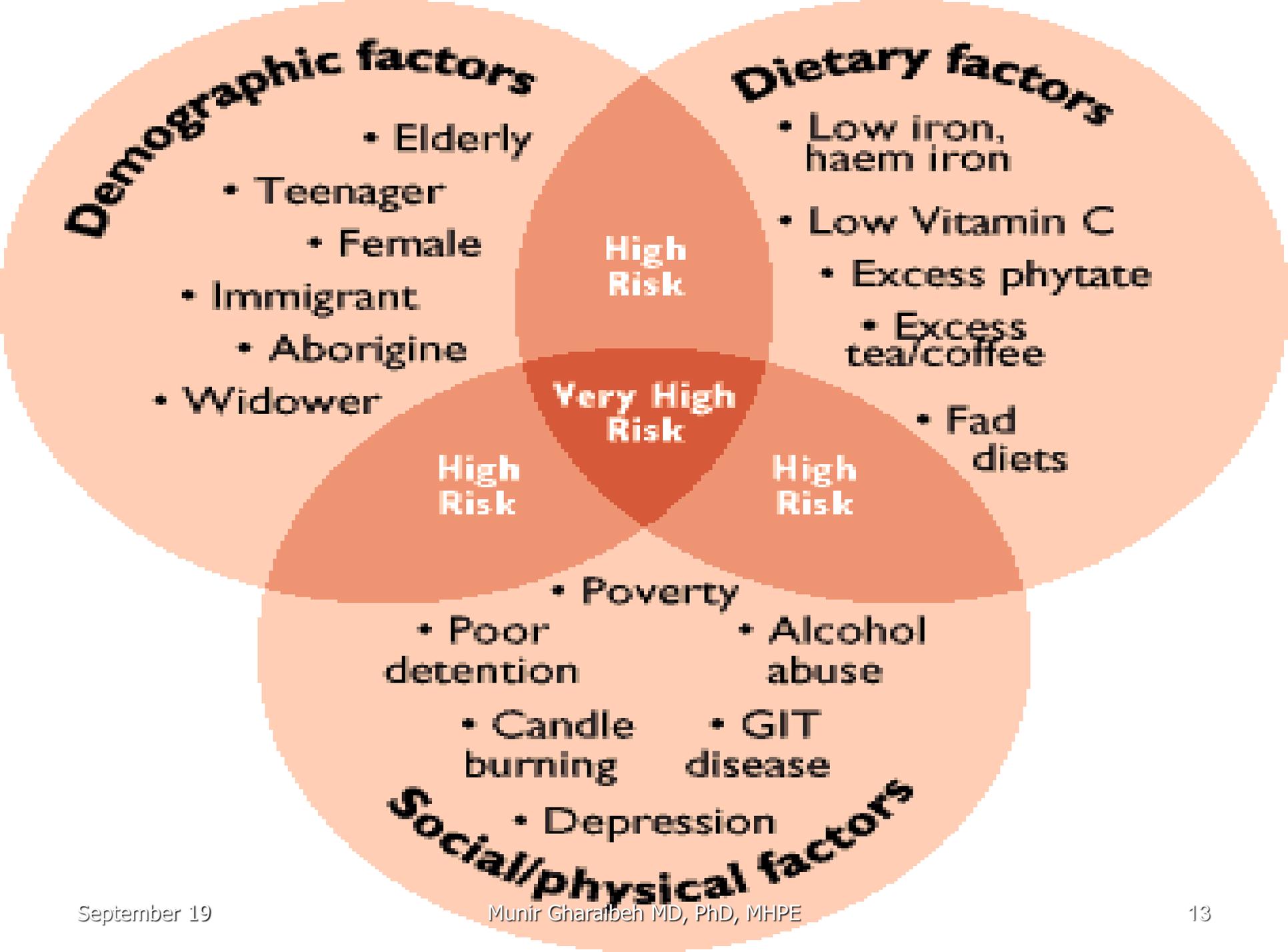
- There is no mechanism for excretion.
- Small amounts are lost by exfoliation of intestinal mucosal cells, bile, urine and sweat.



IRON THERAPY

Indications:

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



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



Oral Iron Preparations:

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

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 can not be effectively maintained with oral iron alone.
- Carry the risk of iron overload.

■ **Iron dextran:**

- 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.**

■ **Iron sodium gluconate.**

- Given only IV , less likely to cause hypersensitivity.

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.
- **Whole Bowel Irrigation;** to flush out unabsorbed pills.
- **Activated charcoal is ineffective.**
- **Supportive therapy is also necessary.**

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.

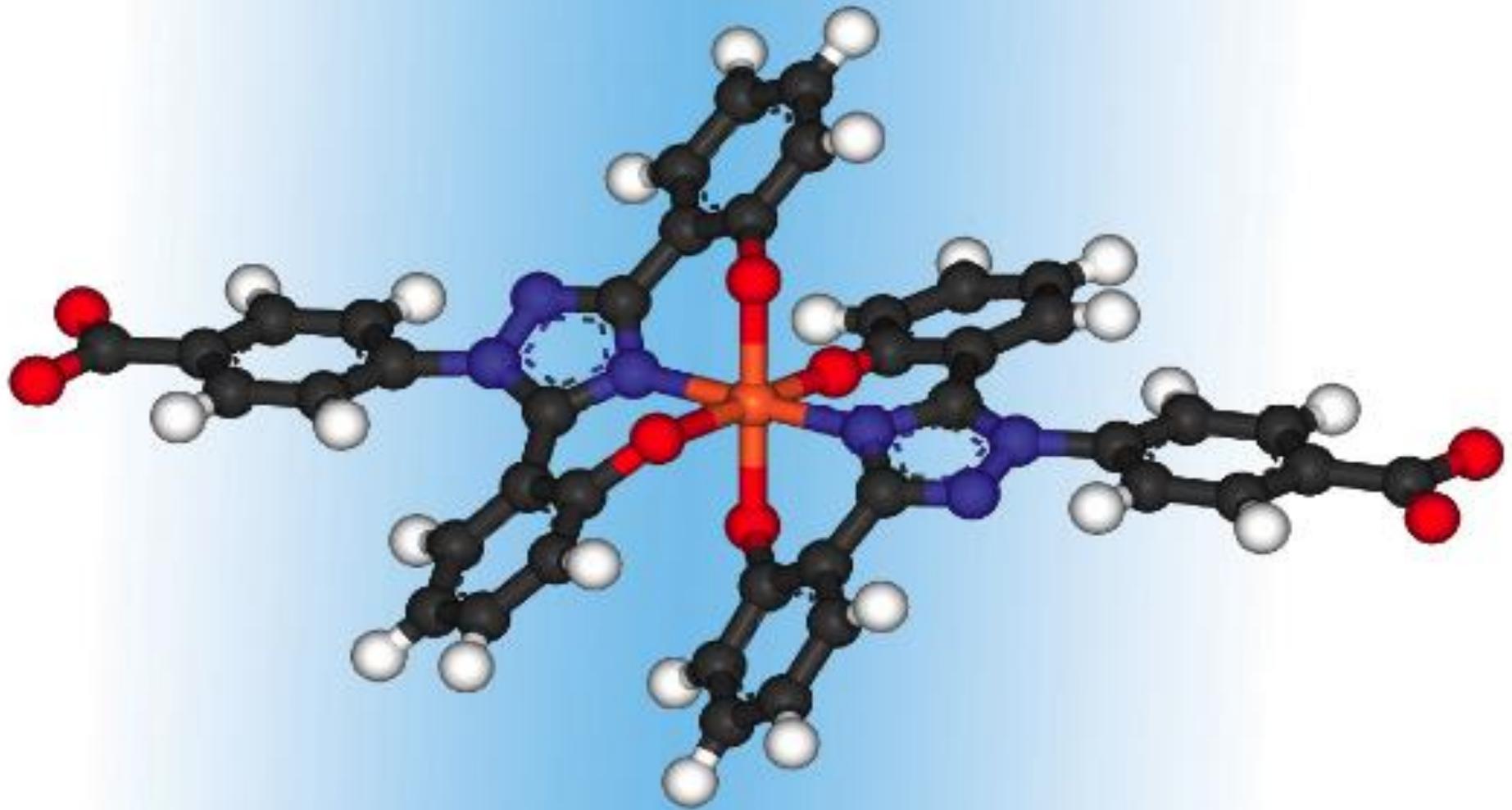
2. Patients with frequent transfusions e.g. in patients with hemolytic anemias

Treatment of Chronic Iron Toxicity:

Intermittent phlebotomy (الفصد).

Deferoxamine: is much less efficient than phlebotomy.

Deferasirox " Exjade": oral, more convenient than deferoxamine.



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>

Vitamin B₁₂

- Porphyrin-like ring with a central cobalt atom.
 - Methylcobalamine
 - Deoxyadenosyl cobalamine.
 - Cyanocobalamine.
 - Hydroxocobalamine.
-
- Meat, liver, eggs, and dairy products.
 - Nutritional deficiency only occurs in strict vegetarians.

Vitamin B₁₂

- Daily requirement : 2mcg
- Storage pool: 300-5000mcg.
- It would take about 5 years to exhaust all the stored pool and for megaloblastic anemia to develop after stopping absorption.

Pharmacokinetics of Vitamin B₁₂

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

Schilling's Test:

- Measures absorption and urinary excretion of radioactively labeled Vitamin B₁₂.

Vitamin B₁₂ Deficiency

Pernicious anemia.

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 B₁₂

Actions of Vitamin B₁₂

1. Transfer of a methyl group from N⁵-methyltetrahydrofolate to homocysteine, forming methionine.

N⁵-methyltetrahydrofolate is the major dietary and storage folate.

2. Conversion of N⁵-methyltetrahydrofolate to tetrahydrofolate. Deficiency leads to accumulation of N⁵-methyltetrahydrofolate cofactors and depletion of tetrahydrofolate .

Vitamin B₁₂

Megaloblastic anemia of Vitamin 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*.

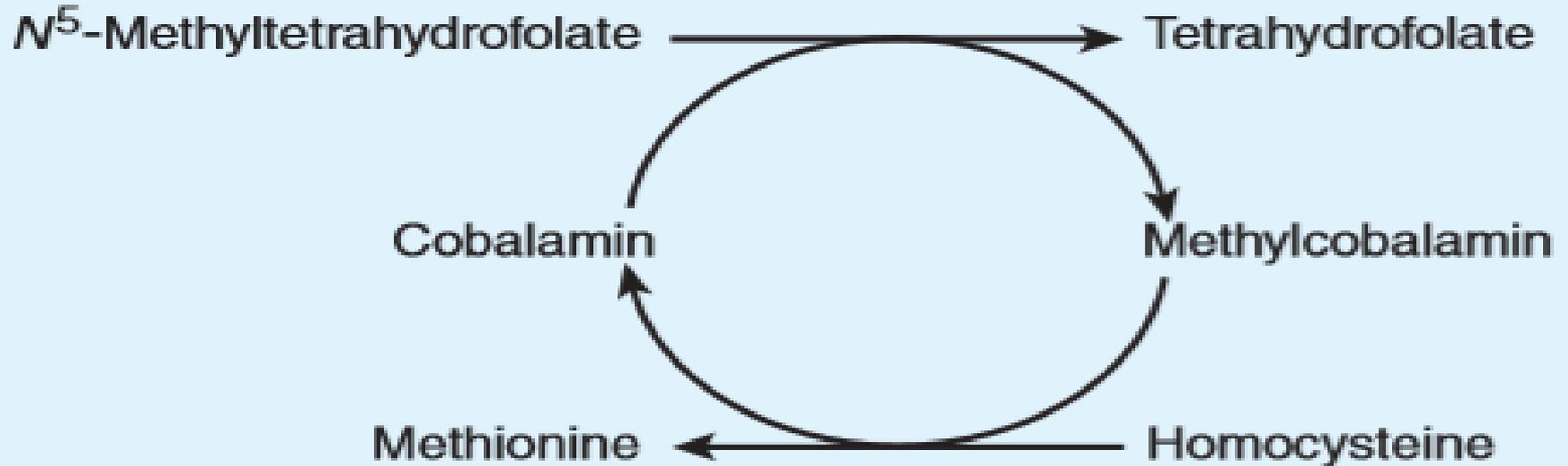
Actions of Vitamin B₁₂

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

Vitamin B₁₂ depletion leads to the accumulation of methylmalonyl-CoA, thought to cause the neurological manifestations of Vitamin B₁₂ deficiency.

Enzymatic reactions that use vitamin B 1

A. Methyl transfer



B. Isomerization of L-Methylmalonyl-CoA



Therapy with Vitamin B₁₂

Parenteral :

Life-long treatment.

Daily or every other day for 1-2 weeks to replenish the stores.

Maintenance: injections every 1-4 weeks.

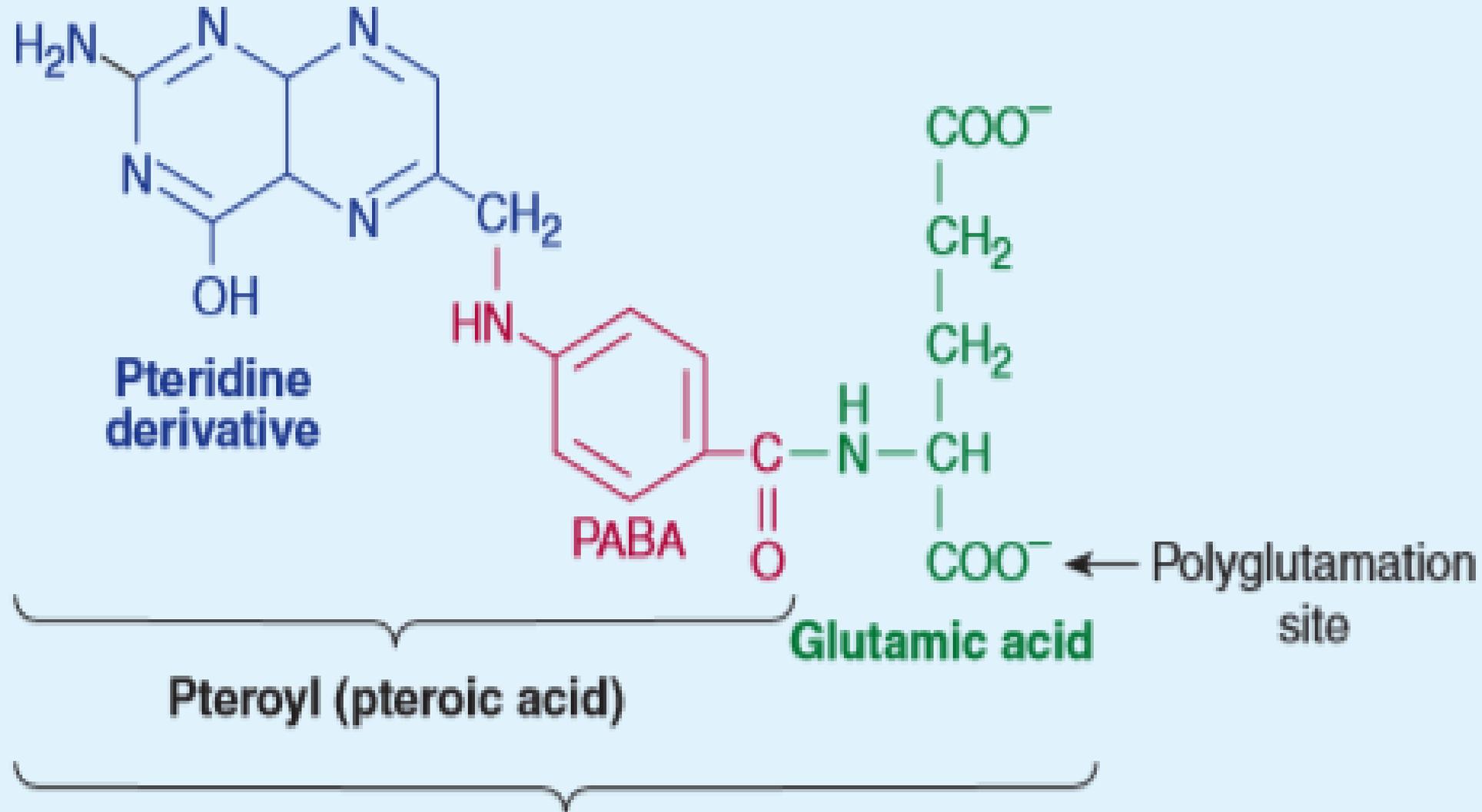
Oral:

Only for patients who refuse or can not tolerate injections.

Intranasal:

For patients in remission

The structure of folic acid



Folic Acid

- Reduced forms of folic acid are required for the synthesis of amino acids, purines and DNA.
- Deficiency is common but easily corrected.
- Deficiency can result in:
 - Megaloblastic anemia.***
 - Congenital malformations.**
 - Occlusive Vascular disease due to elevated homocysteine.**

Chemistry of Folic Acid

- Folic acid = Pteridine + PABA + Glutamic acid.
- Folic acid is reduced to Di and Tetra hydrofolate 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 B₁₂.

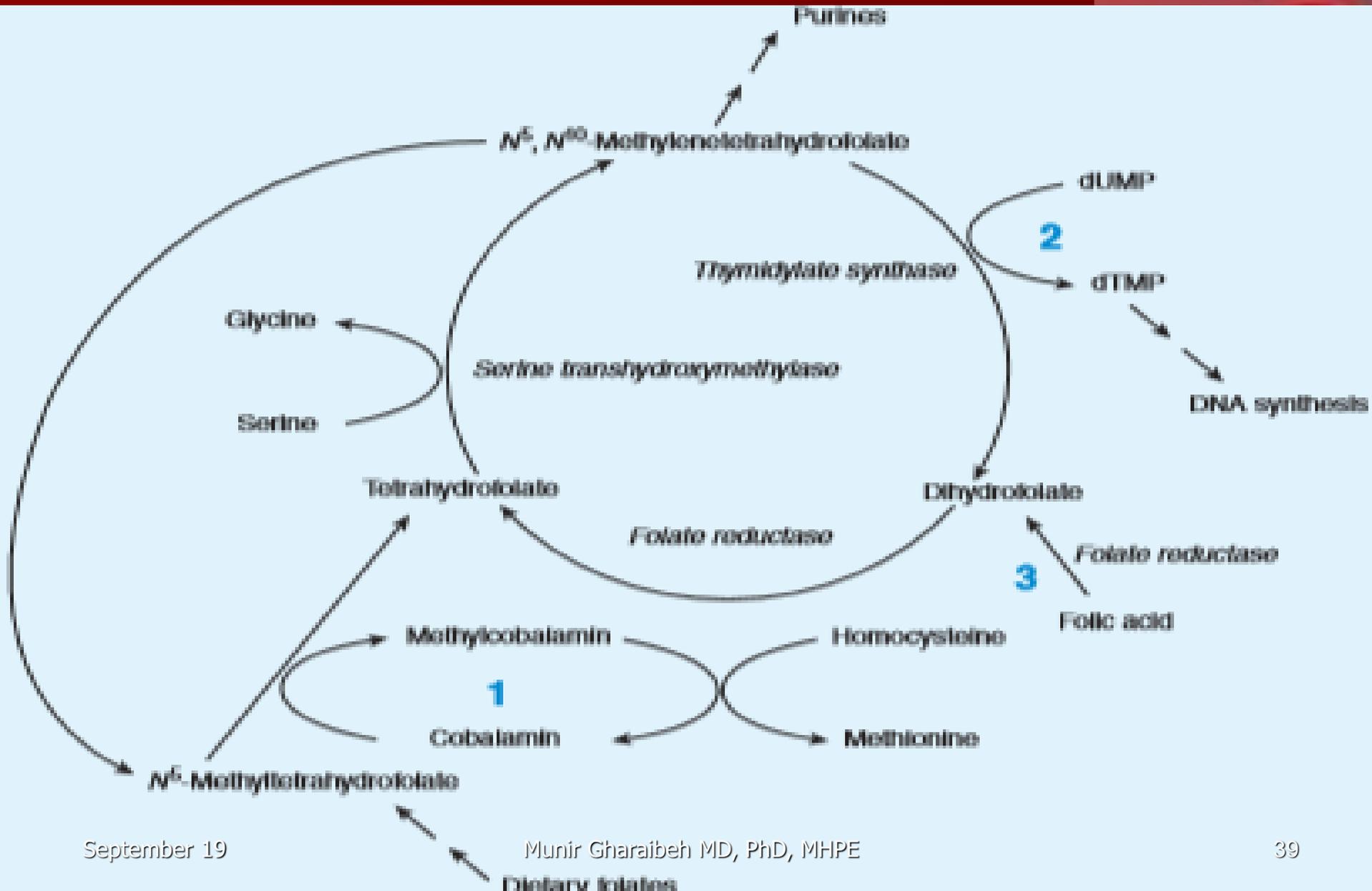
Kinetics of Folic Acid

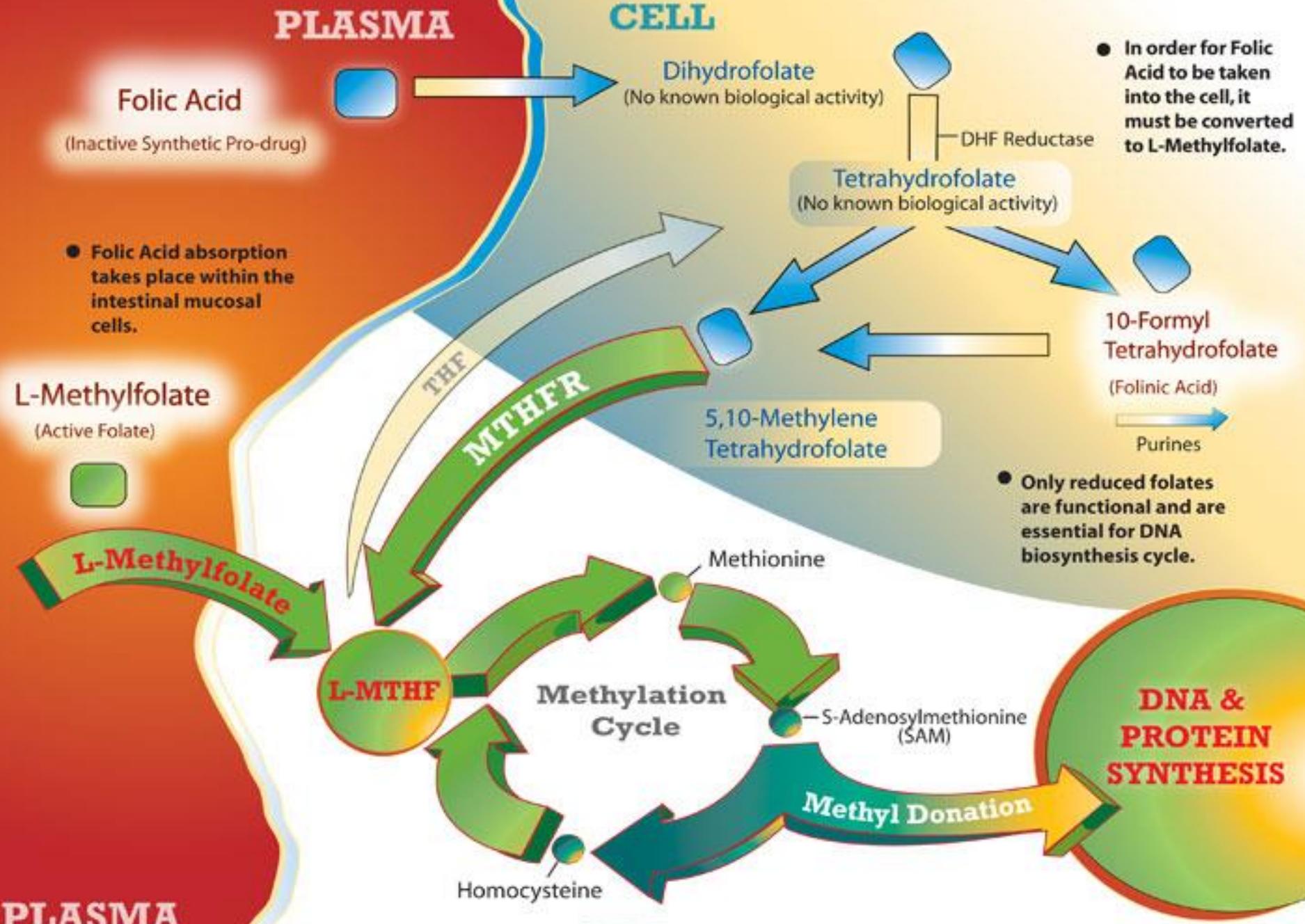
- Only 5-20 mcg are stored in the liver.
- Excreted in urine and stool and also destroyed by catabolism.
- Megaloblastic anemia can develop within 1-6 months after stopping intake.
- Present in yeast, liver, kidney and green vegetables.

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.**

Enzymatic reactions that use folates





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: Methotrxate, Trimethoprim and Phenytoin.**

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.
- Recently supplemented to foods.