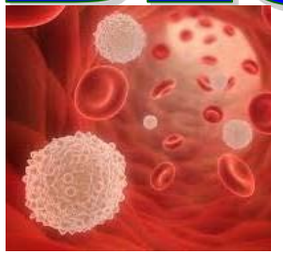
Odessa State Medical University

Department of general and clinical pharmacology and pharmacognosy

AGENTS, ACTING ON ERYTHROPOIESIS. BLOOD SUBSTITUTES.



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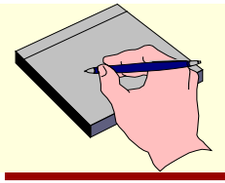


MAIN BLOOD DISEASES

- **Erythropoiesis disorders - ANEMIA:**
  - **iron deficiency (hypochromic)**
  - **megaloblastic (hyperchromic)**
- **Leukopoiesis disorders**
  - **Leukosis**
  - **Leukemia**
- **Blood clotting disorders:**

❖ **Bleeding**

↓ **blood clotting**

↑ **Fibrinolysis**

↓ **platelet aggregation**

❖ **thrombosis**

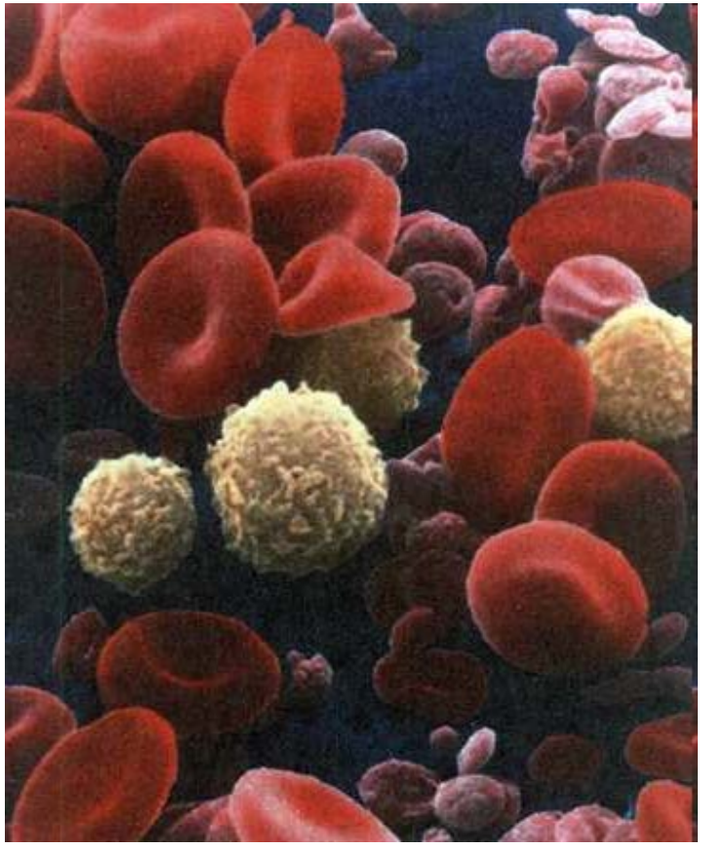
↑ **coagulation**

↓ **fibrinolysis**

↑ **platelet aggregation**

ANEMIA

- **Hypochromic anemia - anemia in which the blood color index due to a lack of hemoglobin is less than 0.8.**
- Color Indicator - reflects the hemoglobin content in the erythrocyte
- **in men erythrocytes4.5-5.5 million in 1 mm^3**
- **in women - 3.7-4.7 million in 1 mm^3**
- **In hypochromic anemias, hemoglobin synthesis is impaired with a slight decrease in the number of erythrocytes.**



Erythrocytes are shaped like rings with a clearing in the middle.

CAUSES OF IRON DEFICIENCY ANEMIA

- **Chronic blood loss of various localization: gastrointestinal, uterine, nasal, renal, pulmonary, iatrogenic and artificial blood loss**
- **Iron absorption disorders: enteritis of various genesis, malabsorption syndrome, small bowel resection, gastric resection excluding the duodenum**
- **Increased iron requirement: pregnancy, lactation, intensive growth and puberty, B12 deficiency anemia, treated with vitamin B12**
- **Iron transport disorders (hypoproteinemia of various genesis).**
- **Nutritional deficiency**

MEGALOBLASTIC ANEMIA

Causes

- **insufficient intake of vitamin B12 in the body with food (vegetarianism, fasting, etc.)**
- **impaired absorption of vitamin B12 in the body (gastrointestinal diseases, parasites, etc.)**

B12 is found in meat, eggs, cheese, liver, milk, kidneys.

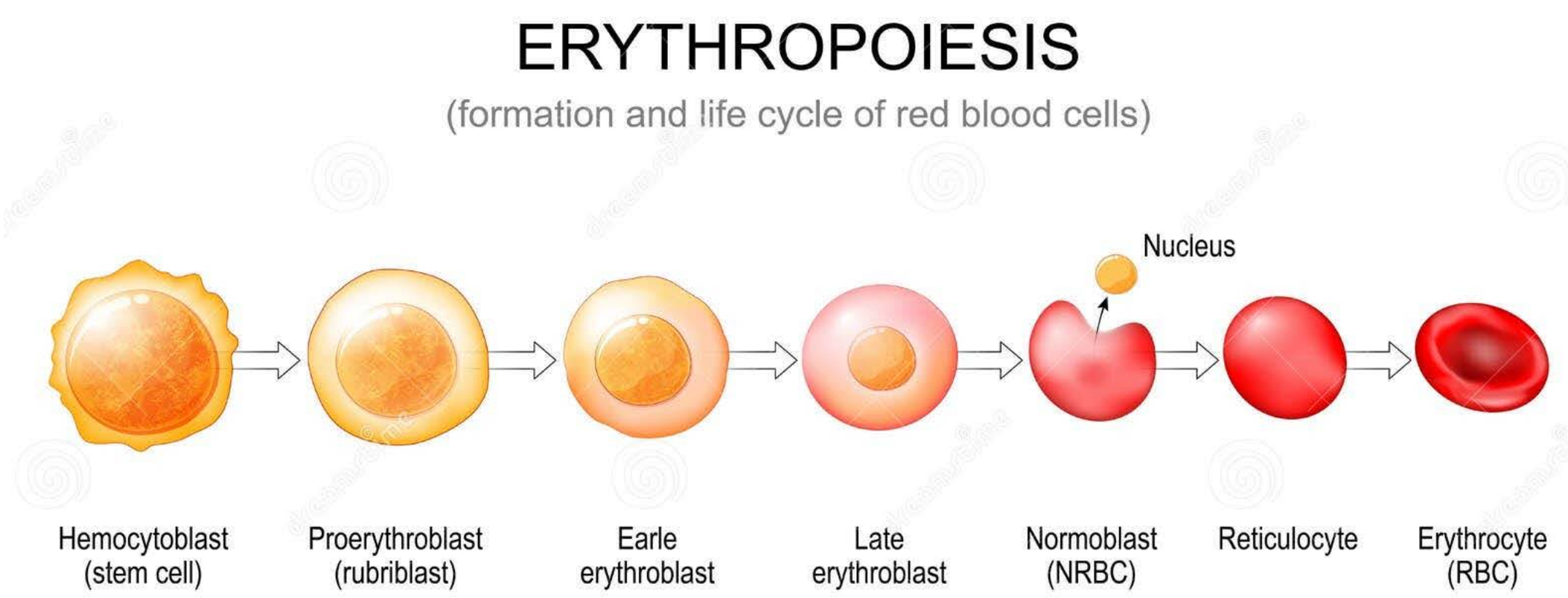
- **Vit. B12 forms a complex with a glycoprotein synthesized in the stomach and is absorbed into the blood - the "external factor" of anemia**
- **The parietal cells of the stomach synthesize the "intrinsic factor" of Castle (glycoprotein)**
- **The complex of the vitamin and glycoprotein binds to specific receptors of the cells of the ileum mucosa and enters the blood**

MEGALOBLASTIC ANEMIA

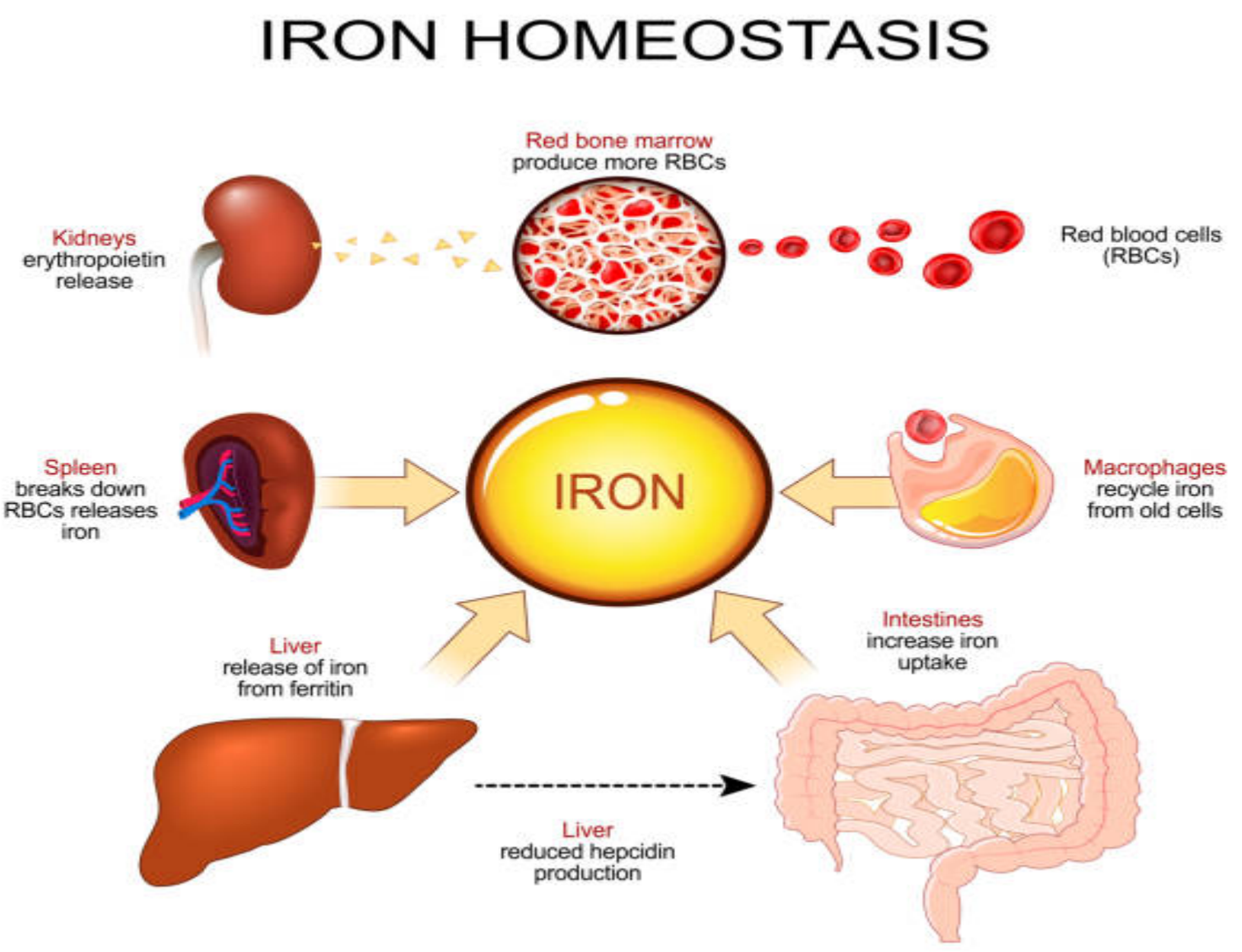
Mechanism:

- **B12 deficiency causes a decrease in the synthesis and structure of DNA, a disorder of the processes of division and maturation of erythrocytes**
- **erythrocytes increase in size (megaloblastics and megalocytes)**
- **Erythrocytes formed under conditions of vitamin B12 deficiency are the result of pathological megaloblastic erythropoiesis**
- **are characterized by low mitotic activity and low resistance, short life span.**
- **Most of them (up to 50%, normally about 20%) are destroyed in the bone marrow.**
- **The number of erythrocytes in the peripheral blood is also significantly reduced**

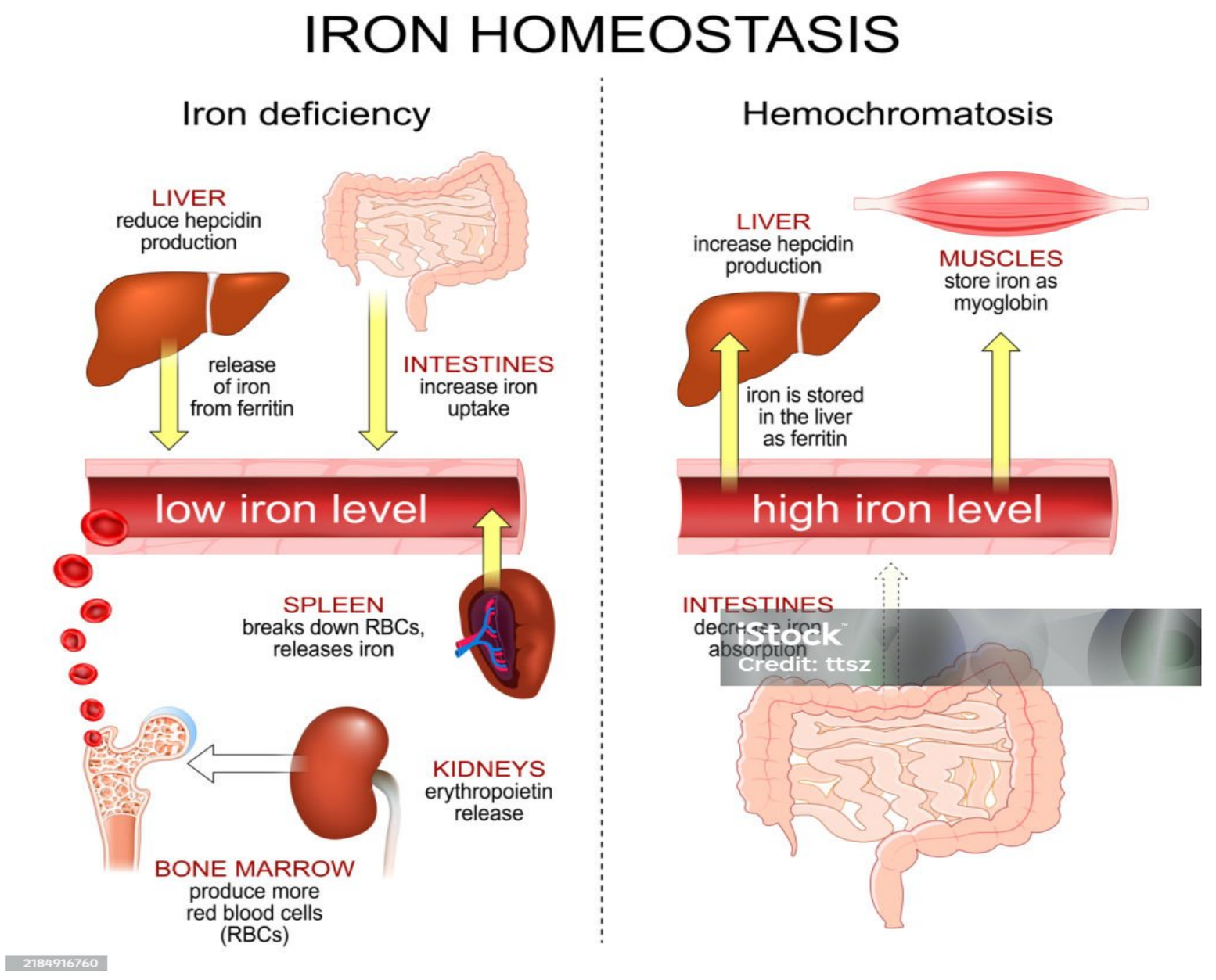
MEGALOBLASTIC ANEMIA

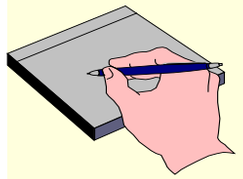


IRON HOMEOSTASIS



IRON HOMEOSTASIS

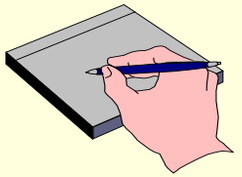




CLASSIFICATION OF AGENTS, ACTING ON ERYTHROPIESIS

- **stimulators of erythropoiesis:**
  - **for hypochromic (microcytic) anemia – iron-containing agent for oral and parenteral administration**
  - **for hyperchromic (megaloblastic) anemia– cyanocobalamine, folic acid**
  - **for anemias of different origin (cancer, AIDS, renal failure etc.) – hemopoietic factors of growth: *erythropoietin* (epoetin-alfa), *colony-stimulating factors of granulocyt* (filgrastim) & *of granulocytes-macropha* (molgramostim)**

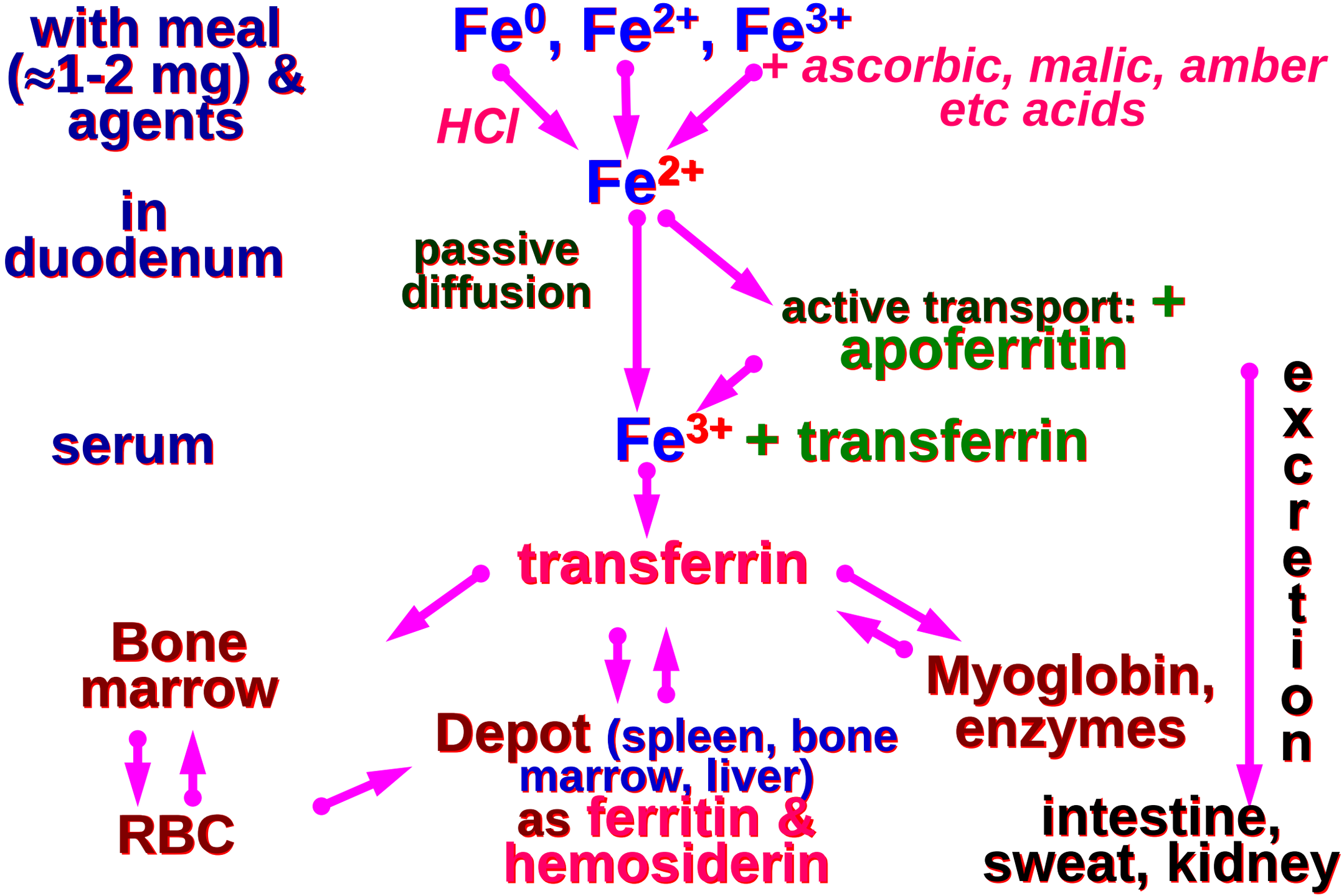
- **inhibitors of erythropoiesis : radioactive phosphorus-32 isotope (^{32}P)**



IRON-CONTAINING AGENTS

- **for oral intake:**
  - ✓ **mono-compound:** **ferronal** ***(ferrous gluconate)***, **actiferrin** ***(ferrous sulfate)***, **heferol** ***(ferrous fumarate)***, **hemofer** ***(ferrous chloride)*** **etc;**
  - ✓ **complex:** **ferroplex** ***(+ascorbic acid),*** **hemostimulin** ***(+copper),*** **multiferrol** ***(+folic acid) etc*****.**
- **for parenteral usage:** **ferbitol** ***(ferric-sorbitol complex),*** **fercoven, ferum-lek** ***(ferric saccharate),*** **coamide** ***(+cobalt)***

PHARMACOKINETICS OF IRON



PRINCIPLES OF IRON-CONTAINING AGENTS THERAPY

- **it isn't wise to treat iron-containing anemia with diet only** (hem iron has the best absorption: 10-30 %; for non-organic iron: 1-10 %)
- **improve absorption:** organic acids, cysteine, proteins; **decrease absorption:** ingestion during or just after meal, milk, eggs, cereal grains, calcium salts, phosphates, antacids, tetracyclines, etc. Better absorption have fumarate, sulfate; worse – gluconate
- **for hemoglobin synthesis daily required 50-100 mg of iron**
- **prescribed iron 1 hr before** (better absorption) **or 2 hrs** (better tolerance) **after meal**
- **the treatment is successful at hemoglobin growth on 1-2 g/l daily**
- **the therapeutic effect – after 2-4 weeks, restoring of iron depot – after 2-3 months**

TOXICITY OF IRON-CONTAINING AGENTS

- **oral forms:** loss of appetite, nausea, vomiting, diarrhea, constipation (binding with hydrogen sulfide); teeth discoloration (powder), dark discoloration of stool (binding with hydrogen sulfide)
- **parenteral forms:**
  - I.M. – headache, painful infiltrates
  - I.V. – phlebitis, dizziness, metallic taste, arthralgia, fever, anaphylactic shock, leukocytosis, nephrotoxicity, hemolysis
- **at prolong us :** hemosiderosis

the treatment should be proved by real iron deficiency!

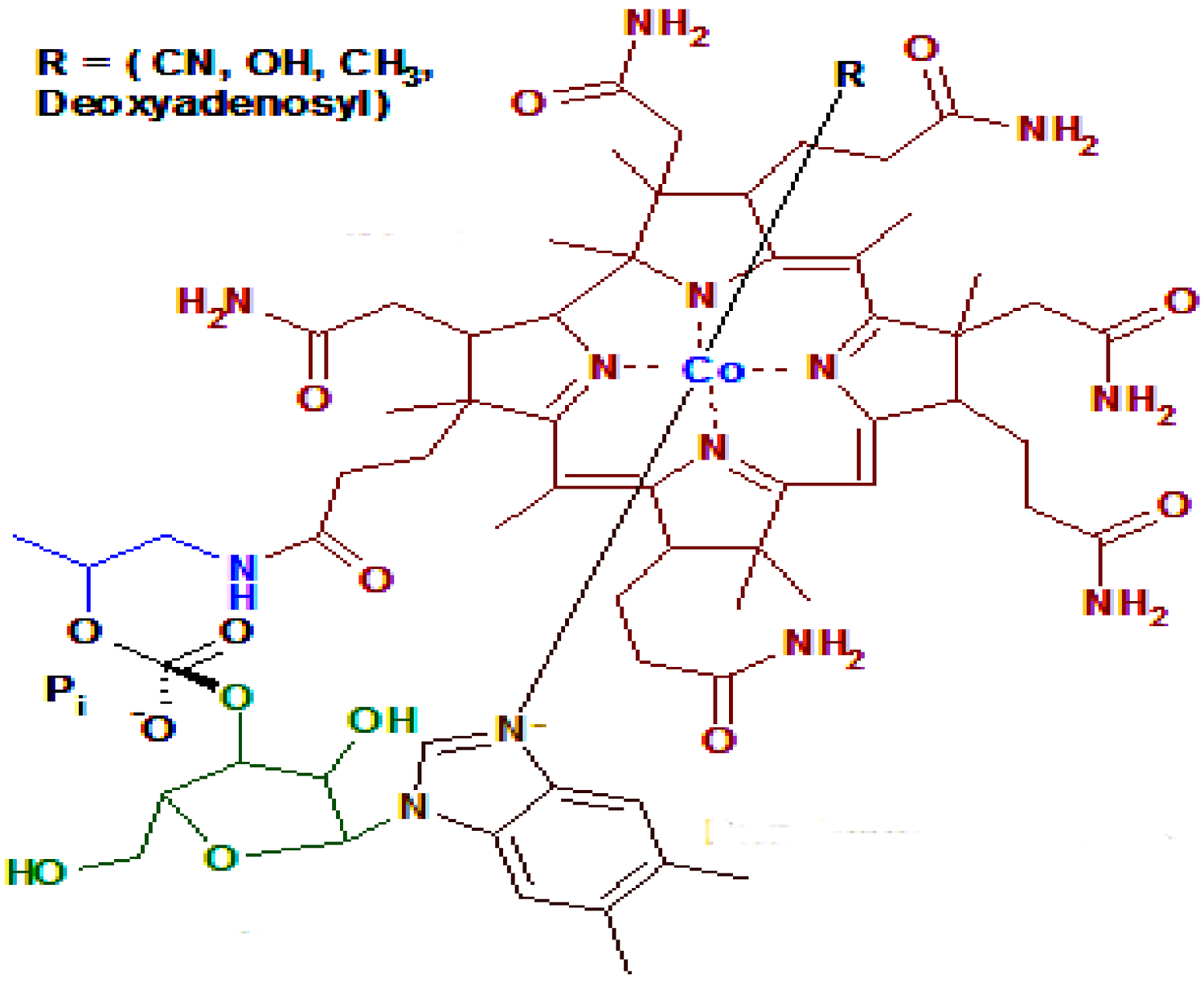
TOXICITY OF IRON-CONTAINING AGENTS

treatment:

- antidote – deferoxamine I.M. or I.V.
- stomach washing with sodium bicarbonate
- correction of collapse, dehydration and acidosis

VITAMIN B_{12}

cyanocobalamin, hydroxycobalamin



Present **– in meat, milk, liver, fish** ***synthesized*** **by intestinal microflora.** ***Daily demand*** **– 2-5 mcg**

CYANOCOBALAMIN

pharmacokinetics

Absorption **– in small intestine and distal part of cecum after binding with intrinsic Castle's factor (intestinal transport is maintained by folic acid)**

Distribution **– transported in blood by plasma protein**

Deposition **– in liver 1-10 mg (store for 2-5 years), in bone marrow etc., daily used 0,5-8 mcg.**

Excretion **with bile into intestine daily 3 mcg; enterohepatic circulation (50-60 % absorbed back); also via kidney (especially at excess)**

CYANOCOBALAMIN

pharmacodynamics

basic reactions:

1. **catalyze conversion of methylmalonic acid into amber acid ⇒ at B_{12} deficiency ↑ content of methylmalonic acid that inhibits myelin synthesis ⇒ neurologic disturbances**

2. **demethylate of tetrahydrofolic acid and regulate:**
   - ✓ **DNA (nucleoproteins) synthesis ⇒ at deficiency there is disturbances of hemopoiesis (DNA replication, maturation of RBC nuclei ⇒ megaloblasts)**
   - ✓ **methionine synthesis: ⇒ synthesis of proteins, phospholipids, choline, betain**

3. **maintaining sulfhydryl (SH) groups in the reduced form**

CYANOCOBALAMIN

pharmacodynamics

- **anabolic action: ↑ protein and nucleic acid synthesis**
- **metabolism: ↑ fat & carbohydrate metamolism, ↓ cholesterol level in blood**
- **activate erythropoiesis (with B_c): DNA replication, maturation of RBC and prevention of their hemolysis**
- **↑ immunity, ↑ blood coagulation**
- **hepatoprotective & neuroprotective action (cognitive function)**
- **reproduction (↑ spermatozoids level)**

Deficit at: **↓ content of Castle's factor (chronic gastritis), enteritis, pancreatitis, helmenthiasis etc**

CYANOCOBALAMIN

inidcations:

- **substitutive: hypovitaminosis – anemia megaloblastic (pernicious, B_{12}-deficient, Addison-Birmer), neurologic disturbances: myelosis; gait disturbances, dementia etc; glossitis – treatment (with B_c) 100 mcg daily during 1 week, than once a week during 1 month and than once a month during all live; prophylaxis (once a month) at vegetarians, stomach resection etc.**

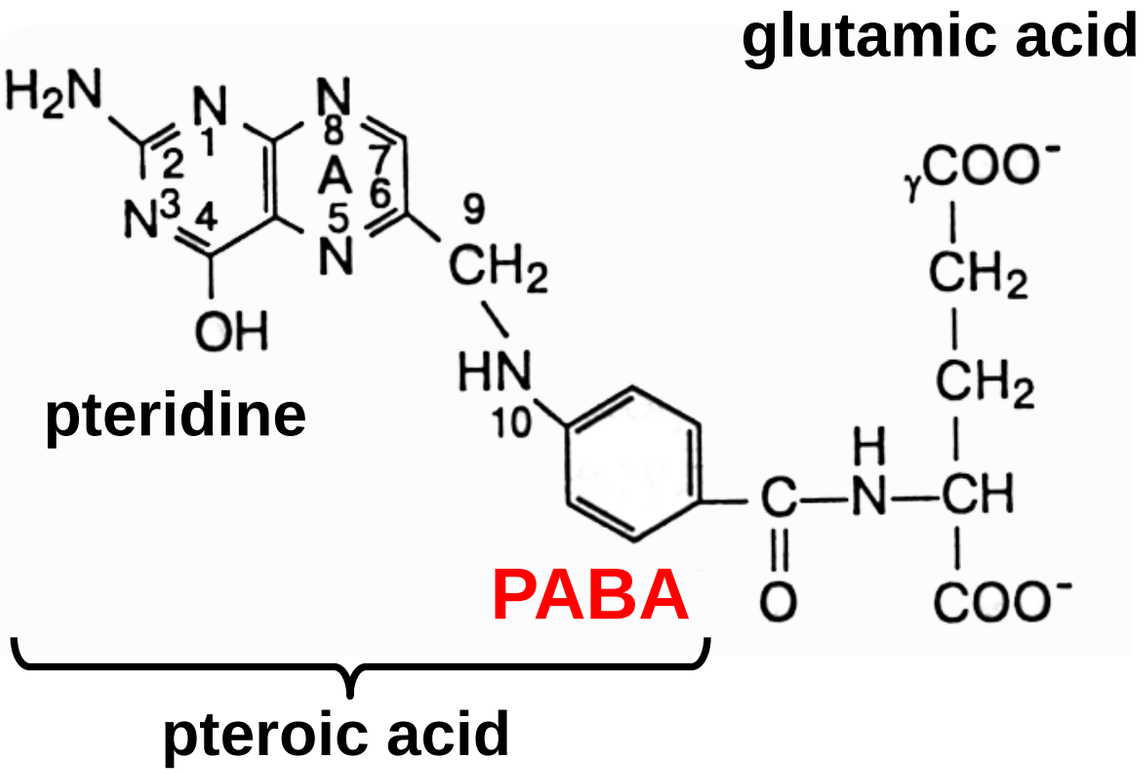
- **pharmacodynamic:**
  - ✓ **anemia (posthemorrhagic, aplastic etc.)**
  - ✓ **polyneuritis, paresis**
  - ✓ **hepatitis, liver cirrhosis**
  - ✓ **myocardiodystrophy**
  - ✓ **skin diseases (psoriasis)**

CYANOCOBALAMIN

adverse effects

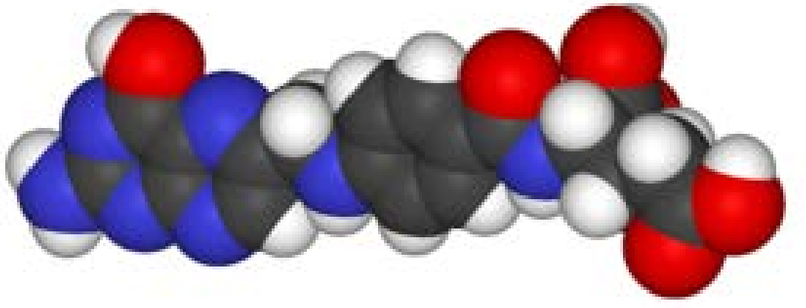
- psychical excitement
- chest pain, tachycardia, arrhythmia (↓ K^+)
- ↑ blood coagulation, ↑ thrombocytes, leucocytes, erythrocytes
- anaphylactic shock (rarely)

FOLIC ACID (B_c)



structure

pteridine heterocycle, PABA, glutaminic acid



Present **– yeast, liver, kidney, cheese, green vegetable, *synthesized* by intestinal microflora**

Daily demand **– 50 mcg, during pregnancy – 400-800 mcg, children 2-12 years – 200mcg**

FOLIC ACID

pharmacokinetics

Absorption: **mainly in form of monoglutamate tetrahydrofolate (THF); alcoholism, spru decrease its absorption; absorption take place in proximal тонкого small intestine кишечника; the best absorption from liver, beer yeast, eggs**

Plasma protein binding **– 60-70 %**

Distribution **– in liver, CSF is the highest concentration; total content – 5-10 мг; actively transported through placenta**

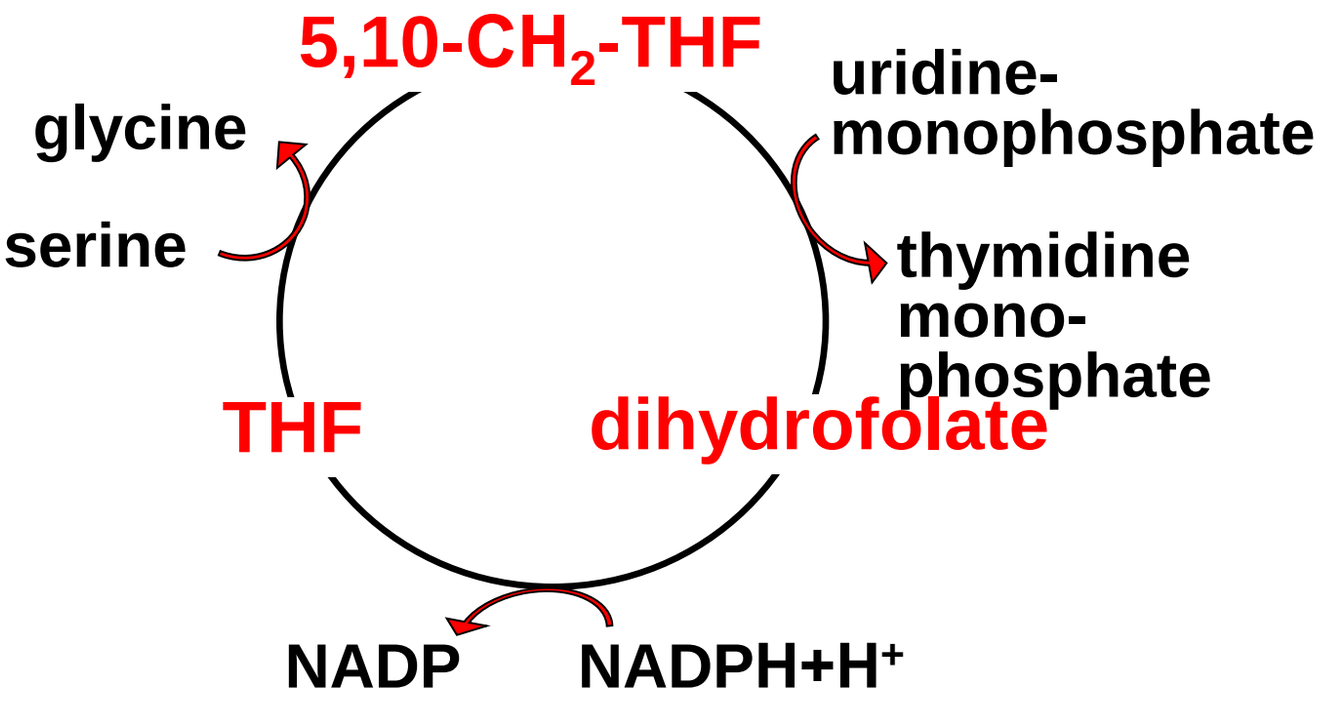
Excretion **via kidney, also with breast milk**

фармакодинамика

main function tetrahydrofolic acid & its derivatives — carrier (acceptor) of monocarbon groups, i.e., methyl from one organic compounds to another

FOLIC ACID

pharmacodynamics



1. conversion of serine into glycine
2. histidine metabolism
3. inclusion of carbon atoms into purine base circle
4. conversion of homocysteine into methionine with B_{12}, as co-factor

↑ erythro-, leuco-, thrombocytosis, plastic and regenerative processes in all organism

FOLIC ACID

indications

- **substitutive: hypovitaminosis – at chronic alcoholism, liver and intestinal diseases, antibiotics therapy, malabsorption, vit. B_{12}-deficient anemia; for treatment – 15 mg I.M. or orally once a day, for prophylaxis – daily demand**
- **adaptative (pregnancy, breast-feeding, premature infants)**
- **pharmacodynamic:**
  - ✓ **hypochromic, hypoplastic etc anemias**
  - ✓ **for stimulation of regenerative processes at peptic ulcer of stomach & duodenum, burns, wounds**

adverse effects

- **dyspepsia, allergic reaction**
- **in high doses ↑ CNS excitement up to seizers, ↓ renal function**

ERYTHROPOIETIN (α, β, ω)

recombinant human erythropoietin – epoetin-alpha

pharmacodynamics

glucoproteid hormone (synthesized in kidney):

↑ **erythrocytes & reticulocytes, hemoglobin, hem synthesis (after 3-4 weeks of regular use)**

indications

- **anemia of different etiology (chronic renal failure, chemotherapy of cancer, AIDS)**

adverse effects

- ***initial:*** **ifluenza-like symptoms (at the beginning), hypetension, thrombosis, myocardial infarction**
- ***delayed:*** **immune disturbances, tumor of bone marrow**

CLASSIFICATION OF BLOOD SUBSTITUTES according to content

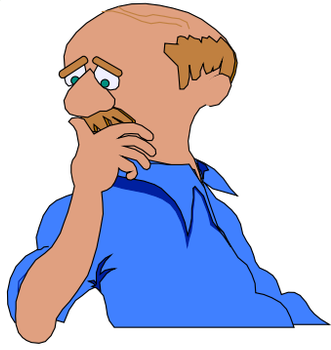
- **protein:** ***from blood cells*** **– erythrocyte, thrombocyte mass ;** ***from plasma*** **– serum, antihemophilic plasma**
- **protein hydrolysate – casein hydrolysate, hydrolysine, aminocrovin etc.; aminoacids derivatives – polyamine**
- **lipid emulsion – lipofundin**
- **colloid:** ***animal origin*** **– gelatinol;** ***plant origin*** **– gumiarabic;** ***synthetic*** **– dextrans (polyglucin, reopolyglycin), polyvinylpyrrolidone derivative (neohemodes)**
- **crystalloid:** ***salt*** **– 0,9 % sodium chloride solution, Ringer's solution, potassium chloride, quantasol, acesol etc; buffer – sodium bicarbonate;** ***solutions of polyatomic alcohols*** **- glucose, fructose, sorbitol**

CLASSIFICATION OF BLOOD SUBSTITUTES according to application

- **hemodynamic *(antishock)*** – **polyglucin** (T1/2≈3-4 days), **reopolyglucin** (T1/2≈1 day), **geltinol**
- **detoxification** – **neohemodes, enterodes, repolyglucin, gelatinol**
- **correctors of acid-alkaline and water-salt balance** – **crystalloid, buffer solutions**
- **for parenteral nutrition** – **protein hydrolysate, aminoacids' solutions, sugars, lipid emulsion**
- **agents that has oxygen-transport system** – **perftoran**
- **multifunctional** – **polyfer** (hemodynamic, hemopoietic), **reogluman** (hemodynamic, hemopoietic, detoxification, diuretic)

ADVERSE EFFECTS OF TRANSFUSION

- **immediate:**
  - ***volume-independent:*** **anaphylaxia, hemolysis, fever, hypercaliemia,**
  - ***at massive transfusion:*** **hypokaliemia, fever, ↓ coagulation**



- **delayed: hypokaliemia, hypothermia, ↓ coagulation**