DRUGS USED IN ANEMIA

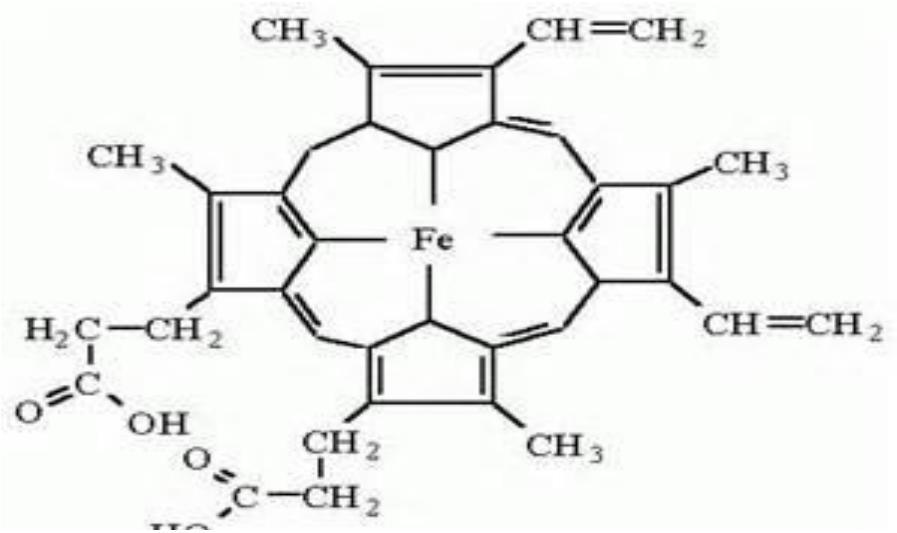
DR SHAMS SULEMAN

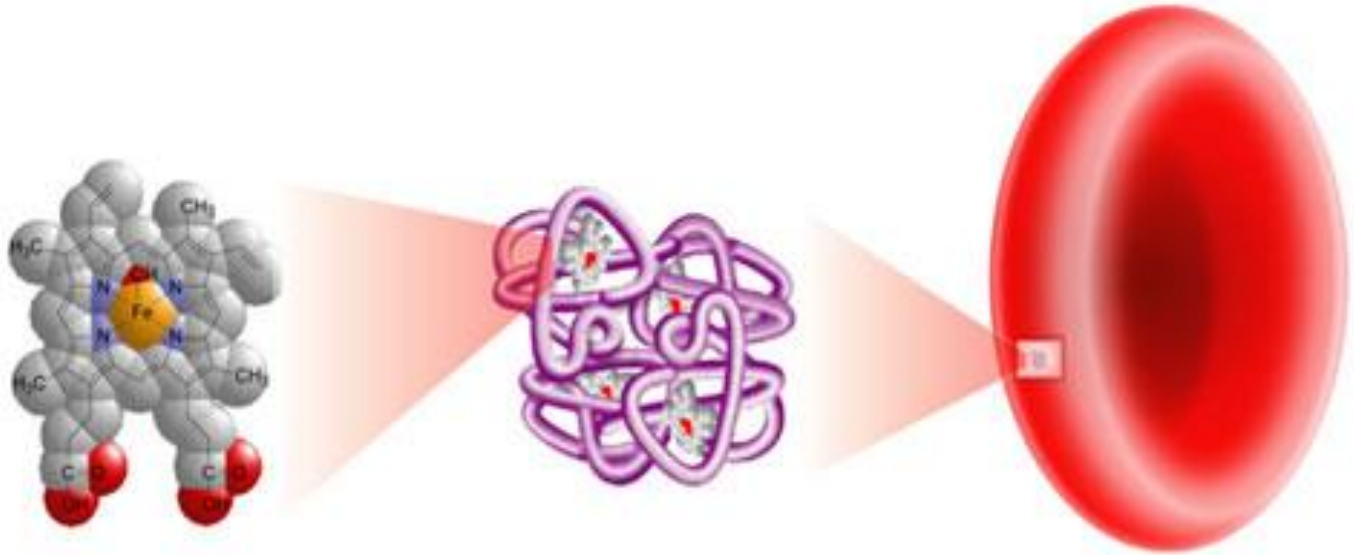
LEARNING OBJECTIVES

- Enlist the drugs used in the treatment of iron deficiency & Megaloblastic anemia
- Describe the various preparations of iron, vitamin B12 and Folic acid
- Describe the pharmacological basis/ role of iron in iron deficiency anemia (hypochromic normocytic anemia)
- Describe the pharmacological basis/ role of vitamin B12 and folic acid in megaloblastic anemia

LEARNING OBJECTIVES

- Classify the drugs used in anaemia
- Describe pharmacokinetics of Iron
- Describe the various oral and parenteral formulations of iron
- Describe the adverse effects of iron therapy
- Describe the drug treatment of Iron toxicity


CH3
CH=CH2
CH3
CH3
Fe
H2C—CH2
CH=CH2
O=C
OH
CH2
CH3
O=C—CH2


Heme
Hemoglobin
Erythrocyte

Types of anemia

Normochromic normocytic

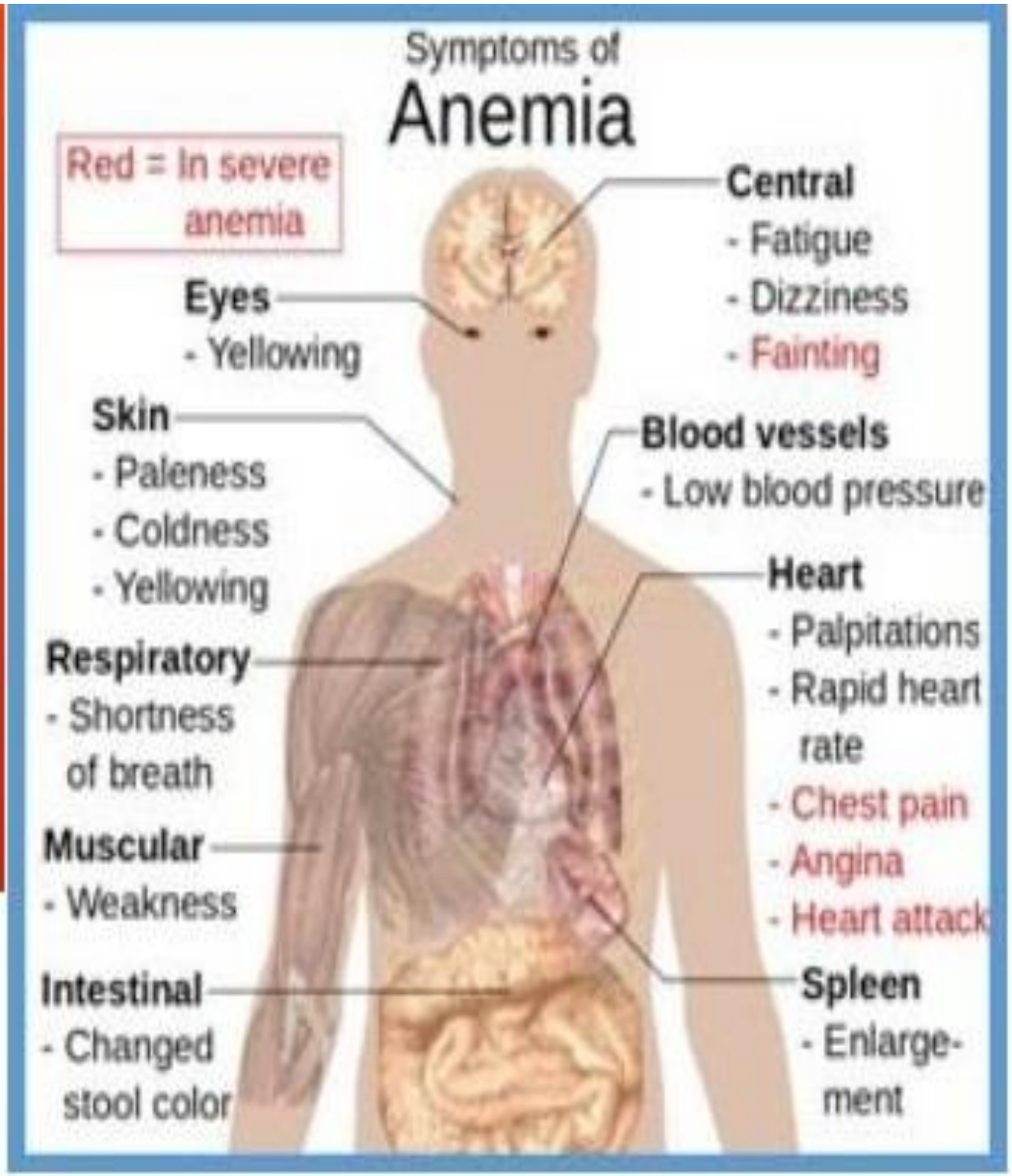
- Anemia of chronic disease
- Hemolytic anemia
- Aplastic anemia

Normochromic macrocytic

- Vitamin B12 deficiency
- Folate deficiency

Hypochromic microcytic

- Iron deficiency
- Thalassemia
- Anemia of chronic disease

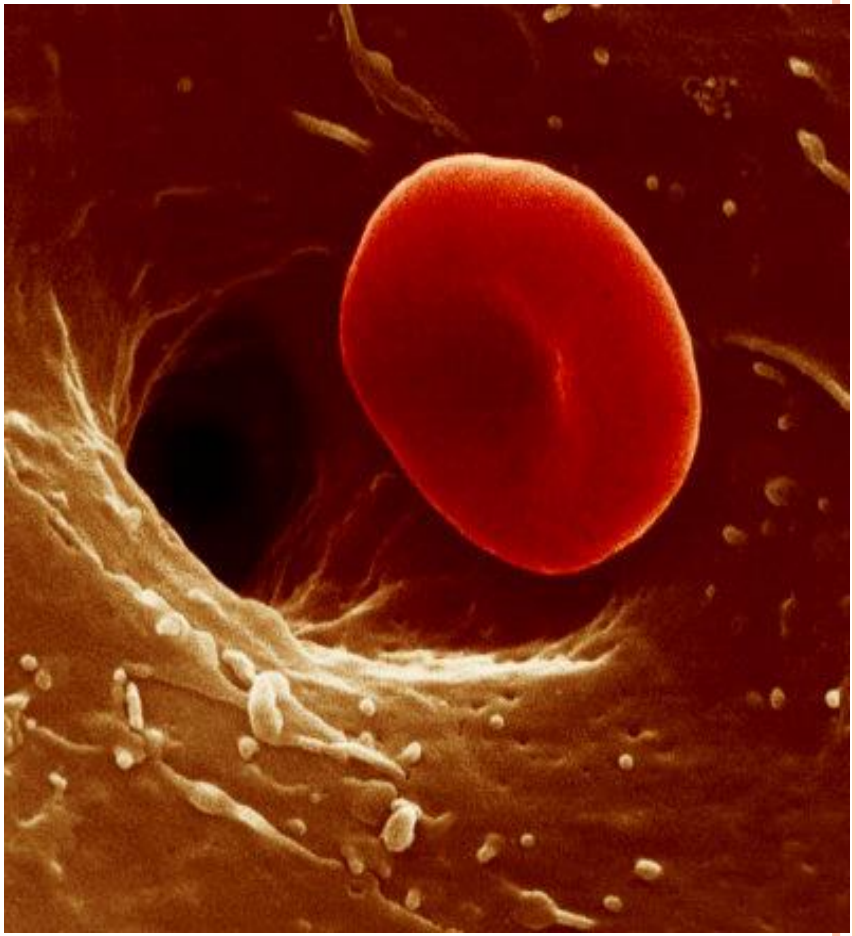

Symptoms of
Anemia
Red = In severe anemia
Central
- Fatigue
- Dizziness
- Fainting
Eyes
- Yellowing
Skin
- Paleness
- Coldness
- Yellowing
Blood vessels
- Low blood pressure
Heart
- Palpitations
- Rapid heart rate
- Chest pain
- Angina
- Heart attack
Respiratory
- Shortness of breath
Muscular
- Weakness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

IRON DEFICIENCY ANEMIA

Definition:

too low a body iron stores support RBC production

- Hemoglobin
  - Women <12
  - Men <13.5
- Hematocrit
  - Women <36
  - Men <41



PATHOPHYSIOLOGY

- Total iron body stores in 70 Kg adult man: 4 g
- A person with 5L of blood has 2.5 g of iron incorporated into Hb.
- Daily iron requirement : 20 – 25 mg
- Total daily intake : 10-15 mg
- Total daily absorption : 1 mg
- Daily iron destroyed 0.8%

MANAGEMENT

- Diet

Indications for therapy

Prevention of anemia

- Pregnancy
- Lactation
- Mennorhagia
- Patients with chronic renal disease
- Postoperative therapy

Treatment of anemia

Iron preparations

- **Oral**

- Ferrous sulphate
- Ferrous gluconate
- Ferrous fumerate

- **Parenteral**

  - Iron dextran (IM/IV)
  - Iron sucrose(IV)
  - Sodium ferric gluconate(IV)
  - Iron Sorbitol

ORAL

HEMATINICS

Oral iron preparations

- Avoid enteric coated or SR iron
- Avoid giving with food
- 250 mg ascorbic acid enhances absorption
- Ferrous sulphate, fumarate gluconate equal efficacy and side effect profile
- Low dose as efficacious with fewer side effects
- Use in patients with IBD controversial

2. ORAL IRON THERAPY

- Adequate in asymptomatic patients with established anemia iron deficiency anemia
- Common used iron salts:
  - Ferrous sulphate (30% elemental iron tabs.)
  - Ferrous gluconate (12% elemental iron tabs.)
  - Ferrous fumarate (33% elemental iron tabs.)
- DOSE
  - 1 tab. 2 to 3 times a day
  - Ideally, in empty stomach since food inhibit absorption

Pharmacokinetics

Absorption…25%

- Promoters
- Inhibitors

Elimination

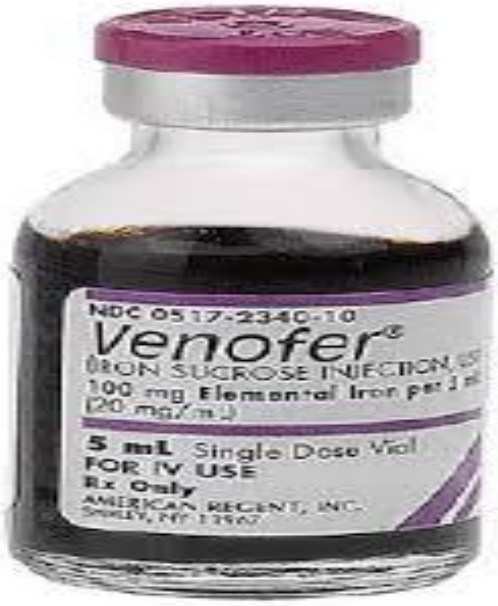
Duration of treatment

- 3-6months

Adverse effects (dose related)

- Nausea
- Epigastric discomfort
- Abdominal cramps
- Constipation
- Diarrhea
- Black stools

Parenteral therapy



Compound	Recommended dosing/ administration	Test dose recommended*
Iron dextran	100–200 mg IV; or total dose IV replacement if <1,500 mg	Yes
Ferric gluconate	125 mg IV	Yes
Iron sucrose	200–250 mg IV	No
Ferric carboxymaltose	15 mg/kg IV to total of 1,000 mg	No
Ferumoxytol	510 mg IV	No
Iron isomaltoside	500 mg IV	No

Pharmacokinetics

- **TDI…**
- Total dose iron Dextran infusion
- Office one-stop therapy.

- **Calculations ==** Ganzoni formula

  Total **iron** dose =

  [actual body weight × (15-actual Hb)] × 2.4
  + **iron** stores)

- **Adverse effects**
  - Local pain & tissue staining
  - Headache
  - Light-headedness
  - Fever
  - Arthralgias
  - Nausea, vomiting
  - Hypersensitivity reactions
- **Duration of treatment**

Acute Iron toxicity

Cause .....

Toxic doses:

- GI Toxicity:
  20mg/kg
- Moderate toxicity:
  40mg/kg
- Lethal toxicity:
  60mg/kg

Acute Iron toxicity

CLINICAL PRESENTATION

- Vomiting, Diarrhea
- Abdominal cramps
- Shock
- Dyspnea
- Severe metabolic acidosis
- Coma, death

Management of acute iron toxicity

- Gastric lavage
- General measures
- Iron chelation therapy

DEFEROXAMINE

- Source: Streptomyces pilosus
- MOA
  - ✓ Binds free iron in blood
- DOSE
  - ✓ 100mg binds 8mg iron

Clinical Pharmacology

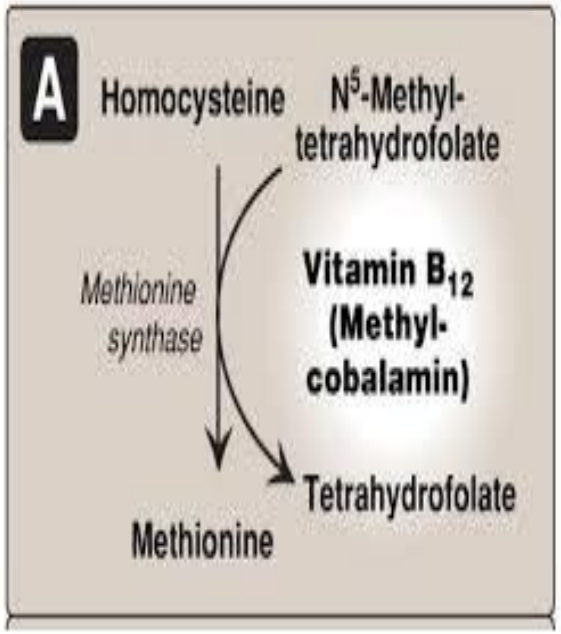
- **Parenteral iron therapy**
- Parenteral therapy should be reserved for
  - patients unable to tolerate or absorb oral iron
    - patients with various postgastrectomy conditions
    - patients with previous small bowel resection
    - inflammatory bowel disease
    - malabsorption syndromes
  - patients with extensive chronic blood loss who cannot be maintained with oral iron alone:
    - advanced chronic renal disease including hemodialysis and treatment with erythropoietin

COBALAMIN

(VITAMIN B 12)

- **Functions:**
- There are three vitamin B12 dependent enzymes using the vitamin B12 as a coenzyme.

1) Leucine transmutase.
2) Methyl malonyl CoA isomerase: which converts methyl malonyl CoA to succinyl CooA which is the final step in oxidation of odd number fatty acids required for myelin sheath formation, so vit B12 deficiency interfere with myelin sheath formation → progressive demyelination of nervous tissue → neurological disorders.
3) Methionine synthase:



Vit B 12 (Cobalamin)

- **Active forms:**
  - Deoxyadenosylcobalamin
  - Methylcobalamin
- **Therapeutically used:**
  - Cyanocobalamin
  - Hydroxocobalamin.
- **Source:** microbial synthesis from liver, eggs and dairy products.
- Chemistry: porphyrin like ring with a central cobalt atom attached to nucleotide.

Types of Vitamin B12 Compared

Cobalamin	Natural Form?	Bioactive Coenzyme?	Conversion steps necessary	Sustained Release	Special Effect
Cyanocobalamin 'the synthetic B12'	no	no	4	average to poor	No particular effect
Hydroxocobalamin 'the long lasting B12'	yes	no	3	very good	Detoxification of cyanide & NO
Methylcobalamin 'the DNA & nerves B12'	yes	yes	0	average	DNA, brain, nerves, blood, detoxification
Adenosylcobalamin 'the energy B12'	yes	yes	0	average	Energy, muscles, brain, DNA

METHYLCOBALAMIN Vs CYANOCOBALAMIN

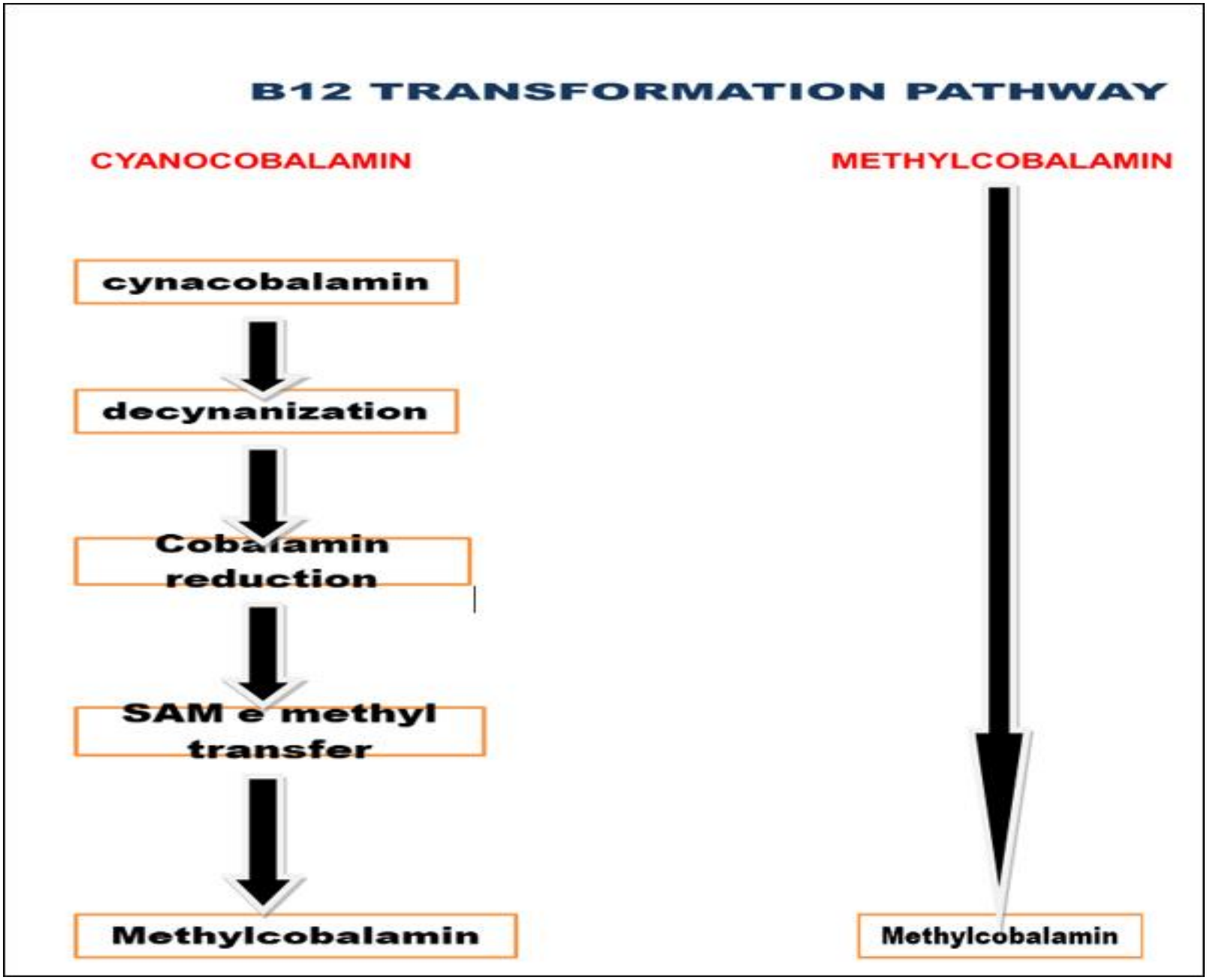
	Methylcobalamin	Cyanocobalamin
Nature	Natural	Synthetic
Chemistry	active form	inactive form, cyanide group, slightly toxic form
Absorption	low absorption rate	Stable, high absorption rate
Distribution	High plasma protein binding	Low protein binding
Metabolism	Direct active form	Converted to methylcobalamin and adenosylcobalamin taking almost 48hrs. Detoxification required for cyanide
Excretion	Higher retension time. Can be used in liver and renal toxicity.	Not advised in renal or liver toxicity. Eliminated fastly
Safety	Safe when compared to other forms	Least safe of all forms
Efficacy	Good compared to other forms	Least efficacious.
Commercial	Costly	Very cheap

	Methylcobalamin	Adenosylcobalamin
Functions[1]	• Required for synthesis of methionine, from homocysteine • Required for methyl donor used in methylation reactions (including within DNA, RNA, and proteins) to prevent alterations in gene expression	• Required by the citric acid cycle (for ATP production) • Required for energy production from lipids and proteins • Required for synthesis of hemoglobin
Metabolic fate[2]	• Found in the cytoplasm, and it predominates in blood and in other body fluids	• Major form in cellular tissues stored in the mitochondria

VIT. B 12 (COBALAMIN)

FORMULATIONS

- Tablets
- Injections : 1000 mcg/ml

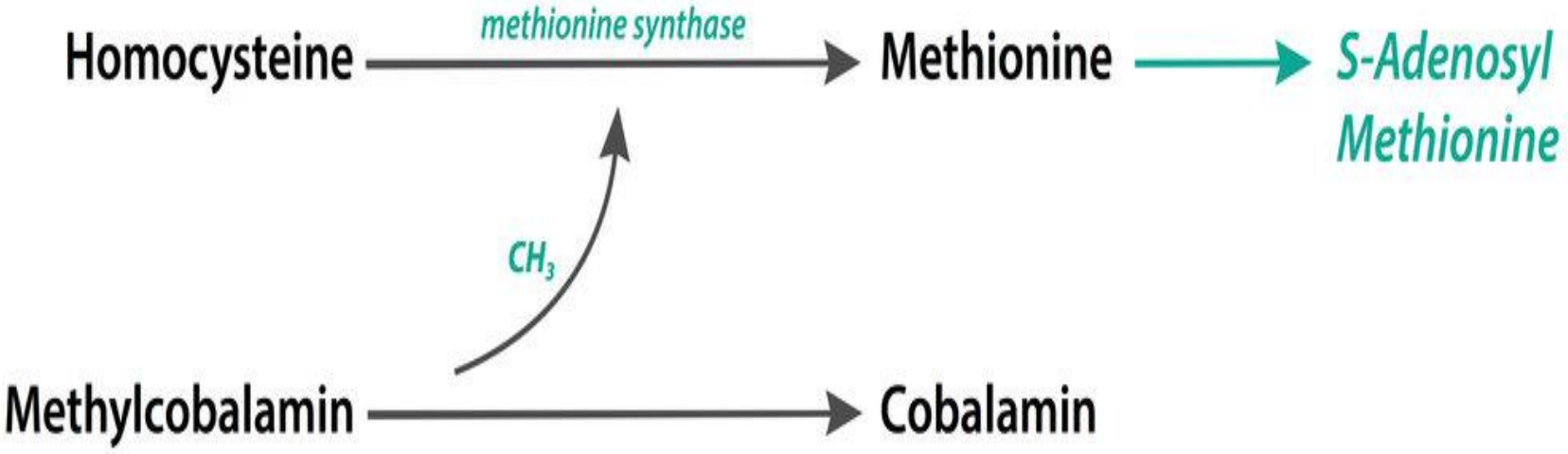

B12 TRANSFORMATION PATHWAY
CYANOCOBALAMIN
METHYLCOBALAMIN
cynacobalamin
decynanization
Cobalamin reduction
SAM e methyl transfer
Methylcobalamin
Methylcobalamin

VITAMIN B12 DEFICIENCY

- Megaloblastic, macrocytic anemia
- Mild or moderate leukopenia or thrombocytopenia
- Neurologic syndrome (paresthesias in peripheral nerves, weakness)
- Progresses to spasticity, ataxia and CNS dysfunction.

MECHANISM OF PERIPHERAL NEUROPATHY

- Methionine _____ S-adenosyl methionine (SAM)
- SAM is required as a methyl donor in myelin synthesis reactions



PERNICIOUS ANEMIA

- Defective secretion of intrinsic factor.

Treatment :

- Treatment depends upon the cause of the deficiency
  - If the cause is malabsorption,
  - Parenteral injections of vit B12 cyanocobalamine or hydroxocobalamine.
  - vitamin B12 can be administered intranasally as a spray or gel.

FOLIC ACID

(Pteroyl monoglutamic acid)

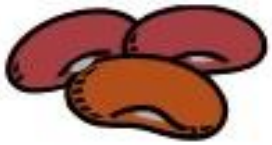
Folic acid

Needed for

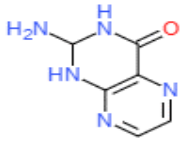
1. Synthesis of DNA
2. Normal maturation of RBC and WBC
3. Synthesis of Purine and Pyrimidine

Folate VS Folic acid

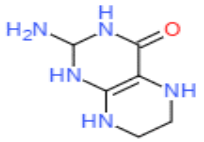
- Natural (complex) form
  - ✓ Foods such as dark-green leafy vegetables, broccoli, asparagus, lentils, beans, peanuts, strawberries, kiwi, orange juice, liver
  - ✓ Can be lost throught processing and cooking
  - ✓ ***Absorption : 50%***



- Synthetic (simple) form
  - ✓ Fully oxidized form, Pteroylmonoglutamic acid
  - ✓ Have only one glutamate molecule attached
  - ✓ Used in nutritional supplements and food fortification
  - ✓ Only form that can be transported across membranes
  - ✓ ***Absorption : ~93%***



Folic Acid

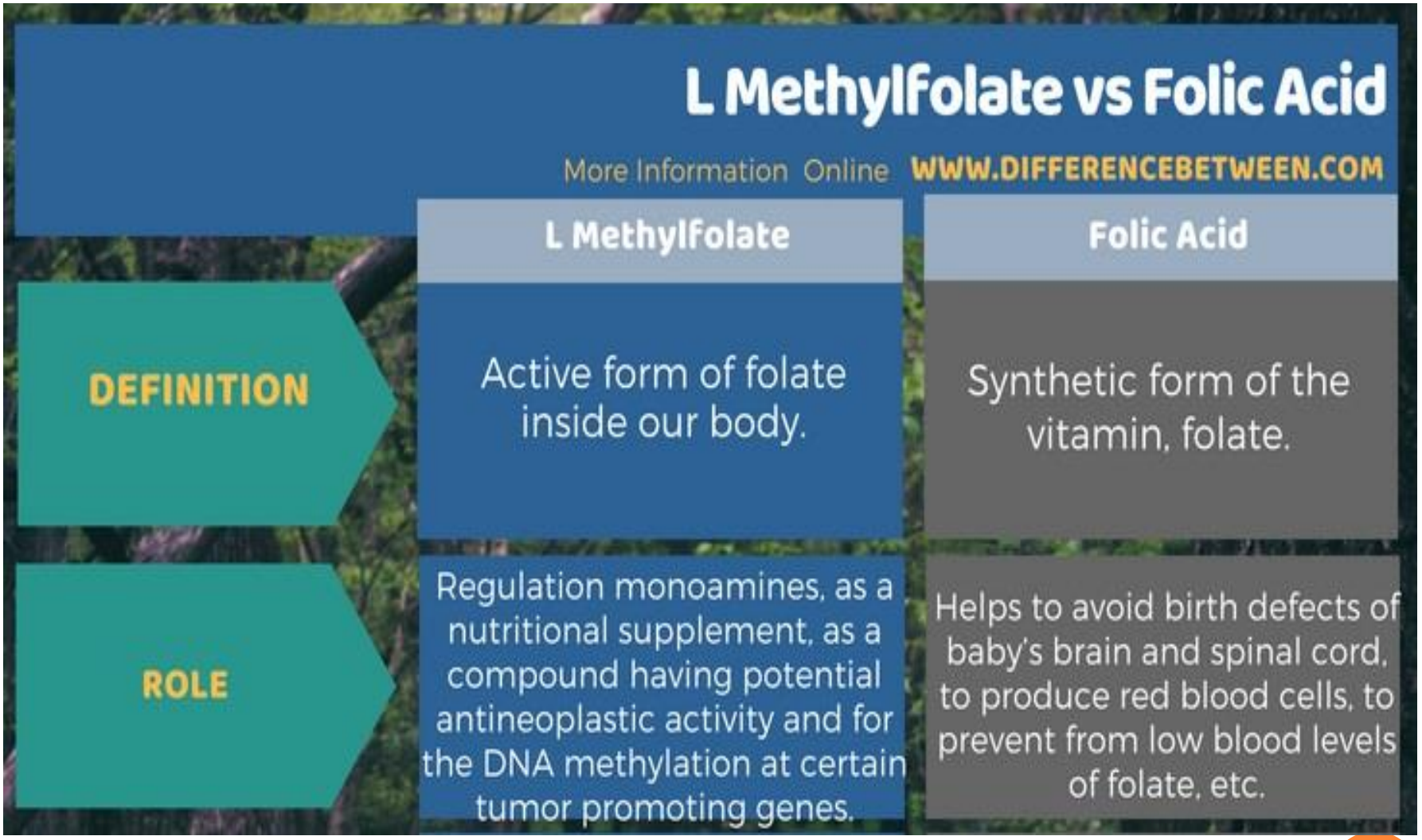


Folate

Folate transporter

- **Folic acid is actively transported across the jejunum, and perhaps the duodenum, by an Na^+-coupled, carrier-mediated process that is stimulated by glucose and shows a pH maximum at about pH 6.**
- **The transporter is a transmembrane protein with much greater affinities for folic acid than for reduced folates.**

Combs GF. The Vitamins. Fundamental Aspects in Nutrition and Health. Elsevier Inc. 2008.


L Methylfolate vs Folic Acid
More Information Online WWW.DIFFERENCEBETWEEN.COM
L Methylfolate
Folic Acid
DEFINITION
Active form of folate inside our body.
Synthetic form of the vitamin, folate.
ROLE
Regulation monoamines, as a nutritional supplement, as a compound having potential antineoplastic activity and for the DNA methylation at certain tumor promoting genes.
Helps to avoid birth defects of baby's brain and spinal cord, to produce red blood cells, to prevent from low blood levels of folate, etc.

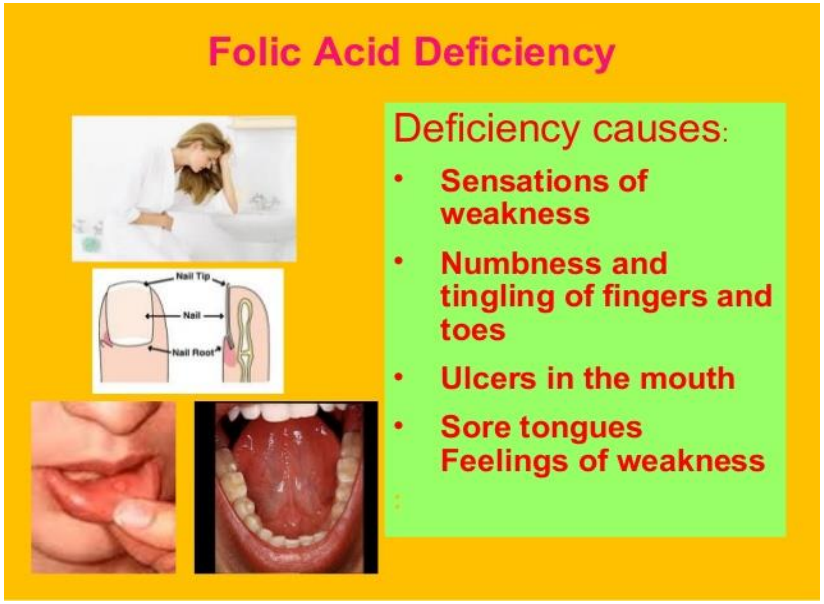
FOLIC ACID DEFICIENCY

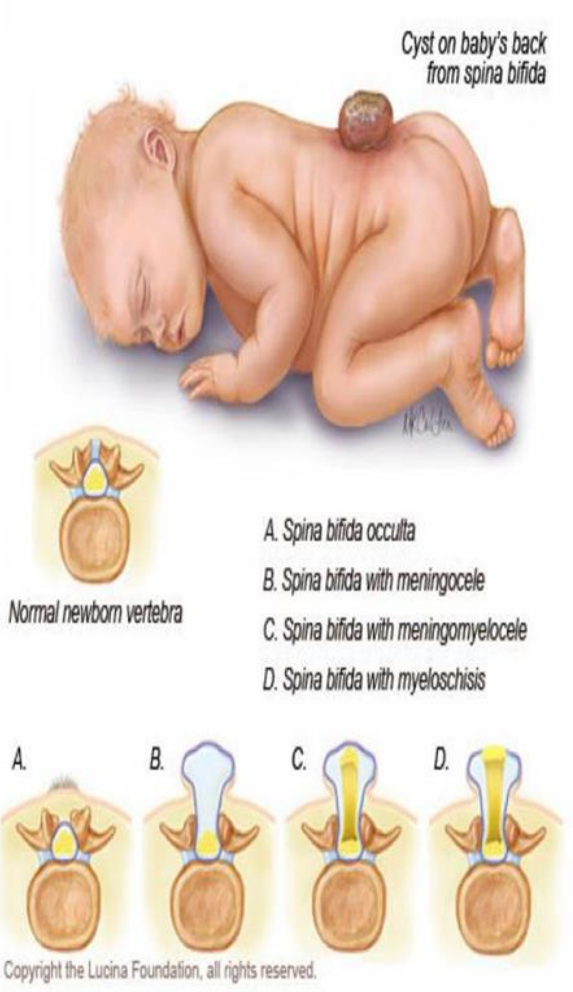
SEEN IN:

- Inadequate dietary intake of folates
- Prolong cooking
- In alcoholics & in pt. with liver diseases
- Pregnancy
- Hemolytic Anemias
- Malabsorption Syndrome

Clinical features

- Megaloblastic anemia
- Epithelial damage
- Neural tube defects

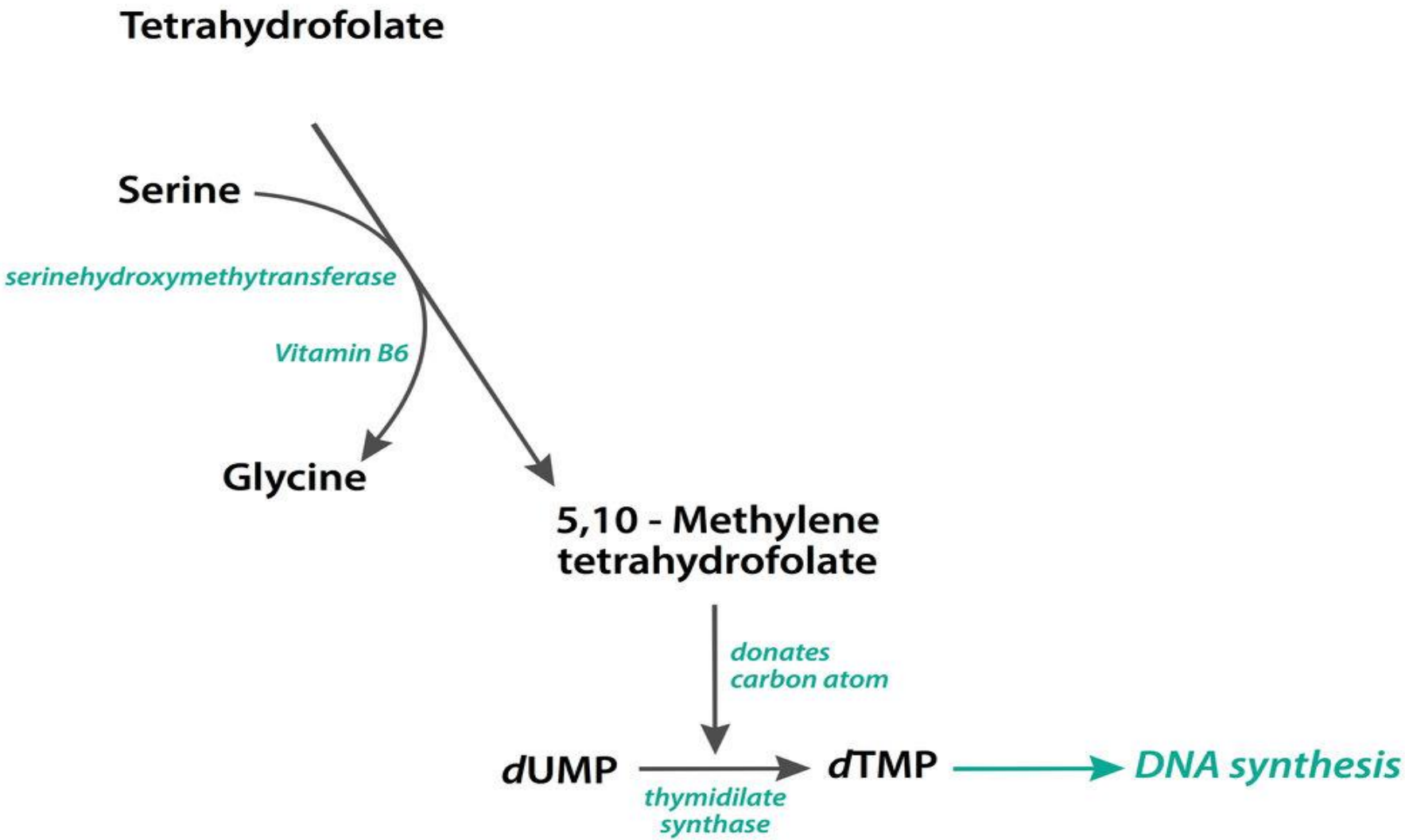




Pharmacokinetics:

- Site of absorption: Proximal jejunum
- Polyglutamates _____ Monoglutamate
- Folic acid reduced to dihydrofolate and tetrahydrofolate
- Transported in blood as methyl-THFA
- Stored in the liver as methyl-THFA
- Enterohepatic circulation occurs

PHARMACODYNAMICS:



PHARMACODYNAMICS

- Functions as a coenzyme
- FA→DHFA →THFA
- THFA mediates one carbon transfer reactions (methyl group)
- Purines :de novo synthesis requires THFA
- Also required for the synthesis of Amino acids: conversion of serine to glycine

THERAPEUTIC USES

- Folic acid deficiency; diet / malabsorption
- Gestation
- Drugs: interfering in absorption& metabolism
  - Methotrexate
  - Trimethoprim
  - Phenytoin
  - Anti-convulsants
  - Oral contraceptives
  - Isoniazid.

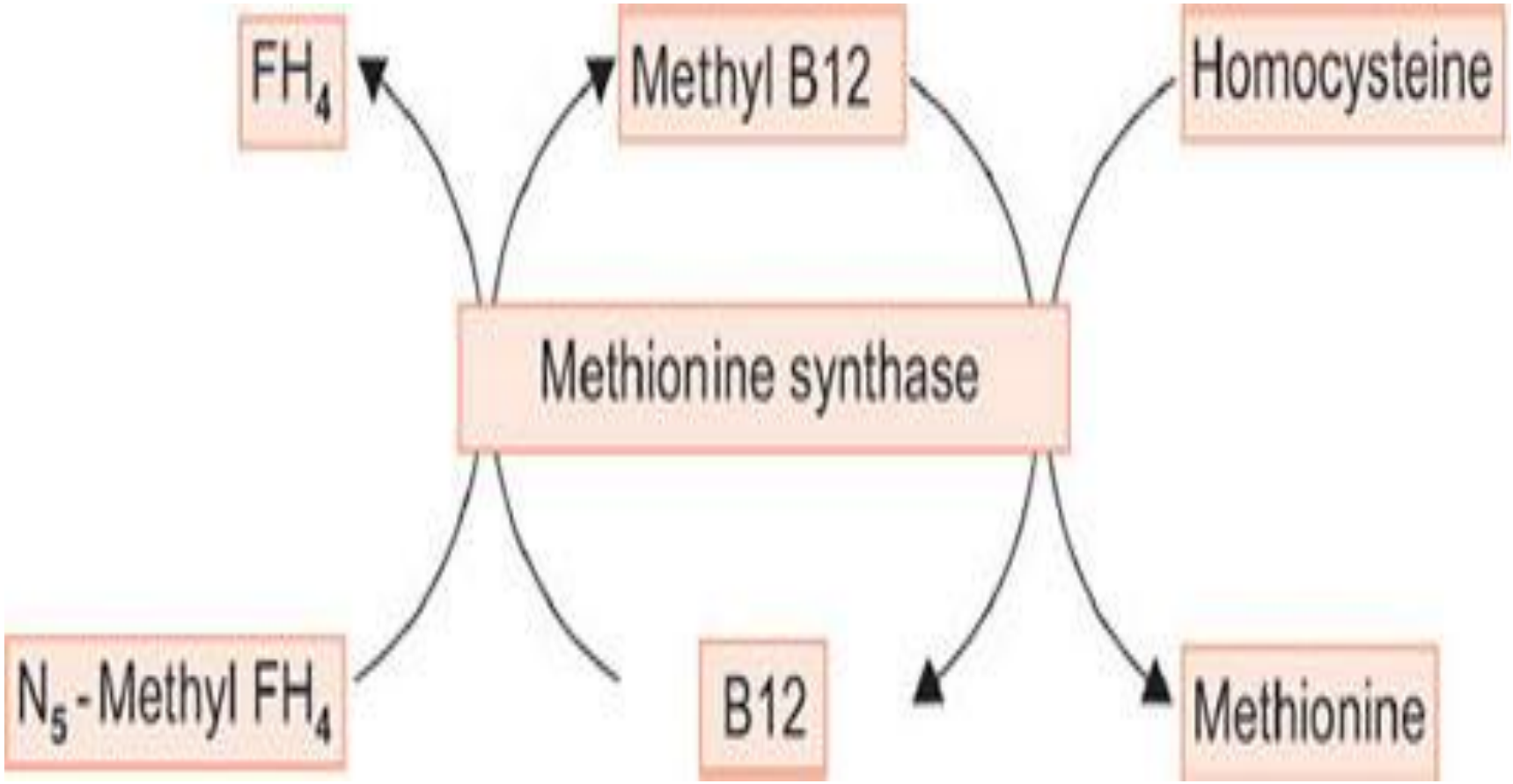
THERAPEUTIC USES

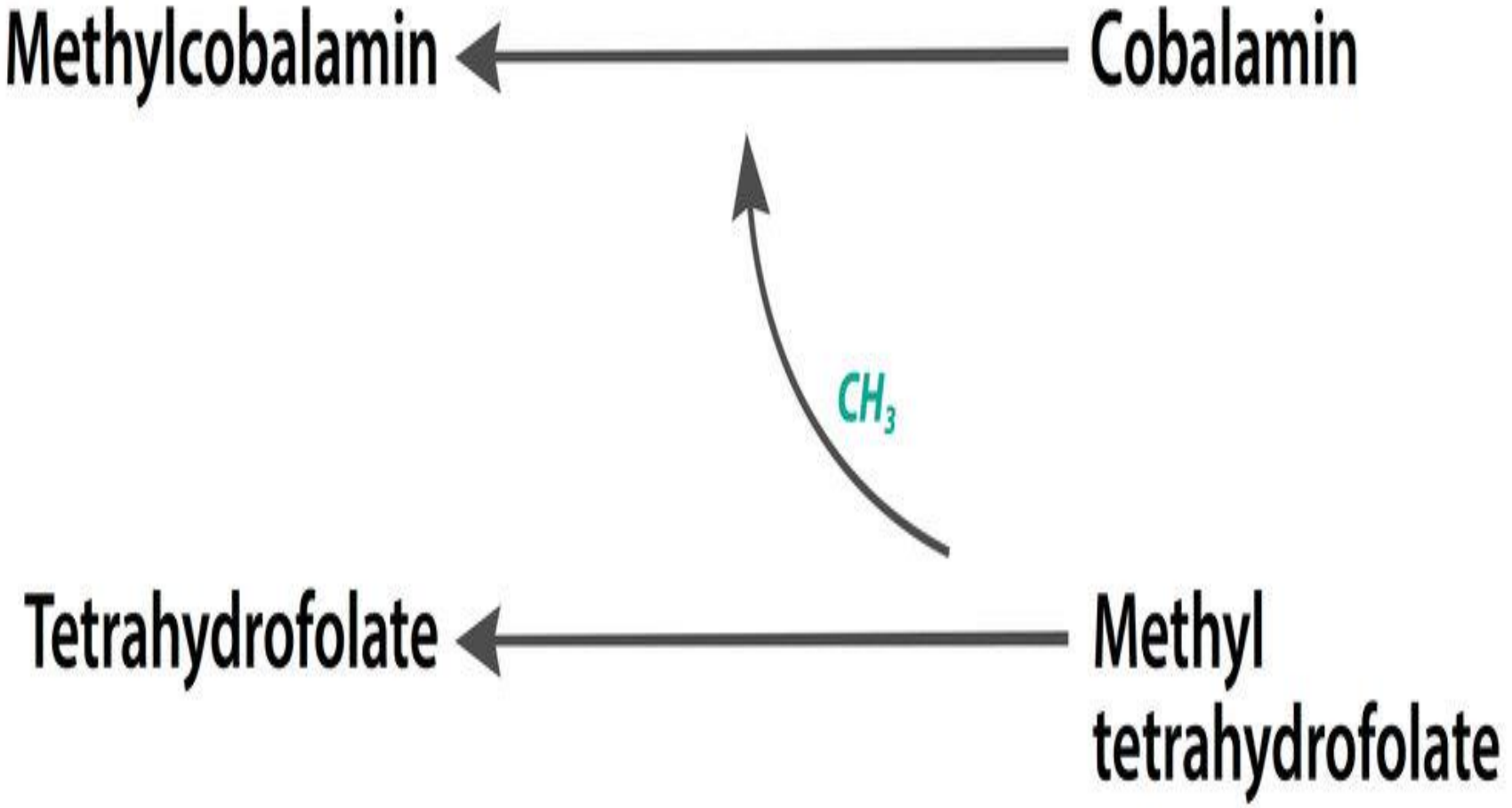
- Patients on Hemodialysis
- Deficiency associated with
  - Cancers
  - Leukemia
  - Certain skin disorders
  - Chronic debilitating disease

METHYL FOLATE TRAP

- Accumulation of folate as N5 – methyltetrahydrofolate and the associated depletion of tetrahydrofolate co-factors in vitamin B12 deficiency.

- Metabolism of vit B12 and folic acid is linked


FH4
Methyl B12
Homocysteine
Methionine synthase
N5-Methyl FH4
B12
Methionine


Methylcobalamin
Cobalamin
CH_3
Tetrahydrofolate
Methyl
tetrahydrofolate

CLINICAL PHARMACOLOGY

Methotrexate – Folate Antagonist

- MOA:
  - Structures MTX and folic acid similar
  - MTX actively transported mammalian cells and inhibits dihydrofolate reductase
  - the enzyme that normally converts dietary folate to the tetrahydrofolate form required for thymidine and purine synthesis
- Leucovorin rescue:
  - Administered as a plan in MTX therapy
  - Leucovorin (Folinic acid) is directly converted to tetrahydrofolic acid - production of DNA cellular protein inspite of presence of MTX
  - Used to rescue bone marrow and GIT mucosal cells

Folinic Acid vs Methylfolate

More Information Online WWW.DIFFERENCEBETWEEN.COM

	Folinic Acid	Methylfolate
DEFINITION	Folinic acid or leucovorin is a medication used to decrease the toxic effects of methotrexate and pyrimethamine.	Methylfolate or Levomefolic is a medication used for DNA reproduction, cysteine cycle and regulation of homocysteine.
NATURE OF THE DRUG	A metabolically active form of folate.	Primary biologically active form of folate.
CHEMICAL FORMULA	C20H23N7O7	C20H25N7O6
MOLAR MASS	473.44 g/mol	459.46 g/mol
ROUTE OF ADMINISTRATION	Via oral, injection to muscle or vein	Via oral, transdermal, subcutaneous routes.
SIDE EFFECTS	Trouble sleeping, allergic reactions and fever	Irritability, sore muscles, achy joints, acne, rash and other allergic reactions.

ERYTHROPOETIN

TYPES

- Recombinant human erythropoietin (epoetin alfa)
- Darbepoetin alfa
- Methoxy polyethylene glycol epoetin beta

PHARMACODYANAMICS

- Erythropoietin stimulates proliferation and differentiation
- Erythropoietin receptors on red cell progenitors.
- Erythropoietin receptor: cytokine receptors (JAK/STAT)
- Increased production of RBCs

REFERENCES

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  Bertram G. Katzung

- **Katzung & Trevor's Pharmacology: Examination & Board Review, 12th Edition**

- **Lippincott illustrated review Pharmacology: 6th Edition**

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