biochemistry

LEC.2

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22/9/2013

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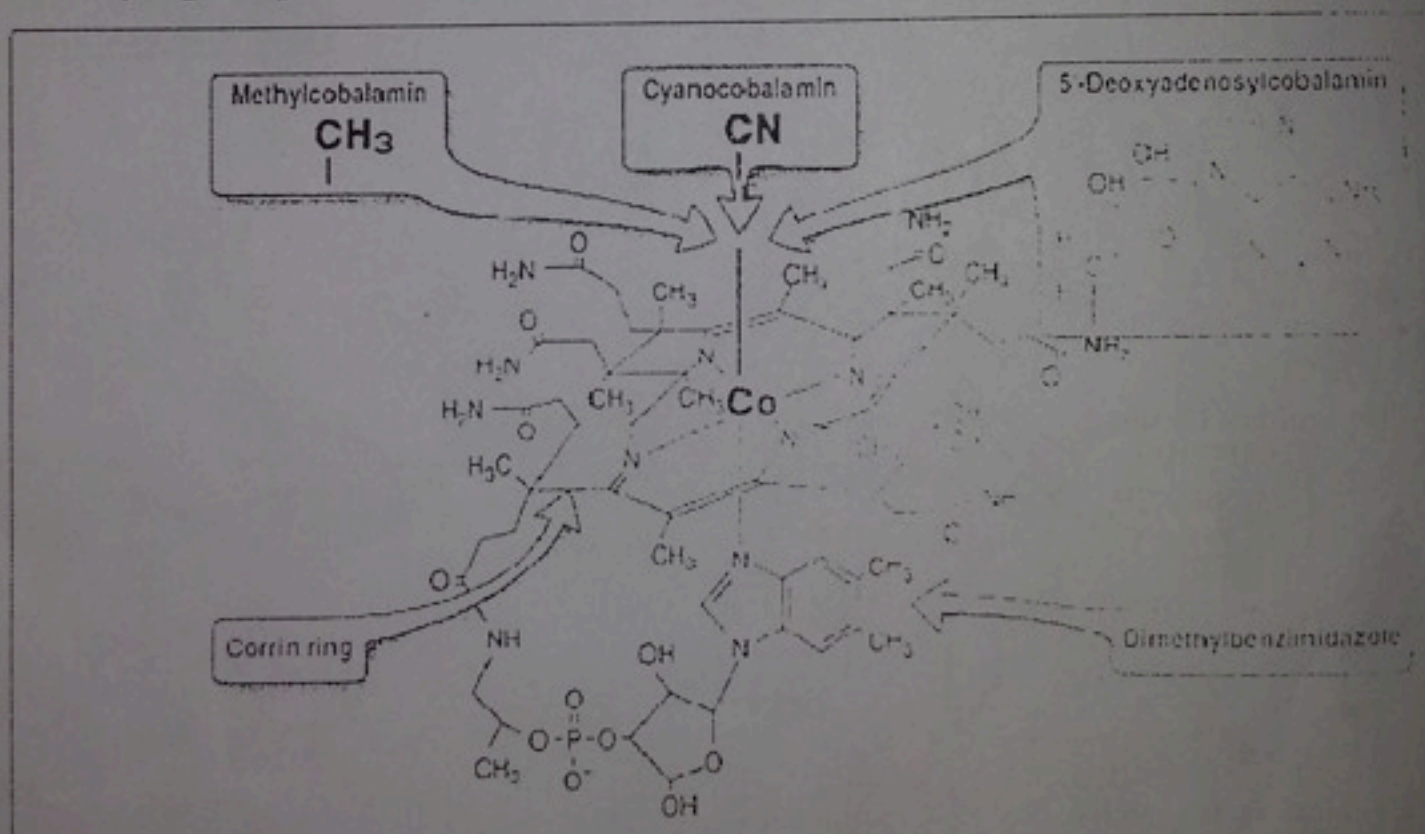
Lec.:٢

Cobalamin:

Cobalamin is more commonly known as **vitamin B١٢**. Vitamin B١٢ is composed of a complex tetrapyrrol ring structure (corrin ring) and a cobalt ion in the center. Cobalt bond to cyanide in commercial preparations of the vitamin in the form of cyanocobalamin.

Active form of vitamin B١٢:

The coenzyme forms of cobalamin are 5'-deoxyadenosylcobalamin, in which cyanide is replaced with 5'-deoxyadenosine (forming an unusual carbon-cobalt bond), and methylcobalamin, in which cyanide is replaced by a methyl group

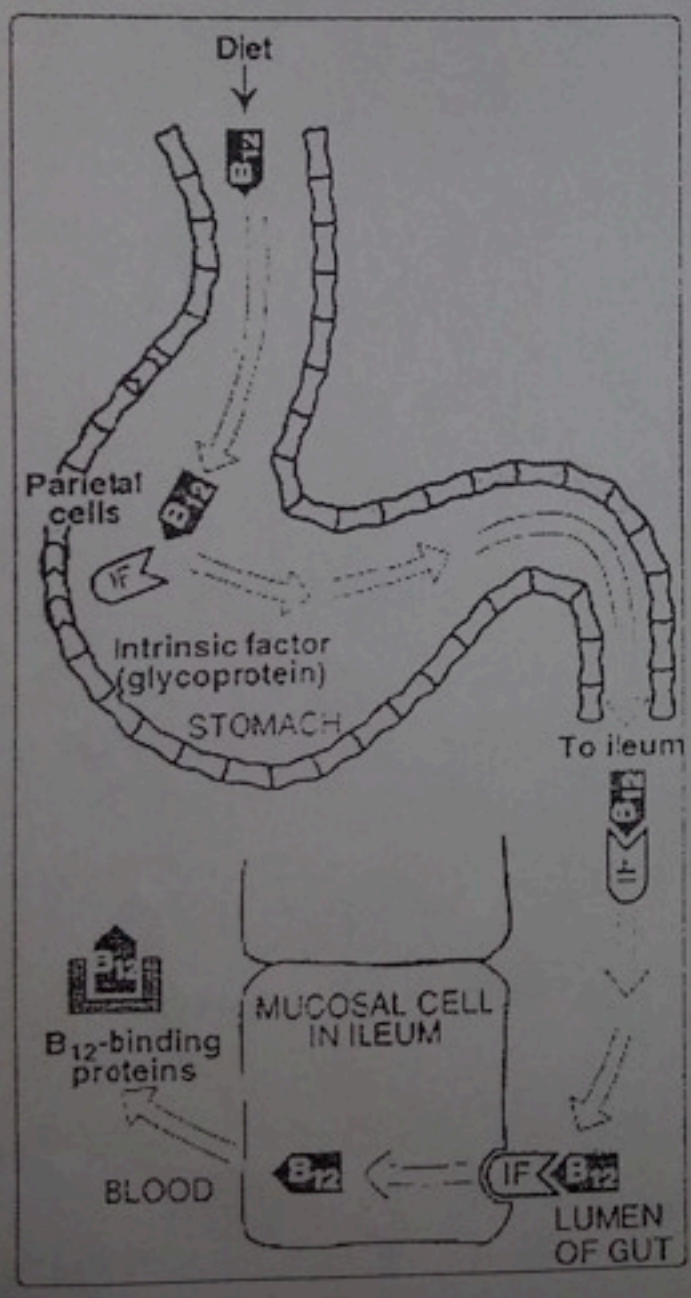


Distribution of cobalamin:

Cobalamin is present in appreciable amounts in liver, whole milk, eggs, oysters, fresh shrimp, and chicken.

metabolism of vitamin B١٢:

- Normally, vitamin B١٢ obtained from the diet binds to a glycoprotein called intrinsic factor (gastric parietal cells are responsible for the synthesis of the intrinsic factor) . The cobalamin–intrinsic factor complex travels through the gut and eventually binds to specific receptors on the surface of mucosal cells of the ileum.
- The bound cobalamin is transported into the mucosal cell and, subsequently, into the general circulation, where it is carried by B١٢-binding proteins which is called **transcobalamin II which is needed for transport to the tissues. It is stored in the liver bound transcobalamin I.**

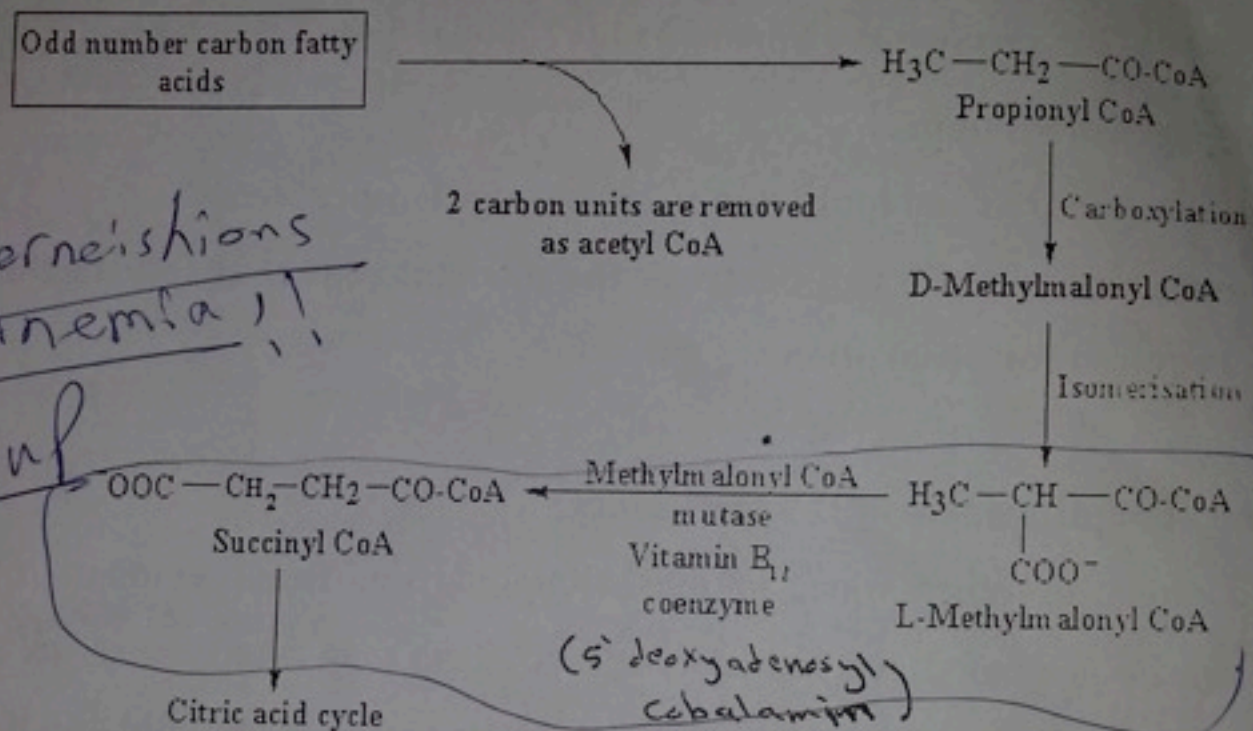


Deficiency of B12 is not easy !!

Biochemical Function of B١٢:

There are only two clinically significant reactions in the body that require vitamin B١٢ as a cofactor:

١. During the catabolism of fatty acids with an odd number of carbon atoms and the amino acids valine, isoleucine and threonine . One of the enzymes in this pathway, ***methylmalonyl-CoA mutase***, requires vitamin B١٢ as a cofactor (5` deoxyadenosylcobalamin).



Pernicious Anemia !!

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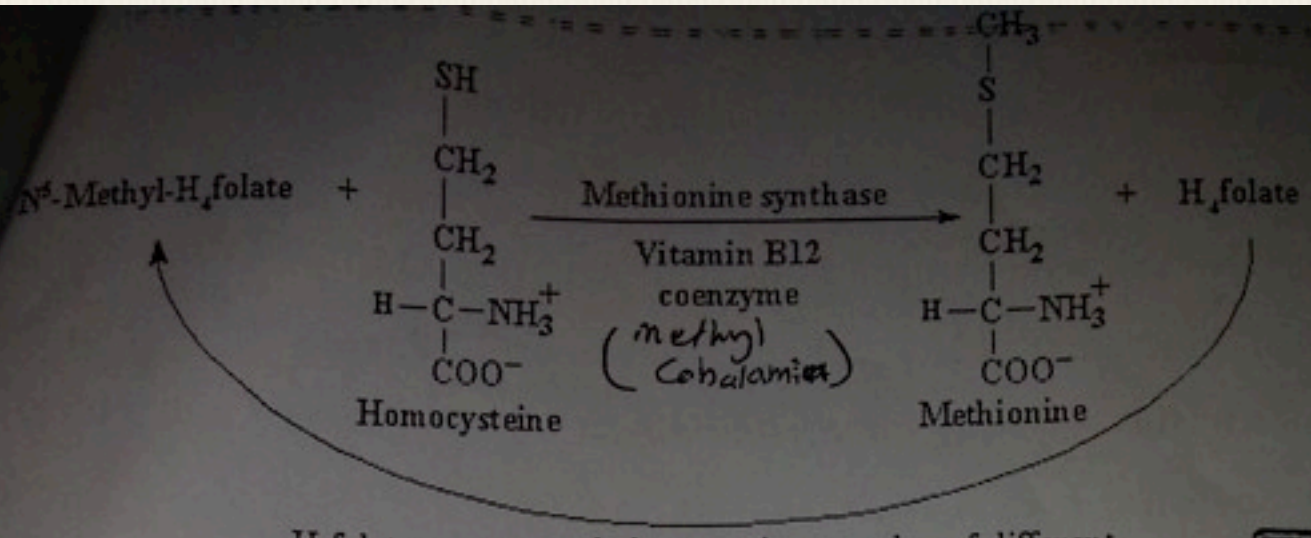
٢. The second reaction requiring vitamin B١٢ catalyzes the conversion of homocysteine to methionine and is catalyzed by ***methionine synthase***.

Homocystine —methylcobalamin→ methionine

N^5-Methyl-H4Folate (CH3) The active form of folic acid



Deficiency of vitamin B_{12}

Deficiency more commonly due to an absorption problem.

Auto immune disease can destroys the parietal cells that secrete the I.F. required for absorption.

Clinical Significances of B_{12} Deficiency:

In contrast to other water-soluble vitamins, significant amounts of vitamin B_{12} are stored in the body. As a result, it may take several years for the clinical symptoms of B_{12} deficiency to develop in individuals who have had a partial or total gastrectomy (who, therefore, become intrinsic factor-deficient), and can no longer absorb the vitamin.

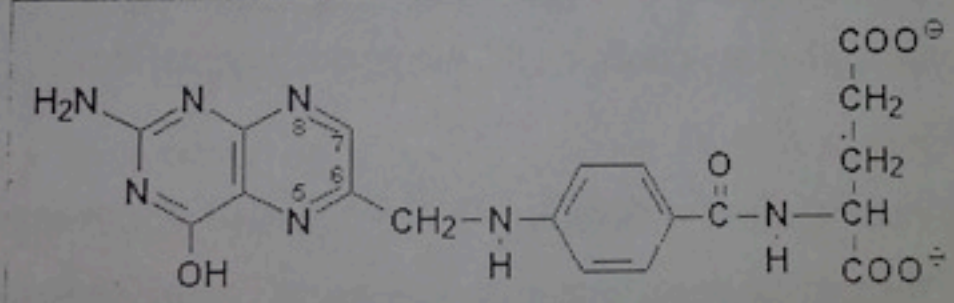
When the vitamin is deficient, abnormal fatty acids accumulate and become incorporated into cell membranes, including those of the nervous system. This may account for some of the neurologic manifestations of vitamin B_{12} deficiency.

- The effects of cobalamin deficiency are most in rapidly dividing cells, such as the erythropoietic tissue of bone marrow and the mucosal cells of the intestine.

- cobalamin deficiency is hypothesized to lead to a deficiency of the tetrahydrofolate forms needed in purine and thymidine synthesis. resulting in the symptoms of megaloblastic anemia.
- Pernicious anemia: is a megaloblastic anemia resulting from vitamin B_{12} deficiency that develops as a result a lack of intrinsic factor in the stomach leading to malabsorption of the vitamin. The anemia results from impaired DNA synthesis due to a block in purine and thymidine biosynthesis. The block in nucleotide biosynthesis is a consequence of the effect of vitamin B_{12} on folate metabolism. When vitamin B_{12} is deficient essentially all of the folate becomes trapped as the N^5-methylTHF derivative as a result of the loss of functional ***methionine synthase***.

Neurological complications also are associated with vitamin B_{12} deficiency and result from a progressive demyelination of nerve cells.

Folic Acid:



Folic **Acid**

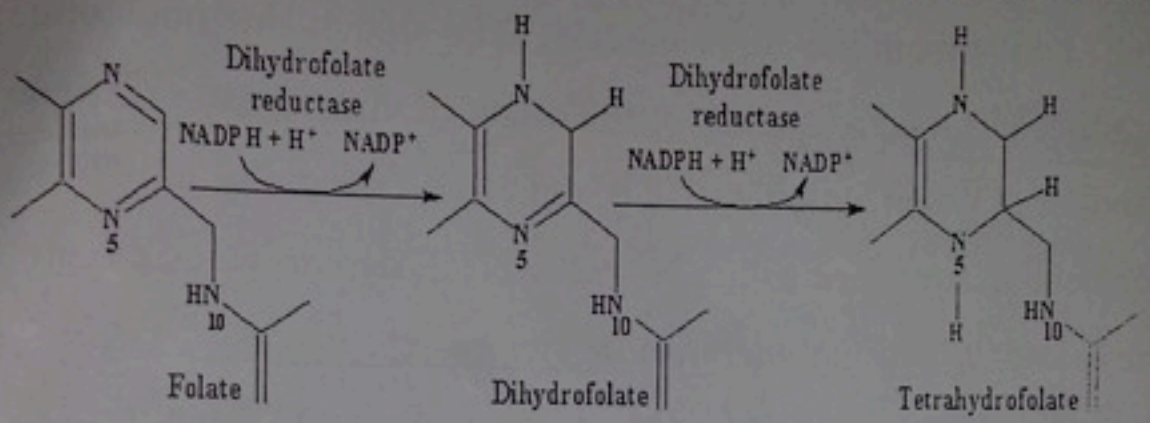
positions ٧ & ٨ carry hydrogens in dihydrofolate (DHF)

positions ٥-٨ carry hydrogens in tetrahydrofolate (THF)

Folic acid is a conjugated molecule consisting of a pteridine ring structure linked to para-aminobenzoic acid (PABA) that forms pteroic acid. Folic acid itself is then generated through the conjugation of

glutamic acid residues to pteroic acid. Folic acid is obtained primarily from yeasts and leafy vegetables as well as animal liver. Animal cannot synthesize PABA nor attach glutamate residues to pteroic acid. thus. requiring folate intake in the diet.

Folic acid is reduced within cells (principally the liver [illegible]) to tetrahydrofolate (THF also H_4folate) through the action of ***dihydrofolate reductase*** **(DHFR)**, an NADPH-requiring enzyme.



The function of THF derivatives is to carry and transfer various forms of one carbon units during biosynthetic reactions. The one carbon units are either methyl, methylene, methenyl, formyl or formimino groups. These one carbon transfer reactions are required in the biosynthesis of serine, methionine, glycine, choline and the purine nucleotides .

[illegible]

also cause anemia!

Clinical Significance of Folate Deficiency

Folate deficiency results in complications nearly identical to those described for vitamin B_{12} deficiency. The most pronounced effect of folate deficiency on cellular processes is upon DNA synthesis.

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١. The result is **megaloblastic anemia** as for vitamin B١٢ deficiency. The due to inability to synthesize DNA during erythrocyte maturation leads to abnormally large erythrocytes term of macrocytic anemia.

٢. **Folate and neural tube defects in the fetus:** Spina bifida and anencephaly, the most common neural tube defects, in fetus of mother with folic acid deficiency, so Folic acid supplementation before conception and during the first trimester has been shown to significantly reduce the defects. Therefore, all women of childbearing age are advised to consume ٠.٤ mg/day of folic acid to reduce the risk of having a pregnancy affected by neural tube defects.

Causes of folate deficiency:

Folate deficiencies are rare due to the adequate presence of folate in food. Poor dietary habits can lead to folate deficiency. The predominant causes of folate deficiency are: impaired absorption or metabolism or an increased demand for the vitamin. The predominant condition requiring an increase in the daily intake of folate is pregnancy. This is due to an increased number of rapidly proliferating cells present in the blood. The need for folate will nearly double by the third trimester of pregnancy. Certain drugs such as anticonvulsants and oral contraceptives can impair the absorption of folate. Anticonvulsants also increase the rate of folate metabolism.

Summary:

١. Active form of vitamin B ١٢ are : ٥'-deoxyadenosylcobalamin. and methylcobalamin.

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٢. Impaired methylmalonyl CoA mutase causes accumulation of unusual odd number carbon fatty acids. These accumulate in nerve cell membranes causing irreversible neurological disorders.

٣. Impaired methionine synthase traps H^4folate as N^5-methyl-H^4folate ("folate trap").This can lead to a secondary or artificial deficiency of folic acid.

٤. One of the main symptoms of folic acid deficiency is anaemia.
Anaemia due to a true folic acid deficiency it is megaloblastic anaemia.
Anaemia due to secondary folic acid deficiency caused by primary B_{12} deficiency is pernicious anaemia

٥. Anaemia could be due to folic acid deficiency or vitamin B_{12} deficiency.

٦. In either case folic acid would cure the anaemia but if the true underlying deficiency involved vitamin B_{12} the patient would still go on to develop the irreversible neurological disorders.

٧. For this reason such patients are always given folic acid and vitamin B_{12} supplements until the true cause of the anaemia is identified.

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