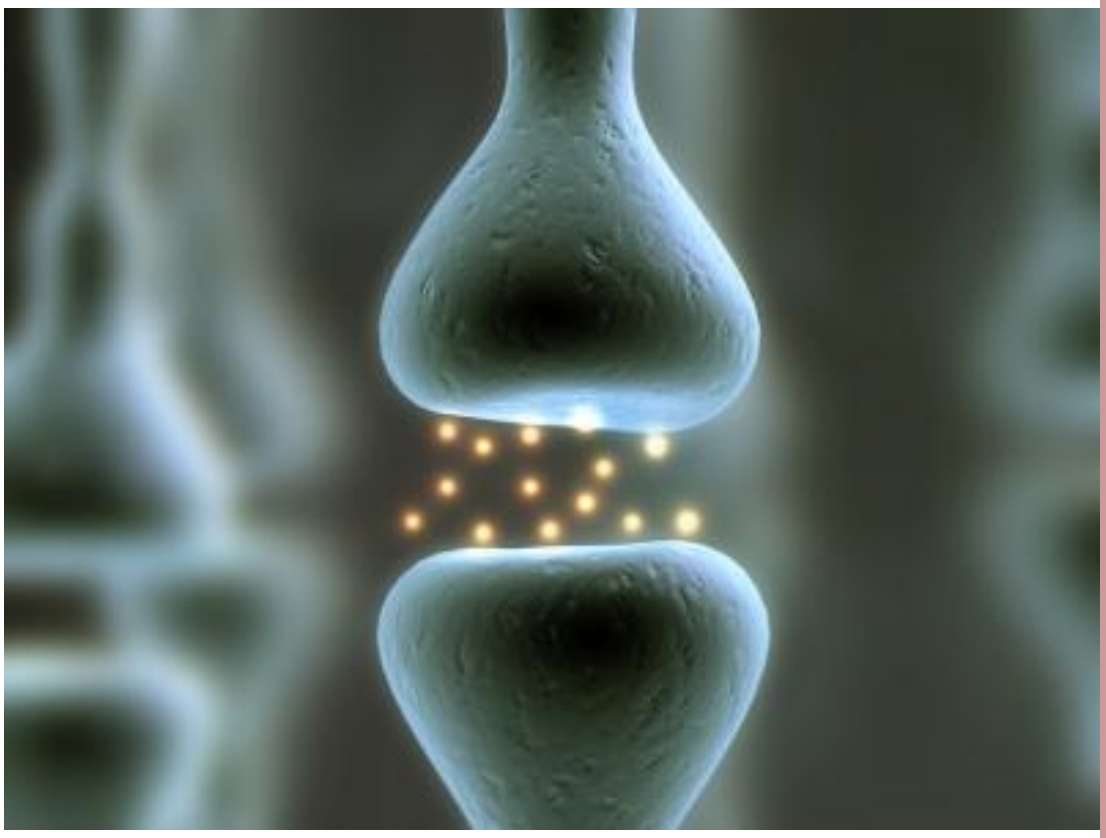
Biochemistry of the CNS



6th lecture:

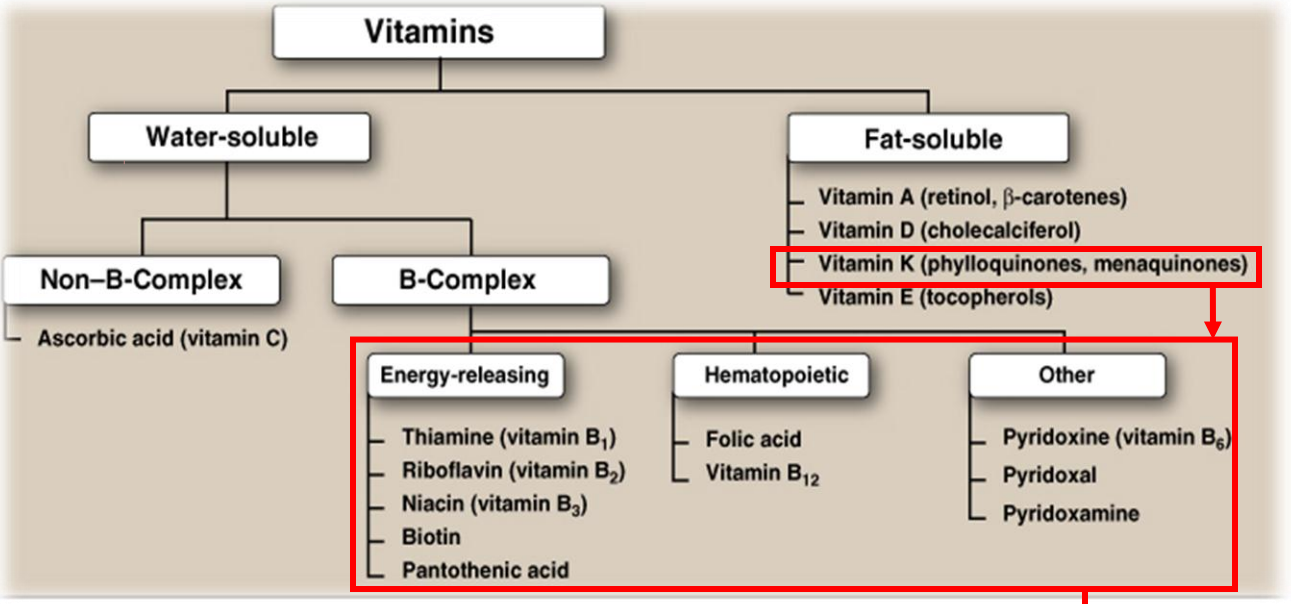
Vitamins B_6 and B_{12}

Done by:

Aliya Alawaji

Mohammed Alanazi

Classification of Vitamins: *very important*



Hematopoietic = involved in blood cell formation.

They are functioning as **co- enzyme,** BUT only one vitamin of the **fat soluble** vitamins acts as **co-enzyme→ vitamin K**

Water-soluble vitamins:

- B vitamins:
  - Thiamin (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), cobalamin (B_{12}), folate.
- Not significantly **stored** in the body **EXCEBT** (Vit. B_{12}), diseases are caused by either **deficiency (↓amount)** or **toxicity (↑amount)** but Toxicity is **rare** because it is water soluble and can be easily excreted out.
- Must be supplied regularly in the **diet.**
- Excess **excreted** in the urine.
- Present in small quantities in different **types of food.**
- **Important** for **growth** and good **health**.

- Help in various **biochemical processes** in the cell by functioning as **co-enzymes** or sometimes as **co-factors.**

Vitamin B6:

- It has ***three*** forms which are present in diet:
  1. Pyridoxine → is present only in **plants**.
  2. Pyridoxal → its main source from **animals**.
  3. Pyridoxamine → its main source from **animals.**
- Active form:
  - All 3 are converted to **pyridoxal phosphate (PLP).**

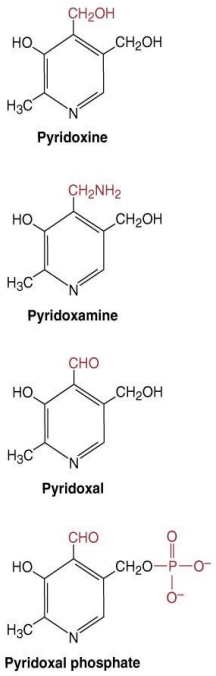


Figure 28.11. Structures of vitamin B_6.

the structure is not important

Functions of Vitamin B6:

- As coenzyme for:
  - **Transamination reactions**: involved in the enter conversion or ***transferring*** of amino group in ***amino acids***.
  - **Deamination reactions**: involved in ***amino acid*** metabolism by ***removing*** amino group.
  - **Decarboxylation reactions:** involved in ***amino acid*** metabolism by ***removing*** carboxyl group and it requires **pyridoxal phosphate**.(e.g. glutamate by decarboxylation reaction to GABA and Histidine by decarboxylation reaction to histamine).
  - **Condensation reactions:** it is a chemical reaction in which **two molecules *combine*** to form **one single molecule** (e.g. form hem part of hemoglopin).

Disorders of Vitamin B6 Deficiency:

- ***Dietary deficiency is rare***, but it was observed in:

- **Newborn infants** fed on formulas **low in B_6**
- **Women** on oral **contraceptives** → vit B_6 **interact** with ***steroid hormones*** in such drugs. (still in debate)
- **Alcoholics:** because they have **low** dilatory intake and vitamin metabolism is **impaired**.

- **Isoniazid:** used for treatment of **tuberculosis** can lead to **vitamin B_6 deficiency** by forming **inactive** derivative with **PLP. (therefore, patient with TB have to take B6 together with Isoniazid)**
- ***Deficiency*** leads to poor activity of ***PLP-dependent enzymes*** Causing: (if there is deficiency, everything that require PLP will be affected)
  - Deficient ***amino acid*** metabolism
  - Deficient ***lipid*** metabolism
  - Deficient ***neurotransmitter synthesis*** [serotonin, epinephrine, noradrenaline and gamma amino butyric acid (GABA)] → that's why **children** with ***vitamin B_6 deficiency*** have **convulsions**.
- **PLP** is involved in the synthesis of **sphingolipids**. Its **deficiency** leads to **demyelination** of nerves and consequent ***peripheral neuritis***.
- ***Mild deficiency*** involves:
  - Irritability
  - Nervousness
  - Depression → due to deficient neurotransmitter synthesis
- ***Severe deficiency*** involves: *(specially in children)*
  - Peripheral neuropathy
  - Convulsions

Vitamin B12: *it's the only vitamin that can be stored in the body that's why Manifestations appear after several years*

- It has **cobalt (Co)** and it's a **vitamin** so it's called → ***Cobalamin***.

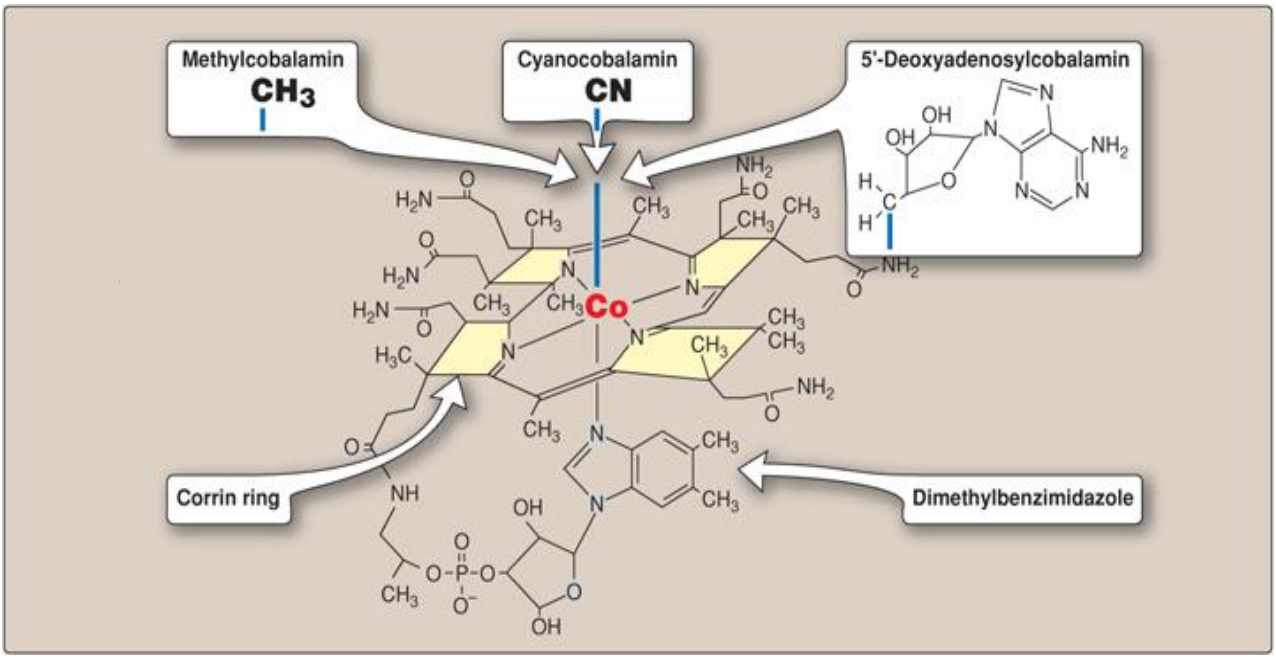
Forms of Vitamin B_{12}:

- Cyanocobalamin → ***cyanide group*** + ***cobalamin***
- Hydroxycobalamin → ***hydroxyl group*** + ***cobalamin***
- Adenosylcobalamin (major storage form in the ***liver***) → adenosyl ***group*** + ***cobalamin*** **(**the **storage** form of **vit B_{12}).**
- Methylcobalamin (mostly found in ***blood circulation***) → ***methyl group*** + ***cobalamin***

❖ The **first two** (***Cyanocobalamin*** and ***Hydroxycobalamin*** "injectable form") are commercially made BUT the **last two "the active form of vit B_{12}"** (***Adenosylcobalamin*** and ***Methylcobalamin***) are present in the body.

Coenzyme forms of B12:

- **Adenosylcobalamin** and **Methylcobalamin** are ***coenzymes*** for metabolic reactions
- Body can **convert** other cobalamins (***Cyanocobalamin*** and ***Hydroxycobalamin***) into **active coenzymes**. →But to do so it needs to be **hydrolyzed** first.



- **Cobalt** (Co) has a coordination state of **six** that means that it can ***bind to 6 different groups***.
- {4 ***Pyrrole rings*** (corrin rings) + 1 ***Dimethylbenzimidazole*** }+ {1 **CN** or **CH_3**}
- **Co** and **corrin ring** (Its name reflects that it is the "core" of vitamin B_{12})
  - ***Methylcobalamin*** = add CH_3 (methyl group)
  - ***Cyanocobalamine*** = add CN (cyanide group)

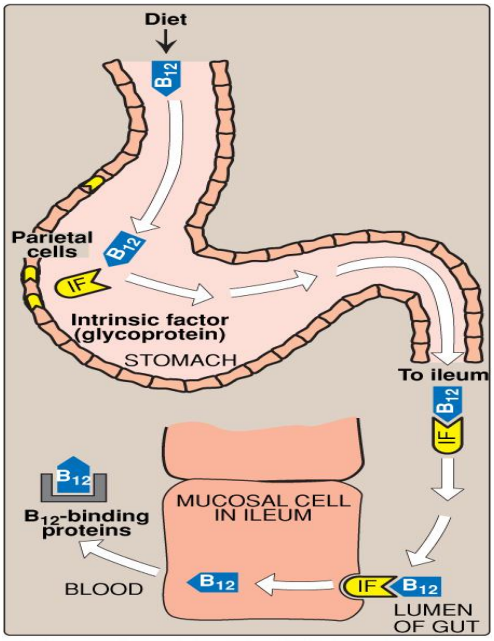
Vitamin B12 (Cobalamin):

- It cannot be synthesized in the human body must be supplied diet; it is synthesized only by microorganisms so it's either from animal products or normal flora or commercially available.
- Mainly found in animal liver bound to protein as:
  - Methylcobalamin or
  - 5'-deoxyadenosylcobalamin

Vegetarian is more deficient

- Essential for normal nervous system function and red blood cell maturation.
- Binds to intrinsic factor and absorbed by the ileum.
- Intrinsic factor is a protein secreted by cells in the stomach.

** There is a glycoprotein **"Intrinsic factor"** which is present in the stomach and is required for B_{12} absorption in the ileum. Intrinsic factor is a protein secreted by cells in the stomach. So what happens is when you take B_{12} in the diet, it comes to the stomach, the parietal cells of the stomach release the intrinsic factor and B_{12} binds to this intrinsic factor and that carries it to the ileum. When it reaches the ileum, the mucosal cells of the ileum have a receptor for this intrinsic factor. So the **"intrinsic factor B_{12} complex"** binds to this receptor and B_{12} is unloaded inside the mucosal cells of the ileum. From there it goes to the circulation and it binds to transcorrin again.



Vitamin B12 Storage:

in 1920's, the doctors were worried about ***pernicious anemia*; people were dying without known reason. However, doctors found out that these patients are cured after ***feeding the liver***. This leads to the conclusion that there are two things are required: one is the extrinsic factor "which is vitamin B_{12}" that is coming from the liver that has been fed to the patient; the other is the intrinsic factor.

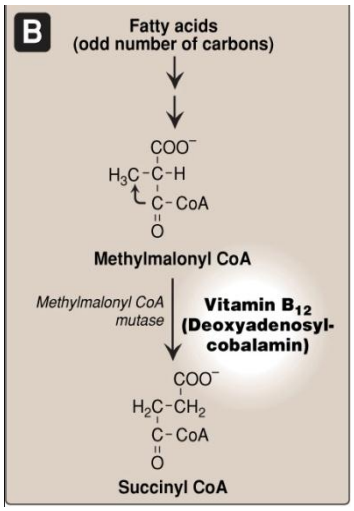
- Liver stores vitamin B_{12} (4-5 mg)
- Other B vitamins are not stored in the body.
- Vitamin B_{12} deficiency is observed in patients with Intrinsic factor deficiency due to autoimmunity or by **partial** or **total gastrectomy**.
  - Clinical deficiency symptoms develop in several years

** so most of the time the deficiency is due to poor absorption.

Functions of Vitamin B12:

- Two reactions require B_{12}:

(1) **Conversion of propionyl-CoA to succinyl-CoA**:



- The enzyme in this pathway, ***methyl-malonyl-CoA mutase***, requires B_{12}

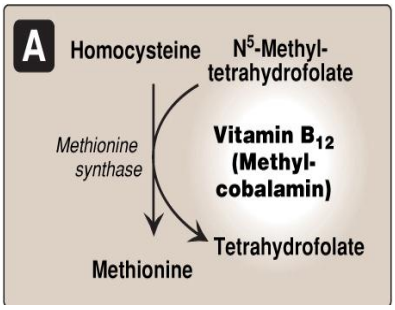
Addition Require: deoxyadenosylcobalamin (coenzym), Odd number of fatty acid (15 carbons).

It will break down into 6 acetyl-CoA and 1 propionyl-CoA

Propionyl-CoA converts to methylmalony CoA

So, in deficiency of vitamin B_{12} the patient will have ***abnormal fatty acids*** in the body, these fatty acids will ***accumulate*** in the cell membrane including the cell membranes of the nervous system leading to ***neuropathy***.

(2) **Conversion of homocysteine to methionine**:



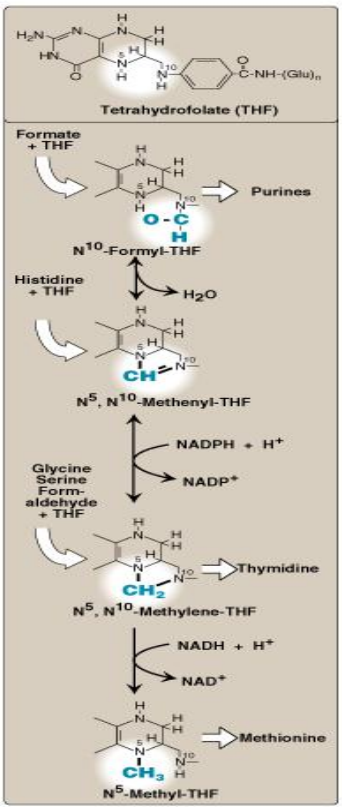
- Methionine synthesis requires B_{12} (in the form of methyl-cobalamin) in converting homocysteine to methionine by methionine synthase.
- **N^5 –methyltetrahydrofolate** is required for the previous conversion and it will get converted into ***tetrehydrofolate*** which is the functional form of ***folic acid***.
- **Tetrehydrofolate** acts as a receptor or a carrier for 1 carbon unit such as methyl group and it is required in the metabolism of fatty acids and specially in the synthesis of nucleotides the purines and pyrimidines.

B12 Deficiency and Folate Trap:

- Homocysteine re-methylation reaction is the only pathway where N^5-methyl TH4 can be returned back to tetrahydrofolate pool.
- Hence folate is trapped as:
  - N^5-methyltetrahydrofolate (folate trap) due to vitamin B_{12} deficiency.

TH4: Tetrahydrofolate

- This leads to folate deficiency and deficiency of other TH4 derivatives (N^5-N^{10} methylene TH4 and N^{10} formyl TH4) required for purine and pyrimidine syntheses.



Interconversion between TH4 carrier of "one-carbon units

you do not need to memories these steps

Disorders of Vitamin B12 Deficiency:

- **Pernicious anemia.**
- **Megaloblastic anemia:**
  - Vitamin B_{12} deficiency is mainly due to the deficiency of intrinsic factor.
- **Demyelination:**
  - Myelin sheath of neurons is chemically unstable and damaged.
- **Neuropathy:**
  - Peripheral nerve damage.

- Deficiency of vitamin B_{12} leads to accumulation of methylmalonyl CoA.
- High levels of methylomalonyl CoA is used instead of malonyl CoA for fatty acid synthesis.
- Myelin synthesized with these abnormal fatty acids is unstable and degraded causing neuropathy.

- ***Neurological symptoms:***
  - ✓ Paraesthesia (abnormal sensation) of hands and feet.
  - ✓ Reduced perception of vibration and position.
  - ✓ Absence of reflexes.
  - ✓ Unsteady gait and balance (ataxia).
- ***Psychiatric symptoms:***
  - ✓ Confusion and memory loss.
  - ✓ Depression.
  - ✓ Unstable mood.