

VITAMIN B6 & B12

Color index:

- **Important**
- Extra explanation
- Lippincott's notes

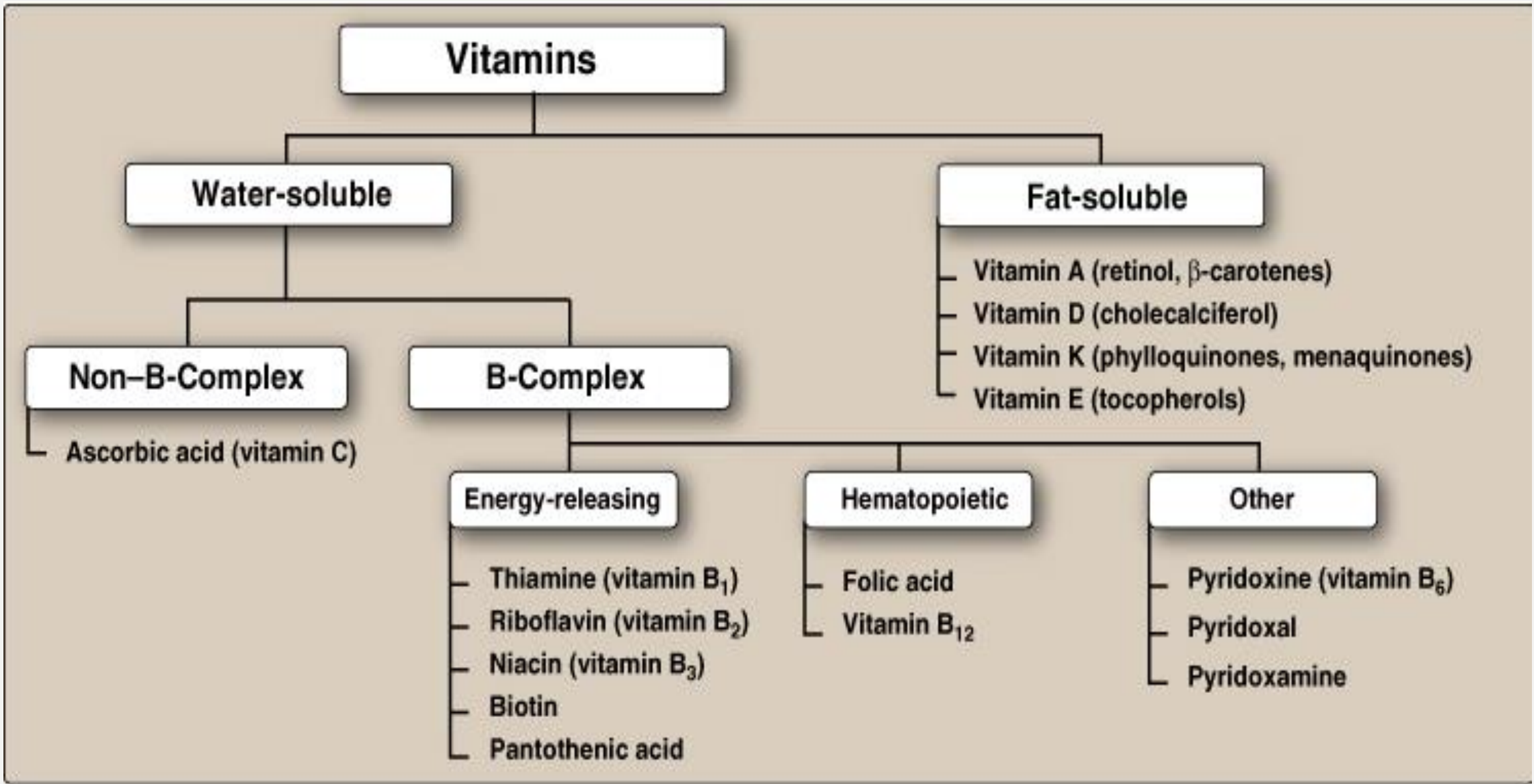
“ALWAYS DO YOUR BEST. WHAT YOU PLANT NOW, YOU WILL HARVEST LATER.”

Check [this link](#) before studying to know if there is any corrections in the teamwork

OBJECTIVES:

By the end of this lecture the Second Year students will be able to:

- Understand the types and functions of vitamins B6 and B12
- Recognize the role of these vitamins in maintaining the myelin sheath of nerves and their function
- Discuss the consequences of vitamin B6 and B12 deficiency that can lead to nerve degeneration and irreversible neurological damage



Water Soluble Vitamins

Types of Vitamin B :

Thiamin (B₁), riboflavin (B₂), niacin (B₃), pantothenic acid (B₅), **pyridoxine (B₆)**, biotin (B₇), **cobalamin (B₁₂)**, Folate. The eight vitamins B types together (and folic acid) are called : B complex.

Function:

They function as coenzymes.

Most Vitamins in vitamin B complex act as precursors for coenzymes (involved with enzymes that catalyze the reactions involved in energy synthesis).

-There are two types of enzymes: **holoenzyme** and **apoenzyme**.

-What are coenzymes?

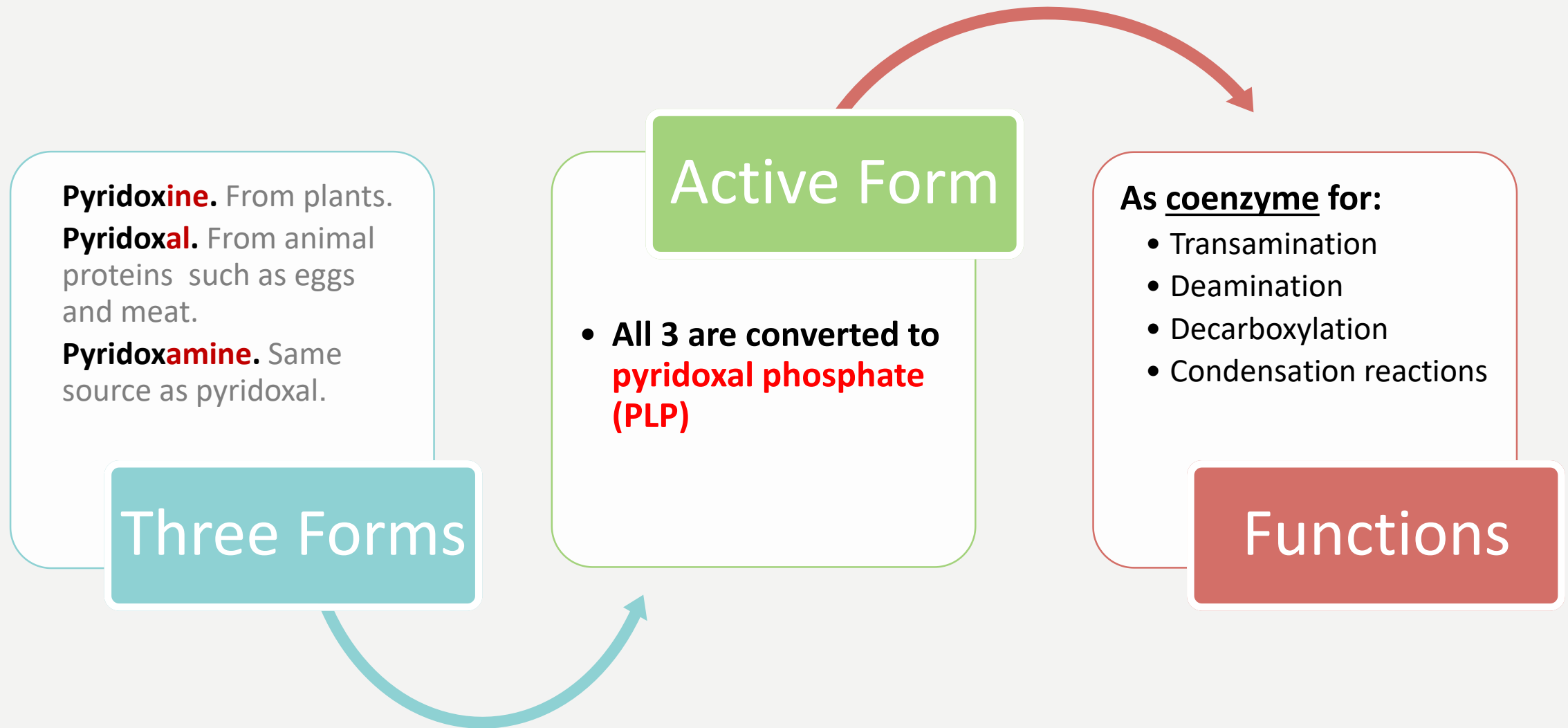
Holoenzyme: some enzymes require a non protein part to become active, this part can either be a cofactor or a coenzyme.

-The coenzyme is bound transiently (not permanent) with the enzyme.

Characteristics of B complex:



Vitamin B6



Pyridoxine. From plants.
Pyridoxal. From animal proteins such as eggs and meat.
Pyridoxamine. Same source as pyridoxal.

Three Forms

Active Form

- All 3 are converted to **pyridoxal phosphate (PLP)**

As coenzyme for:

- Transamination
- Deamination
- Decarboxylation
- Condensation reactions

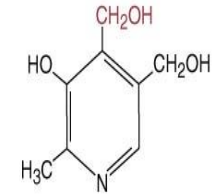
Functions

- Transamination** :the amino group is being transported from one molecule to another.
- Deamination** is the removal of the amino group from a molecule.
- Decarboxylation** :is the removal of CO₂ from a molecule.
- Condensation** reactions of two molecules combining together to form a third molecule.



Note that the red structures, they show the difference between the 4 forms of vitamin B6. They differ only in the nature of the functional group attached to the ring.

All these forms are derivatives of pyridine.



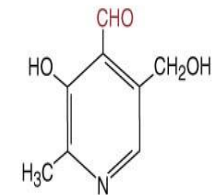
Pyridoxine

OH = alcohol



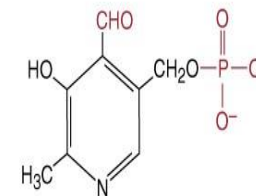
Pyridoxamine

NH₂ = amino acid



Pyridoxal

CHO = aldehyde



Pyridoxal phosphate

Figure 28.11. Structures of vitamin B₆.

*In this image we find some of the important roles which pyridoxal plays in metabolic reactions:

*glycogen is giving you glucose phosphate and then finally giving you pyruvate .

So glycogenolysis and finally entering Krebs cycle.

The transamination reactions are involved in both the synthesis and breakdown of amino acids because they are reversible reactions, these reactions are also involved in energy synthesis because the resulting molecules enter Krebs.

*In order to form neurotransmitters ,decarboxylation must occur.

Glycine and succinyl coA join to form aminoluvilinic acid which then forms heme.

*What is the principle concept for the test used to diagnose for B6 deficiency ?

When tryptophan is degraded it gives you ammonium and carbon dioxide and energy, but this reaction needs vitamin B6 to occur. This reaction actually makes the basis of the test used to check for vitamin B6 deficiency.

So if vitamin b6 is deficient you will have a build up of a molecule called xanthurenic acid, this molecule is found (accumulated) in the blood of the patients who have vitamin B6 deficiency.

Note that at the beginning of the test you give the patient tryptophan (to check if xanthurenic acid will accumulate or not).

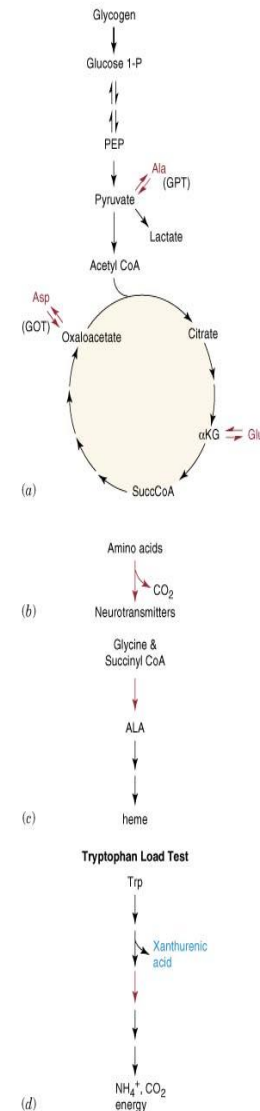
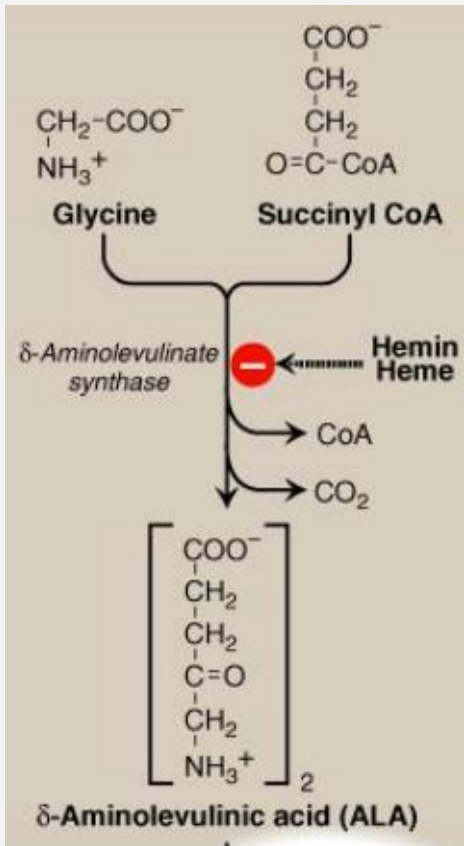


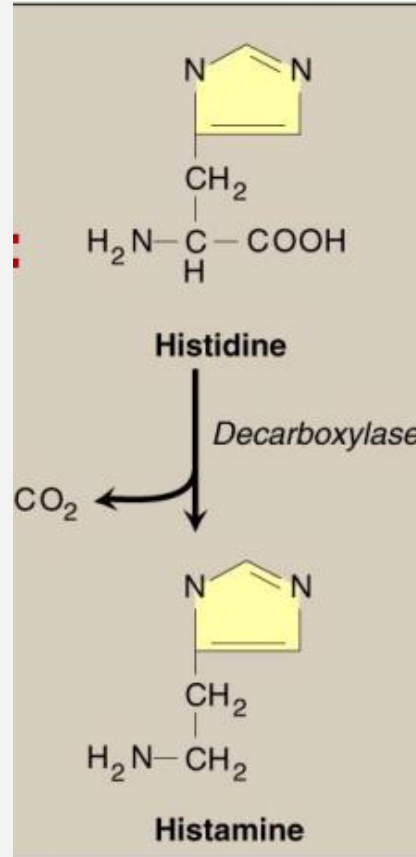
Figure 28.12. Some important metabolic roles of pyridoxal phosphate.

Condensation Reaction
Formation of ALA by ALA synthase, The regulatory step in hemoglobin synthesis



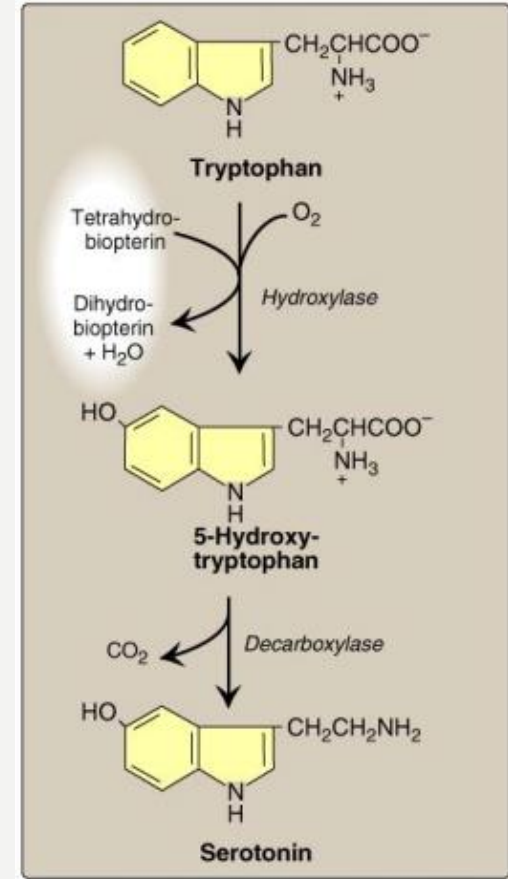
Note that this reaction requires glycine and succinyl CoA to join together.

Decarboxylation Reaction:
Formation of Histamine



Important note: The decarboxylation of histidine yields histamine.

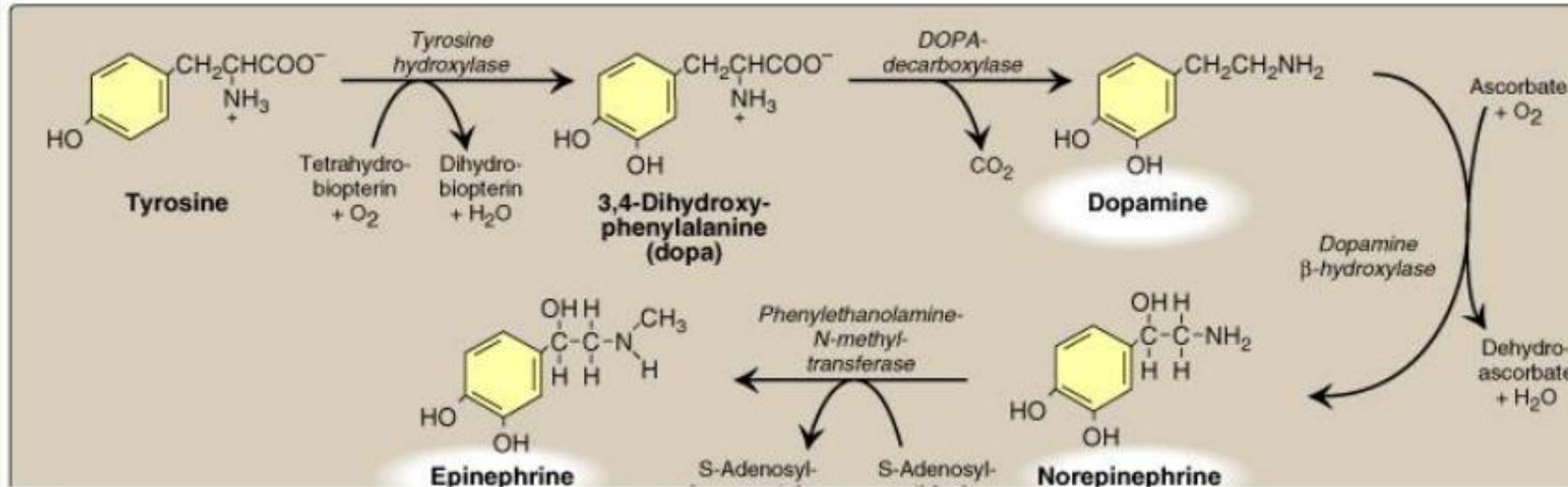
Decarboxylation Reaction:
Formation of Serotonin



Important note: the decarboxylation of tryptophan yields serotonin.

Decarboxylation Reaction:

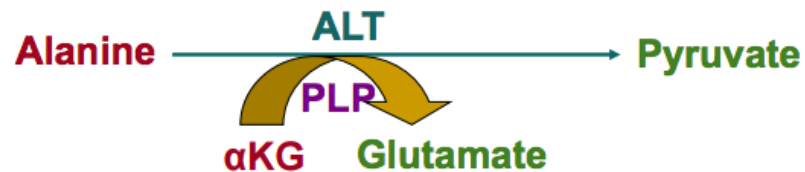
Formation of Catecholamines: Dopamine, norepinephrine and epinephrine



Note :Tyrosine is the parent compound here ,then it gets decarboxylated into dopamine which is then converted into epinephrine and norepinephrine So if there is a deficiency is vitamin B6 ,the catecholamine synthesis will decrease or stop.

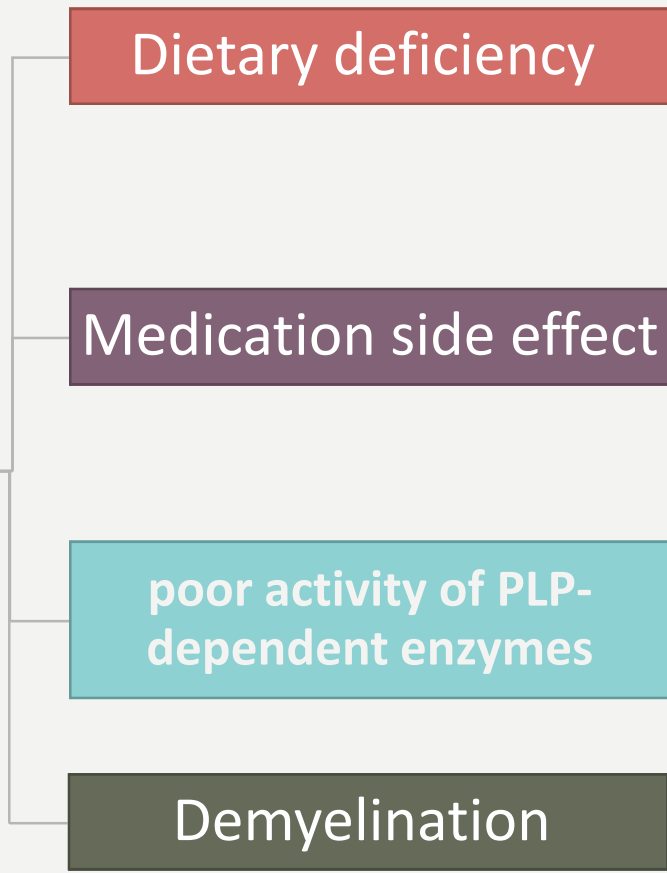
Transamination Reaction

Alanine transfers its amino group to alpha keto glutarate which then turns into glutamate (catalyzed by alanine transaminase which needs PLP) What is left from alanine? pyruvate



The transfer of amino groups is important when a nonessential amino acid (alanine) is converted into an essential amino acid (pyruvate).
*Essential Amino Acids: are those that can't be synthesized by the body so we must get it in the diet.

Disorders Of Vit B6 Deficiency



It is rare , but it is observed in :

- 1- Newborn infants fed on **formulas low** in **B6**.
- 2- Women on oral contraceptives (حبوب منع الحمل).
- 3-Alcoholics.

*Alcohol and oral contraceptives will interfere with absorption of Vitamin B6.

Isoniazid treatment for tuberculosis (by pyridoxine) can lead to vitamin B6 deficiency by forming **inactive derivative** with PLP.

Basically isoniazid forms a complex with pyridoxal phosphate (this complex is an inactive derivative). Which leads to depleted levels of B6(PLP) in the blood. Hence vitamin B6 is given to patients being treated for TB with isoniazid.

Disorders Of Vit B6 Deficiency

Dietary deficiency

Medication side effect

poor activity of PLP-dependent enzymes

Demyelination & neurogenic symptoms

Deficiency leads to poor activity of PLP-dependent enzymes
Causing:

- 1- Deficient amino acid metabolism.
- 2- Deficient lipid metabolism.
- 3- Deficient neurotransmitter synthesis:
Serotonin, epinephrine, norepinephrine and gamma amino butyric acid "GABA".

* PLP is involved in the synthesis of **sphingolipids** so its deficiency leads to **demyelination** of nerves and consequent peripheral neuritis .

Pyridoxine is the only water-soluble vitamin with significant toxicity.

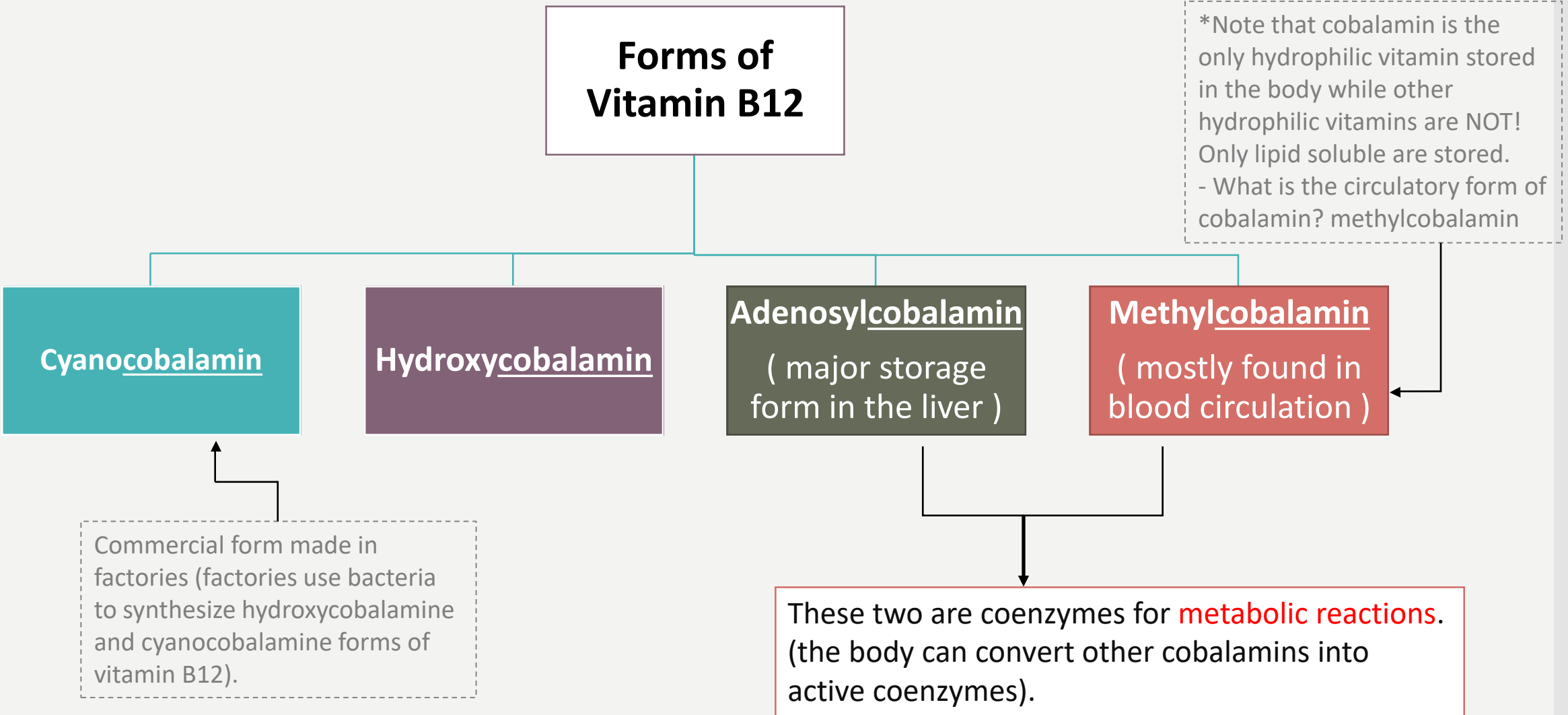
* **Mild deficiency leads to:**

- 1- Irritability
- 2- Nervousness
- 3- Depression

* **Severe deficiency leads to:**

- 1- Peripheral neuropathy (sensory neuropathy), occurs at intakes above 500 mg/day.
- 2- Convulsions

Vitamin B12



Vitamin B12

In the center of the Corrin ring, we have cobalt
And cobalt can make six bonds.

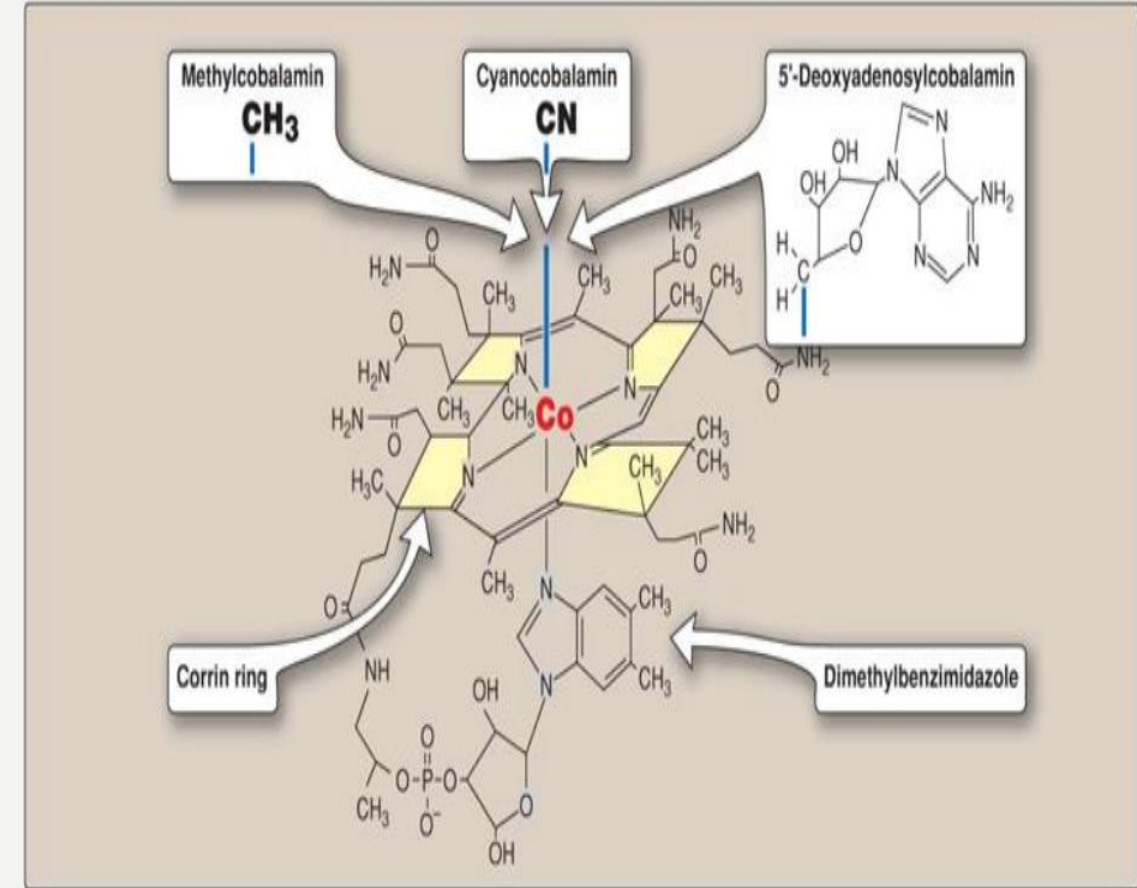
Four of these bonds can attach to the nitrogen found in the Corrin ring, and one is attached to the dimethylbenzimidazole, and the sixth bond :

If it is made with cyanide it is called **cyanocobalamin**.

If a methyl group is attached, its **methylcobalamin**.

Or if adenosyl group is attached it is called **adenosylcobalamin**.

So the form of cobalamin changes according to the change in the sixth group while the other 5 bonds remain the same



الكوبالت نوع من المعادن الموجودة في الأرض ، يستخدم في اعداد السبائك الصلبة.
(تقدر تربط بين الشكل في منتصف الصورة وبين شكل المعدن ☺)

الكوبالت عشان يكون فيتامين بي ١٢ يشبك مع ٤ ذرات نيتروجين، ومع داي ميثيل بينز ايميدازول (٢ ميثان ، حلقة بنزين وحدة ومركب ايميدازول) ، وفي الرابطة السادسة يرتبط مع احد ثلاثة : مع سيانيد ، او ميثان ، او ادينوسين ، ونضيف اسم الي ارتبط معه في بداية اسم المركب.



Vitamin B₁₂ (Cobalamin)

- Mainly found in animal liver bound to protein as:
 - Methylcobalamin or
 - 5'-deoxyadenosylcobalamin
- **Essential** for:
 1. normal nervous system function
 2. red blood cell maturation

*note that folic acid and vitamin B 12 are both required in hematopoiesis .
Deficiency in B12 leads t megaloblastic marocytic anemia.
- **Not synthesized in the body** and must be supplied in the diet.

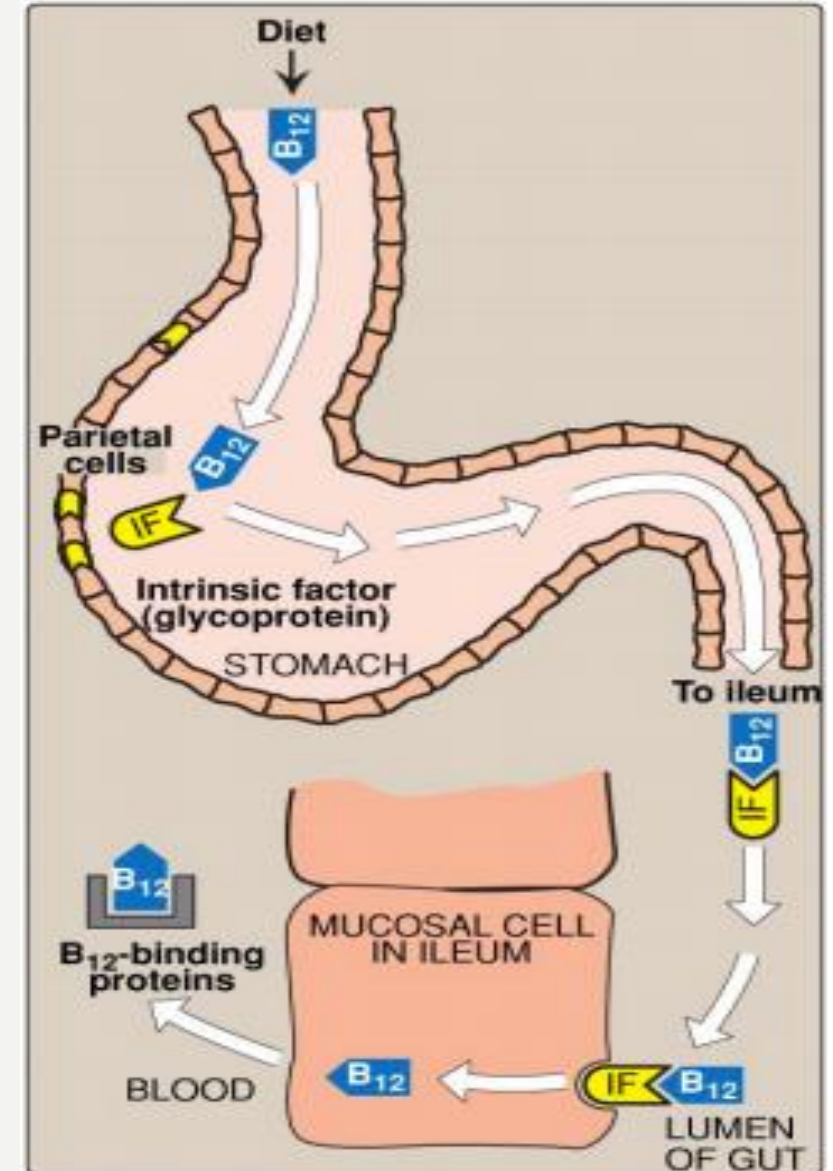
*So this vitamin is synthesized by bacteria either the bacteria found in our gut(normal flora) or the bacteria in animals which we eat. It is not present in plants AT ALL!!
- Binds to intrinsic factor⁽¹⁾ and absorbed by the ileum.

*If a condition in which GIT flora are decreased such as in people taking antibiotics, vitamin B12 deficiency may occur

* it may also occur in older people because their stomach acidity is decreased which impairs the absorption of vitamin B12

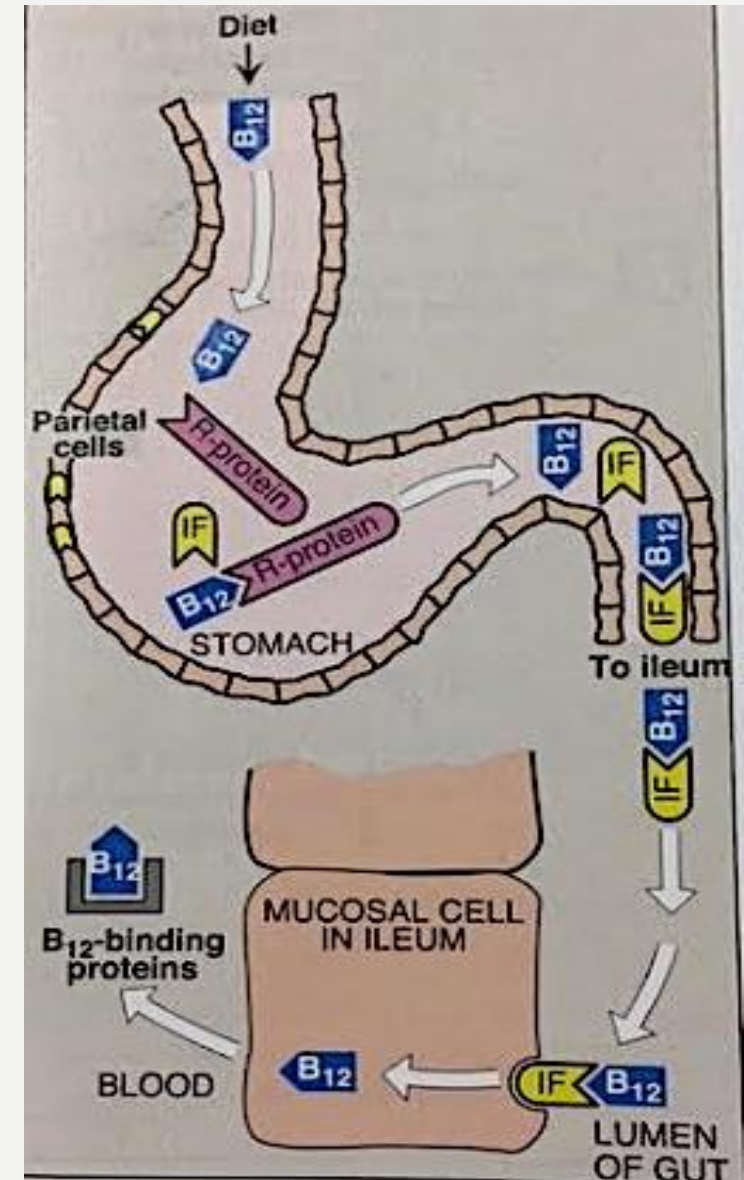
[Further information in the next slide]

(1)Intrinsic factor is a protein secreted by cells in the stomach.



This slide was added by doctor Sumbul
***What's new? R-protein.**

1. Vitamin B¹² is released from food in the acidic environment of the stomach.
2. Free B¹² then binds a glycoprotein (R-protein), and the complex moves into the intestine.
3. B¹² is released from the R-protein by pancreatic enzymes and binds another glycoprotein, intrinsic factor (IF).
4. The cobalamine-IF complex travels through intestine and binds to specific receptors on the surface of mucosal cell and, subsequently, into the general circulation, where it is carried by its binding protein (transcobalamine). B¹² is taken and stored in the liver, primarily.
5. It is **released** into the **bile** and efficiently **reabsorbed** in the **ileum**.
6. Severe malabsorption of vitamin B¹² leads to **pernicious anemia**.
7. This disease is most commonly a result of an autonomic destruction of the gastric parietal cells that are responsible for the synthesis of IF (lack of IF prevents B¹² absorption)
8. [Note: Supplementation works even in the absence of IF because approximately 1% of B¹² uptake is by IF-independent diffusion]



Vitamin B₁₂

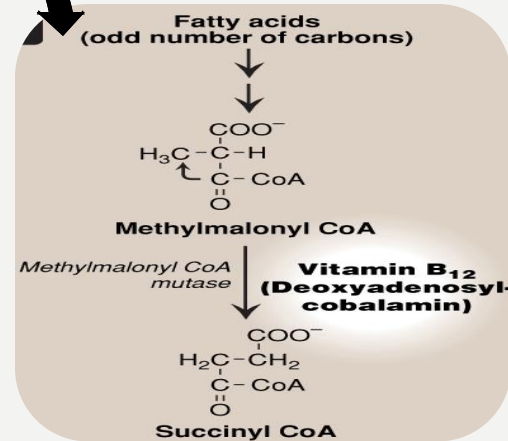
Storage

- ◆ Liver stores vitamin B₁₂ (4-5 mg), while other B vitamins are not stored in the body.
- ◆ Vitamin B₁₂ deficiency is observed in patients with intrinsic factor (IF) deficiency due to autoimmunity or by partial or total gastrectomy
 - Clinical deficiency symptoms develop in several years.

Functions

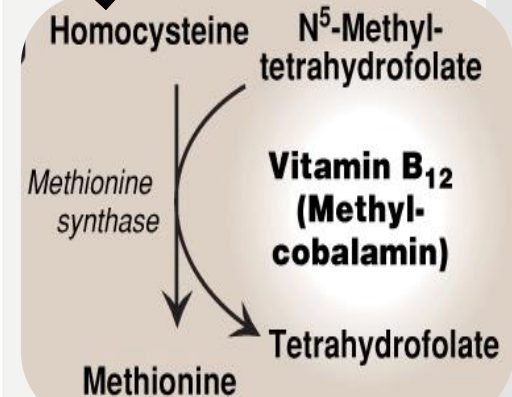
1. Conversion of methylmalonyl-CoA to succinyl-CoA.

The enzyme in this pathway, methylmalonyl-CoA mutase, requires B₁₂.



2. Conversion of homocysteine to methionine.

Methionine synthase requires B₁₂ in converting homocysteine to methionine



Note that this reaction requires vitamin B12 in the form of methyl cobalamin. If deficiency occurs there will be accumulation of homocysteine which may lead to spina bifida or heart defects.

Vitamin B₁₂ is used in the breakdown of fatty acids. Methylmalonyl-CoA is converted into succinyl-CoA by methylmalonyl-CoA mutase, which is actually Vitamin B₁₂ in the form of deoxyadenosyl cobalamin. **-note that all of these points are important!!!!**
-if there is a deficiency in Vitamin B₁₂ this will lead to accumulation of methylmalonyl-CoA

B₁₂ Deficiency And Folate Trap

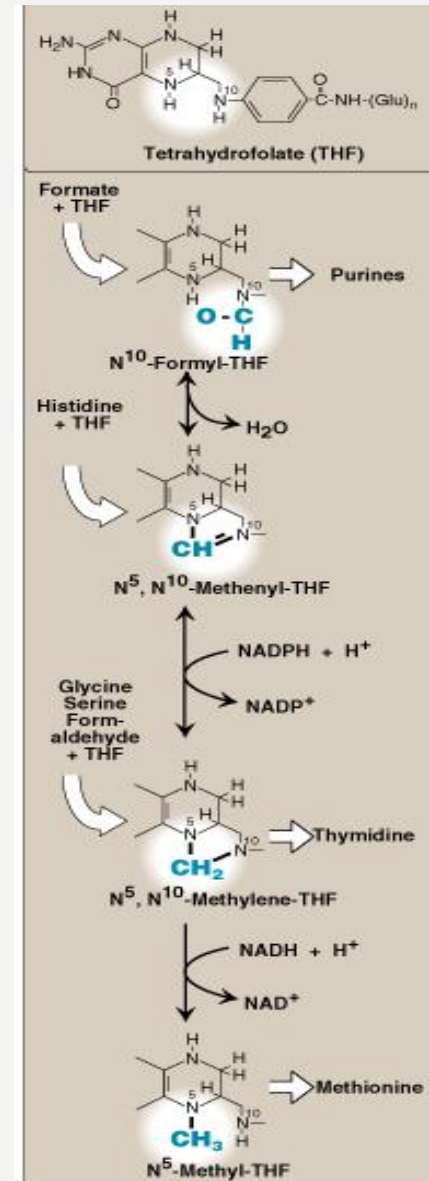
- Homocysteine re-methylation reaction is the only pathway where N⁵-methyl TH4 can be returned back to tetrahydrofolate pool
- Hence folate is trapped as N⁵-methyltetrahydrofolate (folate trap)
- This leads to folate deficiency and deficiency of other TH4 derivatives (N⁵-N¹⁰ methylene TH4 and N¹⁰ formyl TH4) required for purine and pyrimidine syntheses
- TH4: Tetrahydrofolate
- Due to trapping of TH4 all of these reactions can't go on.

-The functional form of folate is tetrahydrofolate.

- other causes of folate deficiency:

Folate deficiency is either due to increased demand as in pregnancy or due to impaired absorption.

B12 deficiency can be determined by the level of methylmalonic acid in blood, which is elevated in individuals with low intake or decreased absorption of the vitamin



B₁₂ Deficiency And Folate Trap

Further explanation:

When homocystein gets converted into methionine ,N5 methyl TH4 gets converted into tetrahydrofolate.

How? methyl group from N5 methyl TH4 donates its methyl group hence it becomes tetrahydrofolate

While the methyl group combines with homocystein ,which yields methionine

This process is the only way to replenish tetrahydrofolate

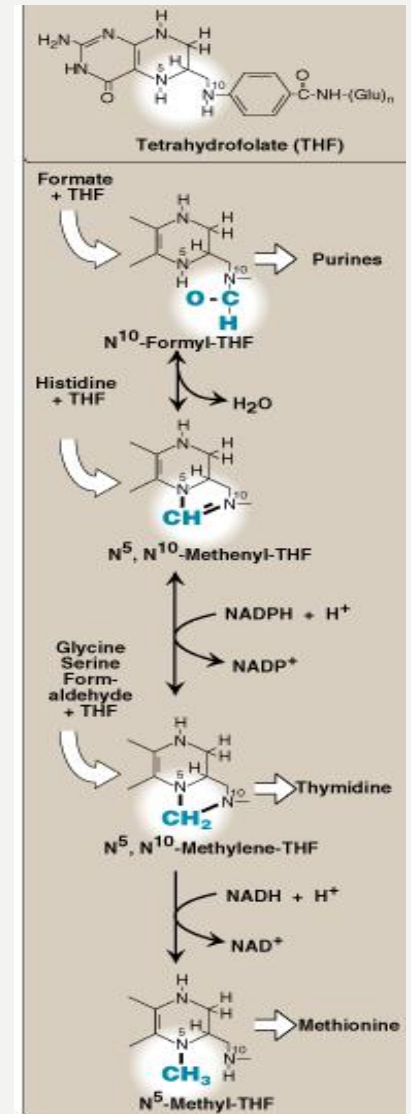
So when there is deficiency of vitamin B12 we wont have replenishment of tetrahydrofolate

So it is trapped in the form of N5 methyl TH4 (folate trap)=folate deficiency

This is the reason that when vitamin B12 deficiency develops ,folate deficiency also develops

So when you treat B12 deficiency you also have to give folate supplements.

Note that folic acid is involved in the synthesis of :
purines,thymidine,methionine.



Interconversion between TH4 carrier of "one-carbon units"

Disorders of Vitamin B₁₂ Deficiency

Pernicious anemia

Megaloblastic anemia (RBC can't divide because of no DNA synthesis so it keeps on growing).

Vitamin B₁₂ deficiency is mainly due to the deficiency of intrinsic factor.

Can be corrected with b12 supplements .

Demyelination

Myelin sheath of neurons is chemically unstable and damaged.

Causes Neuropathy.

Neuropathy

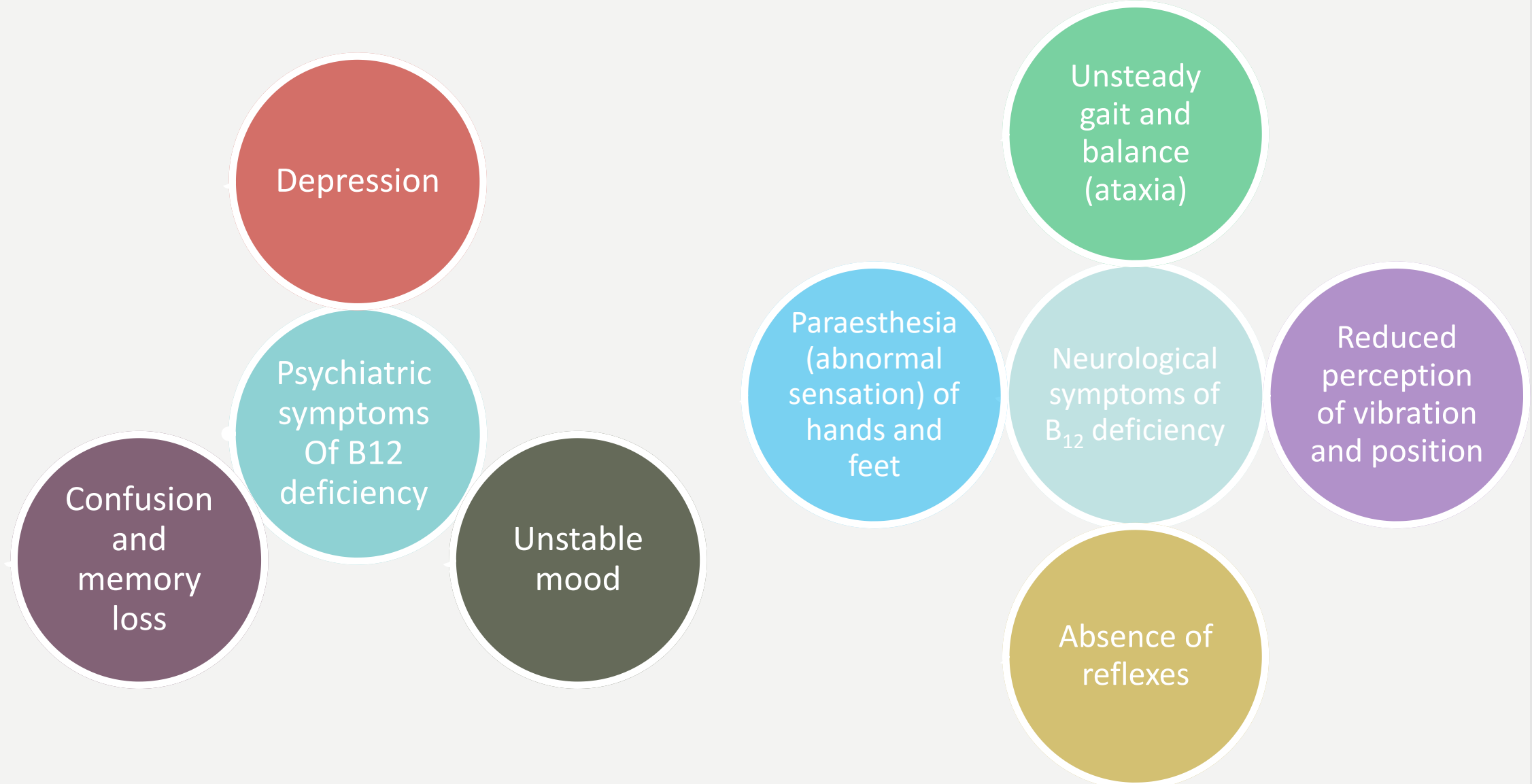
Peripheral nerve damage.

Why demyelination occurs?

If there is deficiency there will be accumulation of methyl malonyl coA then - when the myeline sheath is being synthesized- lots of fatty acids instead of getting methyl coA ,they will get methylmalonyl coA in their structure which will lead to an unstable form of myelin thus demyelination occurs.

- Causes of neuropathy:
- Deficiency of **vitamin B₁₂** leads to accumulation of **methylmalonyl CoA**.
- High levels of **methylmalonyl CoA** is used instead of **malonyl CoA** for fatty acid synthesis.
- Myelin synthesized with these abnormal fatty acids is unstable and degraded causing neuropathy.

Symptoms of B12 deficiency



Psychiatric symptoms = اعراض نفسية

Neurological symptoms = اعراض متعلقة بالاعصاب

1-Vitamin b7 is also known as:

- A. Folate
- B. Biotin
- C. Riboflavin
- D. Pyrodoxine

2-The active form of vitamin B6 is:

- A. Pyridoxine
- B. Pyridoxal
- C. Pyridoxamine
- D. PLP

3-Which one of the following symptoms is caused by severe deficiency of vitamin B6?

- A. Irritability
- B. Depression
- C. Convulsion
- D. Nervousness

4-Which one of the following is NOT caused by vitamin B12 deficiency?

- A. Megaloblastic anemia
- B. Demyelination
- C. Convulsions
- D. Neuropathy

5-Which one of the following vitamins is NOT fat soluble?

- A. Vitamin A
- B. Vitamin B
- C. Vitamin K
- D. Vitamin D

6-Vit B12 is mainly stored in liver in the form of:

- A. Adenosylcobalamin
- B. Methylcobalamin
- C. Cyanocobalamin
- D. Phylloquinone

7-Vitamin B6 works as a coenzyme in the formation of hemoglobin by which one of the following reactions:

- A. Transamination
- B. Deamination
- C. Decarboxylation
- D. Condensation

8-Isoniazid causes deficiency of which one of the following vitamins:

- A. B1
- B. B2
- C. B3
- D. B6

9- Demyelination is Caused by:

- A. Vitamin B6 deficiency
- B. Vitamin B12 deficiency
- C. Toxicity of Vitamin B6
- D. A+B

10-Which of the following is not a characteristic of B Vitamins:

- A. Not significantly stored in the body.
- B. Can be formed in the body
- C. Excess is secreted
- D. unusual to get toxicity.

❖ **Q1: What are the reactions in which vitamin B6 is a required coenzyme? Give an example for each reaction.**

Transamination: as in transforming alanine into pyruvate

Deamination: removing an amino group

Decarboxylation: as in the formation of catecholamines, histamines, serotonin.

Condensation reactions: formation of ALA by ALA synthase

❖ **Q2: A 23 year old patient is being treated for TB by the following antibiotics: isoniazid, Rifampin, and ethambutol with pyrazinamide .**

What is the necessary vitamin supplement that should be given to this patient?

Vitamin B6.

Why is this supplement necessary?

Because isoniazid forms inactive derivatives with PLP causing deficiency of B6.

❖ Q3 : A 45 year old patient came to the ER complaining from paresthesia in his hands and feet. An extensive history was taken from the patient which revealed that he has been suffering from depression for the past 3 weeks. Upon examination patient displayed an absence of reflexes. The doctor ordered a standard blood workup for the patient . The results revealed that the patient is anemic with a vitamin b12 deficiency.

What is the type of anemia in this case?

Pernicious anemia (macrocytic megaloblastic anemia)

List other symptoms of vitamin B12 deficiency.

Ataxia, confusion, unsteady mood.

What is the cause of the patient's paresthesia and loss of reflexes?

--neuropathy which is caused by accumulation of methylmalonyl CoA which leads to the synthesis of fatty acids using this accumulated enzyme instead malonyl CoA. The use of methylmalonyl CoA leads to the formation of unstable fatty acids that are degraded causing neuropathy. This neuropathy is manifested in this case by lose of reflexes and paresthesia.

❖ **Q4: List some of the mild and severe manifestations of pyridoxine deficiency.**

- In mild cases:

1-irritability

2-nervousness and depression.

- In severe cases:

1-Peripheral neuropathy

2-convulsions

Team Members:

Team Leaders:

- عبدالله الغزي.
- نواف العبدالكريم.

Revised by
هشام الغفيلي & خولة العماري

* نستقبل اقتراحاتكم وملاحظاتكم على:

 [@435biochemteam](https://twitter.com/435biochemteam)

 435biochemistryteam@gmail.com

 [@biochemteam435](https://www.whatsapp.com/channel/0029vaq35biochemteam435)

- ليلى اسماعيل.
- سارة الخليفة.
- ربي السليمي.
- ملاك الشريف.
- مروج الحربي.
- نواف الرشيد.
- رفان هاشم.
- ثاني معافى.
- خالد النعيم.
- فارس المطيري.
- أحمد الرويلي.
- إبراهيم الشايع.
- فراس المؤمن.
- محمد الصهيل.
- عبدالله الشنيفي.