

# B12 & Cobalamin

## Learning objectives

- Define vitamins
- Classify fat soluble and water soluble vitamins.
- Study chemical structure and “ biological active ” coenzyme form of vitamin B12.
- List the dietary sources and daily requirement of vitamin B12.
- Biochemical functions of vitamin B12 in the body.
- How it is digested and absorbed, transported and stored;
- Its characteristic deficiency symptoms and disease.

## VITAMINS

### *Definition*

Vitamins are organic nutrients that are required in small quantities for a variety of biochemical functions and which generally cannot be synthesized in the body and must be supplied by the diet

## VITAMINS

### Classification

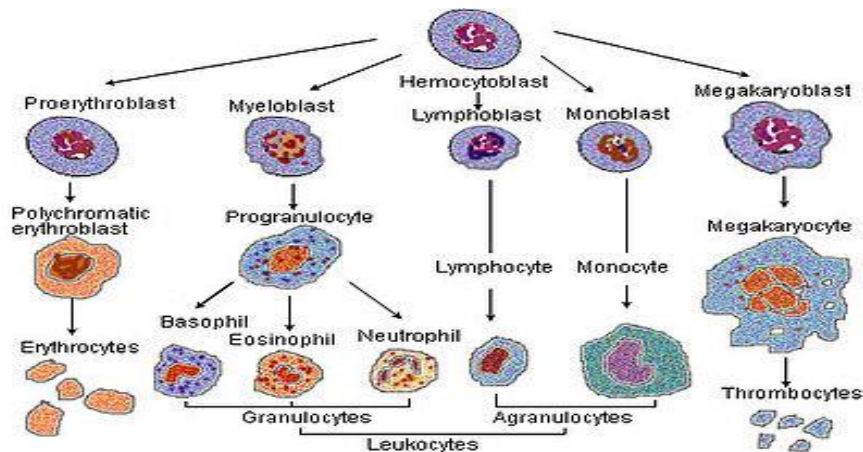
Water soluble	<ul style="list-style-type: none"><li>• B complex</li><li>• C or Ascorbic acid</li></ul>
Fat soluble	<ul style="list-style-type: none"><li>• A or Retinol</li><li>• D or Cholecalciferol</li><li>• E or Tocopherol</li><li>• K</li></ul>

# Requirements of Haemopoiesis

- **Endogenous factors:**
  - **Haematopoietic growth factors**
    - Stem cell factor (SCF).
    - Glycoprotein growth factors.
    - Colony-Stimulating factors (CSFs).
  - **Transcription factors in hematopoiesis.**
- **Exogenous (Dietary) factors:**
  - Proteins and other macro-molecules
  - Minerals
  - Vitamins

## Formation of Blood Cellular Components (Haemopoiesis)

- All cellular blood components are derived from haematopoietic stem cells

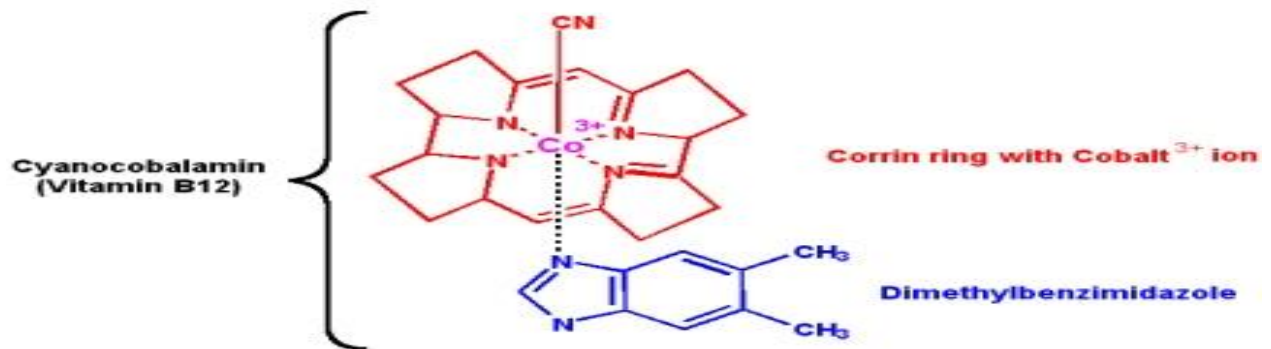


## Vitamin B-12, also called Cobalamin

- Water soluble vitamin
- Key role in the normal functioning of the brain and nervous system , and for the hemopoiesis.
- Is a coenzyme for enzymes that transfer methyl groups and produce red blood cells.

## Vitamin B12 is composed of a:

Complex tetrapyrrol ring structure (corrin ring)  
Cobalt ion in the center.



## Vitamin B12 Derivatives

- Cyanocobalamin (digested form)
- Hydroxycobalamin
- Chlorocobalamin
- Methylcobalamin
- Adenosylcobalamin
- (5'-deoxyadenosylcobalamin)

## Sources of Vitamin B12

- Natural forms
  - Produced by microorganisms (bacteria/fungi) may inhabit in gut
  - Plants do not produce or contain Vit B12
- Food sources rich in Vit.B12
  - Liver , Kidney , Muscle
  - Egg , Milk ,Cheese and other diary products
  - Seafood
  - Foods fortified with B12 are also sources of the vitamin B12.

## Vitamin B12 Stores

- Normal body stores of vitamin B12 about 3-4 mg, primarily in liver.
- This would be sufficient for 3 years if dietary intake ceased or if the ability to absorb the vitamin was lost.

## Plants are not sources of Vit.B12

## Vitamin B12; Dietary requirement

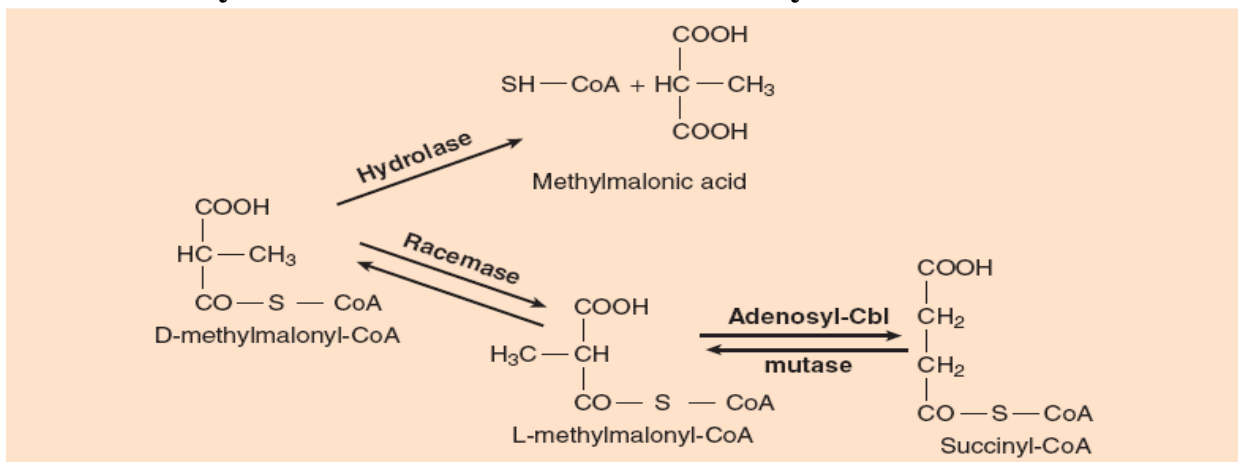
- Recommended intake (RDA) 3µg/day
- 6µg/day in pregnancy & Lactation

## Vitamin B12; Biochemical functions

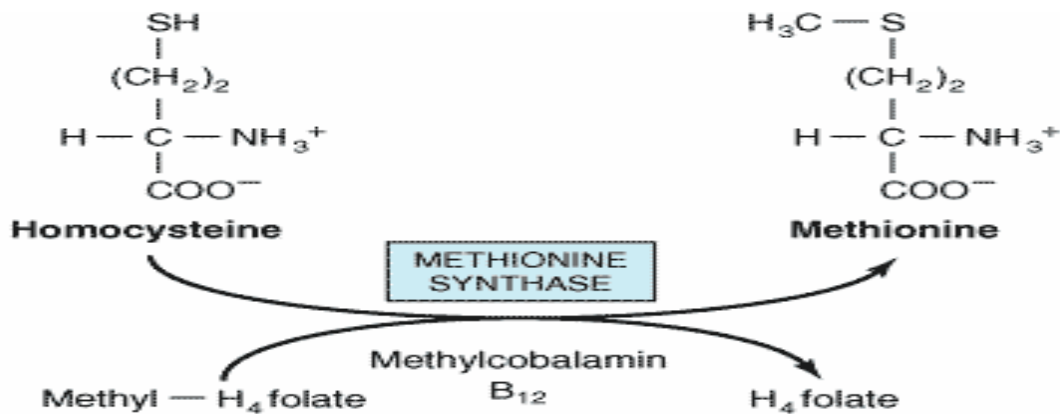
- Vitamin B12 normally plays a significant role in the One carbon transfer reactions which in turn required for:
  - DNA synthesis
  - Fatty acid synthesis
  - Energy production.
  - **One carbon transfer reactions are required in the biosynthesis of:**
    - Amino Acids
    - Serine,
    - Methionine
    - Glycine,
    - Purine nucleotides
    - dTMP (Deoxy Thymidine Mono Phosphate).

## Enzymes that require vitamin B12 as cofactor

- **Methylmalonyl-coa mutase:**
  - Isomerization of methyl malonyl CoA from odd C. numbered fatty acids.
  - Above reaction is an essential step for:
    - Catabolism of fatty acids with an odd number of carbon atoms.
    - Amino acids (Valine, Isoleucine and Threonine).
    - When B12 is deficient odd C. numbered fatty acids accumulate in cell membrane of C.N.S Causing Neurologic symptoms.
- **Methionine synthase:**
  - Synthesis of Methionine from Homocysteine



## Enzyme methionine synthase requires vitamin B12 as a cofactor.



## ABSORPTION OF B12

- **Vitamin B12 Absorption Requires Two Binding Proteins:**
  - Gastric acid and pepsin release the vitamin from protein binding in food and make it available to bind to **cobalophilin**, a binding protein secreted in the saliva.
  - Vitamin B12 is absorbed bound to **intrinsic factor**, a small glycoprotein secreted by the parietal cells of the gastric mucosa.
  - In the duodenum, cobalophilin is hydrolyzed, releasing the vitamin for binding to intrinsic factor.

## **Vitamin B12 Requires intrinsic factor:**

- **In the duodenum, proteases digest B12 binding proteins and release B12, which then binds to IF, to form a complex (IF/B12).**
- **B12 must be attached to IF for it to be absorbed, as receptors in the terminal ileum of the small bowel only recognize the B12-IF complex;**
- **in addition, intrinsic factor protects the vitamin from catabolism by intestinal bacteria.**
- **Once the IF/B12 complex is recognized by specialized ileal receptors, it is transported into the portal circulation.**
- **Following absorption the vitamin is transported to the liver in the blood bound to transcobalamin II (TC-II/B12).**
- **The transcobalamin-II is degraded within a, and free B12 is finally released into the cytoplasm, where it may be transformed into the proper coenzyme.**

## **Absorption of food vitamin B12 thus requires an intact and functioning stomach, exocrine pancreas, intrinsic factor, and small bowel**

- **Problems with any one of these organs makes a vitamin B12 deficiency possible.**
- **Individuals who lack intrinsic factor have a decreased ability to absorb B12.**
- **Gastric acid releases the vitamin from food particles:**
  - **Therefore antacid and acid-blocking medications may inhibit absorption of B12.**
- **In addition some elderly people produce less stomach acid as they age thereby increasing their probability of B12 deficiencies.**

## **Vitamin B12 and/or folate deficiency can cause a characteristic megaloblastic anemia with ineffective erythropoiesis**

- **The anemia of Cobalamin deficiency may be accompanied by characteristic neurologic abnormalities.**
- **The megaloblastic features are identical in deficiencies of FA and Cbl.**
- **The two vitamins are intertwined biochemically so that the final common pathway that impairs DNA synthesis in hematopoietic cells is the same when either vitamin is deficient**
- **However, neuropathy occurs only with Cbl deficiency,.**
- **Megaloblastic anaemia results from impaired nucleotide biosynthesis (DNA Synthesis) due to a block in purine and thymidine biosynthesis.**
- **Block in purine and thymidine biosynthesis is consequence of vitamin B12 deficiency as it prevents the synthesis of THF derivatives (Folate metabolism) required for the purine and thymidine nucleotide.**

## **Vitamin B12; Deficiency**

- **Liver can store up to six years worth of vitamin B12, hence deficiencies are rare.**
- **B12 deficiency develops as a result of a lack of intrinsic factor in the stomach leading to malabsorption of the vitamin.**
- **Vitamin B12 Deficiency Results in:**
  - **Pernicious anaemia.**
  - **Neurological complications (Neuro psychiatric symptoms).**
  - **Gastrointestinal symptoms**



## **Vitamin B12 Deficiency Causes Pernicious Anemia**

- **Pernicious anemia** arises when vitamin B12 deficiency impairs the metabolism of folic acid, leading to functional folate deficiency that disturbs erythropoiesis, causing immature precursors of erythrocytes to be released into the circulation (megaloblastic anemia).
- The most common cause of pernicious anemia is failure of the absorption of vitamin B12 rather than dietary deficiency. This can be the result of failure of intrinsic factor secretion caused by autoimmune disease affecting parietal cells.
- **symptoms such as :**
- fatigue, depression, and poor memory may be experienced.
- **Neurological complications :**
- from a progressive demyelination of nerve cells.
- **Demyelination result from :**
- the increase in methylmalonyl-CoA that result from vitamin B12 deficiency

### **Treatment of B12 deficiency**

- **Folic acid & B12 deficiency symptoms mimic therefore Folic acid & B12 both must be given to halt CNS Symptoms.**
  - Supplements
  - Oral pills
  - Intramuscular
  - Intranasal
  - Sublingual