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**College of Medicine Lec.12(1-8)**

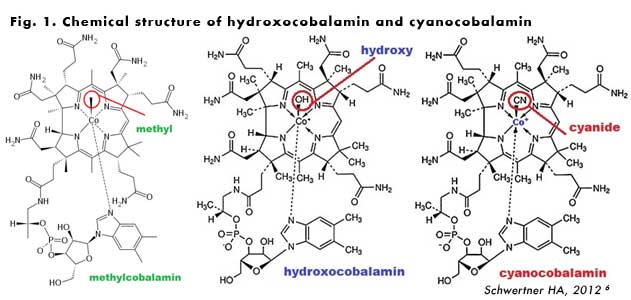
**Medical Biochemistry Dept. 2017-2018**

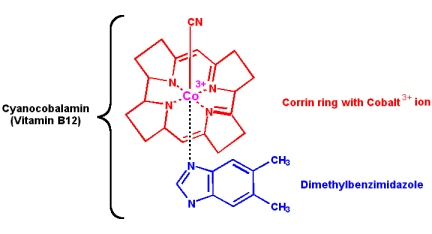
**Vitamin B12**, also called **cobalamin**, is a water soluble [vitamin](http://en.wikipedia.org/wiki/Vitamin) with a key role in the normal functioning of the [brain](http://en.wikipedia.org/wiki/Brain) and [nervous system](http://en.wikipedia.org/wiki/Nervous_system), and for the formation of [blood](http://en.wikipedia.org/wiki/Blood). It is one of the eight [B vitamins](http://en.wikipedia.org/wiki/B_vitamins).

It is normally involved in the [metabolism](http://en.wikipedia.org/wiki/Metabolism) of every [cell](http://en.wikipedia.org/wiki/Cell_(biology)) of the human body, **especially affecting** [**DNA**](http://en.wikipedia.org/wiki/DNA) **synthesis and regulation, but also** [**fatty acid**](http://en.wikipedia.org/wiki/Fatty_acid) **synthesis and energy production**. As the largest and most structurally complicated vitamin, it **can be produced industrially only through bacterial fermentation-synthesis.**

Vitamin B12 consists of a class of chemically-related compounds ([vitamers](http://en.wikipedia.org/wiki/Vitamer" \o "Vitamer)), all of which have vitamin activity. It contains the biochemically rare **element** [**cobalt**](http://en.wikipedia.org/wiki/Cobalt). [Biosynthesis](http://en.wikipedia.org/wiki/Biosynthesis) of the basic structure of the vitamin in nature is only accomplished by simple organisms such as some [bacteria](http://en.wikipedia.org/wiki/Bacteria) and algae, but conversion between different forms of the vitamin can be accomplished in the human body. **A common synthetic form of the vitamin,** [**cyanocobalamin**](http://en.wikipedia.org/wiki/Cyanocobalamin)**, does not occur in nature**, but is used in many pharmaceuticals and supplements, and as a food additive, because of **its stability and lower cost.**

Vitamin B12 is a collection **of** [**cobalt**](http://en.wikipedia.org/wiki/Cobalt) **and** [**corrin ring**](http://en.wikipedia.org/wiki/Corrin_ring) molecules which are defined by their particular vitamin function in the body. All of the substrate cobalt-corrin molecules from which B12 is made must be synthesized by bacteria. However, after this synthesis is complete, the body has a limited power to convert any form of B12 to another, by means of enzymatically removing certain prosthetic chemical groups from the cobalt atom. The various forms ([vitamers](http://en.wikipedia.org/wiki/Vitamer" \o "Vitamer)) of B12 are all deeply red colored, due to the color of the cobalt-corrin complex.

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Vitamin B12 was discovered from its relationship to the disease [**pernicious anemia**](http://en.wikipedia.org/wiki/Pernicious_anemia)**,** which is an [autoimmune disease](http://en.wikipedia.org/wiki/Autoimmune_disease) in which [parietal cells](http://en.wikipedia.org/wiki/Parietal_cell) of the stomach responsible for secreting [intrinsic factor](http://en.wikipedia.org/wiki/Intrinsic_factor) are destroyed. **Intrinsic factor is crucial for the normal absorption of B12,** so a lack of intrinsic factor, as seen in pernicious anemia, causes a [vitamin B12 deficiency](http://en.wikipedia.org/wiki/Vitamin_B12_deficiency).

**Medical uses**

Vitamin B12, is used **to treat** [**vitamin B12 deficiency**](http://en.wikipedia.org/wiki/Vitamin_B12_deficiency)**,** [**cyanide poisoning**](http://en.wikipedia.org/wiki/Cyanide_poisoning)**, and** [**hereditary deficiency of transcobalamin II**](http://en.wikipedia.org/wiki/Hereditary_deficiency_of_transcobalamin_II). It is also given as part of the [schilling test](http://en.wikipedia.org/wiki/Schilling_test) for detecting [pernicious anemia](http://en.wikipedia.org/wiki/Pernicious_anemia).

For [cyanide](http://en.wikipedia.org/wiki/Cyanide) poisoning, large amount may be given [intravenously](http://en.wikipedia.org/wiki/Intravenously), and sometimes in combination with [sodium thiosulfate](http://en.wikipedia.org/wiki/Sodium_thiosulfate). The mechanism of action is straightforward:

the hydroxycobalamin hydroxide [ligand](http://en.wikipedia.org/wiki/Ligand) is displaced by the toxic cyanide ion, and the resulting harmless B12 complex is excreted in [urine](http://en.wikipedia.org/wiki/Urine).

High vitamin B12 level in elderly individuals may protect against [brain](http://en.wikipedia.org/wiki/Brain) [atrophy](http://en.wikipedia.org/wiki/Atrophy) or shrinkage, associated with [Alzheimer's disease](http://en.wikipedia.org/wiki/Alzheimer%27s_disease) and impaired cognitive function.

**Structure**

Vitamin B12 is a collection of [**cobalt**](http://en.wikipedia.org/wiki/Cobalt) **and** [**corrin ring**](http://en.wikipedia.org/wiki/Corrin_ring) **molecules**,B12 is the most chemically complex of all the vitamins.

The structure of B12 is based on a [corrin](http://en.wikipedia.org/wiki/Corrin) ring, which is similar to the [porphyrin](http://en.wikipedia.org/wiki/Porphyrin) ring found in [heme](http://en.wikipedia.org/wiki/Heme), [chlorophyll](http://en.wikipedia.org/wiki/Chlorophyll), and [cytochrome](http://en.wikipedia.org/wiki/Cytochrome). The central metal ion is [**cobalt**](http://en.wikipedia.org/wiki/Cobalt).

Four of the six coordination sites are provided by the corrin ring, and a fifth by a dimethylbenzimidazole group. The sixth coordination site, the center of reactivity, is variable, being a [cyano](http://en.wikipedia.org/wiki/Cyano) group (-CN), a [hydroxyl](http://en.wikipedia.org/wiki/Hydroxyl) group (-OH), a [methyl](http://en.wikipedia.org/wiki/Methyl) group (-CH3) or a 5'-deoxy[adenosyl](http://en.wikipedia.org/wiki/Adenosine) group (here the C5' atom of the deoxyribose forms the covalent bond with Co), respectively.

[**Cyanocobalamin**](http://en.wikipedia.org/wiki/Cyanocobalamin) is one such "[vitamer](http://en.wikipedia.org/wiki/Vitamer)" in this [B complex](http://en.wikipedia.org/wiki/B_vitamins), the cyanocobalamin form of B12 is **easy to crystallize** and is **not sensitive to air-oxidation**; it is typically used as a form of B12 for food additives and in many common multivitamins.

**All cyanocobalamin is vitamin B12, but not all vitamin B12 is cyanocobalamin**. Pure cyanocoblamin possesses the deep pink colour associated with most octahedral cobalt(II) complexes and the crystals are well formed and easily grown up to milimetre size.

[**Hydroxocobalamin**](http://en.wikipedia.org/wiki/Hydroxocobalamin) is another form of B12 commonly encountered in pharmacology, but which is not normally present in the human body. Hydroxocobalamin is sometimes denonoted **B12a** . It is supplied typically in water solution for injection. Hydroxocobalamin is thought to be converted to the active enzymic forms of B12 more easily than cyanocobalamin.



**Hydroxycobalamine (B12a) is superior as:**

**1-**It is more active in enzyme systems.

**2-**It is retained longer in the body when given orally.

Hence,B12a is more useful for theraptic administration of B 12a by mouth.

**Metabolism**

**Absorption**

Vitamin B12 is absorbed from ileum,for its proper absorption it requires:

Presence **of HCL**, and **Intrinsic factor(IF)** of Castle, a constituent of normal gastric juice.

Mechanism of absorption, it has been shown that **two binding proteins** are required:

**Cobalophilin**: a binding protein secreted in the saliva.

**Intrinsic factor(IF)** : a glycoprotein secreted by parietal cells of gastric mucosa.

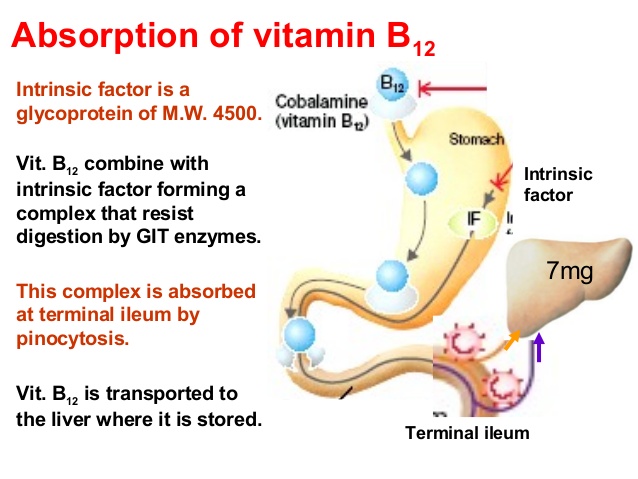
1-Gastric acid (HCL) and **pepsin release the Vit B12** from protein binding in food and make it **available to bind to salivary protein, cobalophilin**.

2-In the duodenum, **cobalophilin is hydrolyzed**, releasing the vitamin for binding to **Intrinsic factor (IF).**

3-Vitamin B12 is **absorbed** from the distal third of the ileum via specific binding site (receptors) that binds the B12-IF complex.

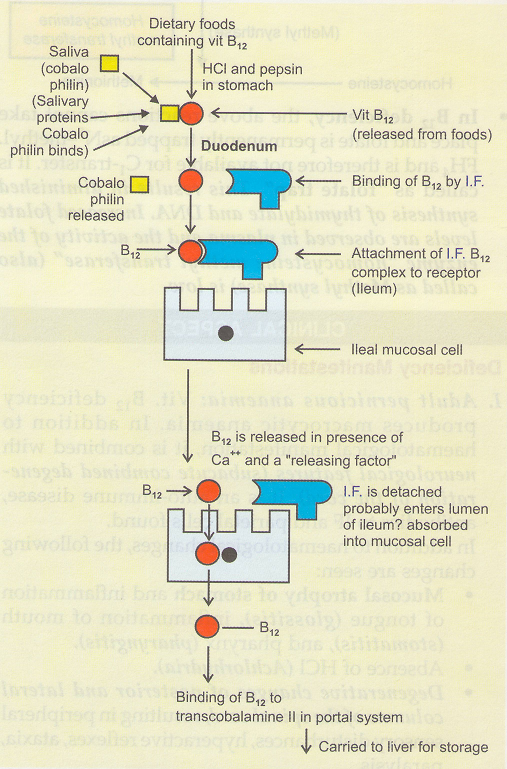
The removal of B12 from intrinsic factor (IF) in presence of **Ca++ ions and a releasing factor(RF)** secreted by duodenum take place and B12 enters the ileal mucosal cells for absorption into the circulation.

If ileal absorptive mechanism is functioning, it can adequately transport 0.5 to 10.0 µg of B12, small amount (1-3%) may be absorbed by simple diffusion.



**In supplements**, B12 is not bound to protein, and therefore does not need digestive enzymes or stomach acid to be detached from a protein. Stomach acid is needed to dissolve some B12 tablets, especially if not chewed. When taken in large enough doses, unbound B12 can overcome intrinsic factor defects because so much can be absorbed through passive diffusion.

There is some preliminary evidence that unbound B12, especially when combined with an absorption enhancer, can be directly absorbed through the membranes under the tongue at higher rates than through passive diffusion in the digestive tract.



**Transport in blood**

Vitamin B12 is transported in blood in association with specific proteins named **Transcobalamine I** and **Transcobalamine II and III.**

**Physiologically** **Transcobalamine II** is more **important.**

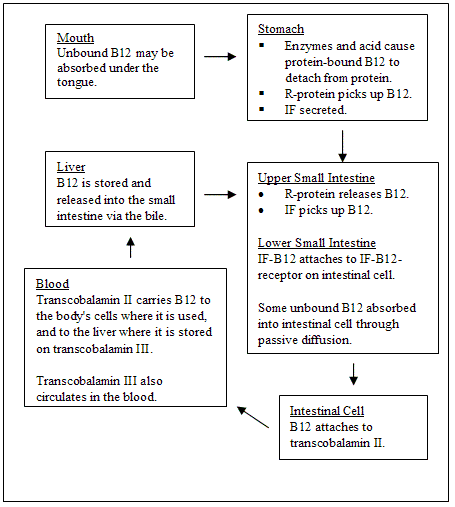
After B12 is absorbed into the intestinal cells, it attaches to transcobalamin II (TC2). Transcobalamin II is made in the intestinal cells , where it picks up B12 and transports it to all body tissues through the blood and cerebrospinal fluid . Cyanocobalamin appears in the blood no longer than 5 hours after ingestion of B12.

While transcobalamin II transports B12 to cells, about 3/4 of the B12 in the blood is stored on haptocorrin (aka transcobalamin I and cobalophilin).

Once the B12-TC2 complex arrives at the cell where it is needed, B12 is released from TC2 in the form of hydroxocobalamin. It is then turned into methylcobalamin or adenosylcobalamin and used for their respective enzymes.

Transcobalamin II also transports B12 to the liver for storage on transcobalamin III.

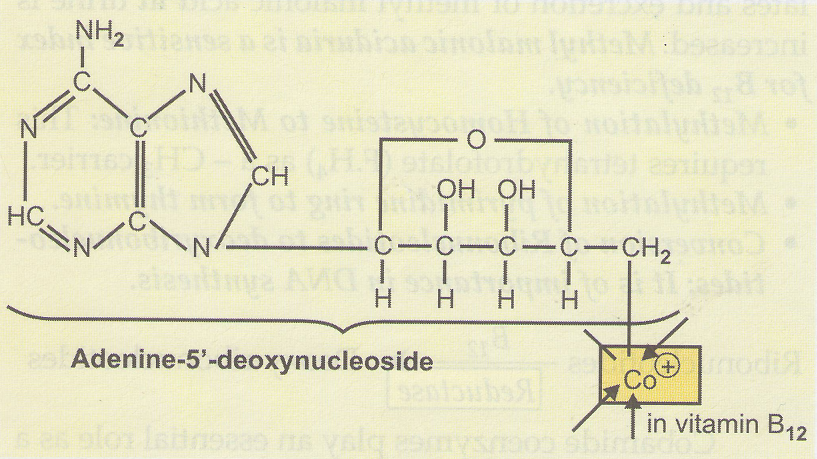
If the circulating B12 exceeds the binding capacity of the blood, the excess is excreted in the urine. This normally happens only after a B12 injection.



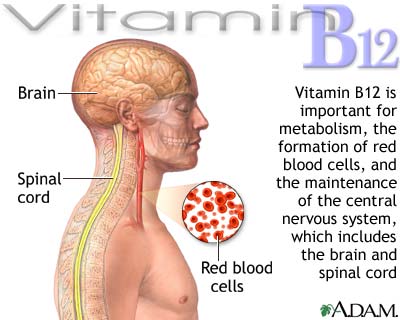
**Biological Active Forms of B12**

Biologically active forms **are cobamide coenzymes** act as coenzyme with various enzymes.

Cobamide coenzyme does not contain the cyano group attached to cobalt but instead there is an **Adenine Nuceoside** (5´-deoxyadenosine) which is linked to cobalt by a C→CO bond.



Vitamin B12 is normally involved in the metabolism of every cell of the body, especially affecting the DNA synthesis and regulation but also fatty acid synthesis and energy production. However, many (not all) of the effects of functions of B12 can be replaced by sufficient quantities of [folic acid](http://en.wikipedia.org/wiki/Folic_acid) (vitamin B9), since B12 is used to regenerate [folate](http://en.wikipedia.org/wiki/Folate) in the body.

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**Deficiency**

May be due to dietary factors, gastric factors as in post gastrostomy and in strict vegetarians.If absorption is prevented by lack of intrinsic factor it will cause pernicious anemia. Megaloblastic anemia appears due to B12 deficiency.

Vitamin deficiencies often go unnoticed until they are severe mostly because the symptoms overlap with many other diseases. Diagnosis of vitamin B12 deficiency is typically based on measurement of serum vitamin B12 levels.

Vitamin B12 deficiency can lead to a multitude of symptoms based on the degree of deficiency. The symptoms are mild to start with but can progressively worsen if the deficiency is not addressed with oral or sub-muscular replenishment of Vitamin B12.

**Clinical Symptoms of vitamin B 12 deficiency:**

**1-**Cardiovascular- increased risk of stroke or heart attack.

**2-**Psychiatric- a- Irratability and overall personality change.

b-Mild memory impairment,,occasional dementia.

c-Psyhosis.

d-Depression.

**3-**Hematologic- a-Megaloblastic anemia.

b-Pancytopenia.

**Symptoms**

Anemia as result from impaired DNA synthesis affecting the formation of the nucleus of new erythrocytes.

Homocystinuria and methylmalonic aciduria occur.

Neurological disorder is secondary to a relative deficiency of Methionine.