To start then

Vitamin B12 is the only, metal-containing vitamin - it is also a water-soluble vitamin that is stored in the liver and must come from the diet.

Vitamin B12 is a collective term for a group of cobalt-containing compounds known as corrinoids which when assembled with 5th and 6th position ligands are known as cobalamins. This is a corrin - notice just 1 proton - sorry about this but the nomenclature gets worse...a corrinoid (not so bad) just means a ring with peripheral decoration so the outer edges—"1" is the 1st carbon then go around up to 19 - (there's no "20" that would be the 4th linker, methane bridge). and the N's are numbered 21-24

Cobalamin is the specific

The principal cobalamins are:
- cyanocobalamin, hydroxocobalamin
- and the two coenzyme forms:
  - methylcobalamin and 5-deoxyadenosylcobalamin
- (adenosylcobalamin).
Vitamins are organic compounds required in the diet in, usually, very small amounts. They are conveniently classed as fat soluble (A, D, E and K) or water soluble (C and the B complex).

We need to consider

1. Vitamins in general
2. Chemical nature of Vit B12
3. Sources
4. Function in brief
5. Consequences of deficiency
6. Function of Vit B12 in detail

Just to be clear about how important B12 is – it is in every cell in humans and controls metabolism because the cobalamin complex is a cofactor in many enzymes – for example – and see below – the synthesis of the myelin sheath arounds nerves and in the synthesis of DNA, and on and on…we have to eat B12 – from animals and sea foods that consume the microorganisms that produce the B12. Deficiencies are common with poor diet and lead to numerous issues, the most obvious being the lack of red blood cells → anemia – pernicious because Fe tablets won’t cure it.

Ferrous fumarate, ferrous sulfate, and ferrous gluconate - notice Fe(II)!

https://www.nhs.uk/conditions/vitamin-b12-or-folate-deficiency-anaemia/symptoms/
https://www.nhs.uk/conditions/vitamin-b12-or-folate-deficiency-anaemia/
https://www.independent.co.uk › LIFE › PULSE
https://www.express.co.uk/life-style/health/1068365/vitamin-B12-deficiency-foods-diet-symptoms

Vitamin B12 deficiency: The best foods containing vitamin B12 to add to your diet

1. VITAMIN B12 deficiency can sometimes be caused by not including enough vitamin B12 in your diet. If you are experiencing symptoms of a deficiency, eat more of these B12-rich foods.

By KAROLINA KAMINSKA
PUBLISHED: 12:24, Mon, Jan 7, 2019 | UPDATED: 12:34, Mon, Jan 7, 2019

Vitamin B12 is involved in the production of red blood cells in the body and keeping the nervous system healthy. It also helps to release energy from food and is involved in the use of folic acid. Folic acid, otherwise known as vitamin B9, helps the body to form healthy red blood cells, and reduces the risk of central neural tube defects. Red blood cells carry oxygen around the body but will be prevented from doing so if there are too few of them or if they are abnormally large. The production of abnormally large red blood cells can happen in people who have a vitamin B12 deficiency.

* Check the nutrition labels while food shopping to see how much vitamin B12 different foods contain

The most common cause of vitamin B12 deficiency is pernicious anaemia, an autoimmune condition affecting the stomach. Pernicious anaemia causes the immune system to attack the cells in the stomach, so they are unable to absorb vitamin B12. However, in some cases, vitamin B12 deficiency can be caused by not getting enough B12 in your diet.

Good sources of vitamin B12 include meat, salmon, cod, milk, cheese, eggs and some fortified breakfast cereals.

A diet including meat, fish and dairy usually provides enough vitamin B12. However, people who don’t regularly eat these foods can become deficient.

* In some cases vitamin B12 deficiency is caused by a lack of B12 in your diet (Image: Getty Images)
As well as breakfast cereals fortified with vitamin B12, people who don’t eat meat, fish or dairy can get the vitamin from yeast extract like Marmite and some soy products.

“Check the nutrition labels while food shopping to see how much vitamin B12 different foods contain,” said the NHS.
According to the NHS, stores of vitamin B12 in the body can last for around two to four years without being replenished, so it can take a long time for any problems to develop after a dietary change. If vitamin B12 deficiency is diet-related, you may be prescribed vitamin B12 tablets to take every day between meals. Once vitamin B12 levels have returned to normal and your diet has improved, you may be advised to stop taking the tablets.

However, people who find it difficult to get enough vitamin B12 in their diets may need to take tablets for life. For people with a vitamin B12 deficiency related to pernicious anaemia or other non-diet-related causes, eating more B12-rich foods won’t help. Instead, the condition will usually be treated with injections of vitamin B12. At first these will be administered every other day for two weeks or until symptoms have started improving. After this, injections may be needed every months for the rest of your life. Symptoms of vitamin B12 deficiency include a pale, yellow tinge to the skin, a sore and red tongue, mouth ulcers, and pins and needles. Other symptoms include disturbed vision, irritability, depression, and a decline in mental abilities.

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**Vitamins in general**

The **13 Essential Vitamins**

- Vitamins - are organic compounds essential to health that must be supplied in small amounts in the diet
- Provide no energy and are unchanged by the reaction they catalyse
- Body does not synthesize vitamins - must be part of the diet

**Vitamins a Definition**

- A group of substances essential to normal metabolism (see below), growth and development, and regulation of cell function; vitamins work together with enzymes, co-factors, and other substances.
- Each vitamin has specific functions. If a certain vitamin is deficient, a deficiency disease results
- Enzymes - are proteins that serve as catalysts in biological synthesis and degradation reactions
- Called a Coenzyme because: it is a chemical that is required for an enzyme to function -

<table>
<thead>
<tr>
<th>remembering:</th>
<th>Apoenzyme + Cofactor$^1$ $\rightarrow$ Holoenzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>(protein only = inactive)</td>
<td>(active)</td>
</tr>
<tr>
<td>Light-mass and small Cofactor/CoEnzyme$^2$ (determines the type of reaction that the Holoenzyme carries out)</td>
<td>Heavy-large ApoEnzyme (determines the biochemistry)</td>
</tr>
<tr>
<td>$\rightarrow$ Heavier-larger (see next page) Holoenzyme (fully functional)</td>
<td></td>
</tr>
</tbody>
</table>

$^1$ Cofactor: An atom, organic molecule, or molecular group that is necessary for the catalytic activity (see catalysis) of many enzymes. A cofactor may be tightly bound to the protein portion of an enzyme and thus be an integral part of its functional structure, or it may be only loosely associated and free to diffuse away from the enzyme. Cofactors of the integral kind include metal atoms — such as iron, copper, or magnesium — or moderately sized organic molecules called prosthetic groups = heme; many of the latter contain a metal atom, often in a coordination complex (see transition element). Removal of the cofactor from the enzyme’s structure causes loss of its catalytic activity. From: Britannica Concise Encyclopedia.

$^2$ Loosely associated cofactors are sometimes called coenzymes; examples include most members of the vitamin B complex. Rather than directly contributing to the catalytic ability of an enzyme, coenzymes participate with the enzyme in the catalytic reaction. From: Britannica Concise Encyclopedia.
Larger (?) - not necessarily - the Coenzyme might fit - probably fits - into a pocket in the apo-enzyme - so may actually reduce the size/volume of the enzyme

**Metabolism**

1. Physical and chemical processes within the body related to body functions.
2. Processes of energy generation and use.
3. Processes that include digestion of food, absorption, elimination, respiration (the process or organs of breathing), blood circulation, and temperature regulation.

**Coenzymes (cofactors) act as group-transfer reagents**
- Hydrogen, electrons, or other groups can be transferred
- Two types of coenzymes:
  - **metabolite coenzymes**
  - **vitamin-derived coenzymes**

### Functional aspects of cofactors

<table>
<thead>
<tr>
<th>Activator ions - transient</th>
<th>Permanent metals – part of the enzyme</th>
<th>Transient cofactors – coenzymes – molecular species</th>
<th>Permanent cofactors – part of the enzyme – coenzymes – molecular species</th>
<th>Prosthetic groups – remain unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺; Ca⁺⁺; K⁺⁺; Mg⁺⁺; Mn⁺⁺</td>
<td>Fe-S centres – see the Fe₄S₄ from aconitase³</td>
<td>ATP</td>
<td>adenosylcobalamin AND methyl-cobalamin</td>
<td></td>
</tr>
</tbody>
</table>

³ Aconitase – has 4 Fe’s Fe₄S₄, 2Fe’s (Fe₂S₂) were seen in the photosystem of chlorophyll.

**Vitamin-derived coenzymes**

Vitamins are conveniently classed as [fat soluble](A, D, E and K) or [water soluble](C and the B complexes).

**Water-soluble B-complex vitamins** - thiamin (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pyridoxine (vitamin B6), folic acid, vitamin B12, and biotin, pantothenic acid and vitamin C - odd ones

**Chemical nature of Vitamin B12**

Vitamin B12 is also called cobalamin based on cobalt-containing compounds known as corrinoids.

Structure: Co-bound to a corrin ring; 5ᵗʰ position is bound a dimethylbenzimidazole – connected via a ribose sugar unit to one of the reduced pyrroles of the corrin ring. The 6ᵗʰ position of the cobalt can have one of 4 different groups attached. The cobalt cycles between Co³⁺, Co²⁺ and Co¹⁺ in its catalytic activity.

Cobalamins are cyanocobalamin, hydroxocobalamin and the two coenzyme forms methylcobalamin (note CH₃⁻) and 5'-deoxyadenosylcobalamin (adenosylcobalamin).

Vitamin B12 is a dark red multiple ring complex structure - see right

Different derivatives N-Co³⁺-R:
- methylcobalamin (R=CH₃) (= coenzyme B12 form ), cyanocobalamin (R=CN) - the vitamin, hydroxycobalamin (R=OH), aquacobalamin (R=H₂O); and, 5'-deoxyadenosylcobalamin (adenosylcobalamin) R= alkyl attached. 5'-deoxyadenosine (= coenzyme B12 →)
As we can see from the structure on the right, cobalamins comprise a nucleotide (base, ribose and phosphate) attached to a corrin ring. The corrin ring is made up of four pyrrole groups and an atom of cobalt in its centre. The cobalt atom attaches to one of: a methyl group, a deoxyadenosyl group, an hydroxyl group, water or a cyano group, to yield the five cobalamin forms mentioned above.

Sources and requirements

Vitamin B12 (cobalamin) only synthesised by bacteria and micro-organisms. Animals ingest it from their natural bacterial flora or eat other animals who have stores of the vitamin. Humans do the same.

Cyanocobalamin is the principal form of the vitamin used for fortification of foods and in supplements. Liver, brain, kidneys richest sources, then eggs; and lower in general meats, milk, tuna, cottage cheese, yogurt. Not in plants which makes it a problem for vegans who are at risk from deficiency. Recommend Daily Allowance (USA): 2-3 µg/day.
Hydrochloric acid in the stomach releases B12 from proteins in foods during digestion. Vitamin B12 is then absorbed from the ileum as a complex with intrinsic factor which is produced by the gastric mucosa - for a large figure see last few pages.

Dietary vitamin B12 is released from ingested proteins in the stomach through the action of pepsin and acid.

It is rapidly bound by one of two vitamin B12-binding proteins that are present in gastric juice; at acid pH, these binding proteins have a greater affinity for the vitamin than does intrinsic factor.

In the small intestine, pancreatic proteases digest the binding proteins, releasing vitamin B12 which then becomes bound to intrinsic factor.

Finally, there are receptors for intrinsic factor on the ileal mucosa which bind the complex, allowing vitamin B12 to be absorbed into portal blood. (from Richard.Bowen@colostate.edu)

**In summary: Transport:** Vitamin B12 binds to proteins in the stomach to protect the B12 from degradation by the pH 2 acidity - then in the small intestines, it is bound to the IF glycoprotein - deficiency of the intrinsic factor leads to B12 deficiency and pernicious anaemia. The vitamin B12-intrinsic factor complex recognises surface receptors of mucosal cells in the ileum and is absorbed.

The Cbl molecule is bound at the interface between the α and β domains of IF. X-RAY OF THE b12 BINDING SITE IN THE Intrinsic factor (IF) - see below for whole picture. Note - no 6th position ligand - just the 5th position benzimidazole - "tail" attached to the Co(III).
It is transported around the body bound to transcobalamin, a specific Vit B12 binding protein. An interesting paper - http://clinchem.aaccjnls.org/content/52/2/263

"The Cobalamin-Binding Proteins Transcobalamin and Haptocorrin in Maternal and Cord Blood Sera at Birth"

"Background: Two proteins carry vitamin B12 in plasma. Transcobalamin (TC) carries ~25% of total plasma vitamin B12 and is 6% to 20% saturated with cobalamin. Haptocorrin (HC) binds ~80% of total cobalamin and is largely saturated with cobalamin."

The Cbl molecule is bound to TC between the a and b domains in a manner very similar to that in IF, but now with its cobalt ion coordinated by the four nitrogen atoms of the corrin ring and by the N3B atom of the dimethylbenzimidazole ring as the fifth ligand on the a side of the corrin ring.

The sixth coordination site of the cobalt is occupied by the Nε2 atom of a histidine side chain, at position 175 in TC, which is located on a loop between helices a 7 and a 8.

B12 enters the blood stream and is taken up by the liver, bone marrow and blood cells prior to intracellular release. The vitamin is then converted into its coenzyme forms, as above. 3-5 mg is stored mainly in the liver in amounts sufficient to last up to 5 years. The requirement of vitamin B12 is (with vitamin D) the smallest of all the vitamins, only 2-3 micrograms per day.
4. Function in brief

Vitamin B₁₂ is important for the normal functioning of the brain and nervous system and for the formation of blood.

It is involved in the metabolism of every cell of the body, especially affecting DNA synthesis and regulation but also fatty acid synthesis and energy production.

Its effects are still not completely known.

Vitamin B₁₂ (cobalamin) derived cofactors are used for two important reactions in humans:

1. **Methylmalonyl CoA mutase** requires 5-deoxyadenosylcobalamin (known as adenosylcobalamin – mol structure above) - Mutase carbon chain rearrangement - shifts CH₃'s about. Involved in fat metabolism.

2. Methionine synthase (cofactor methylcobalamin) catalyses the conversion of homocysteine to methionine and tetrahydrofolate is also formed - see below) - this is a Methyl Transferase (MTA) - important in production of red blood cells. The second reaction taking Methionine back to Homocysteine (see last slide) is catalysed by Methionine Synthase Reductase (cofactor adenosylcobalamin) and forms

**5-adenosylmethionine (SAM)** - SAMs control myelin sheath covering of nerves - this deficiency leads to neurological problems - depression - because of neural problems.

Therefore, Vit B₁₂ controls:

- 1. production of blood platelets and red and white blood cells
- 2. normal nerve cell activity - formation of myelin basic protein,
- 3. DNA and RNA replication, and
- 4. production of the mood-affecting substance SAM (**S-adenosyl-L-methionine**),
- 5. One electron reduction and oxidation

Co(III) is d⁶ - the Co(III) can be reduced in 1e steps to Co(I) - d⁸

So starting with (N)₄-Co(III) - CH₃R homolysis results in CH₃R a radical and leaves a low spin d⁷ the alkyl radical is very reactive.
6. Vitamin B12 works closely together with vitamin B9 (folate) to regulate the formation of red blood cells and to assist in the function of iron.
7. Vitamin B12 is important for the activity of enzymes within cells that control fat, amino acid and carbohydrate metabolism.
8. Both vitamin B12 and the vitamin folate are essential for the production of DNA and RNA.
9. Cyanocobalamin promotes normal growth and development; treats pernicious anaemia.
10. Vitamin B12 helps in the maintenance of the central nervous system:
11. B12 plays a vital role in the metabolism of fatty acids essential for the maintenance of myelin.

Nerves are surrounded by an insulating fatty sheath comprised of a complex protein called myelin.

**Vitamin B12 participates with folic acid in DNA synthesis so its deficiency leads to a similar anaemia.**

**NOTE:** Nomenclature!! 5 6 7 8 = tetra but with 5-Me 1 6 7 8 tetra

**be able to explain (see next page)**
5. **Summary of the Effects of Vit B12 Deficiency (12 points)**

1. Deficiency results in fatigue, anaemia, impaired nervous system functioning, and can increase the risk of infection. Anaemia due to a true folic secondary folic acid deficiency caused by primary B12 deficiency is pernicious anaemia.
2. Folic acid deficiency is common in hospital patients - lack of absorption of B12 containing foods.
3. Deficiency most often afflicts elderly whose diets are not sufficiently rich in B12 foods.
4. Impaired methylmalonyl CoA mutase causes accumulation of unusual odd number carbon fatty acids. These accumulate in nerve cell membranes causing irreversible neurological disorders.
5. Vitamin B12 also has a separate biochemical role, unrelated to folate, in the synthesis of fatty acids in the myelin sheath that surrounds nerve cells. So, vitamin B12 deficiency has a severe effect on the nervous system.
6. Degeneration of spinal cord neurons.
7. Prolonged B12 deficiency can lead to nerve degeneration and irreversible neurological damage.
8. Vitamin B12 deficiency leads to irregular destruction of the myelin sheaths, which eventually causes paralysis and death.
9. Vitamin B9 (folate) and vitamin B12 are critical to the health of the nervous system and to a process that clears homocysteine from the blood. Elevated plasma homocysteine concentrations are considered to be a risk factor for vascular disease and birth defects such as neural tube defects.\(^4\)
10. Vitamins B12, B6, and B9 (folate) work closely together to control blood levels of the amino acid homocysteine - see also above - small here --
11. The most important use of vitamin B12 is to treat the symptoms of pernicious anaemia.
12. Vitamin B12 levels decrease with age and various measures of cognitive impairment are associated with reduced B12 status.

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\(^4\) The American Heart Association, and the National Institutes of Health’s (NIH) National Heart, Lung, and Blood Institute (NHLBI), have both recognized that elevated homocysteine levels are a potential risk factor for cardiovascular disease.
Pernicious anaemia due to a primary deficiency of vitamin B12 gives rise to a secondary deficiency of folic acid because all the folate ends up trapped as N5-methyl-tetrahydrofolate -- see next page --

Or following stomach surgery the small intestine (the ileum) has been removed... and more.

Or in the case of severe digestive problems, such as sprue (also called celiac disease), Crohn's disease, bacteria growth in the small intestine, or a parasite.

Or when drugs are taken to treat heartburn and ulcers for a long time. For example, omeprazole (Prilosec) and lansoprazole (Prevacid) - these are generally proton pump inhibitors.

Or people who eat a strict vegetarian (vegan) diet, and older adults who don't eat a variety of foods, and people with chronic alcoholism. Breast fed infants of vegan mothers are particularly at risk for B12 deficiency.

FOLIC ACID

The importance of folic acid during early pregnancy is the closure of the neural tube occurs around the 28th day of pregnancy.

Incidence of neural tube defects (spina bifida and anencephaly) is reduced by 400µg folic acid supplement/day before conception and during the first month of pregnancy.

Folic acid is a precursor for tetrahydrofolate that is used as a carrier of one carbon units at different levels of oxidation.

Effect of Deficiency: Megaloblastic anaemia, GI

Adequate levels of folate are particularly critical during the development of the nervous system. A shortage of folate in this period can cause neural-tube defects, including spina bifida. Anaemia caused by folate deficiency is very similar to that caused by B12 deficiency (pernicious anaemia).

Sources of folic acid: Intestinal bacteria, liver, yeast and green vegetables

Folate deficiency is probably the most common vitamin deficiency. Since addition of folate to flour in the U.S. began in 1996, neural-tube birth defects have decreased by ~20%.

RDA: 200 µg/day.

For the next slides:
6. **A function of coenzyme B12 - in detail**

In summary here – molecular details next page and at the end.

Only about 15 reactions in humans absolutely require cobalamin coenzymes – but without it – death. Methylcobalamin is the cofactor or coenzyme in Methionine Synthase (MS) - formation of methionine.

**Adenosylcobalamin (B12)** is a coenzyme in the reaction involved in methionine metabolism using methionine synthase reductase (MSR) - that is further reactions after methionine has been formed.

In the MS reaction below - CH₃-cobalamin is the cofactor.

\[ \text{N⁵-Methyl-} \text{Hfolate} + \text{CH₃-cobalamin} \rightarrow \text{Methionine synthase coenzyme} \rightarrow \text{CH₃-cobalamin} + \text{Hfolate} \]

*Hfolate* accepts methyl groups in a number of different reactions and is converted back to N⁵-Methyl-Hfolate.

*Hfolate* is converted to N⁵-methyl-Hfolate in a number of different reactions as it accepts methyl groups. The methyl group can only be removed and the Hfolate regenerated by the above reaction. (See folic acid).
We have seen that there are three main carriers of reduced one-carbon units—THF, SAM and cobalamin derivatives of tetrahydrofolic acid (= THF) or here N5-methyl-H4-folate. 

More detail on the MS and MSR cycles mentioned above: Methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MS) and methionine synthase reductase (MSR or sometimes MTRR) in the folate cycle. The three enzymes of folate metabolism play an essential role in both DNA synthesis and methylation processes.

SAM: S-adenosylmethionine


Folate Metabolism
Intrinsic factor with bound B12\textsuperscript{5}, notice no 6\textsuperscript{th} position binding of the cobalt, contrast transcobalamin below.

Transcobalamin – with B12 embedded
Vitamin B12 may protect older brains from shrinking: study

Elderly people who have higher levels of vitamin B12 in their blood may gain some protection against brain shrinkage, a new study suggests.

The brain normally shrinks about 0.5 per cent per year in normal elderly brains, compared with 1 per cent in those with mild cognitive impairment and 2 per cent in the same time for those with Alzheimer's, said the study's lead author, pharmacology Prof. David Smith of the University of Oxford in Britain.

In Tuesday's issue of the journal Neurology, Smith and his colleagues report that people in the upper third of vitamin B12 levels were six times less likely to experience brain shrinkage compared with those who had the lowest levels.

While the latest results suggest that modifying B12 might protect the brain and possibly prevent cognitive decline, the researchers cautioned the findings to date do not prove a benefit.

"Many factors that affect brain health are thought to be out of our control, but this study suggests that simply adjusting our diets …may be something we can easily adjust to prevent brain shrinkage and so perhaps save our memory," agreed study author Anna Vogiatzoglou, also at Oxford.

Smith and Vogiatzoglou used a more accurate way of testing for vitamin B12 compared with previous studies that showed mixed results.

"The result is novel as it is the first time that something in the blood which is related to our diet has been shown to be related to brain shrinkage," Smith said.

Vitamin B12 helps in the formation of red blood cells and is important to help maintain the central nervous system.

A full-blown deficiency of vitamin B12 is rare in developed countries, but elderly people may not absorb it well and vegetarians may not get enough from their diet.

Vitamin B12 deficiency is a serious problem in less developed countries such as India. Deficiency can lead to anemia and neurological damage.
Summary of information about B12 from these notes

1. Vitamin B12 is the only, metal-containing vitamin –
2. The principal cobalamins are: cyanocobalamin, hydroxocobalamin and the two coenzyme forms methylcobalamin and 5-deoxyadenosycobalamin (adenosylcobalamin).
3. Structure: Co-bound to a corrin ring; 5th position is bound a dimethylbenzimidazole –connected via a ribose sugar unit to one of the reduced pyrroles of the corrin ring. The cobalt cycles between Co3+, Co2+ and Co1+ in its catalytic activity.
4. Called a Coenzyme because: it is a chemical that is required for an enzyme to function – remembering: Apoenzyme+Cofactor6 → Holoenzyme
5. Transport: Vitamin B12 binds to a glycoprotein, the intrinsic factor, in the stomach. The vitamin B12-intrinsic factor complex recognises surface receptors of mucosal cells in the ileum7 and is absorbed. The Cbl molecule is bound at the interface between the α and β domains of IF as shown.

It is transported around the body bound to transcobalamin (TC) - see RHS. - bottom - all 6 positions occupied now...

6. The Cbl molecule is bound to TC between the α and β domains in a manner very similar to that in IF, with its cobalt ion coordinated by the four nitrogen atoms of the corrin ring and by the N3B atom of the dimethylbenzimidazole ring as the fifth ligand on the α side of the corrin ring. The sixth coordination site of the cobalt is occupied by the N ε2 atom of a histidine side chain, at position 175 in TC.
7. Vitamin B12 (cobalamin) derived cofactors are used for two important reactions in humans:
   - Methylmalonyl CoA mutase requires 5-deoxyadenosylcobalamin (known as adenosylcobalamin) - Mutase= carbon chain rearrangement – shifts CH3’s about. – involved in fat metabolism.
   - Methionine synthase (cofactor methylcobalamin) catalyses the conversion of homocysteine to methionine and tetrahydrofolate is also formed - this is a Methyl Transferase (MTA) - important in production of red blood cells. The second reaction taking Methionine back to Homocysteine (see last slide) is catalysed by Methionine Synthase Reductase (cofactor adenosylcobalamin) and forms S-adenosylmethionine (SAM) - SAMs control myelin sheath covering of nerves - this deficiency leads to neurological problems - depression - because of neural problems.

Adenosylcobalamin (B12) is a coenzyme in the reaction involved in methionine metabolism using methionine synthase reductase (MSR). In the MS reaction - CH3-cobalamin is the cofactor.

8. Vitamin B12 works closely with vitamin B9 (folate) to regulate the formation of red blood cells and to assist in the function of iron, and in the production of DNA and RNA, and in the maintenance of the central nervous system and a vital role in the metabolism of fatty acids essential for the maintenance of myelin.

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7 The ileum is the final section of the small intestine. It is about 2-4 m long in humans, follows the duodenum and jejunum and is separated from the cecum by the ileocecal valve (ICV). The pH in the ileum is usually between 7 and 8 (neutral or slightly alkaline). Its function is mainly to absorb vitamin B12 and bile salts and whatever products of digestion were not absorbed by the jejunum. Ref: Wikipedia.
### Expectations from this unit

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Coenzyme B12 is based on the Co(III)-corrin ring with a 5’-deoxyadenosyl group bound to the Co(III).</td>
</tr>
<tr>
<td>2</td>
<td>Many reactions involve moving a CH₃ group around – called mutase reactions. Reactions involve adding a CH₃ group (methyl transferase - MTA) include the formation of methionine from homocysteine.</td>
</tr>
<tr>
<td>3</td>
<td>Other MTA reactions involve addition of CH₃ to Hg²⁺ in anaerobic bacteria. B12 deficiency reduces folic acid so setting off folic-acid deficiency symptoms.</td>
</tr>
<tr>
<td>4</td>
<td>Key features – the vitamin taken as a pill has a CN⁻ as the 6ᵗʰ position. This is replaced by the 5’-deoxyadenosyl group in the coenzyme (one of the active form of the molecules (in mutases)). Coenzymes bind to an apo-enzyme to form a holoenzyme that is biologically active. The Co changes between Co(I), Co(II), and Co(III) in its reactions.</td>
</tr>
</tbody>
</table>