Biochemical Aspects of Vitamin B Deficiency

Objectives

- Characterize the biochemical functions of different vitamin B substances.
- Investigate the causes of vitamin B deficiency and its effects in the body
- Understand the importance of vitamin B deficiency and factors affecting vitamin b deficiency

Vitamins

Definition

- Vitamins are organic compounds that are essential in the diet to promote and regulate the chemical reactions and processes needed for growth, reproduction and maintenance of health.
- Organic compounds classified as vitamins if the lack of a compound in the diet results in deficiency symptoms that are relieved by the addition to the diet.

Functions

- Vitamins aid in chemical reactions that produce energy from carbohydrates, fat proteins and alcohol.

Outline

- **Vitamins**
  - **Definition**
  - **Classification – vitamin, A,B,C,D,E and K**
  - **Role of vitamins as coenzymes and cofactors**
- **Vitamin B - B1, B2, B3, B5, B6, B7, B9, and B12**
- **Vitamin B1 – Thiamine**
  - **Sources**
  - **Chemical and physical properties**
  - **Recommended Dietary Allowance (RDA)**
  - **Factors affecting Thiamine requirements**
  - **Deficiency diseases**
  - **Supplements**
- **Vitamin B2 or Riboflavin**
  - **Food sources and RDA**
  - **Factors affecting riboflavin deficiency**
  - **Ariboflavinosis**
  - **Deficiency Symptoms**

Outline (con't)

- **Vitamin B3 or Niacin**
  - **Coenzyme role**
  - **Chemical and physical properties**
  - **Functions**
  - **Food sources and RDA**
  - **Niacin deficiency**
  - **Deficiency symptoms**
- **Vitamin B5 or Pantothenic Acid**
  - **Food sources and RDA**
  - **Functions**
  - **Pantothenic Deficiency**

Outline (con't)

- **Vitamin B6 or Pyridoxine, pyridoxal, pyridoxamine**
  - **Functions**
  - **Coenzyme role**
  - **Metabolic Roles of PP**
  - **Vitamin B6 Deficiency**
  - **Drug Interactions**
- **Vitamin B7 or Biotin - H**
  - **Functions**
  - **Coenzyme role**
  - **Biotin Deficiency**
  - **Deficiency symptoms**

Outline (con't)

- **Vitamin B9 or Folic Acid**
  - **Functions**
  - **Activation of Folic**
  - **Coenzyme role**
  - **Vitamin B9 Deficiency**
  - **Deficiency symptoms**
  - **Inbitors of folate synthesis**
  - **Supplements**
- **Vitamin B12 or Cobalamin**
  - **Functions**
  - **Coenzyme role**
  - **Cobalamin Deficiency**
  - **Deficiency symptoms**
  - **Effects of Deficiency**

Classification of Vitamins

- Vitamins were named alphabetically and classified in the order to which they were identified: A, B, C, D and E. The B vitamins were named with numbers because they were later found to be many substances. Vitamins B consists of thiamin (B1), riboflavin (B2), niacin (B3), B6 and B12.

Grouping based on fat and water solubility

1. Water-soluble vitamins include Vitamin B and C.
2. Fat-soluble vitamins include vitamins A, D, E and K.

Grouping based on function

3. Coenzyme or components of coenzymes – Vitamin B and vitamin C
4. Red Blood Cell synthesis – Folate, Vitamin B6 and B12.

Classification of Vitamins (continued)

Grouping based on function (con't)

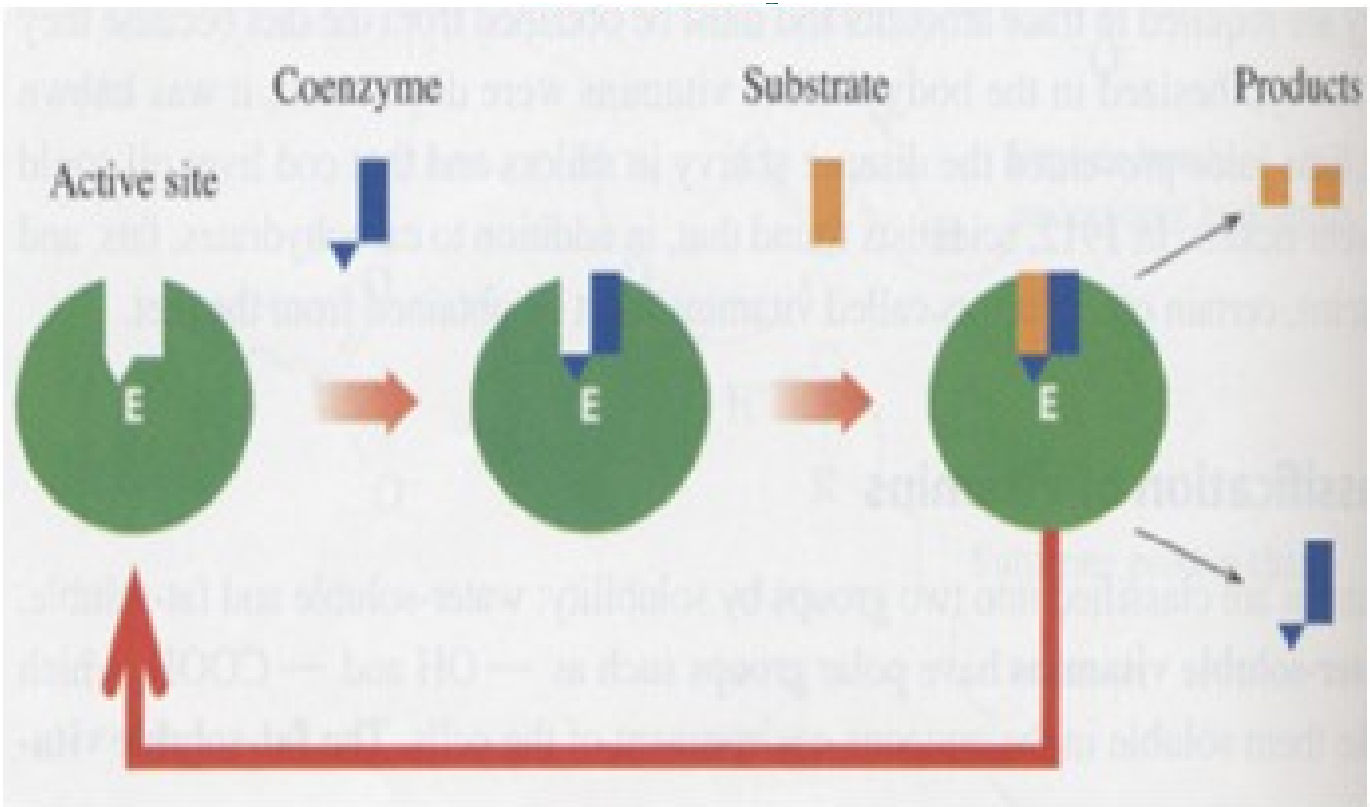
3. Metabolism of energy-yielding nutrients –
   Thiamin, riboflavin, niacin, pantothenic acid and vitamin B6
4. Amino acid/homocysteine metabolism – Folate, Vitamin B6 and B12.
5. Fatty acid synthesis - Biotin, pantothenic acid and niacin
6. Antioxidant protection – Vitamin C and E
7. Nerve transmission - Thiamin, vitamin B6 and B12
8. Gene Expression – Vitamin A and D

Coenzymes

- Definition – small non protein organic molecules that act as carriers of electrons or atoms in metabolic reactions and are necessary for the proper functioning of enzymes

- Many vitamins act as coenzymes. The active coenzyme form of a vitamin serves as a carrier of electrons or chemical groups. The coenzymes combines with the incomplete enzyme to form the active enzyme. When the enzyme function in a reaction, the chemical group (or electrons) is transferred from the coenzyme to a molecule to form a new molecule. The enzyme and coenzyme are then released and reused in subsequent reactions.

The active form of many enzymes require the combination of the protein (enzyme) with a coenzyme usually vitamins



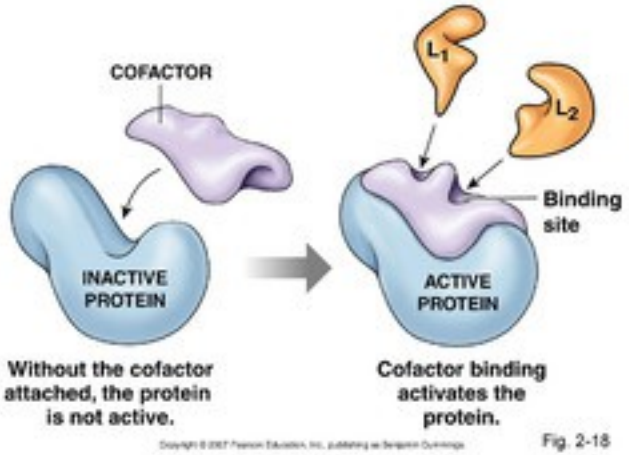
Coenzyme role of Vitamin B

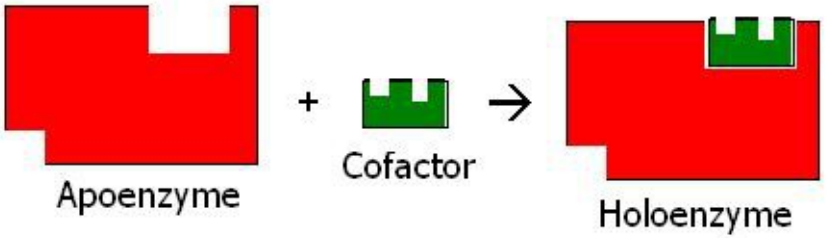
The B vitamins have important metabolic roles as coenzyme partners with cell enzymes that control energy metabolism and build tissues

Eight Vitamins in this group

1. Associated with classic deficiency diseases – thiamin, riboflavin and niacin
2. Coenzyme factors – panthothenic acid, biotin and pyridoxine (vitamin B6)
3. Blood forming factors - folate and vitamin B12 or cobalamin

Vitamins as Cofactors of Enzymes (Protein)





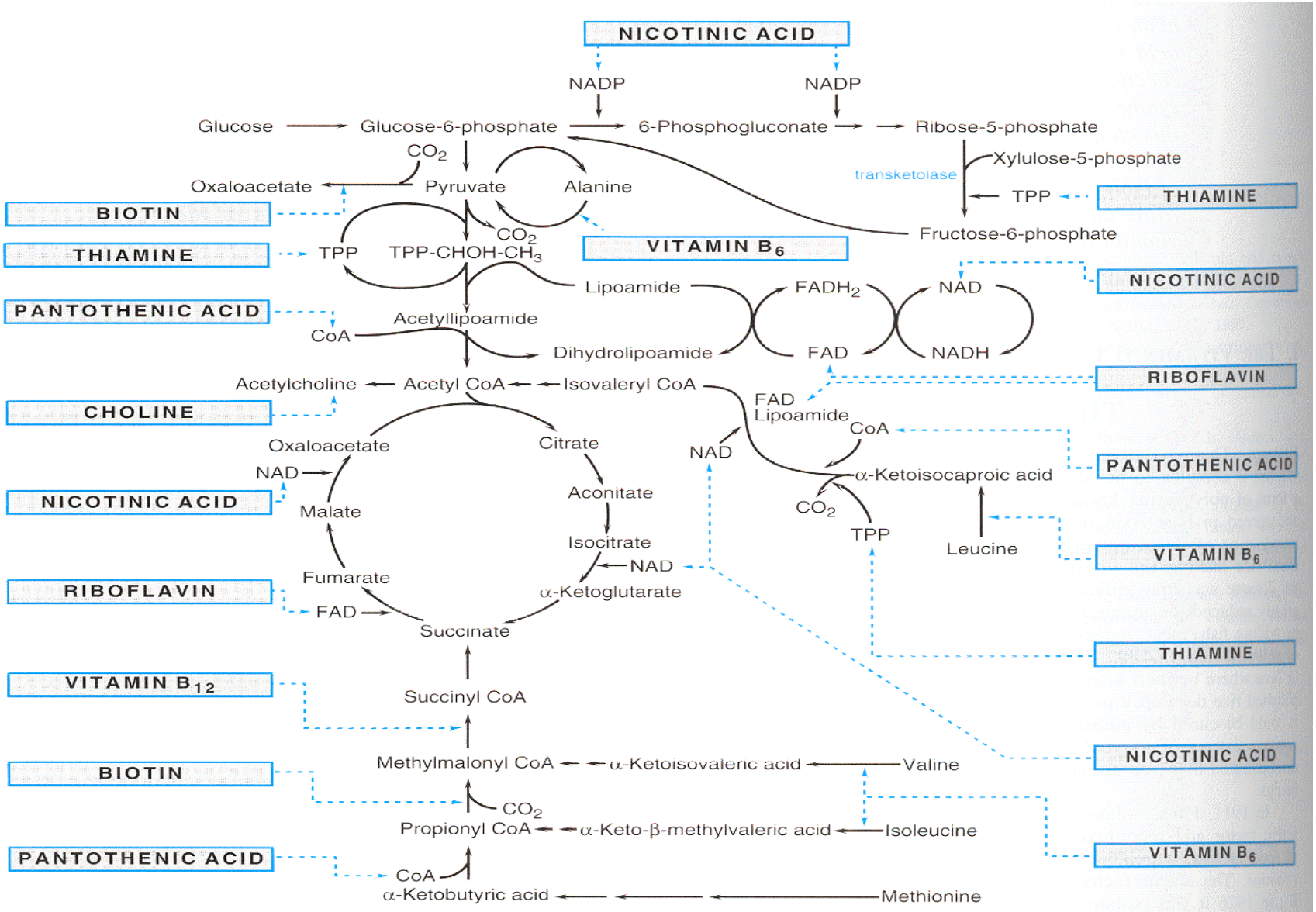
Enzymes and cofactors

- A **holoenzyme** refers to a catalytically active enzyme that consists of both **apoenzyme** (enzyme without its cofactor(s)) and cofactor. There are two groups of cofactors: metals and small organic molecules called coenzymes. Coenzymes are small organic molecules usually obtained from vitamins.

- **Prosthetic groups** refer to tightly bound coenzymes, while **cosubstrates** refer to loosely bound coenzymes that are released in the same way as substrates and products. Loosely bound coenzymes differ from substrates in that the same coenzymes may be used by different enzymes in order to bring about proper enzyme activity.

- Enzymes without their necessary cofactors are called apoenzymes, which are the inactive form of an enzyme. Cofactors with an apoenzyme are called a holoenzyme, which is the active form.

Vitamins in cellular respiration

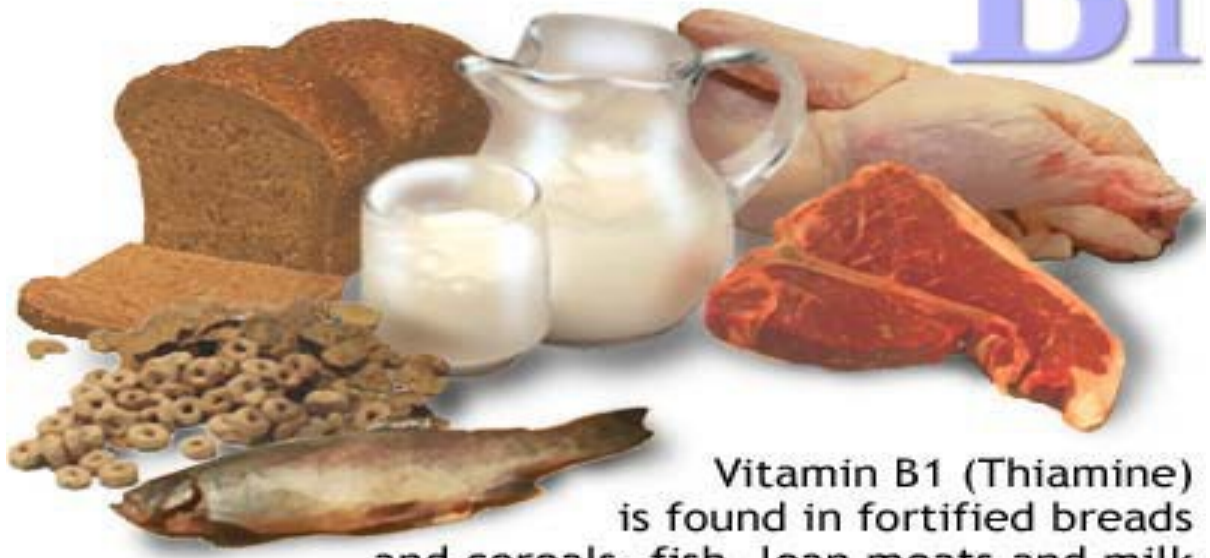


Different kinds of Vitamin B

Vitamin	Name	Deficiency of Symptoms or Disease
Vitamin B1	Thiamine	Beriberi, Wernicke-Korsakoff syndrome
Vitamin B2	Riboflavin	Angular stomatitis, dermatitis, photophobia
Vitamin B3	Niacin, Nicotinic acid	Pellagra
	Niacinamide, Nicotinamide	
Vitamin B5	Pantothenic Acid, Calcium Pantothenate	Acne and paresthesia, although it is uncommon
Vitamin B6	Pyridoxine, pyridoxal, pyridoxamine	Epileptiform convulsions, dermatitis, hypochromic anemia
Vitamin B7	Biotin	Dermatitis
Vitamin B9	Folic Acid / Pteroylglutamic acid	Megaloblastic anemia
Vitamin B12	Cyanocobalamin	Pernicious and megaloblastic anemia, neuropathy

Sources of Vitamin B

Vitamin B1



Vitamin B1 (Thiamine)
is found in fortified breads
and cereals, fish, lean meats and milk

A.D.A.M.

Thiamin, Aneurin or Vitamin B1

- **Sources**
- Thiamine comes from enriched grains such as cereals, baked goods, pork, whole grains, legumes, nuts, seeds and organ meats (liver, kidney and heart).
- **Availability**
- Thiamine is destroyed by cooking and storage because it is sensitive to heat, oxygen and low acid conditions. Its availability may be also affected by antithiamin factors that destroy the vitamins. Tea, coffee, betel nuts blueberries and red cabbage contain antithiamin factors. Frequent consumption of these antithiamin factors increases risk of thiamin or vitamin B1 deficiency.

Thiamin or Vitamin B1

- **Thiamin in the body and its physiological functions**
- Thiamin is important in energy producing reactions in the body. The active form **thiamin pyrophosphate (TPP),** is a coenzyme in the decarboxylation (carboxyl, COOH removal) and transketolation (ketoaldehyde removal)
- During cellular respiration TPP is required in the reaction that forms acetyl-CoA from pyruvate in the mitochondria before its entry into the citric acid cycle to produce energy for cell functions. Likewise, it is also integral in the **lipogenesis** pathway when fatty acids are synthesized.
- Adequate thiamine is required as a **cofactor to drive this key multi-enzyme complex** in the citric acid cycle in the mitochondria as a cofactor.
- Thiamin is also needed for the metabolism of other sugars and certain amino acids for the synthesis of the neurotransmitter acetylcholine, and for the production of sugar ribose, which is needed to synthesize RNA (ribonucleic acid)

Sources of thiamin

Thiamin occurs in small quantities in many nutritious foods that people like to eat every day. Sunflower seeds, watermelon, pork, black beans, and green peas are all exceptionally rich in thiamin. Thiamin-enriched foods like breads and cereals are also good sources.

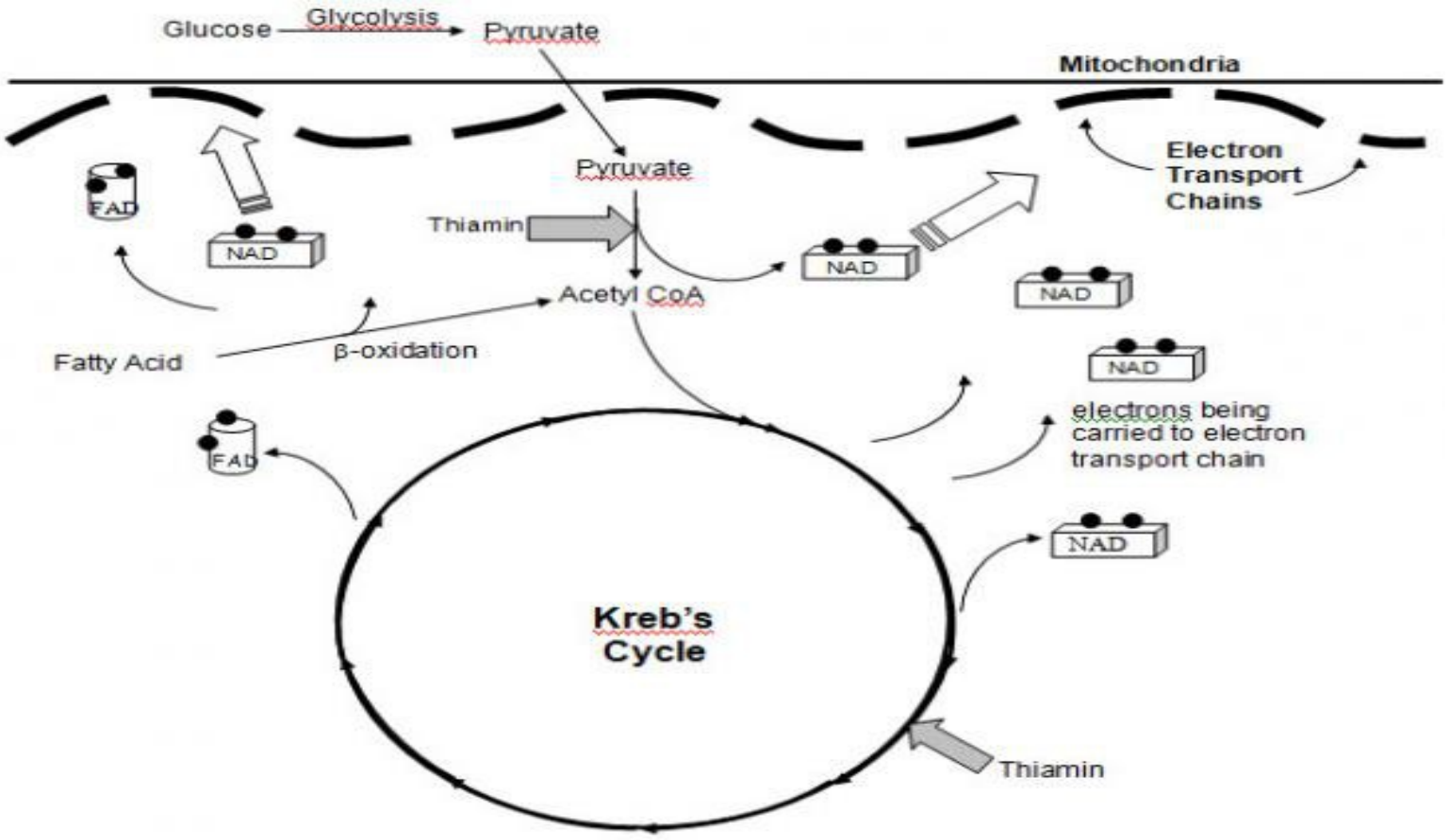
Vitamin B1

- Its phosphate derivatives are involved in many cellular processes. The best-characterized form is thiamine pyrophosphate (TPP), a coenzyme in the catabolism of sugars and amino acids and is comprises 80% of the total thiamin in the body. Thiamine is rapidly absorbed in the duodenum and is combined with phosphate in the jejunal mucosa

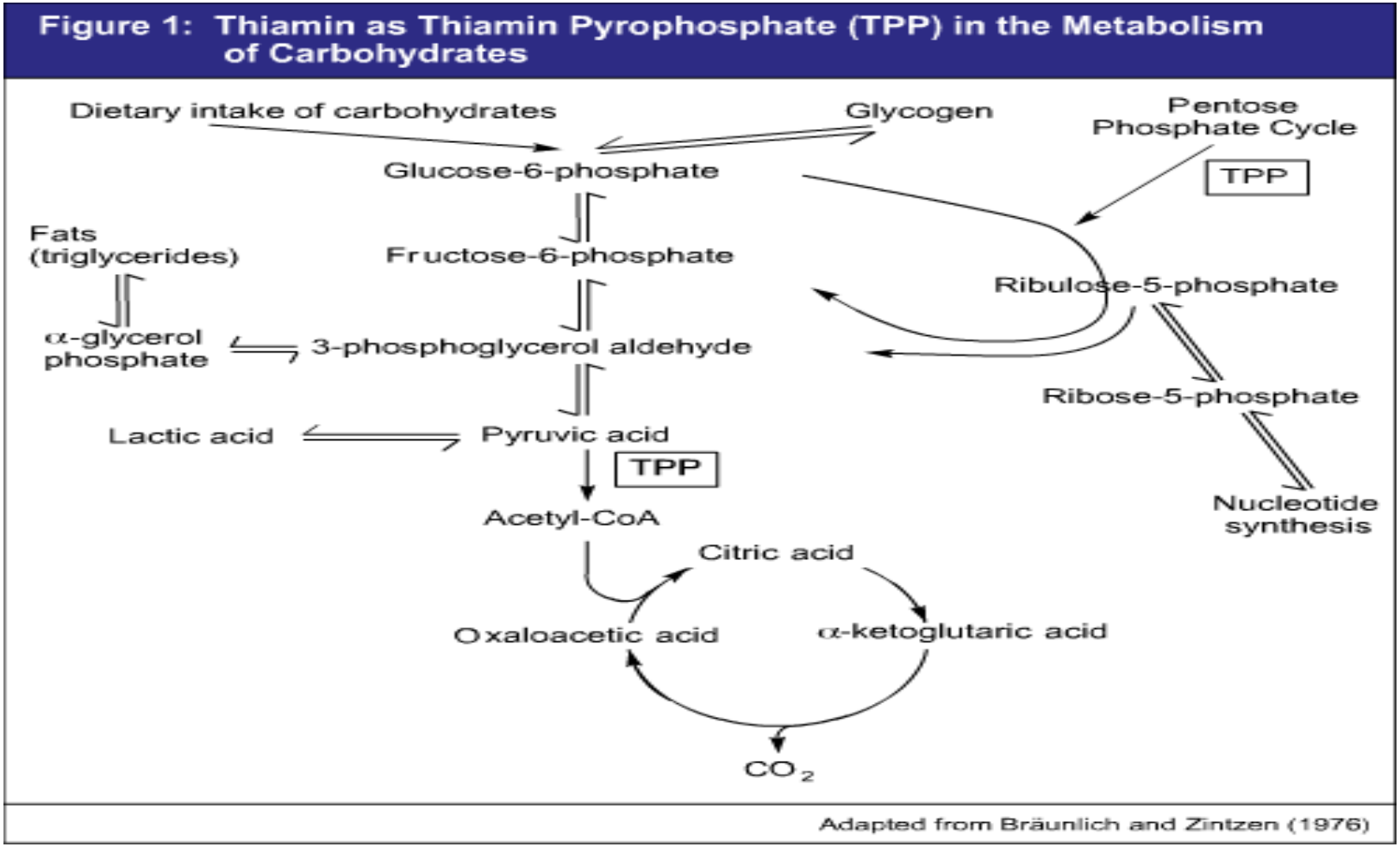
- Thiamine is used in the biosynthesis of the neurotransmitter acetylcholine and gamma-aminobutyric acid (GABA).

- All living organisms use thiamine in their biochemistry, but it is synthesized only in bacteria, fungi, and plants. Animals must obtain it from their diet, and thus, for them, it is an essential nutrient.

Thiamin or Vitamin B1 in cellular respiration



Thiamin or Vitamin B1 in cellular respiration



Thiamin – chemical and physical nature

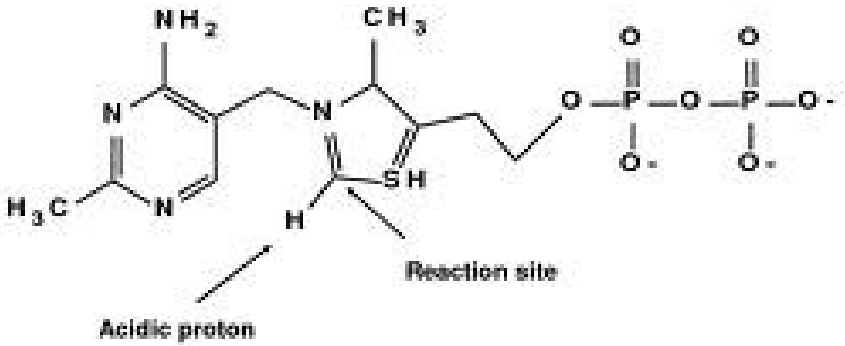
- Thiamin is a water-soluble and fairly stable vitamin, although it is destroyed in alkaline solution.
- Its name comes from its ring-like structure

- Molecular Formula
- C12H17CIN4OS

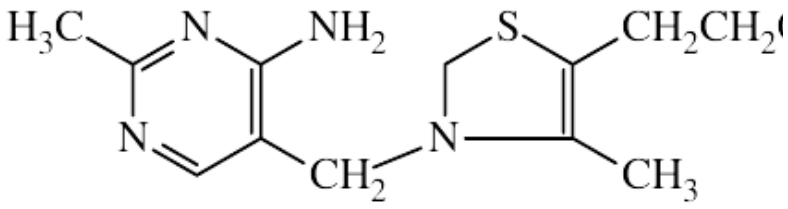
- Molar Mass
- 300.81 g mol

Formula

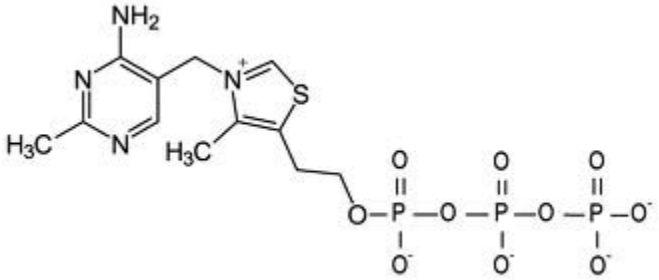
2-[3-[(4-Amino-2-methyl-pyrimidin-5-yl)methyl]-4-methyl-thiazol-5-yl] ethanol



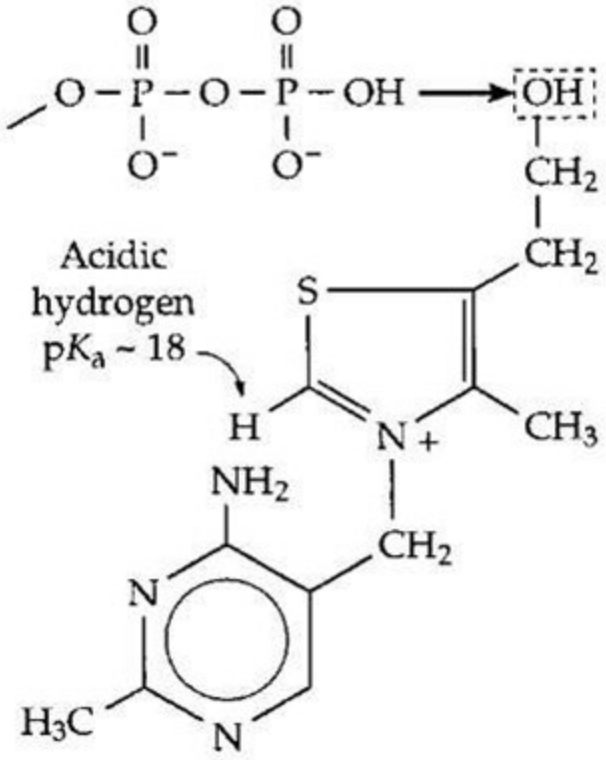
Chemical formula of thiamin and thiamin pyrophosphate (TPP)



THIAMINE



In the coenzyme thiamin diphosphate (thiamin pyrophosphate) the –OH group is replaced by



Thiamin or Vitamin B1 requirement

- Recommend daily intakes or recommended daily allowance (RDA)
- Dietary Reference Intakes for Thiamin:
- Infants
- 0 - 6 months: 0.2* milligrams per day (mg/day)
- 7 - 12 months: 0.3* mg/day
- *Adequate Intake (AI)
- Children
- 1 - 3 years: 0.5 mg/day
- 4 - 8 years: 0.6 mg/day
- 9 - 13 years: 0.9 mg/day
- Adolescents and Adults
- Males age 14 and older: 1.2 mg/day
- Females age 14 to 18 years: 1.0 mg/day
- Females age 19 and older: 1.1 mg/day
- The best way to get the daily requirement of essential vitamins is to eat a balanced diet that contains a variety of foods. Requirement is increased during pregnancy and lactation

Vitamin B1 Deficiency Diseases

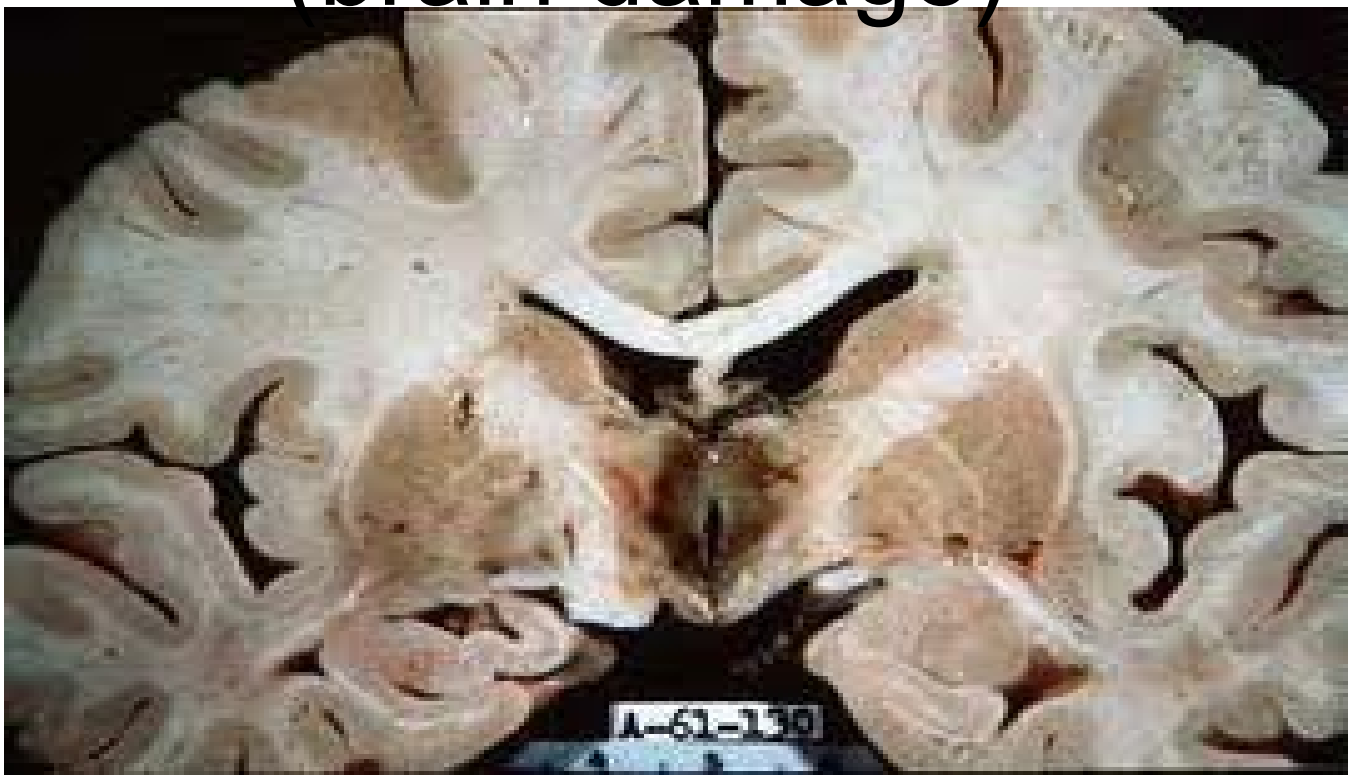
- A lack or deficiency of thiamin can cause weakness, fatigue, psychosis, and nerve damage.

- Thiamin deficiency in the United States is most often seen in people who abuse alcohol (alcoholism). A lot of alcohol makes it hard for the body to absorb thiamin from foods. Unless those with alcoholism receive higher-than-normal amounts of thiamin to make up for the difference, the body will not get enough of the substance. This can lead to a disease called **beriberi.**

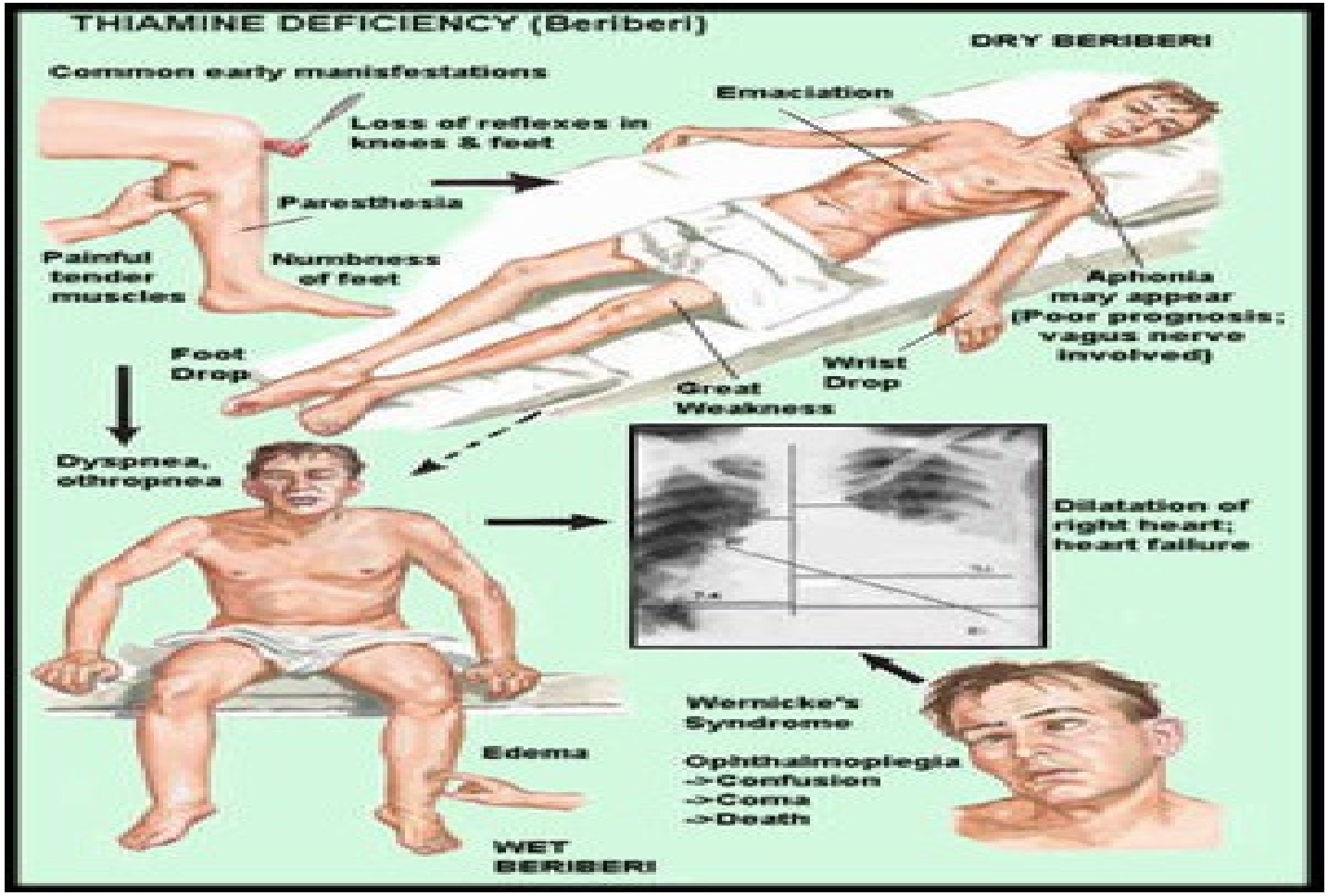
- **Beriberi** affects the nervous and cardiovascular systems. It is called the disease of the peripheral nerves and is characterize by pain (neuritis) in and paralysis of the extremeties, cardiovascular changes and edema. The symptoms of weakness and depression is probably due to the inability to completely use glucose. Brain and nerve tissue rely only on glucose for energy.

- In severe thiamin **deficiency, brain damage can occur. One type is called Korsakoff syndrome**. The other is **Wernicke's disease.** Either or both of these conditions can occur in the same person. Both conditions involve loss of specific functions in the brain and in nerves thought out the body. Both disease are characterized by mental confusion, psychosis, memory disturbances and eventually coma.

Wernicke-Korsakoff – (brain damage)



Beri-beri and Wernicke's syndrome



BERI-BERI

Factors that influence thiamin requirements and personal care of patients

Alcoholism

- Both primary (lack of adequate diet) and conditioned (effect of alcohol) malnutrition develop and may bring serious neurologic disorders. Alcoholics are vulnerable because thiamin absorption is decreased due to the effect of alcohol on the gastrointestinal tract. Likewise, the liver damage that occurs with chronic alcohol consumption reduces conversion of thiamin to active coenzyme forms. Thiamin intake may also be low due to a diet high in alcohol and low in nutrient-dense foods.

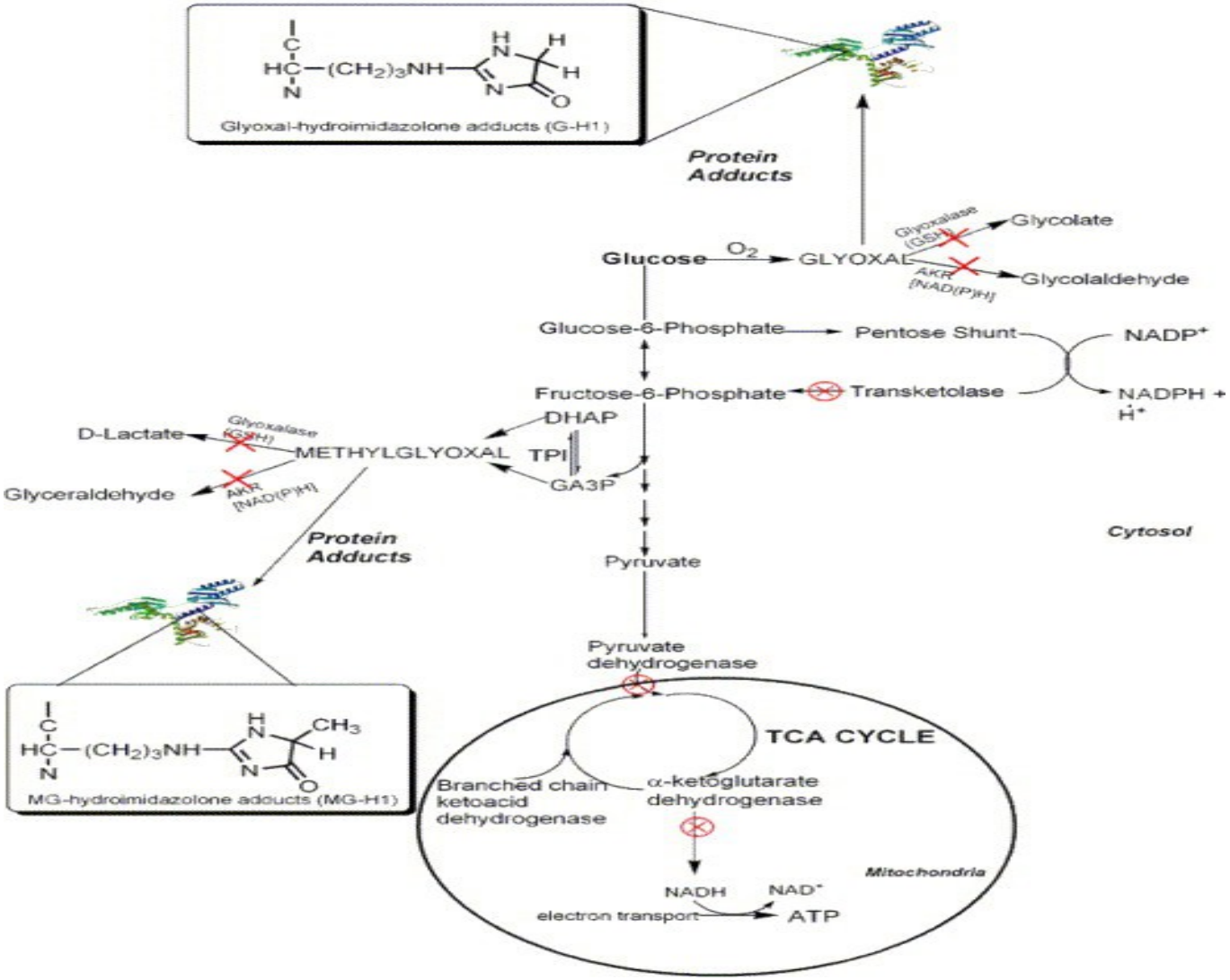
Other disease

- Fevers and infections increase cellular energy requirements. Elderly and persons with chronic illness require particular attention.

Normal growth and development

- Increase of 50% increase of thiamin supplements during gestation and lactation because of the rapid fetal growth and rapid metabolic rate
- Continuing growth in infancy, childhood, adolescence increase the thiamin demand. The larger the body, tissue volume, greater cellular requirements

Deficiency


Glyoxal-hydroimidazolone adducts (G-H1)
Protein Adducts
Glucose
O_2
GLYOXAL
Glycolase (GSH)
Glycolate
AKR [NAD(P)H]
Glycolaldehyde
Glucose-6-Phosphate
Pentose Shunt
$NADP^+$
Fructose-6-Phosphate
Transketolase
NADPH + H^+
DHAP
D-Lactate
Glyoxalase (GSH)
METHYLGLYOXAL
TPI
GA3P
Glyceraldehyde
AKR [NAD(P)H]
Cytosol
Protein Adducts
Pyruvate
Pyruvate dehydrogenase
TCA CYCLE
MG-hydroimidazolone adducts (MG-H1)
Branched chain ketoacid dehydrogenase
α-ketoglutarate dehydrogenase
Mitochondria
NADH
NAD^+
electron transport
ATP

Effects of vitamin B1 deficiency

Gastrointestinal system

- Cells of the smooth muscle and secretory glands do not receive sufficient energy from glucose, they are unable to function in their digestive role to provide glucose when thiamin is deficient.
- Symptoms include anorexia, indigestion, severe constipation, gastric atony (lack of muscle tone), and deficient hydrochloric acid secretion in thiamin deficiency condition.

Nervous system

- The central nervous system depends only on glucose for energy. If thiamin is deficient, neuronal activity is impaired, alertness and reflex responses are impaired resulting to apathy and fatigue.
- If untreated, lipogenesis is hindered and damage to the myelin sheath (lipid tissue) covering nerve fibers.
- Effects include nerve irritation, pain and prickly heat or deadening sensations and could lead to paralysis if untreated.

Effects of Vitamin B1 Deficiency (con't)

Cardiovascular System

- If thiamin is deficient, the heart muscle weakens and may lead to cardiac failure. Then edema in the extremities results.
- Common in patients with congestive heart failure
- Dilation of the peripheral blood vessels as smooth muscles of the vascular system may be involved.

Musculoskeletal

- Chronic painful musculoskeletal condition called primary fibromyalgia due to inadequate amounts of TPP.
- TPP therapy – reduces muscle pain and thiamin status is measured by transketolase activity in red blood cells.
- (Transketolation is the transfer of the first unit two-carbon group from one sugar to another in glucose oxidation)

Possible Interactions

- If you are currently being treated with any of the following medications, you should not use vitamin B1 without first talking to your health care provider.

- **Digoxin** -- Laboratory studies suggest that digoxin, a medication used to treat heart conditions, may reduce the ability of heart cells to absorb and use vitamin B1. This may be particularly true when digoxin is combined with furosemide (Lasix, a loop diuretic).

- **Diuretics (water pills)** -- Diuretics, particularly furosemide (Lasix), which belongs to a class called loop diuretics, may reduce levels of vitamin B1 in the body. It's possible that other diuretics may have the same effect. If you take a diuretic, ask your doctor if you need a thiamine supplement.

- **Phenytoin (Dilantin)** -- Some evidence suggests that some people taking phenytoin have lower levels of thiamine in their blood, and that may contribute to the side effects of the drug. However, that is not true of all people who take phenytoin. If you take phenytoin, ask your doctor if you need a thiamine supplement.

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Supplement

- Vitamin B1 can be found in multivitamins (including children's chewable and liquid drops), B complex vitamins, or if can be sold individually. It is available in a variety of forms, including tablets, softgels, and lozenges. It may also be labeled as thiamine hydrochloride or thiamine mononitrate.

How to Take It:

- As with all medications and supplements, check with a health care provider before giving vitamin B1 supplements to a child.
- Daily recommendations for dietary vitamin B1 according to the National Academy of Sciences were presented earlier.

- There is no known poisoning linked to thiamin as excesses is easily cleared by the kidney.

Thiamin Supplements

- Thiamin supplements containing up to 50 mg per day.
- Thiamin deficiency causes metal confusion and damages the heart, supplements promise to improve mental function and prevent heart disease

Riboflavin – Vitamin B2

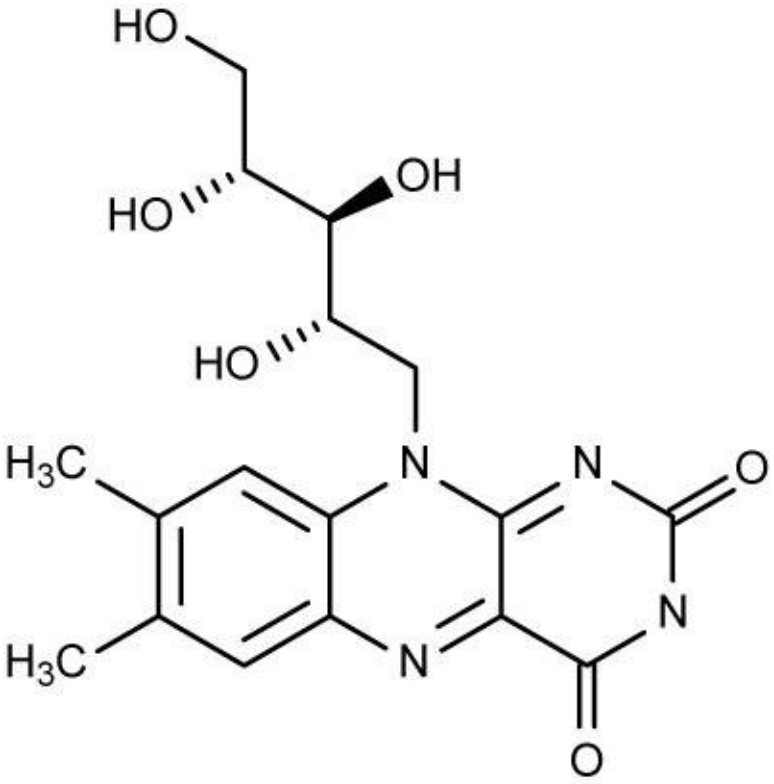
- Riboflavin is a yellow-green fluorescent pigment that forms yellowish-brown, needlelike crystals.
- It is water soluble and relatively heat stable but easily destroyed by light and radiation. It is absorbed in the in the brush border membrane in the upper section of the small intestine.
- Riboflavin is involved in the energy production for the *electron transport chain,* the citric acid cycle, as well as the catabolism of fatty acids (beta oxidation). It of carbohydrates, proteins and fats. It is constituent of the enzyme flavoproteins. Ribolflavin is converted to two enzymes, Flavin mononucleotide (FMN) and then to flavin adenine dinucleotide (FAD).

- Precursor for Flavin coenzymes
  - Flavin mononucleotide and flavin adenine dinucleotide which play key roles in hydrogen transfer reactions associated with glycolysis, the TCA cycle and Oxidative phosphorylation.
  - FMN is required for deamination, the reaction that removes the amino group (NH2 from certain amino acids. FAD is required in the deamination of gycine and in oxidizing some of the fatty acids such as butyric acid. It is therefore considered an antioxidant.

Food Sources and RDA of Vitamin B2

- Milk is the most important source of riboflavin. There are several flavins in milk but the most abundant one is lacto flavin.
- Other sources are organ meats such as liver, kidney and heart, whole or enriched grains and vegetables. It is loss in open cooking with excess water.
- Recommended Daily Allowance (RDA) or Intake
- The recommended daily allowances for riboflavin is 0.6 mg/1000 kcal for all ages.
- Persons at risks may require increase riboflavin. These include persons who live in poverty, have gastrointestinal disease in which the appetite is poor. Children, pregnant and lactating mothers would need more of riboflavin.

Riboflavin Formula



Factors affecting Vitamin B2 or Riboflavin Deficiency

Poor Diet

Not following a healthy diet is one of the primary reasons behind low vitamin B2 in the body. Bad food choices deprives the body of its essential nutrients. So, one has to be very careful what one prefers to eat during meals. Diet lacking in riboflavin foods like green vegetables, milk and dietary products such as yogurt and cheese is one of the main factors responsible for causing vitamin B2 deficiency.

Alcoholism

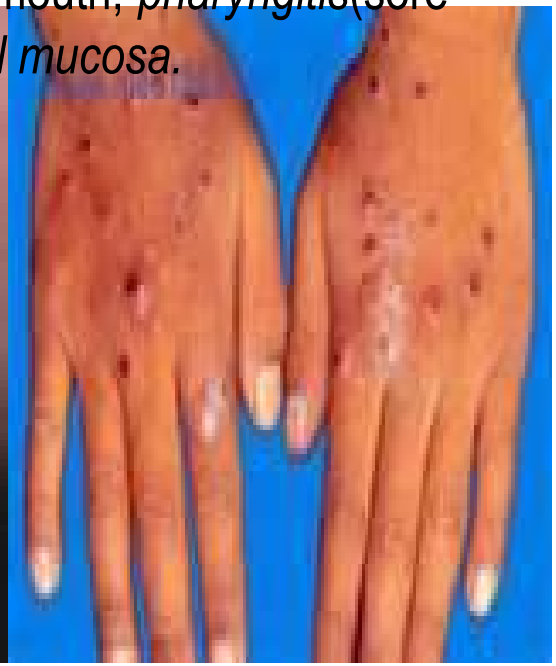
Too much alcohol or coffee consumption also increases the risk of low vitamin B2 levels. Apart from alcohol, excessive smoking or intake of other tobacco based products can also lead to sharp fall in vitamin B2 levels.

Diseases

Chronic illnesses are yet another culprits behind sudden deviation of vitamin B2 levels. People who have had suffered from prolonged illnesses of the liver or other chronic infections may be diagnosed with vitamin B2 deficiency

Ariboflavinosis or Vitamin B2 Deficiency

Symptoms may include *cheilosis* (cracks in the lips), high sensitivity to sunlight, angular *cheilitis, glossitis* (inflammation of the tongue), *seborrheic dermatitis* or *pseudo-syphilis* (particularly affecting the scrotum or labia majora and the mouth, *pharyngitis*(sore t*[illegible]* *edema of the pharyngeal and oral mucosa.*



Symptoms of Riboflavin Deficiency

Eye Problems

- Signs of eye irritation and watery eyes
- It is likely to trigger unusual painful burning sensations in the eyes
- Persistent redness and itchy feeling in the eyes followed by increased sensitivity to light
- Long-standing vitamin B2 deficiency can also make adults prone to eye diseases like cataracts, amblyopia and corneal vascularization.

Mouth Problems

- Distinctly visible cracks at the corners of the mouth
- Sores may also erupt in the mouth followed by inflammation in the lining of the mouth and throat, making it difficult to swallow food.

Hair Problems

- Moderate to severe vitamin B2 shortage can also make a person susceptible to hair loss problems.

Skin Problems

- Deficiency can lead to formation of skin lesions.
- The presence of skin problems like dermatitis
- Flaky, peeling skin near the nose can be observed with vitamin B2 deficiency.
- It accelerates aging of skin, wrinkles getting formed on the facial skin.

Niacin -Vitamin B3

- **Coenzyme role**

- Like thiamin and riboflavin, niacin plays a critical role in energy metabolism.
- The two niacin coenzymes are *nicotinamide-adenine dinucleotide* (NAD) and *nicotinamide adenine dinucleotide phosphate* (NADP) are used in oxidation reduction reactions in the cell.
  - NAD carries hydrogen and their electrons during metabolic reactions, including the pathway from the citric acid cycle to the electron transport chain.
  - NADP is a coenzyme in lipid and nucleic acid synthesis
- These coenzymes:
  - accept energy released during the breakdown of glucose and transfer it as ADP.
  - used in fatty acid synthesis and
  - in processes that lead to the formation of water, a major end product of energy metabolism.
- Niacin partners with riboflavin in the cellular coenzyme systems that convert proteins and small amount of glycerol from fats to glucose and then oxidize the glucose for release of controlled energy.

Chemical and physical properties

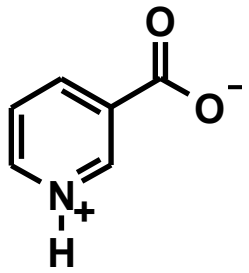
- Two forms of Niacin exist:
  (1) nicotinic acid
  (2) nicotinamide

- Nicotinic acid is easily converted to nicotinamide which is water soluble, stable to acid and heat, and forms a white powder when crystallized.
- Niacin bears a close connection to the essential amino acid tryptophan. Tryptophan is a precursor of niacin.
- Dietary tryptophan can be metabolized to niacin and foods rich in tryptophan (e.g., dairy products) can compensate for inadequate dietary niacin.

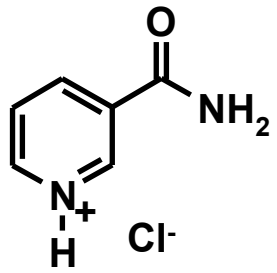
Niacin (Vitamin B3)

- Niacin is composed of two structures: nicotinic acid and nicotinamide.

- There are two co-enzyme forms of niacin: nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Both play an important role in energy transfer reactions in the metabolism of glucose, fat and alcohol



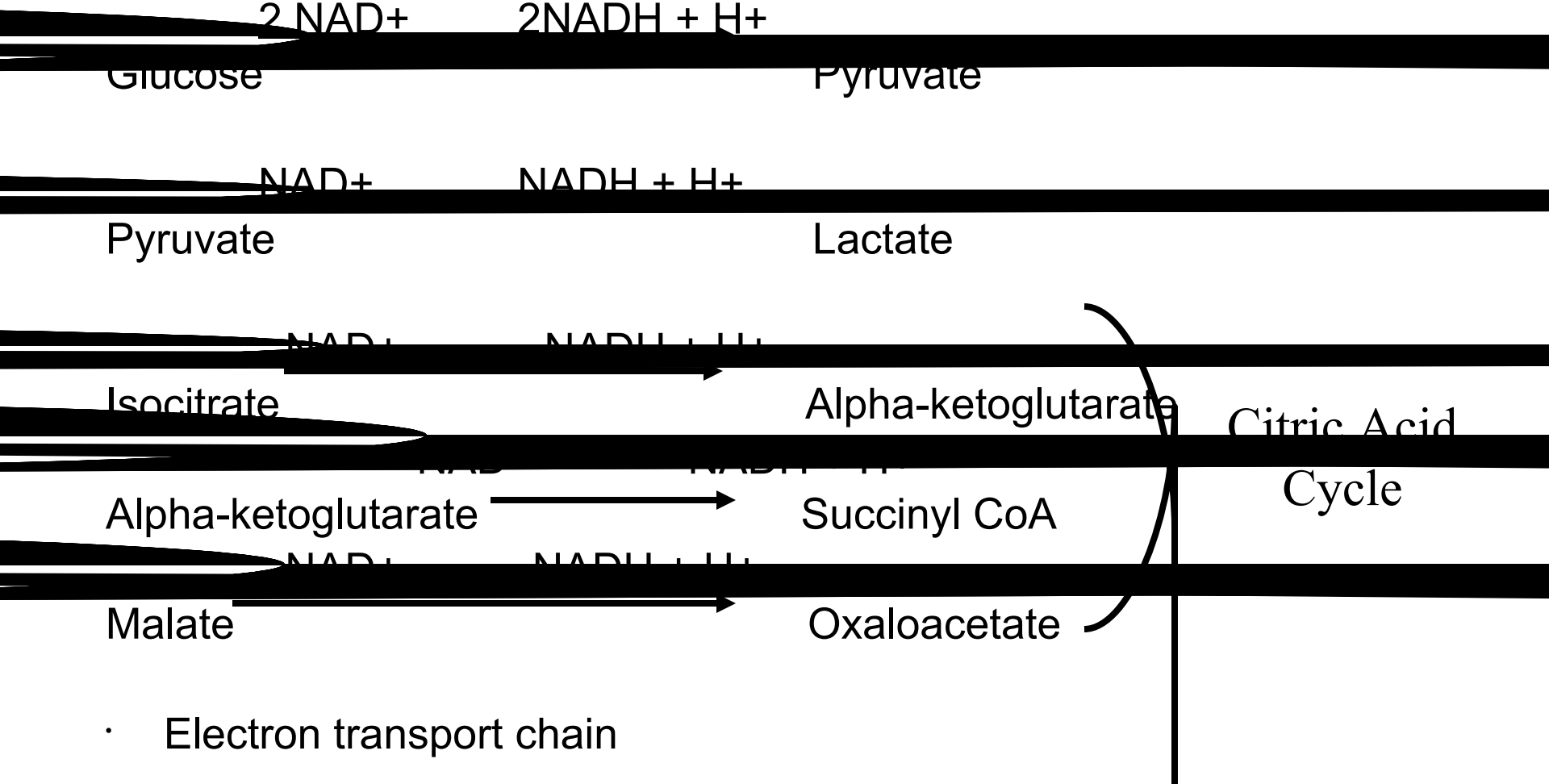
Niacin



Niacinamide HCl

Functions of Niacin

- NAD and NADP participates in 200+ reactions in the body



- Electron transport chain

Niacin food sources and RDA

- Meat and dairy products are the major sources of niacin and also high in tryptophan.
- Other foods include peanuts, dried beans and peas, and whole grains or enriched bread and cereals.

- Recommended Daily Allowance (RDA)
- a. 16 MG NE/day for adolescent and adult
- b. 14 mg NE/day for adolescent and adult women

- Niacin equivalent (NE): The tryptophan-iniacin relation led to the development of the unit of measure called NE. In general, 60 mg of tryptophan can produce I mg of niacin, the amount designated as NE this is the unit used in the DRI or RDA for niacin.

- Increase requirement for pregnant and lactating women,
  increased physical activity and during trauma and surgery for tissue repair

Vitamin B3

Food sources of Niacin (vitamin B3) include dairy, poultry, fish, lean meat, nuts and eggs

A.D.A.M.

Niacin or Vitamin B3 deficiency

- Deficiency results from:
  1. extremely inadequate intake of both niacin and tryptophan,
  2. may be due to diarrhea, cirrhosis, or alcoholism.

- Pellagra also may occur in carcinoid syndrome (tryptophan is diverted to form 5-hydroxytryptophan and serotonin) and in Hartnup disease (absorption of tryptophan by the intestine and kidneys is defective).

- Pellagra is characterized by skin, mucous membrane, CNS, and GI symptoms. Advanced pellagra can cause a symmetric photosensitive rash, stomatitis, glossitis, diarrhea, and mental aberrations. Symptoms may appear alone or in combination.

Niacin - B3 deficiency

- **Skin symptoms**:

include several types of lesions, which are usually bilaterally symmetric. The distribution of lesions—at pressure points or sun-exposed skin—is more pathognomonic than the form of the lesions. Lesions can develop in a glovelike distribution on the hands (pellagrous glove) or in a boot-shaped distribution on the feet and legs (pellagrous boot). Sunlight causes Casal's necklace and butterfly-shaped lesions on the face.

- **Mucous membrane symptoms:**

affect primarily the mouth but may also affect the vagina and urethra. Glossitis and stomatitis characterize acute deficiency. As the deficiency progresses, the tongue and oral mucous membranes become reddened, followed by pain in the mouth, increased salivation, and edema of the tongue. Ulcerations may appear, especially under the tongue, on the mucosa of the lower lip, and opposite the molar teeth.

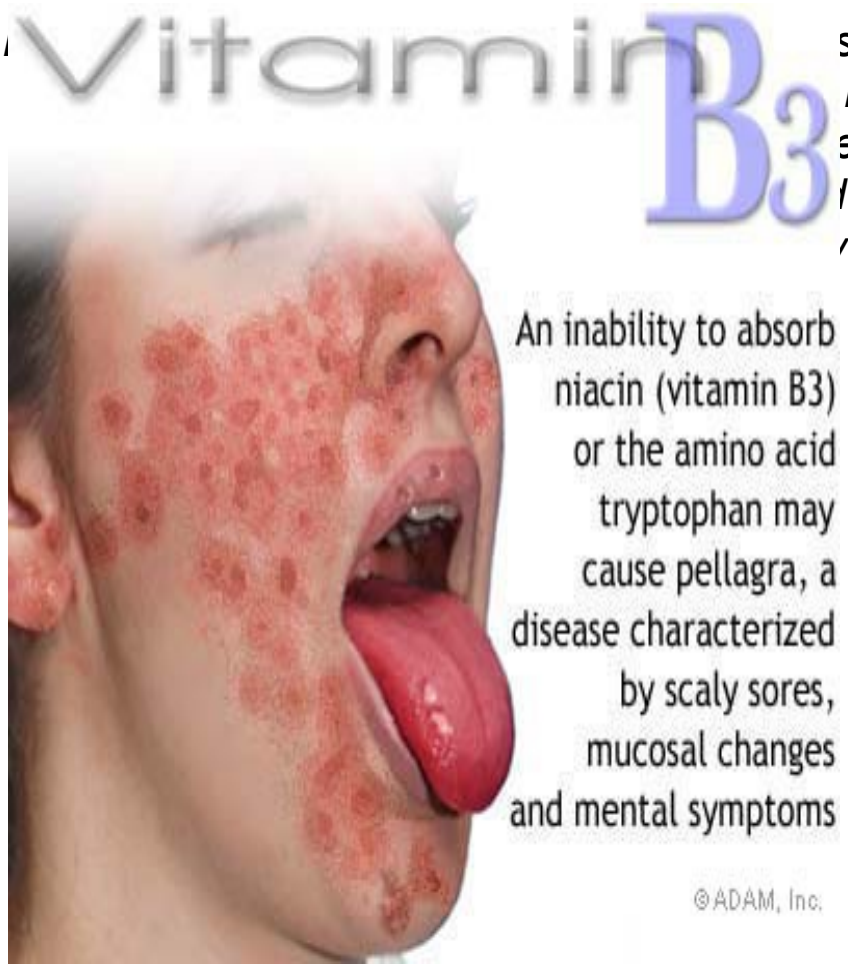
Niacin - B3 deficiency

- **GI symptoms**

early in the deficiency include burning in the pharynx and esophagus and abdominal discomfort and distention. Constipation is common. Later, nausea, vomiting, and diarrhea may occur. Diarrhea is often bloody because of bowel hyperemia and ulceration.

- **CNS symptoms**

include psychosis, encephalopathy (characterized by impaired consciousness), and cognitive decline (dementia). Psychosis is characterized by memory impairment, disorientation, confusion, and confabulation; the predominant symptom may be excitement, depression, mania, delirium, or paranoia.



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localiz

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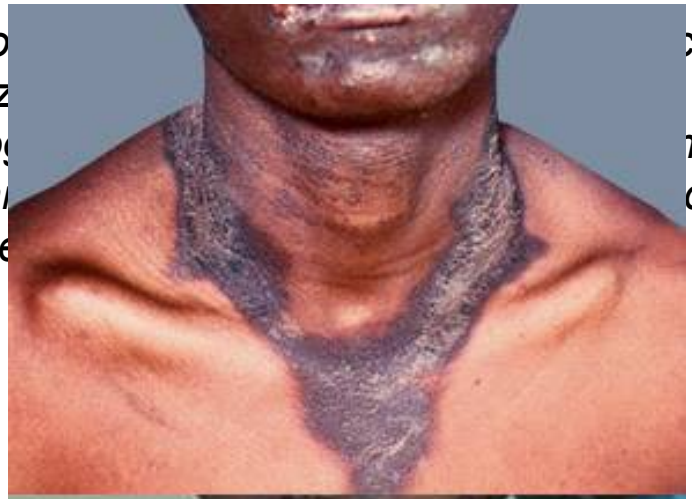
succe



Pantothenic Acid, Calcium Pantothenate Vitamin B5

- **Sources**

It is widely found in both plants and animals including meat, vegetables, cereal grains, legumes, eggs, and milk.

Availability

Vitamin B5 is commercially available as D-pantothenic acid, as well as dexpanthenol and calcium pantothenate, which are chemicals made in the lab from D-pantothenic acid.

Chemical and Physical nature

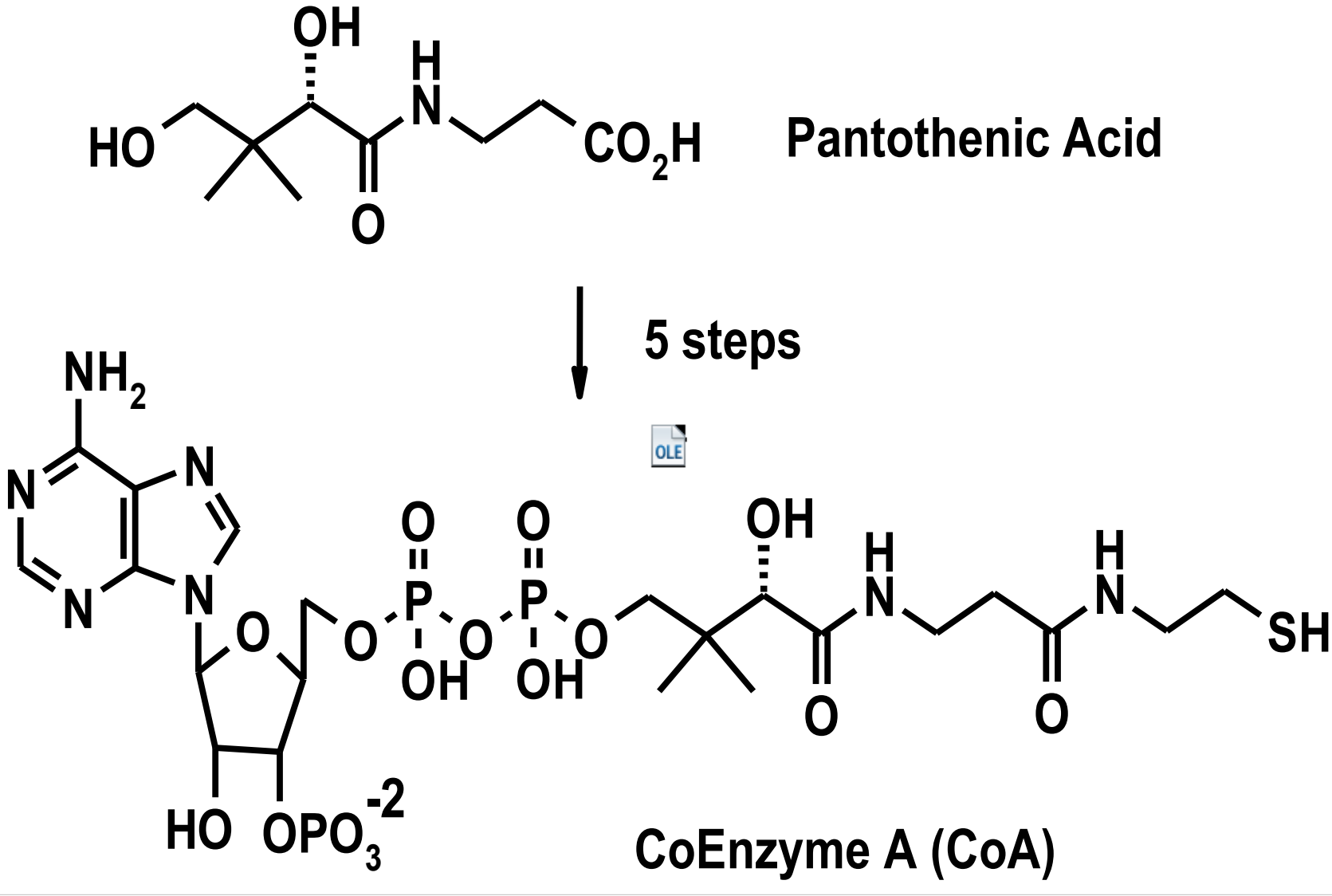
Panthothenic acid is a white crystalline compound. It is readily absorbed in the intestines and combines with phosphorus to make the active molecule acetyl coenzyme (CoA).

Functions of Pantothenic acid (B6)

- Pantothenic Acid is involved in the oxidation of fatty acids and carbohydrates.

- Pantothenic acid is used to synthesize Coenzyme A
- Coenzyme A is involved in the synthesis of amino acids, fatty acids, ketones, cholesterol , phospholipids, steroid hormones, neurotransmitters (such as acetylcholine and antibodies function.

- Deficiency: Dermatitis, enteritis, alopecia, adrenal insufficiency


OH
H
N
HO
CO2H
O
Pantothenic Acid
5 steps
NH2
N
N
N
N
O
O
P
O
P
O
O
OH
OH
OH
H
N
H
N
SH
O
O
HO
OPO3-2
CoEnzyme A (CoA)

Food Sources and RDA

Panthothenic Acid Requirements
The RDA is 4-7 mg/day of pantothenic acid for adults.

About 5 mg/day is lost daily in the urine

Food Sources

Pantothenic acid is both found in animal and plant food.

Good sources include egg, yolk, milk and broccoli.

It is also abundant in animal tissues (liver and kidney).

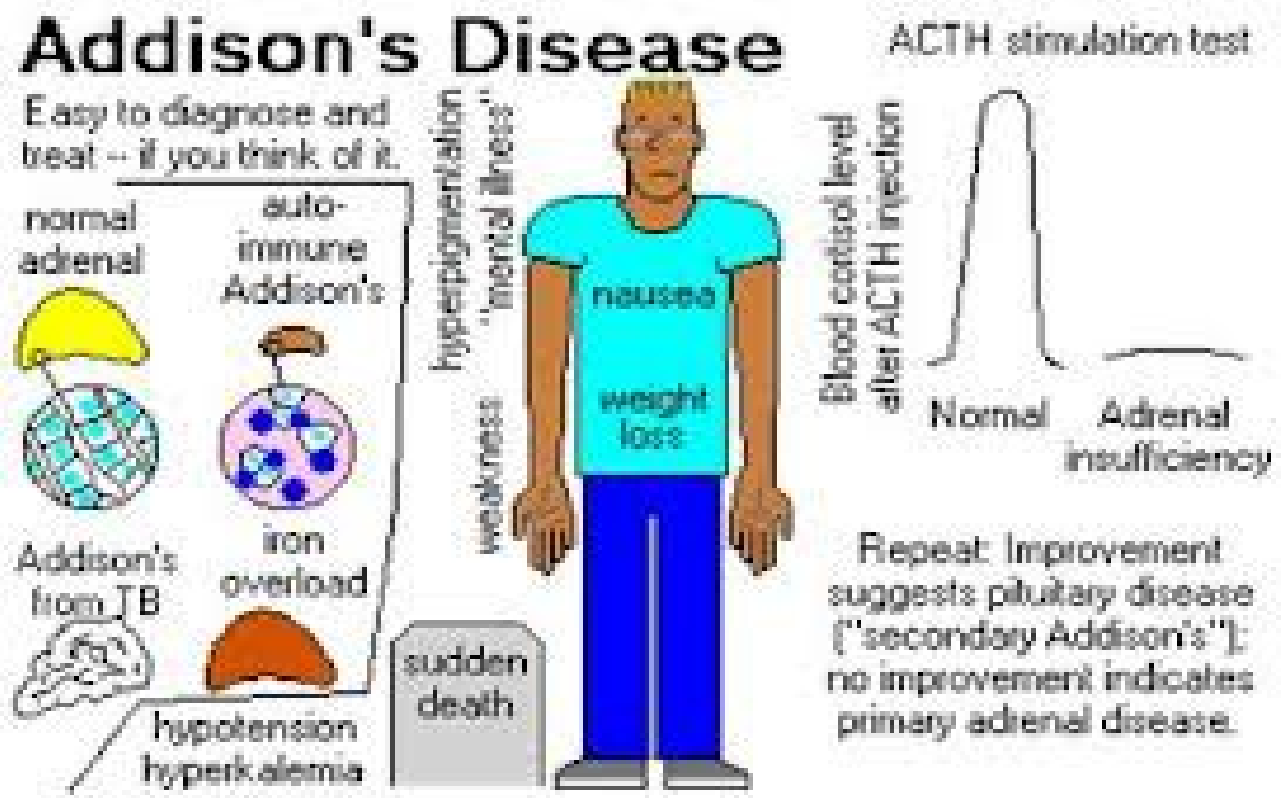
Deficiency

Deficiency is unlikely because intestinal bacteria synthesize considerable amounts. This source, along with its occurrence in a wide variety of foods, makes pantothenic acid deficiency unlikely.

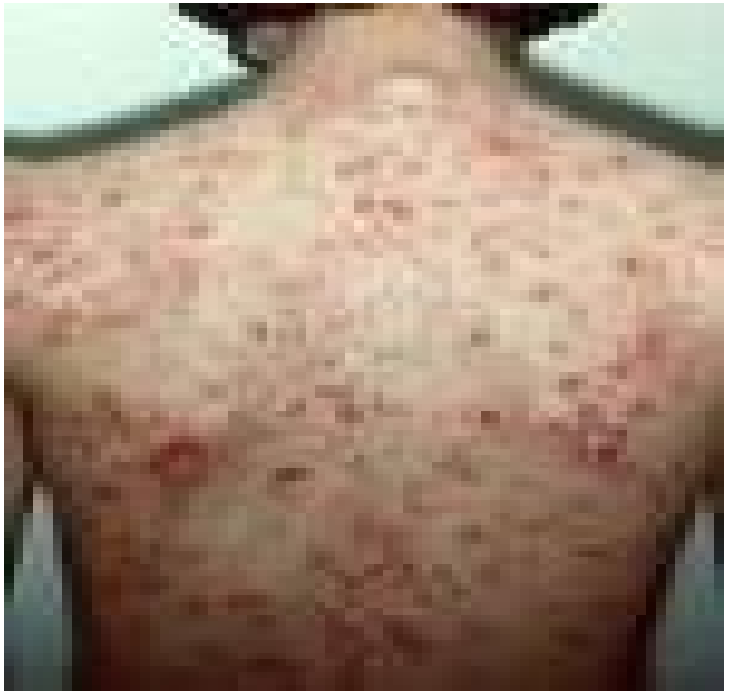
However, to those who don't eat enough food deficiency may result to dermatitis (Acne), enteritis, alopecia and adrenal insufficiency

Food Sources of Pantothenic Acid

Addison's Disease



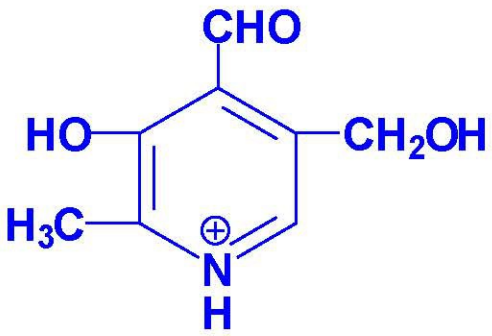
Acne

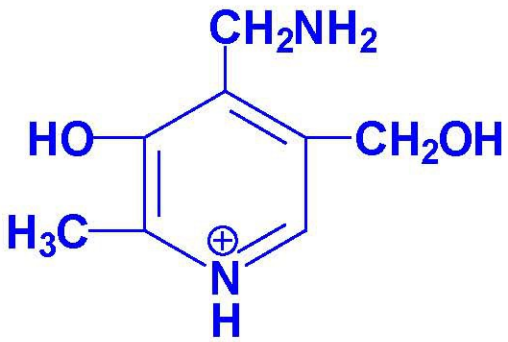


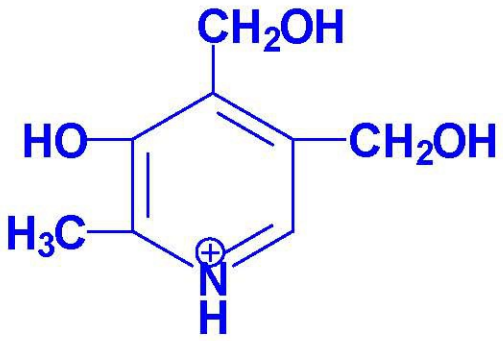
Vitamin B6

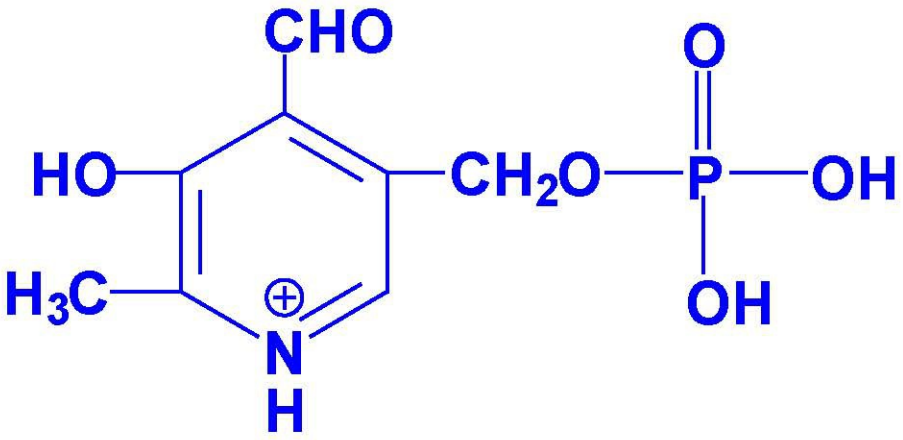
- Pyridoxal, pyridoxamine and pyridoxine and their 5'-phosphates are collectively known as vitamin B6.
- All three are collectively converted to the biologically active form, pyridoxal phosphate by the ATP-requiring enzyme pyridoxal kinase.
- 80% of the body's total B6 is present in muscle bound to glycogen phosphorylase(the major enzyme of glycogen degradation)
- B6 is a coenzyme in nearly 100 enzymatic reactions involving proteins,carbohydrates and lipids.

Pyridoxal, Pyridoxamine, Pyridoxine (the B_6s)









Pyridoxal phosphate

Functions of Vitamin B6

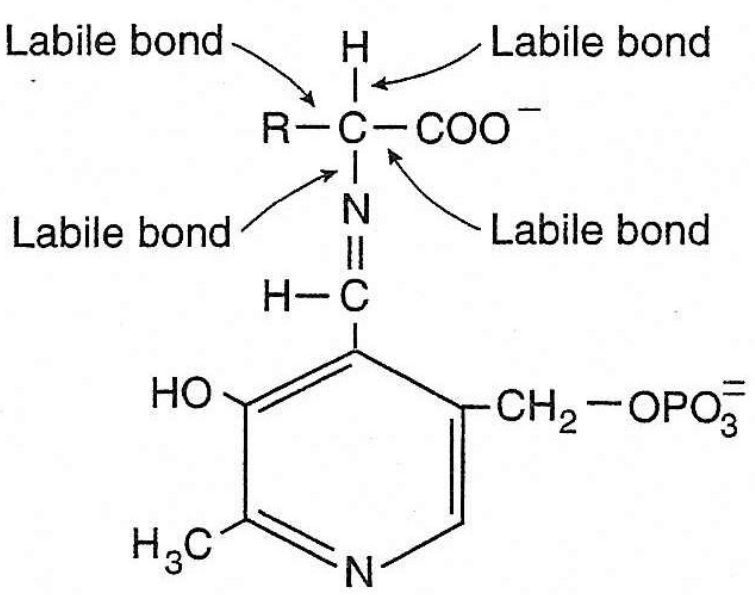
- Vitamin B6 includes a group of closely related compounds: pyridoxine, pyridoxal, and pyridoxamine.
- They are metabolized in the body to pyridoxal phosphate, which acts as a coenzyme in many important reactions in blood, CNS, and skin metabolism.
- Vitamin B6 is important in heme and nucleic acid biosynthesis and in lipid, carbohydrate, and amino acid metabolism.
- Pyridoxine is usually stored in the body as pyroxidal-5-phosphate (PLP), which is the co-enzyme form of vitamin B6.
- Pyridoxine is involved in the *metabolism of amino acids* and *lipids*; *in the synthesis of neurotransmitters and haemoglobin*, as well as in the *production of nicotinic acid*.

Vitamin B6

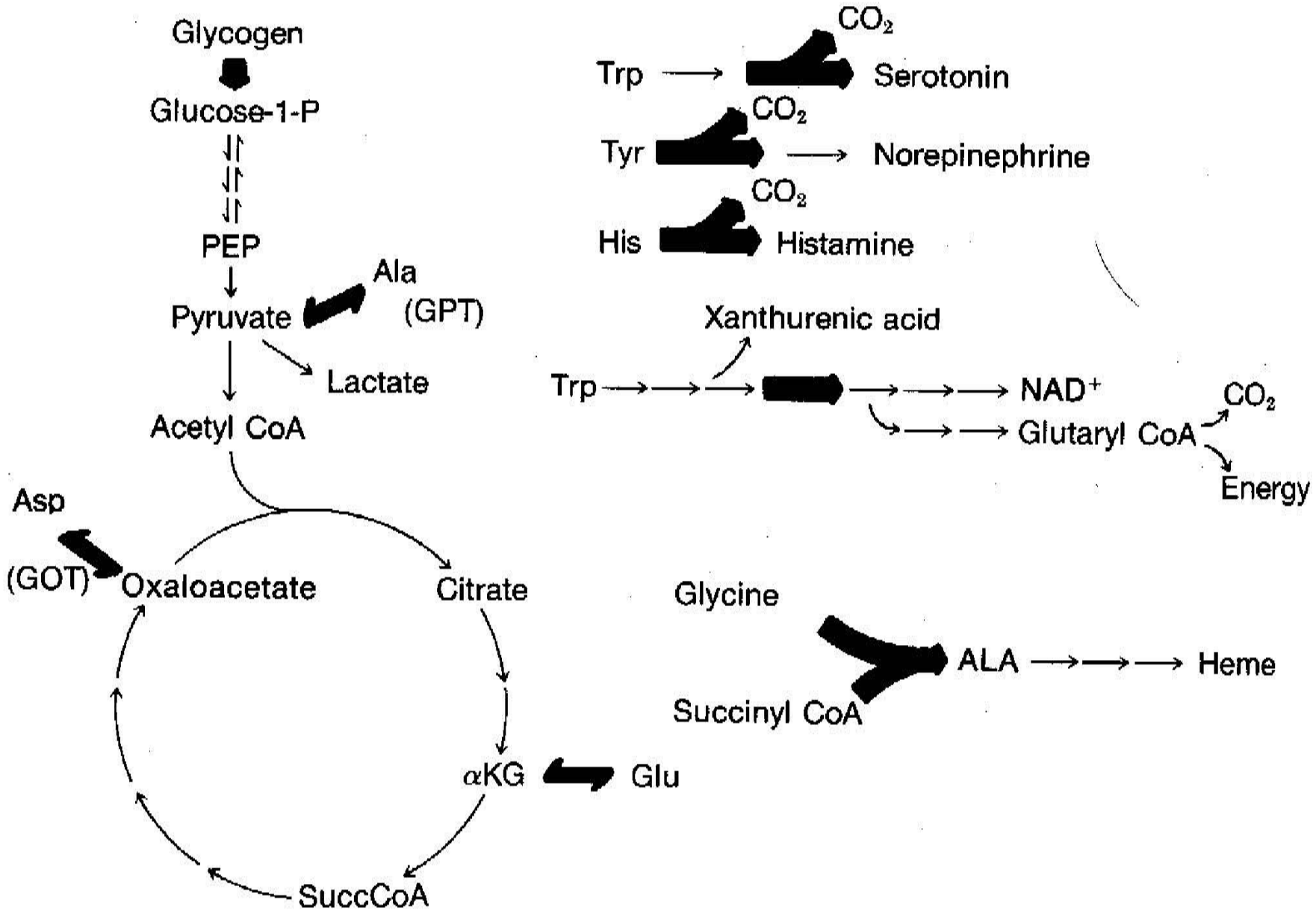
- Within Enterocyte
  - PN phosphorylated to PNP
    - pyridoxine kinase (ATP)
  - PL phosphorylated to PLP
    - kinase (ATP)
  - PNP may be converted to PLP
    - pyridoxine phosphate oxidase (FMN)
- Blood
  - PLP is main form (~60%) of vitamin in blood
    - PL also exists
    - both PL and PLP are bound to albumin

Vitamin-Coenzymes in Amino Acid Metabolism

- Vitamin B-6 : pyridoxal phosphate
  - Enzymes that bind amino acids use PLP as coenzyme for binding
    - Transaminases
    - Amino acid decarboxylases
    - Amino acid deaminases



Metabolic Roles of PP



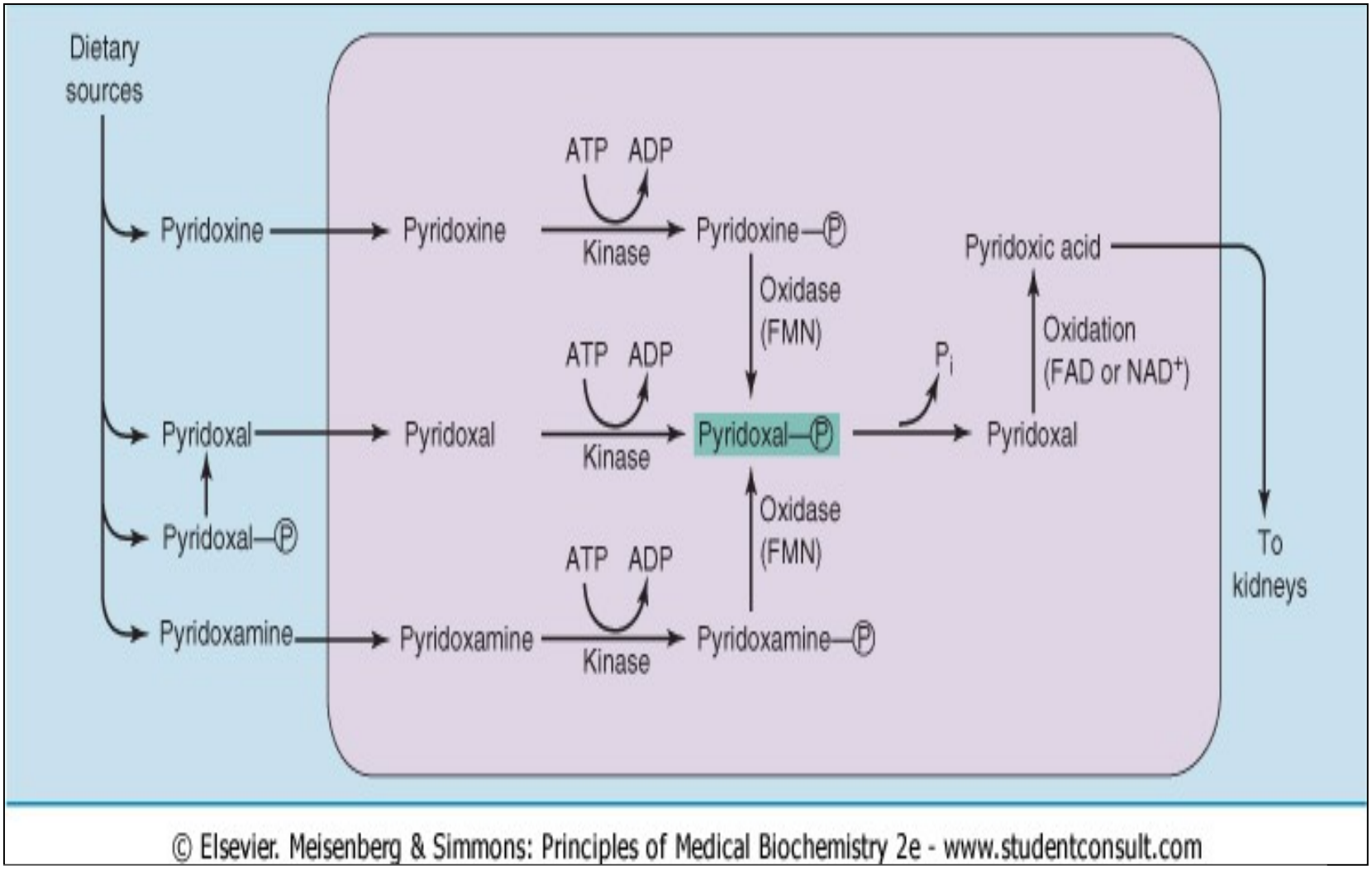


Figure 29.4 The molecular forms of vitamin B6. All vitamin forms can be converted to the coenzyme form pyridoxal phosphate in the human body.

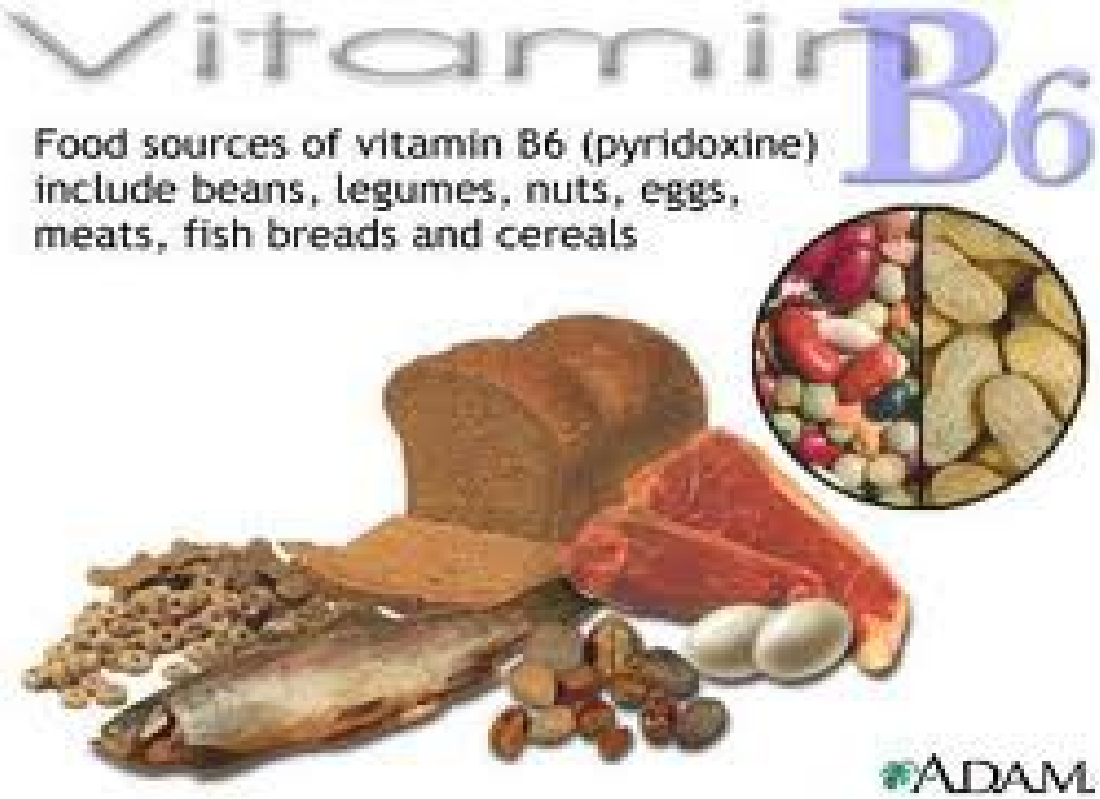
Vitamin B6 deficiency

- Because vitamin B6 is present in most foods, **dietary deficiency**, though rare, can develop because extensive processing can deplete foods of vitamin B6.
- **Secondary deficie*ncy*** may result from various conditions.
  - Symptoms can include peripheral neuropathy, a pellagra-like syndrome, with seborrheic dermatitis
  - Normocytic, microcytic, or sideroblastic anemia can also develop (because pyridoxyl phosphate is the cofactor for heme synthesis),
  - In adults can cause depression, confusion, EEG abnormalities, and seizures. high blood pressure (hypertension), water retention, elevated levels of homocysteine
- **Diagnosis** is usually clinical; no laboratory test readily assesses vitamin B6 status.
- **Treatment** consists of giving oral vitamin B6 and, when possible, treating the cause.

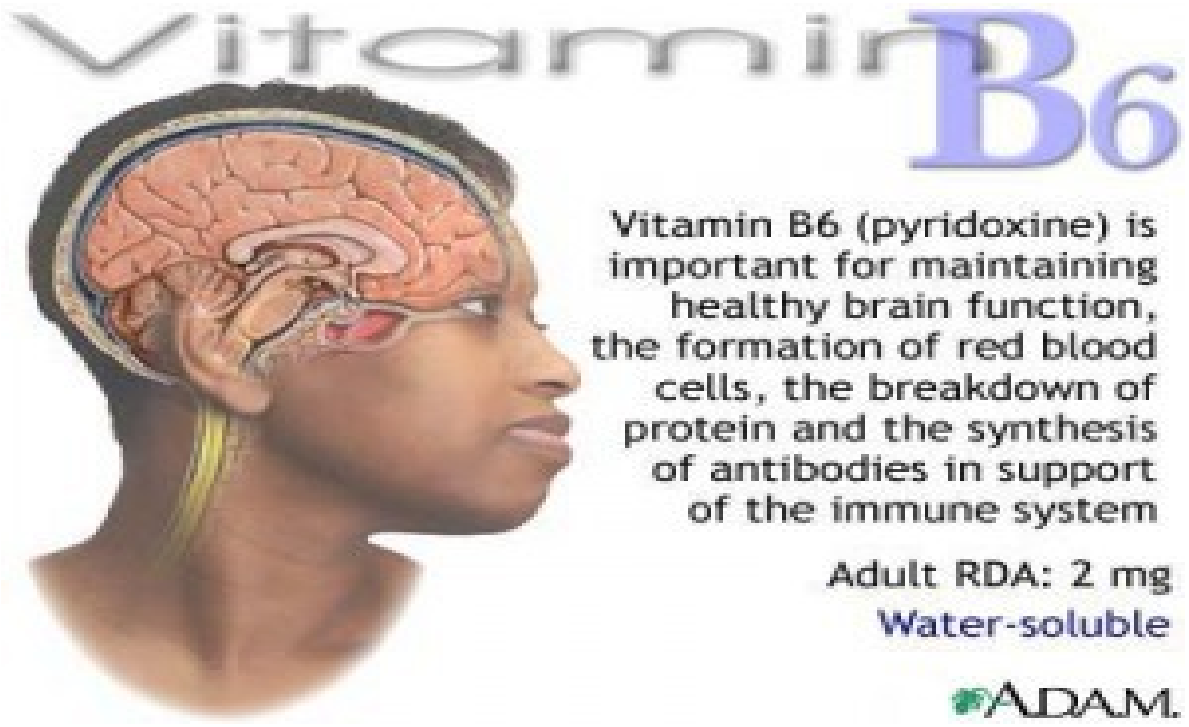
Pyridoxal

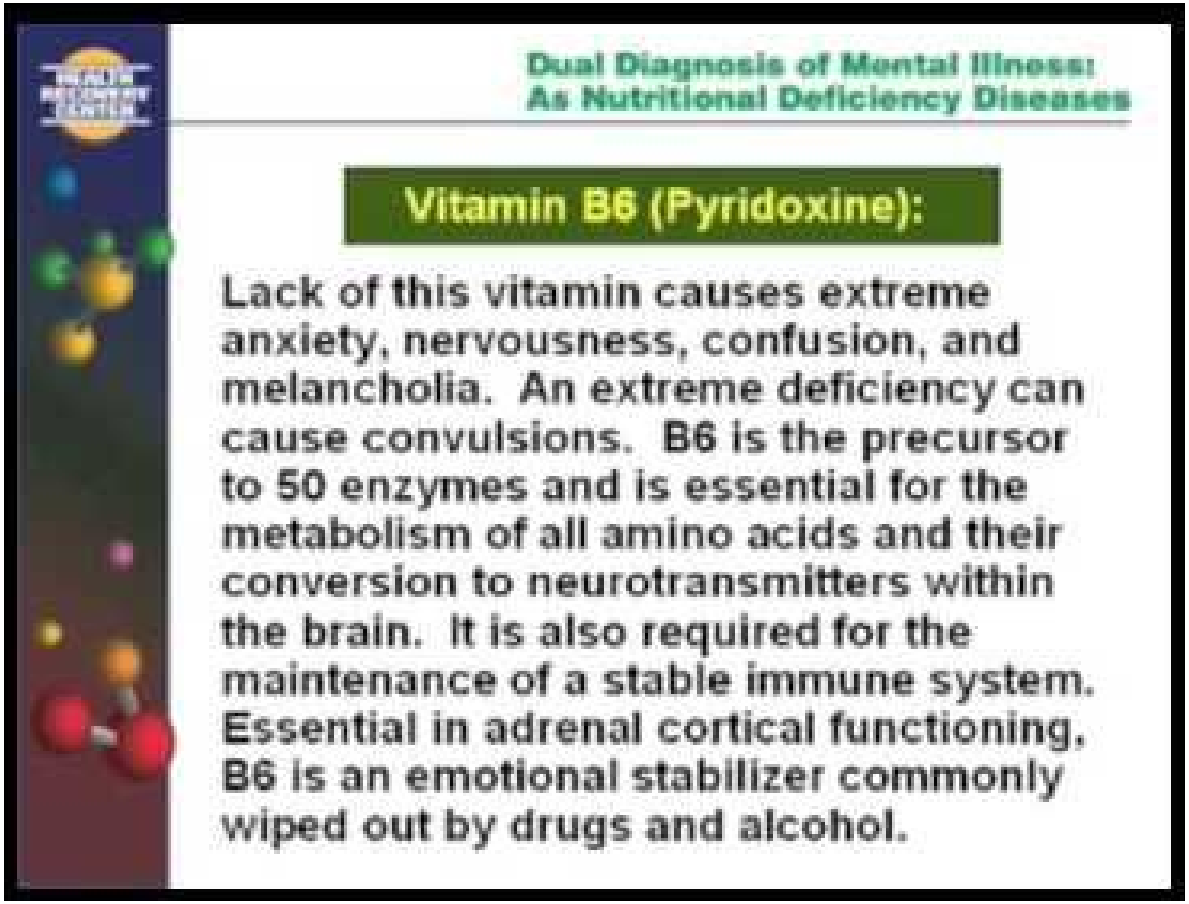
- Drug interactions:
  - Drugs that are ***hydrazines*** such as isoniazid, hydralazine can react with pyridoxal resulting in depletion of the vitamin
  - Oral contraceptives can lead to an abnormality in tryptophan metabolism which resembles pyridoxine deficiency →responds well to supplementation
    - Depression like symptoms due to low levels of serotonin caused by the estrogens in the OC
    - Appears that the vitamin blocks the steroid receptor site by reacting with lysine amino groups at the site → preventing steroid binding

Food Sources



Vitamin B6

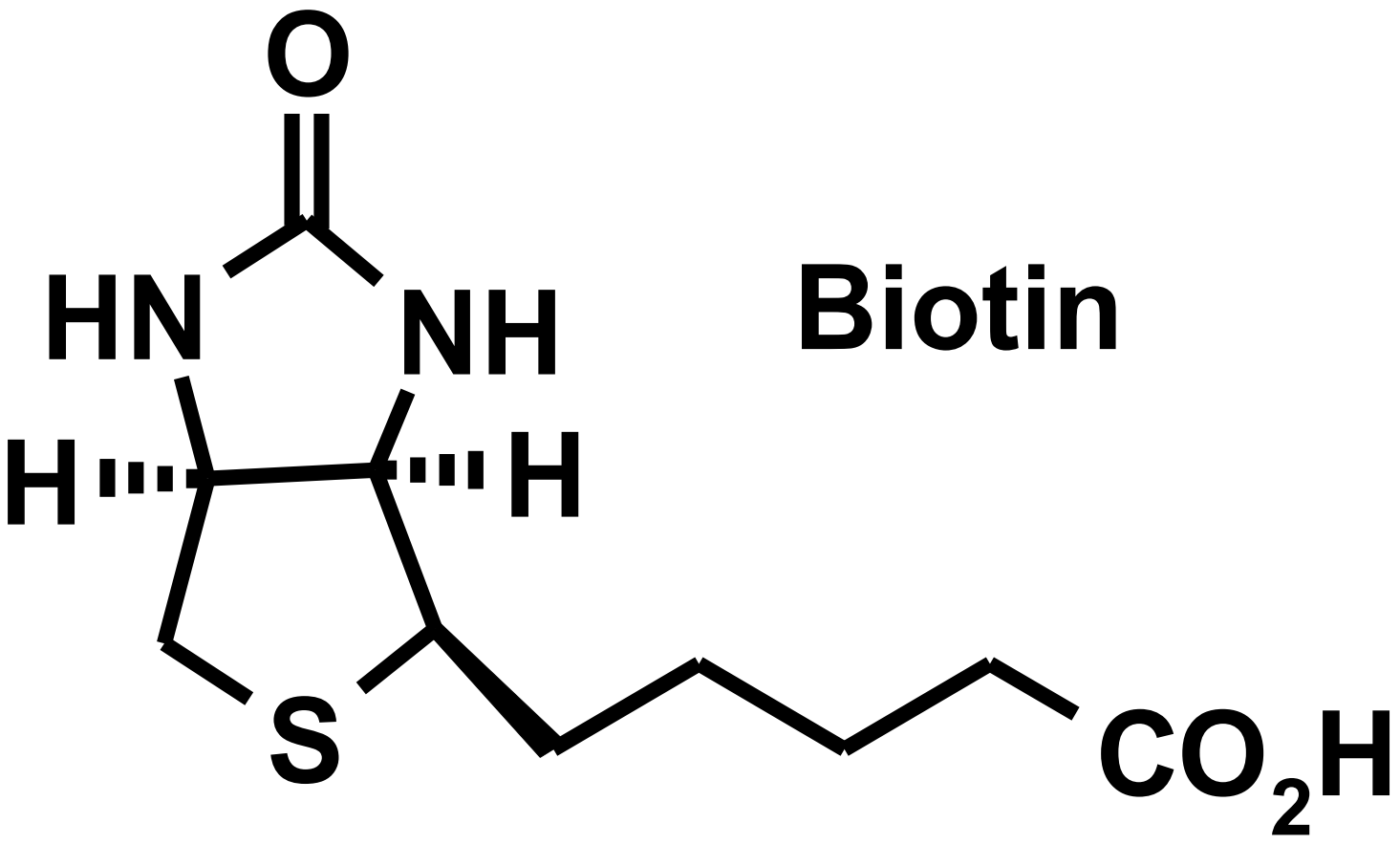

Vitamin B6
Vitamin B6 (pyridoxine) is important for maintaining healthy brain function, the formation of red blood cells, the breakdown of protein and the synthesis of antibodies in support of the immune system
Adult RDA: 2 mg
Water-soluble
A.D.A.M.


Dual Diagnosis of Mental Illness:
As Nutritional Deficiency Diseases
Vitamin B6 (Pyridoxine):
Lack of this vitamin causes extreme anxiety, nervousness, confusion, and melancholia. An extreme deficiency can cause convulsions. B6 is the precursor to 50 enzymes and is essential for the metabolism of all amino acids and their conversion to neurotransmitters within the brain. It is also required for the maintenance of a stable immune system. Essential in adrenal cortical functioning, B6 is an emotional stabilizer commonly wiped out by drugs and alcohol.

Biotin - H

- **Function:**
- coenzyme in **carboxylation reactions-pyruvate,acetylCoA and propionyl CoA carboxylases.**
- **Carbohydrate & fat metabolism**
- Often used in tandem with Pantothenic acid and Folic Acid
- Bacteria in our intestines produce biotin in excess of daily requirements.

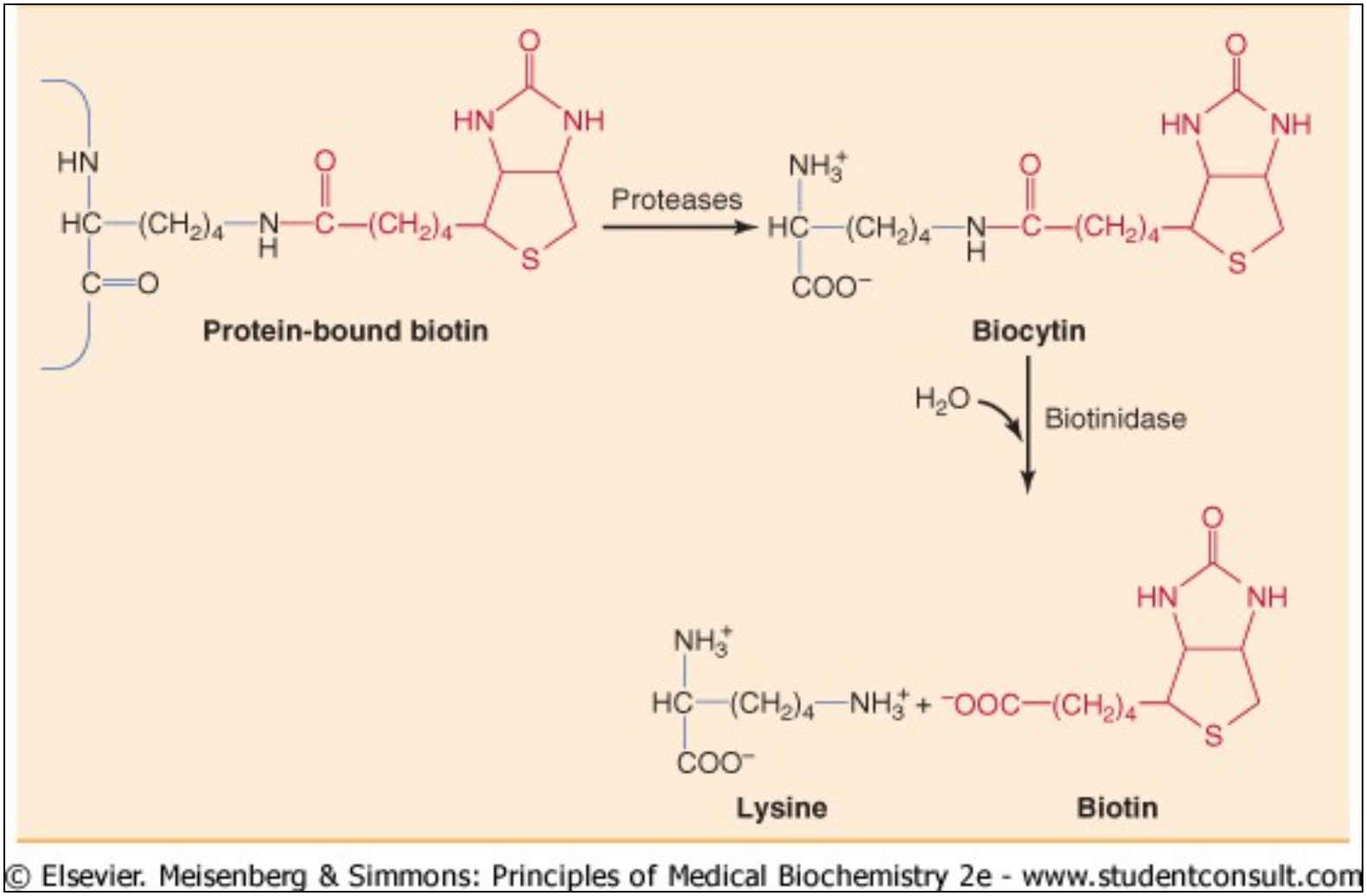
- **Biotin deficiency** may be found in individuals who eat more than 20 egg whites per day. These contain the substance **avidin**, which "ties up" the body's biotin.
- A deficiency of biotin is rare but can cause:
  - Skin disorder called **scaly dermatitis**
  - Hyperesthesia
  - Glossitis
- Found in beef liver, egg yolk, brewer's yeast, peanuts, cauliflower and mushrooms.
  - No RDA has been established to date



Biotin

Coenzyme role of Biotin - B7

- Biotin plays a key role in the metabolism of lipids, proteins and carbohydrates.
- Critical co-enzyme of four carboxylases:
  - acetyl CoA carboxylase, which is involved in the synthesis of fatty acids from acetate;
  - propionyl CoA carboxylase, involved in gluconeogenesis;
  - β-methylcrotonyl Coa carboxylase, involved in the metabolism of leucin; and
  - pyruvate CoA carboxylase, which is involved in the metabolism of energy, amino acids and cholesterol.
- .



Recycling of biotin. These reactions are required both for the utilization of dietary biotin and for the recycling of biotin during the degradation of biotin-containing carboxylase enzymes in the tissues.

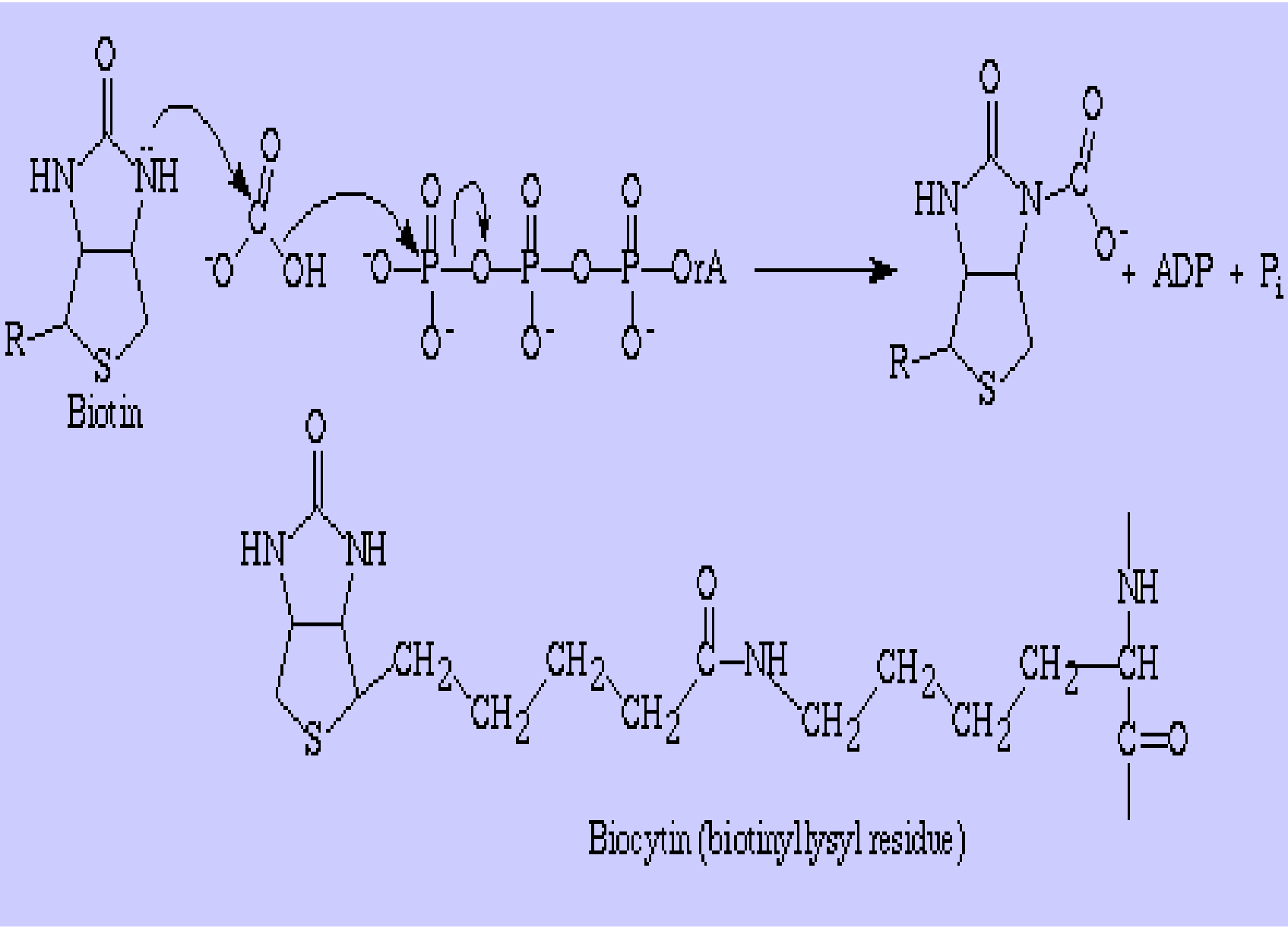
Biotin - B7 Deficiency

- Multiple carboxylase (biotidinase) deficiency, an inborn error of metabolism, can lead to biotin deficiency even when dietary biotin intake is normal

- Biotinidase deficiency seen in infants who present with hypotonia, seizures, optic atrophy, dermatitis and conjunctivitis (impaired growth and neurological disorders)

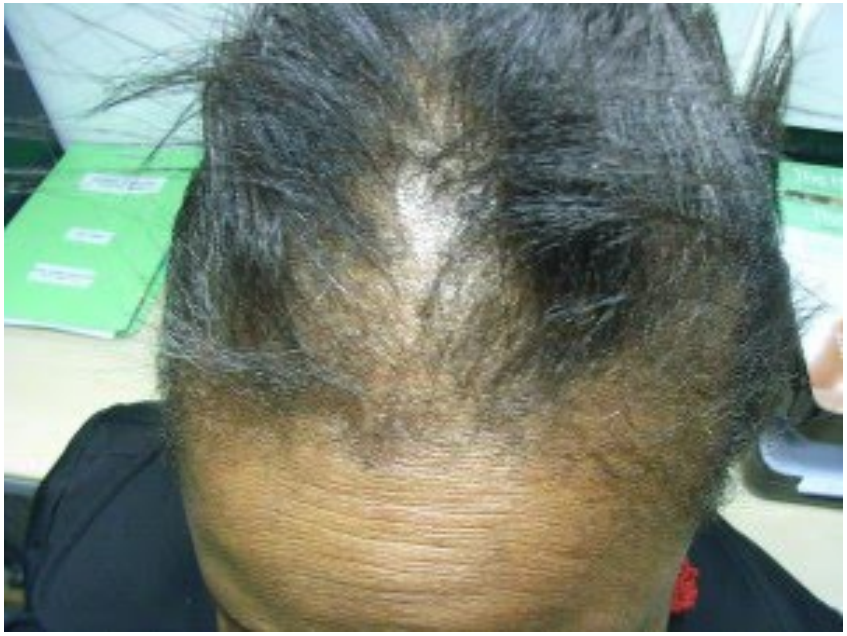
Food Sources

Egg yolk and nuts

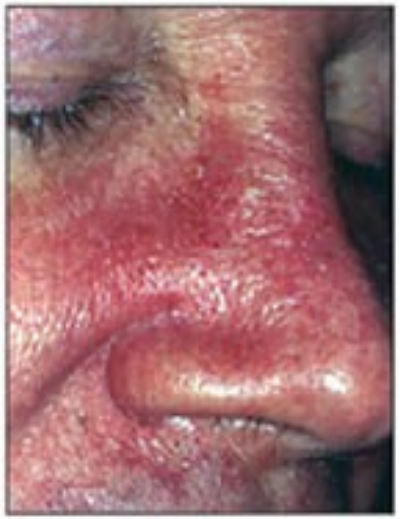

HN
NH
R
S
Biotin
OH
OrA
+ ADP + P_i
Biocytin (biotinyllysyl residue)

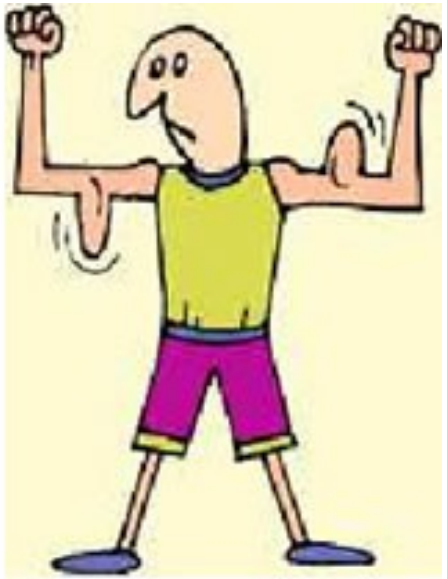
Dry and brittle nails

Hair Loss

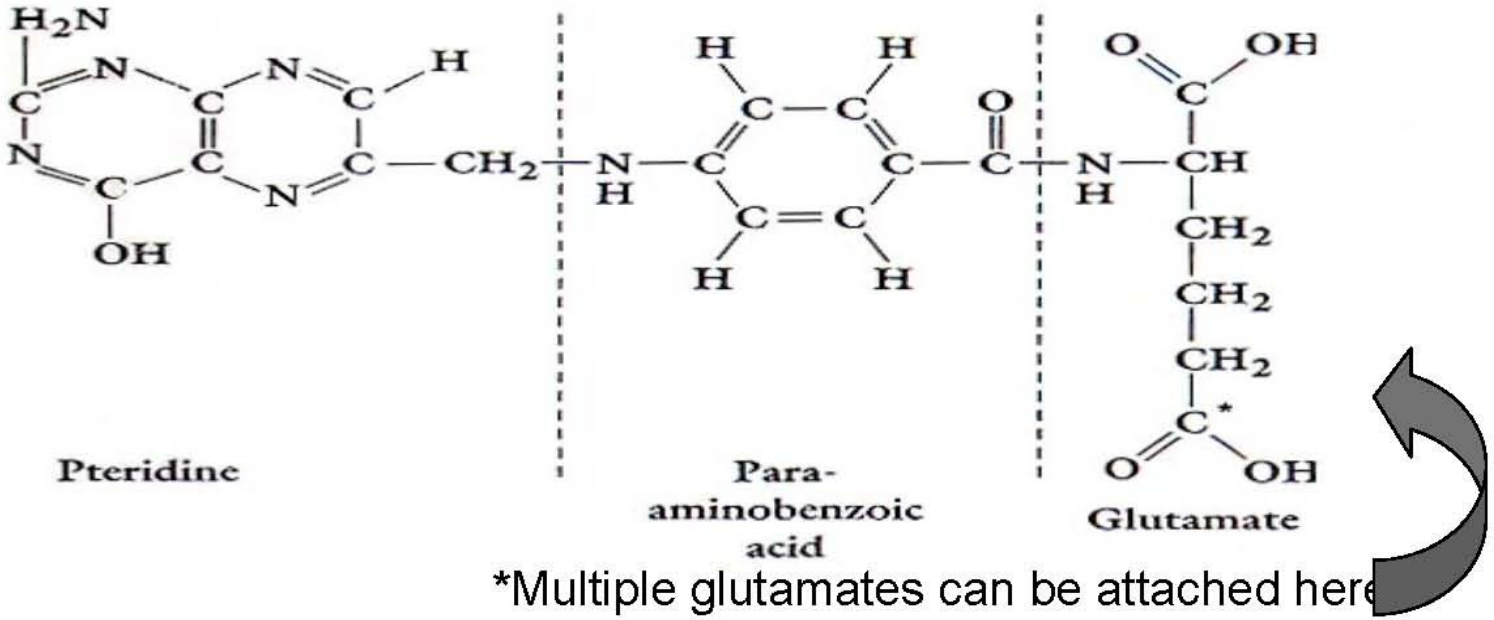


Dermatitis





Folic Acid Biochemistry



Coenzyme form

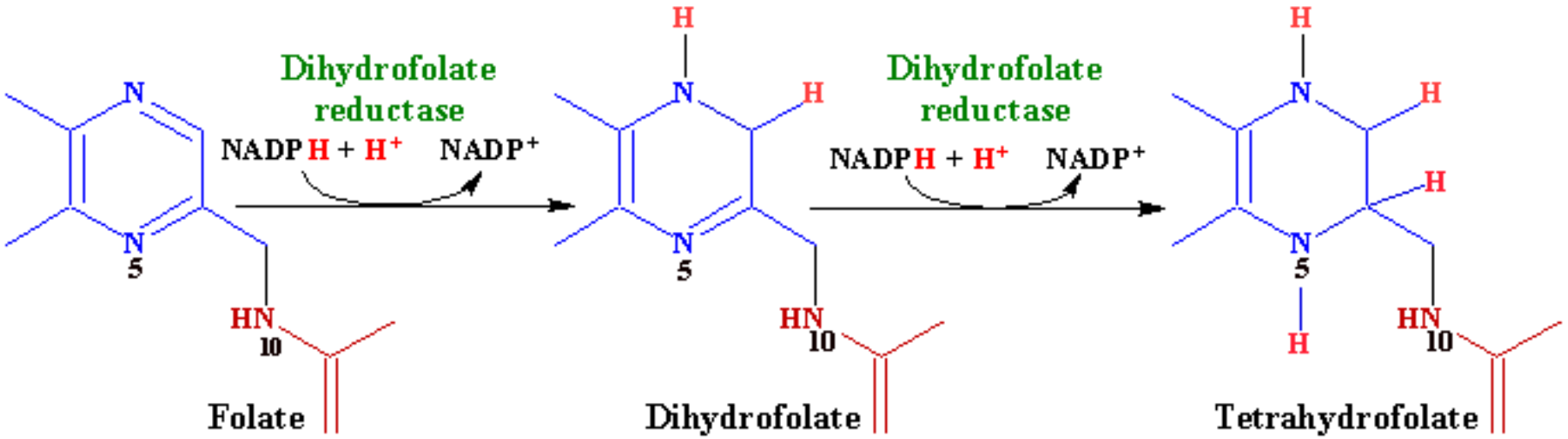
(**THFA**) tetrahydorfolic acid

Folic Acid – B9

- Folic acid consists of pteroic acid and one to seven γ-linked glutamate residues.
- Dietary polyglutamate forms of folic acid are hydrolyzed to pteroyl monoglutamate in the intestinal lumen. The monoglutamate is reduced to the active coenzyme form THF by dihydrofolate reductase in the intestinal mucosa.
- THF functions metabolically as coenzymes that transport single carbon fragments from one compound to another in amino acid metabolism and nucleic acid synthesis.
- Major one-carbon sources are serine, glycine and formimino-glutamate
- Synthesis of purine nucleotides, the thymidylate synthase reaction and the methylation of homocysteine to methionine.
- Folate is essential for DNA synthesis, which is critical in governing maturation of erythrocytes.
- N.B.-all of the one carbon-substituted THF's may also be present in foods.

Activation of folic acid

Folic acid is not the active form of the vitamin. It needs to be reduced to tetrahydrofolate (H4folate). Just the "business" part of the folic acid is shown for ease of illustration:



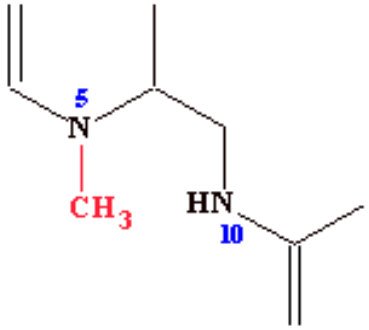
Dihydrofolate reductase found in some micro-organisms (e.g. the malarial parasite) is quite different to the human form and can be inhibited with drugs (e.g. trimethoprim) that have little effect us. This enzyme is also targeted by anti-cancer drugs (see below).

Folic Acid – B9

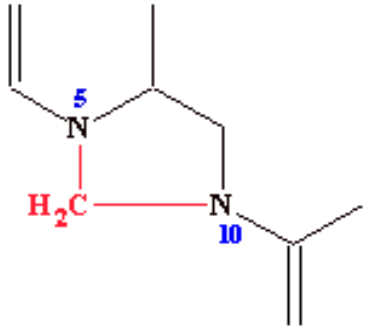
- Folic acid acts as a co-enzyme in the form of tetrahydrofolate(THF), which is involved in the transfer of single-carbon units in the metabolism of nucleic acids and amino acids.
- THF is involved in pyrimidine nucleotide synthesis needed for normal cells division during pregnancy and infancy.
- Folate also aids in erythropoiesis, the production of red blood cells .

Function of Folic Acid

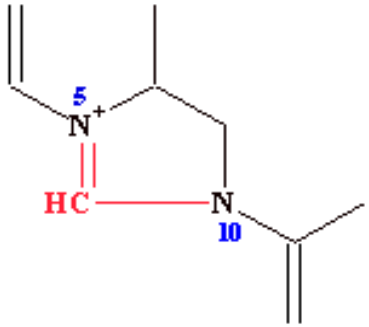
Coenzyme in many reactions involving transfer 1 carbon atom to other compounds. The single carbon groups can be carried on N5, N10 or bridged between both these nitrogens:



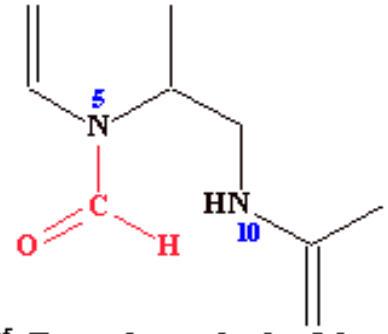
N^5-Methyl-tetrahydrofolate
carries methyl groups



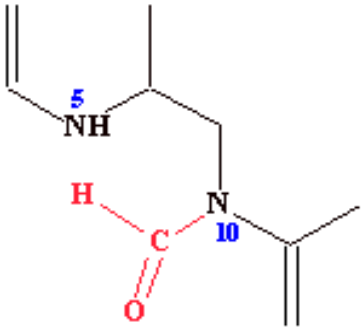
N^5-N^{10}-Methylene-tetrahydrofolate
carries methylene groups



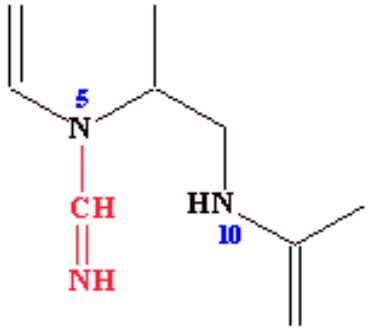
N^5-N^{10}-Methenyl-tetrahydrofolate
carries methenyl groups



N^5-Formyl-tetrahydrofolate
carries formyl groups



N^{10}-Formyl-tetrahydrofolate
carries formyl groups



N^5-Formimino--tetrahydrofolate
carries methenyl groups

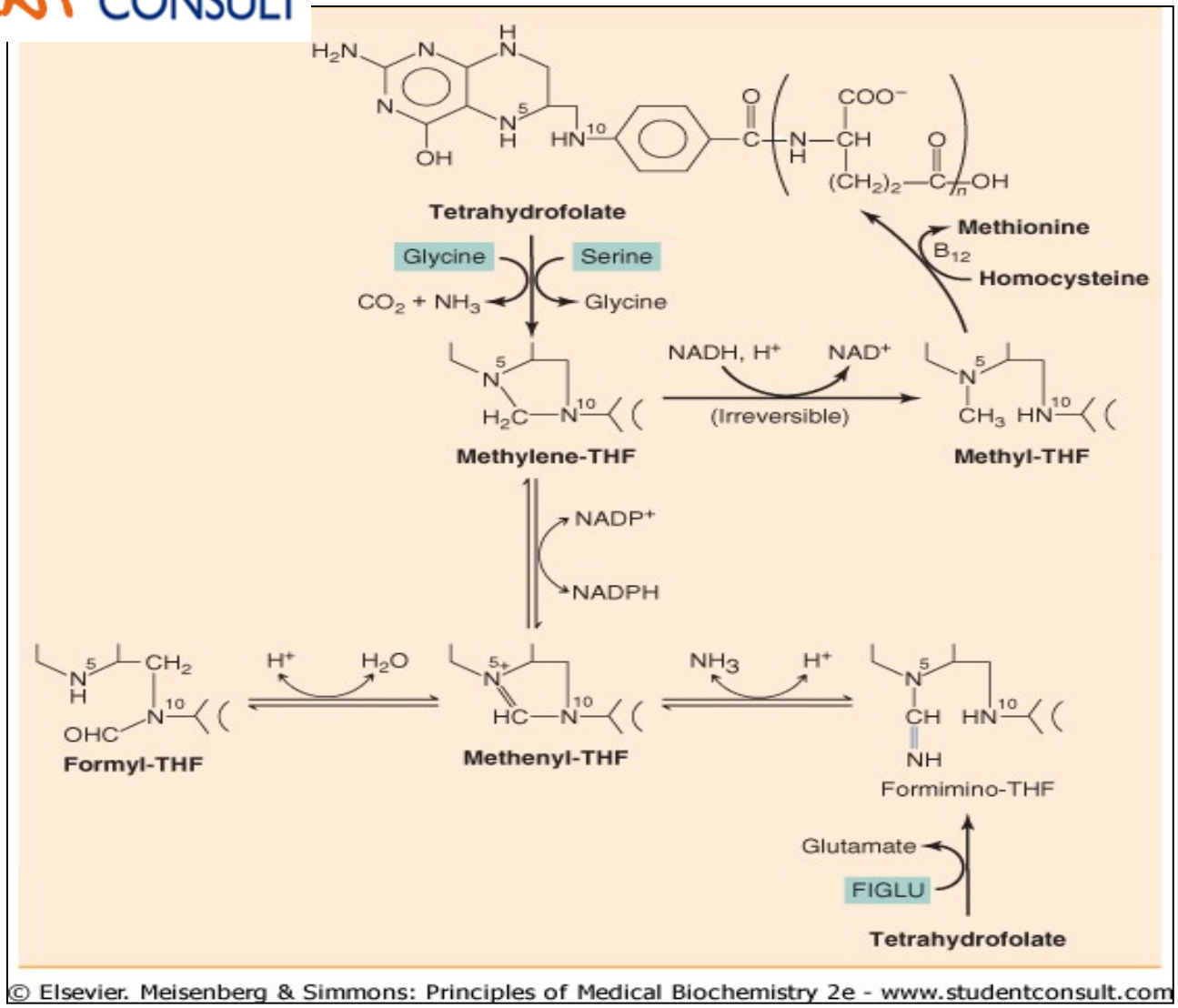


Figure 29.9 Tetrahydrofolate (THF) as a carrier of one-carbon units. FIGLU, formiminoglutamate (formed during histidine degradation).

Folic Acid Deficiency

- In folic acid deficiency, the patients present as if they have pernicious anemia but are not responsive to administration of intrinsic factor.

- In folate deficiency, replacement of RBC's and GI tract cells is reduced. First signs are anemia and GI tract deterioration.

- Megaloblastic anemia(Macrocytic anemia).-primary defect is a reduction in DNA synthesis, leading to unbalanced cell growth in all rapidly proliferating cells. Over-sized cells with an abnormal amount of cytoplasm.

Folic Acid – B9 Deficiency

- Folate deficiency is common.
- It may result from inadequate intake, malabsorption, or use of various drugs.
- Deficiency causes megaloblastic anemia (indistinguishable from that due to vitamin B12 deficiency).
- Maternal deficiency increases the risk of neural tube birth defects..
- The most common causes are:
  - inadequate intake (patients with under nutrition or alcoholism),
  - increased demand (e.g., due to pregnancy or lactation), and
  - impaired absorption (e.g. in tropical spruce or due to certain drugs).

Folic Acid – B9 Deficiency

- Deficiency can also result from inadequate bioavailability and increased excretion
- Deficiency results in a macrocytic anemia, and elevated levels of homocysteine.
- Deficiency in pregnant women can lead to birth defects. Supplementation is often recommended during pregnancy.
- Researchers have shown that folic acid might also slow the insidious effects of age on the brain
- Treatment with oral folate is usually successful

Symptoms and Signs

- Prolonged cooking destroys folate, predisposing to inadequate intake.
- Intake is sometimes barely adequate (e.g., in alcoholics). Liver stores provide only a several-month supply.
- Alcohol interferes with folate absorption, metabolism, renal excretion, and enterohepatic reabsorption, as well as intake. 5-Fluorouracil
- In the US, many dietary staples (e.g., cereals, grain products) are routinely enriched with folate, tending to reduce risk of deficiency.
- Folate deficiency may cause glossitis, diarrhea, depression, and confusion.
- Anemia may develop insidiously and, because of compensatory mechanisms, be more severe than symptoms suggest.
- Folate deficiency during pregnancy increases the risk of fetal neural tube defects and perhaps other brain defects

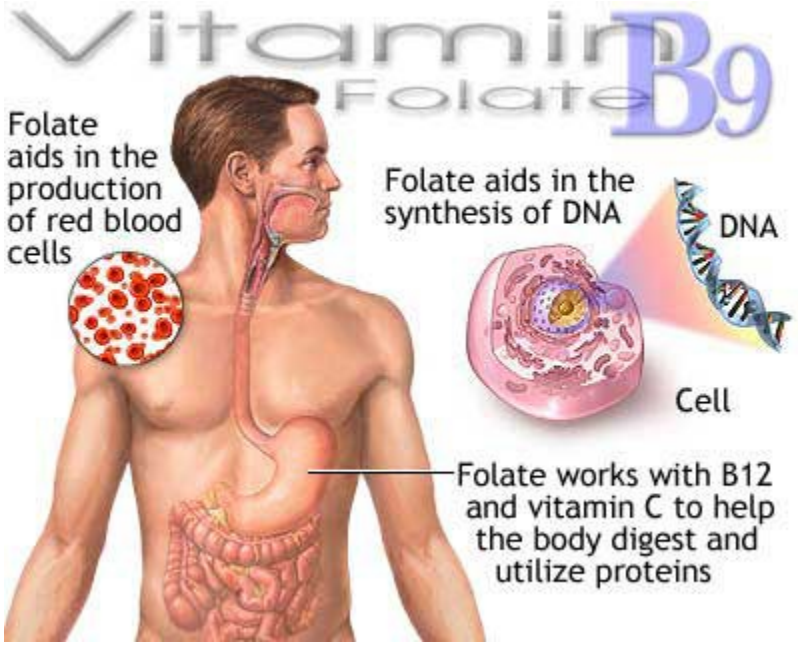
Folate Deficiency Causes

- The most common cause is dietary deficiency, especially among alcoholics, indigents and vegans.
- Malabsorption or increased requirement for folate (pregnancy, lactation, malignancy) can also cause a deficiency and anemia.
- Folic acid is absorbed in the jejunum, but malabsorption only occurs with diffuse intestinal disease.

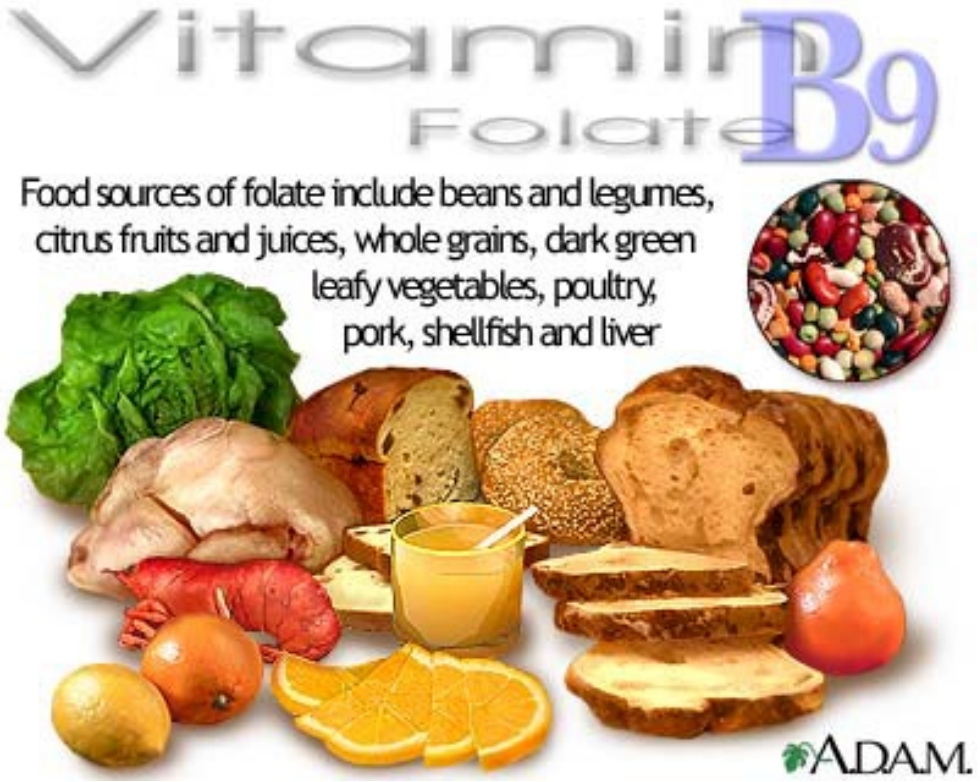
Folic Acid – B9

- Folate (folic acid) is now added to enriched grain foods in the US. Folate is also plentiful in various plant foods and meats, but its bioavailability is greater when it is in supplements or enriched foods than when it occurs naturally in food.
- Folates are involved in RBC maturation and synthesis of purines and pyrimidines. They are required for development of the fetal nervous system. Absorption occurs in the duodenum and upper jejunum. Enterohepatic circulation of folate occurs.
- Folate supplements do not protect against coronary artery disease or stroke (by lowering homocysteine levels); their role in reducing the risk of various cancers is unclear.
- The upper limit for folate intake is 1000 μg; higher doses (up to 5 mg) are recommended for women who have had a baby with a neural tube defect. Folate is essentially nontoxic.

Functions


Vitamin B9
Folate
Folate aids in the production of red blood cells
Folate aids in the synthesis of DNA
DNA
Cell
Folate works with B12 and vitamin C to help the body digest and utilize proteins

Food Sources



Folic Acid deficiency symtoms

Inhibitors of Folate Synthesis in Bacteria

- Inhibitors of folate synthesis in bacteria are bacteriostatic.

- Sulfonamides act as structural analogs of para-aminobenzoic acid (PABA) to inhibit synthesis of pteroic acid from pteridine and PABA in bacteria.Trimethoprim inhibits bacterial but not human dihydrofolate reductase

Megaloblastic anemia:

- Vitamin B12/Folic acid deficiency
- Second most common type of anemia.
- Multi System disease – All organs with increased cell division.
- Pernicious anemia –
  - autoimmune, Gastric atrophy, VitB12 def.

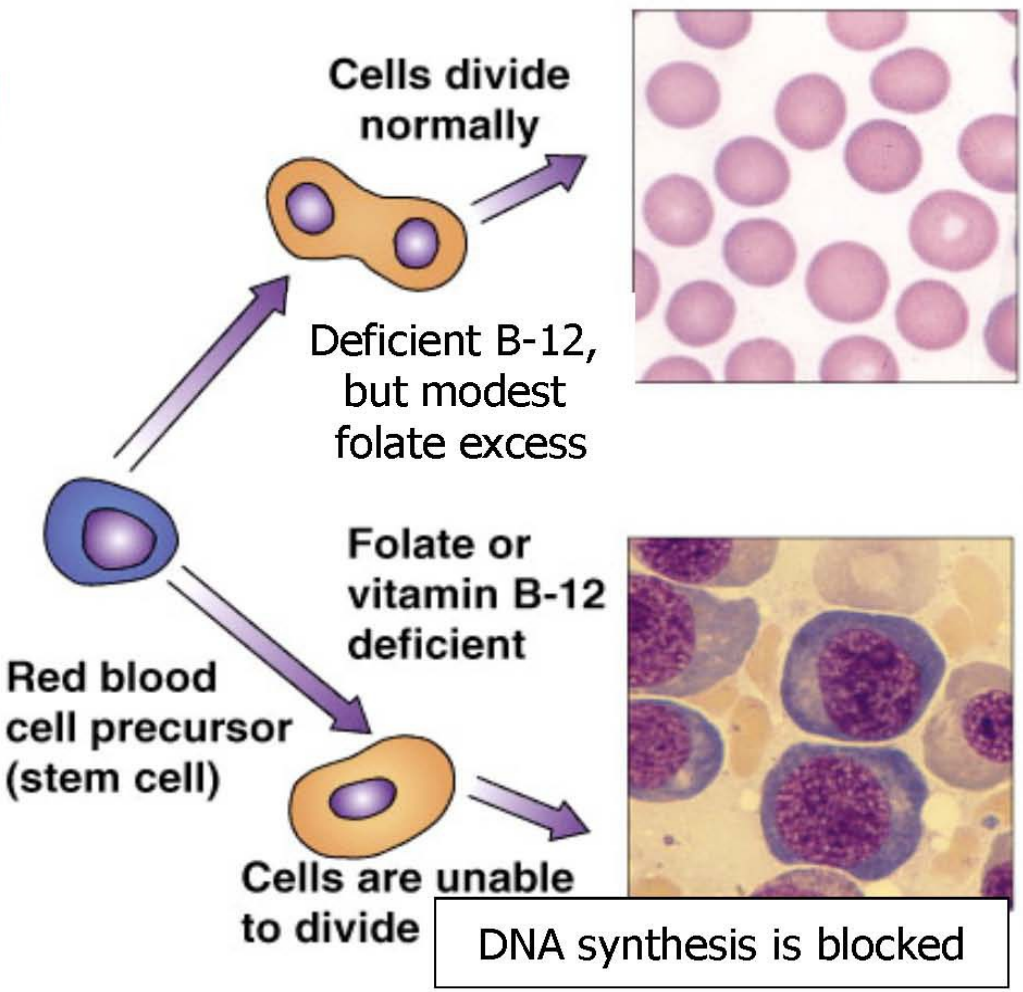
Megaloblastic anaemia and folic acid deficiency

Folic acid deficiency reduces the capacity of the body to make dTMP which affects the rapidly dividing bone marrow cells associated with red blood cell production.

Pernicious anaemia due to primary deficiency of vitamin B12 giving secondary deficiency of folic acid because all the folate ends up trapped as N5-methyl-tetrahydrofolate

Importance of folic acid during early pregnancy:
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.

Megaloblastic Anemia



Normal blood cells in the bloodstream. The size, shape, and color of the red blood cells show that they are normal. Mature red blood cells have lost their nuclei.

Megaloblastic blood cells seen here in the bone marrow are arrested at an immature stage of development. They still have their nuclei and are slightly larger than normal red blood cells.

N5,N10-methylene tetrahydrofolate is absolutely essential for DNA synthesis. This is important in cells that are dividing rapidly such as red blood cell producing bone marrow cells, hair follicles, intestinal mucosa cells and **cancer cells** (rapidly dividing cells need to replicate their DNA often).

Methotrexate (analogue of folic acid) binds to dihydrofolate reductase 1000 times more tightly than folate.

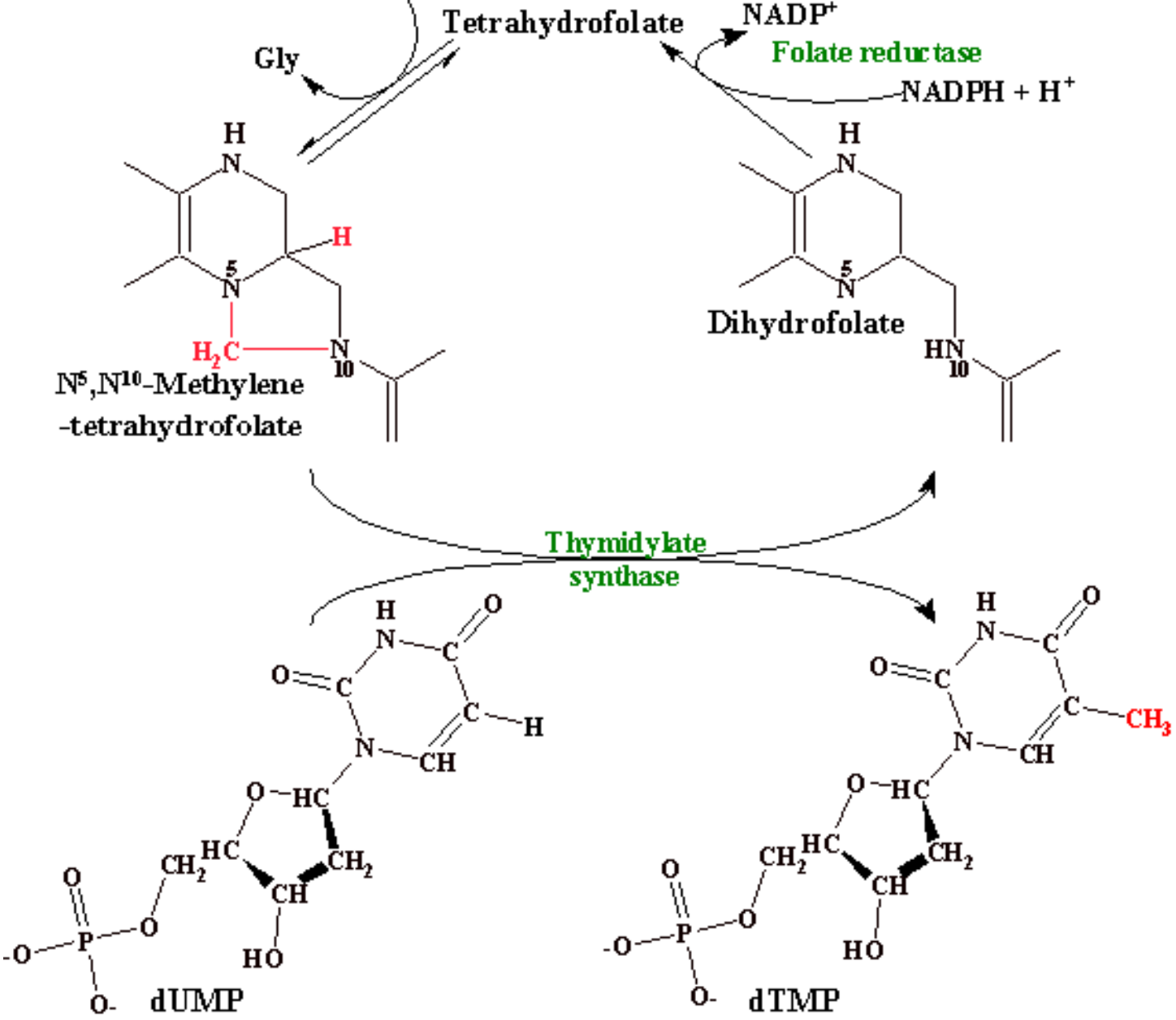
This inhibits the conversion of folate and dihydrofolate into active tetrahydrofolate

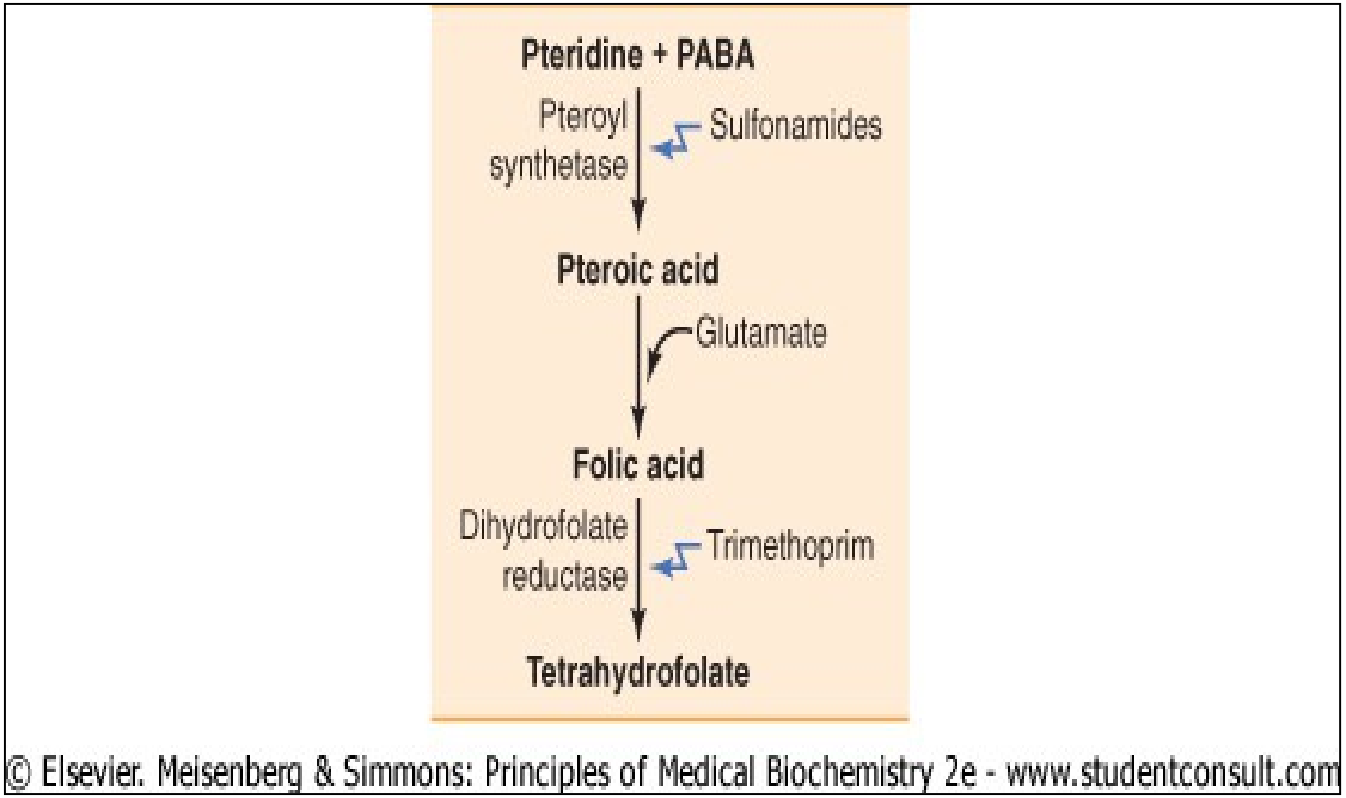
Methotrexate is used to treat leukemia. It works by inhibiting the production of tetrahydrofolate which in turn limits the amount of N5,N10-methylene tetrahydrofolate available for dTMP synthesis

5-FormylTHF (Leucovorin) is a drug to enhance efficacy of methotrexate

Supplement

- Folate 400 to 1000 µg po once/day replenishes tissues and is usually successful even if deficiency has resulted from malabsorption.
- The normal requirement is 400 µg/day.
- *In patients with megaloblastic anemia, vitamin B 12 deficiency must be ruled out before treating with folate.*
- *If vitamin B 12 deficiency is present, folate supplementation can alleviate the anemia but does not reverse, and may even worsen,neurologic deficits*
- For pregnant women, the recommended daily allowance (RDA) is 600 µg/day. For women who have had a fetus or infant with a neural tube defect, the recommended dose is 1000 to 5000 µg/day


Tetrahydrofolate
NADP+
Folate reductase
Gly
NADPH + H+
Dihydrofolate
N5,N10-Methylene
-tetrahydrofolate
Thymidylate
synthase
dUMP
dTMP



Pharmacological inhibition of tetrahydrofolate synthesis in bacteria. PABA, para-aminobenzoic acid.

Cyanocobalamin – B12

- Cobalamin are compounds with biologic vitamin B12 activity:
  - nucleic acid metabolism,
  - methyl transfer
  - myelin synthesis and repair
  - Necessary for the formation of normal RBCs.
- Food-bound vitamin B12 is
  1. released in the stomach's acid environment and is bound to R protein (haptocorrin)
  2. Pancreatic enzymes cleave this B12 complex (B12-R protein) in the small intestine
  3. After cleavage, intrinsic factor, secreted by parietal cells in the gastric mucosa, binds with vitamin B12.
  4. Intrinsic factor is required for absorption of vitamin B12, which takes place in the terminal ileum.

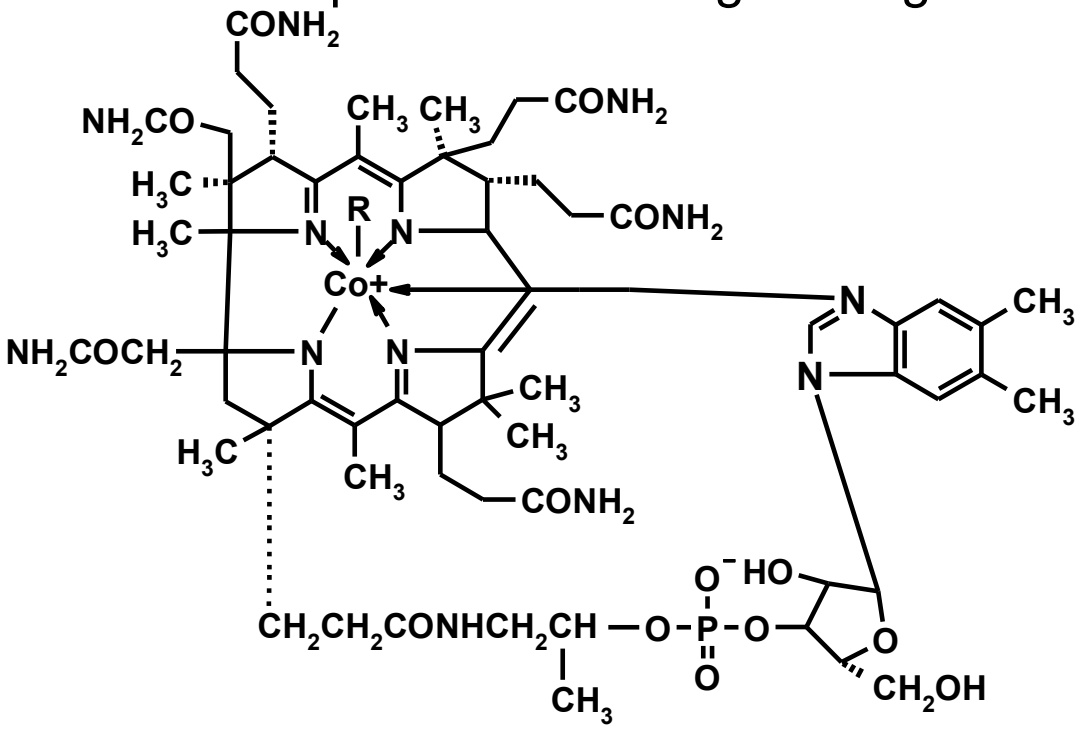
Cyanocobalamin – B12

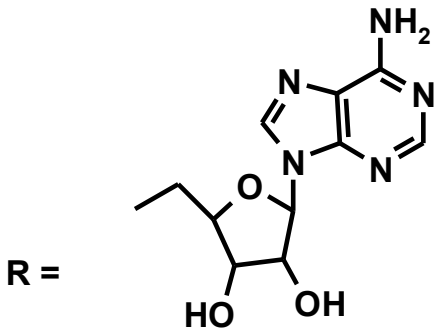
- Vitamin B12 in plasma:
  1. Binds to transcobalamins I and II.
  2. Transcobalamin II is responsible for delivering vitamin B12 to tissues.
  3. The liver stores large amounts of vitamin B12.
  4. Enterohepatic reabsorption helps retain vitamin B12.

- Liver vitamin B12 stores can normally sustain physiologic needs for 3 to 5 yr if B12 intake stops and for months to 1 yr if enterohepatic reabsorption capacity is absent.

Cyanocobalamin – B12

- Commercially isolated from fermentation cultures, dark red solid
- Not found in any plant food sources and is produced almost solely by bacteria, such as ***streptomyces griseus***.
- Rich sources of B12 include liver, meat, egg yolk, poultry and milk.
- Animals depend on microorganism gut bacteria to synthesize





Adenosylcobalamin

R = CN Cyanocobalamin

R = OH Hydroxocobalamin

R = CH_3 Methylcobalamin

Cyanocobalamin – B12

- **Only Two reactions require B12 as a coenzyme**
- Synthesis of blood cells
- Required for maintenance of our **nerve myelin sheaths**
- Acts as a coenzyme in the synthesis and repair of DNA
- Absorption is dependent on **intrinsic factor**, a glycoprotein secreted by parietal cells of the gastric mucosa
  - In the ileum the complex binds to receptors and carried across the membrane by an active transport process, also some passive absorption
  - Once in the intestinal cells the complex is degraded and the compound binds to transcobalamin II (∩-globulin) for transport in the blood
  - Transported to the liver for storage (5-11 mg) and activated by reduction of Co+3 to Co+1
  - As we age we have an difficult time producing intrinsic factor.
    - Recommend people over 60 have their vitamin B12 levels checked

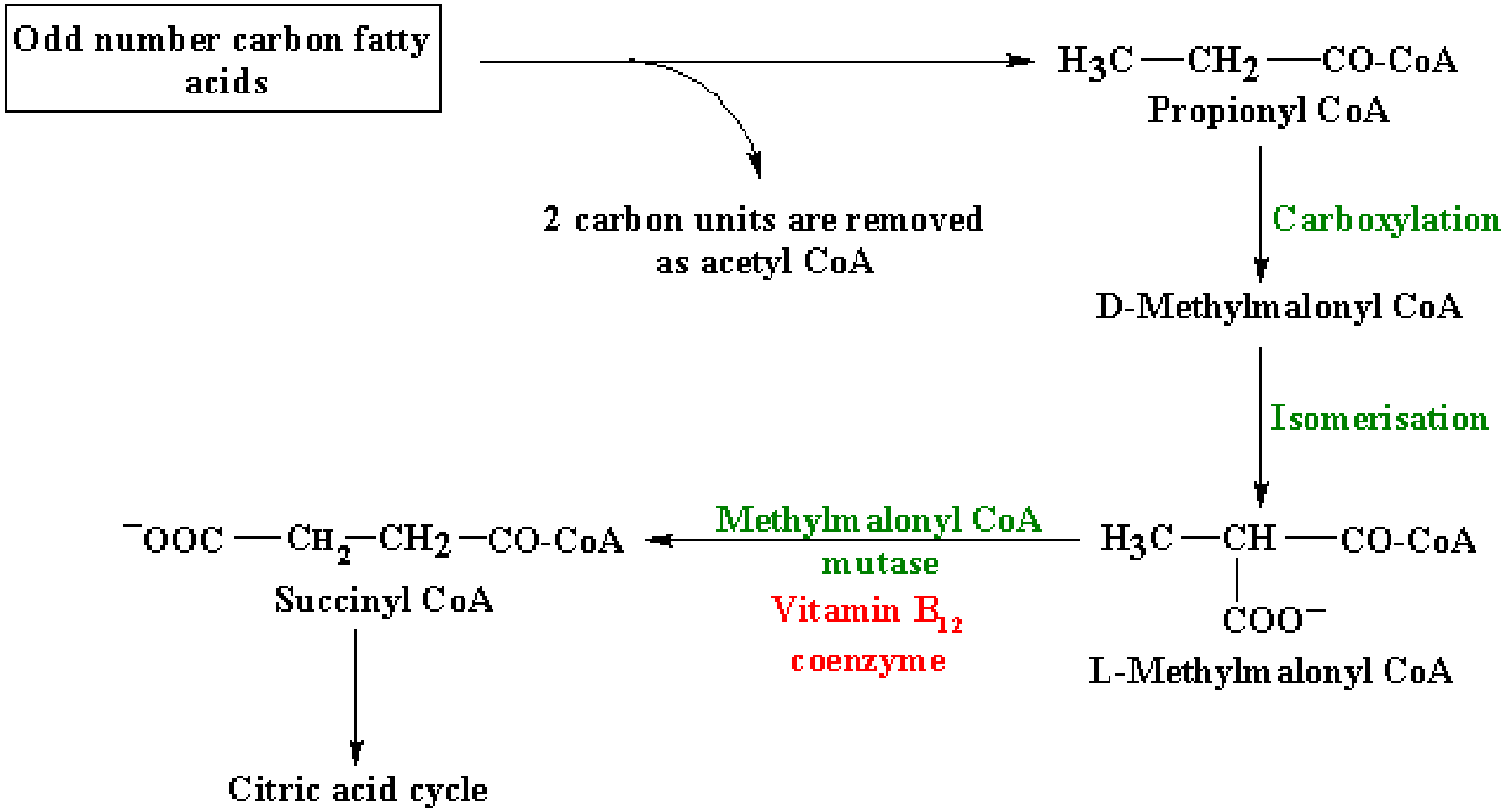
Only 2 reactions require B_{12}:

Conversion of propionyl-CoA to succinyl-CoA. One enzyme in this pathway, methyl-malonyl-CoA mutase, requires B_{12}.

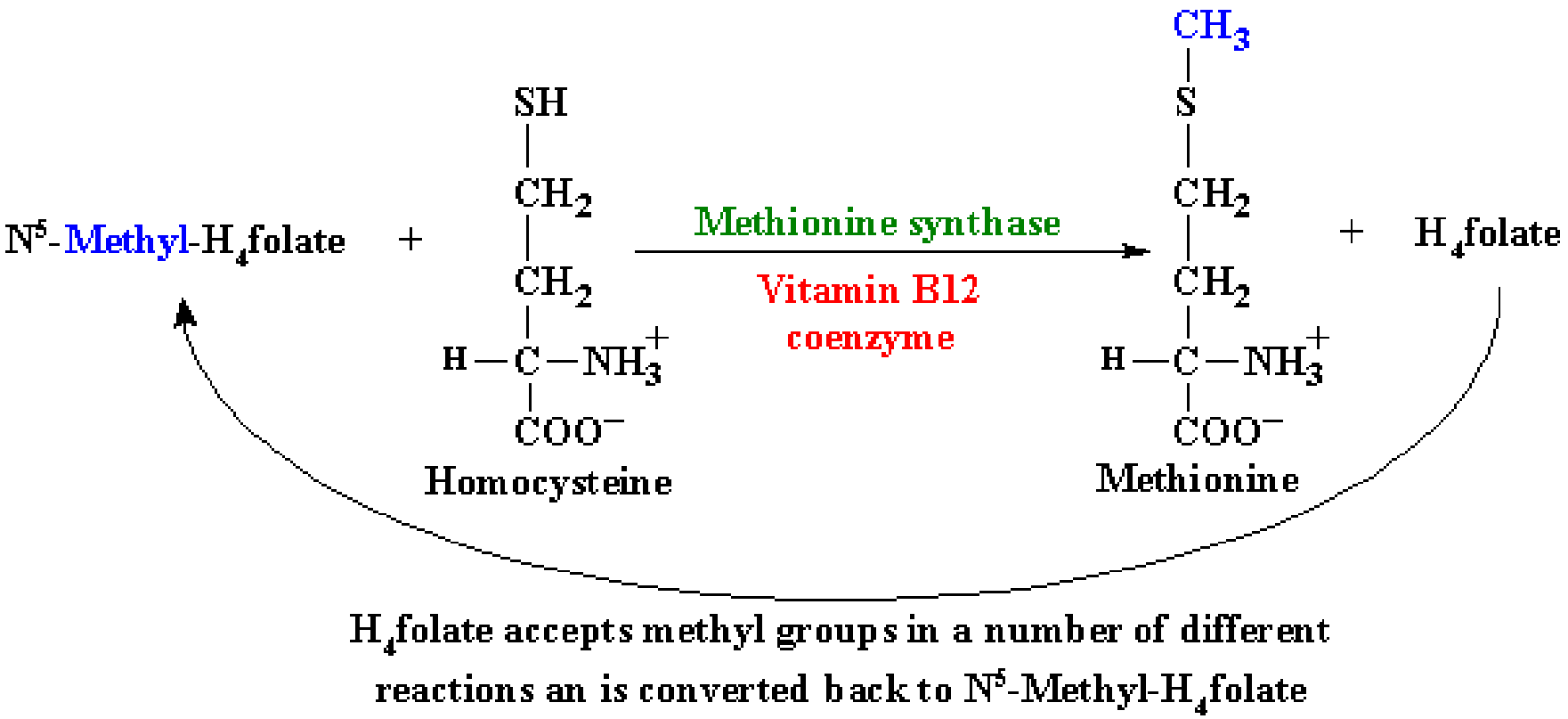
Methionine synthase needs B_{12} in converting homocysteine to methionine. The reaction transfers a methyl group from N^5-THF to OH-cobalamin.

Function of vitamin B12

1) Vitamin B12 (as deoxyadenosylcobalamin) is a co-enzyme methylmalonyl CoA mutase.



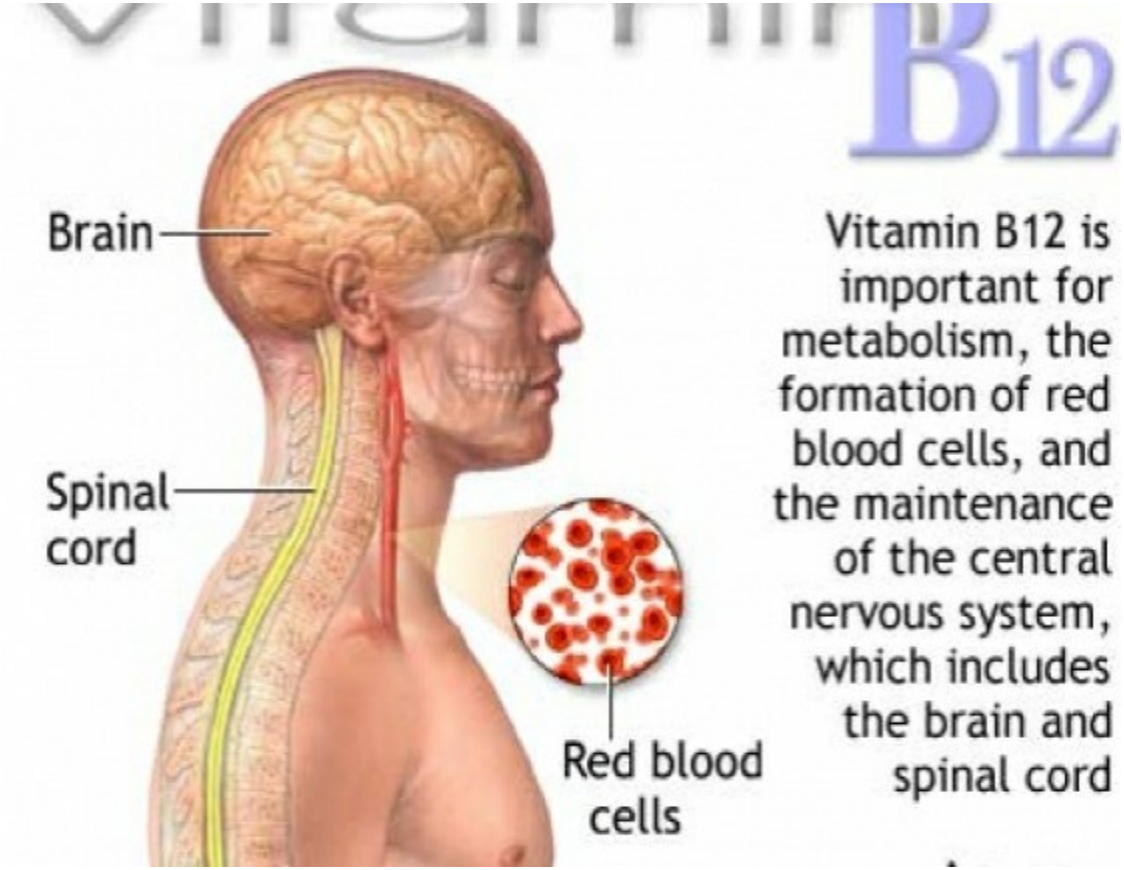
2) Vitamin B12 is also a coenzyme in a reaction involved in methionine Metabolism.



H4folate is converted to N5-methyl-H4folate in a number of different reactions as it accepts methyl groups. **The methyl group can only be removed and the H4folate regenerated by the above reaction. (See folic acid)**

Food sources

Function of vitamin B12



Vitamin B12 Deficiency

- Dietary vitamin B12 deficiency usually results from inadequate absorption, but deficiency can develop in vegans who do not take vitamin supplements.
- Deficiency causes megaloblastic anemia, damage to the white matter of the spinal cord and brain, and peripheral neuropathy.
- Diagnosis is usually made by measuring serum vitamin B12 levels.
- Treatment consists of oral or parenteral vitamin B12. Folate (folic acid) should not be used instead of vitamin B12 because folate may alleviate the anemia but allow neurologic deficits to progress.
- Large amounts of vitamin B12 seem to be nontoxic but are not recommended for regular use (ie, as a general tonic).

Vitamin B12 Deficiency

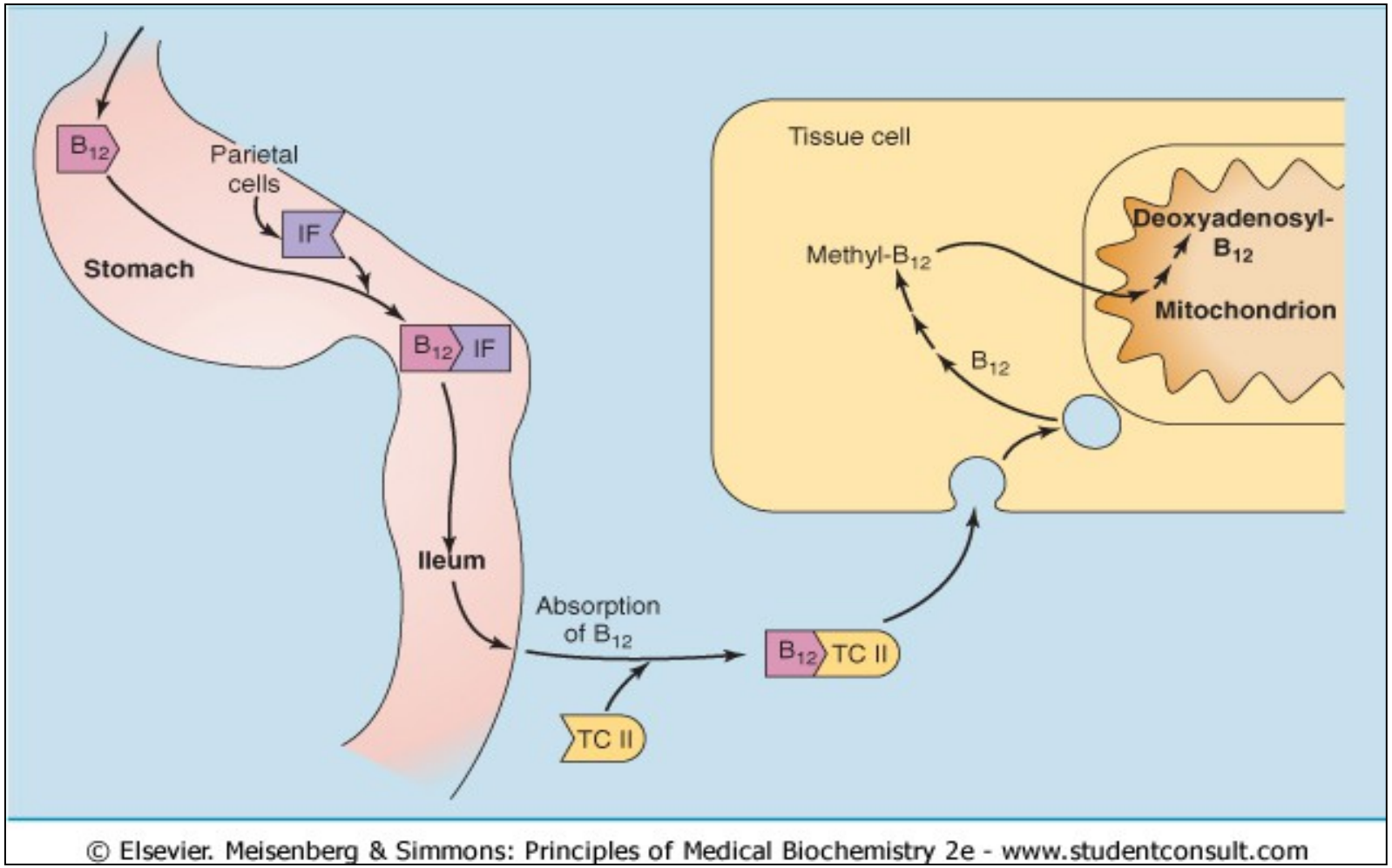
- Inadequate vitamin B12 intake is possible in vegans but is otherwise unlikely.
- Breastfed babies of vegan mothers may develop vitamin B12 deficiency by age 4 to 6 mo because their liver stores (which are normally extensive) are limited and their rapid growth rate results in high demand.
- **Pernicious anemia** (vitamin B12 deficiency) results from vitamin B12 deficiency caused by an autoimmune metaplastic atrophic gastritis with loss of intrinsic factor
  - Patients are at increased risk of stomach and other GI cancers.
- **Subacute combined degeneration**a, vitamin B12 deficiency affects mostly brain and spinal cord white matter
  - Demyelinating or axonal peripheral neuropathies can occur.

Symptoms and Signs

- Pernicious anemia-characteristic signs:
- Megaloblastic anemia
- Diminished gastric secretion
- Neurologic dysfunction as a result of peripheral nerve and spinal cord demyelination. Combined system degeneration of PNS and CNS.
- Treatment of B12 deficiency-large oral supplements or monthly injections of more moderate doses.
- B12 creates a “methyl-folate trap” that prevents dietary folate from activating. This halts synthesis of thymidylate and DNA.

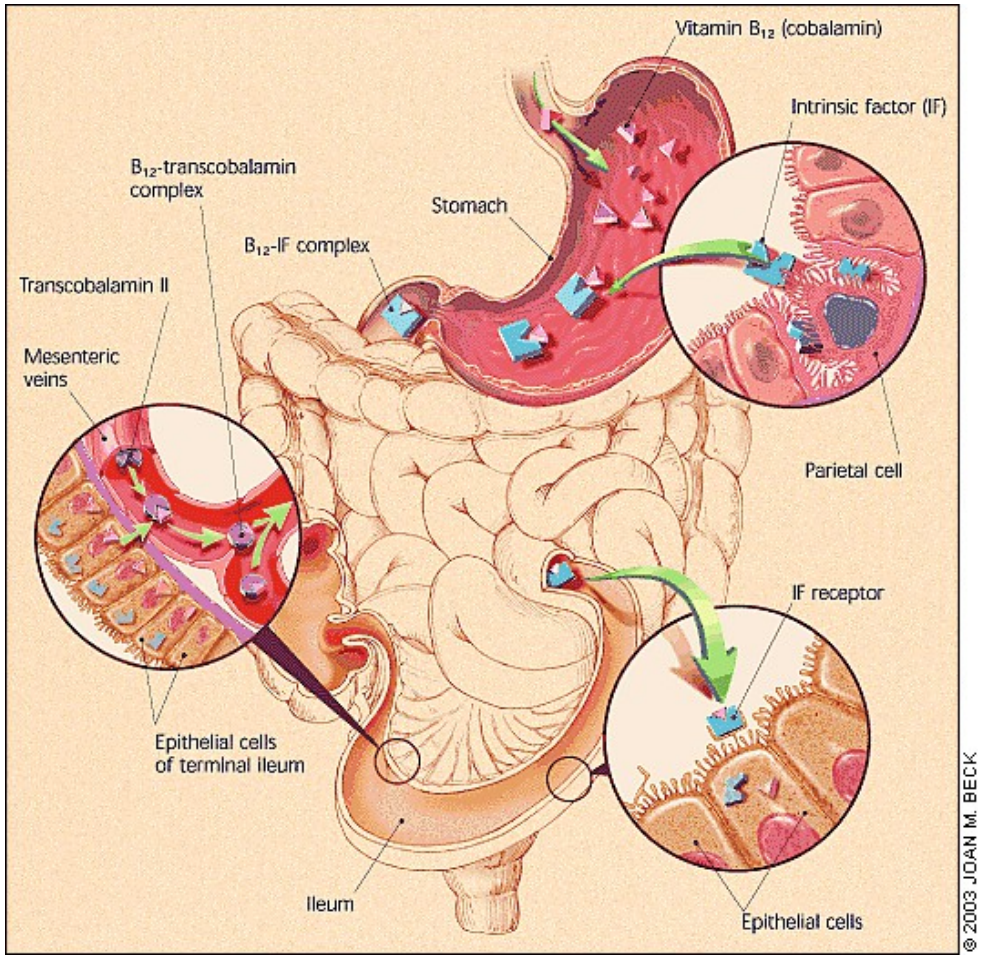
Symptoms and Signs

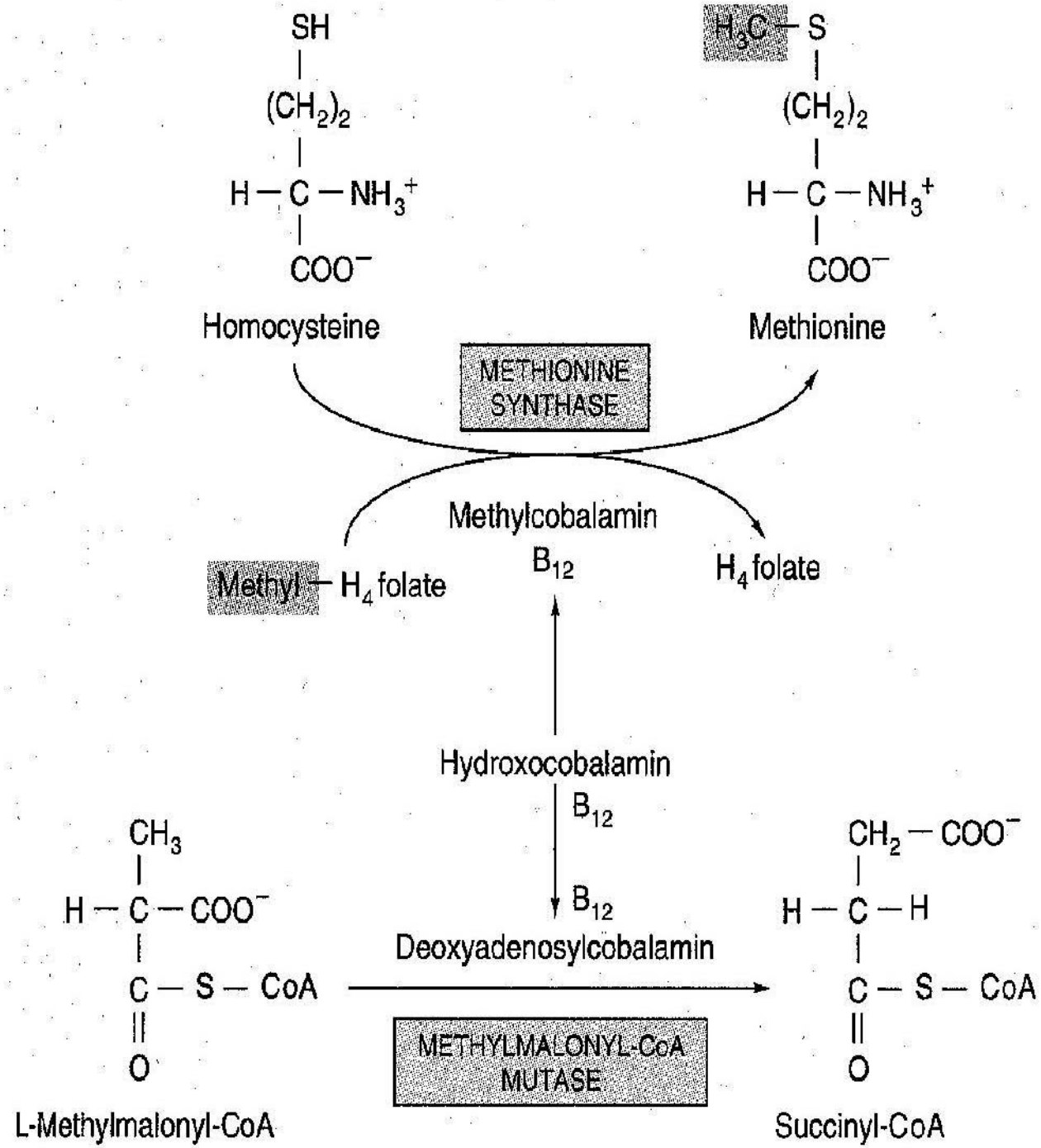
- Anemia usually develops insidiously. splenomegaly and hepatomegaly occurs occasionally.
- Various GI symptoms, including weight loss and poorly localized abdominal pain, may occur.
- Neurologic symptoms develop independently from and often without hematologic abnormalities.
  - Early stages, decreased position and vibratory sensation in the extremities is accompanied by mild to moderate weakness and hyporeflexia.
  - Later stages, spasticity, extensor plantar responses, greater loss of position and vibratory sensation in the lower extremities, and ataxia emerge.
- Paranoia (megaloblastic madness), delirium, confusion, spastic ataxia, and, at times, postural hypotension may occur in advanced cases.



Absorption, transport, and tissue utilization of vitamin B12. IF, intrinsic factor; TC II, transcobalamin II.

Vitamin B12 absorption and transport




SH
(CH2)2
H — C — NH3+
COO−
Homocysteine
H3C — S
(CH2)2
H — C — NH3+
COO−
Methionine
METHIONINE SYNTHASE
Methylcobalamin
B12
Methyl — H4 folate
H4 folate
Hydroxocobalamin
B12
B12
Deoxyadenosylcobalamin
CH3
H — C — COO−
C — S — CoA
O
L-Methylmalonyl-CoA
METHYLMALONYL-CoA MUTASE
CH2 — COO−
H — C — H
C — S — CoA
O
Succinyl-CoA

Effects of B12 Deficiency

Impaired methylmalonyl CoA mutase causes accumulation of unusual odd number carbon fatty acids.
These accumulate in nerve cell membranes causing irreversible neurological disorders.

Impaired methionine synthase traps H4folate as N5-methyl-H4folate ("folate trap").
This can lead to a secondary or artificial deficiency of folic acid.
One of the main symptoms of folic acid deficiency is anaemia.

Anaemia due to a true folic acid deficiency it is **megaloblastic anaemia.**

Anaemia due to a true folic secondary folic acid deficiency caused by primary B12 deficiency is **pernicious anaemia**

Megaloblastosis

Biochemical Basis of Megaloblastosis

The transfer of the methyl group of N^5-methyl-tetrahydrofolate to homocysteine in methionine synthesis requires cobalamin as a coenzyme.

The cobalamin-deficient individual "traps" folate in the N^5-methyl form and becomes compromised in the use of one-carbon derivatives of tetrahydrofolate for metabolic reactions. One particularly sensitive reaction is a diminished synthesis of pyrimidine nucleotide dTMP.

Major consequences of folate and/or cobalamin deficiency in proliferating cells are abnormal DNA structure (elongated chromosomes, increased fragility, and reduced methylation) and perturbation of cell cycle (arrest in S phase).

Relationship of B12 & Folate

	B12 deficiency	Folate deficiency
Megaloblastic anemia	Yes	Yes
Combined system degeneration	Yes	No
Intrinsic factor	Yes	No
Due to dietary deficiency	Rare	Often
absorption	Terminal ileum	jejunum

Supplement

- Vitamin B12 1000 to 2000 µg po can be given once/day to patients who do not have severe deficiency or neurologic symptoms or signs.
- A nasal gel preparation of vitamin B12 is available.
- For more severe deficiency, vitamin B12 1 mg IM is usually given 1 to 4 times/wk for several weeks until hematologic abnormalities are corrected
- Although hematologic abnormalities are usually corrected within 6 wk (reticulocyte count should improve within 1 wk), resolution of neurologic symptoms may take much longer.
- Neurologic symptoms that persist for months or years become irreversible.
- In most elderly people with vitamin B12 deficiency and dementia, treatment must be continued for life unless the pathophysiologic mechanism for the deficiency is corrected.
- Infants of vegan mothers should receive supplemental vitamin B12 from birth.

Consequences of Vitamin Deficiency (1)

folate

(1) megaloblastic anemia (may be due to insufficient methionine or cobalamin in tissues)
(2) neural tube defects (during fetal development)
(3) homocysteinemia

cobalamin

(1) pernicious anemia (chronic atrophic gastritis). This is usually attributed to a lack of or reduced secretion of intrinsic factor, a stomach protein needed for B_{12} absorption. It may also be secondary to other intestinal diseases (*e.g.*, tropical sprue).
(2) megaloblastic anemia
(3) neuropathy (axon degeneration in peripheral and central nervous systems)

Summary

- Vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 pyridoxine, B12 (cobalamin), C (ascorbic acid, biotin, folate
- All except B12 and folate wash out from body, low risk of toxicity

- **Vitamin B1 (thiamine)**
  - Function: Component of thiamine pyrophosphate,
    - cofactor in:
      - Pyruvate dehydrogenase (glycolysis)
      - α-ketoglutarate dehydrogenase (TCA cycle)
      - Transketolase (HMP shunt)
    - Branched chain amino acid dehydrogenase
  - Deficiency:
    - Wernike-Korsakoff syndrome

      Alcoholism and malnutrition

      Mental confusion, psychosis, memory disturbances and eventually coma.

- Beriberi (dry)
  Polyneuritis, symmetrical muscle wasting
- Beriberi (wet)
  High-output cardiac failure (dilated cardiomyopathy) edema

- **Vitamin B2 (riboflavin)**
  - Function: Cofactor in oxidation and reduction (FAD, FMN) B2=2 ATP
  - Deficiency: Cheilosis, corneal vascularization

- **Vitamin B3 (niacin)**
  - Function: Constituent of NAD, NADP, used in redox reactions, B3=3 ATP
    - Derived from tryptophan, requires B6 for synthesis
  - Deficiency: Pellagra (diarrhea, dermatitis, dementia), glossitis
    - Hartnup disease (decreased tryptophan absorption)
    - Malignant carcinoid syndrome (increased tryptophan metabolism
  - Clinical use: Treatment of hyperlipidemia (decrease LDL, increase HDL)
  - Excess: Facial flushing, treat with aspirin

- **Vitamin B5 (pantothenate)**
  - Function: Component of CoA (cofactor in acyl transfers) and fatty acid synthase
  - Deficiency: Dermatitis, enteritis, alopecia, adrenal insufficiency

- **Vitamin B6 (pyridoxine,pyridoxal, and pyridoxamine)**
  - Function: Converted to pyridoxal, phosphate, cofactor in transamination (ALT/AST), decarboxylation reactions, glycogen phosphorylase, heme synthesis
    - Required for synthesis of B3 (niacin)
  - Deficiency: Convulsions, hyperirritability, peripheral neuropathy

- **Vitamin B7 (H) Biotin**
  - Function: Cofactor for carboxylation enzymes, pyruvate carboxylase, acetyl-CoA carboxylase, propionyl-CoA carboxylase
    - Raw egg whites binds biotin and prevents absorption
  - Deficiency: Dermatitis, alopecia, enteritis.
    - Antibiotic use or excessive raw eggs

- **Vitamin B9 (Folic Acid)**
  - Function: Converted to tetrahydrofolate (THF), coenzyme used in 1-carbon transfer/methylation reaction.
    - Used in synthesis of nitrogenous bases in DNA/RNA
  - Deficiency:
    - Macrocytic-megaloblastic anemia
      Without neurological symptoms
    - Neural tube defects
      Prevent with prenatal supplements
    - Much smaller liver stores than B12
    - Most common US vitamin deficiency
      Especially in pregnancy, alcoholism
      Can be caused by phenytoin, sulfonamides, methotrexate Folic Acid
- **Vitamin B12 (cobalamin)**
  - Found: Only in animal products, synthesized by microorganisms (large reserves in liver)
  - Function: Cofactor for homocysteine methyltransferase (transfers CH3 groups) and methylmalonyl-CoA mutase

- **Vitamin B12 (cobalamin) cont.**
- Deficiency:
  - Macrocytic-megaloblastic anemia
  - Neurological symptoms
    - Irreversible if prolonged
    - Paresthesias
    - Sub acute combined degeneration
      - Posterior and lateral spinal columns
  - Causes of deficiency
    - Intestinal malabsorption
      - Sprue, enteritis, fish tapeworm
  - Lack of intrinsic factor
    - Pernicious anemia
  - Absence of terminal ileum
    - Crohn's disease, surgical

    - Schilling test to detect etiology of deficiency

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