Water soluble vitamins

Vitamins

- Vitamins are vital low-molecular organic compounds, which required in very small quantities.
- Vitamins are chemically unrelated organic compounds that cannot be synthesized in adequate quantities by humans and, therefore, must be supplied by the diet.

- Ten vitamins (folic acid, cobalamin, ascorbic acid, bioflavonoids, pyridoxine, thiamine, niacin, riboflavin, biotin, and pantothenic acid) are classified as water soluble. Because they are readily excreted in the urine, toxicity is rare. However, deficiencies can occur quickly.

- Four vitamins (A, D, K, and E) are termed fat soluble . They are released, absorbed, and transported (in chylomicrons) with dietary fat. They are not readily excreted, and significant quantities are stored in the liver and adipose tissue. In fact, consumption of vitamins A and D

in excess of the Dietary Reference Intakes can lead to accumulation of toxic quantities of these compounds.

- Vitamins are required to perform specific cellular functions. For example, many of the water-soluble vitamins are precursors of coenzymes for the enzymes of intermediary metabolism.

In contrast to the water-soluble vitamins, only one fatsoluble vitamin (vitamin K) has a coenzyme function.

Water soluble vitamins

- B Complex

  - Energy releasing: thiamine, niacin, riboflavin, biotin, pantothenic acid
  - hematopoietic: folic acid, cobalamin
  - other: pyridoxine

Non-B Complex

- ascorbic acid
- bioflavonoids

B Complex vitamins

- Mainly contained in plant foods, especially in shells and embryos of cereal grains. Therefore, they are many in flour and bran, as well as in yeast.
- In much smaller quantities are found in food of animal origin (liver, kidneys, brain, egg yolk).

Exceptions

- Leafy, dark green vegetables are a good source of folic acid.
- Cobalamin is present in appreciable amounts in liver, red meat, fish, eggs, dairy products, and fortified cereals.
- A metabolite of tryptophan, quinolinate, can be converted to NAD(P). In comparison, 60 mg of tryptophan = 1 mg of niacin.

The daily requirement of adult healthy person in vitamins B

- Vitamins B_1, B_2-1,5-2,0 mg
- Pyridoxine – 2-4 mg
- Pantothenic acid -10 mg
- Niacin-15-25 mg
- B_{12}- 0,025-0,05 mg
- Bc -0,18-0,4 mg
- Vitamins H – 0,115-0,120 mg

The concept of hypovitaminosis and avitaminosis

- **Avitaminosis** – are disease that occurs at complete absence in food or complete violation absorption of a vitamin.
- **Hypovitaminosis** – are conditions due to insufficient intake of vitamins with food or incomplete its digestion.
- Hypovitaminosis and avitaminosis can be **primary and secondary.**

The reasons of primary hypovitaminosis and avitaminosis

Insufficient intake or complete absence of vitamins in food.

The reasons of secondary hypovitaminosis and avitaminosis

- Vitamins are present in food, but do not enter the inner medium of the organism.
- **Reasons** :

-Diseases of the gastrointestinal tract in which absorption of vitamins is violated.

-The lack of fats in the diet, which are necessary for absorption fat-soluble vitamins.

-Diseases of liver and biliary tract, which leads to violation absorption of fat-soluble vitamins.

The reasons of secondary hypovitaminosis and avitaminosis

- Parasitic diseases because parasites absorb vitamins or destroy them.
- Violation of activation absorbed vitamins as a result diseases internal organs (liver, kidneys).
- Treatment by antibiotics and sulfanilamide preparations for a long time, these drugs suppress the intestinal microflora and reduce the synthesis of vitamins.

The reasons of secondary hypovitaminosis and avitaminosis

- Application of antivitamins.
- Relative insufficiency with increased need for vitamins in pregnancy, breastfeeding, heavy physical labor.

Antivitamins

- **Antivitamins –** are structural analogs of vitamins.
- Bacteria for their growth and reproduction require the presence of many vitamins for the synthesis of coenzymes.
- Injection in the body of antivitamins leads to the death of microorganisms. Antivitamins usually block the active sites of enzymes and cause competitive inhibition of enzymes.

Vitamers

- **Vitamers are** structural analogs of vitamins, which have vitamin activity.
- For instance, vitamers of vitamin B_6 - pyridoxol, pyridoxal, pyridoxamine.

B VITAMINS

- Thiamin (Vitamin B1)
- Riboflavin (Vitamin B2)
- Niacin (B3)
- Pyridoxine Vitamin B6)
- Biotin
- Folic acid
- Cyanocobalamin (Vitamin B12)
- Pantothenic acid

- These vitamins are chemically not related to one another.
- They are grouped together because all of them function in the cells as precursors of coenzymes.

Vitamin	RDA/ AI		Best Sources
	Men	Women	
Thiamin (B1)	1.2mg	1.1mg	Fortified cereals and oatmeals, meats, rice and pasta, whole grains, liver
Riboflavin	1.3mg	1.1mg	Whole grains, green leafy vegetables, organ meats, milk, eggs
Niacin	16mg	14mg	Meat, poultry, fish, enriched cereals, peanuts, potatoes, dairy products, eggs
Pantothenic acid	5mg	5mg	Lean meats, whole grains, legumes
Folate	400ug	400ug	Green leafy vegetables, organ meats, dried peas, beans, lentils
B6	1.3mg	1.3mg	Fish, poultry, lean meats, bananas, prunes, dried beans, whole grains, avocados
B12	2.4ug	2.4ug	Meats, milk products, seafood
Biotin	30ug	30ug	Cereal/grain products, yeast, legumes, liver
Vitamin C	90mg	75mg	Citrus fruits, berries, and vegetables- especially peppers

Biochemical Role of Coenzymes and Vitamins

Coenzyme	Related vitamin	Chemical reaction
NAD^+, $NADP^+$	Niacin	Oxidation-reduction
FAD	Riboflavin (B_2)	Oxidation-reduction
Thiamine pyrophosphate	Thiamine (B_1)	Aldehyde group transfer
Coenzyme A	Pantothenate	Acyl group transfer
Tetrahydrofolate	Folate	Transfer of one-carbon groups
Biotin	Biotin	Carboxylation
Pyridoxal phosphate	Pyridoxal (B_6)	Transamination


B1

THIAMINE (VITAMIN B1)

Box 37.1: Thiamine and thymine are different

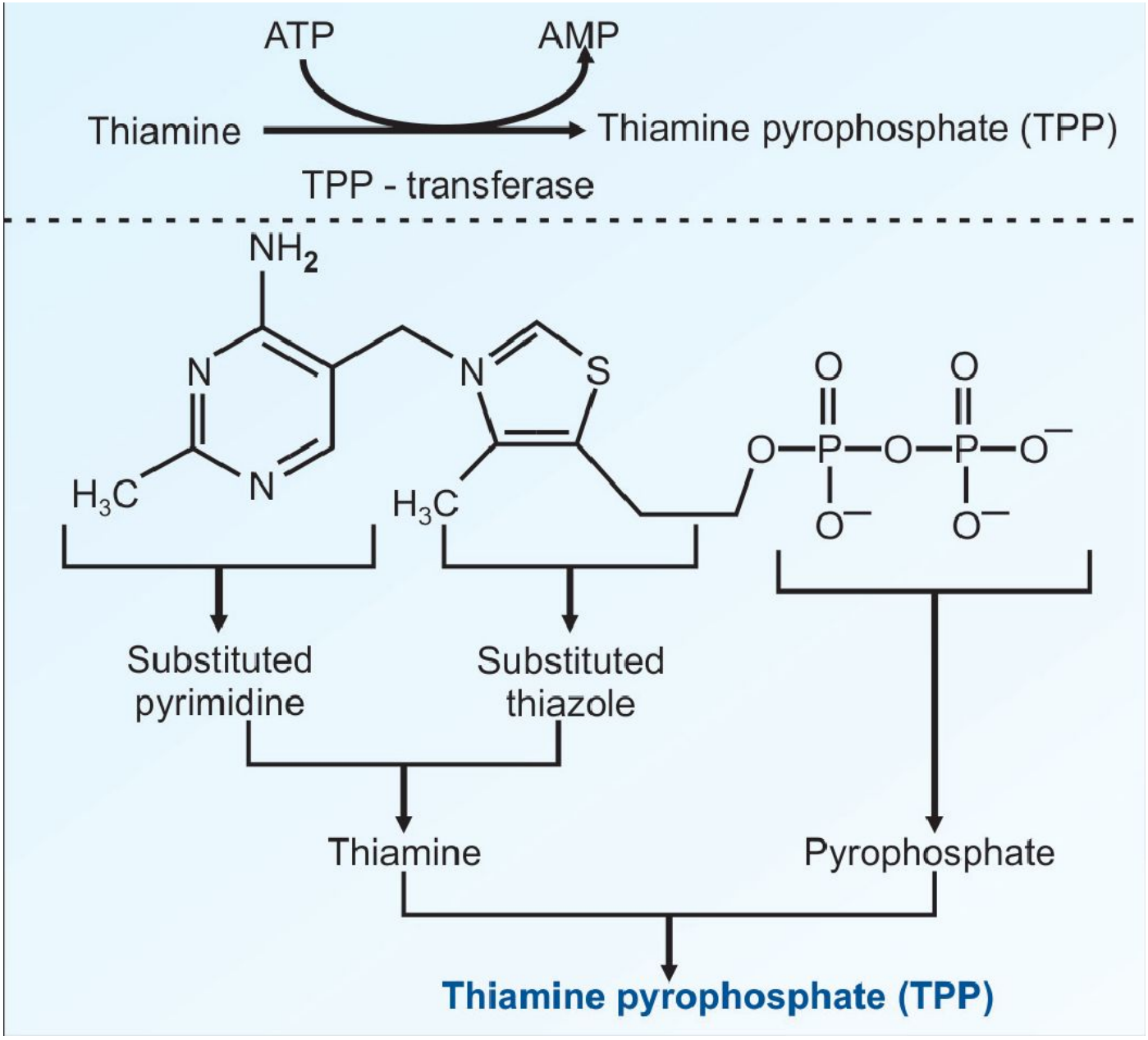
THYMINE is the base present in DNA.
THIAMINE is vitamin B_1.

- Thiamine is also called as vitamin B1 In old literature, it is designated as Aneurine (it can relieve neuritis) or anti Beri Beri factor.

- Its active co-enzyme(major function) form is thiamine pyrophosphate (TPP)

- It is formed by addition of two phosphate groups, with the help of ATP

Thiamine : B1


ATP
AMP
Thiamine
Thiamine pyrophosphate (TPP)
TPP - transferase
NH2
N
N
S
H3C
N
H3C
O
O
O
P
O
P
O
O
O
Substituted pyrimidine
Substituted thiazole
Thiamine
Pyrophosphate
Thiamine pyrophosphate (TPP)

Functions of B1:

1. Enzyme cofactor: (Thiamine pyrophosphate TPP or TDP)

A. Decarboxylation reactions

Pyruvate dehydrogenase

α-ketoglutarate dehydrogenase

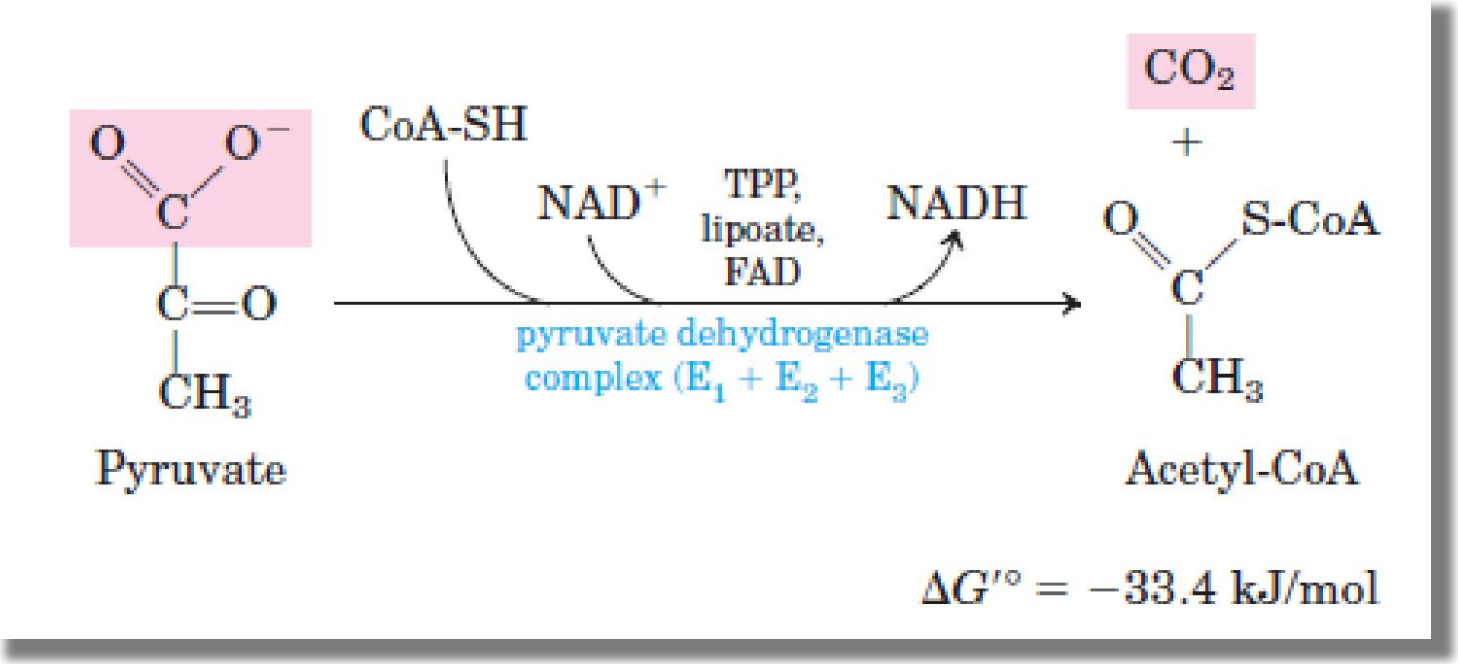
α-keto acid dehydrogenase – branched chain amino acid metabolism.

B. Transketolation reactions

Transketolase – Pentose Phosphate pathway

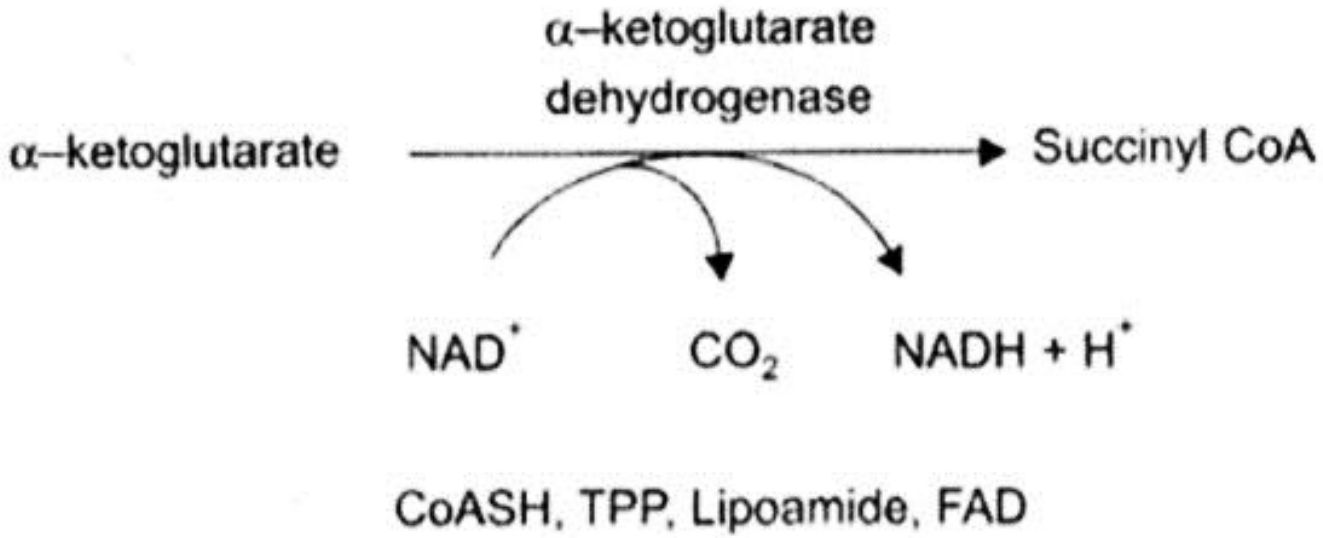
A. Decarboxylation reactions

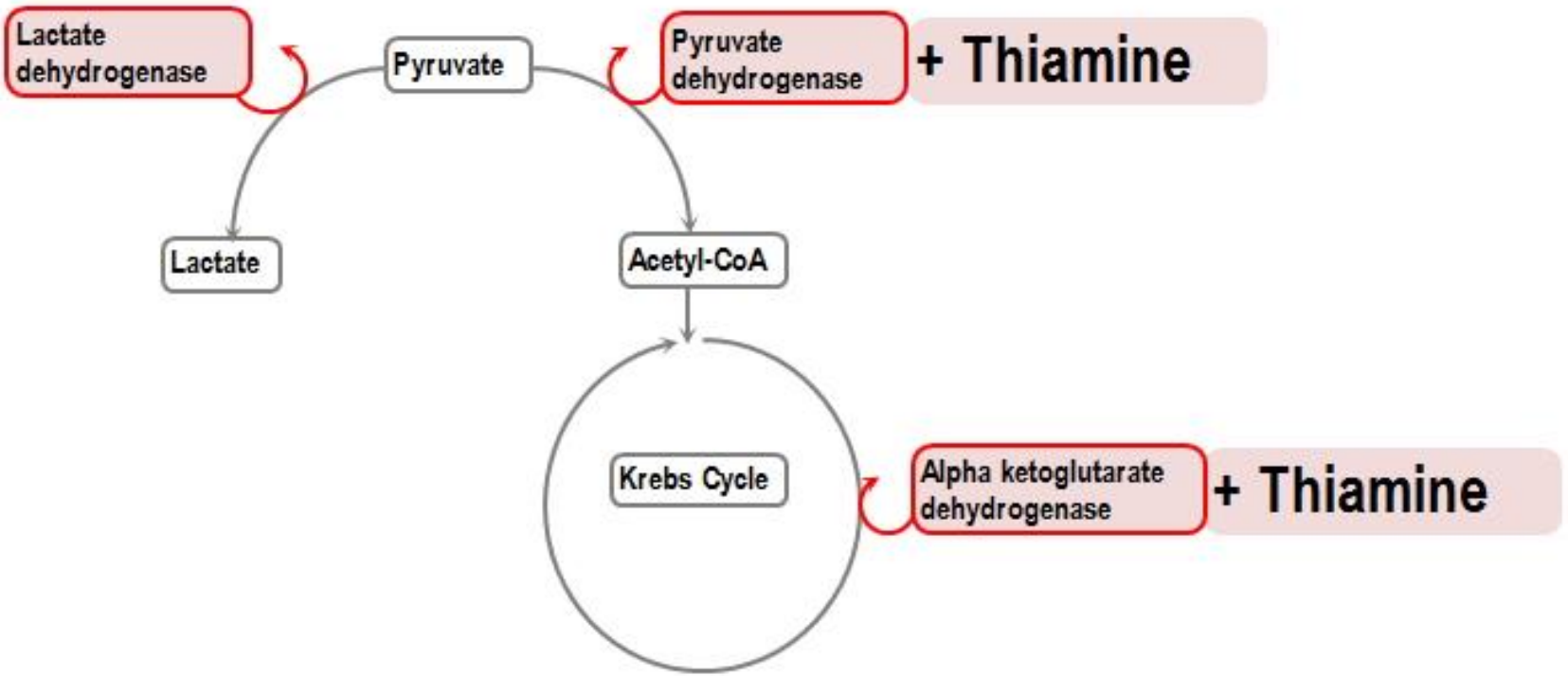
- **Pyruvate dehydrogenase complexed to TPP:** it catalyzes the breakdown of pyruvate, to acetyl CoA, and carbon dioxide



A. Decarboxylation reactions

- **II. Alpha ketoglutarate dehydrogenase:** requires TPP is the decarboxylation of **alpha ketoglutarate** to succinyl CoA and CO_2




Lactate dehydrogenase
Pyruvate
Pyruvate dehydrogenase
+ Thiamine
Lactate
Acetyl-CoA
Krebs Cycle
Alpha ketoglutarate dehydrogenase
+ Thiamine

A. Transketolation reactions

- III. **Transketolase:** The second group of enzymes that use TPP as co-enzyme are the transketolases, in the Pentose phosphate pathway(PPP) of glucose

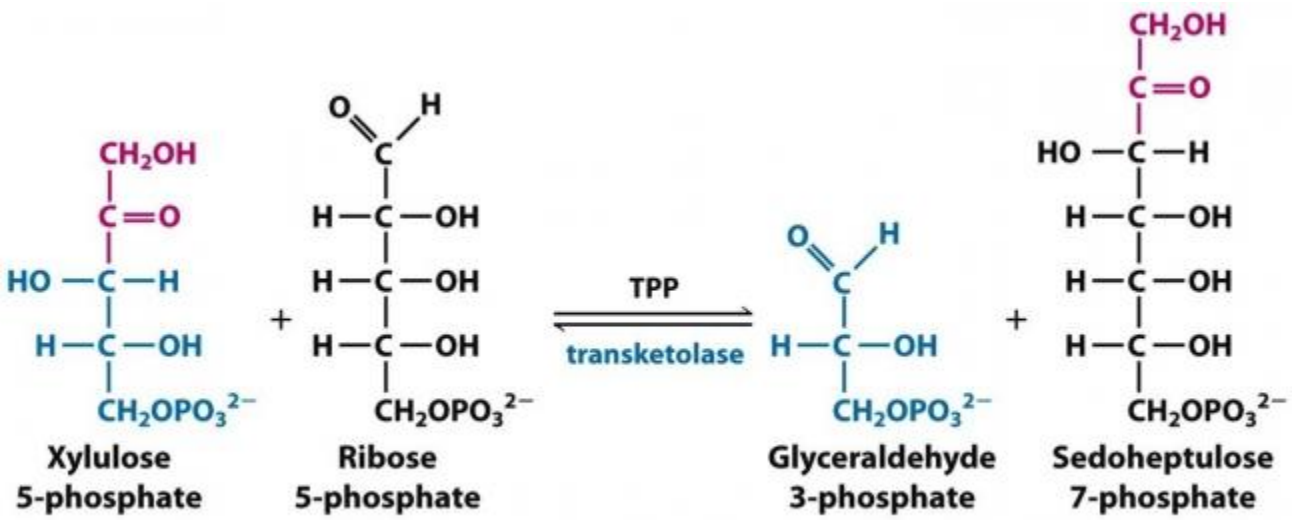


Figure 14-23b
Lehninger Principles of Biochemistry, Fifth Edition

Thiamin status is affected by:

1. Food processing – washing, polishing etc.

2. Ethanol ingestion / alcoholism
   - Reduces thiamin intake
   - Impaired intestinal absorption
   - Alters phosphorylation of thiamine
   - Increases excretion

Thiamine deficiency

- In thiamine deficiency, the activity of these two dehydrogenase-catalyzed reactions is decreased, resulting in decreased production of ATP and, therefore, impaired cellular function.

Vitamin B1

Thiamine deficiency is diagnosed by an increase in erythrocyte transketolase activity observed on addition of TPP.

Beriberi: This is a severe thiamine-deficiency syndrome found in areas where polished rice is the major component of the diet.

Adult beriberi is classified as dry (characterized by peripheral neurologic deficits) or wet (characterized by edema due to cardiac

dysfunction).

Wernicke-Korsakoff syndrome

- In the United States, thiamine deficiency, which is seen primarily in association with chronic alcoholism, is due to dietary insufficiency or impaired intestinal absorption of the vitamin.
- Some alcoholics develop Wernicke-Korsakoff syndrome, a thiamine deficiency state characterized by confusion, ataxia, and a rhythmic to-and-fro motion of the eyeballs (nystagmus) with Wernicke encephalopathy as well as memory problems and hallucinations with Korsakoff dementia.
- The syndrome is treatable with thiamine supplementation, but recovery of memory is typically incomplete.

Deficiency Diseases of B1:

- Beriberi
  - Wet beriberi
  - Dry beriberi
  - Infantile beriberi

- Wernicke-Korsakoff syndrome: inability to coordinate voluntary muscle movements; unsteady movements and staggering gait

- Polyneuritis: inflammation of a nerve accompanied by pain and sometimes loss of function

Wet Beri Beri:

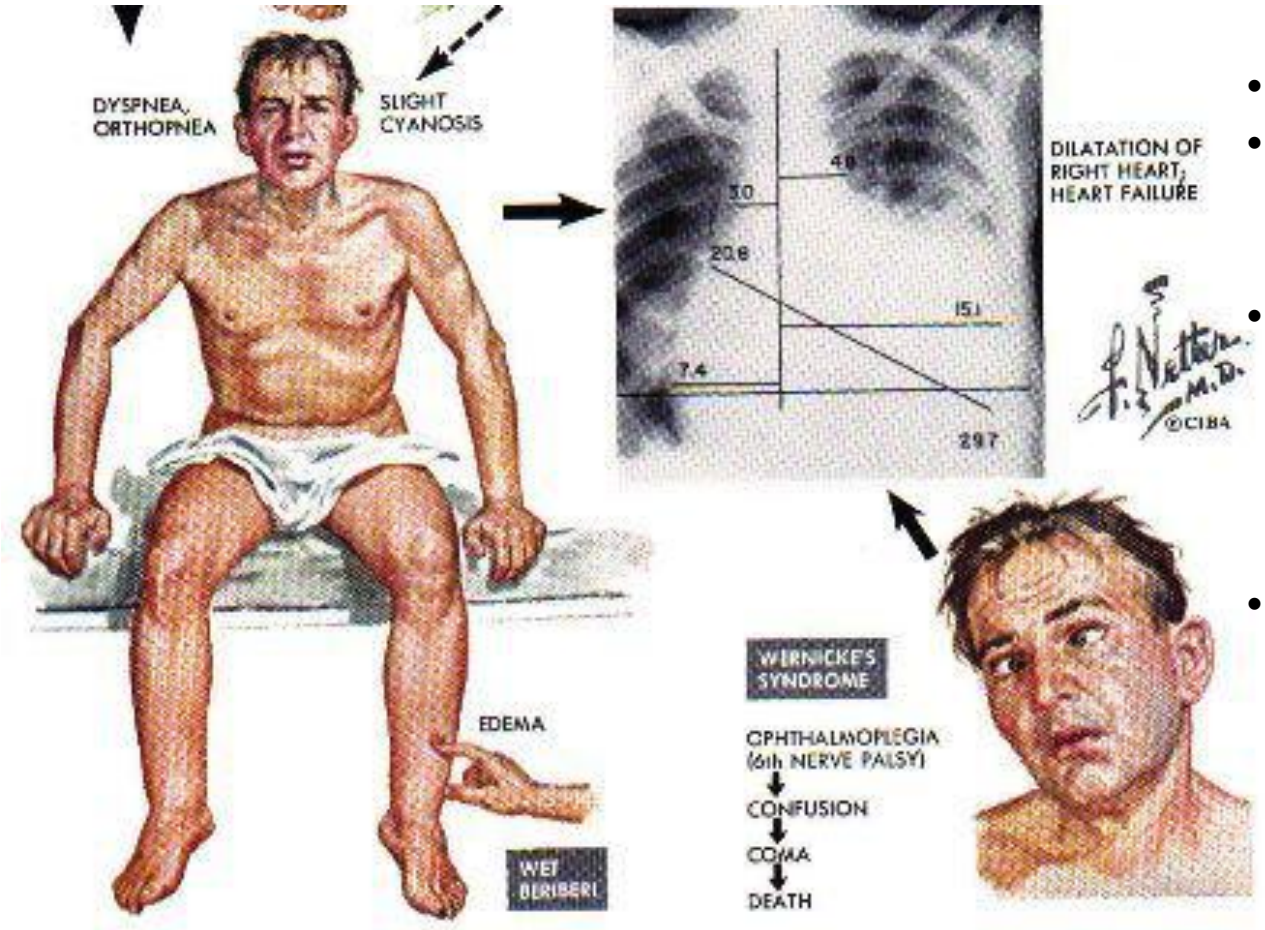
Cardiovascular manifestations

- edema
- palpitations
- breathlessness
- fatigue
- distended neck veins

cause of death: cardiac failure

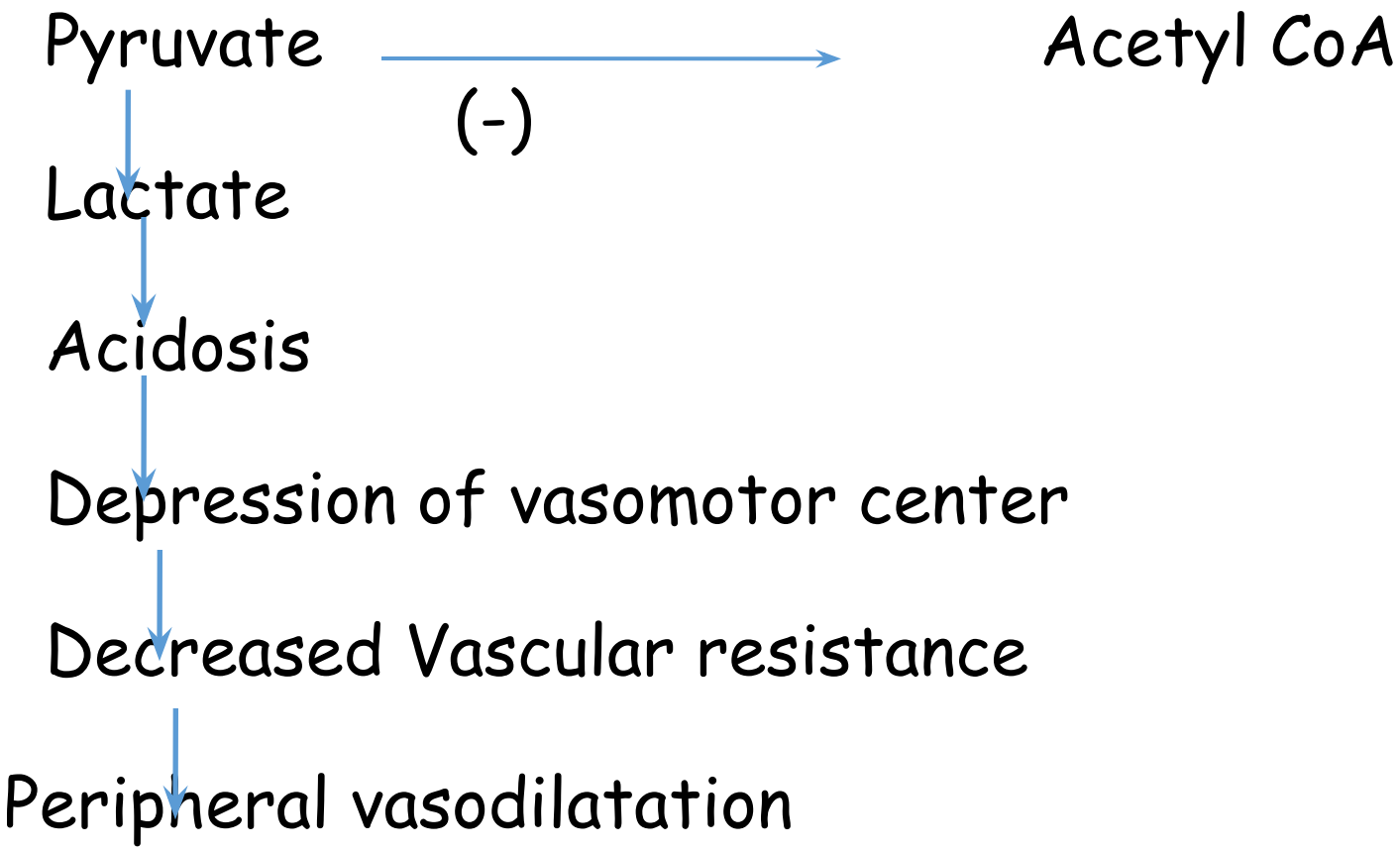
Deficiency Manifestations of Thiamine

- B. **Wet beriberi:. cardiac beriberi**



- Edema of legs
- face, trunk and serous cavities
- Palpitation, breathlessness distended neck veins
- Death occurs due to heart failure.

Biochemical basis of wet beriberi:



Dry Beriberi (paralytic / nervous)

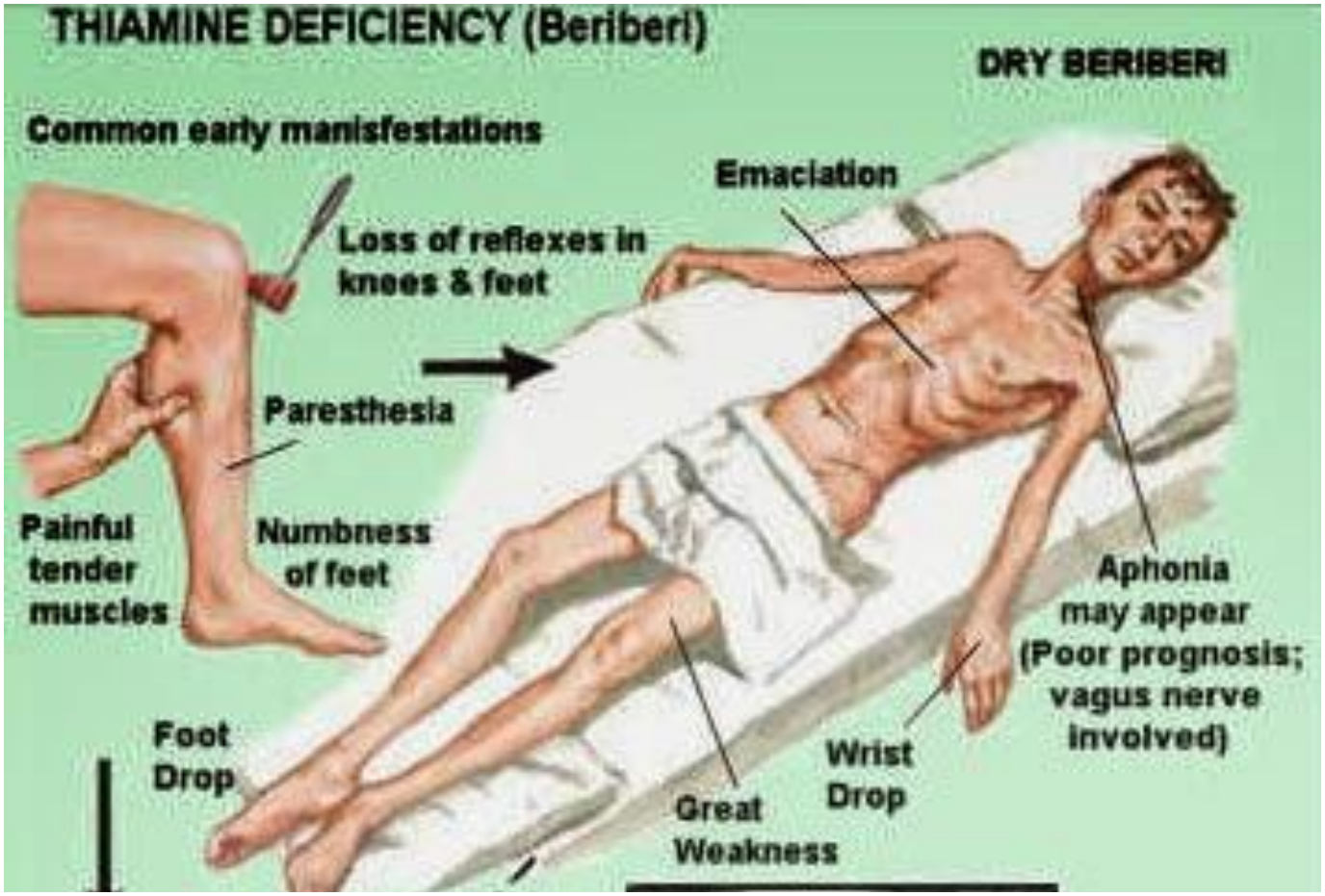
CNS manifestations:

- muscle weakness
  - gait disturbance
  - paralysis
  - calf muscle tenderness
  - impairment of sensory, motor and reflex functions

    (distal segment of limbs > proximal segment)

Deficiency Manifestations of Thiamine

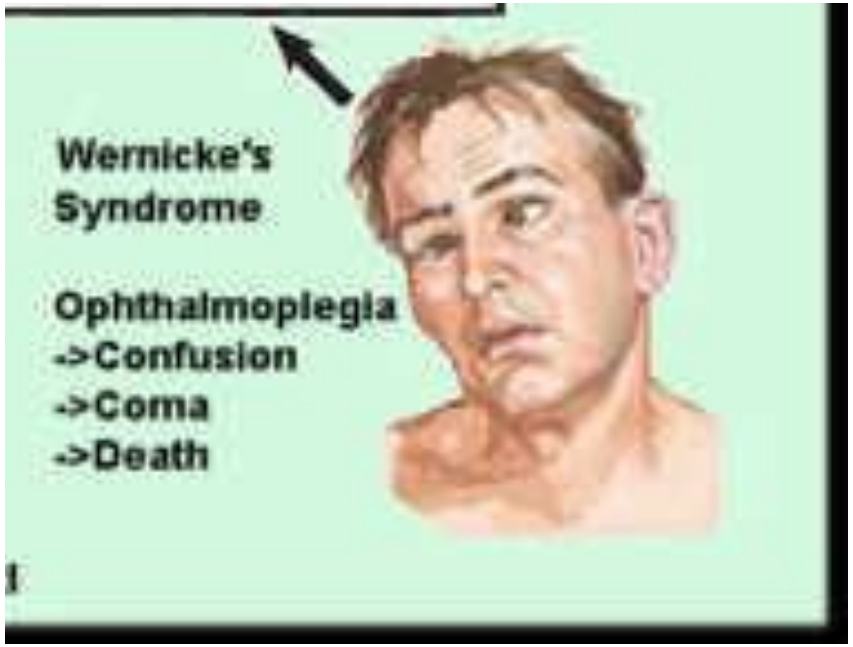
- Dry **Beriberi (peripheral neuritis):** Walking becomes difficult. Peripheral neuritis with sensory disturbance leads to complete paralysis



Infantile beri-beri:

- Maternal malnutrition
- Age group: 2 – 3 months
- 3 forms
  - Cardiac (acute fulminating)
  - Aphonic
  - Pseudomeningitic

Cerebral Beri beri:



High risk groups:

Alcoholism

Chronic dialysis

Clinical features:

Wernicke's encephalopathy – ataxia, confusion and opthalmoplegia.

Korsakoff psychosis – amnesia and confabulation – impairment of conceptual function decreased spontaneity and initiative

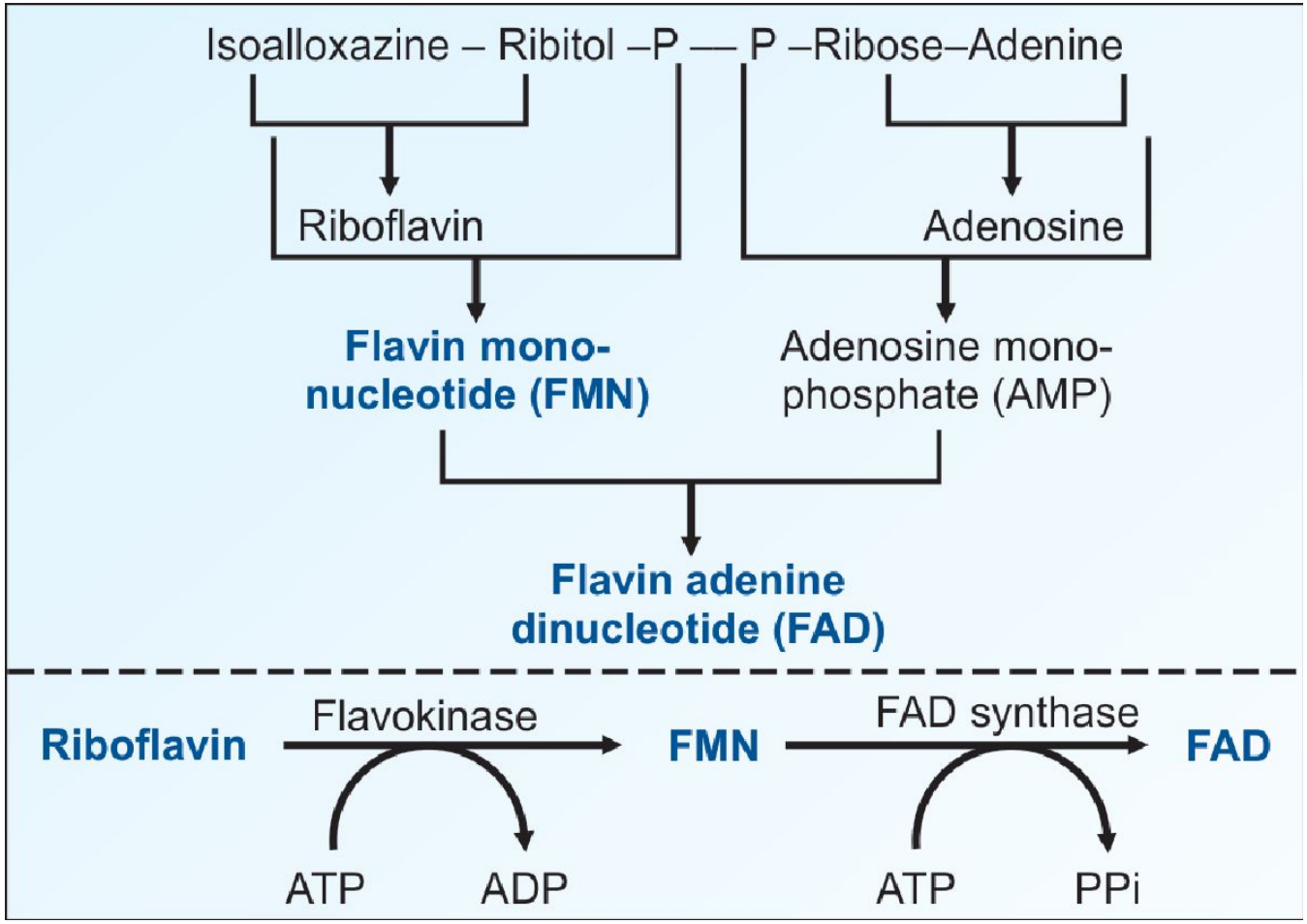

B
2

Riboflavin : B2

- Heat stable, light sensitive , luminescent vitamin – UV light
- Vitamin B_2 , lactoflavin, Warburg's yellow enzyme
- Source – whole cereals, legumes (beans), eggs , milk
- **Daily Requirement**
- Riboflavin is concerned mainly with the metabolism of **carbohydrates** and requirement is related to calorie intake.
- Adults on sedentary work require about 1.5 mg per day. During pregnancy, lactation and old age, additional 0.2 to 0.4 mg/day are required.

Co-enzyme forms:

- FMN – Flavin Mono Nucleotide
- FAD – Flavin Adenine Dinucletide



Functions:

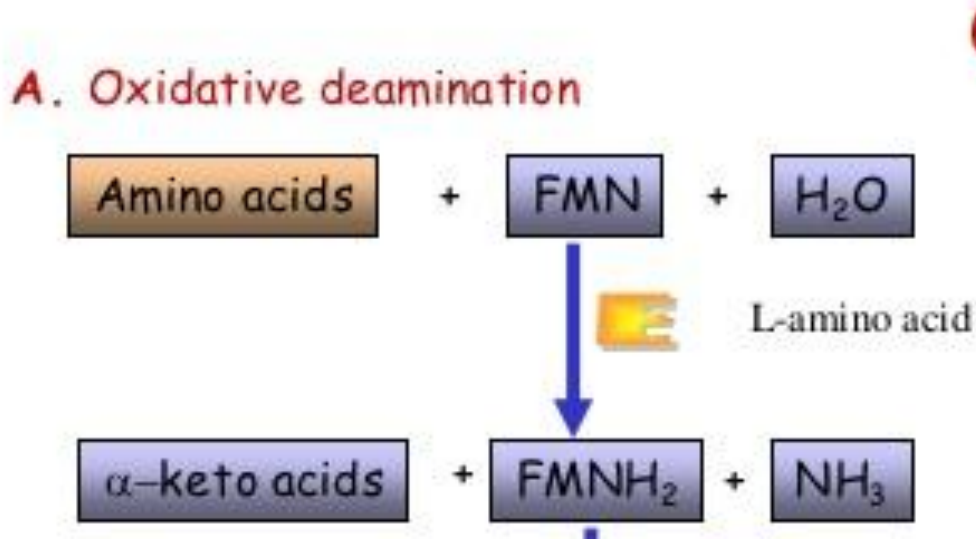
- Integral component of electron transport chain ATP Synthesis ----*NAD FMN CoQ*

- *Component of several enzymes in the metabolic pathway*

  - TCA cycle succinate dehydrogenase
  - Fatty Acid Oxidation acyl CoA dehydrogenase
  - **Amino acid oxidation** As a part of alpha ketoglutarate
  - Isocitrate dehydrogenase complex (dihydrolipoate dehydrogenase)

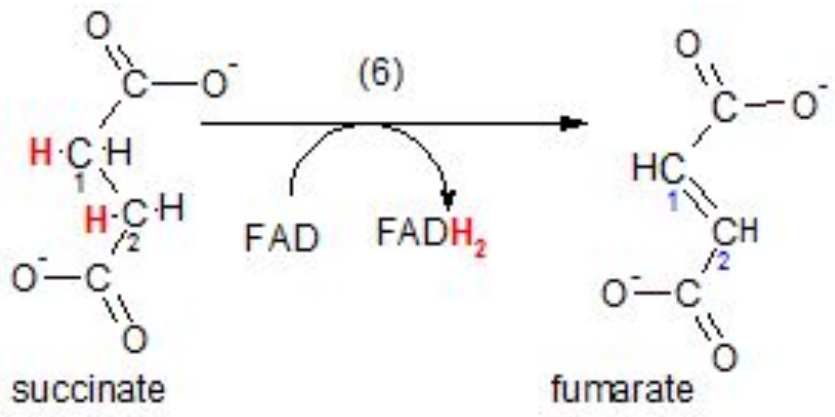
FMN-dependent Enzymes

- i. During the **amino acid oxidation**, FMN is reduced. It is reoxidized by molecular oxygen to produce hydrogen peroxide



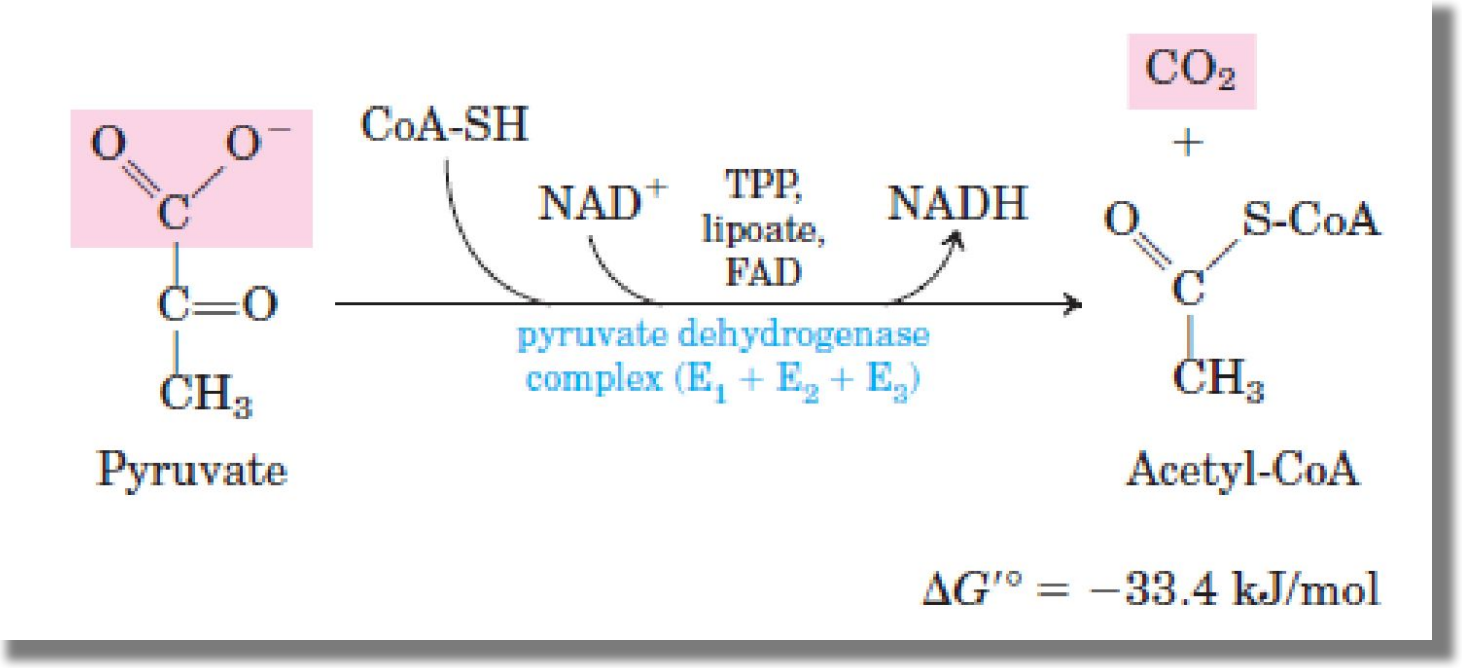
FAD-dependent enzymes

- 1. Succinate to fumarate by succinate dehydrogenase in TCA

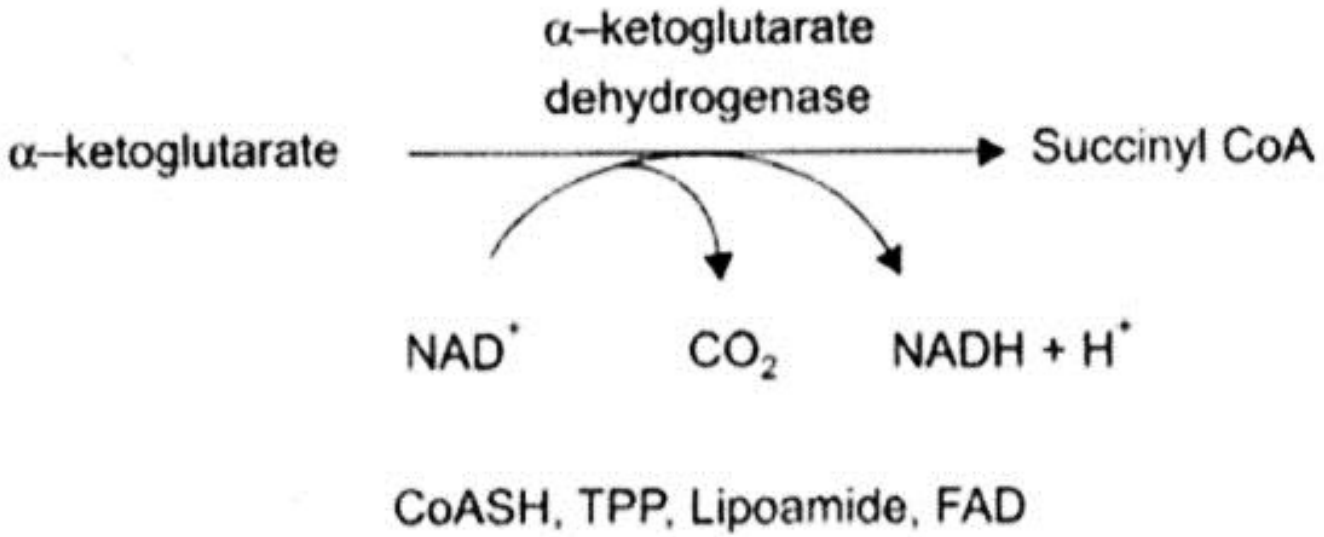


FAD-dependent enzymes

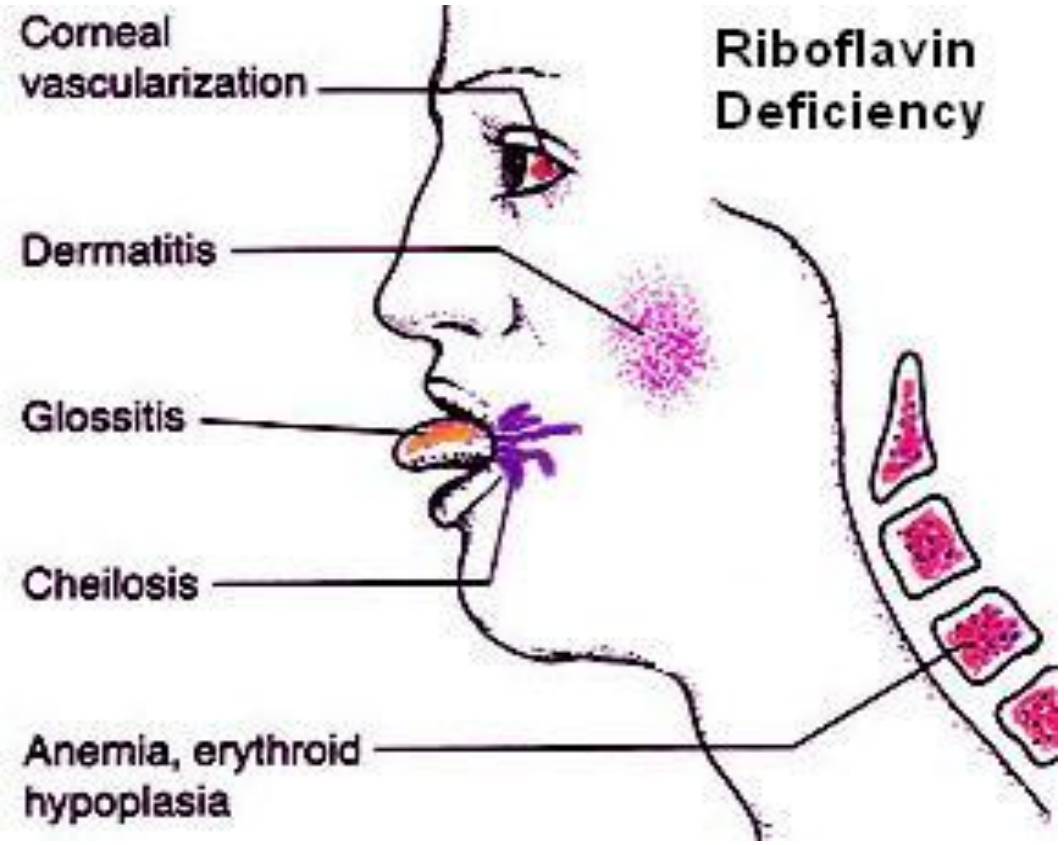
- Pyruvate dehydrogenase (Pyruvate to acetyl CoA)



α-Ketoglutarate dehydrogenase (Alpha ketoglutarate to succinyl) CoA by alpha in TCA cycle



Riboflavin deficiency:



Deficiency manifestations:

- Glossitis - inflammation of tongue

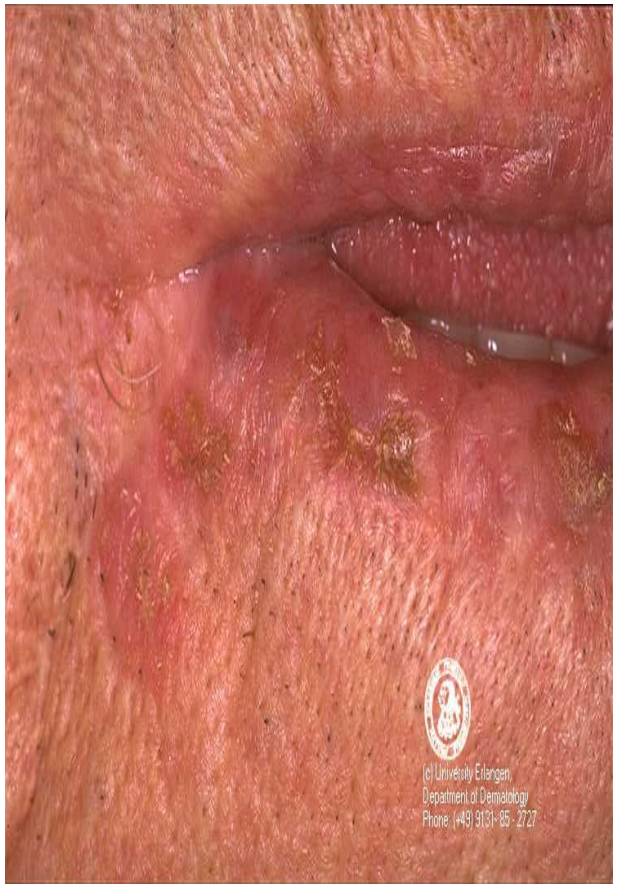
  Magenta red colour(glossitis), Fissures, Atrophy of lingual papillae

- Cheilosis: fissures in lips

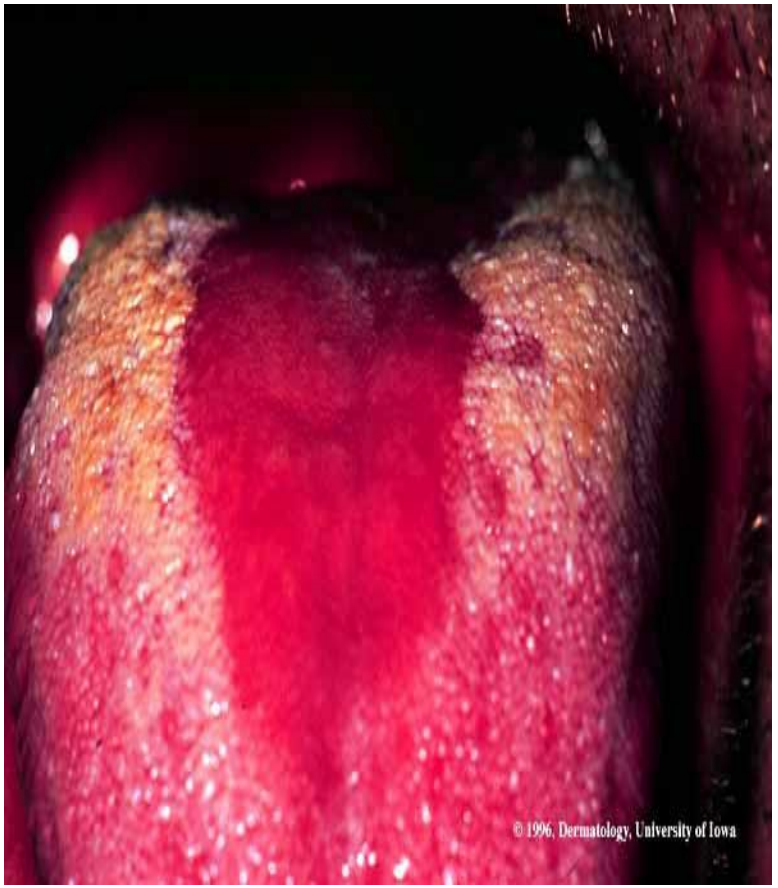
- Angular stomatits: inflammation at corners of mouth

- Conjunctivitis

Riboflavin Deficiency



Riboflavin Deficiency (Cheilosis)



Riboflavin Deficiency (Glossitis

B3

Niacin

Niacin

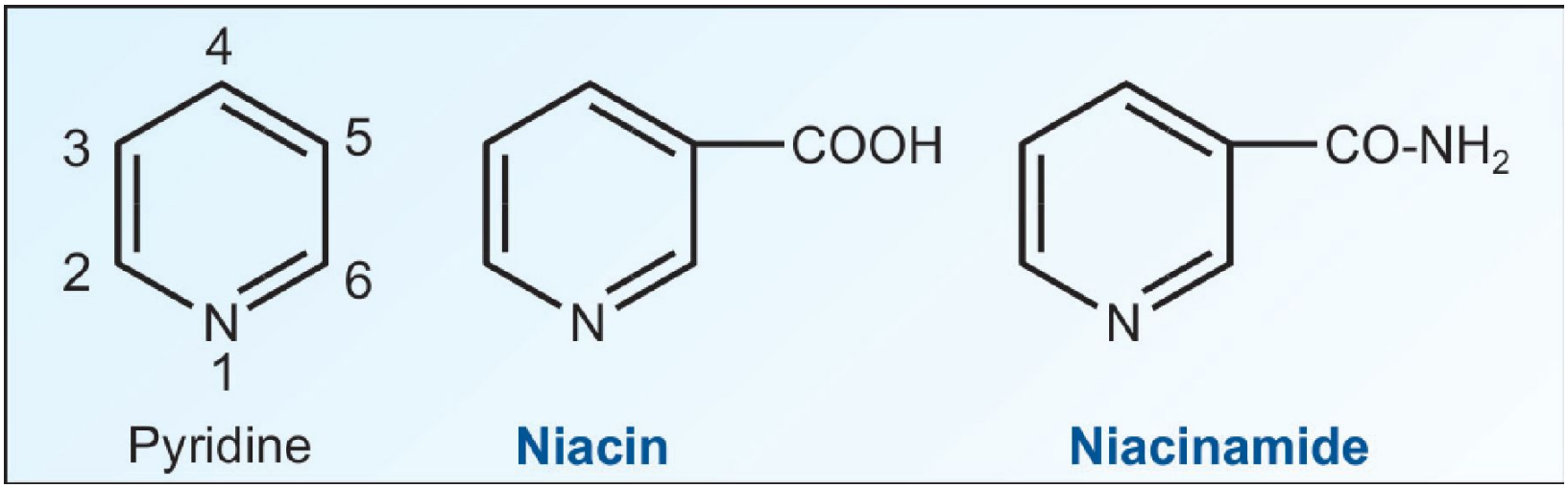
- Niacin is found in unrefined and enriched grains and cereal; milk; and lean meats, especially liver.
- Corn is low in both niacin and tryptophan.

  Corn-based diets can cause pellagra.

Niacin: B3

- Exists in two forms
  - Nicotinic acid (Niacin)
  - Nicotinamide (Niacinamide)

- Two coenzyme forms of niacin
  - NAD+
  - NADP+



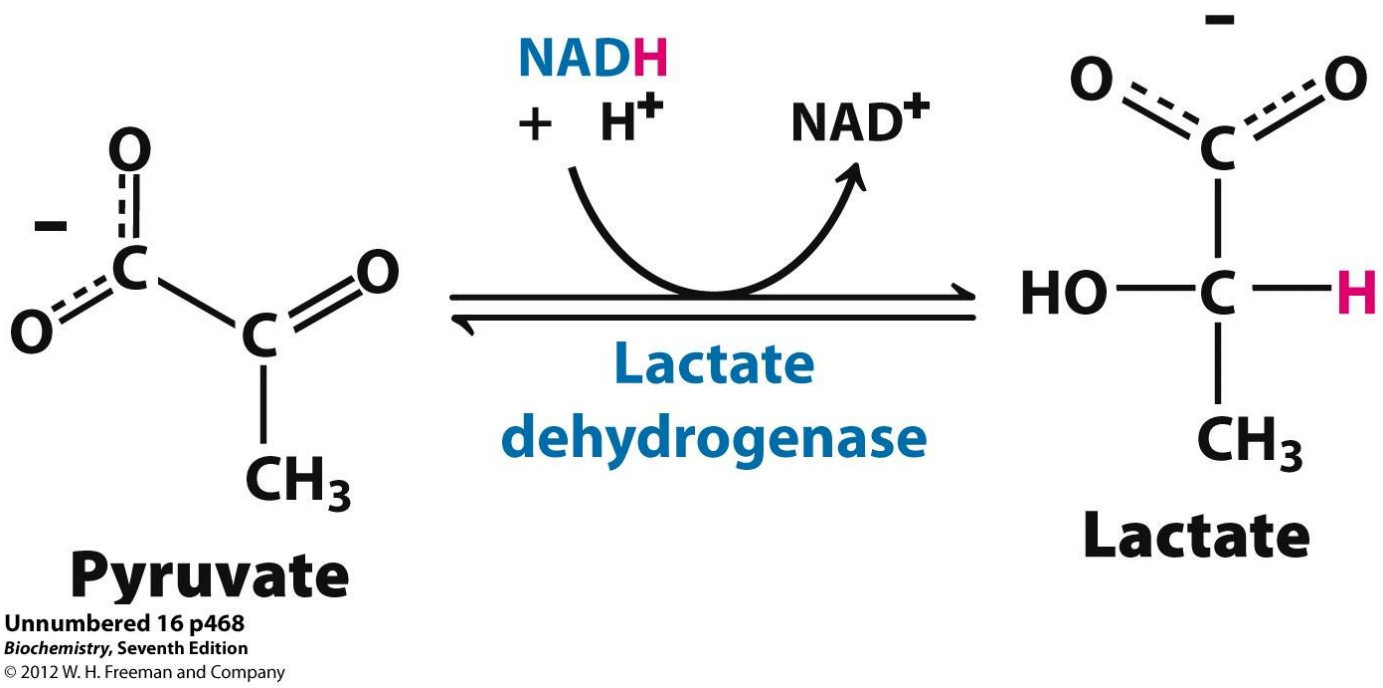
Function:

- Coenzymes are active participants in oxidation-reduction reactions – Dehydrogenases

- Function in at least 200 reaction in cellular metabolic pathways
- NAD+
  - Participates in catabolic reactions
  - Electron and hydrogen ion acceptor
- NADP+
  - Anabolic reactions
  - Important in biochemical pathway for fatty-acid synthesis, steroid and bile acid synthesis.

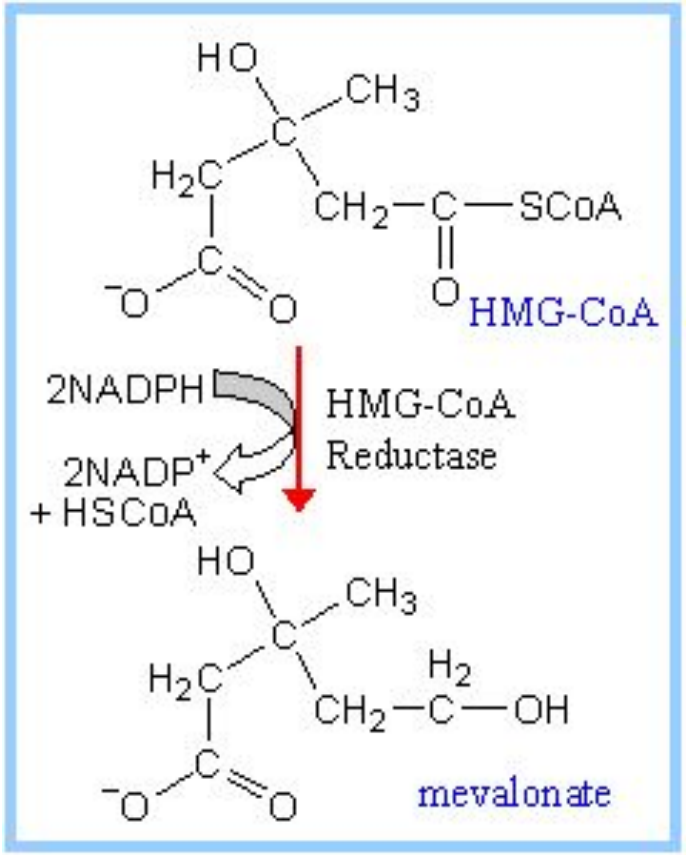
NAD+ dependent enzymes

- Lactate dehydrogenase (lactate → pyruvate)

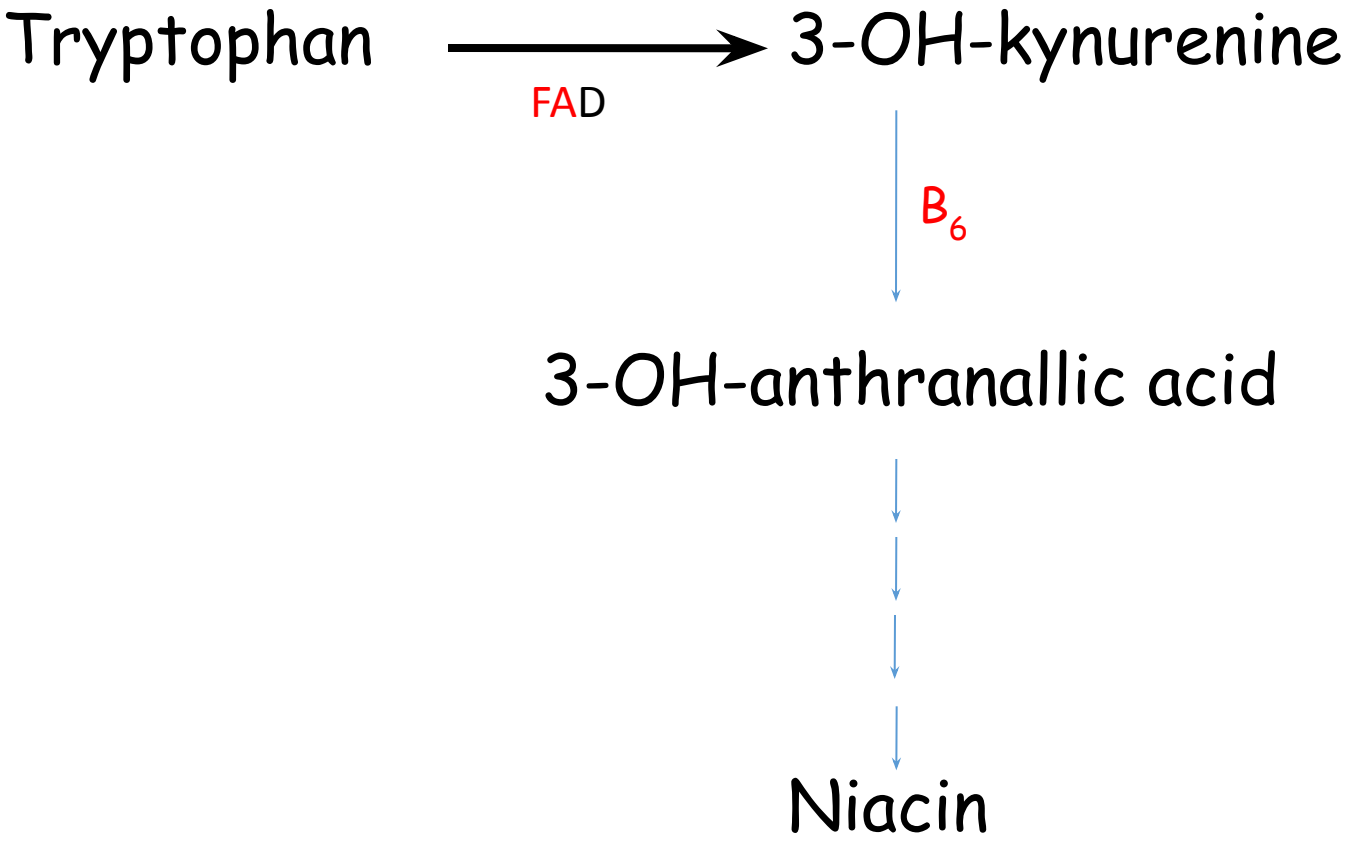


NADPH utilizing reactions

- 3. HMG CoA reductase (HMG CoA → mevalonate) in Fatty acid metabolism



Tryptophan can be converted to Niacin:



Deficiency manifestation:

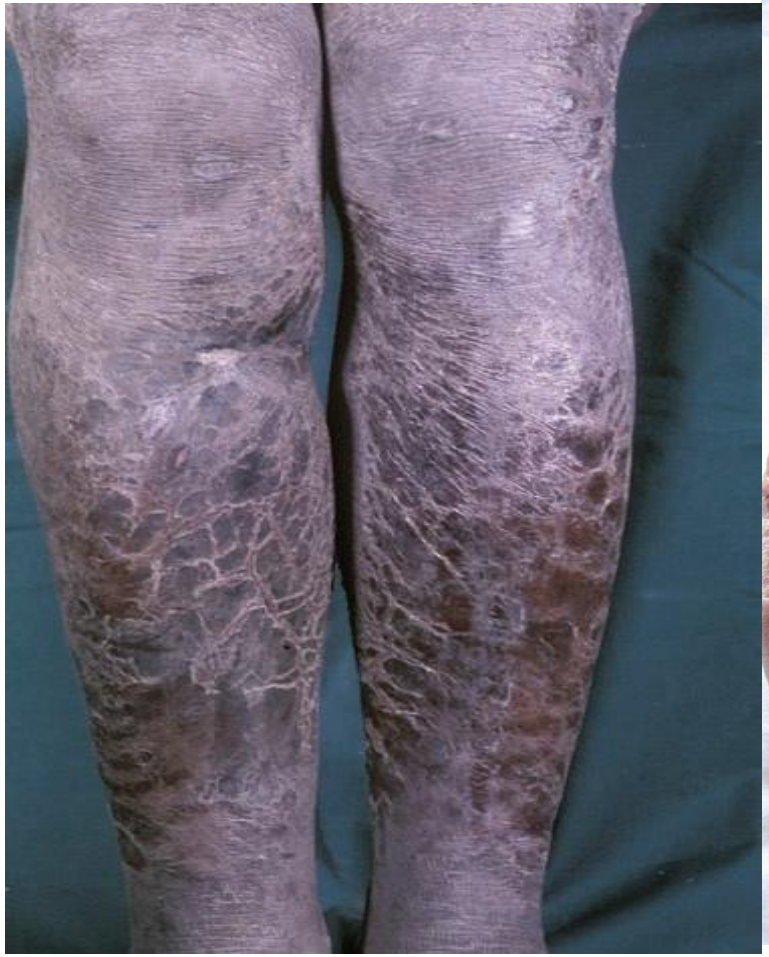
- Pellagra , a disease involving the skin, gastrointestinal tract, and CNS:
  - Dementia, Diarrhea, Dermatitis
  - If not treated can cause death
  - Develops about 50 to 60 days after a niacin deficient diet

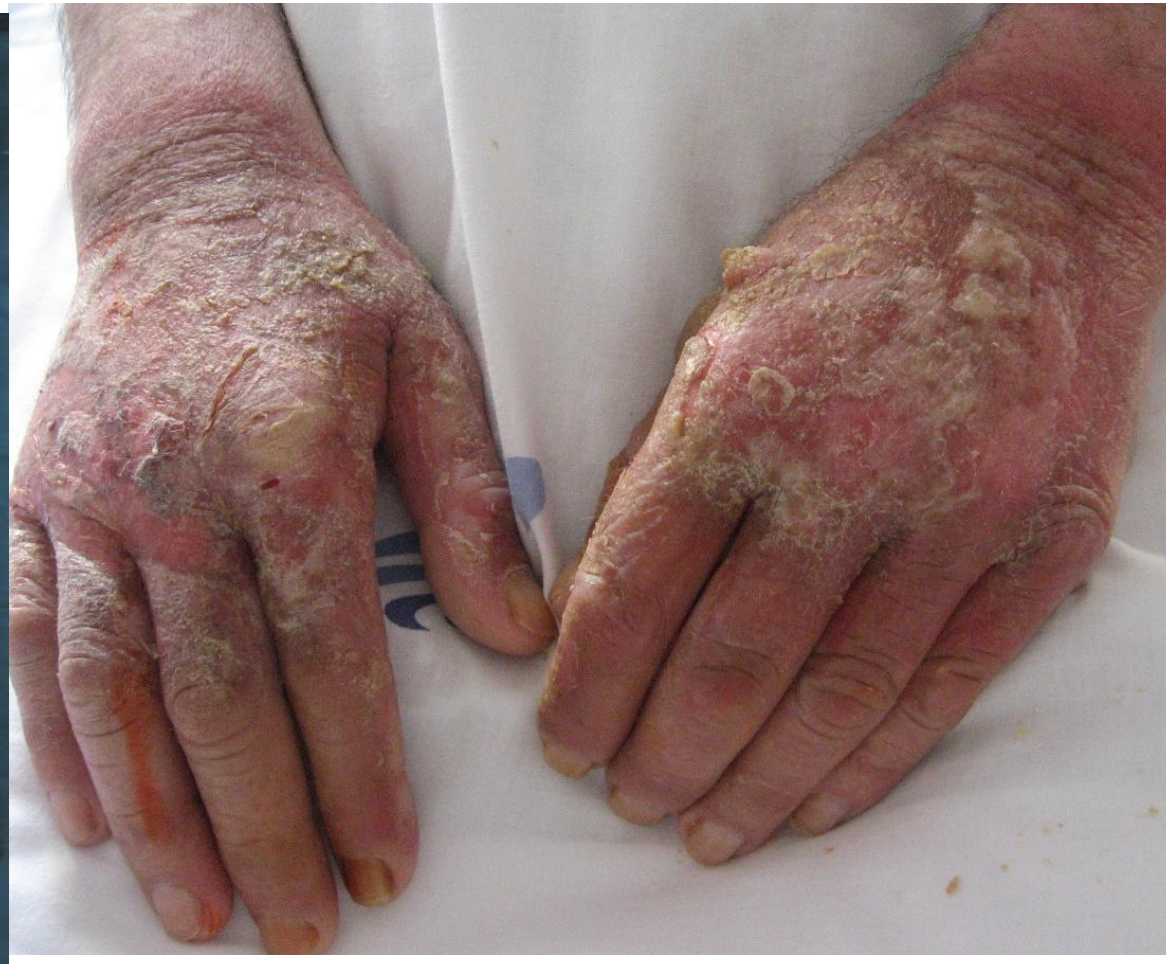
- Early symptoms
  - Loss of appetite, weight loss, and weakness

- Mild symptoms
  - Indigestion, canker sores, vomiting, depression and fatigue

Pellagra
niacin deficiency

Pellagra
Niacin deficiency





Pellagra like symptoms can be seen with:

- Niacin deficiency
- Hartnup disease Less absorption of Trp
- Carcinoid syndrome excess Trptophan going for Serotonin synthesis and less for Niacin synthesis
- Pyridoxine deficiency Kynureninase is not working
- Isoniazid administration ANTI-TUBERCULOUS DRUG damages liver and increased AST/ALT activity + directly inhibits PLP formation

Niacin

Treatment of hyperlipidemia: Niacin at doses of 1.5 g/day, strongly inhibits lipolysis in adipose tissue, the primary producer of circulating free fatty acids (FFAs). The liver normally uses these circulating FFAs as a major precursor for triacylglycerol (TAG) synthesis. Thus, niacin causes a decrease in liver TAG synthesis, which is required for very-low-density lipoprotein [VLDL] production. Low-density lipoprotein (LDL, the cholesterol-rich lipoprotein) is derived from VLDL in the plasma.

Thus, both plasma TAG (in VLDL) and cholesterol (in LDL) are lowered.

Niacin

Therefore, niacin is particularly useful in the treatment of type llb hyperlipoproteinemia, in which both VLDL and LDL are elevated. The high doses of niacin required can cause acute, prostaglandin- mediated flushing. Aspirin can reduce this side effect by inhibiting prostaglandin synthesis. [Note: Niacin raises high-density lipoprotein levels.]

B5

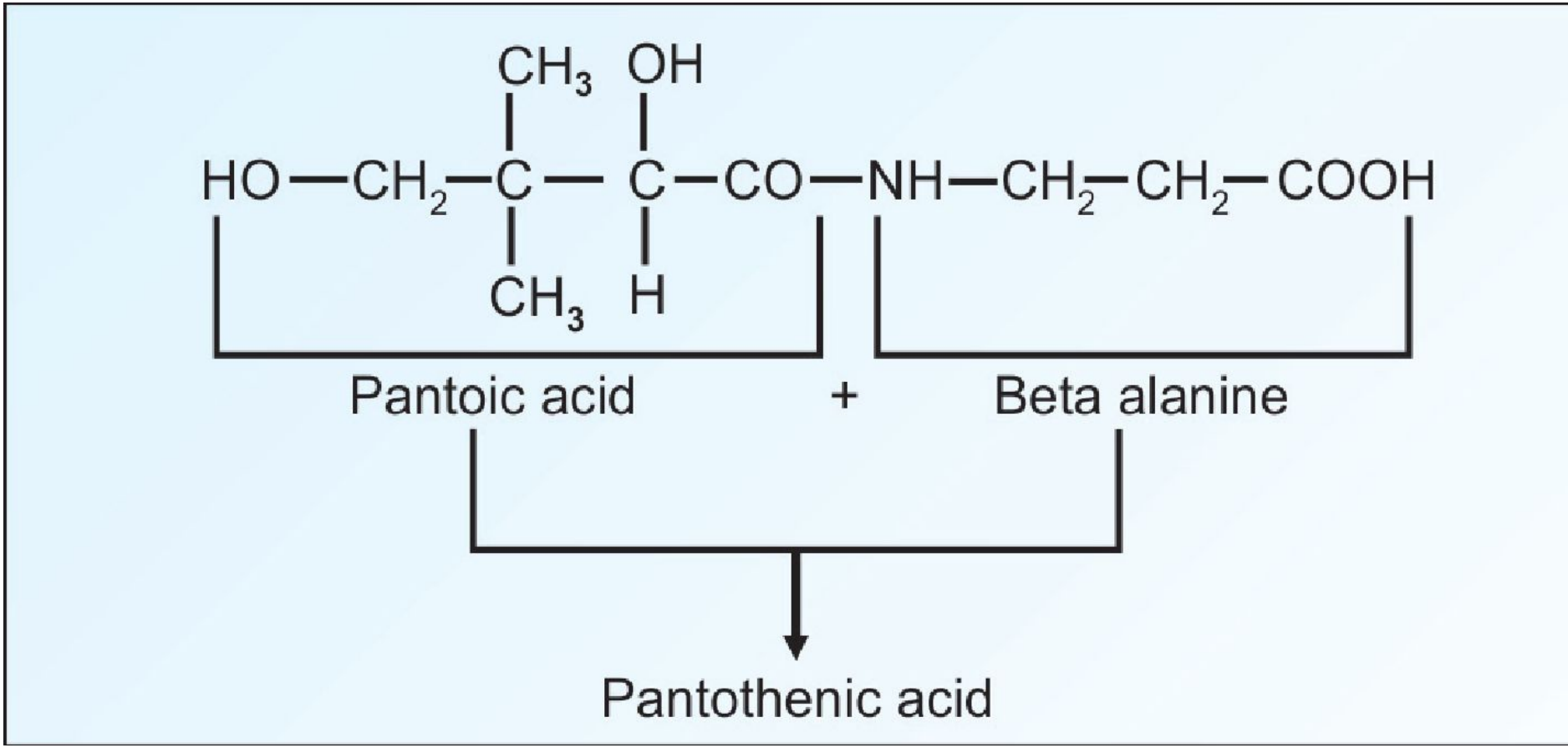
Panothenic Acid

Pantothenic acid: B5

- Contains Pantoic acid (derived from valine) and β-alanine (derived from aspartate)
- Carrier of acyl groups
- Involved in the metabolism of fat, proteins and carbohydrates
- **Active form – Coenzyme A (Co-A)**

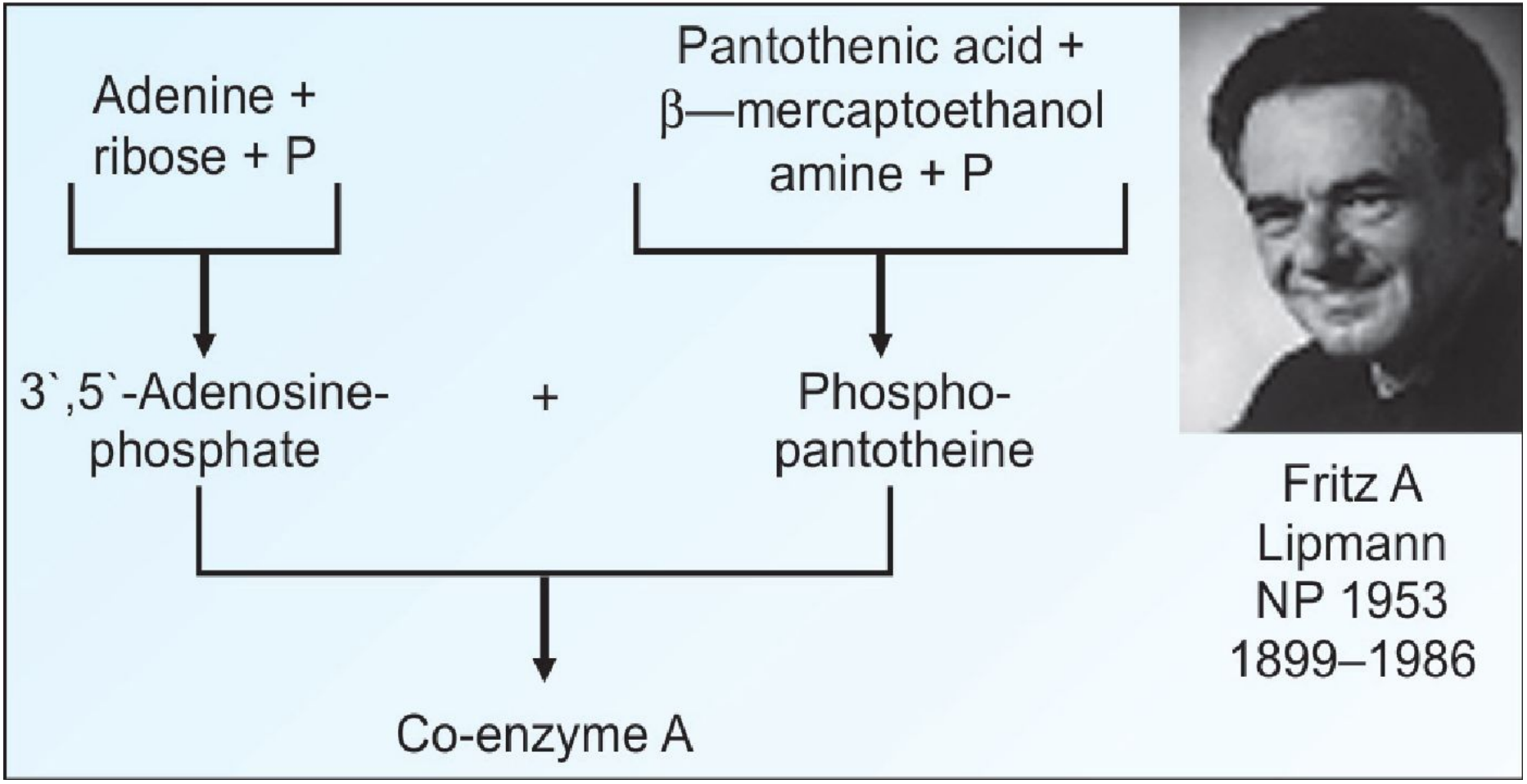
  Acyl carrier protein.

Pantothenic acid: B5



- **Sources of Pantothenic Acid**
- It is widely distributed in plants and animals. Moreover, it is synthesized by the normal bacterial flora in intestines. Therefore, deficiency is very rare. Yeast, liver and eggs are good sources.

Pantothenic acid: B5 and Co-enzyme A



Functions of Co-A:

1. Cellular metabolism – Co-A derivatives

ii. The thio ester bond in acyl-CoA is a high energy bond.
These acyl groups are transferred to other acceptors,

- Acetyl CoA + Choline ⟶ Acetylcholine + CoA

- iii. Acyl groups are also accepted by CoA molecule during the metabolism of other substrates, for example:'

- Pyruvate+CoA+NAD+ ⟶ AcetylCoA+CO_2+NADH

Functions of Co-A:

1. Cellular metabolism – Co-A derivatives

iv. The important CoA derivatives are:

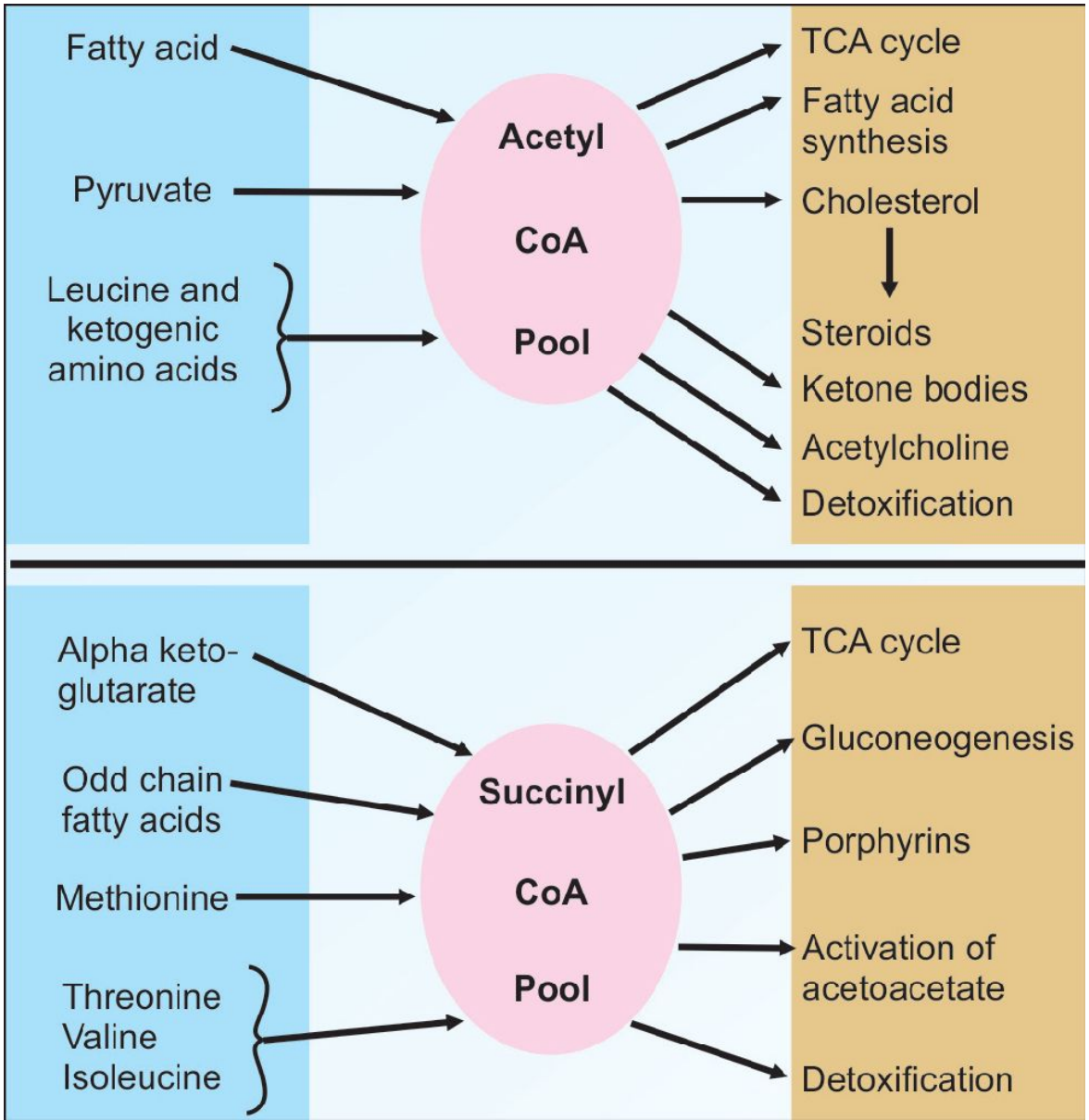
a. Acetyl CoA

b. Succinyl CoA

c. Hydroxyl beta methyl glutaryl CoA (HMG CoA)

d. Acyl CoA.

Sources and Uses of Co-A in Cellular metabolism



Deficiency manifestations;

- Fatigue, irritability

  low CoA levels ⟶ energy production ↓

- Neurological symptoms

  Numbness, muscle cramps

  ↓ acetyl choline formation

- Burning foot syndrome :paresthesia (burning, lightning pain) in lower extremities, staggering gait due to impaired coordination and sleep disturbances.

- Hypoglycemia : decreased acylation of receptors – increased binding of insulin.

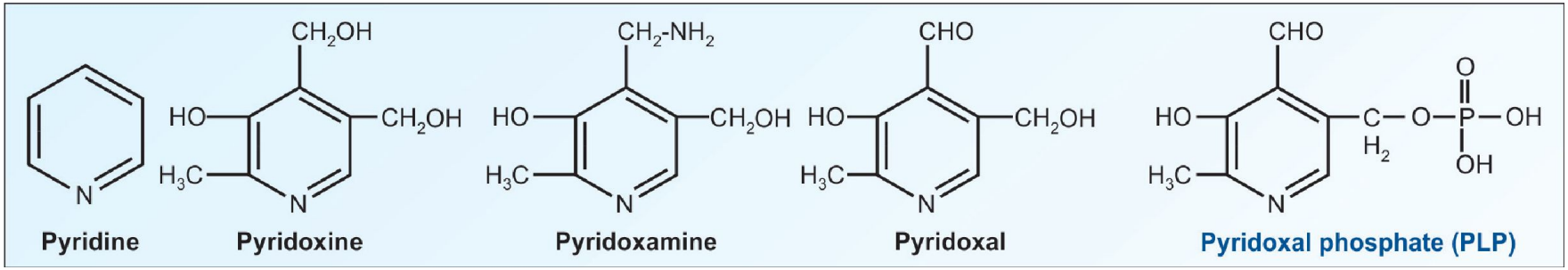

B
6

Pyridoxine: B6

- Three forms :

1. Pyridoxine
2. Pyridoxal
3. Pyridoxamine – antioxidant

Active form of B6 – Pyridoxal phosphate (PLP)



Functions of B6: central role in metabolism

- **Aminoacid metabolism:**

1. Transamination
2. Deamination
3. Decarboxylation
4. Transulfuration

- **Lipid metabolism** :

1. Sphingomyelin synthesis
2. Carnitine synthesis

- **Carbohydrate metabolism** :

1. Glycogenolysis – glycogen phosphorylase
2. Gluconeogenesis –formation of alpha keto acids

Other minor functions of B6

- Heme synthesis
- Catecholamine synthesis
- Niacin synthesis
- Modulation of hormone action – mainly steroids

Transamination reactions : PLP prosthethic group of animo transferases

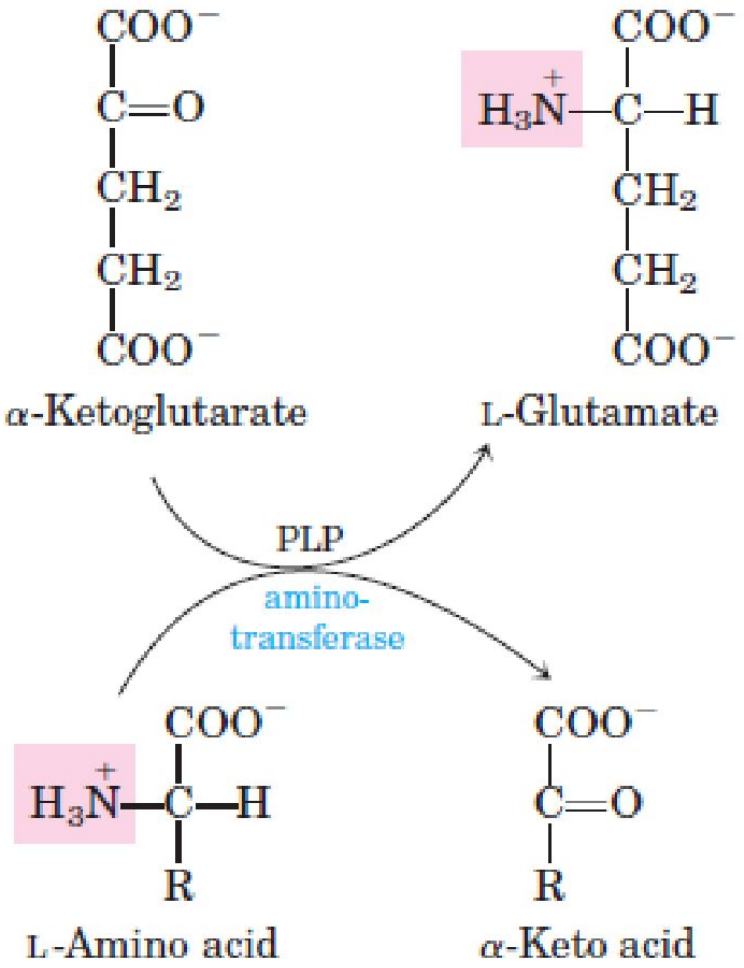
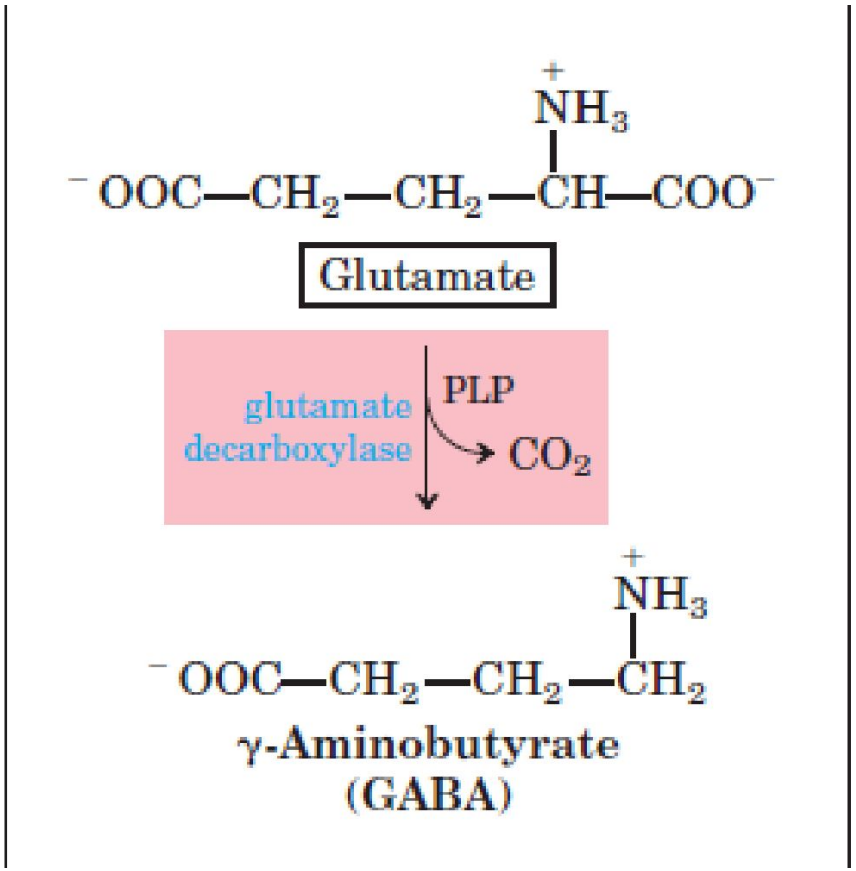


FIGURE 18–4 Enzyme-catalyzed transaminations. In α

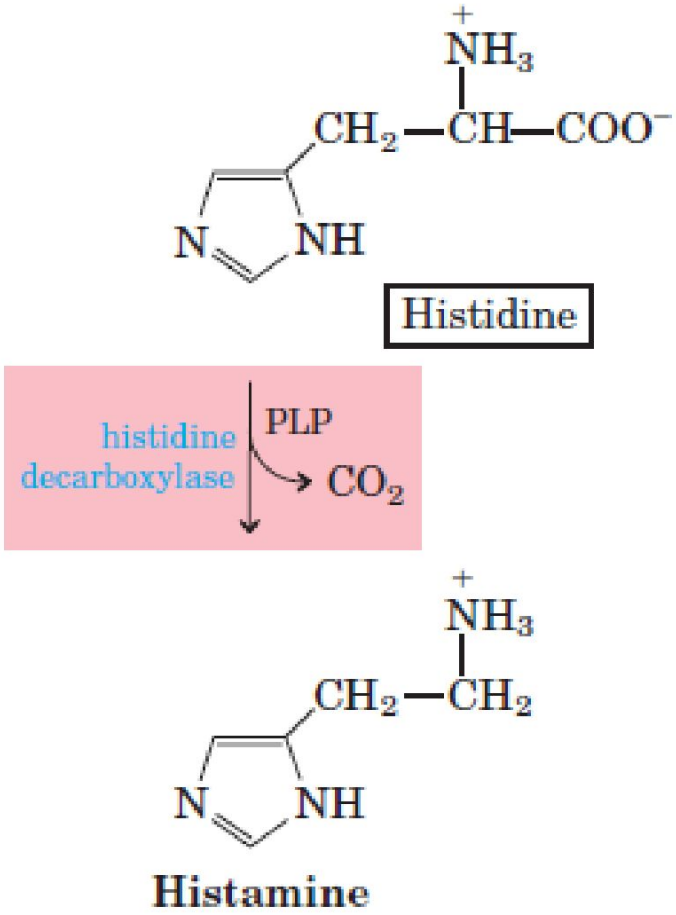
Decarboxylation reactions:

- Glutamate decarboxylase :

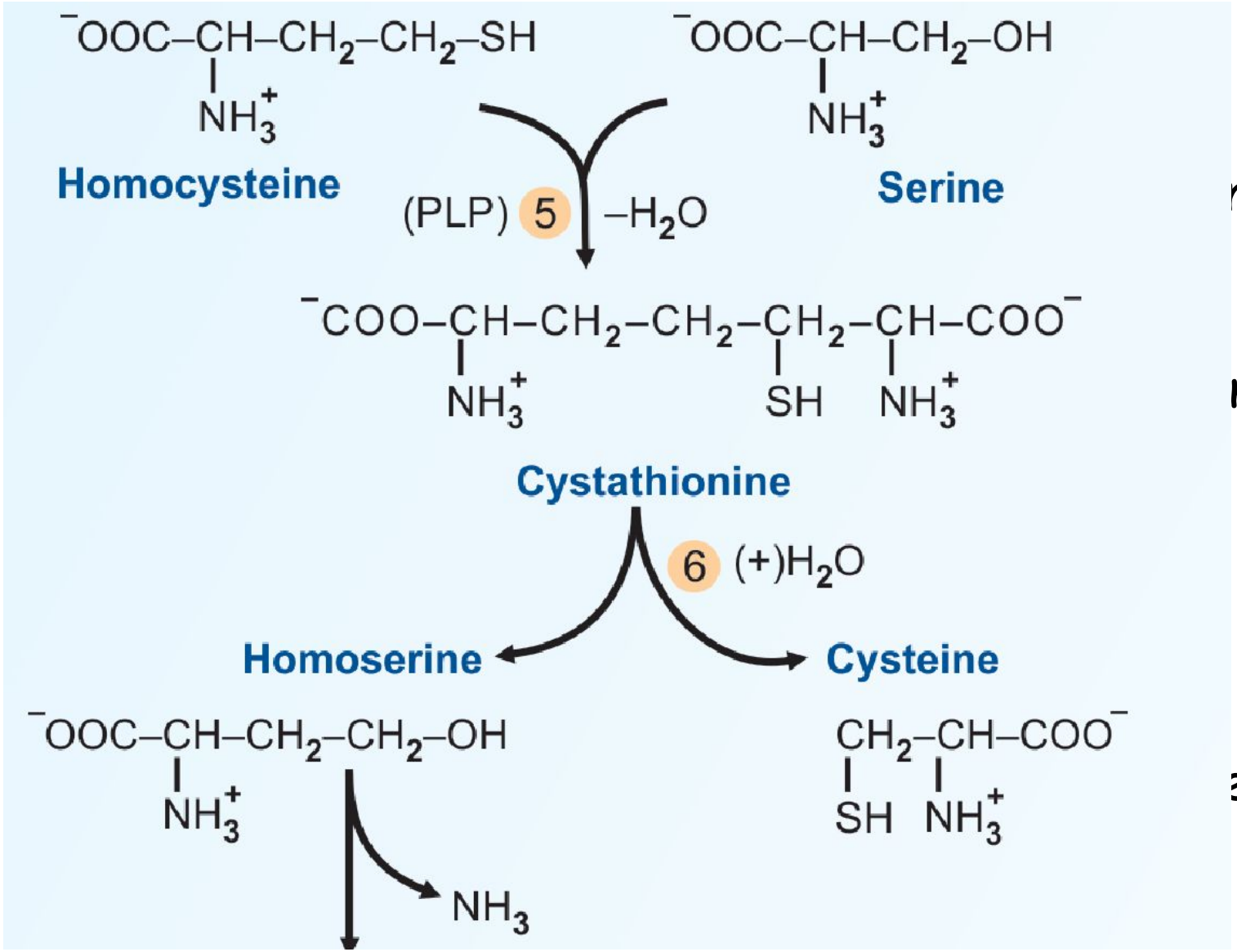
  Glutamate → GABA (inhibitory neurotransmittor)



Histidine decarboxylase :
Histidine → Histamine



Transsulfuration :



Modulation of hormone action

B6 - Remove hormone-receptor complex from DNA binding

Terminate the action of steroid hormone

B_6 deficiency:

- Enhances steroid hormone sensitivity
- Increases risk for hormone dependent cancers of breast and uterus

Drugs inactivating PLP:

- Alcohol
- Isoniazid - Anti tubercular
- Carbidopa – used with DOPA in parkinsonism
- Penicillamine – chelating agent
- Oral contraceptive pills

Clinical indications for pyridoxine

- Isoniazid, a drug commonly used to treat tuberculosis, can induce a vitamin B6 deficiency by forming an inactive derivative with PLP.
- Dietary supplementation with B6 is, thus, an adjunct to isoniazid treatment. Otherwise, dietary deficiencies in pyridoxine are rare but have been observed in newborn infants fed formulas low in B6, in women taking oral contraceptives, and in alcoholics.

Deficiency manifestation:

- Neurological manifestations:
  Peripheral neuritis
  convulsions

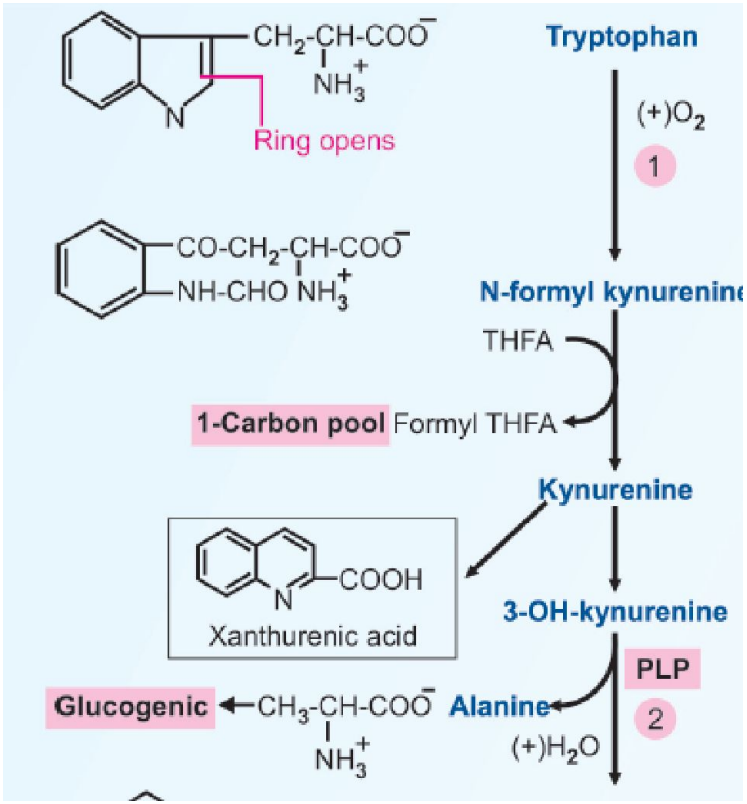
Basis: ↓ Formation of catecholamine
↓ GABA levels
↓ Sphingolipid synthesis → Demyelination

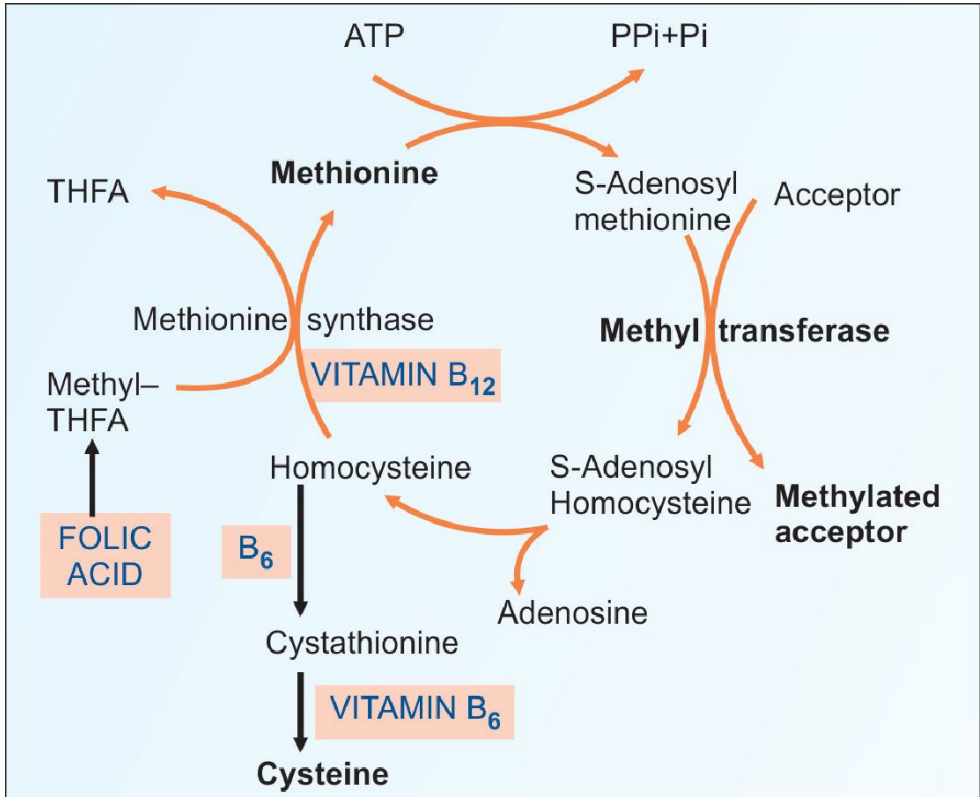
- Dermatitis - (pellagra like symptoms)

- Microcytic hypochromic Anemia – decreased formation of Heme

Diagnosis of B6 deficiency:

- Decreased AST and ALT activity
- Methionine load test – Homocysteine and cystathionine in urine.
- Tryptophan load test – Xanthurenic acid





Toxicity of Vitamin B6

- **Toxicity of Vitamin B6.** Pyridoxine is the only water-soluble vitamin with significant toxicity.

  Doses over 100 mg may lead to **sensory neuropathy**.

  Further excess is manifested by imbalance, numbness,

  muscle weakness and nerve damage.

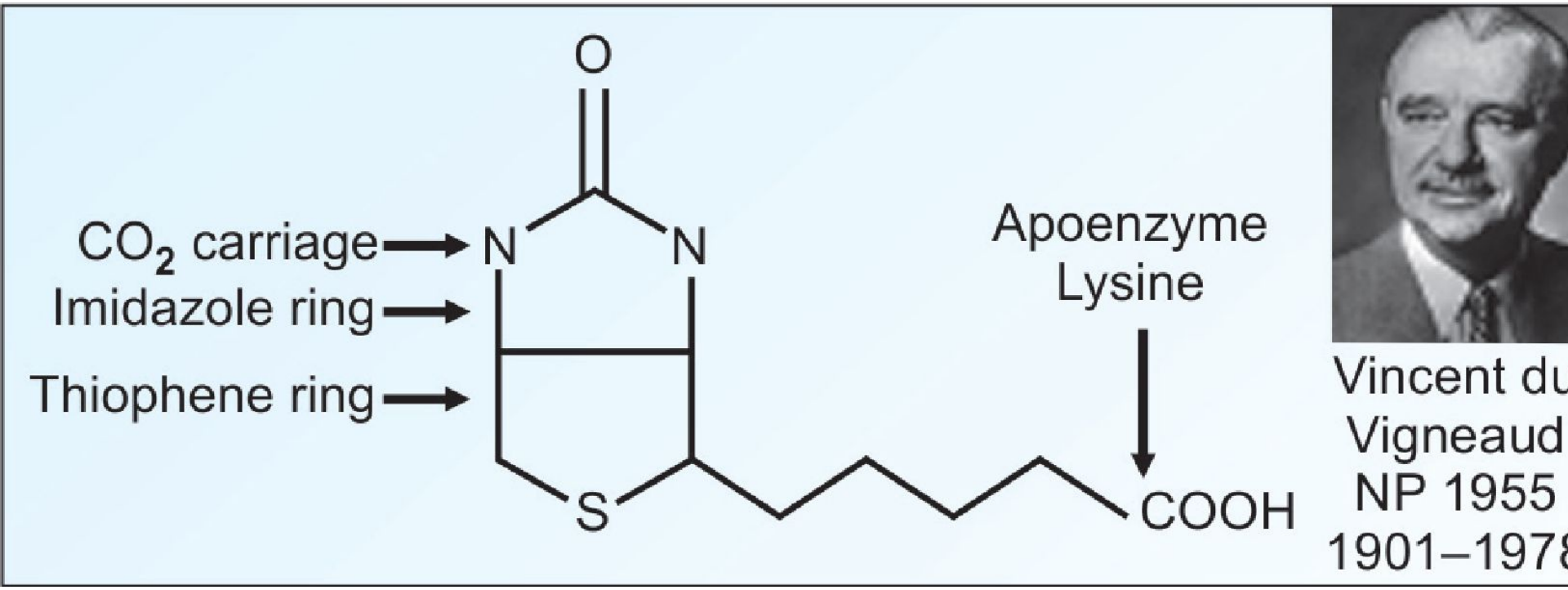
  Substantial improvement, but not complete recovery, occurs when the vitamin is discontinued.

biotin

The hair, skin, and nail vitamin.

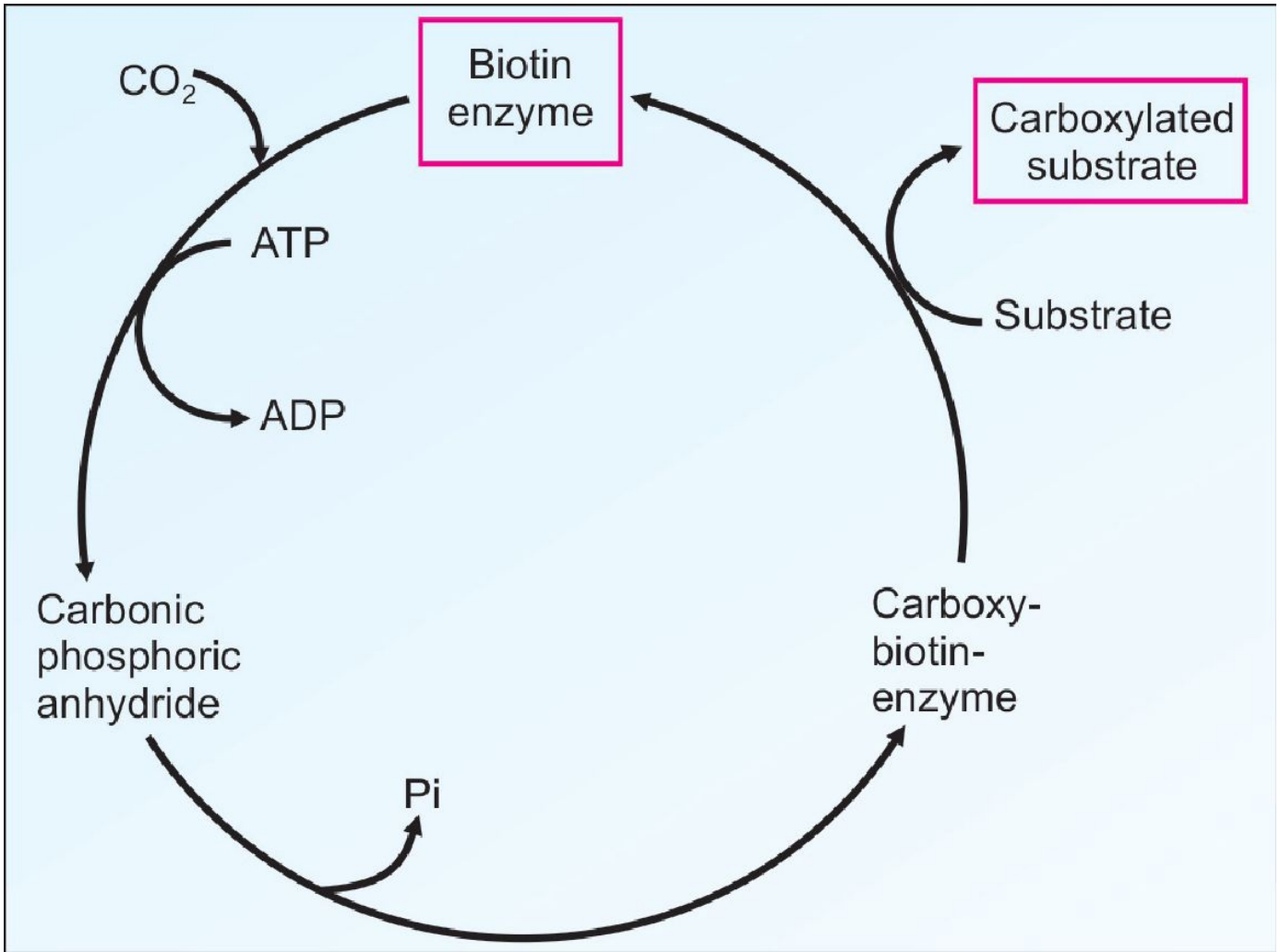
Biotin: B7

- Co-enzyme for carboxylation reaction:
- Carboxylation require Bicarbonate, ATP and Biotin.



Biotin acts as co-enzyme for **carboxylation reactions**.

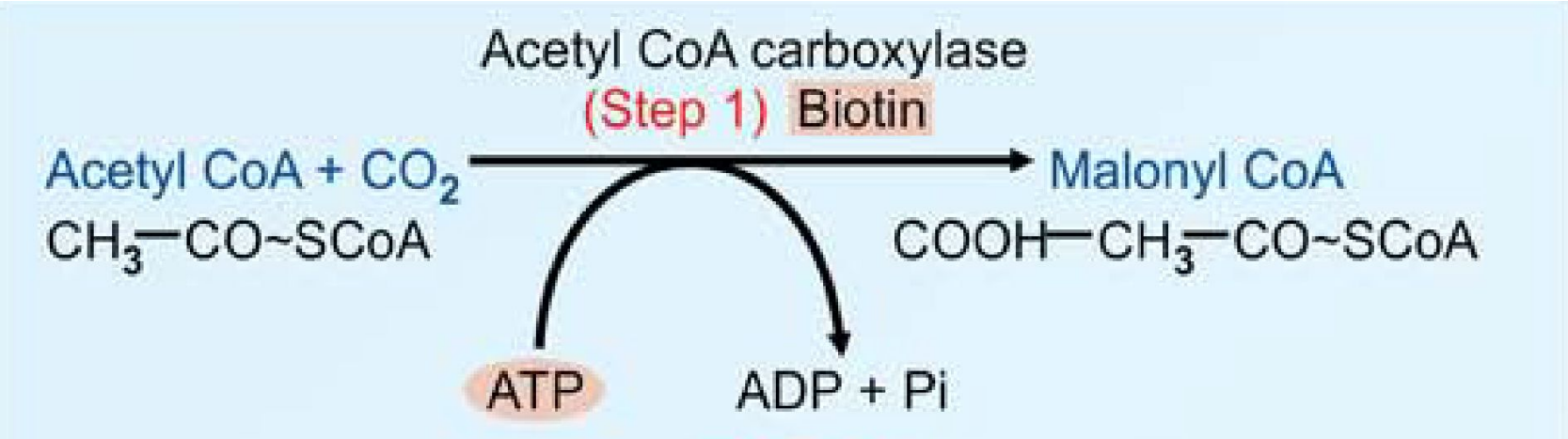
- Biotin captures a molecule of CO2 which is attached to nitrogen of the biotin molecule. The energy required for this reaction is provided by ATP.



Biotin Requiring CO_2 Fixation Reactions

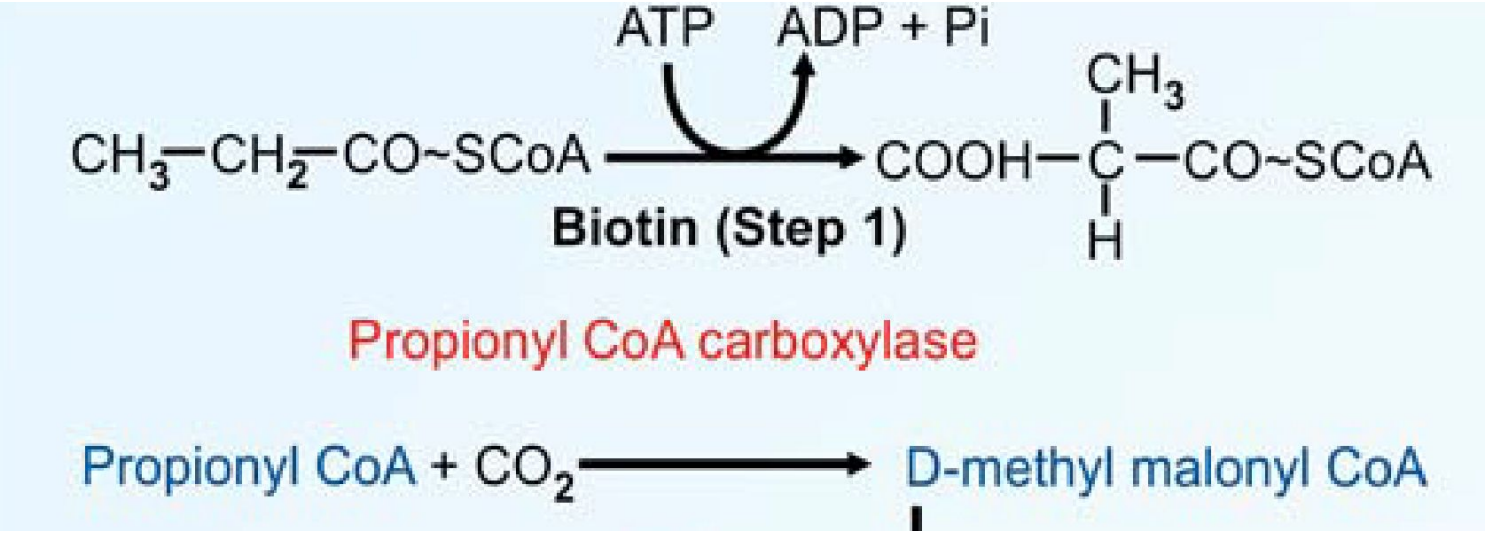
- *Acetyl CoA carboxylase*
- This enzyme adds CO_2 to acetyl CoA to form malonyl CoA. This is the rate limiting reaction in biosynthesis of fatty acids

- Acetyl CoA +CO2+ATP→ Malonyl CoA + ADP+Pi



Biotin Requiring CO_2 Fixation Reactions

- *Propionyl CoA Carboxylase*
- Propionyl *CoA* +*CO2*+*ATP*→ Methyl malonyl *CoA* +*ADP*+Pi

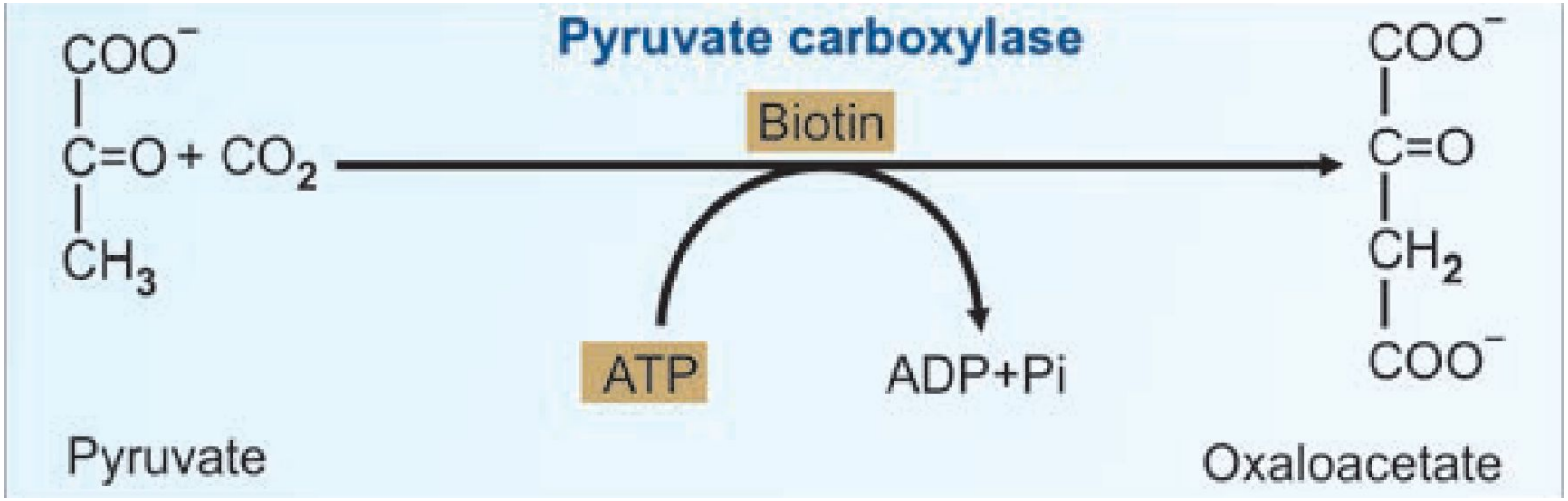


Biotin Requiring CO_2 Fixation Reactions

Pyruvate Carboxylase

- Pyruvate + CO2 +ATP→ Oxaloacetate +ADP +Pi This is important in two aspects.

- One, it provides the oxaloacetate, which is the catalyst for TCA cycle.
- Second, it is an important enzyme in the gluconeogenic pathway



Biotin deficiency: causes

- Consumption of raw egg – Avidin (binds biotin)

- Dialysis

- **Requirement of Biotin**
- About 200–300 mg will meet the daily requirements

Features of biotin deficiency

- Vitamin H – (Haar and Haut) Hair and skin in German
- Biotin deficient faces – unusual fat distribution with a characteristic rash.

Symptoms :

1. Periorificial dermatitis
2. Conjunctivitis
3. Alopecial (loss of hair (especially on the head)
4. Neurological – Tingling and numbness , depression , lethargy.

Biochemical basis:

- CNS features : Defect in Pyruvate carboxylase lactic acidemia.

- Skin rash and hair loss – due to abnormal fatty acid metabolism mainly of omega -6 – fatty acids.

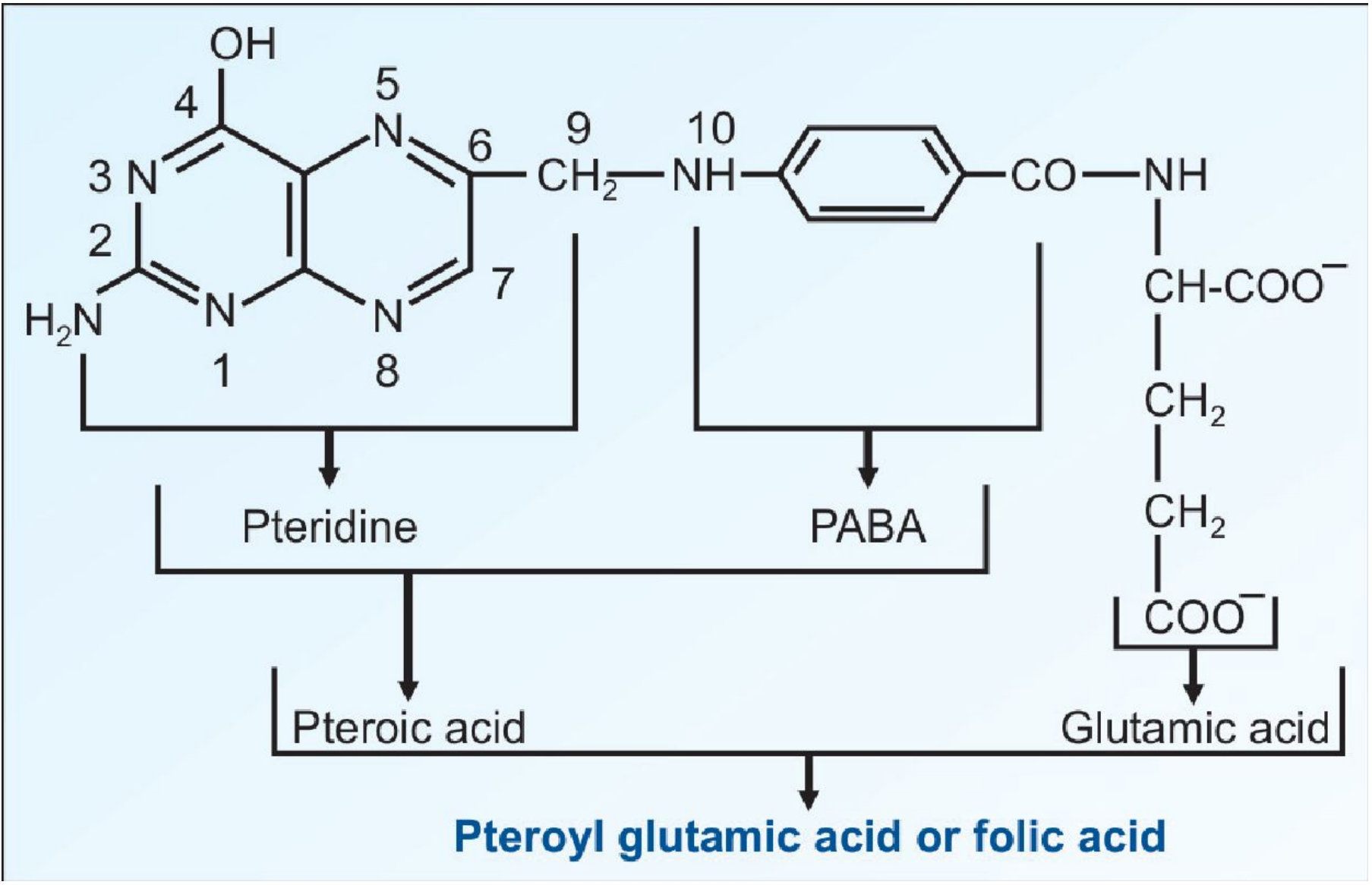
- Biotinylation of histones – regulation of transcription and cell proliferation – is affected.

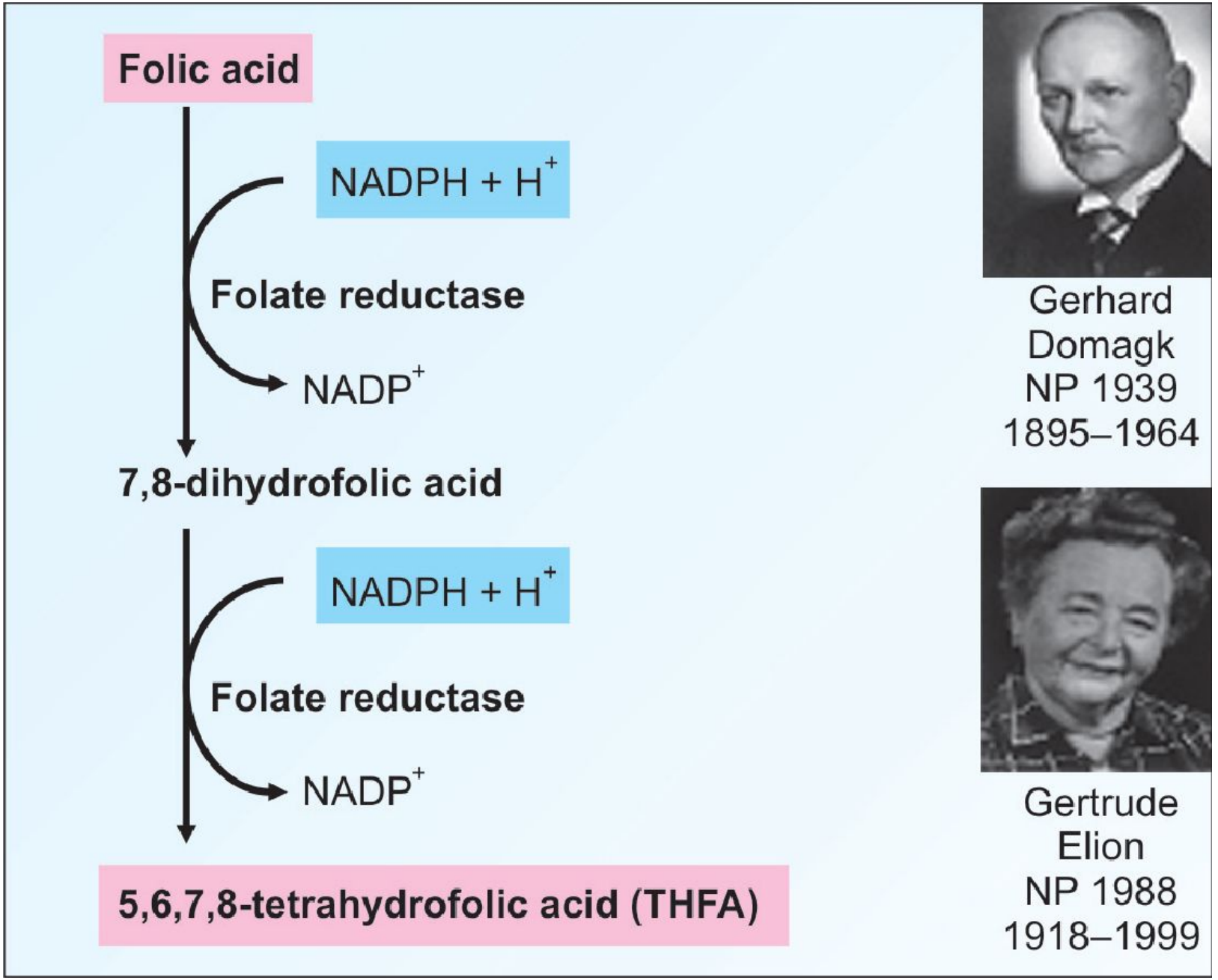
Biotin

- Biotin deficiency does not occur naturally because the vitamin is widely distributed in food. Also, a large percentage of the biotin requirement in humans is supplied by intestinal bacteria. However, the addition of raw egg white to the diet as a source of protein induces symptoms of biotin deficiency, namely, dermatitis, glossitis, loss of appetite, and nausea.
- Raw egg white contains a glycoprotein, avidin, which tightly binds biotin and prevents its absorption from the intestine.
- With a normal diet, however, it has been estimated that 20 eggs/day would be required to induce a deficiency syndrome. Thus, inclusion of an occasional raw egg in the diet does not lead to biotin deficiency, although eating raw eggs is generally not recommended due to the possibility of salmonella infection.


folic acid
FOLIC ACID
400mcg
B9

Folic Acid


OH
4
5
N
6
9
10
3 N
CH2
NH
CO
NH
2
7
H2N
N
N
CH-COO−
1
8
CH2
CH2
Pteridine
PABA
COO−
Pteroic acid
Glutamic acid
Pteroyl glutamic acid or folic acid



Gerhard
Domagk
NP 1939
1895–1964

Gertrude
Elion
NP 1988
1918–1999

Folate metabolism:

- Folic acid is present as various forms of Tetrahydrofolate :

- Acts as a co-enzyme by accepting, transfering, or modyfying one carbon units that are attached to N5 or N10 position of folate.

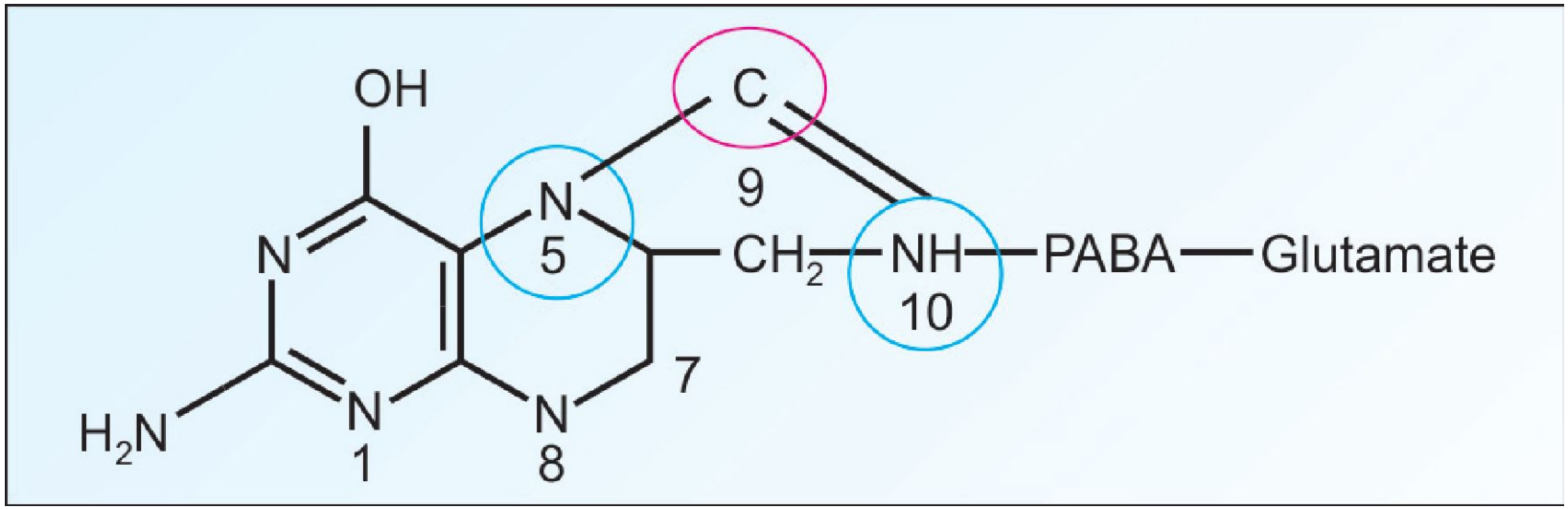


Fig. N_5, N_{10}-methenyl THFA. One carbon unit (red ring) is attached to N_5 and N_{10} groups (blue rings) of tetrahydrofolic acid

Active one carbon donors

- :

1. Formyl THF – purine synthesis
2. Methylene THF – pyrimidine synthesis
3. Methenyl THF
4. Formimino THF

Intermediates

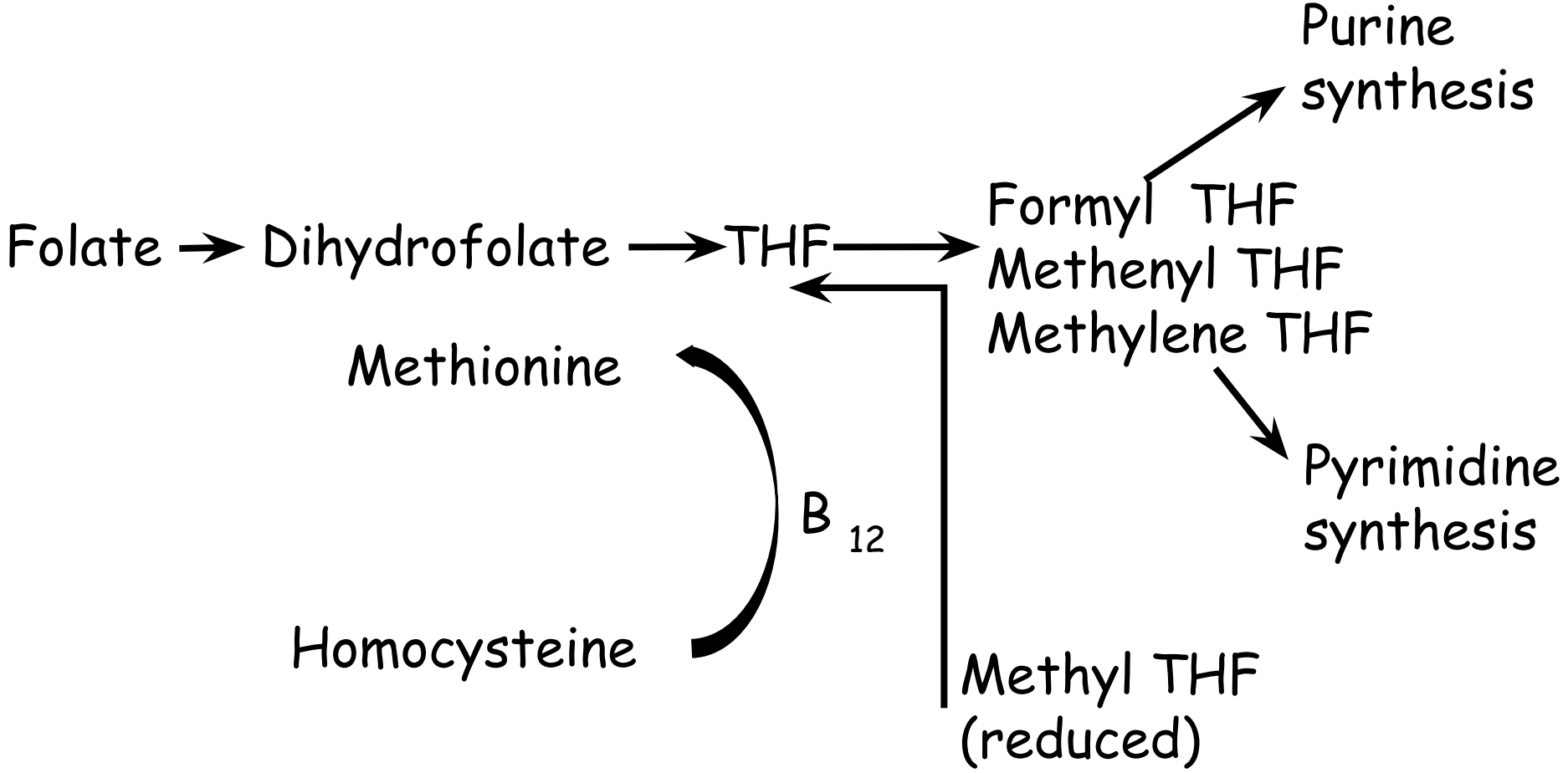
- Predominant form in plasma – methyl THF (reduced) and inactive.

Folic acid (B_c)

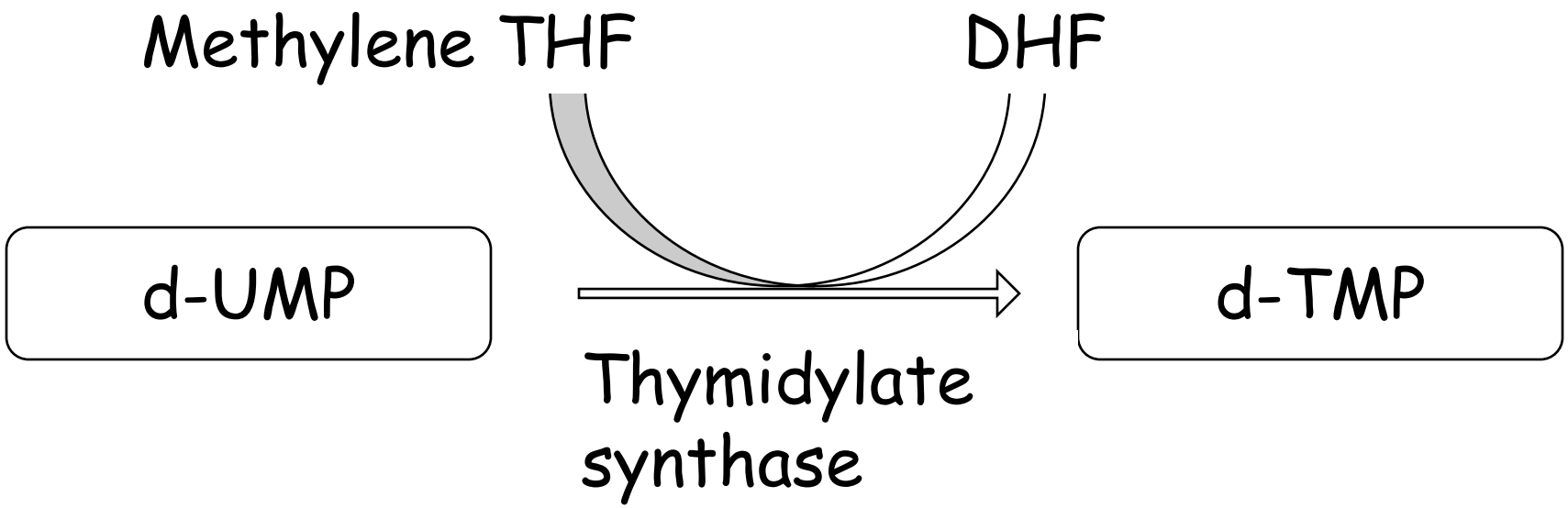
- Function of folic acid:

  Tetrahydrofolate (THF), the reduced, coenzyme form of folate, receives one-carbon fragments from donors such as serine, glycine, and histidine and transfers them to intermediates in the synthesis of amino acids, purines, and thymidine monophosphate (TMP), a pyrimidine nucleotide found in DNA.

Functions of Folate:
1. DNA synthesis
2. Conversion of Homocysteine to methionine



Pyrimidine synthesis:



Purine synthesis:

Carbon 2 and 8 of the purine ring is donated by formyl THF

Deficiency of Folate :

Causes :

- **Malabsorption syndromes**-poor absorption caused by pathology of the small intestine, alcoholism
- Drugs –

  Valproic acid – Neural tube defects

  Sulfasalazine

  Methotrexate – that are dihydrofolate reductase inhibitors.

- Increased demands – Pregnancy

  Lactation

Deficiency manifestation:

- *Reduced DNA synthesis*
- *Macrocytic Anemia* – results from a deficiency in folic acid, or vitamin B12. These macrocytic anemias are commonly called megaloblastic because a deficiency of either vitamin (or both) causes accumulation of large, immature RBC precursors, known as megaloblasts, in the bone marrow and the blood.
- Homocysteinuria
- Neural tube defects in fetus.

Deficiency manifestation

- A folate-free diet can cause a deficiency within a few weeks.
- *Reduced DNA synthesis*
- In folate deficiency, THFA is reduced and thymidylate synthase enzyme is inhibited.

- Hence dUMP is not converted to dTMP. So dTTP is not available for DNA synthesis.

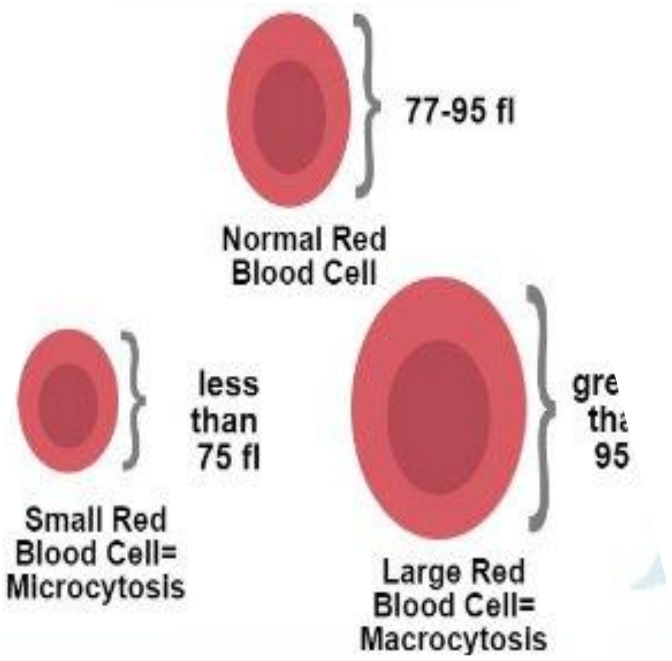
- Thus cell division is arrested. Very rapidly dividing cells in bone marrow and intestinal mucosa are therefore most seriously affected.

Deficiency manifestation

- *Macrocytic Anemia*
- It is when RBC's are larger than their normal volume.

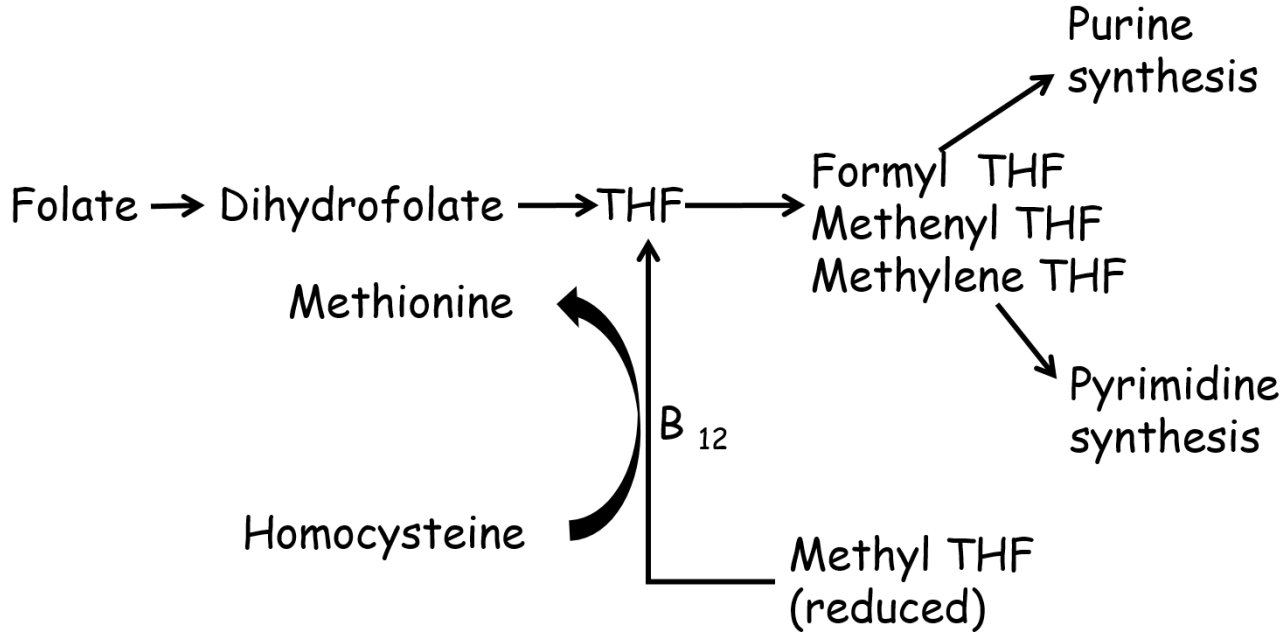
- Cells are larger because they cannot produce DNA quickly enough to divide at the right time as they grow, and thus grow too large before division

- there is insufficient *numbers* of cells and hemoglobin content per cell



Deficiency manifestation

- *Hyperhomocysteinemia*
- Folic acid deficiency may cause increased homocysteine levels in blood since remethylation of homocysteine Is affected.




eggs
meat
B12
oysters
poultry

Vitamin B_{12}

- Only animal source – vegetarians ??
- Only water soluble vitamin that can be stored up to some extent
- Contains cobalt.

- Synthetic preparation : injectables

1. Hydroxycobalamin
2. Cyanocobalamin – easily crystalized and extracted from bacteria.

Vitamin B_{12}

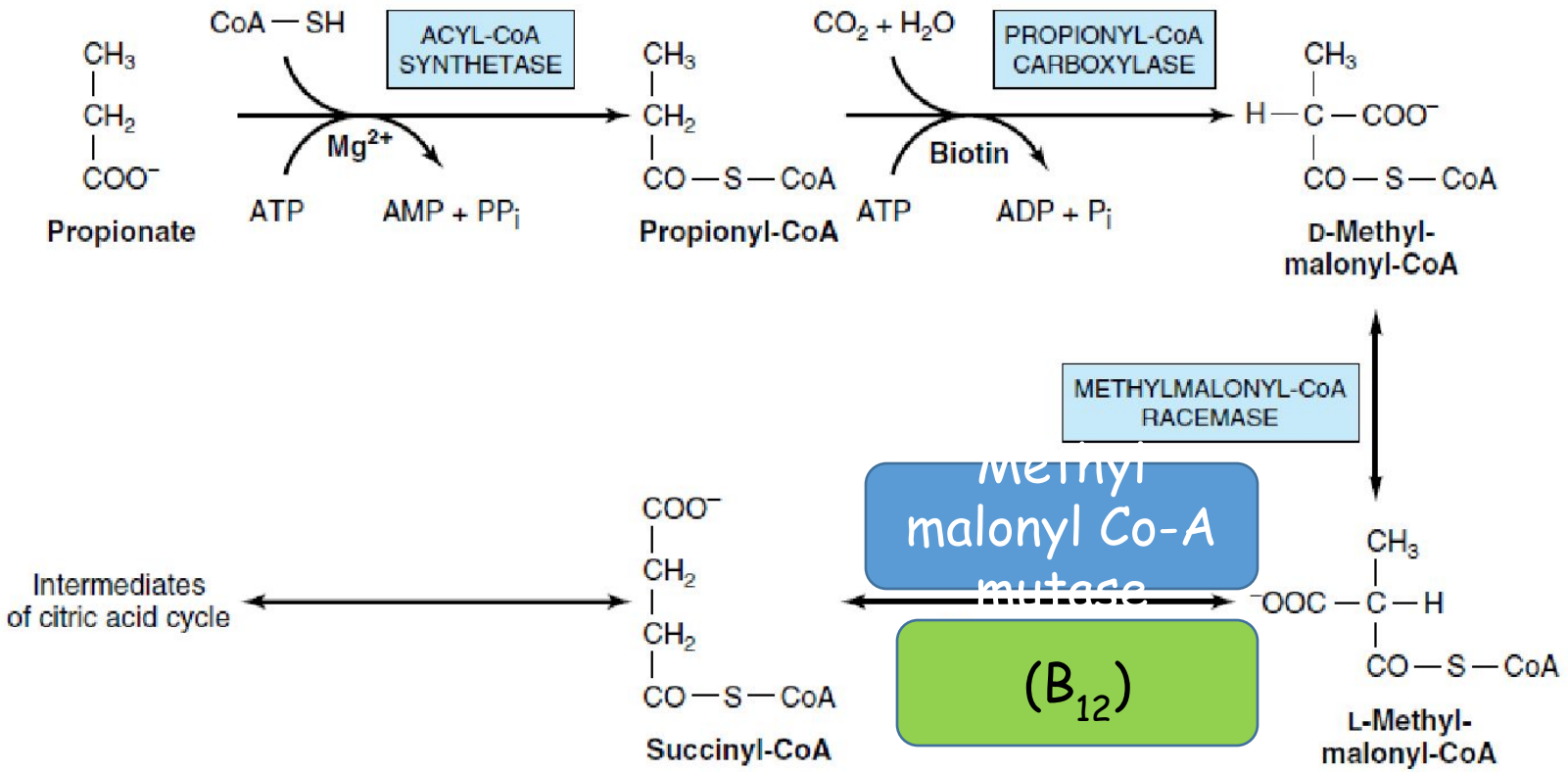
1. Methyl cobalamin – predominant function in plasma

- Converts homocysteine to methionine with transfer of methyl group from Methyl THF.
- Enzyme – homocysteine methyl transferase/methionine synthase

2. Deoxyadenosylcobalamin – mitochondrial

- Converts methylmalonyl Co-A to succinyl co-A
- Enzyme – methyl malonyl Co-A mutase

Conversion of methyl malonyl Co-A to succinyl Co-A



Deficiency manifestation:

- Megaloblastic anemia
- Methylmalonic aciduria
- Neurological manifestation:

a) Myelopathy – myelin loss, axonal degeneration and Gliosis
b) Larger fibres are affected – posterior and lateral columns – Subacute combined degeneration of spinal chord.
c) Loss of vibratory and position sense, ataxia. Intact motor fibres

Biochemical basis:

- Hematological - Folate trap – decreased methylation of DNA

- Neurological –

1. Abnormal propionate metabolism
2. Accumulation of methyl malonyl Co-A –toxin
3. Abnormal fatty acid synthesis and myelination

Megaloblastic anemia:

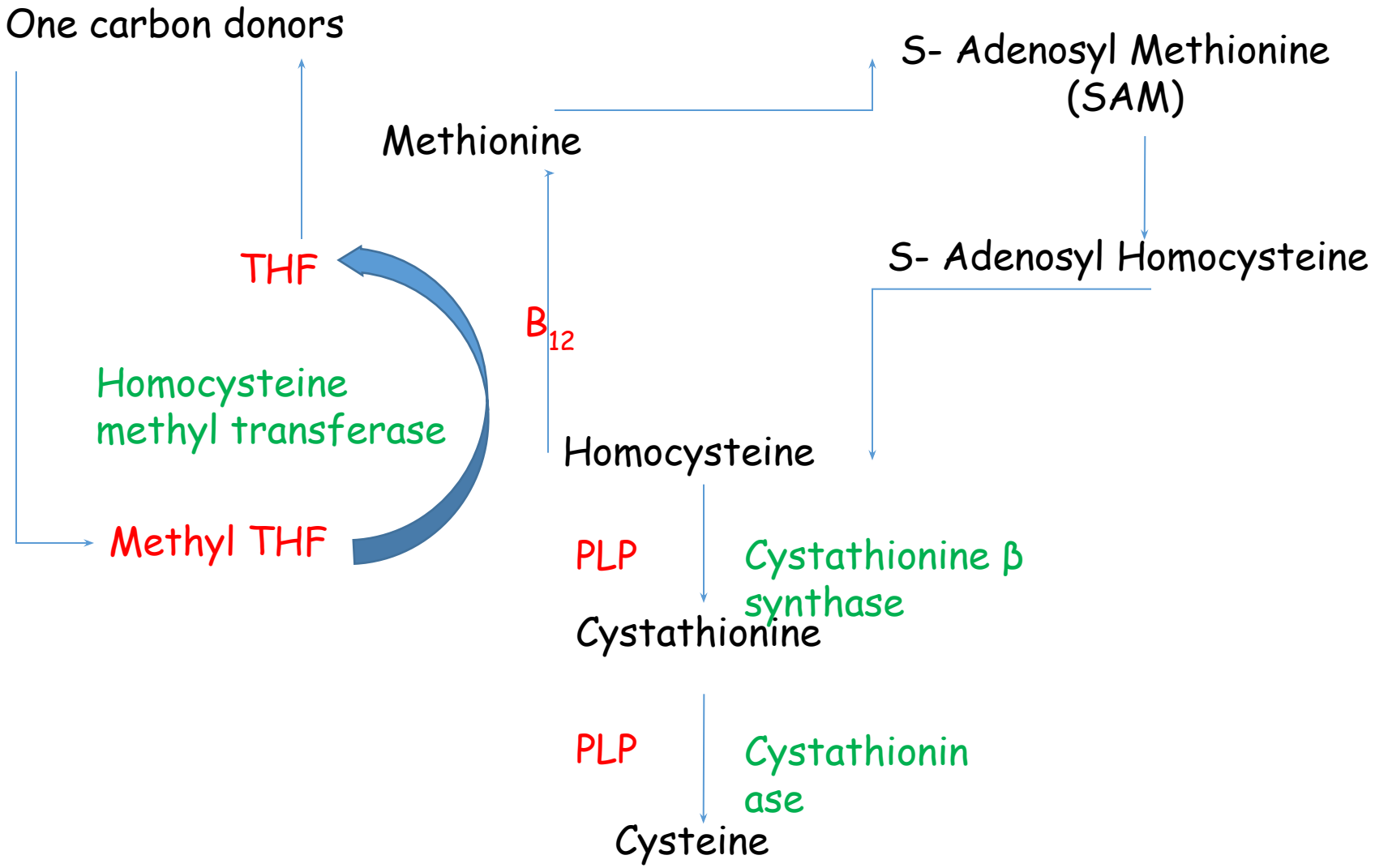
Vitamin B12 def

- Neurological manifestations present
- Methylmalonic aciduria
- Pernicious anemia
- Develops in years
- Vegan diet
- Absent

Folate Def

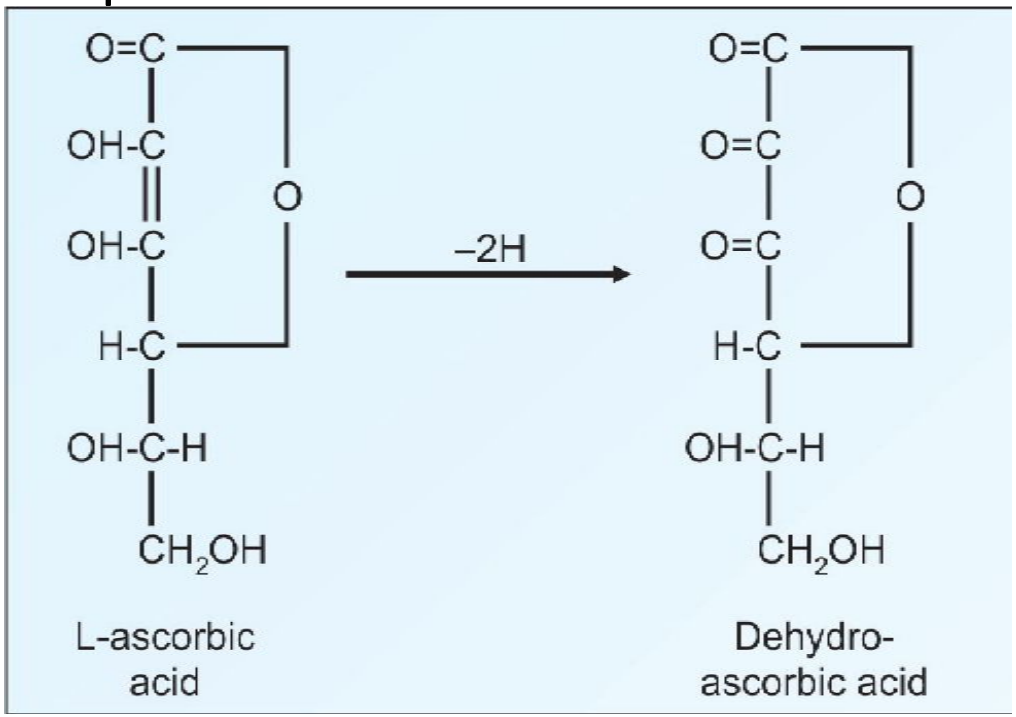
- Absent neurological manifestations
- Absent
- Not related
- Develops in months
- Alcoholism
- Neural tube defects in foetus

Homocysteine metabolism:



VITAMIN C (ASCORBIC ACID)

- **Chemistry**
- It is a sugar acid known as hexuronic acid. Ascorbic acid is easily oxidized by atomospheric O_2 to dehydroascarobic acid .
- High temperature (cooking) accelerates oxidation. Light and alkali also promotes oxidation



Functions

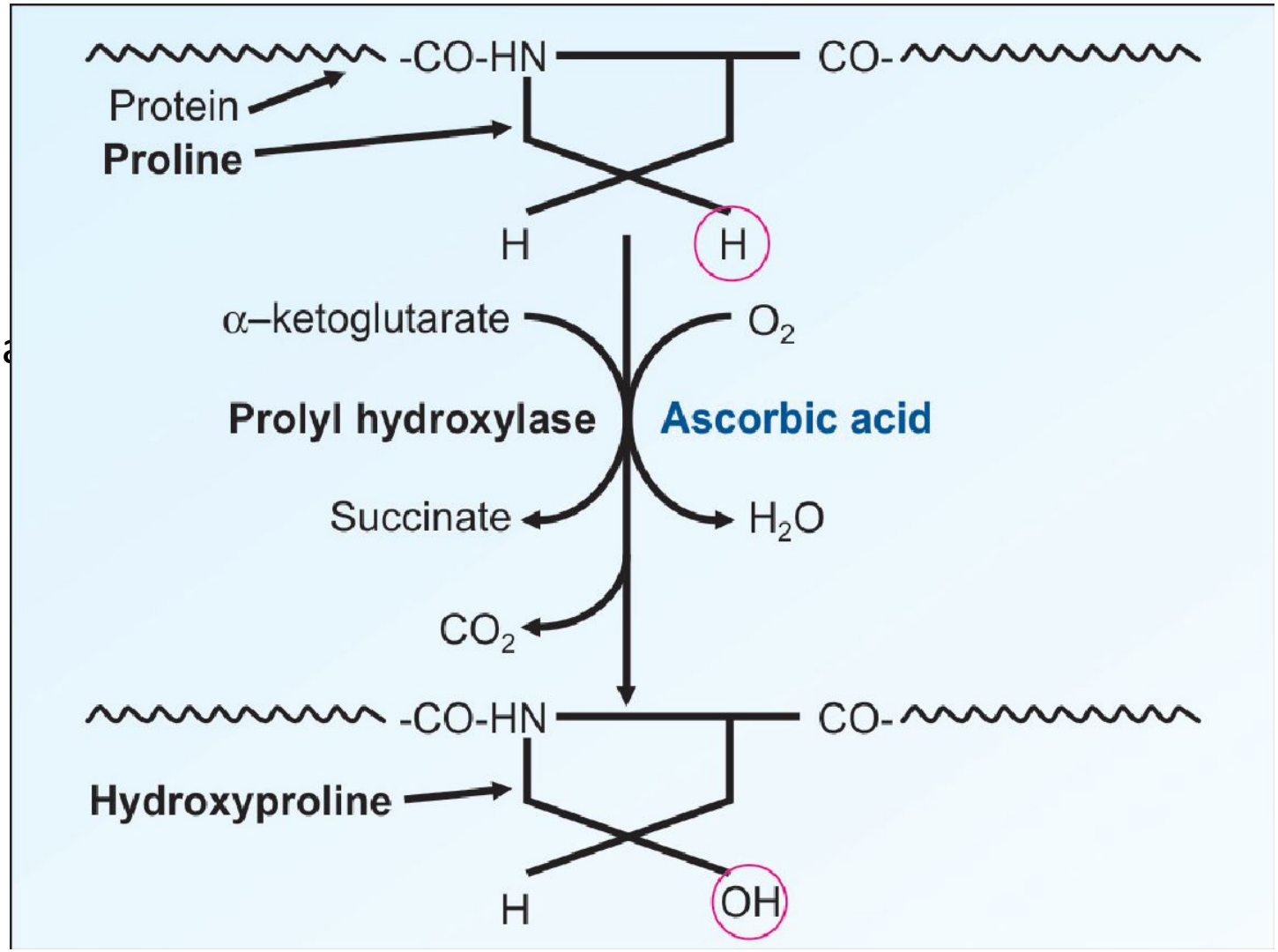
- 1. Ascorbic acid act as antioxidant. It is free radical scavenger. Since it is a strong reducing agent it protects carotenes, vitamin E and other B vitamins of dietary origin from oxidation.

- 2. It is required for the hydroxylation of proline and lysine residues of collagen. Since collagen is component of ground substance of capillaries, bone and teeth vitamin C is required for proper bone and teeth formation also.

- 3. It participates in hydroxylation reactions of steroid biosynthesis.

- 4. It is required for catecholamine synthesis from tyrosine.

- 5. In the liver bile acid synthesis requires ascorbic acid.



Hydroxylation of proline to hydroxyproline needs ascorbic

Functions

- 6. Ascorbic acid participates in the synthesis of carnitine.
- 7. It is required for the absorption of iron in the intestine. It maintains iron in ferrous form.
- 8. Catabolism of tyrosine requires ascorbic acid.
- 9. When given in large doses it reduces severity of cold. However evidence is lacking.
- 10. Vitamin C is effective in controlling bacterial invasion by inhibiting activity of bacterial hyaluronidase enzyme. It acts as inhibitor of this enzyme due to structural similarity to glucuronate of hyaluronin, the substrate of hyaluronidase.


vitamin

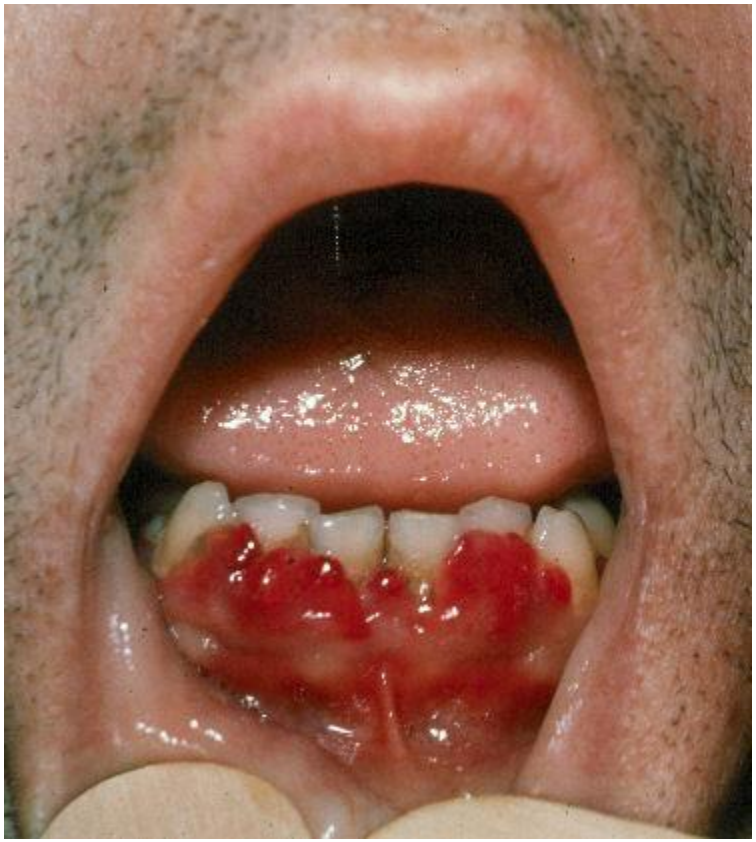
Vitamin C deficiency

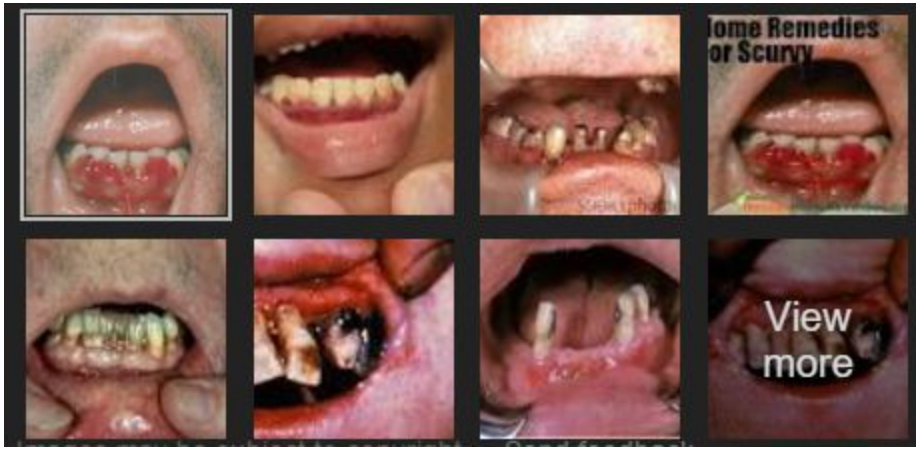
- 1. In adults deficiency of vitamin C causes scurvy.

But it rarely occurs in normal people.

- The symptoms of scurvy are
  (*a*) Haemorrhages in various tissues particularly in inside of thigh, calf and forearm muscles. It may be due to capillary fragility.
  (*b*) General weakness and anaemia.
  (*c*) Swollen joints, swollen gums and loose tooth.
  (*d*) Susceptible for infections.
  (*e*) Delayed wound healing.
  (*f*) Bone fragility and osteoporosis.

- 2. Vitamin C deficiency in infants gives rise to infantile scurvy. It occurs in weaned infants who are fed on diets low in vitamin C.





(A) Gingivitis and bleeding gum in vitamin C deficiency;
(B) Lime and (C) Gooseberry are good sources of vitamin C

- **Sources**
- Amla (indian gooseberry), guava, coriander and amarnath leaves, and cabbage are rich sources.
- Fruits like lemon, orange, pineapple, papaya, mango and tomato are good sources. Apples, bananas and grapes are fair sources.

- **Daily requirement (RDA)**
- Adults : 60-80 mg/day.

Therapeutic uses

- Large doses of Vit C are used to treat common cold, soft tissue infections.

- Since it is an antioxidant it reduces incidence of cancer, cardiovascular diseases and act as anti aging agent also.

Bioflavonoids (“vitamin of Permeability”)

- **Bioflavonoids are a group of naturally occurring plant compounds, which act primarily as plant pigments and antioxidants. They exhibit a host of biological activities, most notably for their powerful antioxidant properties.**
- Bioflavonoids work with other antioxidants to offer a system of protection. Numerous studies have shown their unique role in protecting vitamin C from oxidation in the body, thereby allowing the body to reap more benefits from vitamin C.
- **Bioflavonoids inhibit hyaluronidase, resulting in increase of vessels strength (decrease of permeability)**

Bioflavonoids (vitamin P) continue

- **Bioflavonoids Health Benefits**
  The main health benefits of bioflavonoids fall into two categories: health-promoting effects and therapeutic effects. The health-promoting effects include better eyesight, improved cardiovascular health, increased capillary strength, improved structure of connective tissues and appearance of skin, and a stronger immune system.
- Bioflavonoids also offer the health-promoting effect of lowering the risk of some diseases, such as atherosclerosis, cancer, arthritis, and gastrointestinal disorders. The therapeutic applications include treating a variety of diseases and disorders. Several of these are coronary heart disease, allergies, inflammation, hemorrhoids, respiratory diseases, viral infections, some types of cancer, and peptic ulcers.

Bioflavonoid Superstars

- Different bioflavonoids tend to have different health effects on the body. Some of the common bioflavonoids and their benefits are outlined below.
- Quercetin's primary use is for the relief of allergies and inflammation. In scientific experiments, it was found to be an effective inhibitor of histamine release from mast cells – the cause of allergic reactions.
- Pycnogenol™ has cardiovascular benefits, boosts the immune system, helps improve the appearance of the skin, helps varicose veins, provides relief from arthritic pain, and helps reduce inflammation.
- Rutin (and drug as ascorutin) for blood vessels and immune system

Bioflavonoid Superstars (continue)

- Grape seed extract has beneficial effects on the circulatory system. Some of these include improvements to cardiovascular health, protective antioxidant effects, improved eye health, and anti-inflammatory action.
- Green tea extract plays a beneficial role in protecting against certain infections, improving cardiovascular health, promoting better dental hygiene, and offering protection from the development of some types of cancer.
- Daily needs 25-50 mg/day

Avitaminosis and sources of vit.P

- Bioflavonoids are present in all **botanical supplement** products and foods. In fact, many medicinal herbs owe their curative actions to the bioflavonoids they contain. Besides the important antioxidant effects, bioflavonoids help the body maintain health and function in many ways. They have been shown to be anti-mutagenic, anti-carcinogenic, anti-aging, and promote structure and function in the circulatory system.
- Avitaminosis is exhibited by **petehii** (subcutaneous bleeding points due to increased permeability), however there is no separate avitaminosis P. More often is avitaminosis of vitamin C and P (scurvy)

TABLE 6–2 Some Coenzymes That Serve as Transient Carriers of Specific Atoms or Functional Groups

Coenzyme	*Examples of chemical groups transferred*	*Dietary precursor in mammals*
Biocytin	CO_2	Biotin
Coenzyme A	Acyl groups	Pantothenic acid and other compounds
5′-Deoxyadenosylcobalamin (coenzyme B_{12})	H atoms and alkyl groups	Vitamin B_{12}
Flavin adenine dinucleotide	Electrons	Riboflavin (vitamin B_2)
Lipoate	Electrons and acyl groups	Not required in diet
Nicotinamide adenine dinucleotide	Hydride ion ($:H^-$)	Nicotinic acid (niacin)
Pyridoxal phosphate	Amino groups	Pyridoxine (vitamin B_6)
Tetrahydrofolate	One-carbon groups	Folate
Thiamine pyrophosphate	Aldehydes	Thiamine (vitamin B_1)

TABLE 37.1: Summary of water soluble vitamins discussed in this chapter

Name	*Co-enzyme form*	*RDA*	*Main reaction using the co-enzyme*	*Deficiency disease*
Thiamine	Thiamine pyrophosphate (TPP)	1–1.5 mg	Oxidative decarboxylation of alpha keto acids	Beriberi
Riboflavin	Flavin adenine dinucleotide (FAD)	1.5 mg	Dehydrogenation, oxidized in ETC (1.5 ATP)	Glossitis, angular stomatitis
Niacin	Nicotinamide adenine dinucleotide (NAD and NADP)	20 mg	Dehydrogenation, oxidized in ETC (2.5 ATP), reductive biosynthetic reactions and hydroxylation	Pellagra
Pyridoxine	Pyridoxal phosphate (PLP)	1–2 mg	Transamination, decarboxylation of amino acids	Seizures, anemia, homocystinuria
Pantothenic acid	Co-enzyme A, ACP	10 mg	CoA derivatives, acyl carrier proteins	Burning foot syndrome
Biotin	Biotin	200–300 mg	Carboxylation	No specific disease

Note: The requirements are significantly higher in pregnancy and lactation. See also Table 38.1 for other water soluble vitamins.

Table I-10-1. Water-Soluble Vitamins

Vitamin or Coenzyme	Enzyme	Pathway	Deficiency
Biotin	Pyruvate carboxylase	Gluconeogenesis	MCC* (rare): excessive consumption of raw eggs (contain avidin, a biotin-binding protein)
	Acetyl CoA carboxylase	Fatty acid synthesis	
	Propionyl CoA carboxylase	Odd-carbon fatty acids, Val, Met, Ile, Thr	Alopecia (hair loss), bowel inflammation, muscle pain
Thiamine (B_1)	Pyruvate dehydrogenase	PDH	MCC: alcoholism (alcohol interferes with absorption)
	α-Ketoglutarate dehydrogenase	TCA cycle	Wernicke (ataxia, nystagmus, ophthalmoplegia)
	Transketolase	HMP shunt	Korsakoff (confabulation, psychosis)
			Wet beri-beri (high-output cardiac failure) and dry beri-beri (without fluid retention)
	Branched chain ketoacid dehydrogenase	Metabolism of valine isoleucine and leucine	

A- ATP
B- BIOTIN
C- CO_2

REM - VOMIT

MAIN □ATP SYNTHESIS

DECREASEDATP □ Na+K+ PUMP FAILURE □CELLS SWELL AND DIE

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Niacin (B_3) NAD(H) NADP(H)	Dehydrogenases V.Imp □SOURCE OF e_0^{-1} for ETC Left untreated □death !!	Many	Pellagra: diarrhea, dementia, dermatitis, and, if not treated, death Pellagra may also be related to deficiency of tryptophan (corn major dietary staple), which supplies a portion of the niacin requirement.
Folic acid THF	Thymidylate synthase U□ T Enzymes in purine synthesis need not be memorized DNA and RNA synthesis	Thymidine (pyrimidine) synthesis Purine synthesis	MCC: alcoholics and pregnancy (body stores depleted in 3 months) Homocystinemia with risk of deep vein thrombosis and atherosclerosis Megaloblastic (macrocytic) anemia Deficiency in early pregnancy causes neural tube defects in fetus

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Table I-10-1. Water-Soluble Vitamins (*continued*)

Vitamin or Coenzyme	Enzyme	Pathway	Deficiency
Cyanocobalamin (B_{12})	Homocysteine methyltransferase Methylmalonyl CoA mutase	Methionine, SAM Odd-carbon fatty acids, Val, Met, Ile, Thr	MCC: pernicious anemia. Also in aging, especially with poor nutrition, bacterial overgrowth of terminal ileum, resection of the terminal ileum secondary to Crohn disease, chronic pancreatitis, and, rarely, vegans, or infection with *D. latum* Megaloblastic (macrocytic) anemia Progressive peripheral neuropathy
Pyridoxine (B_6) Pyridoxal-P (PLP)	Aminotransferases (transaminase): AST (GOT), ALT (GPT)	Protein catabolism	MCC: isoniazid therapy Sideroblastic anemia
	δ-Aminolevulinate synthase	Heme synthesis	Cheilosis or stomatitis (cracking or scaling of lip borders and corners of the mouth) Convulsions

SUBACUTRE COMBINED DEGENERATION

1)Regeneration of TETRAHYDROFOLATE (ACTIVE FOLATE)□DNA and RNA synthesis

ANYTHING THAT DAMAGES LIVER
OR ANYTHING THAT INCTREASED AST/ALT ACTIVITY □INCREASED NEED FOR PLP

LESS HEME□SMALL RBCs□ IRON NOT USED □ IRON DEPOSITED IN PRECURSORS OF RBCS□SIDEROBLASTS

Riboflavin (B_2) FAD(H_2) ATP	Dehydrogenases	Many	Corneal neovascularization Cheilosis or stomatitis (cracking or scaling of lip borders and corners of the mouth) Magenta-colored tongue
Ascorbate (C)	Prolyl and lysyl hydroxylases Dopamine hydroxylase	Collagen synthesis Catecholamine synthesis Absorption of iron in GI tract STOMACH ACIDITY AND VIT C Fe^{+3} □ Fe^{+2}	MCC: diet deficient in citrus fruits and green vegetables Scurvy: poor wound healing, easy bruising (perifollicular hemorrhage), bleeding gums, increased bleeding time, painful glossitis, anemia
Pantothenic acid CoA CoA	Fatty acid synthase Fatty acyl CoA synthetase Pyruvate dehydrogenase α-Ketoglutarate dehydrogenase	Fatty acid metabolism PDH TCA cycle	Rare