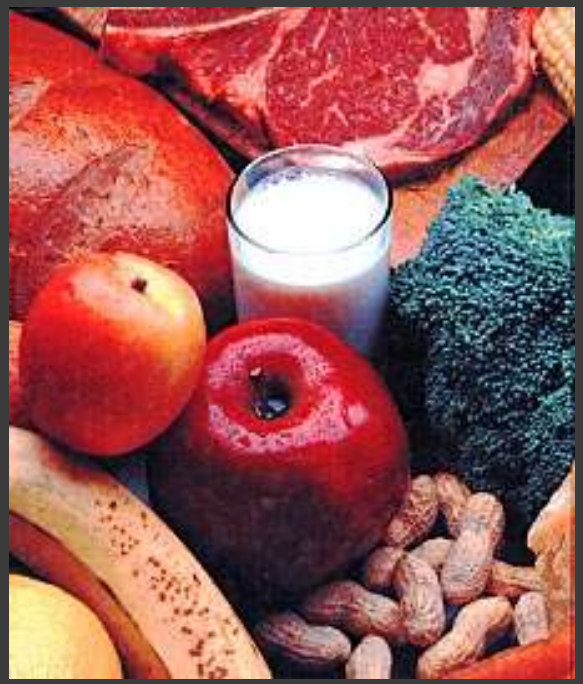
Water Soluble Vitamins



Dr Aparna Chaudhari

VITAMINS

- **Vitamins are required in diet in small amounts- absence of which leads to a deficiency disease.**

- **Vitamins cannot be synthesized by humans.**
- **They are organic compounds occurring in natural foods.**
- **They are necessary to maintain good health.**

- **Vitamins are useful to correct vitamin deficiency manifestations but taking higher doses will not boost up health, but cause some toxic effects.**

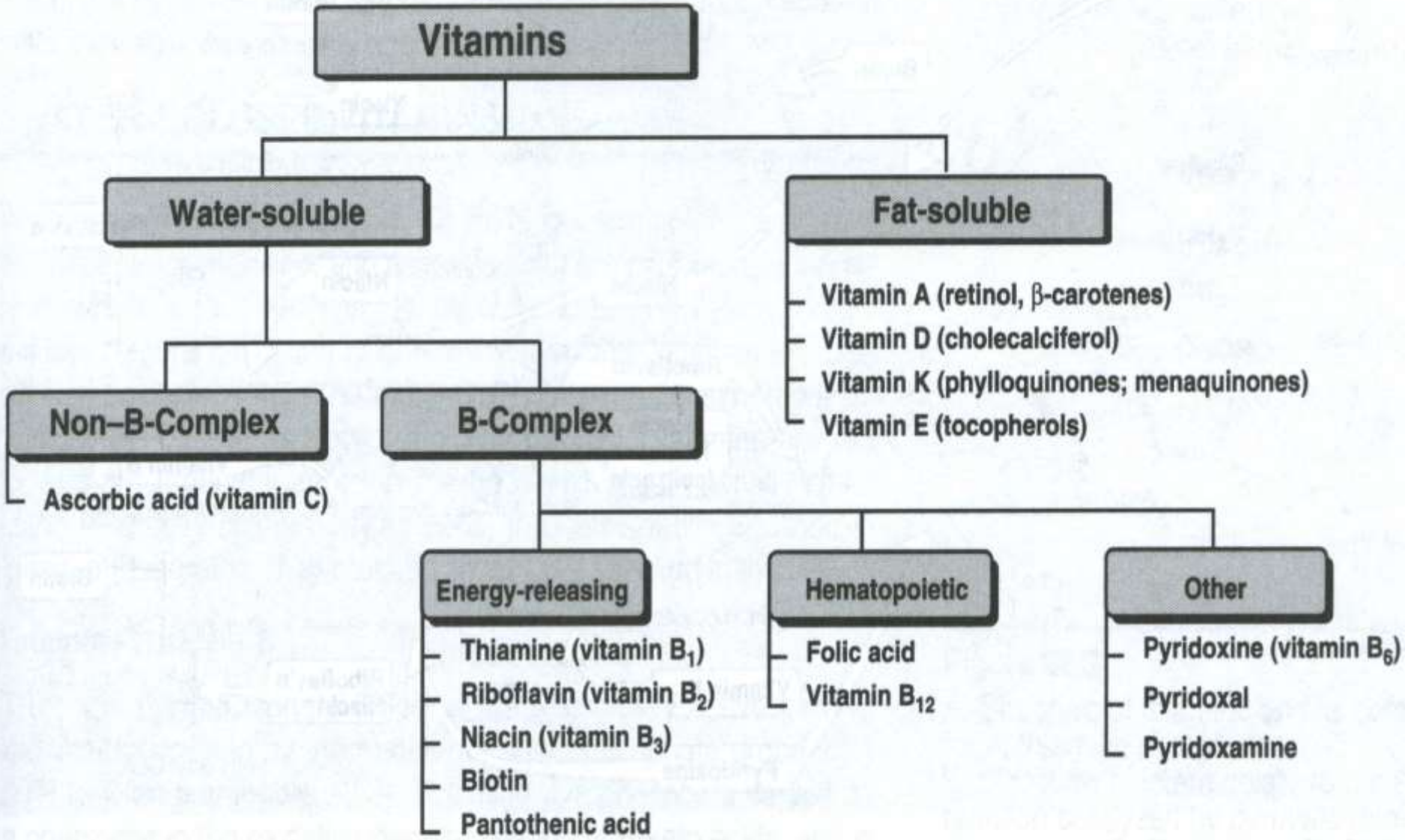


Figure 28.1
Classification of the vitamins.

Vitamin c

- k/as Ascorbic acid
- Man Cannot synthesize
- heat labile so destroyed by cooking
- Involved in formation of collagen , major component of connective tissues

Chemistry

- Similar to monosaccharide
- Strong reducing agent
- Forms- L ascorbic acid and dehydroascorbic acid
- D ascorbic acid inactive
- Oxidized finally to oxalic acid

Biosynthesis and kinetics

- Humans cannot synthesize ascorbic acid due to lack of enzyme L- gulonolactone oxidase.
- Readily absorbed from GI tract
- Body pool – 1500mg
- N level- 0.7 – 1.2 mg/dl
- Smokers, alcoholics, OC pills- low levels seen
- Excretion- oxalic acid, diketogluconic acid

Biochemical role

- Collagen formation
  - Structural protein
  - supporting matrix for connective tissue, blood vessels, bone, cartilage,dentine.

Proline hydroxylase

- Proline → Hydroxyproline
- vit C, O2, Fe2+

lysyl hydroxylase

- Lysine → Hydroxylysine
- vit C, O2, Fe2+

Contd...

- Essential for wound healing
- Prescribed for post op cases
- Bone formation
- collagen also in ground substance surrounding capillary wall- def leads to capillary fragility

Antioxidant

- eliminates free radicals.
- prevents heart diseases, cancer, ageing, cataract

Role in amino acid metabolism

- Tyrosine and tryptophan metabolism.
- required for oxidation of parahydroxy phenyl pyruvate – homogentisate – maleylacetoacetate in tyrosine degradation.
- essential for hydroxylation of tryptophan to serotonin.

Role in lipid metabolism

- Formation of carnitine

- Fatigue in vit C def is due to decreased carnitine levels

- Stimulates 7alpha- hydroxylase – syn of bile acids.

Role in iron metabolism

- converts ferric ions to ferrous form – facilitates absorption.
- formation of ferritin
- mobilization of iron from it.

Role in hemoglobin metabolism

- degradation of Hb to bile pigments

- Reconversion of methemoglobin to Hb

Effect on other vitamins

- Spares vit A ,E and B complex vitamins from oxidation.
- Required for conversion of folic acid to THF.
- Involved in maturation of RBCs.

Phagocytosis

- Increases synthesis of immunoglobulins.

SYNTHESIS OF HORMONES

- synthesis of corticosteroids
- synthesis of epinephrine

Drug metabolism

- Cytochrome P450 – detoxification reactions

CELL RESPIRATION

- Cytochrome oxidase

Daily requirement and sources

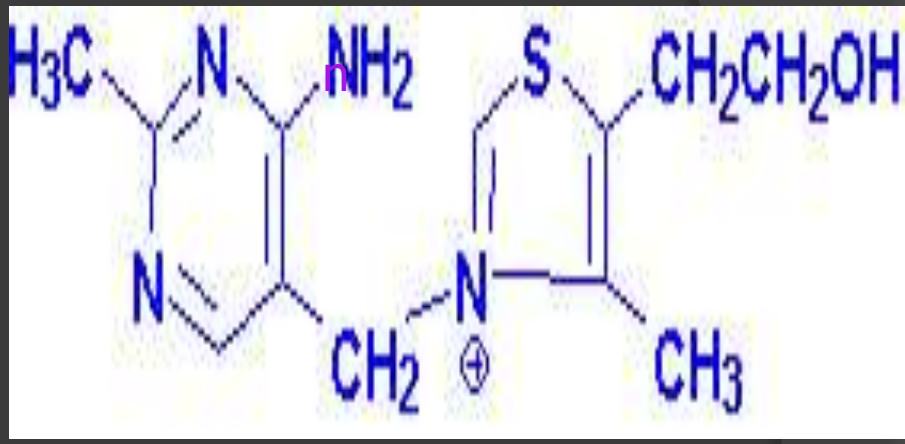
- 60-75mg/day

- Sources-
  - Fresh fruits
  - green leafy vegetables
  - citrus fruits
  - gooseberry
  - Guava
  - Cabbage
  - Spinach
  - Germinating seed

Deficiency - scurvy

- Symptoms reflect impaired collagen synthesis resulting in defective connective tissue.
  - Capillary fragility- petechiae,ecchymosis, hematomas, hemarthrosis. Epistaxis, hematuria, malena.
  - Swollen painful gums. Teeth loosened and lost.
  - Poor wound healing and anemia.
  - Demineralisation and osteoporosis.
  - Weakness, early fatigue, depression.

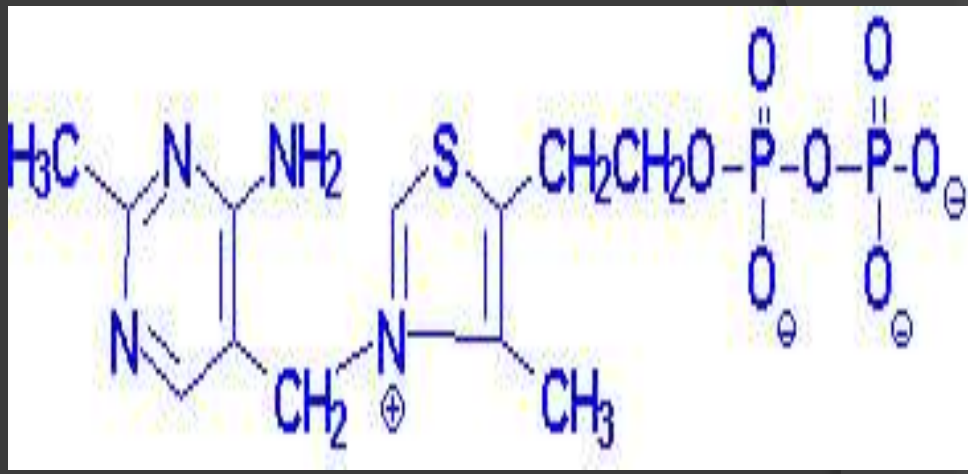
Thiamine



- Anti beri beri or antineurotic vitamin
- It has a specific coenzyme – TPP
- It contains a pyrimidine ring and a thiazole ring held by methylene bridge

Thiamine pyrophosphate

- The active form is formed by addition of two phosphates groups



- Thiaminase in sea foods can destroy thiamin (cleaving both the rings)

FUNCTIONS OF THIAMINE :

Functions of thiamine is through the cofactor Thiamine Pyrophosphate or TPP

- **Oxidative decarboxilation**: Pyruvate dehydrogenase requires TPP

- **Decarboxylation:** Branched chain amino acid α-keto acid dehydrogenase also requires TPP
- **Transketolase reaction:** Transketolase (pentose phosphate pathway)
- **Thiamine triphosphate** is known to be involved in nerve conduction.

Reactions that uses thiamine pyrophosphate

A) Transketolase

Ribose – 5- P + Xylulose –5 P

Transketolase
TPP

Sedoheputlose-7-P + Glyceraldehyde 3- P

B) Pyruvate dehydrogenase & α ketoglutarate dehydrogenase

Pyruvate

Acetyl CoA

The requirement of thiamine is increased along with higher intake of carbohydrate.

α KG
TPP

TCA cycle

α Ketoacid decarboxylase also requires TPP

Succinyl CoA

Thiamine

Sources

Cereals, pulses, oil seeds, nuts & yeast are good sources
Polished rice removes 80 % of thiamine.
Animal foods like pork, liver, heart kidney and milk also contains thiamine

RDA

1- 1.5 mg / day for adults, requirement increases during pregnancy & lactation

Deficiency of thiamine leads to Beriberi

Early symptoms are
Anorexia ,constipation , nausea, weakness, mental depression.

Thiamine Deficiency

Wet Beriberi – CVS manifestation are prominent
Edema of legs, face, trunk and serous cavities
Palpitation, breathlessness, distended neck veins

Dry Beriberi – CNS manifestation are major features
Muscles get wasted, walking becomes difficult
peripheral neuritis with sensory disturbance

- Infantile Beriberi – Occurs in infants – Restlessness, sleeplessness, bouts of screaming
- Wernicke-Korasakoff syndrome – known as cerebral beriberi
- Encephalopathy (ophthalmoplegia, nystagmus, cerebral ataxia) ,delirium& psychosis
- Alcoholic polyneuritis – Poly neuritis with motor and sensory defects in chronic alcoholics.

DEFICIENCY MANIFESTATIONS

Decreased activity of
pyruvate dehydrogenase and
α-ketoglutarate dehydrogenose causes:
→
a. accumulation of pyruvate and lactate

b. decreased acetyl CoA and ATP
formation leading to →
decreased acetylcholine level which alters
→ central nervous system activity.

DECREASED TRANSKETOLASE LEVELS:

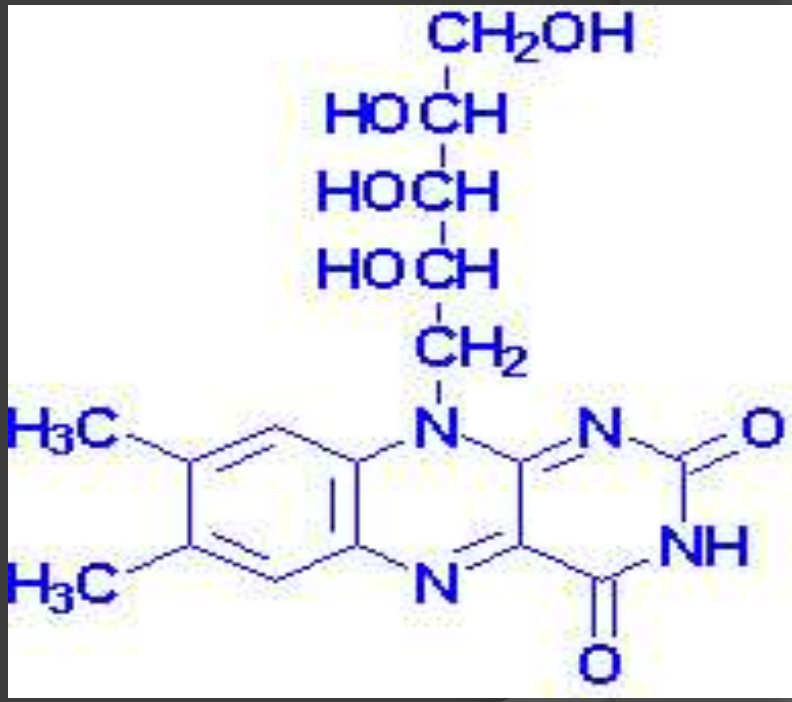
- decreased activity of pentose phosphate pathway due to TPP deficiency results in low levels of NADPH - necessary for fatty acid synthesis; → this leads to a decrease in synthesis of myelin, which may cause peripheral neuropathy.

Assessment of thiamine status:

- By estimating urinary thiamine excretion and plasma levels of pyruvate and lactate
- Determination of erythrocyte transketolase activity which requires TPP as coenzyme confirms the deficiency

RIBOFLAVIN

First B complex component to be isolated in a pure state.



• Has dimethyl isoalloxazine ring to which D-ribitol is attached by a nitrogen atom

• It is stable to heat but sensitive to light.

COENZYMES OF RIBOFLAVIN

- Two active coenzymes
  FMN & FAD

- FMN is formed by the transfer of phosphate from ATP.

- FAD is formed by transfer of an AMP moiety from ATP to FMN.

- Both are capable of reversibly accepting two hydrogen atoms.
- Both are bound tightly to flavoenzymes

- Catalyze oxidation /reduction reactions

Riboflavin

FMN dependent enzymes

- L- amino acid oxidase
- NADH dehydrogenase

FAD –dependent enzymes

- Succinate dehydrogenase
- Acyl CoA dehydrogenase
- Xanthine oxidase
- Dihydrolipoate dehydrogenase

FUNCTIONS OF RIBOFLAVIN:

- FAD [Flavin adenine Dinucleotide] and FMN [Flavin mononucleotide]
  are co-enzymes for a number of oxidases and dehydrogenases
- they can accept two hydrogen ions to form FADH2 and FMNH2 and take part in redox reactions,
  eg. electron transport chain or act as antioxidants

Niacin metabolism- oxidation of NAD and NADP.

Iron mobilisation.

Riboflavin

Sources – Milk and dairy products.
Liver, dried yeast, egg, whole milk, milk powder are rich sources
Fish, whole cereals, germinating plants, legumes and green leafy vegetables are good sources **.**

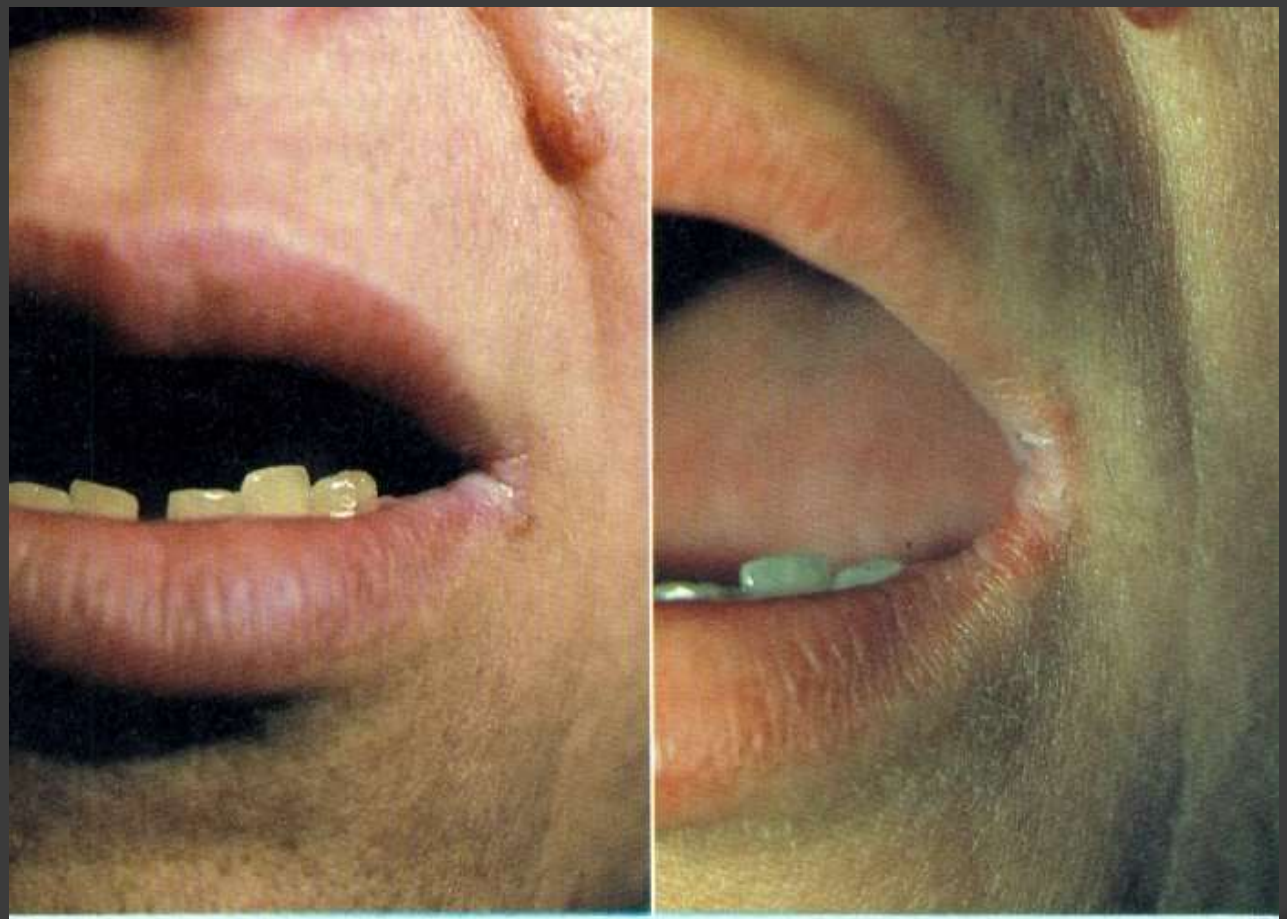
Daily requirement
Adults on sedentary work require 1.5 mg
During pregnancy & lactation – 1.7 – 1.9 mg
Above 60 years – needs supplementation

DEFICIENCY MANIFESTATIONS

Rare except in elderly or alcoholic individuals - no specific deficiency disease

Symptoms of deficiency-

- **angular stomatitis (inflammation at the sides of the mouth)**
- **cheilosis (fissures at corners of mouth)**
- **glossitis (inflamed tongue)**
- **conjunctival congestion(earliest sign)**



A From "Fundamentals of Clinical Nutrition" by R. L. Weinsier copyright 1993 by Mosby-Year Books N.Y. B

Fig. 6-9 Angular stomatitis of riboflavin deficiency before (**A**) and after (**B**) therapy.

NIACIN

- Niacin or nicotinic
•acid is known as pellagra preventing factor.

It is a pyridine derivative (pyridine 3-carboxylic acid)

•Amide form is nicotinamide

- Can be synthesized from Tryptophan

- 60 mg of Trp = 1 mg of niacin

Structure of NAD^+ & $NADP^+$

- Coenzymic forms NAD^+ & $NADP^+$

- Involved in oxidation and reduction reactions

NIACIN

- **The coenzyme forms of Niacin and their functions are:**

(1) Oxidation and reduction:

Nicotinamide adenine dinucleotide [NAD^+] is converted to NADH. This compound is used for oxidation reactions to generate ATP.

Nicotinamide adenine dinucleotide phosphate [$NADP^+$] is converted to NADPH and this compound is used for Reductive biosynthesis.

(2) ADP ribosylation : NAD and NADP required for ADP-ribose transfer reactions involved in DNA repair, regulation, DNA replication and cell cycle.

Niacin

NAD^+ dependent enzymes

1) Lactate dehydrogenase
2) Glyceraldehyde –3-phosphate dehydrogenase
3) Pyruvate dehydrogenase
4) β hydroxyacyl CoA dehydrogenase

$NADPH$ generaters ($NADP^+$ dependent enzymes)

1) Glucose –6-phoshate dehydrogenase
2) 6-phosphogluconate dehydrogenase
3) Malic enzyme
4) Cytoplasmic isocitrate dehydrogenase

NAD^+ or $NADP^+$ dependent

1) Glutamate dehydrogenase
2) Isocitrate dehydrogenase

- NADPH utilizing reactions

1) β keto acyl ACP → β hydroxy acyl ACP- Fatty acid synthesis
2) HMG CoA → mevalonate – Cholesterol synthesis
3) Folate → tetrahydrofolate

- 4) Biosynthesis of Vit D, Steroids and Neurotransmitters.

Niacin

Sources

Liver, yeast, whole grains, cereals, pulses are rich sources
Milk, fish, eggs and vegetables – moderate sources.

RDA

Adult 15 – 20 mg
Children 10 – 15 mg
Pregnancy and lactation – requires more

Clinical effects of Niacin deficiency

- Results in pellagra
- Symptoms of pellagra leads to dermatitis, diarrhoea, Dementia
- Other features - achlohydria , vaginitis

- **Causes of nicotinamide deficiency**
- Lack of tryptophan
- Lack of vitamin B6-PLP coenzyme
- Isoniazid drug – inhibits PLP formation.
- Hartnup's disease
- Carcinoid syndrome

DEFICIENCY MANIFESTATIONS of NIACIN

- **Deficiency leads to the clinical condition called PELLAGRA - characterised by,**

3 “Ds” --→4 “Ds”

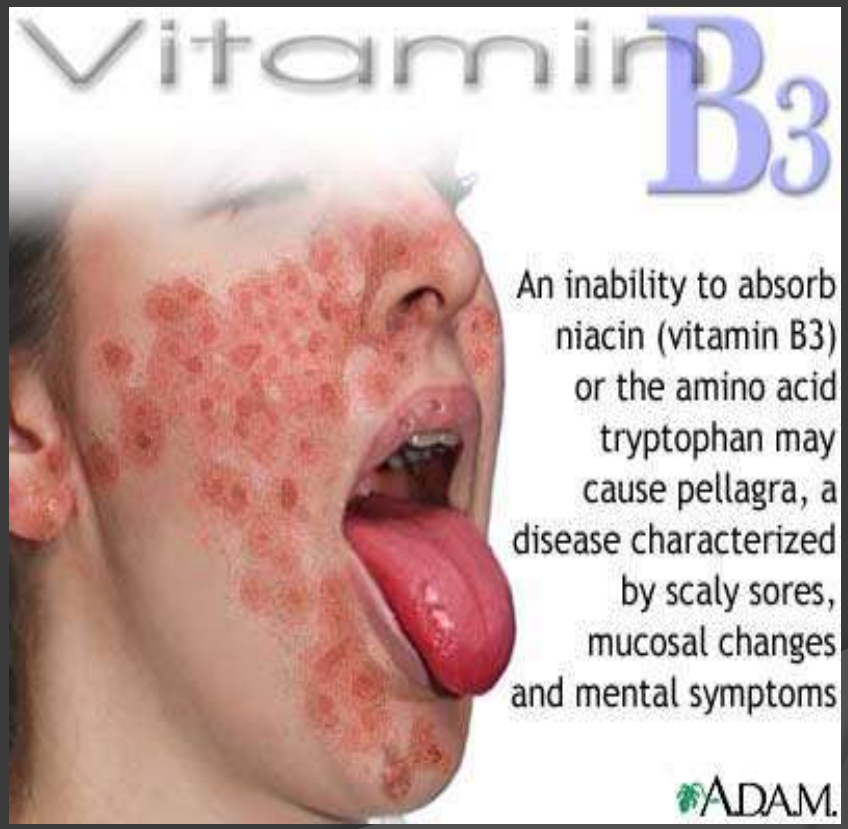
Dermatitis
Diarrhoea
Dementia

Dermatitis: In early stages, bright red erythema occurs, especially in the feet ankles and neck. Increased pigmentation around the neck is known as **Casal's necklace**. The dermatitis is precipitated by exposure to sunlight

Diarrhoea: may be mild or severe with blood and mucus. This may lead to weight loss.

Dementia: seen in chronic patients. Irritability, Inability to concentrate and poor memory

Pellagra (rough skin)



PYRIDOXINE

- Vitamin B_6 compounds are pyridine derivatives.
- Pyridoxine has a primary alcohol as functional group
- Pyridoxal has aldehyde
- pyridoxamine amine functional group.
- Pyridoxine can be converted to pyridoxal and pyridoxamine.
- Pyridoxine to Pyridoxal- dehydrogenase
- Pyridoxal to PLP by Kinase

Pyridoxal phosphate

Coenzymic form is PLP

By entering into schiff base
with the amino acid it can permit
-Transamination
-Decarboxylation
-Deamination
-Transsulfuration

Pyridoxal phosphate

Biochemical function : As a coenzyme for

- Transamination: ALT & AST
- Decarboxylation (formation of)
  - GABA
  - Histamine
  - Serotonin
  - Taurine
  - Ethanolamine
  - ALA synthase – PLP dependent required for Haem biosynthesis
- Homocysteine --to-- Cysteine
- Phosphorylase
- Involved in formation of ceramide,sphingolipids

- Synthesis of Co A from Pantothenic acid
- Transport of K ions across cell membrane from outside to inside
- Intramitochondrial FA synthesis : As a coenzyme with condensing enzyme for elongation of Fatty acid
- For biosynthesis of arachidonic acid from Linoleic acid
- Involved in Immune response

DEFICIENCY MANIFESTATIONS

- primary deficiency is very rare
- Abnormal amino acid metabolism, Hypochromic microcytic anemia
- secondary pellagra
- convulsions and depression
- Peripheral neuritis
- Demyelinating diseases
- Drug treatment with INH & Penicillamine
- Oral contraceptives
- Alcoholism- Acetaldehyde compete with PLP for protein binding.

Pyridoxal phosphate

Sources

Egg yolk, fish, milk (rich sources)

Good sources – Wheat,corn, cabbage, roots and tubers

Highest concentration in honey

RDA

Adult : 2 – 2.2 mg

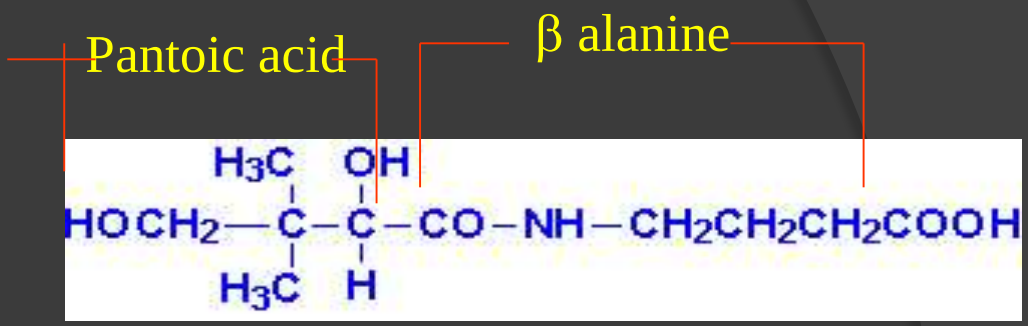
During pregnancy, lactation, old age : 2.5 mg

Therapeutic value :

Nausea & vomiting of pregnancy ; Radiation sickness,

Muscular dystrophies, to treat oxalate stones of kidney

Structure of Pantothenic acid



- Pantos means
- "everywhere"

& widely distributed in nature

- It consist of two components pantoic acid & β- alanine held together by peptide linkage

- Coenzyme form is CoA

which is a nucleotide.

- Reduced form is CoA-SH.

PANTOTHENIC ACID

Functions as co-enzyme A [COA-SH]

It is involved in the synthesis of

e.g. acetyl CoA,

succinyl CoA,

fatty acyl CoA

It is also a component of fatty acid synthase; acyl carrier protein

- Acetyl CoA pool : TCA cycle,FA synthesis,Cholesterol, Ketone body,Acetyl choline, detoxification

- Succinyl CoA pool : TCA cycle, Gluconeogenesis, Porphyrin,Activation of acetoacetate,detoxification

Pantothenic acid

Biochemical function

- CoA serves as carrier of activated acetyl or acyl group as thiol ester

Pyruvate → Acetyl CoA

αKeto glutarate→ Succinyl CoA

Fatty acid → Acyl CoA

Acyl carrier protein

Group transfer reactions

- Formation of acetyl Choline, citrate, succinate

Sources

- Widely distributed. Rich sources are egg, liver, yeast, It is also synthesized by normal bacterial flora in intestine

RDA –10 mg / day

Deficiency

- **Rare**
- **Deficiency of pantothenic is associated with Burning feet syndrome (pain, numbness in toes, sleeplessness)**
- **In experimental animals, deficiency results in anemia, fatty liver, decreased steroidogenesis**

Biotin

- It is known as anti-egg white injury factor.
- It is a sulfur containing vitamin.
- It consists of imidazole ring fused with thiophene ring with valeric acid side chain.
- It is bound to ε- amino group of lysine to form biocytin in enzymes
- It participates as a coenzyme in the carboxylation reactions

BIOTIN

Functions;_It is an activated carrier of CO2.

Functions as co-enzyme(CARBOXYBIOTIN) for:

1. ***pyruvate carboxylase*** **in gluconeogenesis**
2. ***Acetyl CoA carboxylase*** **in fatty acid synthesis**
3. ***Propionyl CoA carboxylase*** **in β oxidation of odd-numbered fatty acids**

Biotin

Biotin dependent enzymes

1. **Pyruvate carboxylase – pyruvate to oxaloacetate**
2. **Acetyl CoA carboxylase – acetyl CoA to Malonyl CoA**
3. **Propionyl CoA carbozylase – propionyl CoA to D-methyl malonyl CoA**

Deficiency :

very rare on a normal diet,

- **may lead to dermatitis,atrophic glossitis,anorexia,hallucinations,depression.**
- **can be induced by:**

  eating lot of raw egg whites,

  which contain glycoprotein ‘avidin’

  that binds to biotin in the intestine

  preventing its absorption.
- **long-term antibiotic therapy**

  which kills intestinal bacteria

Biotin

Sources

- Liver, yeast, peanut, milk, egg yolk , soya bean are rich sources.
- Normal bacterial flora will provide adequate quantities of biotin

RDA

200 – 300 μg

VITAMIN B12 [COBALAMINE] :

The only vitamin synthesised neither by plants nor by animals, but only by a few species of bacteria

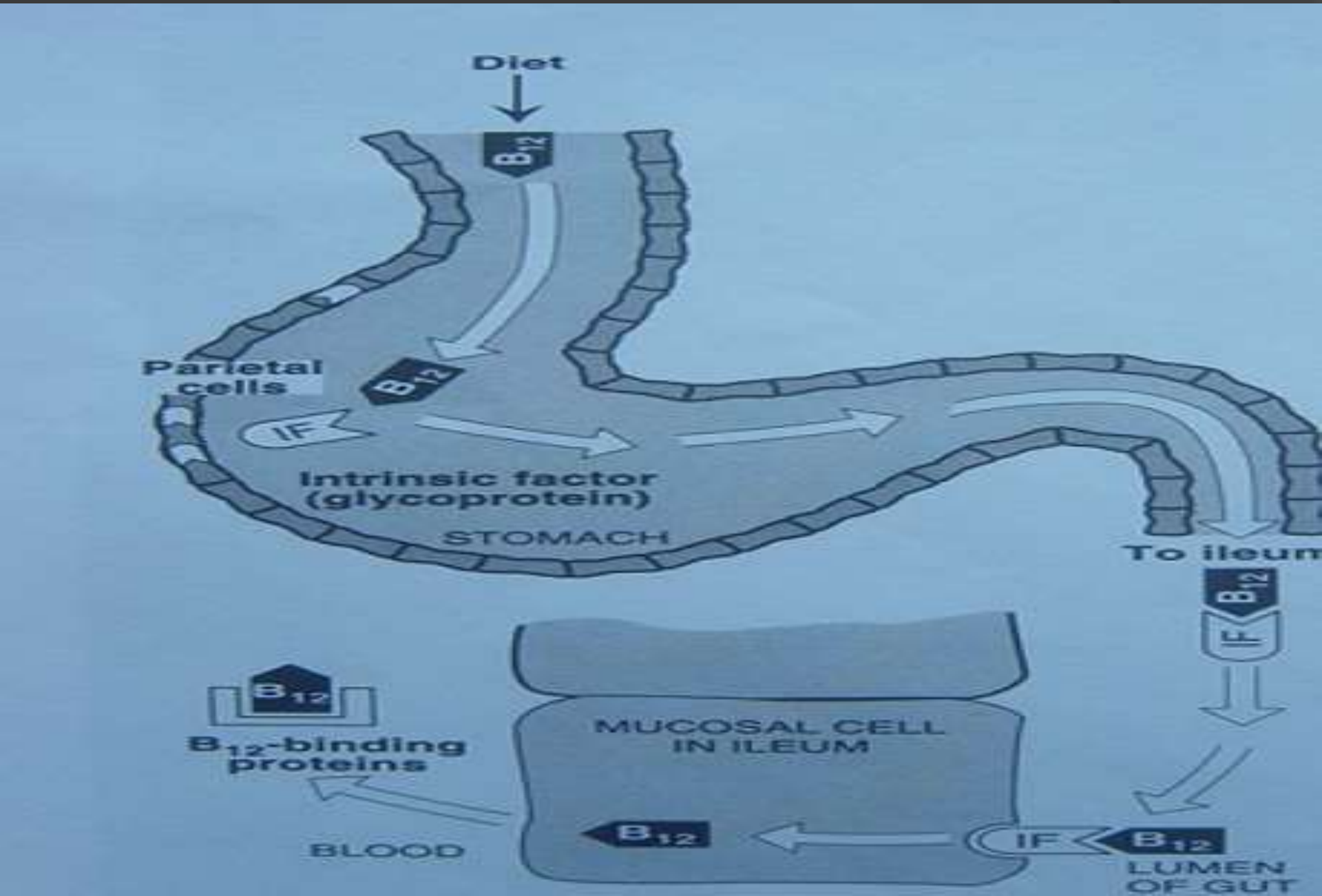
Two active forms;

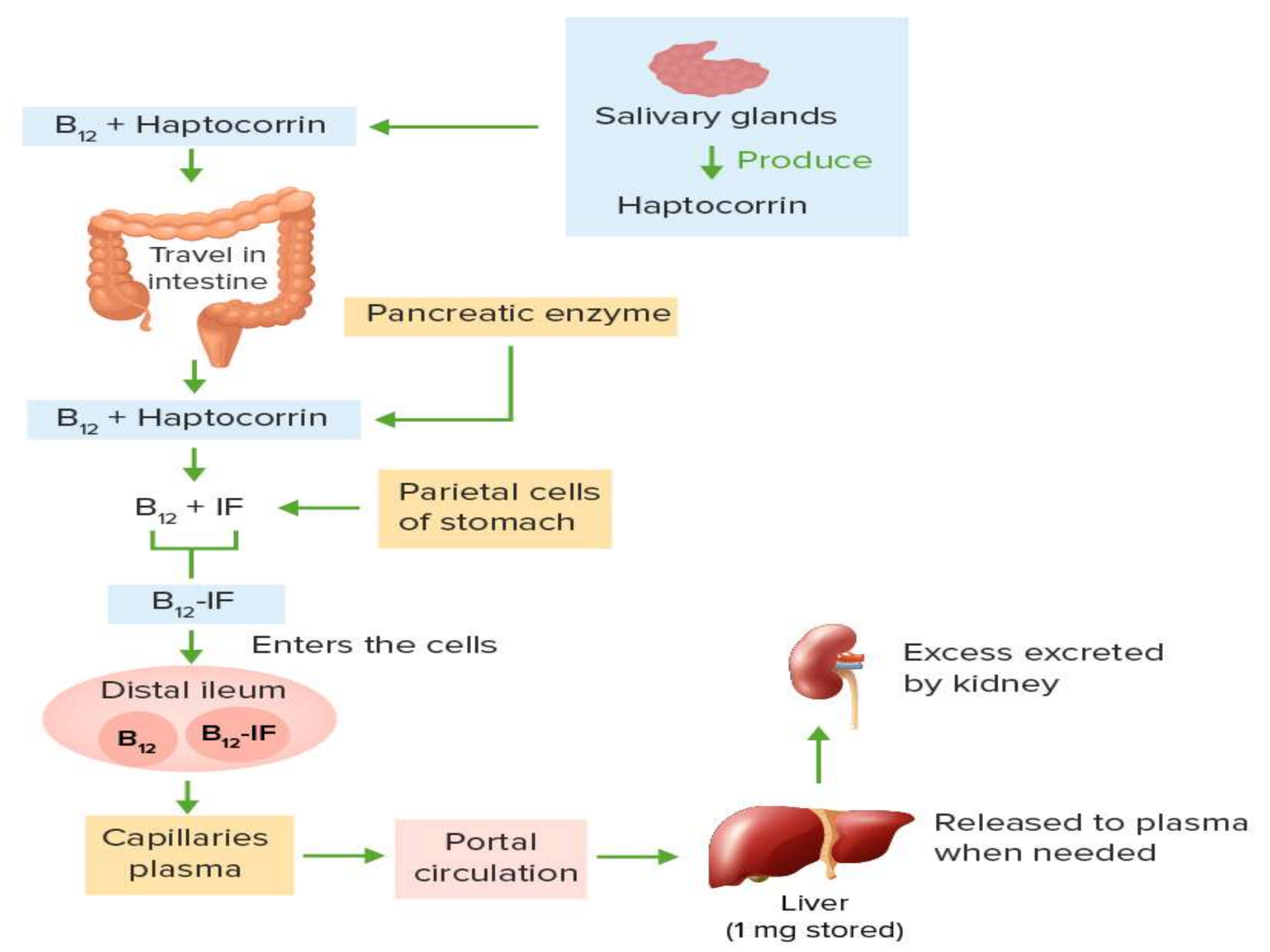
- **Deoxy adenosyl cobalamin and**
- **methyl cobalamin**

Cobalamin

- Heat stable, red colour, synthesized by microorganisms
- Anti-pernicious anemia vitamin
- Corrin ring with central cobalt atom
- Cyanocobalamin, Hydroxy cobalamin
- Active form – deoxy adenosyl cobalamin & methyl cobalamin

Absorption of Vitamin B_{12}




Salivary glands
Produce
Haptocorrin
B_{12} + Haptocorrin
Travel in intestine
Pancreatic enzyme
B_{12} + Haptocorrin
B_{12} + IF
Parietal cells of stomach
B_{12}-IF
Enters the cells
Distal ileum
B_{12}
B_{12}-IF
Capillaries plasma
Portal circulation
Liver
(1 mg stored)
Released to plasma when needed
Excess excreted by kidney

Vitamin B 12 can be stored :

- water soluble vitamins can not be stored but it can be stored in liver .
- Transcobalamin 1 and 3 provoides excellent form of storage.
- liver contains about 2 mg of vitamin which is sufficient for requirement of 2 to 3 years.

Functions

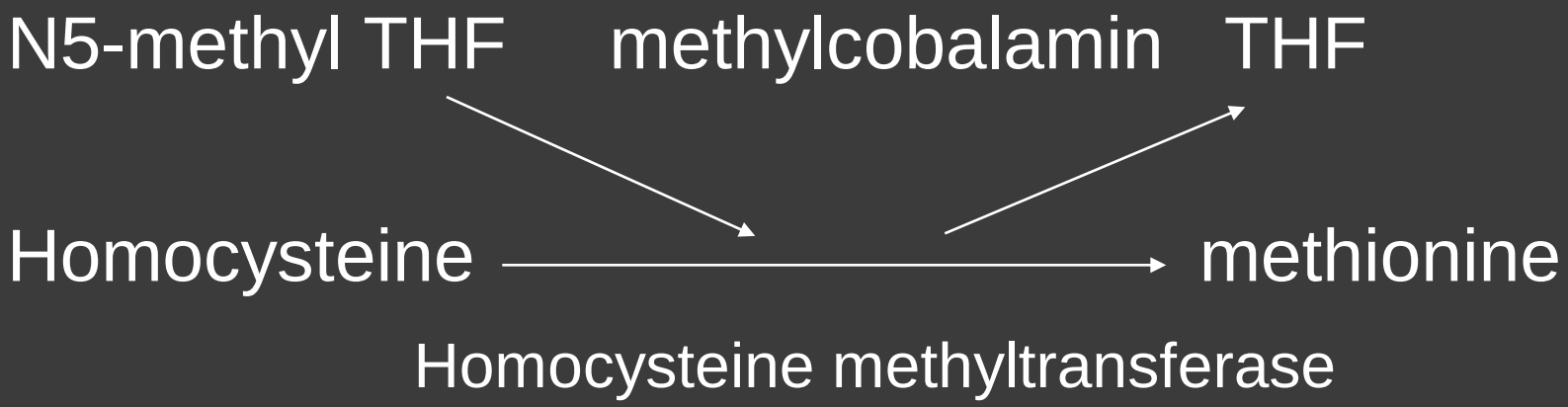
- **coenzyme for two enzyme actions.**

  1. *Methylmalonyl CoA mutase*, with deoxyadenosyl Cobalamin- assists in the breakdown of odd-numbered fatty acids

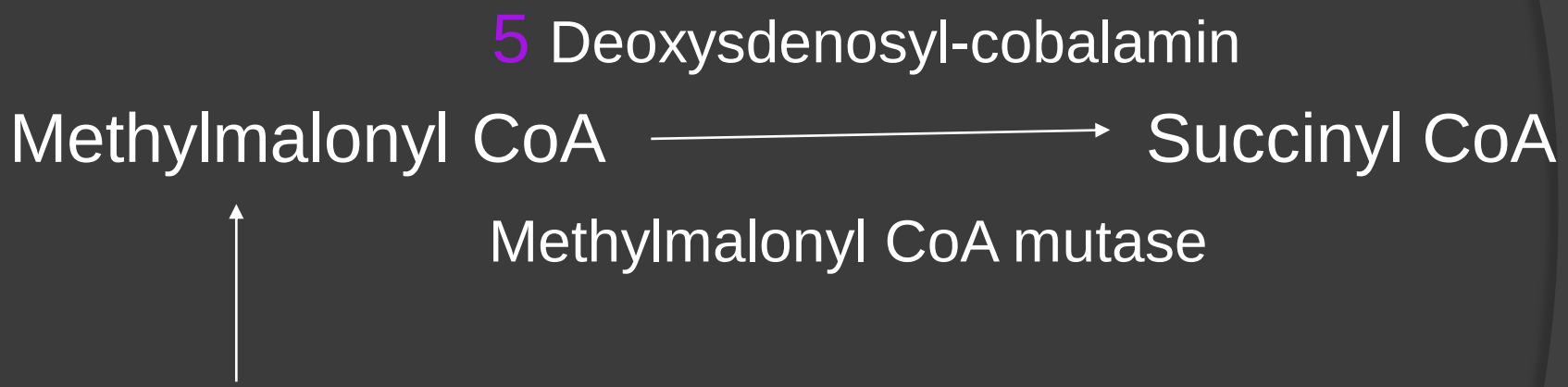
  2. *Homocysteine methyl transferase*, with methyl cobalamin- assists in the synthesis of methionine. This reaction also reverses the methyl folate trap, regenerating THF

Biochemical function

- Synthesis of methionine from homocysteine



- Isomerization of methylmalonyl CoA to succinyl CoA



Sources

Foods of animal origin are the only sources for the vitamin.

Rich sources – liver, kidney, milk, curd, eggs, fish, pork and chicken.

Curd is better source of Vitamin B_{12}

This vitamin is synthesized only by microorganism.

RDA

Adult – 3 μg

Children – 0.5 – 1.5 μg

Pregnancy – 4 μg / day

Therapeutic dose:

100-1000 microgram by injection.

Causes of vit B 12 deficiency:

- Nutritional
- Decrease in absorption
- Pernicious anemia
- Gastric atrophy
- Pregnancy
- Fish tape worm

DEFICIENCY MANIFESTATION

As a significant amount of vitamin B_{12} is stored in the body it takes about 2 years for symptoms of deficiency to develop.

Deficiency can cause :

- The **accumulation of abnormal odd-numbered fatty acids** incorporated into the cell membranes of nerves resulting **in neurological symptoms, inadequate myelin synthesis, and nerve degeneration.-combined degeneration**

- Secondary **'artificial' folate deficiency since folate is 'trapped' as methyl-THF.**

- This causes a decrease in nucleotide synthesis, resulting in **megaloblastic anaemia.**

- **Abnormal Homocysteine level :**

  homocysteine is accumulated leading to homocysteinuria.

  It s level in blood is related to myocardial infarction .

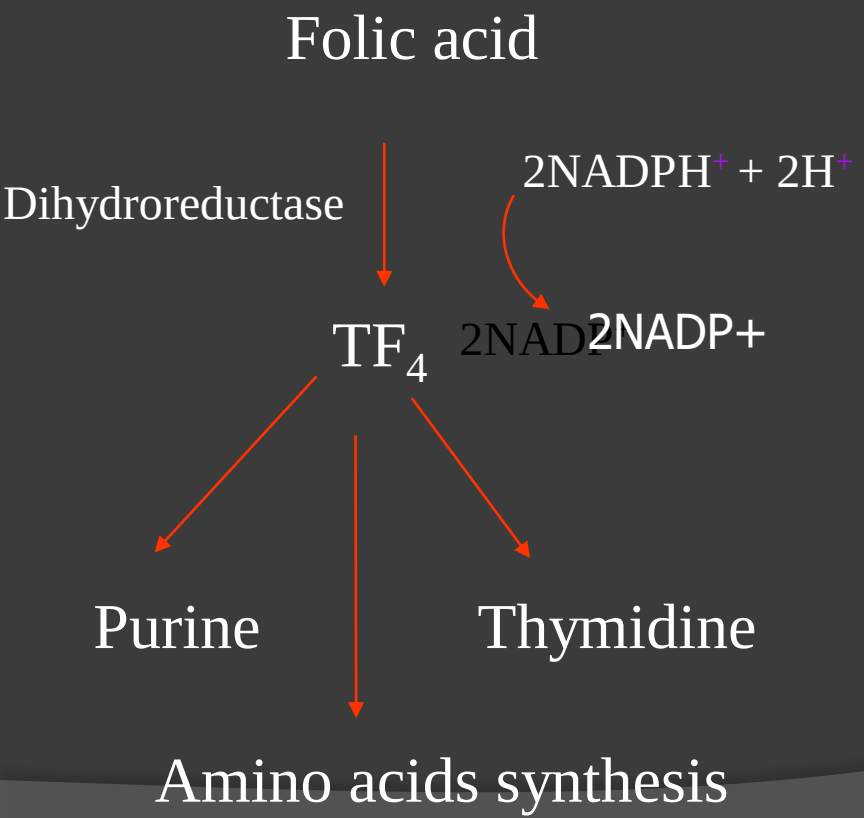
  so vit B 12 is protective against ishemic heart disease.

Assessment

- Serum B12: Elisa ; RIA
- Schilling test : Radioactive labelled B12
- Methylmalonic acid in urine
- Peripheral smear :megaloblasts
- Homocystinuria

Folic acid

- Folic acid has three components
  - Pteridine nucleus
  - p-aminobenzoic acid
  - Glutamic acid – (1-7)



Important for one carbon metabolism

FOLIC ACID

- **Folic acid (or folate) plays a key role in one-carbon metabolism**
- **Essential for the biosynthesis of the purines, pyrimidine and, thymine .**
- **Folic acid deficiency is common among pregnant women and alcoholics.**

FOLIC ACID...

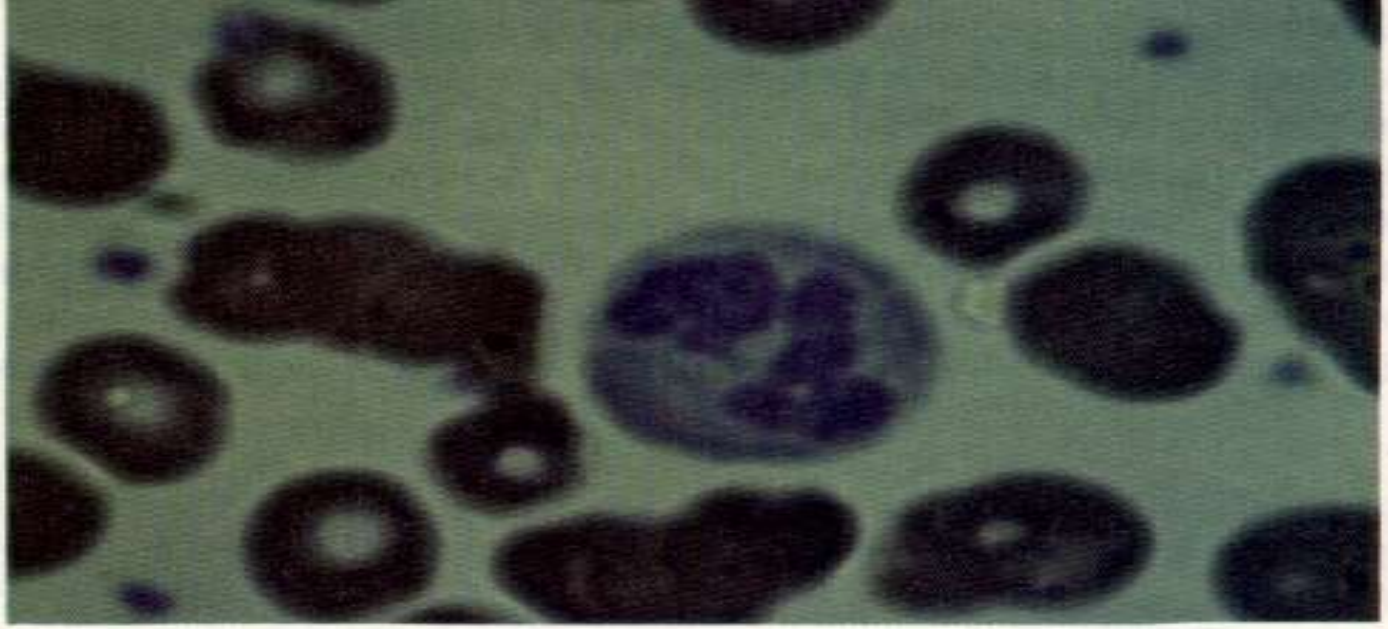
1. **The biologically active form of folic acid is tetra hydrofolic acid (THF).**
2. **THF is produced by the two-step reduction of folate by *dihydrofolate reductase* .**
3. **Folic acid is composed of a pteridin ring attached to p-aminobenzoic acid (PABA) and conjugated with one or more glutamic acid residues.**

- THF exists in various forms : methyl, Methylene,methenyl ,formyl & formimino

- All are metabolically interconvertible.

Folic acid

Rich Sources – green leafy vegetables,
whole grains, cereals, liver, kidney, yeast & egg
Milk – poor source
RDA
Adult – 100 μg
Pregnancy – 300 μg
Lactation – 150 μg
Deficiency – Most common
Growth failure & megaloblastic anemia.
Caused by increased demand or by poor absorption or by treatment with drugs
Early fetal development of neural tube is critically dependent on folic acid.
Deficiency during early pregnancy may lead to neural tube defects .



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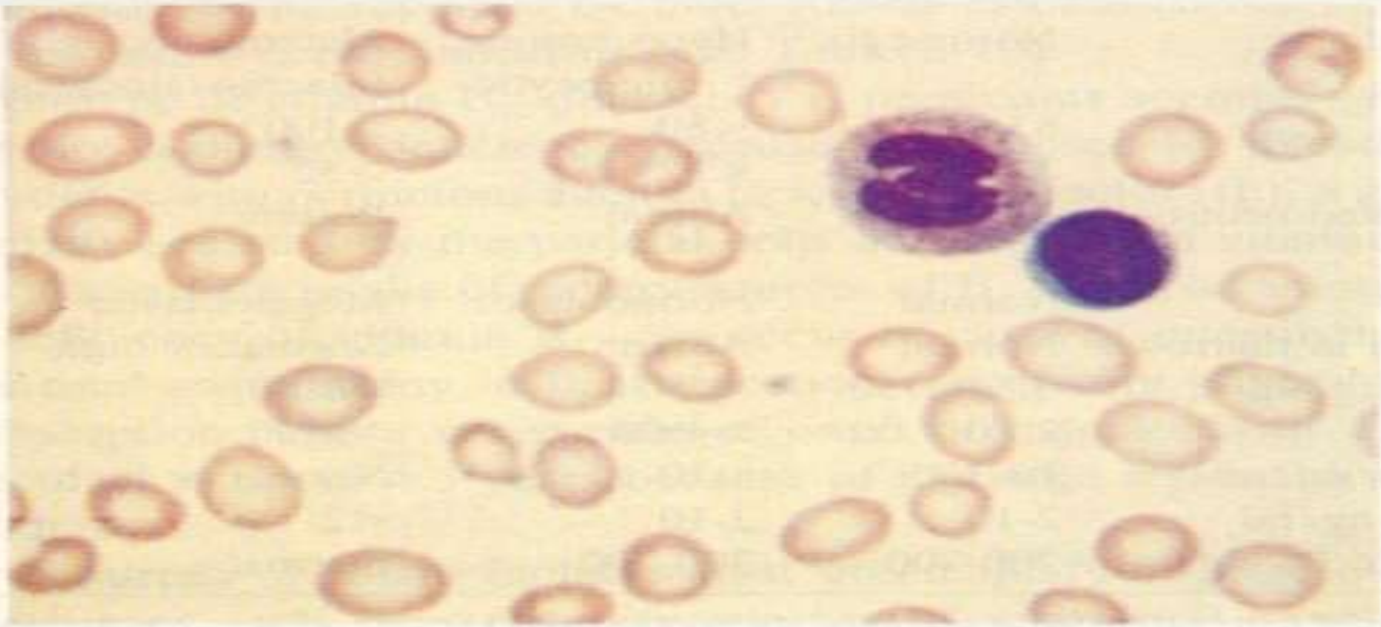


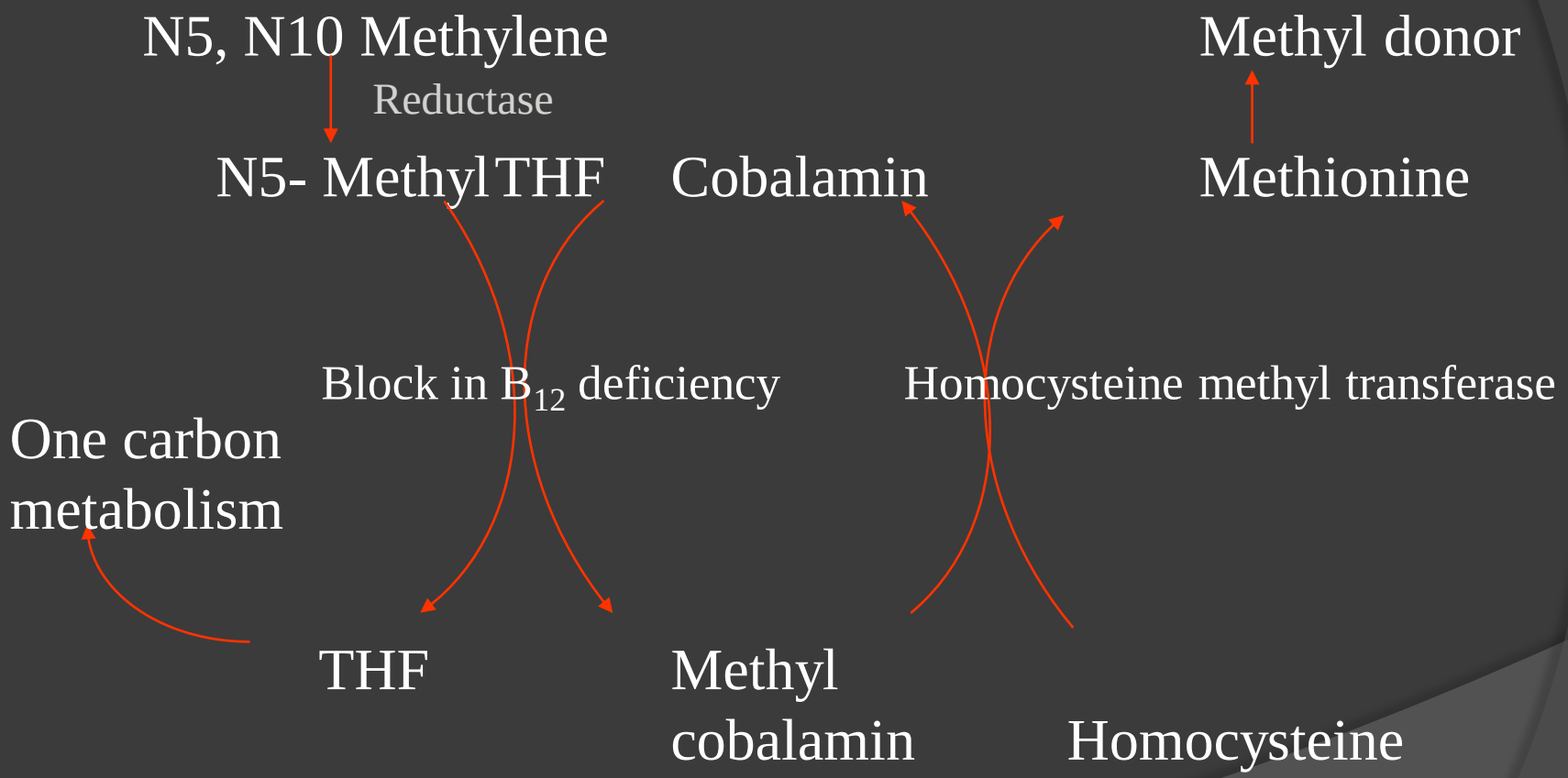
B

Fig. 2-6 **A**, Blood cells in macrocytic anemia; notice the hypersegmented polymorphonuclear leukocytes. **B**, Blood cells in microcytic anemia.

Metabolic reactions of THF

- THF ---- N5,N10 methylene THF by serine hydroxy methyl transferase(plp) [serine --- Glycine]
- N5,N10 methylene THF is oxidised to N5,N10 methenyl THF .On hydrolysis forms N5 formyl THF (Folinic acid) stable form for admns.of THF
- N5,N10 methylene THF is reduced to N5 methyl THF

Interrelationship between Folic acid & Vitamin B_{12} __ Folate trap – methyl trap



- L-Histidine + Glutamic acid ---N-FIGLU
- N-Formimino glutamic acid + THF ---N5 formimino THF
- N5 Formimino THF on deamination gives N5,N10 methenyl THF which on hydrolysis gives N5 formyl THF (stable form)

Fundamental role of Folic acid

- Growth : synthesis 0f Purines & pyrimidines.
- Haemopoesis

INHIBITORS OF FOLIC ACID COENZYME SYNTHESIS :

- **Methotrexate, a folic acid analogue competitively inhibits *Dihydrofolate reductase.***
- **It has been used to effect the remission of acute leukemia in children.**

INHIBITORS OF FOLIC ACID COENZYME SYNTHESIS...

- **Sulfanilamide and its derivatives are structural analogs of para aminobenzoic acid. - competitively inhibit the synthesis of folic acid. Thus decreasing the synthesis of critical nucleotides needed for the replication of DNA and RNA.**

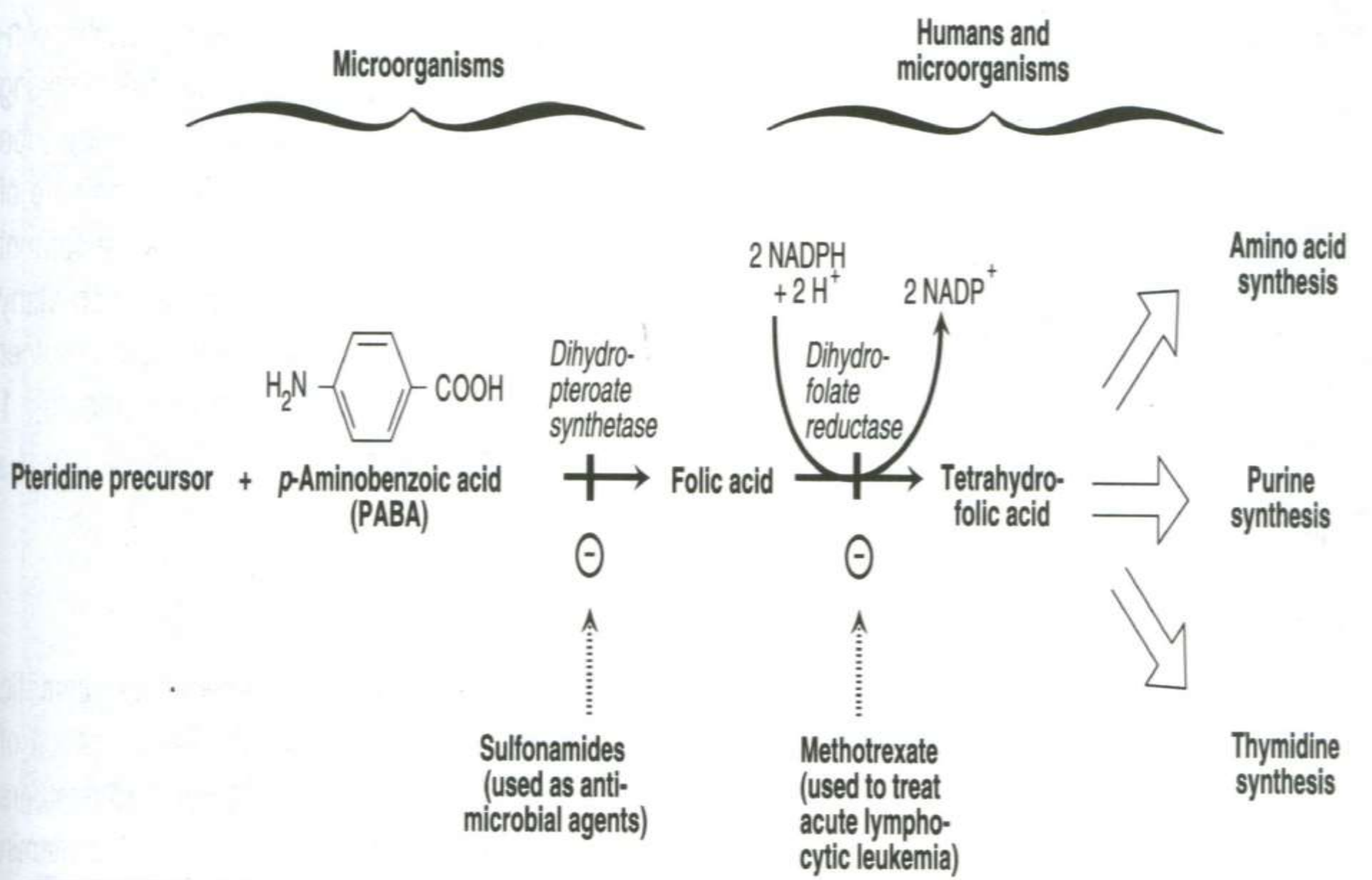


Figure 28.9
Inhibition of tetrahydrofolate synthesis by sulfonamides and methotrexate.

Thank you