Vitamins
Polish biochemist Casimir Funk discovered vitamin B1 in 1912 in rice bran.

He proposed the complex be named "Vitamin" (vital amines).

By the time it was shown that not all vitamins were amines, the word was already universal.
Vitamin - definition

- An organic compound required as a nutrient in tiny amounts by an organism.
- It cannot be synthesized in sufficient quantities by an organism, and must be obtained from the diet.
- Vitamins have diverse biological function:
  - hormone-like functions as regulators of mineral metabolism (vit. D),
  - regulators of cell and tissue growth and differentiation (some forms of vit. A)
  - antioxidants (vit. E, C)
  - enzyme cofactors (tightly bound to enzyme as a part of prosthetic group, coenzymes)
Vitamin classification

**Lipid-soluble vitamins** (A, D, E and K)

- hydrophobic compounds, absorbed efficiently with lipids,
- transport in the blood in lipoproteins or attached to *specific binding proteins*,
- more likely to accumulate in the body,
- more likely to lead to *hypervitaminosis*
Vitamin classification

**Water-soluble vitamins** - 8 B vitamins and vitamin C

- Function: mainly as enzyme cofactors,
- hydrophilic compounds dissolve easily in water,
- not readily stored, excreted from the body,
- their consistent daily intake is important.

Many types of water-soluble vitamins are synthesized by bacteria.
Lipid-soluble vitamins

Vitamin A

Retinol

- Biologically active forms - retinoids: retinol, retinal, retinoid acid.

- Major vit. A precursors (provitamins) → plants carotenoids.

- Foodstaf of animals origin contain most of vit. A in the form of esters (retinylpalmitates) – retinol and long fatty acid.
Vitamin A and vision

- Vit. A is necessary to form **rhodopsin** (*in rods, night vision*) and **iodopsins** (*photopsins, in cones – color vision*) - visual pigment.
- Retinaldehyde is a prosthetic group of light-sensitive opsin protein.
- In the retina, all-*trans*-retinol is isomerized to 11-*cis*-retinol → oxidized to 11-*cis*-retinaldehyde, this reacts with opsin (Lys) → to form the holoprotein **rhodopsin**.
- Absorption of light → conformation changes of opsin → photorhodopsin.
Vitamin A and vision

- The following is a series of isomerisation → initiation of nerve impulse.

- The final step is hydrolysis to release all-trans-retinaldehyde and opsin.

- Deficiency of vit. A leads to night blindness.

- Vitamin A is an important antioxidant.
Vitamin A and other functions

Transcription and cell differentiation

- Retinoic acid regulates the transcription of genes - acts through nuclear receptors (steroid-like receptors).
- By binding to various nuclear receptors, vit. A stimulates (RAR – retinoid acid receptor) or inhibits (RXR- retinoid „X“ receptor) transcription of genes transcription. All-*trans*-retinoic acid binds to RAR and 9-*cis*-retinoic acid binds to RXR.
- Retinoic acid is necessary for the function and maintenance of epithelial tissues.
Vitamin A - deficiency

- The early sign → a loss of sensitivity to green light,
  - prolonged deficiency → impairment to adapt to dim light
  - more prolonged deficiency leads to night blindness

- Ever escalated deficiency leads to **squamous metaplasia** - columnar epithelia are transformed into heavily keratinized squamous epithelia.

- The conjunctiva loses mucus-secreting cells → glykoprotein content of the tears is reduced → **xeroflalmia** ("dry eyes")
  - Often complication - bacterial or chlamidial infection which results in perforation of the cornea and blindness
Vitamin A - deficiency

- Transformation of respiratory epithelium – *loss of protective airway function* (antibacterial properties) → bronchitis.
- Conversion of the urinary tract epithelium → *higher frequency of urinary stone formation*

- Immunosuppression
- Impairment of reproductive function (both in men and women).

- Worldwide deficiency of vit. A
- 3 – 10 mil. children become xerophtalmic every year
  - 250 000 to 500 000 go to blindness
  - 1 million die from infections
Vitamin A - toxicity

- Toxic dose:
  - single dose of more than 200 mg
  - more than 40 mg per day

- Acute symptoms - headache, vomiting, impaired consciousness.

- Chronic intoxication – weight loss, vomiting, pain in joints, muscles, blurred vision, hair loss, excessive bone growth.

- Both vit. A excess and deficiency in pregnancy are teratogenic – retinoic acid is gene regulator during early fetal development.

- *Carotenoids* are non toxic - accumulation in tissues rich in lipids (the skin of babies overdosed with carrot juice may be orange).
Metabolic functions of vitamin A

- Vision
- Gene transcription
- Immune function
- Embryonic development and reproduction
- Bone metabolism
- Haematopoiesis
- Skin health
- Antioxidant activity
Sources of vitamin A

- cod liver oil
- meat
- egg
- milk
- dairy products
- carrot
- broccoli
- spinach
- papaya
- apricots

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Vitamin D

- Calciol, vitamin D$_2$ (cholecalciferol) → precursor of calcitriol, D$_3$ (1,25-dihydroxycalciferol).

- Regulates with PTH calcium and phosphate level (absorption, reabsorption, excretion).

- Synthesis in the skin (7-dehydrocholesterol) UV → further transformation in the liver and kidneys.
Synthesis

UV irradiation 270 – 300 nm

Photolysis

Non-enzymatic reaction in the skin

Transport to the liver
Liver

Cholecalciferol (calcioi; vitamin D₃) → Calcidiol-25-hydroxylase → Calcidiol (25-hydroxycholecalciferol) → Calcidiol-24-hydroxylase → 24-hydroxycalcidiol

Kidneys

Calcidiol-1-hydroxylase → Calcidiol (25-hydroxycholecalciferol) → Calcidiol-24-hydroxylase → 24-hydroxycalcidiol → Calcidiol-1-hydroxylase → Calcitriol (1,25-hydroxycholecalciferol) → Calcitirol (Inactive form)
Effects of vitamin D

- Transported in the blood on a carrier (vitamin-D binding protein, VDBP).

- $1,25(\text{OH})_2\text{D}$ binds to intracellular receptors (intestine, bone, kidney).

- The main function is to maintain plasma levels of calcium (essential for neuromuscular activity) and phosphate levels:
  - increase Ca absorption in the intestine,
  - reduce the excretion of calcium (stimulates parathyroid hormone-dependent Ca reabsorption in the distal tubule),
  - mobilizing bone mineral, together with parathyroid hormone
Vitamin D - deficincy

- Failure of absorption in the intestine.
- The lack of the liver and the renal hydroxylation of vit. D (congenital deficiency of 1-hydroxylase).

- The lack of UV irradiation.

- The main manifestation - impaired ossification of the newly created osteoid, abundance of non mineralized matrix.
- Vit. D is necessary for the prevention of skeletal changes (rickets in growing individuals, osteomalacia in adults).
Vitamin D and immunity

- It increases the activity of natural killer cells (cytotoxic lymphocytes).
- Increases the phagocytic ability of macrophages.
- Reduces the risk of virus diseases (colds, flu).
- Reduces the risk of many cancers (colon, breast and ovarian cancer).
- Reduces the risk of cardiovascular disease → have a positive impact on the composition of plasma lipids.
Sources of vitamin D

- In addition to sunbathing:
  - various fish species (salmon, sardines and mackerel, tuna, catfish, eel), fish oil, cod liver
  - eggs, beef liver, mushrooms
Vitamin E

- Vitamin E is a family of $\alpha$, $\beta$, $\gamma$, $\delta$ tocopherols and corresponding tocotrienols isomers.
- They are formed from chroman ring and hydrophobic ftyyl side chain.
- The highest biological activity has $\alpha$-tokoferol.
Vitamin E

- Adsorption from the small intestine.
- Its absorption is dependent on the presence of lipids in the diet.
- Associated with plasma lipoproteins → liver uptake through receptors for apolipoprotein E.
- $\alpha$-tocopherol is bind to $\alpha$-tocopherol transport protein ($\alpha$-TTP) → transported to the target organs (the excess is stored in adipocytes, in muscle, liver).
- $\beta$, $\gamma$, $\delta$-tocopherols are transferred into the bile and degraded.
Vitamin E as antioxidant

- Stops free radical reactions (peroxyl radicals ROO•, oxygen radicals HO•, lipoperoxid radicals LOO•). Chroman ring with OH group → uptake radicals.
Vitamin E as enzyme cofactor

- \(\alpha\)-tocopherol quinon generated by oxidation of \(\alpha\)-tocopherol can acts as a cofactor of mitochondrial unsaturated fatty acids.

- \(\alpha\)-tocopherol quinon + cytochrom B\(_5\) + NADH+H\(^+\) initiate formation of double bonds in FA – temporarily changes to \(\alpha\)-tocopherol-hydroquinon (in the presence of O\(_2\) changes back to \(\alpha\)-tocopherol quinon).
Vitamin E – deficiency and toxicity

- The lack of $\alpha$-tocopherol in plasma is often associated with impaired fat absorption or distribution (in patients with cystic fibrosis, in patients with intestine resection).

- Deficit of vit. D exhibit - neurological problems, impaired vision, eye muscle paralysis, platelet aggregation, impairment of fertility in men, impaired immunity.

- Toxicity is relatively small.
Sources of vitamin E

- fortified cereals
- seeds and seed oils, like sunflower
- nuts and nut oils, like almonds and hazelnuts
- green leafy vegetables,
- broccoli
- cabbage
- celery

Vitamin E is found in corn, nuts, olives, green, leafy vegetables, vegetable oils and wheat germ.

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Vitamin K

- **Vitamin K** is a group of lipophilic, hydrophobic vitamins.

- They are needed for the posttranslational modification of proteins required for blood coagulation,

- They are involved in metabolism pathways, in bone mineralisation, cell growth, metabolism of blood vessel wall.
Vitamin K

- Vitamin K$_1$ (phylloquinon) – plant origin
- Vitamin K$_2$ (menaquinon) – normally produced by bacteria in the large intestine
- K$_1$ and K$_2$ are used differently in the body
  - K$_1$ – used mainly for blood clotting
  - K$_2$ – important in non-coagulation actions - as in metabolism and bone mineralization, in cell growth, metabolism of blood vessel walls cells.

Synthetic derivatives of Vit.K
Vitamin K - function

- Cofactor of liver microsomal *carboxylase* which carboxylates glutamate residues to $\gamma$-carboxyglutamate during synthesis of prothrombin and coagulation factors VII, IX and X (posttranslation reaction).

- Carboxylated glutamate chelates Ca$^{2+}$ ions, permitting the binding of blood clotting proteins to membranes.

- Forms the binding site for Ca$^{2+}$ also in other proteins – osteocalcin.
Vitamin K - deficiency

- Deficiency is caused by fat malabsorption or by the liver failure.
- Blood clotting disorders – dangerous in newborns, life-threatening bleeding (*hemorrhagic disease of the newborn*).
- Osteoporosis due to failed carboxylation of osteokalcin and decreased activity of osteoblasts.
- Under normal circumstances there is not a shortage, vit. K is abundant in the diet.
Sources of vitamin K

- Green leafy vegetables
- vegetable oil
- broccoli
- cereals

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Water soluble vitamins

- Vitamin $B_1$ (thiamine)
- Vitamin $B_2$ (riboflavin)
- Vitamin $B_3$ or Vitamin P or Vitamin PP (niacin)
- Vitamin $B_5$ (panthotenic acid)
- Vitamin $B_6$ (pyridoxine and pyridoxamine)
- Vitamin $B_7$ or Vitamin H (biotin)
- Vitamin $B_9$ or Vitamin M and Vitamin B-c (folic acid)
- Vitamin $B_{12}$ (cobalamin)
**Vitamin B₁ (thiamine)**

- Thiamin has a central role in energy-yielding metabolism.
- Composed of a substituted pyridine and thiazole ring.
- Active form is thiamine diphosphate (thiamin pyrophosphate, TPP), a coenzyme for three multi-enzyme complex →
- This complex catalyses oxidative decarboxylation of α-ketoacids →
  - *pyruvate dehydrogenase* in carbohydrate metabolism,
  - *α-ketoglutarate dehydrogenase* → cytric acid cycle,
  - *Branched-chain keto-acid dehydrogenase* .
- TPP is coenzyme for *transketolase* – pentose phosphate pathway.
Vitamin B₁ - deficiency

1. Mild deficiency – leads to gastrointestinal complaints, weakness
2. Moderate deficiency - peripheral neuropathy, mental abnormalities, ataxia
3. Full-blown deficiency - beri-beri – characterized with severe muscle weakness, muscle wasting and delirium, paresis of the eye muscles, memory loss.
   - Degeneration of the cardiovascular system.

- Beri-beri causes long-term consumption of foods rich in carbohydrates but poor in thiamine - husked rice, white flour and refined sugar.
Source of vitamin B₁

- paddy grains, cereals
- meat
- yeast
- honey
- nuts
Vitamin B₂ (riboflavin)

- Yellow to orange-yellow natural dye slightly soluble in water.
- Has a central role in energy-yielding metabolism.
- Provides the reactive moieties of the coenzymes *flavin mononucleotide (FMN)* and *flavin adenine dinucleotide (FAD)*.
- Flavin coenzymes are electron carries in oxidoreduction reaction.
Vitamin $B_2$

F MN → ATP-dependent phosphorylation of riboflavin

F AD → further reaction with ATP in which its AMP moiety is transferred to F MN.
FMN a FAD function

FMN and FAD act as prosthetic groups of many oxidoreduction enzymes, flavoprotein:

- *oxydase of α-amino acids* – degradation of amino acids
- *xantinoxidase* – degradation of purines
- *aldehyde dehydrogenases*
- mitochondrial *glycerol-3-phosphate dehydrogenase* – transport of reducing unit (H⁺) from mitochondria to cytosol
- *succinate dehydrogenases* – citric acid cycle
- *succinyl CoA-dehydrogenase* – β-oxidation of FA
- *NADH-dehydrogenase* – part of respiratory chain in mitochondria
- coenzymes in hydrogen transfer – formation of reducing forms - FMNH₂ a FADH₂
Vitamin B$_2$ absorption

- Riboflavin is absorbed in the proximal intestine.

- Riboflavin is stored mainly in the liver, kidney and heart in the form of FAD (70-90%) or FMN.
Causes of vitamin B$_2$ deficiency

- Lack of dietary vitamin B.
- A result of conditions that affect absorption in the intestine.
- The body not being able to use the vitamin.
- An increase in the excretion of the vitamin from the body.
Vitamin B₂ – symptoms of deficiency

- Cracked and red lips.
- Inflammation of the lining of mouth and tongue.
- Dry and scaling skin- keratitis, dermatitis and iron-deficiency anemia
Sources of vitamin B₂

- foods of animal origin (liver, pork and beef, milk, dairy products, fish eggs)
- cocoa,
- nuts,
- yeast,
- of smaller quantities in cereals.

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Vitamin B₃ - niacin

- Active form – nikotinic acid and nikotinamid.
- NAD a NADP → key components of the metabolic pathways of carbohydrates, lipids, amino acids.
- Nicotinic acid prevents the release of fatty acids from adipose tissue, decreases lipoproteins VLDL, IDL a LDL.
- High dose of niacin dilates blood vessels.
Vitamin B₃ - niacin

- Absorption:
  - At low concentration by active transport.
  - At high concentration by passive diffusion.

- Transportation:
  - Both nicotinic acid (NA) and nicotinamide (NAm) bind to plasma proteins for transportation.

- Biosynthesis:
  - The liver can synthesize *Niacin* from the essential amino acid *tryptophan*, but the synthesis is extremely slow and requires vitamin B₆ (60 mg of Tryptophan = 1mg of niacin). Bacteria in the gut may also perform the conversion but are inefficient.
Vitamin B₃ - deficiency

- **Pellagra**: A serious deficiency of niacin.
- The main results of pellagra can easily be remembered as "the four D's": diarrhea, dermatitis, dementia, and death.
- Pelagra is very rare now, except in alcoholics, strict vegetarians, and people in areas of the world with very poor nutrition.

- Milder deficiencies of niacin can cause dermatitis around the mouth and rashes, fatigue, irritability, poor appetite, indigestion, diarrhea, headache.
Sources of vitamin $\text{B}_3$

- foods of animal origin
- yeast
- sunflower seeds, beans, peas
- green leafy vegetable
- broccoli, carrots

[Image: Food sources of Niacin (vitamin B3) include dairy, poultry, fish, lean meat, nuts and eggs.](http://health.allrefer.com/health/nutrition.html)
Vitamin B$_5$ – panthotenic acid

- Part of acetyl-CoA – consists of pantoic acid and $\beta$-alaninem

\[
\text{Pantothenic acid} \quad \text{acetyl group} \quad \text{pantothenic acid}
\]

Acetyl coenzyme A, showing its constituents
Vitamin B₅ — panthotenic acid

- Co-enzyme A assists the following reactions:
  - formation of sterols (cholesterol and 7-dehydrocholesterol).
  - formation of fatty acids.
  - formation of keto acids such as pyruvic acid.

Other reactions are acylation, acetylation, signal transduction, deamination.
Vitamin $B_5$ - deficiency

Rare to occur.

- When occur it leads to paresthesias.

- Disorders of the synthesis of acetylcholine – neurological symptoms (paresthesia).
Sources of vitamin $B_5$

- meat, foods of animal origin,
- yeast,
- wholemeal bread,
- broccoli, avocado
- royal gelly
Vitamin $B_6$

- Prekursor of active coenzyme pyridoxal phosphate – PPL.
Vitamin B₆

- Vitamin B₆ is needed for more than 100 enzymes involved in protein metabolism.
- It is also essential for red blood cell metabolism and hemoglobin formation.
- The nervous and immune systems need vitamin B₆ to function efficiently.
- It is also needed for the conversion of tryptophan to niacin (vitamin B₃).
- Vitamin B₆ also helps maintain blood glucose within a normal range. When caloric intake is low, vitamin B₆ helps to convert stored carbohydrate or other nutrients to glucose to maintain normal blood sugar levels.
Transamination reaction
Vitamin B₆ deficiency

Signs of vitamin B₆ deficiency include:

- **Skin:** dermatitis (skin inflammation), stomatitis (inflammation of the mucous lining of any of the structures in the mouth), glossitis (inflammation or infection of the tongue).
- **Neurological abnormalities:** Depression, confusion, and convulsions.
- Vitamin B₆ deficiency also can cause anemia.
Vitamin B₆ – natural sources

- cereals,
- beans,
- meat,
- liver,
- fish,
- yeast,
- nuts and some fruits as banana
- potatoes.
- It is also produced by bacterial flora in the colon.
Vitamin B₇ - biotin

- Prosthetic group of *pyruvate carboxylase*, *acetyl-CoA carboxylase* and other *ATP-dependent carboxylases*.

![Biotin molecule](image)
Biotin – natural source

- liver
- meat
- kidney
- yeast
- egg yolk
- mushrooms
- milk and diary products.
Vitamin B₉ – folic acid

- Consist of pteroic acid - pteridine + paraaminobenzoic acid (PABA) + glutamic acid

Pteroyl-monoglutamate (the absorbed form of folic acid)
Vitamin B₉ – folic acid

- Active metabolite of folic acid is tetrahydrofolate (THF).
- THF is coenzyme of transferases carrying one carbon unit.
- This reaction participates in nucleotide and nucleic acid synthesis.
- \(N^5,N^{10}\)-THF carries one carbon unit (methylene or methenyl).
Folic acid deficiency

Deficiency results in elevated levels of homocystein.

Deficiency in pregnant women can lead to birth defects.
Sources of vitamin B₉

- sources of animal origin
- milk and milk products
- yeast
- greens
Vitamin B\textsubscript{12} - cobalamin

- Chemically most complex vitamin
- Complex of organic compounds atom within the molecule is Co, similar to the heme.
- In man there are two metabolically active forms: methylkobalamin and adenosylkobalamin.
Vitamin B$_{12}$ - cobalamin

- Cobalamin catalyses two reactions
  - Cytoplasmic *methylation of homocystein to methionin*.
  - Mitochondrial *methylmalonyl-CoA mutase* (methylmalonyl-CoA $\rightarrow$ sukcynyl-CoA) needs *deoxy adenosylkobalamin*. 
Vitamin $\text{B}_{12}$ – cobalamin

- Essential for the maturation of erythrocytes.
- Protects against pernicious anemia.
- Essential for cell growth and reproduction.
- Essential for the formation of myelin and nucleoproteins.
Vitamin $B_{12}$ – cobalamin

- Vitamin $B_{12}$ in food is bound to the protein.

- Hydrochloric acid in the stomach releases free vitamin $B_{12}$.

- Once released vitamin $B_{12}$ combines with a substance called intrinsic factor (IF). This complex can then be absorbed by the intestinal tract.
Sources of vitamin $B_{12}$

- fish and shellfish,
- meat (especially liver),
- poultry,
- eggs,
- milk, and
- milk products

while lacto-ovo vegetarians usually get enough $B_{12}$ through consuming diary products, vegan will lack $B_{12}$
Vitamin C

- Vitamin C is a water-soluble vitamin.

- Almost all animals and plants synthesize their own vitamin C, not man.

- Vitamin C was first isolated in 1928 and in 1932 it was proved to be the agent which prevents scurvy.
Vitamin C

- Vitamin C is a weak acid, called ascorbic acid or its salts “ascorbates”.

- It is the L-enantiomer of ascorbic acid.

- The D-enantiomer shows no biological activity.
The role of vitamin C

- Cofactor in the synthesis of norepinephrine from dopamine.

- Involved in a variety of metabolic processes (oxidation-reduction reactions and cellular respiration, carbohydrate metabolism, synthesis of lipids and proteins).

- Antioxidant and free radical scavenger → maintain proper immune system.
The role of vitamin C

- T-lymphocyte activity, phagocyte function, leukocyte mobility, and possibly antibody and interferon production seem to be increased by vitamin C.

- Involved in the synthesis of collagen, the major component of ligaments, tendons, cartilages and skin.

- Involved in tyrosine metabolism.
Deficiency of vitamin C

- Fatigue, personality changes, decline in psychomotor performance and motivation.

- Vitamin C deficiency over 3-5 months results in *symptomatic scurvy*.

- Scurvy leads to the formation of liver spots on the skin, spongy gums, and bleeding from all mucous membranes.

- In advanced scurvy there are open, suppurating wounds and loss of teeth. Severe scurvy may progress to neuritis, jaundice, fever, dyspnea, and death.
Vitamin C as antioxidant

Alpha Tocopherol (Vitamin E)

(Lipid Free Radicals)

Tocopheroxyl Free Radical (Oxidized Vitamin E)

Ascorbate

Monodehydroascorbate (semidehydroascorbate)

Dehydroascorbate
Vitamin C as antioxidant

\[ \text{ascorbate (Vitamin C)} \rightarrow \text{dehydroascorbate (oxidized Vitamin C)} \rightarrow \text{GSH (reduced glutathione)} \rightarrow \text{GSSG (oxidized glutathione)} \rightarrow \text{dehydroascorbate reductase} \rightarrow \text{ascorbate (Vitamin C)} \]

(R*) (Free Radical)
Vitamin C as pro-oxidant

- Ascorbic acid reduces transition metals - Cu^{2+}, to Cu^+, and Fe^{3+} to Fe^{2+} during conversion from ascorbate to dehydroascorbate. This reaction can generate superoxide and other ROS:

  - Fenton’s reaction:
    1. \( Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^- \)
    2. \( Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OOH^- + H^+ \)

\[ 2 \text{Fe}^{2+} + 2 \text{H}_2\text{O}_2 \rightarrow 2 \text{Fe}^{3+} + 2 \text{OH}^- + 2 \text{OH}^- \]
\[ 2 \text{Fe}^{3+} + \text{ascorbate} \rightarrow 2 \text{Fe}^{2+} + \text{dehydroascorbate} \]