

Schedule of biochemical lectures
Faculty of Pharmacy, 2nd year

Definition and scope of biochemistry

Bioenergetics – Living organism is thermodynamically an open system

Definition of the open system

equilibrium state in biological systems, steady state condition

definition of- enthalpy, entropy, Gibbs free energy

endergonic processes

exergonic processes

role of high energy compounds, macroergic bond, examples for high-energy compounds

central role of ATP

Protein structure

1. Functions of proteins in the organism

2. Protein composition/structure

-amino acids

-formation of peptide bond

* release of water

* alfa carbon atom

* linear chain without branches

- conformation - proper spatial structure for enzyme function

- secondary bonds stabilizing conformation

* exception: disulfide links at Cys residues

* van der Waals interaction

* H bond

- rotation at the peptide bond

- secondary structures

* α -helix

* β -sheet

* random structure

3. Protein conformation

- primary

- secondary

- tertiary

* three dimensional

* determines the characteristics of the protein

- quaternary

- * linkage of several polypeptide chains
- * formation of dimers, tetramers, polymers
- importance of folding

Enzymes

1. Enzymatic action

- catalyzators, biological catalyzators, biocatalyzators
 - a/ materials catalysing access/joining
 - * ensuring proper surface
 - * protein surface: proper orientation, great concentration - speed increases
 - b/ side chains of proteins actively participate in the reaction
 - * separation of charges
 - * catching the substrate temporarily
 - * proper orientation
- binding the active intermediate - not substrate specific!

2. Models

- a/ lock and key model (Emil Fischer)
- b/ induced fit model
 - the real template is produced when the substrate is approaching
 - it can be highly regulated - negative and positive feed back

3. Coenzymes

- role: transfer of energy, charge or acyl group
- role of NAD, FAD, NADP and CoA (derivatives of ADP)
- vitamins - water- and fat-soluble

4. Classification of enzymes

- a/ trivial names
- b/ International Union of Biochemists (IUB)
 - oxidoreductases
 - transferases
 - hydrolyses
 - lyases
 - isomerases
 - ligases

5. Isoenzymes, their clinical importance

6. Units of enzyme activity

- international (standard) unit (IU)
- catal
- specific activity, molar activity

7. Definition of multienzyme complexes

Enzyme kinetics

1. Role of enzymes during catalysis

- reduction of activation energy
- speeding up the approach of the equilibrium state

2. Steady state

- the speed of the enzyme reaction depends on the substrate concentration
- Michaelis-Menten equation
- Briggs-Haldane equation
- definition/determination of v_{\max} and v
- definition/determination of K_M

3. Order and conditions of reactions

- first order
- second order
- pseudo first order
- zero order kinetics

4. Kinetics of inhibition

- competitive
- non-competitive
- uncompetitive

Principles of regulation of metabolic pathways

- committed step
- rate-limiting step, key enzyme
- negative feedback

Regulation of enzymatic reactions (definition and example for each mode)

- compartmentalization
- regulation of enzyme quantity (induction and repression)
- allosteric regulation
- covalent modification
 - phosphorylation
 - limited proteolysis

CARBOHYDRATES

Chemistry and biochemical importance

- monosaccharides (C3-C7); aldoses, ketoses
- stereoisomerism (L and D epimers, α and β anomers)
- furanose, pyranose ring structures
- derivatives of monosaccharides
- disaccharides
- polysaccharides

Digestion and absorption

- carbohydrates in food
- action of digestive enzymes
- absorption and types of transport
- GLUT transporters, types and characterization, insulin dependence!

Normal blood glucose level, **hypo- and hyperglycemia**

Glycolysis

- steps, names of the intermediates, structures!!, names of the enzymes, cofactors, irreversible steps, ATP formation on the substrate level!!, total ATP yield
- comparison of hexo- and glucokinase
- comparison of the aerobic and anaerobic degradation of glucose
- pyruvate dehydrogenase enzyme complex
- regulation

Gluconeogenesis

- steps, especially the 3 irreversible steps (names and structures! of intermediates, enzyme names, cofactors, intracellular localization)
- role, source / precursors
- regulation (allosteric and hormonal), ATP requirement

Glycogen

- its role, characterization of stores
- synthesis and degradation (structures, enzymes, coenzymes)
- regulation of synthesis and degradation, role of hormones and allosteric regulation
- Adaptation (regulation of blood glucose level)

Interconversion of hexoses (6-phosphate forms)

Pentose phosphate pathway (HMP-shunt)

- steps with enzymes, coenzymes and intermediates; hexose part with structures

- importance
- regulation of phases depending on NADPH/ribose requirement

Rappaport-Liebering-shunt

- formation of 2,3 DPG (2,3-bisphosphoglycerate) and its importance in RBC

Special fate of glucose in tissues and organs

- RBC, brain, liver, muscle, adipose cells

Relationship between the carbohydrate metabolism and other metabolisms:

synthesis of amino acids:	glycerol phosphate - serine pyruvate - alanine oxaloacetate - aspartic acid
fatty acid biosynthesis:	source of NADPH + H ⁺
triacylglycerol synthesis:	the role of glycerol phosphate in the adipose tissue
citric acid cycle	pyruvate - acetyl-CoA
nucleotide synthesis	source of ribose-5-phosphate

LIPIDS

Chemistry, classification

Fatty acid derivatives

- glycerides
 - triacylglycerols
 - phospholipids
- sphingolipids

Isoprene derivatives

- steroids
- ubiquinone, dolichol

Common saturated and unsaturated fatty acids, essential fatty acids,

Eicosanoids

- groups, main effects
- their formation from membrane phospholipids (role of PLA₂) and from essential fatty acids
- importance of EPA and DHA
- substances influencing the formation of eicosanoids (especially steroid and non-steroid anti-inflammatory drugs /NSAID, SAID/)

Digestion and absorption of lipids

- lipases, colipase, phospholipase; their activation; cholesteryl ester hydrolase
- role of bile acids
- absorption

Metabolism of lipoproteins

- classification and characterization of lipoproteins
- metabolism of lipoproteins

Lipid mobilization

- characterization of the lipid stores
- phases of lipid mobilization, cases of increased lipid mobilization
- regulation of TG lipase, fate of glycerol

Oxidation of fatty acids

- β -oxidation in detail (localization, phases, carnitine-dependent transport, formulae, enzymes, coenzymes, energy yield)

Synthesis of fatty acids

- „de novo” synthesis in detail (localization, formulae, enzymes, coenzymes, function of the fatty acid synthase multienzyme complex, regulation of the key step, adaptive regulation, importance of ATP-citrate lyase and malate-citrate transporter, sources of NADPH)

Synthesis of triacylglycerols and phospholipids

- steps of TG and phospholipid synthesis (formulae, coenzymes)
- importance of TG and phospholipid synthesis

Metabolism of ketone bodies

- ketogenesis (localization, steps, enzymes, coenzymes, formulae)
- utilization of ketone bodies (localization, main route, cofactor, enzyme)
- circumstances and biochemical background of increased ketogenesis

Steroid metabolism

- cholesterol synthesis (localization, steps /till active isoprenoids with formulae/, cofactors, energy requirement, regulation of the key enzyme, drugs affecting the cholesterol metabolism, regulation at the cellular/tissue level, esterification in the cell and in the blood, structure of cholesterol)
- metabolism of bile acids (importance, main steps of the synthesis, primary and secondary bile acids, cofactors of the key enzyme and its regulation, enterohepatic circulation, composition of bile)
- other bioactive cholesterol derivatives: pathways of steroid hormone synthesis, localization, elimination of steroid hormones; synthesis of vitamin D₃ vitamin, activation, importance of calcitriol

Amino acid metabolism

1. Classification of amino acids (essential - , non essential - , semiessential amino acids)
2. Removal of amino acid nitrogen:
 - transamination
 - oxidative deamination
 - direct deamination
3. The role of glutamine in the transport of ammonia
4. Detoxification of amino acid nitrogen (the main steps of the urea cycle)
5. The fate of the carbon skeleton of amino acids (definition of glucogenic and ketogenic amino acids)
6. Conversion of amino acids to pyruvate
 - to oxaloacetate
 - to alfa - ketoglutarate
 - to fumarate
 - to acetoacetyl - CoA, acetyl - CoA
 - to succinyl - CoA
7. Utilization of amino acids in:
 - energy generation (points of entry of the carbon from the amino acids into the TCA cycle)
 - synthesis of lipid and cholesterol (acetyl - CoA)
 - synthesis of glucose (pyruvate, oxaloacetate)
 - synthesis of coenzymes (SAM, NAD)
 - synthesis of neurotransmitters and hormones (histamine, serotonin, GABA, DOPA, norepinephrine, epinephrine, thyroxine, triiodothyronine)
 - porphyrine synthesis
 - purine synthesis
 - the synthesis of other compounds (creatine, taurine)

Nucleotide metabolism

1. Chemical characterization of nucleic bases (purine - , pyrimidine bases)
2. Participation of nucleotides in the metabolism:
 - energy storage (central role of ATP)
 - nucleotide units for DNA synthesis
 - nucleotide units for RNA synthesis
 - components of cofactors (NAD, FAD)
 - intracellular second messengers (cAMP, cGMP)
 - synthesis of activated intermediates (UDP - glucose, CDP - choline, CDP - diacylglycerol, GDP - mannose)
 - allosteric effectors

3. Some aspects of nucleotide metabolism:
- de novo synthesis of purine nucleotides
 - purine salvage mechanisms
 - degradation of purin bases
 - synthesis of pyrimidine nucleotide
 - pyrimidin salvage mechanisms
 - degradation of pyrimidine bases

4. Drugs influencing nucleotide metabolism

Citric acid cycle, terminal oxidation and oxidative phosphorylation (3 hours)

1. Citric acid cycle as the central pool of the intermediate metabolism
 - The main steps of the discovery of the TCA cycle; role of Albert Szent-Györgyi
 - Localization of the TCA cycle, steps, energy balance
 - Main entry and exit points in the cycle, anaplerotic reactions
 - Regulation of the cycle, its dependence on the general energy balance of the cell
2. Definition of terminal oxidation, redox systems in the organism
 - Thermodynamic characterization of redox reactions
 - Energy balance of NADH and FADH oxidation
 - The structure of mitochondria, mitochondrial transport systems
 - Steps of terminal oxidation (complex I-IV, coenzyme Q, cytochrome c)
 - Vectorial character of proton transport, the process of electron transport, functional groups of redox systems
3. Oxidative phosphorylation
 - Definition and mechanism of oxidative phosphorylation
 - The chemiosmotic theory
 - Structure and function of F_1F_0 ATPase
 - Steps of ATP synthesis in terminal oxidation, their efficacy
 - Action of uncoupling substances
 - Brown adipose tissue and its role in thermoregulation

Biochemical characteristics of the connective tissue and the cytoskeleton

Main components:

1. Fibrillar proteins (collagen, elastin, fibrillin)
2. Proteoglycans (core protein, glycosaminoglycans)
3. Adhesive glycoproteins (fibronectin, laminin, tenascin etc.)

Connective tissue, cytoskeleton, extracellular matrix

Main components: 1. Fibrillar proteins (collagen, elastin, fibrillin)
 2. Proteoglykans (coreprotein, GAG)
 3. Adhesive glycoproteins

1. Fibrillar proteins

Collagen:

synthesis: Preprocollagen - hydroxylation, glycosylation - formation of alfa superhelix (hsp 47) - procollagen -secretion - N- and C-terminal peptidases - tropocollagen - arrangement of fibres - maturation-aging, formation of cross-links (Lys oxidase) aldol condensation, Schiff base

Collagen types:

fibrillar collagens (skin, bone, cartilage, reticular fibre, cell surface)
 facit collagens: IX, XII (fibrillar collagen arrangement)
 basal membrane collagens: IV, VIII (transparency of cornea)
 short collagen
 long collagen: VII (epidermolysis bullosa)
 collagens with non-collagen functions

Elastin:

synthesis - proelastin - loose structure - beta helix formed from beta sheets
 cross-links between 4 chains (1 Lys + 3 Lys aldehydes), desmosin, isodesmosin

Fibrillin:

2 genes: 5. and 15. chromosomes
 component of microfibrils at the periphery of the elastic fibres

2. Proteoglycans

Characterisation

classification

GAG types:

hyaluronic acid
 chondroitin sulfate
 dermatan sulfate
 heparan sulfate + heparin
 keratan sulfate

New classification according to core protein:

1. Great aggregating proteoglycans
 - aggrecan - chondrocyte
 - versican - fibroblast
 - perlecan - epithel, endothel, BM
- domain structure: HABD, GAG-BD, EGF, lectin, complement regulating
2. Small, Leu-rich proteoglycans: fibromodulin, decorin

3. Membrane-bound proteoglycans:
 a/ transmembran PG: syndecan, fibroglycan
 b/ GPI-bound PG: glipican

3. Adhesive glycoproteins

glycoproteins with several different binding domains

1. fibronectin

440 kD (2 x 220 kD -S-S-)

size is 2-fold of that of tropocollagen

cca. 50 exons, mostly duplication -- repeating 4-5 moduls

domains: fibrin-, collagen-, RGD-, heparin-binding sites

(RGD= --Arg-Gly-Asp---Ser)

integrin - transmembrane protein - linked to actin

2. laminin

main component of the BM, adhesive protein

800-1 000 kD, 3 chains

cross-shaped molecule composed from $\alpha\beta\gamma$ chains

high affinity to collagen type IV

domains: polymerization, cell-binding (integrin receptors), dystroglycan-binding, entactin/nidogen-binding etc.

7 types

their role in the control of cell differentiation: s-laminin - inhibits axon growth, induces agrin-AchR aggregation - phosphorylation of the receptor results in stabilization - formation of the motor endplate

3. tenascin

embryonic differentiation

4. nidogen/entactin:

important component of the basal membrane; its role in filtration in the kidney

Tyr-sulfate

4. Adhesive receptors

Integrins (receptors)

their role in the reorganization of the cytoskeleton following activation

5. Cytoskeleton

- Microfilaments
- Intermedier filaments
- Microtubules

Biochemistry of membranes

1. Structure of biological membranes, fluid mosaic model

Composition of membrane lipids, their localization in the membrane

The role of lipids in the maintenance of membrane fluidity, adaptation of membranes to changes in temperature

The role of cholesterol in biological membranes
 Dynamism of membrane lipids, rotation, flip flop, lateral movement
 Interactions between lipids and proteins; definition of annular and bulk lipid

2. Membrane proteins and transport systems

Classification of membrane proteins, extra-, intra- and transmembrane proteins
 Dynamism of membrane proteins, rotation, lateral mobility, its role, experimental techniques
 Modes of transport, transport of lipid soluble materials, structure and function of ionophores, channels, active transport
 General structure of channel-forming proteins
 Classification of channels, according to gating mechanism: voltage-, ligand-, stretch-gated channels, examples
 Active transport systems: P type, F_1F_0 type, V type ATPases, structures and functions

Biochemistry of contractile tissues (2 hours)

1. Types of contractile tissues

Structure and components of the skeletal muscle
 Structure and function of the contractile system, sliding filament theory
 Characteristics of myosin, composition of thick filament
 Components of the thin filament: actin, tropomyosin, troponin complex
 Formation and dissociation of the actin myosin complex, cross-bridge cycling, the role of ATP, ADP+Pi
 Regulatory role of the troponin complex
 Main processes generating energy for muscle contraction

2. Regulation of muscle contraction by calcium

Extra- and intracellular membrane systems of the muscle fibre, role of volume-surface ratio
 Connection of the T tubule and the junctional SR
 Structure and function of the dihydropyridine receptor and the ryanodin receptor
 Mechanism of calcium release
 in heart muscle: calcium induced calcium release
 in skeletal muscle: intramembrane charge movement
 Structure and function of sarcoplasmic reticulum calcium ATPase

Chemical composition and metabolism of the neural tissue

Composition: 40-80 % lipid, cholesterol (25 % of the amount in the organism)
 20-60 % protein (turnover is fast - 80 hours on average)

Main characteristics:

- no energy store (fat, glycogen)
- main glucose consumer of the organism (60 % of the total glucose), its use for ATP and neurotransmitter synthesis
- in the absence of glucose ketone bodies but not fatty acids are metabolized

Blood-brain barrier

Lipids: synthesis of phospho- and sphingolipids in situ

Amino acids: 8-10-fold more are free as pool (75% are Glu and Asp, the rest are mainly glutathion, cystathion and taurine (the functions of these last ones are not known)

Many ketoacid: oxalacetate, α -ketoglutarate (used for NH_4^+ detoxification)

Nucleotides: purines but not pyrimidines are synthesised (there is no carbamoyl-P-synthetase)

Characteristic proteins: S-100 - sclerosis multiplex, appican (amyloid precursor protein) - Alzheimer - disease; neuron-specific enolase - tumor diagnostics

Synthesis, storage, excretion and inactivation of neurotransmitters:

1. Acetylcholine:

synthesis:

Ser -- decarboxylation -- choline + 3 SAAM -- choline

choline + acetyl CoA ---acetylcholine + CoA

stored in the presynaptic vesicles (10-60 000/vesicle) together with ATP

effect: on nicotinic and muscarinic type acetylcholine receptors

neurotoxins: receptor inhibitors - cobra toxin, d-tubocurarine

breakdown: acetylcholine esterase

types of acetylcholine esterase, inhibitors, organic phosphate esters, pesticides

2. Catecholamines:

synthesis: sympathetic nerve terminals + adrenal medulla

Tyr -- dihydroxy-phenylalanin (DOPA) -- decarboxylase -- dopamine

oxidation -- norepinephrine -- SAM -- epinephrin

Parkinson's disease

secretion: to the serum via sympathetic terminals innervating smooth muscle

effect: via receptors (α - and β -adrenergic receptors)

inactivation: through methylation of phenyl-3-OH, COMT (astroglia)

MAO - NH_4^+ cleavage in addition to formation of COOH group -

3,4-dihydroxyphenylglycolaldehyde is produced

3. GABA:

synthesis: astroglia - neuron cooperation

glutamate -- decarboxylase -- GABA

effect: via GABA-receptors (Cl^- channel) - inhibitory neurons

inactivation: transamination

GABA -- succinate semialdehyde -- succinate

4. Serotonine

synthesis:

Trp --hydroxylation on the 5th carbon atom -- decarboxylase --

5-hydroxytryptamine (serotonine)

effect: vasoconstrictor + neurotransmitter of the smooth muscle of the intestine

inactivation: MAO --- NH_4^+ + 5-hydroxyindolacetate

5. Histamine

synthesis: His -- decarboxylase -- histamine

effect: vasodilator, stimulates HCl secretion, mast cells also produce it (allergy)

6. Glutamate

synthesis: astroglia (Glu) neuron interaction

receptors: ionotrop - ion channels (NMDA, AMPA)
 metabotrop - G- protein - adenylate cyclase
 their role (learning processes)
 receptor desensitization - phosphorylation

Biochemistry of the blood

RED BLOOD CELLS

- Special metabolism of red blood cells (metabolic pathways – glycolysis, HMP shunt, GLUT transporter, ATP synthesis and usage, fate of lactate)
- Role of glutathione
- Iron metabolism
- Oxygen transport of hemoglobin (Hb types)
- Factors influencing oxygen binding capacity of hemoglobin
- Synthesis of heme group
- Degradation of heme group

PLASMA PROTEINS

- Serum protein electrophoresis
- Fractions of plasma proteins
- Serum total protein concentration-significance of decreased serum level
- Proteins: albumin
 alfa-1-antitripsin
 ceruloplasmin
 alfa-2-macroglobulin
 transferrin
 ferritin
 fibrinogen
 lipoproteins

WHITE BLOOD CELLS

- Classification of leukocytes
- Special metabolism of neutrophil granulocytes
- Oxidant and antioxidant factors and mechanisms
- Killing mechanisms of neutrophil granulocytes
- Respiratory burst in neutrophil granulocytes

BLOOD CLOTTING-COAGULATION CASCADE

- Characterization of platelets and their role in blood clotting
- Coagulation factors
- Vitamin K dependent factors
- Intrinsic and extrinsic pathways of coagulation cascade
- Inhibitors of coagulation
- Fibrinolysis

Biochemistry of the liver and biotransformation

1. Structure of liver and its microcirculation system

Metabolic pathways in liver, and their localization

Role of liver in carbohydrate and in protein/amino acid metabolism

Role of liver in lipid metabolism, mechanism fat liver formation

Role of liver in steroid metabolism, synthesis and role of bile acids

Formation and turnover of bile pigments

Role of liver in the metabolism of ions and vitamins

2. Biotransformation

Aim and phases of biotransformation

Reactions of the first phase, structure and function of cytochrome P450

Reactions of the second phase, conjugation systems

Removal of the biotransformation products

Induction of the biotransformation system

Interaction of xenogen materials, biochemical mechanism of addiction

3. Biochemical effects of alcohols

Metabolic pathways of alcohol

The effect of ethanol on cell metabolism, acute and chronic effects

Fate of methanol in the organism, effects

Effects of long chain and multivalent alcohols

Biochemical consequences of liver insufficiency

Biochemistry of nutrition

1. Makronutrients
 - Proteins, carbohydrates, lipids
 - Daily requirement (quality and quantity)
2. Dietary fibers
 - Types
 - Diet rich in fibers
3. mikronutrients
 - vitamins
 - minerals

Biochemistry of hormones

1. Chemical and biochemical classification of hormones
 - Classification of hormones according to action
 - Hormones of the hypothalamic- hypophyseal system
 - The somatomammotrop family and its biochemical effects
 - The glycoprotein family and its biochemical effects
 - POMC gene products and biochemical effects
 - Biochemistry of the neurohypophyseal system
2. Biochemistry of thyroid and parathyroid hormones
 - Mechanism of thyroid hormone production
 - Iodine turnover of the organism
 - Role of plasma proteins in the biological effect of thyroid hormones
 - Transport of T3, T4 and iodine, metabolic effects
 - Gene regulatory effects of thyroid hormones
 - Regulation of extracellular calcium
 - Action of the parathyroid hormone (biochemical mechanism)
 - Factors influencing extracellular ionized calcium level
3. Hormonal regulation of blood glucose level
 - Structure and synthesis of insulin
 - Effect of insulin on the intermediate metabolism
 - Insulin receptor: structure and function; somatomedins
 - Early metabolic consequences of diabetes mellitus
 - Pathobiochemical basis for late complications of diabetes mellitus
 - Pathobiochemical and diagnostic significance of protein glycosylation
4. Biochemistry of steroid hormones
 - Biosynthetic pathways, enzymes and compartmentalization of steroid hormones
 - Important metabolites of the different steroid groups
 - Action of steroid hormones, steroid receptors
 - Metabolic effects of steroid hormones

Regulation of gene expression

The structure of DNA, the structure of chromosome, euchromatin, heterochromatin, regulation of transcription, enhancer, silencer, the difference between prokaryotic and eukaryotic gene expression.

Histones and their function, nonhistone proteins, regulation of replication of the eukaryotic cell: exit from G₀ phase, protooncogenes, cytokines, tumor suppressor genes.

Repair mechanisms, tumorous cell proliferation, apoptosis, tumor sensitivity of knock out mutants of the p53 gene.

The structure of eukaryotic genes, exon, intron, splicing, coding and noncoding fragments, classification of genomic sequences by repetitive character, IRE and UTR RNA types, RNA polymerases, the transcription process, maturation of mRNA, the mechanism of splicing, tissue specific and developmental dependent splicing, thalasemias, antisense RNA.

Transcription factors, HLH proteins, Zn-finger proteins, Leu-zipper, intracellular hormone receptors, fos and jun proteins, p53, hox proteins, the connection of transcription and the chromatin structure.

The mechanism of prokaryotic translation, the initiation complex, the three steps of elongation; termination, the signal peptide and signal recognition particle

Second messenger system

General principles of biochemical regulation, adaptation, limits of adaptation

1. Signalling systems

- Intracellular calcium as second messenger
- Factors influencing intracellular calcium level
- Calcium transport systems, intracellular transport stores
- IP₃ as calcium release signal
- Structure and function of calcium-binding proteins

2. Cyclic nucleotide dependent signalling systems

- Structure, types and function of G proteins
- Effect of cholera and pertussis toxin
- ADP ribosylation
- Adenylate and guanylate cyclase systems
- Role of phosphodiesterase in the cyclic nucleotide dependent signalization

3. Phosphorylation and dephosphorylation as regulation mechanisms

- Types and function of protein kinases
- Role of protein phosphatases in signalization
- Phosphorylation and dephosphorylation cascades, their role in the coordinated regulation of physiological functions of the organism

4. General principles of biochemical regulation

- Theoretical differences of control and regulation

Behaviour of open equilibrium systems

Definitions of normal value, normal intervallum

Biochemical adaptation, loading tests

Adaptation on the level of the individual, species, animal kingdom; biochemical evolution

Limits of adaptation, biochemical interpretation of illness, role of drugs in the extension of the limits of biochemical adaptation

Thermodynamic interpretation of death