Human Metabolism

1. Manual

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PRINCIPLES BEHIND THE MAIN MAP

1. Comprises only the *human* metabolism.
2. The size of the individual maps is A3, suitable for study at the desk.
3. Reactions are shown by ⟶ or ⟷. The second arrow indicates that the equilibrium constant is fairly close to 1.
   Substrates and/or coenzymes (also substrates) are indicated with the following symbols: ⟶ or ⟶
4. ⇄ indicates that two different enzymes are involved in the conversions in one direction and its opposite.
5. Anabolic sequences are in general shown by ascending arrows.
6. Catabolic sequences are in general shown by descending arrows.
7. Metabolic sequences with one or more less important metabolite(s) are shown as ⟶ (ATP)
8. ⟶ indicates that the coenzyme ATP donates orthophosphate whereby it is converted to ADP. The other reaction mechanisms of ATP, UTP, CTP are shown in full as

   ATP ⟶ PP or ATP ⟶ AMP

   For reactions involving NAD, NADP and FAD these coenzymes are shown on the reduced form. One exception is the reusage of NAD^+ at the glycolysis.
9. Pyridoxalphosphate-dependent transaminations and decarboxylations are shown as

   Pyridoxal-P ⟶ and Pyridoxal-P ⟶ CO_2,

   respectively. In other words the transaminations are simplified for topological reasons.
10. Reactions where cytochrom P 450 activates O_2 in hydroxylations are shown as P 450.
11. The numbers adjacent to the arrows refer to the ENZYMES map. Name, classification, regulation etc. can be found here.
12. The intention has been to minimize the crossing of arrows.
13. Whenever possible each of the metabolites is placed only at one spot. An exception to this rule is α-ketoglutarate.
14. End products of metabolism are intentionally placed at the borderline of the maps wherever possible.
15. Names of metabolites with acidic character refer to the anionic form (glutamate instead of glutamic acid).
16. Abbreviations, list of essential amino acids, inborn erros of metabolism, vitamins and hormones are given on this map.
17. The main chart has a coordinate system to which references are made from several of the other maps.
18. Valine, isoleucine and leucine are degraded in essentially the same way. Only the catabolism of leucin is shown. The oxidative decarboxylation (the second step) corresponds to the conversion of pyruvate to acetyl-CoA.
19. Formulas of the most important metabolites and the coenzymes are shown on the FORMULAS map.
20. For details of the subcellular localization of the metabolig processes see the CELLULAR LOCALIZATION map.
21. Inhibitors and hormones are the main topics on separate maps.

ABBREVIATIONS

ACP	Acyl carrier protein
AMP ADP ATP	Adenosine monophosphate di tri
~ CH_3	S-Adenosyl-methionine
CMP CDP CTP	Cytidine monophosphate di tri
CoA = HScoA	Coenzyme A
Cof.	Cofactor
C_1-THFA	C_1-Tetrahydrofolate
de	Deoxy
DHP	Dihydropteridine
DPG	Di-P-glycerate
FAD, $FADH_2$	Flavin adenine dinucleotide
FFA	Free fatty acids
FMN, $FMNH_2$	Flavin mononucleotide
GABA	ϒ-Amino- buturic acid
Gal	Galactose
$GluNH_2$ = gln	Glutamine
GMP GDP GTP	Guanosine monophosphate di tri
HSCoA = CoA	Coenzyme A
IMP	Inosine monophosphate
mRNA	Messenger RNA
$NAD(P)^+$	Nicotinamide adenine dinucleotide (phosphate)
Orn	Ornithine
P	Orthophosphate
P 450	Microsomal cytochrome P 450
PP	Pyrophosphate
rRNA	Ribosomal RNA
SAM	S-Adenosyl-methionine
THFA	Tetrahydrofolate
THP	Tetrahydropteridine
TMP TDP TTP	Thymidine monophosphate di tri
tRNA	Transfer RNA
TPP	Thiamine pyrophosphate
UMP UDP UTP	Uridine monophosphate di tri
XMP	Xanthosine monophosphate

INTERACTIONS BETWEEN THE MAPS

⟶ Main usage
⇢ Alternative usage

2. MAIN MAP
Presents central parts of the metabolism: metabolites, coenzymes and connecting arrows. For further information see elsewhere on this map.

3. ENZYMES
Lists 200 enzymes alphabetically. Each is given a number and a coordinate relating to the main map. Indicates the enzyme-MW, structure, coenzyme requirement, subcellular localization, inhibitors, regulation etc.

4. ENZYME CLASSIFICATION
Classifies the enzymes into 6 classes according to the international system. Shows the coenzymes and their role in the different type reactions. Indicates the role of the vitamins.

5. FORMULAS
Main map with formulas for metabolites and coenzymes instead of names as on main map. Shows the formulas of amino acids, essential amino acids and essential fatty acids.

6. METABOLITES
Main map showing only the metabolites. Is especially useful for self-testing.

7. MAIN PATHWAYS
Expands and explains the uptake and the breakdown of the food and the pathways and regulations involved.

8. OTHER PATHWAYS
TCA-cycle, biosynthesis and usage of ATP, purine and pyrimidine metabolism, phosphatid and cholesterol metabolism and pentose-phosphate-shunt.

9. INHIBITORS
Lists antimetabolites, toxins, pharmaca etc. and explains their role in metabolism.

10. CELLULAR LOCALIZATION
Short description of the mammalian cell and its organelles with main emphasis on biochemical markers.

11. HORMONES
Detailed map of the regulatory factors of hypothalamus and the products of the first and secondary targets. The hormonal regulation of metabolic sequences, the energy conversions and the mineral concentrations in the blood are shown.

ESSENTIAL AMINO ACIDS AND FATTY ACIDS

		Co-ordinate
Isoleucine	(ile)	(H6)
Leucine	(leu)	(F7)
Lysine	(lys)	(F7)
Methionine	(met)	(C8, G6)
Phenylalanine	(phe)	(D3, F7)
Threonine	(thr)	(H6)
Tryptophan	(trp)	(F7)
Valine	(val)	(H6)
Arginine*	(arg)	(F7)
Histidine**	(his)	(F7)

* Essential for growing children
** Essential, but requirement is not known exactly

Linolate	(C11)
Linolenate	(C11)

INBORN ERRORS OF METABOLISM

	See the ENZYMES map
Albinism	(no. 192)
Alcaptonuria	(no. 98)
Argininosuccinic acidemia	(no. 22)
Homocystinuria	(no. 42)
Lesch-Nyhan syndrome	(no. 108)
Maple syrup urine disease (occurs at decreased activity of the decarboxylating enzyme mentioned in "Principles" Part. 18)	
Methylmalonic acidemia	(no. 126)
Phenylketonuria	(no. 145)
Porphyrias	(no. 198)

VITAMINS

Ascorbinate	(C)	(G6)
Biotin	(B)	(D6, E8)
Cholecalciferol	(D_3)	F10)
Cobalamine	(B_{12})	(E4, G5)
Folate	(B)	(G6)
Lipoate	(B)	(H6)
Nicotinamide	(B)	H1)
Pantothenate	(B)	(H3)
Pyridoxine	(B_6)	(F2)
Riboflavine	(B_2)	(H2)
Thiamine	(B_1)	(B4, B5)

HORMONES etc.

Aldosterone	(E12)
Corticosterone	(E12)
Cortisol	(F11)
Cyclic AMP	(G2)
Dopamine	(D4)
Epinephrine	(E4)
Estradiol	(E10)
Estrone	(E11)
GABA	(F5)
Histamine	(F7)
Norepinephrine	(E4)
Progesterone	(F12)
Prostaglandins	(C12)
Serotonin	(E7)
Testosterone	(E10)
Thyroxine	(D4)

Human Metabolism

2. Main Map

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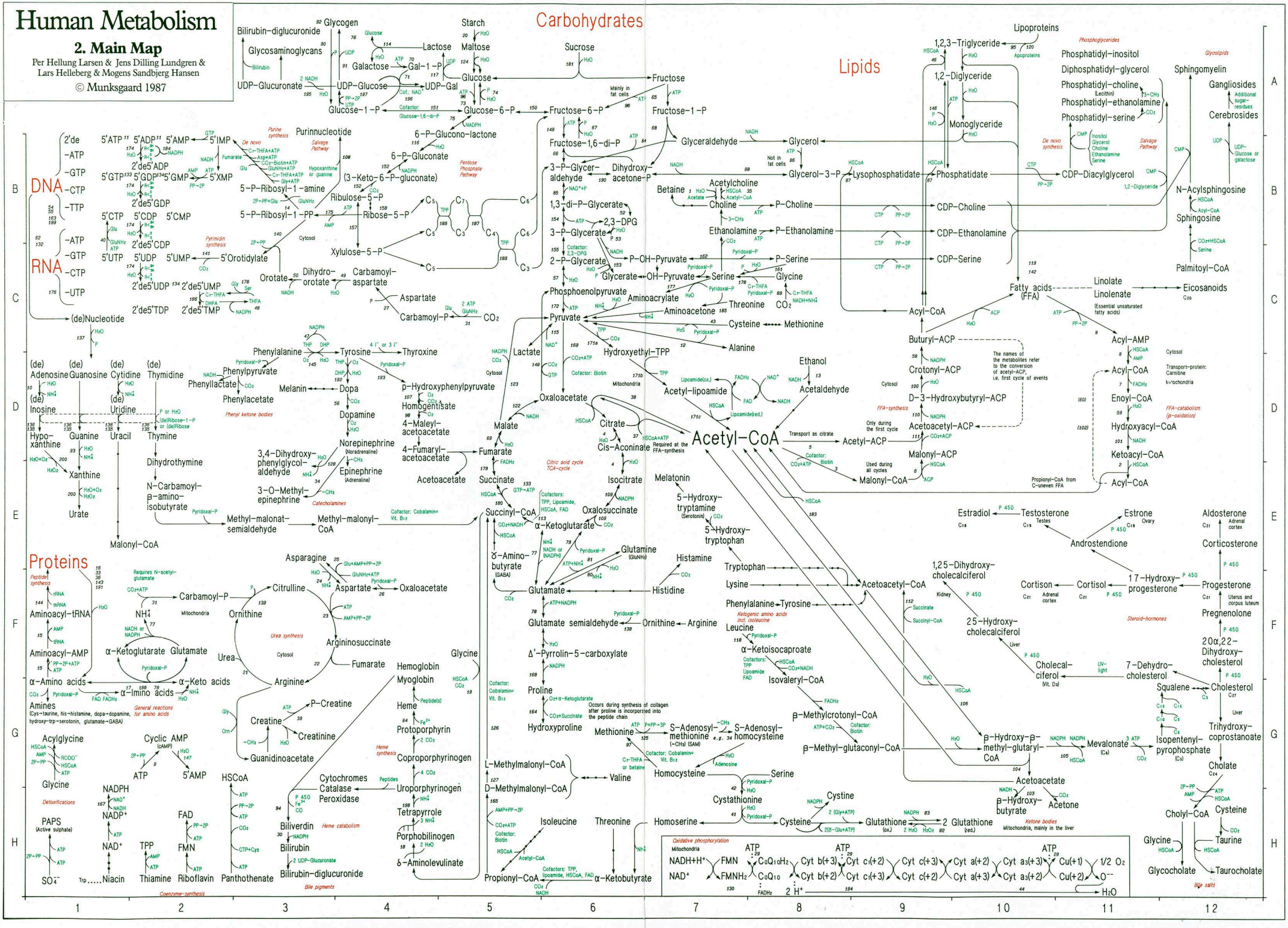

Human Metabolism

3. Enzymes

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ENZYMES IN GENERAL

DEFINITION: Enzymes (E) are proteins with catalytic activity. 2000 different E's are known – 200 are discussed here.

MODE OF ACTION: E's increase the reaction velocity of a certain process by lowering the energy of activation. E's do not change the equilibrium of the reaction.

CLASSIFICATION: E's can be classified into six main classes according to the character of the catalyzed process – see below and compare with the map ENZYME CLASSIFICATION. E's can also be classified in the following ways *a)* E's without requirement for cofactors (e.g. Mg^{2+}, Ca^{2+}) and coenzymes (e.g. pyridoxal-P, biotin). *b)* E's with requirement for cofactors and for coenzymes. *c)* E's with a prosthetic group (e.g. FAD, biotin) which means enzymes strongly bound to their coenzymes.

E's can be further classified according to those which are regulatory and those which are non-regulatory. Within the first group the E may be regulated by an allosteric mechanism (e.g. aspartate transcarbamoylase no. 27), or regulated by covalent modification (e.g. glycogen phosphorylase no. 90).

ENZYME REACTION VELOCITY: The catalytic ability of the E is often expressed by the initial reaction velocity (V_o) under defined conditions. One enzyme unit equals that amount of enzyme which catalyses the conversion of 1 μmole substrate per minute at 25°C. The optimal reaction velocity (V_{max}) is obtained when the E is saturated with substrate under optimal conditions (temp., pH, etc.). The substrate concentration which gives half of the maximal reaction velocity is called K_m, the so-called Michaelis-Menten constant.

REGULATION: In the organism the activity of the E's can be regulated in two different ways: *a)* feedback inhibition of an allosteric E – i.e. the activity is influenced by allosteric effector-molecules (e.g. CTP on enzyme no. 27). *b)* repression – this means reduced synthesis of E (e.g. δ-aminolevulinate synthetase no. 19).

ALLOSTERIC ENZYMES: Defined as E's whose activity is changed following binding of allosteric effectors to the allosteric site of the E. This site is situated on the surface of the molecule and is *not* the catalytic active site of the E. Allosteric effectors may be nucleotides, succinyl-CoA etc. When the reaction velocity is plotted against the substrate concentration for an allosteric reaction a sigmoid curve is obtained.

INHIBITORS: Are classified into irreversible inhibitors (which destroy the catalytic active sites) and reversible inhibitors. The latter are further divided into competitive, where the inhibitor competes with the substrate for the binding to the active site (without being converted after binding), and non-competitive, where the inhibitor binds to the enzyme but not at the active site.

KEY TO THE MAP

The alphabetic list of enzymes presented below is an attempt to show the most important enzymes as they are mentioned in present day textbooks such as A. Lehninger: »Principles of Biochemistry,« 1982 and L. Stryer: »Biochemistry,« 1981.

The overview includes the enzyme name, number on map, map coordinate, systematic code, reference to textbook and a commentary.

ENZYME NAME: In order to facilitate the use of the map as a supplement to the text books, the same nomenclature as in the textbooks is used.

NUMBER CODE: Each enzyme is assigned an arbitrary number (1-200), which can be used when going from the main map to this map.

MAP COORDINATE: If on the other hand one has an enzyme name and wants to know if or where the reaction is to be found on the main map, one can check the alphabetic list to see if there is a coordinate to the main map.

SYSTEMATIC CODE: Enzymes are classified into six main groups as shown in some detail on the map ENZYME CLASSIFICATION:

1. Oxidoreductases
2. Transferases
3. Hydrolases
4. Lyases
5. Isomerases
6. Ligases

On the present map only the first two code numbers are given.

REFERENCE TO TEXTBOOKS: This code indicates the page in the Lehninger (L)/Stryer(S) textbooks, where the enzyme reaction is described.

COMMENTARY NOTES: The following abbreviations are used:

allo	:	Allosteric enzyme
CI	:	Competitive inhibitor
Cof	:	Cofactor (only those not mentioned on MAIN MAP)
Com	:	Composition
Cs	:	Committed step (the enzyme of a metabolic sequence with the lowest reaction velocity)
E	:	Enzyme – the enzyme in question
F	:	Function
I	:	Inhibitor
L	:	Location (site of action)
Los	:	Location of synthesis (e.g. specific cells in a tissue)
Moa	:	Mode of action
NI	:	Non-competitive inhibitor
no	:	Arbitrary number code
pro-E	:	Pro-enzyme
Stim	:	Stimulator
Scl	:	Subcellular localization

Acetylcholin esterase	*1*	B-7	3.1	L700	*Scl:* On the post-synaptic membrane. By activity the resting membrane potential is restored. *NI:* Disopropyl phosphofluoridate (DIPF).
Acetyl-CoA acetyl transferase	*2*		2.3	L516	*Moa:* Also termed thiolase (no. 183).
Acetyl-CoA carboxylase	*3*	E-8	6.4	L586	*Moa:* Allo. *Stim:* Citrate (increases V_{max} 10-fold). *CI:* Palmitoyl-CoA.
Aconitase	*4*	D-6	4.2	L445	*Moa:* One of the terminal carboxylate-groups in citrate is bound to the E and the α-C atom corresponding to this is hydroxylated.
ACP-acetyl transferase	*5*	D-8	2.3	L588	*Com:* Part of the fatty acid acyl synthase complex.
ACP-malonyl transferase	*6*	E-9	2.3	L588	*Com:* Part of the fatty acid acyl synthase complex.
Acyl-CoA dehydrogenase	*7*	D-11	1.3	L515	
Acyl-CoA synthase	*8*	C-11	6.2	L512	*Moa:* The two reactions shown are energetically coupled. Propionate may serve as a substrate too.
Adenylate cyclase	*9*	G-2	4.6	L732	*Scl:* The inner part of the cell membrane. *Stim:* Hormones, which use cAMP as an intracellular messenger (e.g. epinephrine and glucagon) (cf. map HORMONES).
Adenylate deaminase	*10*	D-1	3.5	S531	
Adenylate kinase	*11*	B-2	2.7	L387	*Moa:* ATP + AMP ⇄ 2 ADP. *Cof:* Mg^{2+}.
Alanine transaminase	*12*	C-7	2.6	L532	Serum concentrations are used in the diagnosis of liver and heart diseases.
Alcohol dehydrogenase	*13*	D-8	1.1	L427	*L:* Liver. *Comp:* Contains two Zn^{2+}. *Moa:* Ethanol + NAD^+ ⇄ acetaldehyde + NADH. Cf. no. 170
Amidophosphoribosyltransferase	*14*	B-3	2.4	L628	Cs in the purine synthesis. *CI:* IMP, AMP and GMP.
Aminoacyl-tRNA synthetase	*15*	F-1	6.1	L877	*Moa:* A class of enzymes, which activates amino acids during protein synthesis. Cof: Mg^{++}.
Aminopeptidase	*16*	E-1	3.4	L689	*Los:* Small intestine. *Moa:* Successive hydrolysis of the NH_2- terminal amino acid residue (except for proline).
Aminotransferase	*17*	G-2	2.6	L259	Also termed no. 188. *Moa:* α-Amino $acid_1$ + α-keto $acid_2$ ⇄ α-keto $acid_1$ + α-amino $acid_2$.
δ-Aminolevulinate dehydrase	*18*	H-4	4.2	S505	*CI:* Heme.
δ-Aminolevulinate synthetase	*19*	G-5	2.3	S505	Cs in the heme synthesis. *Moa:* The resulting CO_2-molecule originates from glycine. *CI:* Heme (also inhibits the synthesis of E).
α-Amylase	*20*	A-5	3.2	L288	*Los:* Salivary glands and pancreas. *Moa:* E hydrolyses β 1-4 glycosidic linkages in starch and amylopectin.
Arginase	*21*	F-3	3.5	L550	*Los:* Liver. *Moa:* Consumes four moles of energy-rich phosphate-molecules for the synthesis of one mole urea.
Argininosuccinate lyase	*22*	F-3	4.3	L552	*Moa:* The four C-atoms in the product fumarate stem from the substrate aspartate.
Argininosuccinate synthetase	*23*	F-3	6.3	L552	*Cof:* Mn^{2+}.
Asparaginase	*24*	F-3	3.5	L544	
Asparagine synthetase	*25*	E-3	6.3	L618	
Aspartate aminotransferase	*26*	F-4	2.6	L216	Estimation of serum concentrations is used in diagnosis of liver and heart diseases.
Aspartate transcarbamoylase	*27*	C-4	2.1	L631	Cs in the pyrimidine synthesis. *Moa:* allo. *S:* ATP. *CI:* CTP. *I:* Phosphoacetyl-L-aspartate (PALA).
ATPase	*28*		3.6		*Moa:* ATP + H_2O ⇄ ADP + P. $\Delta G'_o$ = 7.3 kcal/mol.E.g. no. 99 or no. 131.
ATP synthetase	*29*	H-8/10	2.7	L484	Also denoted F_oF_1 ATPase. *I:* Dinitrophenol (drug) uncouples the ATP-synthesis of the oxidative phosphorylation.
Biliverdin reductase	*30*	H-3	1.3	S507	
Carbamoyl phosphate synthetase I	*31*	F-2	2.7	L551	*Scl:*Mitochondria. *Cof:* N-acetylglutamate.
Carbamoyl phosphate synthetase II	*31*	C-5	2.7	L632	*Scl:* Cytosol. *CI:* UMP.
Carbonic anhydrase	*32*		4.2	L710	*Com:* Contains Zn^{2+}. *Moa:* CO_2 + H_2O ⇄ H_2CO_3. *NI:* Acetazolamide (drug).
Carboxypeptidase	*33*	F-1	3.4	L689	*Com:* Contains Zn^{2+}. *Los:* Exocrine cells in the pancreas as pro-E. *L:* Small intestine. *Moa:* Successive hydrolysis of carboxylate-terminal amino acids.
Catechol-O-methyl transferase	*34*	E-3	2.1	S895	*F:* Inactivates catecholamines as enzyme no. 128 does.
Choline-acetyl transferase	*35*	B-8	2.3	S887	*Scl:* At the end of the presynaptic axon. *Moa:* The product is taken up by the synaptic vesicles.
Chymotrypsin	*36*	F-1	3.4	L688	*Los:* Exocrine cells in pancreas as pro-E. *L:* Small intestine. *Moa:* E hydrolyses peptide bonds where phe-, trp- and tyr-residues are involved. Is activated by no. 191.
Citrate lyase	*37*	D-6	4.1	L586	*Scl:* Cytosol. *Moa:* Is used at the FFA synthesis, because acetyl-CoA cannot diffuse over the mitochondria membrane.
Citrate synthase	*38*	D-6	4.1	L444	Cs in the TCA-cycle. *Moa:* Allo. *I:* Oxaloacetate, citrate, succinyl-CoA, NADH, fatty acid acyl-CoA and ATP.
Creatine kinase	*39*	G-3	2.7	L384	*L:* Muscle tissue. *F:* Keeps the ATP at a high level, no. 11 has corresponding F. *Cof:* Mg^{2+}.
CTP synthetase	*40*	B-1	6.3	L631	
Cystathionine lyase	*41*	H-7	4.4	L620	*Com:* Pyridoxal phosphate as functional group.
Cystathionine synthase	*42*	G-7	4.2	L620	As for no. 41.
Cysteine desulfhydrase	*43*	C-7	4.4	S416	As for no. 41.
Cytochrome oxidase= cytochrome aa_3	*44*	H-10	1.9	L482	*Com:* Contains a heme group and Cu. *I for cytochrome* aa_3: CN^-, N_3^- and CO.
Dehydrogenases	*45*		1.1	L256	*Moa:* RH_2 + $NAD(P)^+$ ⇄ R + NAD(P)H + H^+. FAD accepts the two H^+ ions.
Diglyceride acyl transferase	*46*	A-9	2.3	S458	
Dihydrobiopterin reductase	*47*	C-3	1.6	S424	*Moa:* Catalyzes the conversion of the electron-transporting biopterin to its active reduced form.
Dihydrofolate reductase	*48*	C-3	1.5	L261	Also denoted no. 182. *I:* Methotrexate = amethopterin and aminopterin (cancer therapy).
Dihydroorotase	*49*	C-4	3.5	L631	*Moa:* Amide bond is formed and the ring is closed.
Dihydroorotate oxidase	*50*	C-3	1.3	L631	*Moa:* A double bond is formed in the ring.
Dioxygenase	*51*		1.13	L502	*Moa:* The two oxygen atoms (from O_2) are taken up by the organic substrate molecule. E.g. no. 98.
2,3-Diphosphoglycerate mutase	*52*	B-6	2.7	S276	*Moa:* Breaks the acid anhydride bond and forms a phosphoester bond.
2,3-Diphosphoglycerate phosphatase	*53*	B-6	3.1	S276	
DNA ligase	*54*	B-1	6.5	L848	*Moa:* Catalyzes the formation of a diester bond between the 3'OH of Okazaki-fragments and the 5'P of double helix DNA with simultaneous hydrolysis of ATP to AMP and 2P.
DNA polymerase	*55*	B-1	2.7	L843	*Com:* Contains Zn^{2+}. *Moa:* DNA_n + dNTP ⇄ DNA_{n+1} + 2P, direction of synthesis 5' → 3'. Eucaryotic E: *a)* Requires all four nucleotide triphosphates (dNTP) *b)* requires Mg^{2+}, *c)* requires a DNA template and RNA (cf. no. 163), *d)* has nuclease activity (cf. no. 62).
Dopa decarboxylase	*56*	D-4	4.1	S895	*Moa:* An example of the decarboxylation of amino acids (cf. MAIN MAP G-1).
Enolase	*57*	C-6	4.2	L408	*Cof:* Mg^{2+}. *I:* Concommitant presence of F^- and P (binds Mg^{2+}).
Enoyl-ACP reductase	*58*	C-9	1.3	L592	*Com:* Part of the fatty acid acyl synthase complex.
Enoyl-CoA hydratase	*59*	D-11	4.2	L517	*Moa:* If the substrate contains a cis-double bond between C-2 and C-3, the product has to be inverted (by enzyme no. 102) before the oxidation can continue.
Enoyl-CoA isomerase	*60*	D-11	5.3	L520	*Moa:* If the substrate for no. 59 contains a double bond between C-3 and C-4, this must be isomerized to a double bond between C-2 and C-3.
Enterokinase	*61*		3.4	L688	*Los and L:* Small intestine. *Moa:* Converts protrypsin to trypsin (no. 191).
Exonuclease 3'→5' or 5'→3'	*62*	B-1	3.1	L846	*Moa:* Hydrolyses the DNA strand before the formation of hydrogen bonds between the two strands.
Fatty acyl-CoA oxygenase	*63*		1.3	L594	*Moa:* Introduces a C-9 cis double bond in saturated FFA's. Requires NADPH and O_2.
Ferrochelatase	*64*	G-4	4.99	S506	Fe^{2+} is transported in the plasma bound to transferrin and is deposited in the tissues as ferritin molecules. *CI:* Heme.
Fructokinase	*65*	A-7	2.7	L417	*Cof:* Mg^{2+}.
Fructose-1,6-diphosphate aldolase	*66*	B-6	4.1	L406	*Moa:* Aldole cleavage.
Fructose-1,6-diphosphatase	*67*	A-6	3.1	L565	*L:* Liver. *Moa:* Allo. *Cof:* Mg^{2+}. *Stim:* ATP, 3-glycerolaldehyde and citrate. *I:* AMP.
Fructose-1-phosphat aldolase	*68*	A-7	4.1	L417	*Moa:* Aldole cleavage.
Fumarase	*69*	D-5	4.2	L446	*Moa:* Stereo-specific addition of water. This means that only L-malate is formed.
Galactokinase	*70*	A-4	2.7	L418	*Cof:* Mg^{2+}.
Galactose-1-phosphate uridylyl transferase	*71*	A-4	2.7	L418	*L:* Liver. E has decreased activity at galactosemia.
Galactosyl transferase	*72*		2.7	L576	*Moa:* Catalyzes the addition of galactose residues to N-acetylglucosamines and to the hydroxyl-group of hydroxy-glycine residues in collagen fibers.
Glucokinase	*73*	A-5	2.7	L405	*L:* Liver. *Moa: a)* Is specific for D-glucose, *b)* is not inhibited by glucose-6-P as is no. 96, *c)* since K_m~ 10mM the E is active at high blood glucose concentrations. *Stim of synthesis:* Insulin.
Glucose-6-phosphatase	*74*	A-5	3.1	L566	*L:* Primarily in the liver. Not present in muscle and brain tissue. *Scl:* Endoplasmatic reticulum. *Cof:* Mg^{2+}.
Glucose-6-phosphate dehydrogenase	*75*	A-5	1.1	L457	*Cof:* Mg^{2+}.
$\alpha(1\rightarrow6)$-Glucosidase	*76*	A-4	3.2	L416	Also called »branching enzyme«. *Moa:* The product is free glucose and unbranched glycogen.
Glutamate dehydrogenase	*77*	E-5	1.4	L534	*L:* Mainly in the liver. *Scl:* Mitochondria (NADH) and cytosol (NADPH). *Stim:* GDP, ADP. *I:* GTP, ATP.
		F-2			
Glutamate kinase dehydrogenase	*78*	F-5	1.1	L687	Cs in the proline synthesis. *Moa:* Allo. *CI:* Proline.
Glutamate transaminase	*79*	E-6	2.6	L532	*Moa:* Any amino acid can donate an amino group and any α-keto acid can accept it. E.g. no. 12, no. 26 and no. 118.
		G-2			
Glutaminase	*80*	E-6	3.5	L546	*L:* Primarily in the liver.
Glutamine synthetase	*81*	F-6	6.3	L546	*Moa:* Glutamyl-5-P is an intermediary product in the reaction.
Glutathione peroxidase	*82*	H-9	1.11	L272	*F:* Cf. no. 83. *Com:* Contains selenocysteine. *L:* Erythrocytes.
Glutathione reductase	*83*	H-9	1.6	S343	*F of no. 82 and 83:* E keeps the proteins on the reduced form. *L:* Erythrocytes.
Glyceraldehyd kinase	*84*	B-7	2.7	L417	Also termed triose kinase. *Cof:* Mg^{2+}.
Glyceraldehyd-3-phosphate dehydrogenase	*85*	B-6	1.2	L408	*Moa:* Allo. *NI:* Iodoacetate. Arsenate uncouples the substrate phosphorylation catalysed by no. 154 by acting as an analogue to the P, which is a substrate in the reaction.
Glycerol kinase	*86*	B-8	2.7	L596	*Cof:* Mg^{2+}.
Glycerolphosphate acyl transferase	*87*	B-9	2.3	L597	
Glycerolphosphate dehydrogenase	*88*	B-7	1.2	L596	
Glycin synthase	*89*	C-8	2.1	L538	
Glycogen phosphorylase	*90*	A-3	2.4	L414	*Com:* Present in two forms: a (active) and b (inactive). The a- and b-form can be interconverted by enzymes no. 159 and 160. *Moa:* Allo. *Stim* (for the b-form): AMP. Hormonal control, cf. no. 166.

B

Human Metabolism

3. Enzymes

Jens Dilling Lundgren & Per Hellung-Larsen

Glycogen synthase	*91*	A-4	2.4	L572	*Comp:* Present in two forms: a (active) and b (inactive), which can be interconverted by no. 166 and a phosphatase. *Moa:* Allo, E requires a primer. *Stim* (for the b-form): Glucose-6-P. Regarding the hormone control, cf. no. 166.
Glycosyl-(4→6)-transferase	*92*	A-3	2.4	L574	Also denoted »branching enzyme«. *Moa:* E moves six to seven glucosyl-residues.
Guanine deaminase	*93*	D-1	3.5	L634	
Heme oxygenase	*94*	G-4	1.14	S507	
Hepatic lipase	*95*	A-10	3.1	L316	*L:* Liver
Hexokinase	*96*	A-5	2.7	L403	*Moa:* Allo. *Cof:* Mg^{2+}. *CI for the muscular E:* Glucose-6-P. Insulin stimulates the uptake of the substrate in muscle and adipose tissues.
Homocysteine methyl transferase	*97*	G-6	2.1	S494	The cofactor is a derivate of vit. B_{12}: Methylcobalamine.
Homogentisate 1,2-dioxygenase	*98*	D-4	1.13	L540	*Moa:* Breaks the aromatic ring. E has decreased activity at alcaptonuria.
H^+-transporting ATPase	*99*		3.6	L385	*F:* transports H^+ ions and thereby Cl^- over the cell membrane. *L:* The parietal cells in the stomach. *Stim:* The hormone gastrine.
3-Hydroxyacyl-ACP dehydratase	*100*	D-9	4.2	L590	*Comp:* Part of the fatty acid acyl synthase complex.
Hydroxyacyl-CoA dehydrogenase	*101*	D-11	1.1	L517	*Moa:* E is stereospecific for the L-form of the substrate. Cf. no. 102.
Hydroxyacyl-CoA epimerase	*102*	D-11	5.1	L521	*Moa:* If the substrate for no. 101 is on the D-form this E convert it to the L-form.
Hydroxybutyrate dehydrogenase	*103*	H-10	1.1	L525	*Moa:* Stereospecific for the D-form of β-hydroxybutyrate.
Hydroxymethylglutaryl-CoA lyase	*104*	G-10	4.1	L524	
Hydroxymethylglutaryl-CoA reductase	*105*	G-11	1.1	L608	Cs in the cholesterol synthesis. *L:* Primarily the liver but also the intestinal epithelia. *Scl:* Endoplasmatic reticulum. *I:* Cholesterol (inhibits the synthesis and activity of E), mevalonate.
Hydroxymethylglutaryl-CoA synthase	*106*	G-9	4.1	L524	
Hydroxyphenylpyruvate dioxygenase	*107*	D-4	1.13	L540	
Hypoxanthine-guanine phosphoribosyl transferase	*108*	B-4	2.4	L635	*Moa:* Guanine or Hypoxanthine + PRPP → GMP or IMP + PP. The reaction with adenin is catalyzed by another enzyme. E has decreased activity (sex-linked recessive) at Lesch-Nyhan's syndrome.
Isocitrate dehydrogenase	*109*	E-6	1.1	L445	*Moa:* Allo. *Cof:* NADH instead of NADPH, Mg^{2+}, Mn^{2+}. *Stim:* ADP, *I:* NAD(P)H.
3-Ketoacyl-ACP reductase	*110*	D-9	1.1	L590	*Comp:* Part of fatty acid acyl synthase complex.
3-Ketoacyl-ACP synthase	*111*	D-9	2.3	L589	*Comp:* As no. 110. *Moa:* The resulting CO_2 is the same as that accepted by no. 3.
3-Ketoacyl-CoA transferase	*112*	F-9	2.8	L525	Not present in the liver.
α-Ketoglutarate dehydrogenase complex	*113*	E-6	1.2	L445	*Comp and Moa:* In principle as for no. 171. *Cof:* Mg^{2+}. *CI:* Succinyl-CoA and NADH.
Lactase	*114*	A-4	3.2	L419	*L:* In the mucus on the luminal surface of the epithelia of small intestines.
Lactate dehydrogenase	*115*	C-6	1.1	L412	*Comp:* Present in the isoforms A_4, A_3B, A_2B_2, AB_3, B_4. *Moa:* A_4 (*L:* Striated muscle) has the highest affinity for pyruvate, so that of the neccessary formation of NAD^+ to the reaction catalysed by no. 85 under anaerobic conditions can be made. B_4 (*L:* Heart) has the highest affinity for lactate. AB_3 (*L:* Liver).
Lactonase	*116*	B-4	3.1	L457	*Cof:* Mg^{2+}.
Lactose synthase	*117*	A-4	2.4	L577	*Com:* E is a modification of no. 72 by binding of α-lactalbumine (synthesis is stimulated by prolactine). *L:* Mammary glands.
Leucine transaminase	*118*	F-7	2.6	L532	*Com:* Pyridoxal phosphate is the functional group.
Lipase	*119*	C-10	3.1	L702	*L:* Mainly adipocytes. *Scl:* Cytosol. FFA is transported in the plasma bound to albumine. E is hormonally stimulated *Stim:* (Nor) epinephrine, glucagon, ACTH. *I:* Insulin and prostaglandins.
Lipoprotein lipase	*120*	A-10	3.1	L701	*L:* Adipocytes. *Scl:* The outer surface of the cell membrane. *Moa:* Releases triglycerides from chylomicrons and VLDL. *I:* Insulin.
Lysyl oxidase	*121*		1.13	L160	*Com:* Contains Cu. *F:* E catalyzes the condensation of two lysyl-residues in different polypeptide chains in helical collagen.
Malate dehydrogenase (NAD^+)	*122*	D-5	1.1	L447	*Scl:* Mitochondria (and the cytosol at the gluconeogenesis). *Moa:* Oxidoreduction.
Malate dehydrogenase ($NADP^+$)	*123*	D-5	1.1	L593	E also denoted malate enzyme. *L:* Mainly in adipocytes. *Scl:* Cytosol. *Moa:* Oxidative decarboxylation.
Maltase	*124*	A-5	3.2	L419	*L:* In the mucus on the luminal side of the epithelia of small intestines.
Methionine adenosyl transferase	*125*	G-6	2.5	L619	*Moa:* Adenosylmethionine (the product) has a larger transfer potential than C_1-THFA.
Methylmalonyl-CoA mutase	*126*	G-5	5.4	L522	The cofactor is a derivate of vit B_{12} namely deoxyadenosylcobalamine. Decreased activity of E leads to methylmalonic acidose.
Methylmalonyl-CoA racemase	*127*	G-5	5.1	L522	
Monoamine oxidase	*128*	E-3	1.4	S895	*F:* Inactivates catecholamines as does no. 34.
Monooxygenase	*129*		1.14	L503	Also denoted mixed function oxidase. *Moa:* One of the 0 atoms is incorporated into the organic compound, while the other 0 atom becomes a part of H_2O. *Cof:* Cytochrome P 450 or THP.
NADH-ubiquinone reductase	*130*	H-7	1.6	L479	*Com:* Prostetic group: 1) FMN, 2) nonheme iron protein. (FeS). *I:* Retenone, amytal.
Na^+-K^+ transporting ATPase	*131*		3.6	L386	*F of the reaction:* Creates a concentration gradient of ions over the cell membrane. *Scl:* Integral protein in the cell membrane. *Moa:* E is situated in the cell membrane. 3 Na^+ is pumped out and 2 K^+ is pumped in pr. hydrolysis of 1 ATP. E requires Na^+ (inside), K^+ (outside) and Mg^{2+}. *I:* Vanadate (inside) and cardiotonic steroids, e.g. digitalis and ouabain (outside).
Nuclease	*132*		3.1	L800	There is as well an endonuclease (e.g. no. 199) as an exonuclease (e.g. no. 62). *Scl:* Nucleus.
Nucleoside diphosphate kinase	*133*	B-1 E-5	2.7	L389	*Moa:* NTP_1 + (d)NDP_2 ⇌ NDP_1 + (d)NTP_2. *Cof:* Mg^{2+}.
Nucleoside monophosphate kinase	*134*	B-2	2.7	L630	*Moa:* ATP + NMP ⇌ ADP + NDP. *Cof:* Mg^{2+}.
Nucleosidase	*135*	D-1	3.2	L634	
Nucleoside phosphorylase	*136*	D-1	2.4	S531	
5-Nucleotidase	*137*	C-1	3.1	L634	
Ornithine transaminase	*138*	F-6	2.6	S418	See 118.
Ornithine transcarbamoylase	*139*	F-3	2.1	L552	*Scl:* Mitochondria. *Cof:* Mg^{2+}.
Orotate phosphoribosyl transferase	*140*	B-3	2.4	L631	
Orotidylate decarboxylase	*141*	C-2	4.1	L631	
Pancreatic lipase	*142*	C-10	3.1	L690	*Los:* The exocrine glands of pancreas as pro-E. *L:* Small intestine. *Moa:* E is activated by bile salts, Na^+ and lipase.
Pepsin	*143*	F-1	3.4	L687	*Los:* In the stomachal epithelia as pro-E. *L:* Stomach. *Moa:* Hydrolysis of peptide bonds involving tyr- or phe-residues. *Stim:* The E itself (autocatalysis) and low pH. The hormone gastrin stimulates the secretion of E.
Peptidyl transferase	*144*	F-1	2.3	L887	*Scl:* Cytosol, the 50S subunit of the ribosome. *Moa:* Moves the newly synthesized polypeptide from the P-site to the aminoacyl-tRNA of the A-site. *NI:* Cycloheximide (eucaryotes and procaryotes), and chloramphenicol (procaryotes).
Phenylalanine monooxygenase	*145*	D-3	1.14	L540	Decreased activity of E leads to phenylketonuria with production of phenyl ketone bodies.
Phosphatidate phosphatase	*146*	A-9	3.1	L597	
Phosphodiesterase	*147*	G-2	3.1	L734	*Scl:* Cytosol. *Stim:* Ca^{2+})-calmodulin complex. *I:* Caffeine, theophylline, prostaglandins and xanthines.
Phosphoenolpyruvate carboxy kinase	*148*	D-5	4.1	L565	*Moa:* At glucogenesis the resulting CO_2 is the same as that used by no. 169. *Cof:* Mg^{2+}.
Phosphofructo kinase	*149*	A-6	2.7	L406	Cs in the glycolysis. *Moa:* Allo. *Cof:* Mg^{2+}. *Stim:* AMP, fructose-1,6-di-P, ADP, P, K^+, citrate, Mg^{2+}, Ca^{2+}, FFA and 2,3-diphosphoglycerate.
Phosphogluco isomerase	*150*	A-5	5.3	L405	*Cof:* Mg^{2+}.
Phosphogluco mutase	*151*	A-4	2.7	L416	*Moa:* Glucose-6-P_1 + glucose-1,6-di-P_2 ⇌ glucose-1,6-di-P_1 + glucose-1-P_2 .*NI:* DIPF.
6-Phosphogluconate dehydrogenase	*152*	B-4	1.1	L457	*Cof:* Mg^{2+}.
3-Phosphoglycerate dehydrogenase	*153*	C-6	1.1	L620	
3-Phosphoglycerate kinase	*154*	B-6	2.7	L410	*Moa:* Substrate phosphorylation. *Cof:* Mg^{2+}.
Phosphoglycerate mutase	*155*	C-6	2.7	L411	*Moa:* Same principle as no. 151. *Cof:* Mg^{2+}.
Phospolipase	*156*		3.1	L312	*Com:* Several specific types. *L:* Small intestine (*F:* digestion), and lysosomes (*F:* demolition). *Moa:* Hydrolysis of phosphoglycerides.
Phosphopentose epimerase	*157*	B-4	5.1	L666	
Phosphopentose isomerase	*158*	B-4	5.3	L457	*Moa:* Ketose to a aldose through a enediol.
Phosphorylase a phosphatase	*159*		2.7	L422	*Moa:* Changes no. 90 from the a to the b-form. *I:* Ca^{2+} and AMP.
Phosphorylase b kinase	*160*		3.1	L422	*Moa:* Changes no. 90 from the b to the a-form. *Stim:* No. 166 and Ca^{2+}.
Phosphoserine phosphatase	*161*	C-8	3.1	L620	
Phosphoserine transaminase	*162*	C-7	2.6	L620	See 118.
Primase	*163*	B-1	2.7	L848	*Moa:* Forms the RNA-primer which is required by no. 55.
Prolyl hydroxylase	*164*	G-5	1.14	L160	*Com:* Contains Fe^{2+}. Fe is maintained in its reduced form by ascorbate. *Moa:* Hydroxylation of the C-4 of the proline residue.
Propionyl-CoA carboxylase	*165*	H-5	4.1	L522	*Cof:* Mg^{2+}.
Protein kinase	*166*		2.7	L731	*Moa:* Allo, by covalent modification enzyme no. 160 is activated by one P and enzyme no. 91 is changed from its a to its b-form by two P's. All cAMP-dependent regulations have E as a part of the cascade (cf. the map HORMONES). *Stim:* Hormones, which mediate their effect via cAMP, (nor)epinephrine and glucagon.
Pyridine nucleotide transhydrogenase	*167*	H-1	1.6	L478	
Pyrroline carboxylate reductase	*168*	F-5	1.5	L617	
Pyruvate carboxylase	*169*	C-6	4.1	L454	*Moa:* Allo, one of the steps of the gluconeogenesis since the reaction of no 172, is irreversible. *Cof:* Mg^{2+}. *Stim:* Acetyl-CoA.
Pyruvate decarboxylase	*170*		4.1	L426	*L:* Yeast cells. *Moa:* Pyruvate + H_2O ⇌ Acetaldehyde + CO_2. *Cof:* TPP, Mg^{2+}. Cf. no. 13.
Pyruvate dehydrogenase complex:				L437	*Scl:* Mitochondria. *Moa:* Allo. The regulation of the activity of E: 1) Covalent modification by a kinase (*Stim:* NADH) which inactivates E and a phosphorylase (*Stim:* Ca^{2+}, Mg^{2+}) which activates E, 2) allo modification (*C Stim:* CoA, NAD+, *CI:* ATP, acetyl-CoA, FFA). E is stimulated by insulin.
Pyruvate dehydrogenase	*171a*	C-6	1.2		
Dihydrolipoyl transacetylase	*171b*	D-6	2.3		
Dihydrolipoyl dehydrogenase	*171c*	D-7	1.6		
Pyruvate kinase	*172*	C-6	2.7	L412	*Moa:* Allo, substrate phosphorylation. *Cof:* K^+, Mg^{2+}. *Stim:* AMP, ADP, amino acids (especially alanine). *I:* Acetyl-CoA, FFA, ATP. E is stimulated by glucagon.
Restriction endonuclease	*173*		3.1	L823	*L:* Bacteria. *Moa:* Cleaves both strands in the DNA, when a particular sequence is recognized.
Ribonucleotide reductase	*174*	B/C-2	1.7	L633	
Ribose phosphate diphospho transferase	*175*	B-3	2.7	L628	*Com:* Contains S. *Moa:* Allo. *CI:* The products of 5-P-ribosyl-1-PP.
RNA polymerase	*176*	C-1	2.7	L854	*Com:* Contains Zn, one specific enzyme for each type of RNA (I-rRNA, II-mRNA, III-tRNA). *Moa:* RNA_n + NTP ⇌ RNA_{n+1} + PP, direction of synthesis 5' → 3'. *Scl:* E – I in the nucleolus, E – II and E – III in the nucleoplasma. The eucaryotic E requires *1)* The presence of all four nucleotides, *2)* Mg^{2+}, *3)* template. *NI:* Actinomycin D, acridine, rifampicin and α-amanitin (drugs).
Serine dehydratase	*177*	C-7	4.2	S411	See 118.
Serine hydroxy methyl transferase	*178*	C-3/7	2.1	L620	See 118
Succinate dehydrogenase	*179*	E-5	1.3	L447	*Com:* Contains six non-heme proteins (FeS), as does no. 130. *CI:* Malonate.
Succinyl-CoA synthetase	*180*	E-5	6.2	L446	*Moa:* Substrate phosphorylation. *Cof:* Mg^{2+}.
Sucrase	*181*	A-6	3.2	L419	*L:* Mucus on the luminal side of the epithelia of the small intenstine.
Tetrahydrofolate dehydrogenase	*182*		1.5	L634	Also denoted dihydrofolate reductase. Cf. no. 48.
Thiolase	*183*	E-8	2.3	L524	
Thioredoxin reductase	*184*	B-2	1.6	L633	
Threonine dehydratase	*185*	C-7	4.2	S411	See 118.
Thymidylate synthase	*186*	C-2	2.1	L633	*NI:* Fluorouracil (drug).
Transaldolase	*187*	B-5	2.2	L666	Also denoted aldolase. *Moa:* Transfers a C-3 unit to an aldehyde group.
Transaminase	*188*	G-2	2.6	L259	Also denoted aminotransferase. Cf. the explanation at no. 17.
Transketolase	*189*	B/C-5	2.2	L666	*Moa:* Transfers a C-2 unit to an aldehyde group.
Triosephosphate isomerase	*190*	B-6	5.3	L407	The result of this reaction is that C-1 and C-6 get the same »metabolic destiny«. This holds true also for C-2 and C-5 as well as for C-3 and C-4.
Trypsin	*191*	F-1	3.4	L688	*Los:* The exocrine cells in the pancreas as trypsinogen. *L:* Small intestine. Is activated by no. 61 and the E itself (auto catalysis).
Tyrosine monooxygenase	*192*	D-3	1.14	S895	Cs in the synthesis of catecholamines. Decreased synthesis leads to albinism.
Tyrosine transaminase	*193*	D-4	2.6	L540	See 118.
Ubiquinol-cytochrome c reductase	*194*	H-8	1.6	L482	*Com:* Contains non-heme groups (FeS) and Cu. *NI:* Antimycin A.
UDP-glucose dehydrogenase	*195*	A-3	1.1	L458	
UDP-glucose 4-epimerase	*196*	A-4	5.1	L418	*Moa:* The cofactor NAD^+ accepts 2 H^+ which are released again.
UDP-glucose pyrophosphorylase	*197*	A-4	2.7	L418	
Uroporphyrinogen synthetase	*198*	H-4	4.3	S506	Decreased activity of E (autosomal dominant trait) leads to acute intermittent porphyria. At decreased activity of the cosynthetase (autosomal recessive) (cf: MAIN MAP) congenital erythropoietic porphyria is developed.
UV-specific endonuclease	*199*	B-1	3.1	L914	*L:* Especially the skin. *Moa:* 5'→3' endonuclease which recognizes thymin dimers (maybe the result of ultraviolet light) – and hydrolyses the damaged DNA strand on the 5' site. Decreased activity leads to the disease xeroderma pigmentosum.
Xanthine oxidase	*200*	E-1	1.2	L634	*Com:* Contains molybdenum, Fe. Has FAD as prostetic group. *I:* Allopurinol (drug).

Human Metabolism

4. Enzyme Classification

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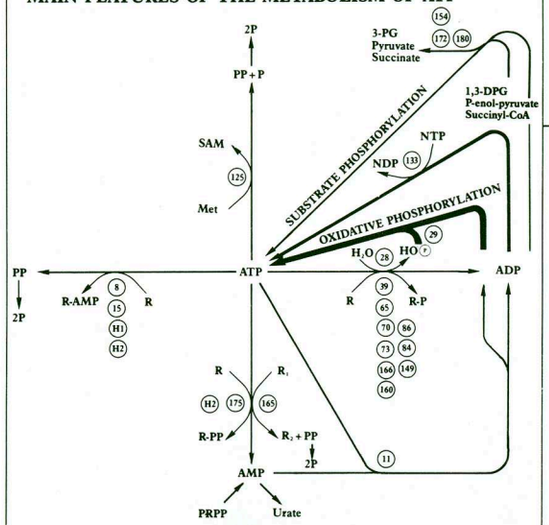
GENERAL

The map shows the main principles behind the classification of the enzymes into 6 classes. The numbering of classes and subclasses follows the proposal from the Enzyme Commission of the International Union of Biochemistry.
For most of the classes, the following is indicated:
1) molecule/group/bond involved
2) formulas to indicate the type of reaction catalyzed
3) trivial names for selected enzymes belonging to the class
4) reference to the map ENZYMES (numbers) and to the MAIN MAP (coordinates).

MAIN FEATURES OF THE METABOLISM OF ATP



VITAMINS AND COENZYMES

Each vitamin is represented by trivial name, chemical name, name of the active compound (A C), water or fat solubility (WS or FS), the effect *(eff)*, referring to the enzyme classification (E C) and deficiency *(D)*.

Vit A = **Retinol.** A C: **Retinal** (FS). *Eff*: Involved in the chemical conversion of light impulses in the retina. *D:* Night blindness.

Vit B_1 = **Thiamine.** A C : **TPP.** (WS). *Eff*: E C 2.2 and 4.1 *D:* Beri-Beri.

Vit B_2 = **Riboflavin.** A C : **FMN and FAD.** (WS). *Eff*: E C 1.2, 1.3 and 1.6.

Vit B_6 = **Pyridoxin.** A C : **Pyridoxal-P.** (WS). *Eff*: E C 2.6, 4.1.1, 4.2. *D:* Anemia.

Vit B = **Nicotinic acid and Niacin.** A C : **NAD and NADP.** (WS). *Eff*: E C : 1.1, 1.2, 1.4, 1.5, 1.6. *D:* Pellegra.

Vit B_{12} = **Cobalamin.** A C : **Deoxyadenosyl-cobalamin** (WS). *Eff*: E C 2.1 and 5.4. *D:* Pernicious anemia.

Vit B **Biotin.** A C : **Biocytin.** (WS). *Eff*: E C 6.4.

Vit B **Folic acid.** A C : **THFA** (WS). *Eff*: E C 2.1.2 *D:* Megaloblastic anemia.

Vit B **Panthothenic acid.** A C : **Co-A.** (WS). *Eff:* Transport of acyl groups. E C 6.2.

Vit C = **Ascorbic acid.** A C : **Ascorbate?** (WS). *Eff*: Cf. no. 164. *D:* Scurvy.

Vit D_3 = **Cholecalciferol.** A C : **1,25-dihydroxy-cholecalciferol.** (FS). *Eff* and *D.:* Cf. the map HORMONES.

Vit E = **α-tocopherol.** (FS).

Vit K = **Menadion.** (FS). *Eff*: Coenzyme in the carboxylation of glutamic acid residues in prothrombin.

1. OXIDOREDUCTASES. Reactions involving redox processes. Classified according to the nature of the substrate.

1.1 *CHOH-groups* — RCH_2OH / R_1R_2CHOH —NAD(P)$^+$→ $RCHO$ / $R_1R_2C{=}O$ — Dehydrogenase — 45

1.2 *CHO-groups or CO-groups*
- $R\text{-}CHO + H_2O$ —NAD(P)$^+$→ $RCOOH$
- $R\text{-}CHO + H_2O + O_2$ —FAD→ $RCOOH + H_2O_2$ — Oxidase — 200

1.3 *CH_2-CH_2-groups* — $R\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}R^1$ —FAD→ $R\text{-}CH{=}CH\text{-}CO\text{-}R^1$ — Dehydrogenase — 7

1.4 *CH-NH_2-groups*
- $R\text{-}CH(NH_2)\text{-}COOH + H_2O$ —NAD(P)$^+$→ $R\text{-}CO\text{-}COOH + NH_3$ — Dehydrogenase — 77
- $R\text{-}CH(NH_2)\text{-}COOH$ —FAD→ $R\text{-}C(=NH)\text{-}COOH$ —H_2O→ $R\text{-}CO\text{-}COOH + NH_3$ — Oxidative deamination

1.5 *C-NH-groups* — R^1R^2NH —NAD(P)$^+$→ R^1R^2N — 48

1.6 *NAD(P)H + H$^+$*
- $NADPH + H^+$ —NAD$^+$→ $NADP^+$
- $NADH + H^+$ —FAD→ NAD^+ — Transhydrogenase — 171 c

1.11 *H_2O_2 as acceptor*
- $H_2O_2 + H_2O_2$ → $O_2 + 2H_2O$ — Catalase
- $RH_2 + H_2O_2$ → $R + 2H_2O$ — Peroxidase — 82

1.13 *Incorporation of O_2* — $R\text{-}R^1 + O_2$ → $R\text{-}O\text{-}O\text{-}R^1$ — Dioxygenase — 51

1.14 *O_2 as oxidant* — $RH + O_2$ —P_{450} or THP→ $ROH + H_2O$ — Monooxygenase or hydroxylase — 29

2. TRANSFERASES. Reactions involving transfer of groups from one molecule to another. Classified according to the nature of the group transferred.

2.1 *C_1 groups*
- 2.1.1 $\text{-}CH_3$ — R_1 —SAM, homocys→ $R_1\text{-}CH_3$ — Transmethylase — 34
- 2.1.2 CH_2OH — $R_1 + R_2\text{-}CH_2OH$ —THFA + Pyr-P→ $R_1CH_2OH + R_2$ — 178
- 2.1.3 $\text{-}CONH_2$ — $R_1 + R_2\text{-}CONH_2$ → $R_1\text{-}CONH_2 + R_2$ — Transamidinase — 139

2.2 *Aldehyde/keto groups*
- 2.2.1.1 $\text{-}CO\text{-}CH_2OH$ — $R_1 + R_2\text{-}CO\text{-}CH_2OH$ —TPP→ $R_1\text{-}CO\text{-}CH_2OH + R_2$ — Transketolase — 189
- 2.2.1.2 $\text{-}CHOH\text{-}CO\text{-}CH_2OH$ — $R_1 + R_2\text{-}CHOH\text{-}CO\text{-}CH_2OH$ → $R_1CHOH\text{-}CO\text{-}CH_2OH + R_2$ — Transaldolase — 187

2.3 *Acyl groups*
- 2.3.1 Acyl- — $R_1 + R_2\text{-}CO\text{-}R_3$ → $R_1\text{-}CO\text{-}R_3 + R_2$ — 87

2.4 *Glucosyl groups*
- 2.4.1 Hexosyl- — $R_1 + R_2$-(hexose) → R_1-(hexose) $+ R_2$ — 91
- 2.4.2 Pentosyl- — $R_1 + R_2$-(pentose) → R_1-(pentose) $+ R_2$ — 140

2.6 *N-containing groups*
- 2.6.1 Amino- — $R_1\text{-}CH(NH_2)\text{-}COOH + R_2\text{-}C(=O)\text{-}COOH$ —Pyr-P→ $R_1\text{-}C(=O)\text{-}COOH + R_2\text{-}CH(NH_2)\text{-}COOH$ — Aminotransferase — 17

2.7 *P-containing groups*

	Acceptor	Transfered group				
2.7.1	Alcohol	P	$R\text{-}CH_2OH$		$R\text{-}CH_2OP$	96
2.7.2	Acid	P	$R\text{-}COOH$	NTP, NDP	$R\text{-}COOP$ — Kinase	154
2.7.3	N-containing	P	$R\text{-}NH_2$		$R\text{-}NHP$	39
2.7.4	P-containing	P	R-P		R-PP	133 + 134
2.7.6		PP	$R\text{-}CH_2OH$	ATP, AMP	$R\text{-}CH_2O\text{-}PP$ — Pyrophosphokinase	175
2.7.7		NMP	$R\text{-}CH_2OH$	NTP, PP	$R\text{-}CH_2O\text{-}NMP$ — Nucleotidyl-transferase	197
2.7.8		N-base -P	$R_1\text{-}CH_2OH$	NMP-P-R_2, NMP	$R_1\text{-}CH_2O\text{-}P\text{-}R_2$	B11

3. HYDROLASES. Reactions involving cleavage of a molecule concommitantly with uptake of water. Classified according to the nature of the substrate.

3.1 *Carboxylic acid esterases*
- 3.1.1. *Esterases* — R_1COOR_2 —H_2O→ $R_1COOH + HOR_2$ — 119
- 3.1.2. *Thiolesterases* — R_1COSR_2 —H_2O→ $R_1COOH + HSR_2$
- 3.1.3. *Phosphomonoesterases* — RO-P —H_2O→ $ROH + HO\text{-}P$ — 53
- 3.1.4 *Phosphodiesterases* — $R_1\text{-}O\text{-}P(OH)(=O)\text{-}O\text{-}R_2$ —H_2O→ $R_1\text{-}O\text{-}P(OH)(=O)\text{-}OH + HOR_2$
- 3.1.6 *Esters of sulphuric acid* — $R\text{-}O\text{-}S(=O)_2\text{-}OH$ —H_2O→ $ROH + H_2SO_4$

3.2 *Glycosides*
- 3.2.1 *Glycosidases* — —H_2O→ $+ ROH$ — 20
- 3.2.2 *N-glycosidases* — —H_2O→ $+ NH_3$

3.1 *Proteins and Peptides*
- 3.4.1 *Aminopeptidases* — $R\text{-}CH(NH_2)\text{-}CO\text{-}$ —H_2O→ $R\text{-}CH(NH_2)\text{-}COOH$ — Aminopeptidase — 16
- 3.4.2 *Carboxypeptidases* — $\text{-}NH\text{-}CH(R)\text{-}CO\text{-}$ —H_2O→ $\text{-}NH_2$ — 33
- 3.4.3 *Dipeptidases* — $\text{-}NH\text{-}CH(R^1)\text{-}CO\text{-}$ → $\text{-}NH_2$ + $CH(R^1)\text{-}CO\text{-}$ — 36, 143
- 3.4.4 *Proteinases* — $\text{-}NH\text{-}CH(R^1)\text{-}CO\text{-}$ → $\text{-}NH_2$ + $CH(R^1)\text{-}CO\text{-}$ — 191

3.5 *C-N bonds in non-peptides (confer group 2.6)*
- $RCONH_2$ —H_2O→ $RCOOH + RNH_2$ — Amidase — 80
- $R\text{-}NH\text{-}C(=NH)\text{-}NH_2$ —H_2O→ $RNH_2 + CO(NH_2)_2$ — Amidinase

3.6 *Acid anhydrides* — $R\text{-}O\text{-}P(OH)(=O)\text{-}O\text{-}P(OH)(=O)\text{-}OH$ —H_2O→ $R\text{-}O\text{-}P(=O)(OH)\text{-}O\text{-}P + HO\text{-}P$ — 28

3.9 *P-N-bonds* — $R\text{-}NH\text{-}P$ —H_2O→ $R\text{-}NH_2 + HO\text{-}P$ — Phosphoamidase

4. LYASES. Reactions involving cleavage/condensation of (a) molecule (s) without simultaneous uptake/elimination of water. Classified according to the nature of the bond.

4.1 *C-C bonds*
- 4.1.1 $R_1\text{-}CO\text{-}COOH$ —TPP, CO_2→ $R_1\text{-}CHO$ — Decarboxylase — 56
- 4.1.1 $R_1\text{-}CH(NH_2)\text{-}COOH$ —Pyr-P, CO_2→ $R_1\text{-}CH_2\text{-}NH_2$
- 4.1.2 $R_1\text{-}CHOH\text{-}CHOH\text{-}R_2$ → $R_1\text{-}CH_2OH + R_2\text{-}CHO$ — Aldolase — 66
- 4.1.3 $R_1\text{-}CO\text{-}COOH + HR_2\text{-}CO\text{-}SCoA + H_2O$ —HSCoA→ $R_1\text{-}C(OH)(COOH)\text{-}R_2\text{-}COOH$ — Condensing enzyme — 38

4.2 *C-O bonds* — $R_1CH_2\text{-}CHOH\text{-}R_2$ —H_2O→ $R_1\text{-}CH{=}CH\text{-}R_2$ — 69

4.3 *C-N bonds* — $R_1\text{-}C(=NH)\text{-}NH\text{-}CH_2\text{-}R_3$ → $R_1\text{-}C(=NH)\text{-}NH_2 + CH{=}CH\text{-}R_3$ — 22

5. ISOMERASES. Reactions involving isomerization of a molecule – including epimerization.

5.1 *Epimerization* — R_1-(ring)-R_2 → R_2-(ring)-R_1 — Epimerase — 196

5.2 *Cis-trans isomerization* — $R_1R_2C{=}CR_3R_4$ → $R_1R_2C{=}CR_4R_3$ — Isomerase — D4

5.3 *Intramolecular oxidoreduction* — $R_1\text{-}C_1(R_2)\text{-}C_2(=O)\text{-}R_3$ → $R_1\text{-}C_1(=O)\text{-}C_2(R_2)\text{-}R_4$ — Isomerase — 190

5.4 *Intramolecular transfer* — $\text{-}C_1(R_1)\text{-}C_2(R_2)\text{-}$ → $\text{-}C_1(R_2)\text{-}C_2(R_1)\text{-}$ — Mutase — 127

6. LIGASES. Reactions involving establishment of a binding between two molecules with simultaneous hydrolysis of an acid anhydride bond. Classified according to the nature of the bond.

6.1 *C-O bonds*
- RCOOH (amino acid) —ATP, PP→ RCO~AMP —t-RNA, AMP→ RCO~tRNA — Synthetase — 15
- RCOOH (fatty acid) —ATP, PP→ RCO~AMP —HSCoA, AMP→ RCO~SCoA — Thiokinase — 8

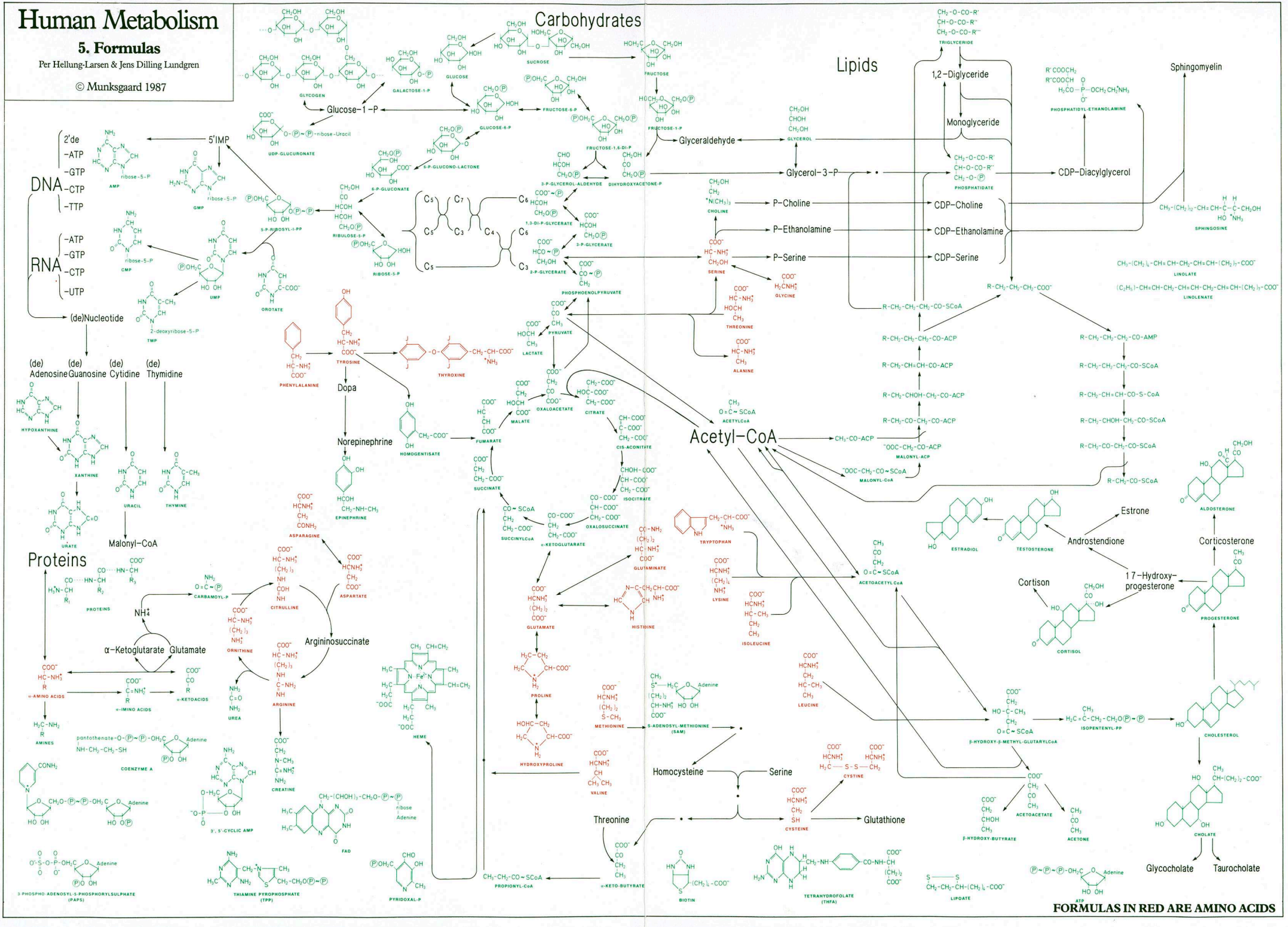
6.3 *C-N bonds* — $RCOOH + NH_2R(H)$ —ATP, ADP + P→ $RCONHR(H)$ — 81

6.4 *C-C bonds* — RCO-SCoA —CO_2~biotin-enzyme→ HOOC-R-CO-SCoA — 3

Human Metabolism

5. Formulas

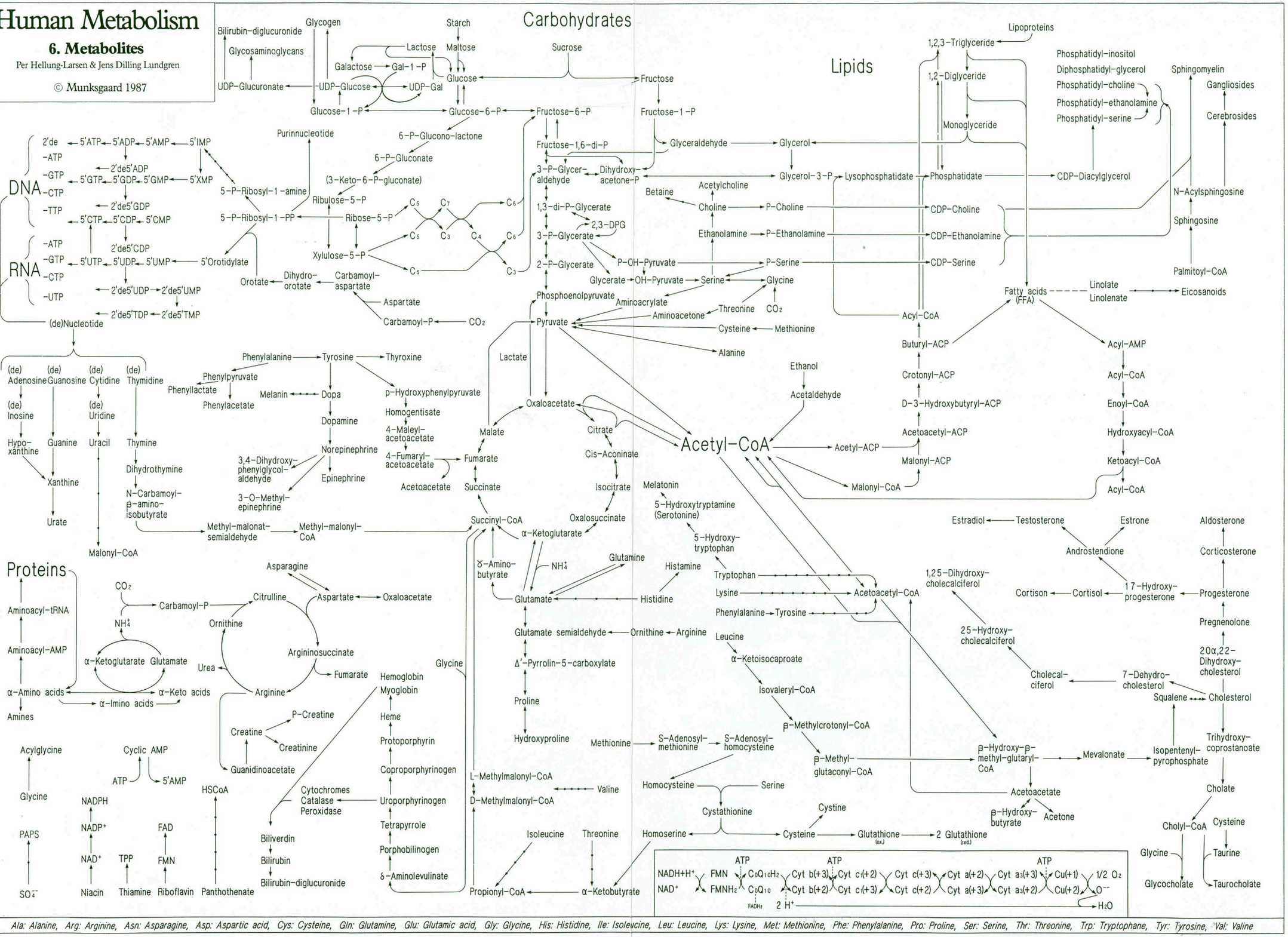
Per Hellung-Larsen & Jens Dilling Lundgren



Human Metabolism

6. Metabolites

Per Hellung-Larsen & Jens Dilling Lundgren



Ala: Alanine, Arg: Arginine, Asn: Asparagine, Asp: Aspartic acid, Cys: Cysteine, Gln: Glutamine, Glu: Glutamic acid, Gly: Glycine, His: Histidine, Ile: Isoleucine, Leu: Leucine, Lys: Lysine, Met: Methionine, Phe: Phenylalanine, Pro: Proline, Ser: Serine, Thr: Threonine, Trp: Tryptophane, Tyr: Tyrosine, Val: Valine

Human Metabolism

7. Main Pathways

Jens Dilling Lundgren & Per Hellung-Larsen

PROTEIN ABSORPTION

With a few exceptions, for example the absorption of immunoglobulins by the infant, proteins in the food are hydrolyzed to their »building stones« – the amino acids – and these are then absorbed through the intestine. The enzymes involved in the catabolism of proteins are pepsin (143) in the stomach and aminopeptidase (16), carboxypeptidase (33), chymotrypsin (36) and trypsin (191) in the small intestine.

The transport of amino acids across the cell membrane of the intestinal epithelial cell is a carrier-facilitated, stereospecific transport, where the driving force is a Na^+-gradient over the membrane. The amino acids are subsequently transported into the blood by simple diffusion and then taken up by cells with a need for amino acids for the synthesis of proteins or by cells with a need for »fuel« substances for energy formation (see map: OTHER PATHWAYS).

The proteins in the food may be substituted by mixtures of amino acids. The human organism requires so-called essential amino acids: (arginine), histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Arginine is essential for infants and growing children. The daily diet must contain these essential amino acids in amounts from 0.5 g/day (trp) to 2 g/day (leu, met, phe) supplemented with nonessential amino acids to yield 50-60 g/day.

The nutritional value of a given protein depends on its content of essential amino acids and its digestibility. It is recommended that the proteins account for at least 12% of the total calories needed. Males, 23-50 years, 70 kg, requires 2700 kcal/day. The average caloric value of a protein is 4.3 kcal/g.

PROTEIN STRUCTURE

Primary structure: The specific sequence of the 20 different amino acids bound together with covalent bonds in the polypeptide chain. The primary sequence of a given protein is determined by the nucleotide sequence in the gene coding for the synthesis of mRNA leading to the synthesis of the protein.

Secondary structure: The relationship between amino acids close to each other in the polypeptide chain. Mediated by chemical forces (hydrogen bonds) between different chains (e.g. pleated-sheet structure) or between groups within a given chain (e.g. α-helix structure).

Tertiary structure: The relationship between amino acids which are distant in the polypeptide chain. Mediated by chemical forces (hydrogen bonds or hydrophobic interactions) between side chain groups.

Quaternary structure: The relationship between different polypeptide chains (e.g. hemoglobin A = $\alpha_2\beta_2$, lactate hydrogenase isoenzymes H_4 , H_3M, H_2M_2 etc.).

Many proteins contain S-S bridges between cysteine residues. Some textbooks see the S-S bridges as part of the primary sturcture, while others consider them to be part of the secondary structure.

PROTEIN CLASSIFICATION

The proteins synthesized by the organism serve many different purposes and relevant examples may be classified accordingly:

1. **Structural proteins:** A number of filaments – collagen-, elastin-, actin-, myosin- and intermediary filaments – and microtubuli (and centrioles) are polypeptide chains or aggregates thereof. The connective tissue contains proteoglycans, which consist of 95% sulfated glycosaminoglycans and 5% protein. Cf. CELLULAR LOCALIZATION.

2. **Enzymes.** Cf. ENZYMES.

3. **Transport proteins:** *Hemoglobin* is the major protein in erythrocytes. A conjugated protein composed of four identical heme groups (see map: FORMULAS) and four peptide chains – 2 α- and 2 β-chains. Binding of one O_2-molecule to the Fe^{++}-containing heme group increases the affinity toward the next O_2-molecule (allosteric effect). Transports O_2 from the lungs to the tissues and H^+ (primarily from H_2CO_3) from the tissues to the lungs, where CO_2 is liberated. *Serum Albumin.* The most abundant protein in plasma. Major carrier of fatty acids in the blood. Also responsible for bilirubin-transport. β_1-*lipoprotein* is one of a number of lipoproteins, which can be classified into a) *Chylomicrons b) Very low density lipoproteins (VLDL),* c) *Low density lipoproteins (LDL)* and d) *High density lipoproteins (HDL).* Consist of hydrophobic- and hydrophilic lipids together with an apoprotein shell. β_1-lipoprotein transports various lipids in the plasma. *Transferrin and transcortin* transport Fe^{+++} and glucocorticoids, respectively.

4. **Proteins of the pore complex:** Facilitate the transport of lipophobic compounds. The transport can be *a)* active under utilization of ATP (e.g. Na^+-K^+ *ATPase* (131)) *b)* carrier-facilitated, where the transport of the carrier results in the transport of the compound in question *c)* due to diffusion and filtration where the driving force is concentration and pressure differences, respectively.

5. **Regulatory proteins:** *Hormones.* Cf. HORMONES. *Receptors for hormones* including neurotransmitters and growth factors have recently been characterized and shown to be proteins. Binding of the ligand changes the functional state of the receptor. *Repressors* which serve as regulators of transcription are proteins which can bind to specific sites on DNA.

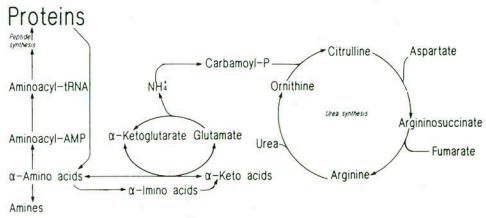
6. **Contractile proteins:** Actin- and myosin-filaments are the basic structures in muscles. The myosin-filaments can slide on the actin-filaments under utilization of ATP.

7. **Storage proteins:** *Myoglobin* contains only one heme group and one peptide chain. Located in the external tissues. Has a high affinity for O_2. *Ferritin* is the protein involved in storage of Fe^{++} (hydroxide and phosphate). Especially present in the liver, spleen and bone marrow.

8. **Defense and protection proteins:** *Antibodies* also called *immunoglobulins.* Present in the so-called γ-globulin fraction of se rum. Y-shaped configuration of four polypeptides. The top of the Y has a capacity to bind a specific antigen (e.g. polypeptide) while the bottom specifies the binding of the molecule to different cell types (e.g. mast cells). Basis of the humoral immunological response towards antigenes. *Fibrinogen:* The substrate for the last step in the blood clotting cascade where thrombin converts fibrinogen into a fibrin clot. The cascade is initiated by either compounds in the blood (intrinsic pathway) or outside the blood (extrinsic pathway) which eventually convert prothrombin into thrombin.

PROTEINS OF THE BLOOD PLASMA

Apart from the role of the plasma proteins in transport, regulation, defense and protection, the plasma proteins create a greater colloid osmotic pressure of the plasma than of the intestinal fluid. This creates the possibility of reabsorption of water from the intestinal fluid.



BIOSYNTHESIS OF PROTEINS

The primary structure of proteins is determined by the nucleotide sequence of a given gene on a specific chromosome. Mechanism: *1)* Transcription of a gene, catalyzed by RNA-polymerase II (176). The specific nucleotide sequence in the gene is converted into a specific sequence in RNA. Takes place in the nucleus. *2)* Simultaneous transcription of genes for a number of tRNA's (RNA-polymerase III) and for rRNA's (RNA-polymerase I). *3)* Loading of specific tRNA's with specific amino acids. Catalyzed by aminoacyl tRNA synthetases (15). Takes place in the cytoplasm. *4)* Attachment of mRNA to the ribosome. A specific sequence of three nucleotides in the mRNA specifies the formation of an initiation complex with the tRNA (with anticodon corresponding to the initiation sequence) in the P site (the so-called peptidyl site on the ribosome surface). *5)* Binding of a new aminoacyl-tRNA to the next codon of the mRNA on the A site (acceptor site) of the ribosome. A peptide bond is formed between the carboxylate-group of the first amino acid and the amino group of the second amino acid. *6)* Removal of the first tRNA. The position of the second amino-acyl-tRNA is changed from the A site to the P site.

NH_4^+ - METABOLISM

Formation: The amino groups of the amino acids are the primary source.

Directly:

a) Oxidative deamination: Glutamate → α-ketoglutarate + NADH.

b) Dehydratase deamination: Serine and threonine → pyruvate.

c) Hydrolytic deamidation: Glutamine → glutamate, asparagine → aspartate.

Via transamination: Every amino acid can transfer its α-aminogroup to α-ketoglutarate or to hydroxypyruvate under the formation of glutamate and serine, which can be directly deaminated.

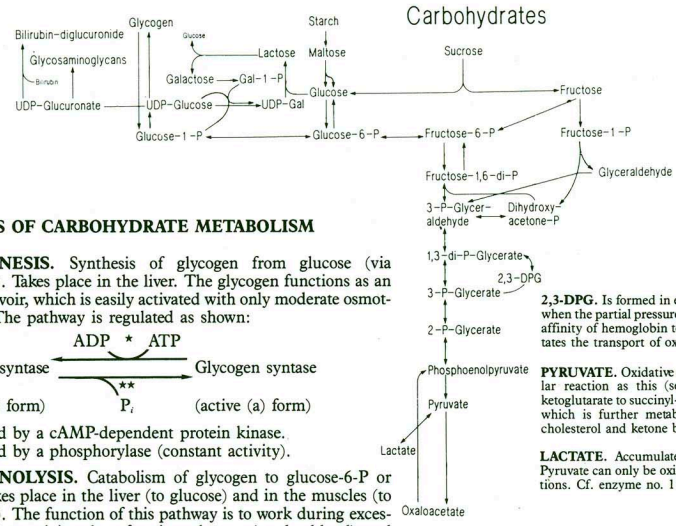
Elimination: NH_4^+ is elimination from the organism because it is toxic in high concentrations: A shift of the equilibrium: α-ketoglutarate ↔ glutamate, to the right leads to a shoot-down of the TCA-cyclus and thereby to lack of energy. The elimination occurs in two ways: *A:* Via a covalent binding to α-ketoacids or to amino acids. *B:* Via the urine: 1) Free NH_4^+-ion, which determines the pH of the urine. 2) Urea synthesis: Located in the liver. Free NH_4^+ is converted to carbamoyl-P before entering the urea cycle. Every amino acid can deliver its amino group to oxaloacetate under the formation of aspartate, which brings the other amino group to the urea molecule. The urea is transported to the kidney with the blood.

NITROGEN BALANCE

The nitrogen balance is an estimate of how much protein is absorbed minus the amount eliminated. During negative N-balance more nitrogen is eliminated than absorbed, indicating that the organism breaks down its own functional proteins.

BILIRUBIN-DIGLUCURONIDE. Exemplifies how the organism is able to reduce or neutralize the effect of a poisonous substance (in this case bilirubin) by conjugating it and thereby increasing its elimination (in this case through the bile).

GLYCOSAMINOGLYCANS. A group of substances which comprise the amorphous substance of connective tissue. They bind water and so facilitate the diffusion of nutrients.



PATHWAYS OF CARBOHYDRATE METABOLISM

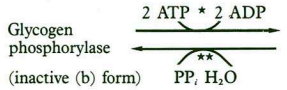
GLYCOGENESIS. Synthesis of glycogen from glucose (via glucose-6-P). Takes place in the liver. The glycogen functions as an energy reservoir, which is easily activated with only moderate osmotic change. The pathway is regulated as shown:

* Catalyzed by a cAMP-dependent protein kinase.

** Catalyzed by a phosphorylase (constant activity).

GLYCOGENOLYSIS. Catabolism of glycogen to glucose-6-P or glucose. Takes place in the liver (to glucose) and in the muscles (to glucose-6-P). The function of this pathway is to work during excessive muscular activity thus forming glucose (to the blood) and glucose-6-P (to the muscles).

Regulation:



* Phosphorylase b kinase (made from an inactive phosphorylase a kinase by a cAMP-dependent protein kinase)

** Phosphorylase phosphatase (inhibited by cAMP).

An increase in the level of cAMP therefore leads to breakdown of glycogen and a concommitant inhibiton of the synthesis.

GLYCOLYSIS. Catabolism of glucose to pyruvate. Takes place in all cells with the initial step catalyzed by hexokinase (95). The liver form is called glucokinase (73). The pathway creates substrate for the TCA cycle under aerobic conditions. In the absence of oxygen the pathway is important as an energy-yielding process. Regulated by phosphofructokinase (149), i.e. the committed step.

Glucose + 2 P_i + 2 ADP + 2 NAD^+ → 2 Pyruvate + 2 ATP + 2 NADH + 2 H^+.

GLYCONEOGENESIS. Synthesis of glucose from pyruvate via oxaloacetate. Only the liver contains glucose-6-P-phosphatase (74). The function of this pathway is to convert energy reservoirs (lactate, glucogenic amino acids) to glucose. Especially important for the brain which is dependent on a constant blood glucose level. Fructose 1,6-diphosphatase is the committed step.

2,3-DPG. Is formed in erythrocytes, where its synthesis is increased when the partial pressure of oxygen decreases. 2,3-DPG decreases the affinity of hemoglobin towards oxygen. Thus, increased DPG facilitates the transport of oxygen from the lungs to the tissues.

PYRUVATE. Oxidative decarboxylation leads to acetyl-CoA. A similar reaction as this (see MAIN MAP) is the conversion of α-ketoglutarate to succinyl-CoA and of α-ketobutyrate to propionyl-CoA which is further metabolized to TCA cycle, synthesis of FFA's, cholesterol and ketone bodies.

LACTATE. Accumulates in muscles under anaerobic conditions. Pyruvate can only be oxidized in the TCA cycle under aerobic conditions. Cf. enzyme no. 115.

CARBOHYDRATE ABSORPTION

The carbohydrates in the food should account for about 50% of the caloric value. The most important nutritional carbohydrates are the polysaccharides starch (composed of amylose and amylopectin) and glycogen, disaccharides starch (composed of amylose and amylopectin) and glycogen, disaccharides (sucrose, maltose and lactose) and the monosaccharides (glucose, galactose and fructose). Only the latter substances can be directly absorbed. The necessary catabolism of the poly- and disaccharides is initiated in the mouth by amylase (20) from the salivary glands. When the food reaches the stomach, the low pH there inhibits the amylase. However, amylase is added from pancreas resulting in breakdown of all carbohydrates to a mixture of mono- and disaccharides. The disaccharides are hydrolyzed in the glycocalyx in the membrane of epithelial intestinal cells by sucrase, maltase and lactase. The absorption is partly carrier-facilitated and partly a specific symport across the luminal membrane. The monosaccharides are then transported with the blood to the liver, where they are metabolized or redistributed to other cells of the body.

Human Metabolism

8. Other Pathways

Jens Dilling Lundgren & Per Hellung-Larsen

ENERGY.
The energetic state of a cell is determined by the intracellular ATP concentration. When this is low the catabolic energy producing processes will be stimulated, either directly (by ADP and AMP) or indirectly by epinephrine and glucagon. Concommitantly, the anabolic pathways are inhibited. On the other hand, if the energy is sufficient, the anabolic processes will dominate either due to the high concentration of ATP or indirectly by the action of insulin.

The energy (ATP) may arise from the metabolism of *a)* carbohydrates (incl. lactate), *b)* amino acids, *c)* lipids and *d)* ketone bodies.

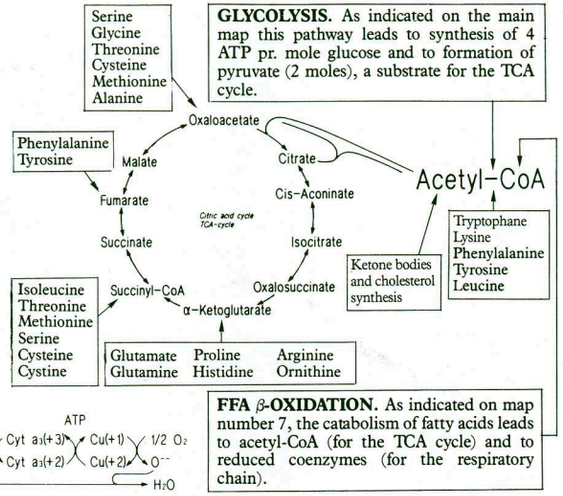
SYNTHESIS OF ATP. Two different mechanisms are available (confer the map: ENZYME CLASSIFICATION): *1) Phosphorylation at substrate level, 2) Oxidative phosphorylation.*

Ad 1) Occurs at 2 processes in the glycolysis and at a single process in the TCA cycle (see MAIN MAP). ATP is formed by transfer of P_i from a metabolite to ADP.

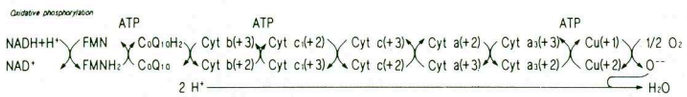
Ad 2) More important from a quantitative point of view is this series of processes, which take place in the inner membrane of the mitochondria. ATP and water are produced and the substrates are reduced coenzymes ($NADH + H^+$, $NADPH + H^+$ and $FADH_2$) and oxygen. The so-called chemiosmotic theory by Mitchell postulates that a gradient of H^+ ions is the basis for the production of ATP. The TCA cycle and the oxidative phosphorylation are coupled, so that the TCA cycle does not work if the oxidative phosphorylation does not use the reduced coenzymes.

TCA CYCLE. Also called the citrate cycle. Every molecule of acetyl-CoA gives rise to 12 ATP + 2 CO_2. It is therefore evident that glucose cannot be synthesized from acetyl-CoA, as both of the two C-atoms become carbon-atoms of CO_2. A number of the amino acids donate metabolites other than acetyl-CoA to the TCA cycle, while the carbohydrates and the lipids donate primarily resp. solely acetyl-CoA. Carbohydrates are also converted to oxaloacetate and to malate, which are of importance for the substitution of the TCA metabolites, for example α-ketoglutarate, succinyl-CoA and oxaloacetate. If there is insufficient catabolism of carbohydrates and/or amino acids the acetyl-CoA cannot enter the TCA cycle and ketone bodies will be synthesized. This is the case with untreated diabetes mellitus, where the low intracellular glucose concentration even triggers secretion of glucagon which increases the β-oxidation of FFA's and leads to a further increase in acetyl-CoA.

The TCA cycle is primarily regulated by the concentration of oxaloacetate. The committed step is citrate synthetase (38).



GLYCOLYSIS. As indicated on the main map this pathway leads to synthesis of 4 ATP pr. mole glucose and to formation of pyruvate (2 moles), a substrate for the TCA cycle.



FFA β-OXIDATION. As indicated on map number 7, the catabolism of fatty acids leads to acetyl-CoA (for the TCA cycle) and to reduced coenzymes (for the respiratory chain).

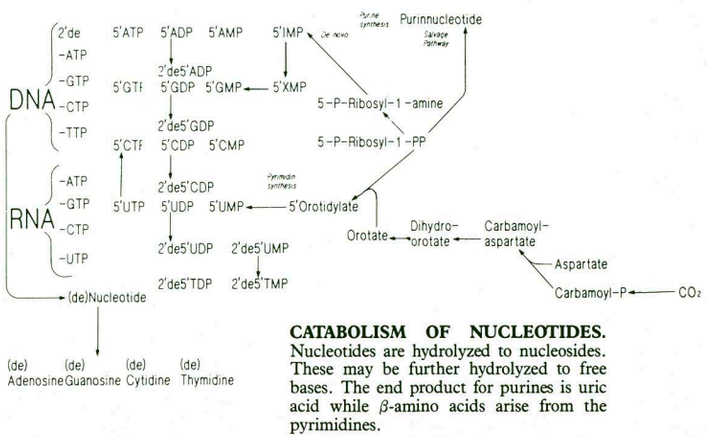
DNA-SYNTHESIS. Also denoted replication. Takes place in the nucleus at a certain period of time in the cell cycle – the S-phase (S = synthesis). The DNA is doubled by so-called semiconservative replication by a complex process where the substrates are 2'deoxy nucleoside 5'triphosphates (dATP, dGTP, dTTP, dCTP). The enzyme is DNA polymerase (55). The regulation is unknown even though several factors capable of stimulating cell proliferation have been isolated.

PYRIMIDINE SYNTHESIS. Condensation of carbamoyl-phosphate and aspartate leads to carbamoyl-aspartate, which can be metabolized to UMP and further to UDP and UTP. The committed step is aspartate transcarbamoylase (27).

RNA-SYNTHESIS. Also called transcription. Takes place in the nucleus – in the nucleoli (synthesis of pre rRNA) and in the nucleoplasm (all other types of RNA). Takes place in all phases of the cell cycle. Genes for pre rRNA's are transcribed by RNA-polymerase I, genes for pre mRNA's = HnRNA's (heterogeneous nuclear RNA's) are transcribed by RNA-polymerase II, whereas the tRNA-genes are transcribed by RNA-polymerase III. All types of RNA except 5S rRNA are modified after their synthesis: *a)* cleavages by specific nucleases *b)* methylations of bases and/or ribose moieties *c)* polyadenylation *d)* formation of pseudouridine and *e)* splicing.

The regulation of RNA synthesis is unknown, but some hormones e.g. glucocorticoids, can induce increased synthesis of a specific protein.

PURINE SYNTHESIS (SALWAGE PATHWAY). Free purines can be rescued from catabolic processes by reactions with 5-phosphoribosyl-1-pyrophosphate (PRPP) to form purine nucleosides, which can then be phosphorylated by kinases.



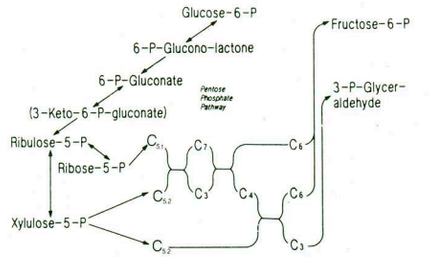
CATABOLISM OF NUCLEOTIDES. Nucleotides are hydrolyzed to nucleosides. These may be further hydrolyzed to free bases. The end product for purines is uric acid while β-amino acids arise from the pyrimidines.

PENTOSE PHOSPHATE PATHWAY. Three initial, successive, oxidative reactions lead to formation of ribose-5-P + 2 NADPH + CO_2 from glucose-6-P. These reactions are followed by non-oxidative processes catalyzed by transketolase (189) and transaldolase (187), whereby 3 moles pentose-phosphates are metabolized to 2 moles hexose-P + 1 mole triose-P. These molecules can then be processed via glycolysis.

Ribose-5-P can also be metabolized to 5-P-ribosyl -1-PP (PRPP) – a precursor for purine and pyrimidine biosynthesis.

The NADPH produced in the pentose phosphate pathway is used in *a)* the biosynthesis of FFA's *b)* hydroxylations with P-450 (steroids, detoxifications) *c)* reduction of oxidized glutathione (especially important in erythrocytes where the pentose phosphate pathway is the only metabolic sequence making NADPH). In case of decreased activity of glucose-6-P-dehydrogenase (75) the harmful effect of oxidative pharmaca on cell membranes will not be eliminated by reduced glutathione; this means that the erythrocytes become fragile and anemia may arise.

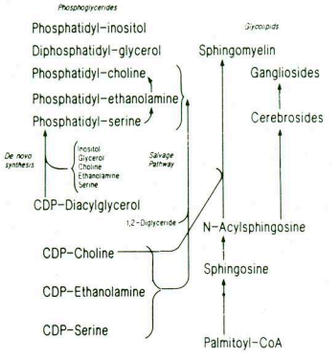
Intermediates:
C_3 = glyceraldehyde-3-P
C_4 = erythrose-4-P
$C_{5,1}$ = ribose-5-P
$C_{5,2}$ = xylulose-5-P
C_6 = fructose-6-P
C_7 = sedoheptulose-7-P



SYNTHESIS OF PHOSPHATIDES (DE NOVO). Phosphatidate reacts with CTP to form CDP-diacylglycerol, which then reacts with inositol, glycerol, choline, ethanolamine or serine to form a phosphatide.

SYNTHESIS OF PHOSPHATIDES (SALWAGE PATHWAY). Reaction between CDP-cholin (or ethanolamine or serine) and 1,2-diglyceride leads to a phosphatide.

MEMBRANE LIPIDS. Consist of *a)* phospholipids (phosphoglycerides and sphingomyelins), *b)* cerebrosides and gangliosides and *c)* cholesterol.

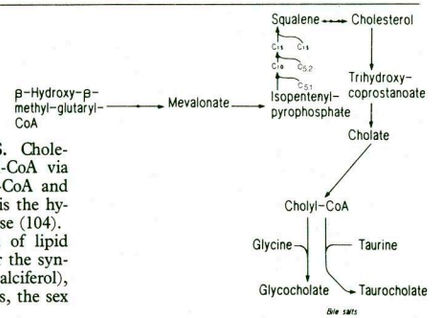


All of the compounds have a hydrophilic end and a lipophilic »tail« and are therefore detergents. Their synthesis takes place in the cytoplasm. The regulation is not known.

MEMBRANES. All composed of a double layer (unit membrane) of membrane lipids with the lipophilic »tails« turned towards the middle of the membrane. Membranes are said to have a *»fluid mosaic structure«*. This means that various proteins are embedded in the double lipid layer with no strong binding between the proteins or between proteins and lipids. Some proteins are *integral* (i.e. they go all the way through the membrane) others are *peripheral* (example: receptors, pore structures).

SYNTHESIS OF BILE ACIDS. Cholesterol (C_{27}) is metabolized to cholic acid (C_{24}), which is conjugated with either glycine or taurine to form bile salts (sodium, potassium). These salts initiate the formation of micelles (FFA, monoglycerides, phospholipids, cholesterol, fat soluble vitamins) in the intestine thereby facilitating the uptake of lipids. The bile salts are synthesized in the liver and are excreted in the bile during meals rich in fat. The excretion is controlled by cholecystokinin. After the absorption of the micelles the lipophilic substances are carried as lipoprotein, whereas the bile salts are bound to albumin and transported back to the liver (the enterohepatic pathway).

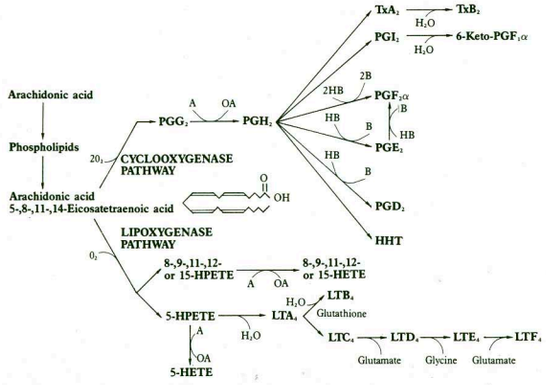
Intermediates:
$C_{5,1}$ = dimethyl-allyl-PP
$C_{5,2}$ = isopentenyl-PP
C_{10} = geranyl-PP
C_{15} = farnesyl-PP



CHOLESTEROL SYNTHESIS. Cholesterol is synthesized from acetyl-CoA via beta-hydroxy-beta-methyl-glutaryl-CoA and mevalonate. The committed step is the hydroxymethyl-glutaryl-CoA reductase (104).

Cholesterol is an integral part of lipid membranes and is a precursor for the synthesis of vitamin D_3 (cholecalciferol), glucocorticoids, mineralocorticoids, the sex hormones and the bile acids.

EICOSANOID METABOLISM.
The metabolites of this pathway have recently been shown to have several important physiological functions. See map: HORMONES. There are two subpathways nominated by the initial enzyme name, namely: 1) cyclooxygenase pathway (generating Tx and PG) and 2) lipoxygenase pathway (generating HPETE, HETE and LT). Regulation: See maps: INHIBITORS (acetylsalicylic acid), and HORMONES (glucocorticoids).



ABBREVATIONS.
A and OA = reduced and oxidized molecule A.
A and HB = oxidized and reduced molecule B.
ETE = 5-,8-,11-,14-eicosatetraenoic acid
H- = hydroxy-
HHT = hydroxy-5-,8-,10-heptadecatrienoic acid
HP- = hydroperoxy-
LT = leukotriene
PG = prostaglandin
Tx = thromboxane

Human Metabolism

9. Inhibitors

Jens Dilling Lundgren & Per Hellung-Larsen

INTRODUCTION. A number of compounds affect the human metabolism. The discipline of pharmacology deals with the effect of various effectors/drugs, which may be classified in the following way:

1. Neurotransmitters and substances which interfere with the receptors for neurotransmitters.
2. Substances with effect on the central nervous system (CNS) *a.* Psychogenic (treatment of manic, psychotic and depressive conditions). *b.* CNS-stimulating. *c.* CNS-depressing (drugs against Parkinsonism, drugs against migraine, anestetica, sleeping medicine and analgetica).
3. Analgetica with local pain releasing effects.
4. Substances with effect on the endocrine balance.
5. Substances with effect on the function of the circulatory system and the gastro-intestinal tract.
6. Chemotherapeutica = substances with effect on *a)* bacterial, *b)* viral, *c)* parasitic infections and on *d)* neoplasms (cancers).
7. Substances dealt with under toxicology, i.e. poisons from bacteria, the air and (chemical) factories.

In the following a number of substances are listed alphabetically within the seven classes. Elsewhere on the map there are definitions of concepts of importance for the understanding of the biochemical/physiological effect of the compounds, such as receptor affinity, synapses, neurotransmitters and bacterial physiology.

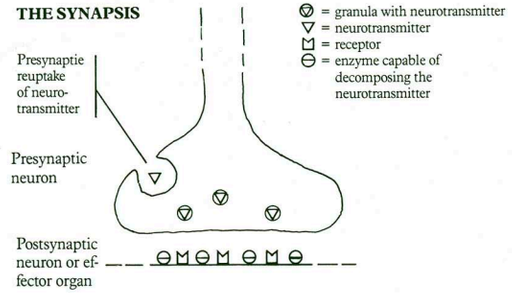
1. **ACETYLCHOLIN.** Agonist to ganglionic neuromuscular and parasymphathetic synapses.
4. **ACETYLCYSTEINE.** Used as an expectorant, due to its capacity for reducing disulphide bridges in sputum thereby lowering its viscosity.
3. **ACETYLSALICYLIC ACID.** Trade name, e.g. aspirin. Inhibits the prostaglandin synthesis, and so acts since the analgesically prostaglandins produced at inflammation sensitivitize pain-conducting nerves against bradykinin which is also produced at inflammation. Inhibits thrombocyte-aggregation and glucosaminoglycane synthesis and increases the elimination of urate through the kidneys (cf. allopurinol).
7. **ACTINOMYCIN D.** Antibiotic inhibitor of transcription. Acts by its tight binding to DNA, thus preventing it from being an efficient template.
3. **ALLOPURINOL.** Used in the treatment of gout, which is caused by increased concentration of urate in the body fluids. Allopurinol is converted to alloxanthin, which is a noncompetitive inhibitor of the enzyme xanthin oxidase (suicidal inhibition).
7. **ALLOXAN.** Analog of pyrimidin. Destroys the Langerhans' Isles of pancreas, thus causing »experimental diabetes«.
6d. **AMINOPURINE.** Analog of purines. After being incorporated into DNA it may cause erroneus replication.
2b. **AMPHETAMINE.** Stimulates α- and β-adrenergic receptors indirectly by stimulating the exocytosis of the secret-granula. Leads to CNS stimulation and inhibition of appetite.
7. **AMYTAL.** Inhibits the NADH-ubiquinone reductase (130).
7. **ANTIMYCIN.** Inhibits the ubiquinol-cytochrome c reductase (194).
7. **ARSENATE.** Analog to phosphate. Inhibits the phosphorylation at substrate level in the glycolysis (85).
3. **ASPIRIN.** See Acetylsalicylic acid.
1. **ATROPIN.** Acetyl-cholin antagonist. Leads to pupil dilatation, dryness of the mouth, decreased motility in the intestinal tube. Decreases the secretion from sweat and other exocrine glands. Has no affinity to the neuromuscular synapse.
7. **AVIDIN.** Protein in egg white. Inhibits the absorption of biotin from the intestine. May induce deficiency syndrome.
7. **AZASERINE.** Chemical structure: 2-0-(2-diazoacetyl)-serin. Inhibits amidotranspherases in the de novo synthesis of purines.
7. **AZIDES.** Salts like NaN_3. Inhibit the cytochrome oxidase.
2c. **BARBITAL.** A hypnotic (sleep inducing) drug. Its mode of action is unknown, but it is interesting that barbiturates induce their own breakdown, by induction of the P-450-cytochrome oxidase enzymes in the liver.
6d. **BROMOURACIL.** Analog of pyrimidines. Effect similar to aminopurine.
7.+2b. **CAFFEINE.** A methylxanthine which inhibits the phosphodiesterase (147) – the enzyme catalyzing the breakdown of cAMP.
1. **CARBACHOL.** Acetylcholin agonist. Leads to pupil contraction and increased secretion from exocrine glands including sweating. Contracts smooth muscles in bronchi and the intestinal tube (confer atropin). Has no affinity to the neuromuscular synapse.
7. **CARBONMONOXIDE.** Poisoneous gas with no odor. Inhibits the cytochrome oxidase. CO reacts with great affinity with heme groups in hemoglobin, so reducing the potential O_2-carrying effect.
6a. **CHLORAMPHENICOL.** Inhibits the peptidyl transferase (144) and hence protein synthesis in bacteria.
2a. **CHLORPROMAZINE.** Has a – not very well understood- antipsychotic effect. It functions as an antagonist to dopamin receptors, and is hence able to induce Parkinson's disease. Cf. synapsis and Levo-dopa.
1. **CIMETIDINE.** Antagonist to some of the histaminergic receptors (H_2), which with a few exceptions are situated on the pariental cells of the stomach. The HCl secretion is thus inhibited.
7. **CYANIDES.** Salts like NaCN. Inhibit the cytochrome oxidase (44).
7. **CYCLOHEXIMIDE.** Antibiotic substance which inhibits the elongation step in protein synthesis of eucaryotic cells.
1. **DECAMETHONIUM.** Depolarizes primarily the muscular membrane of the neuromuscular synapse by stimulating the cholinergic receptors. After this the binding of acetylcholin to the receptors is inhibited and the muscle is paralysed.
2a. **DIAZEPAM.** Trade name, e.g. Valium. An anti-anxiety drug. Increases GABA's hyperpolarizational effect (Cf.: Synapses) and so inhibits the conductivity of all nerves, leading for example to paralysis of muscles.
4. **DICUMAROL.** Antagonist to vit. K. Inhibits the clotting in vivo by inhibiting the vit. K-dependent carboxylation of glutamate in e.g. prothrombin. The binding of Ca^{2+} to prothrombin an obligatory step in the conversion of prothrombin to thrombin is inhibited in this way cf. heparin.
7. **DIPHTERIA TOXIN.** Inhibits protein synthesis by inactivating an elongation factor.
4. **DIGOXIN.** A digitalis glycoside similar to ouabain. Inhibits the $Na^+ - K^+$ – ATP'ase and hence has a specific effect on the heart. The contractility of the heart-walls is increased simultaneously to decreased conductivity of electrical impulses between the atria and the ventricles. Used in the treatment of decreased heart pump function or in the cases where the atria contracts with an abnormally high frequency.
7. **DIISOPROPYLPHOSPHOFLUORIDATE (DIPF).** Inhibits acetylcholin esterase on the postsynaptic membrane. The inhibition can be abolished by excess hydroxyamines.
7. **DINITROPHENOL.** 2,4-dinitrophenol. Inhibits the ATP syntetase thereby uncoupling the oxidative phosphorylation.
4. **DISODIUM CHROMOGLYCATE.** Inhibits the anaphylatic release of histamine and slow-reacting substances of anaphylaxis from mast cells. The mode of action is unknown.
4. **DISULFIRAM.** Trade name, e.g. Antabuse. Inhibits the enzyme capable of converting acetaldehyde – a breakdown product of ethanol – to acetyl-CoA. Acetaldehyde in large concentrations leads to mast cell degranulation and eventually to anaphylactic chock with vasodilatation, increased heart rate and bronchoconstriction.
2c. **DOPA.** See Levo-dopa.
1.+4. **EPINEPHRINE.** See the map: HORMONES.
2c. **ERGOTAMINE.** An ergot alkaloid, which is an antagonist to the serotonergic receptor (similar to LSD). Used in the treatment of migraine, where the drug probably contracts the vessels, which are dilated by serotonin.
7. **ETHANOL.** Is metabolized to acetaldehyde, which is toxic probably because it reacts with biogenic amines. Cf. disulfiram.
2c. **ETHER.** An anestetics. Inhibits the activity of neurons. The degree of inhibition is proportional to the partial pressure of the gas.
7. **FLUORACETATE.** Is metabolized to fluoracetyl-CoA, which reacts with oxaloacetate to form fluorcitrate, which cannot be further processed.
7. **FLUORIDES.** Salts such as NaF. Present in normal drinking water but are poisons if the intake is too big. Inhibit Mg^{2+}-dependent reactions – for example the enolase-reaction (57) – probably by formation of Mg-fluoride-phosphate complexes.
6d. **FLUORURACIL.** Inhibits DNA-synthesis. Used as cancer chemotherapeuticum. Fluoruracil is metabolized to F-dUMP, which inhibits the thymidylate synthetase (186), which converts dUMP to dTMP.
5. **FOLIC ACID/THFA.** See Vitamin B_{12}.
4. **HEPARIN.** A glycosaminoglycane. Found in mast cells. Inhibits the clotting in vivo and in vitro by activating antithrombine III, which inhibits the effect of thrombin conversion of fibrinogen to fibrin. Cf. dicumarol.
1. **HEXAMETHONIUM.** Antagonist towards ganglion receptors and hence inhibits the function of the sympatic and parasympatic nervous system.
5. **HORMONES, OTHER.** Nearly all hormones are available as drugs, or synthetic compounds with some or all of the effects of the natural hormones.
2a. **IMIPRAMINE.** A tricyclic antidepressive drug. Inhibits presynaptic reuptake of norepinephrine and serotonin.
7. **IODOACETATE.** Inhibits the glycolysis by reacting with SH-groups in glyceraldehyde-phosphate dehydrogenase (85).
2c. **LEVO-DOPA.** Dopaminergic agonist. Is converted to dopamine in the axon. Used in the treatment of Parkinson's disease, which is caused by a deficiency of dopamine in the extra-pyramidale tracts. Cf.: Synapses and Chlorpromazine.
3. **LIDOCAINE.** A local anesthetic. Inhibits the activity of neurons by inhibition of the depolarization which is necessary for maintenance of the treshold value and for the release of an action potential.
4. **LOOP DIURETICS.** Increase the elimination of Na^+ and water from the kidneys.
7. **MALONATE.** Competitive inhibitor of succinate dehydrogenase (179).
5. **MENOTROPIN.** A combination of LH and FSH. Used in inducing ovulation in women with infertility.
6d. **6-MERCAPTOPURINE.** Cancer chemotherapeuticum. Inhibits the conversion of 5'IMP → 5'AMP.
7. **METHANOL.** Methanol is metabolized to formaldehyde, which is very toxic. The lethal dose is about 30 ml.
6d. **METHOTREXATE.** Analog of THFA. Cancer drug.
1. **METHYLDOPA.** False neurotransmitter. Is converted to methylnorepinephrine in the axonterminal. Has affinity to the receptor but is without physiological activity.
5. **METYRAPONE.** Inhibits the 11-α-hydroxylase which is neccesary for the synthesis of glucocorticoids. The secretion of the regulatory hormones CRF and ACTH is stimulated in this way, if the negative feed-back mechanism is intact. This results in synthesis of the precursors of glucocorticoids, which can be collected and measured in the urine. The drug is therefore used in the differential diagnosis of either a hypothalamic-pituitary gland disorder or an adrenal disorder.
7. **MONOIODOACETATE.** See Iodoacetate.
2c. **MORPHINE.** A strong analgetic which mediates its function through specific opiate receptors.
2c. **NALOXONE.** Antagonist to the opiate receptors which are stimulated by morphine and the endogenous endorphins.
7. **NITRITES.** Salts like $NaNO_2$. Mutagenic as they may lead to deamination of bases in the DNA. By reaction with amines the nitrosamines are formed.
7. **NITROGEN MUSTARD.** Alkylating mutagen.
4. **NITROGLYCERIN.** Is absorbed through the mouth mucosa. Results in a general vasodilatation causing a decrease in the blood-flow to the heart leading to a decrease in the pumping activity of the heart. Used in the treatment of angina pectoris where pains from the heart are due to deficiency of oxygen in the heart muscle.
7. **NITROSAMINES.** Strong mutagens and carcinogens. Mechanism: As described for nitrites.
1.+4. **NOREPINEPHRINE.** Cf. the map: HORMONES.
7. **OLIGOMYCIN.** Inhibits the ATP syntetase (29) and hence the oxidative phosphorylation.
6a. **PENICILLINS.** Inhibit the stabilisation of the cell wall of newly synthesized bacteria by inhibition of the transpeptidase. The bacteria lyse.
1. **PHYSOSTIGMIN.** Alkaloid. Inhibits the acetylcholin esterase (1), on the postsynaptic membrane.
1.+4. **PROPANOLOL.** Selective antagonist to β 1 and 2 adrenergic receptors. This leads to decrease in the activity of the heart; the bronchi constrict and a slight vasoconstriction occurs.
7. **PUROMYCIN.** Antibiotic substance which inhibits protein synthesis by causing premature chain termination. Acts as an analog of amino-acyl-t-RNA.
7. **ROTENONE.** Inhibits the electron transport between NADH and ubiquinone.
4. **STREPTOKINASE.** Converts the plasma protein plasminogen to plasmin, which is a proteolytic enzyme capable of cleaving fibrin fibers. Clots in vessels are thereby dissolved.
6a. **SULFONAMIDES.** Antagonists to p-amino-benzoic acid.
6a. **TETRACYCLINS.** Inhibit protein synthesis in bacteria by blocking the acceptor site on the ribosomes.
4. **THEOPHYLLINE.** A methylxanthin (cf. caffeine). Used in the treatment of asthma because an increased level of cAMP relaxes the smooth muscles in the bronchi (cf. epinephrine).
5. **THIOURACIL-DERIVATES.** Inhibit the peroxidase reaction of I^- which is necessary in the synthesis of thyroxine. Used in the treatment of diseases with increased levels of T_4 and T_3, e.g. Graves disease.
5. **TOLBUTAMIDE.** A sulfonylurea, which increases the secretion of insulin from the pancreatic isles of Langerhans' β-cells. Used in the treatment of the types of diabetes mellitus where the β-cells are still able to produce small amounts of insulin.
6a. **TRIMETOPRIM.** Inhibits the bacterial dihydrofolate reductase (48).
1. **TUBOCURAINE.** Related to curare. Antagonist to the neuromuscular receptor, induces muscle paralysis. (Cf. decamethonium).
2a. **VALIUM.** See Diazepam.
5. **VITAMIN B_{12}** THFA is an essential compound in the conversion of UMP to TMP (enzyme no. 186). THFA is produced either in the Vit. B_{12}-dependent reaction catalysed by enzyme no. 97 or from folic acid. Pernicious anemia arises if the concentration of Vit. B_{12} in the plasma is low. This leads to decreased synthesis of TMP and inhibition of erythrocyte formation. Some of the symptoms are also observed with lack of folic acid but this does not involve the Vitamin B_{12}-dependent amino acid converting reaction.

RECEPTORS. Protein molecules situated all over the cell, but usually on membranes. They are able to bind specific compounds. The specificity of a receptor is large if only one or a few compounds can be bound. When a compound is bound, the reaction usually initiate a change in physiological parameters.

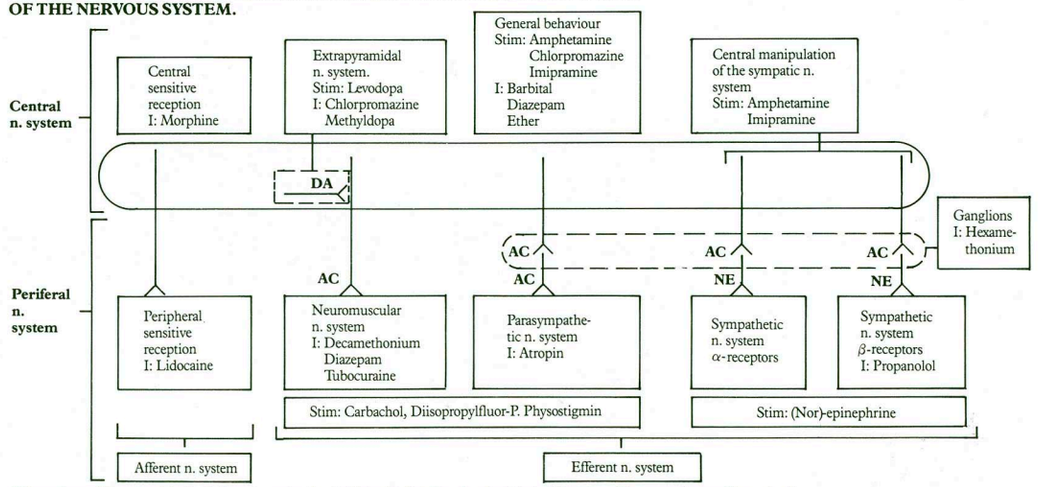
AFFINITY. The ability of a compound to bind to a receptor. The greater amount of the compound bound, the higher the affinity.

SYNAPSES AND NEUROTRANSMITTERS. When a message is to be transformed from a neuron to another or from an effector organ a synapse is located. It converts the electrical message to the release of a chemical compound presynaptic (a neurotransmitter), which effectuates the continuation of the message by binding to receptors on the postsynaptic membrane. There is only one neurotransmitter involved in one synapsis, and it is decomposed by enzymes on the postsynaptic membrane or reabsorbed by the presynaptic neuron after receptor-binding. Examples of neurotransmitters: 1) *Norepinephrine* (the sympathetic nervous system) 2) *acetylcholine* (neuromuscular motor end plate the parasympathetic nervous system and ganglions). 3) *dopamine* (the extrapyramidale nervous system, which inhibits the activity of neurons capable of initiating tremors of arms and legs, as in Parkinsons disease), and 4) *gamma amino butyrate* (GABA) which inhibits the transformation of the message by hyperpolarization of the nerve membrane.

THE SYNAPSIS



THE PRINCIPAL CLASSIFICATION AND PHARMACOLOGICAL REGULATION OF THE NERVOUS SYSTEM.



Abbrevations: AC = acetylcholin, DA = dopamine, I = inhibitor(s). (inhibits the physiological function of the synapsis; specific mode of action is described elsewhere on the map). n. = nervous, NE = norepinephrine, Stim = stimulator(s).

Human Metabolism

10. Cellular Localization

Per Hellung-Larsen & Jens Dilling Lundgren

CELLS IN GENERAL

Cells from eucaryotes (protists, fungi, plants and animals), in contrast to cells from procaryotes,contain a cell nucleus surrounded by a nuclear membrane.

The human organism contains about 10^{14} cells assembled in various tissues, namely epithelia, connective tissue, muscle and nerve tissue. The cells can be classified into at least 200 different types. They may be involved in exocrine secretion (salivary gland), hormone secretion (adrenal gland), contraction (heart), the blood system (red blood cells), the immune system (lymphocytes), specialized metabolic purposes (liver), formation of germ cells (testes)), menstruation (ovarian follicle), sensory processes (taste, smell, pain etc.), movements (ciliated cells in respiratory tract) etc.

A homogenate of cells/tissue can be prepared in various ways: By freezing and thawing, by osmotic shock, by ultrasonication or by mechanical force. If done carefully, the nuclei, mitochondria, lysosomes and microbodies are left intact, whereas the membranes are more or less fragmented. The homogenate can be fractioned by repeated centrifugations at progressively higher speeds. Thus, the whole cells, nuclei and the cytoskeleton are pelleted at low speed (∼ 1000 × g), mitochondria, lysosomes and microbodies at 10-20.000 × g, whereas high speeds (∼ 100.000 × g) are required for pelleting of ribosomes, small vesicles and viruses. Cell-free extracts are supernatants resulting from homogenates centrifuged at a certain speed. An example is the cell-free extract used in *in vitro* protein synthesis, which contains the amino acids, enzymes, factors and ribosomes.

Abbreviations used: *d:* diameter, *F:* function, *l:* length, *M:* marker metabolite (enzyme), *S:* size, structure etc., *Q:* quantitative aspects.

1 mm	=	10^{-3}m	range of light microscopy
100 μm	=	10^{-4}m	
1 μm	=	10^{-6}m	
500 nm	=	$5 \cdot 10^{-7}$m	
1 nm	=	10^{-9}m	range of electron microscopy (EM)
1 Å	=	10^{-10}m	

1. **CELL MEMBRANE.** Also called the plasma membrane. *F:* Functions as a selective permeability regulator. Carries receptors on the outer surface. Regulates the cell volume, the intracellular pH and the concentration and composition of ions. *S:* Unit-membrane consisting of lipids (phospholipids, glycolipids and cholesterol) with embedded proteins in different positions. The proteins are more or less embedded in the membrane and part of them can be located towards the interior of the cells or towards the surface of the cell. The glycoproteins, which are often involved in the receptor-structure, are located at the cell surface. The cell membrane has a »fluid mosaic structure«, which means that there is no covalent binding between the components, i.e. proteins and lipids. The ratio between proteins and lipids varies in different membranes from 4:1 to 1:4. The membrane has a thickness of about 8 nm.

2. **CENTRIOLES.** *F:* Essential for cell division. The number of centrioles is increased 2-fold prior to division. In some cells they differentiate to cilia or flagellae. *S:* Composed of microtubuli (l = 500 nm, d = 200 nm). *Q:* 1 pair of centrioles per interphase cell.

3. **CHROMATIN.** *F:* Chromosomal material. Often classified into euchromatin (transcriptionally active), heterochromatin (transcriptionally inactive and looking dense in the EM) and perichromatin granules. The latter structures are supposed to be the site for synthesis of HnRNA as their number increases with increased activity of transcription. *S:* DNA + protein + small amounts of RNA.

4. **CYTOSOL.** *F:* Site for a number of the main metabolic processes, like glycolysis, pentose phosphate shunt, protein synthesis and glycogen metabolism. *S:* Defined as the cytoplasm without its organelles, i.e. the cell-free extract. The cytosol contains a number of protein filaments constituting the cytoskeleton. *Q:* Constitutes 50-60% of the total cell volume. *M:* Lactate dehydrogenase.

5. **ENDOPLASMIC RETICULUM (ER).** *F:* Site of production of the protein and the lipids of most of the organelles. Two distinct regions of ER can be distinguished in EM - the rough ER with attached ribosomes on the cytoplasmic side of the membrane where the protein synthesis takes place, and the smooth ER without ribosomes, which is not involved in protein synthesis. The smooth ER contains enzymes involved in lipid and steroid synthesis, as well as in detoxification reactions. The NADPH- and cytochrome P 450 - dependent hydroxylations have been well studied. The smooth ER in muscle cells is called the sarcoplasmic reticulum. The microsome fraction is fragmented ER. It can be fractionated into rough and smooth microsomes (less dense). *S:* The diameter of the microsome vesicles is about 50-100 nm. The ER is pelleted by high speed centrifugation. *Q:* ER accounts for about 20% of the total cellular protein and about 60% of the cellular RNA. The RNA is rRNA (80% of whole cell RNA) which in its mature form constitutes the ribosomes together with some specific proteins. *M:* Glucose-6-phosphatase.

6. **GLYCOGEN GRANULES.** *F:* Deposits of glycogen. Serve as energy reservoir. *S:* d = 10-40 nm. *Q:* Appears often in liver and muscle tissue. Other energy deposits are ATP, phospho-creatine and fat droplets.

7. **GOLGI APPARATUS.** *F:* Probably a regulator of the transport of macromolecules (proteins, glycoproteins, glycolipids). It modifies the molecules during their passage. The precise biochemical function is not known. Apart from the modifications, the Golgi apparatus produces secretory vesicles, which can be released to the cell surface (exocytosis). It is postulated that a recycling of vesicles containing membranous material takes place. *S:* Located near the nucleus. Consists of a stack of plates (a few to several hundred per cell). The Golgi apparatus has two sides - proteins enter at one side and leave at the other.

8. **LYSOSOMES.** *F:* Site for intracellular digestion. *S:* Spherical vesicles, d = 500 nm. Heterogenous in size. Often classified into primary (newly formed) and secondary lysosomes. The latter type comprises digestive vacuoles, autophagic vacuoles and multivesicular bodies. Lysosomes contain a unit-membrane enclosing about 50 enzymes, all hydrolytic (proteases, lipases, nucleases, glycosidases, phosphatases, sulfatases) with a pH-optimum around 5. *Q:* There are about 200 lysosomes per cell and they account for 0.2 - 0.5% of the cytoplasmic volume. *M:* Acid phosphatase.

9. **MICROBODIES/PEROXISOMES.** *F:* Perform catabolic reactions by use of oxygen. Discovered around 1960. Present in most eucaryotic cells. Contain enzymes (peroxidases) catalyzing reactions like $RH_2 + O_2 \rightarrow R + H_2O_2$ and also catalase to remove excess hydrogen peroxide, $H_2O_2 \rightarrow H_2O + \frac{1}{2}O_2$. The microbodies are involved in fatty acid catabolism and probably also in detoxification reactions. *S:* Slighly larger than lysosomes. Contains a unit-membrane. *Q:* There are about 500 microbodies per cell. They account for about 1% of the cytoplasmic volume.

MICROTUBULI/FILAMENTS. *F:* The cytoplasm of eucaryotic cells contains a number of filaments which serve as the basic structure of the cytoplasm - called the cytoskeleton. Two of the important filaments are microtubules (made of tubulin) and microfilaments (actin filaments). Apart from these structures, the cytoskeleton contains the so-called intermediary filaments and other proteins. Actin filaments are involved in cell motility together with myosin. Microtubules form a part of the cilial core. Microtubules are located at the center of interphase cells but they disassemble as the mitotic spindle is formed. The drug colchicine blocks the cells in mitosis by preventing polymerization of tubulin molecules into microtubules. The drug cytochalasin inhibits the formation of actin filaments. *S:* Tubulin filaments (microtubules) have d = 25 nm (dimers of α-tubulin and β-tubulin). Actin filaments have d = 7 - 10 nm.

10. **MITOCHONDRIA.** *F:* Site of major energy production in the cell = oxidative phosphorylation of ADP to ATP. Fatty acids are catabolized to acetyl-CoA, NADH and $FADH_2$ and acetyl-CoA is oxidized to CO_2 and H_2O in the TCA-cycle. *S:* A matrix surrounded by two unit-membranes. The inner membrane is folded, thus forming cristae in the matrix. The *matrix* contains > 100 enzymes, including those of the TCA-cycle and those catalyzing the oxidation of pyruvate and fatty acids. Mitochondrial DNA, tRNA's and ribosomes are positioned here. The *inner membrane* contains the respiratory chain components, (i.e. the oxidative phosphorylation) the ATP synthetase and some proteins regulating transport in and out of the matrix. The mitochondria have the following dimensions l = 2 μm d = 500 nm. *Q:* 400 - 1000 mitochondria in a rat liver cell. Account for 15 - 20% of the cytoplasm. 40% of the dry weight of mitochondria is phospholipid. *M:* Succinate dehydrogenase and cytochrome oxidase.

11. **NUCLEAR MEMBRANE.** Also called nuclear envelope. *F:* Regulates the transport into (histones) and out of (mRNA's) the nucleus. *S:* Double unit membrane, with a membrane thickness of about 8 nm and a distance of 20 - 40 nm between the membranes creating the perinuclear space. The nuclear pores have a distance of 100 - 200 nm. The individual pores have d = 30 - 100 nm. *Q:* A typical cell contains 3 - 4000 pores.

12. **NUCLEOLI.** *F:* Site for transcription of genes for ribosomal RNA by means of RNA polymerase I. Certain regions of chromosomes »nucleolar organizer regions« are bound to nucleoli. *S:* Regions within nucleoli are fibrillar components (mainly pre rRNA), granular components (mature rRNA) and pale staining regions. *Q:* In some cells only a few %, in other cells 25% of the nuclear volume. *M:* Pre rRNA.

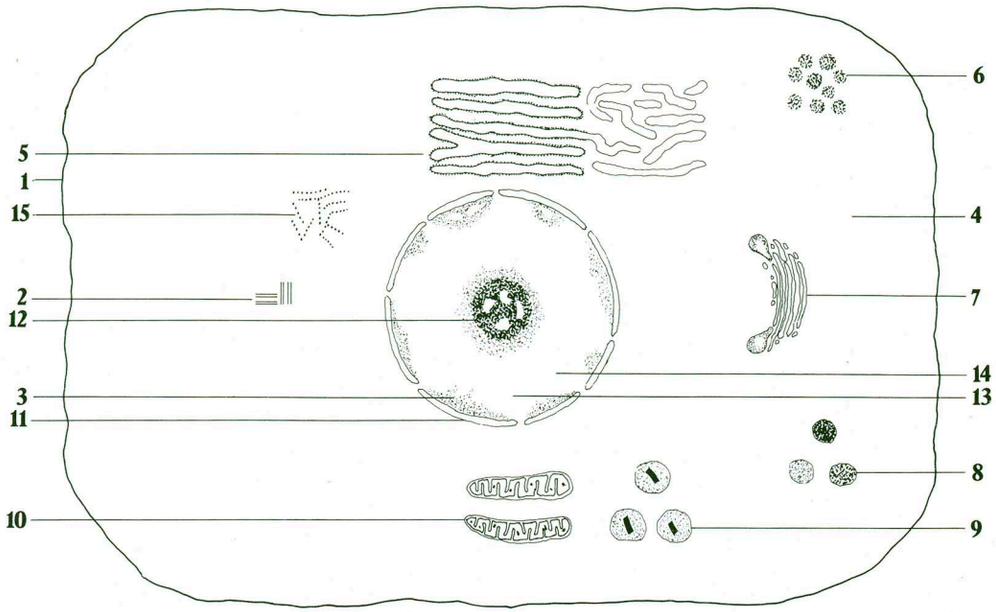
13. **NUCLEOPLASM.** *F:* Site for replication of DNA (DNA-polymerase) and transcription of genes for mRNA's (RNA polymerase II) and for tRNA's (RNA polymerase III). *S:* Contains a number of organelles with more or less known functions. *M:* HnRNA and pre tRNA.

14. **NUCLEUS.** *F:* Contains and protects the genetic material. A number of posttranscriptional modifications take place before the transcripts leave the nucleus (splicing, polyadenylation, methylation, endonuclease cleavage etc.) *S:* 1/20 - 1/10 of the cell volume, d = 5 μm. *Q:* In general 1 nucleus per cell. The nucleus has about 10% of the cell protein and 95% of the DNA. *M:* DNA- and RNA-polymerases and NAD-pyrophosphorylase (NMN → NAD).

NUCLEAR MATRIX. *F:* Unknown. *S:* When purified nuclei (detergent-treated nuclei) are treated with DNase, a fairly defined structure is left - called the nuclear matrix.

15. **RIBOSOMES.** *F:* Site of protein synthesis. The specific mature mRNA's are translated into specific amino acid sequences. The amino acids are »carried« by specific tRNA's. *S:* Ribonucleoprotein particles = 2 subunits (in mammalian cells called 60S and 40S). The 2 subunits from an 80S particle (4.5 × 10^6 Daltons). A ribosome can also be regarded as a large multienzyme complex. These particles consist of a number of specific proteins and 28S rRNA and 18S rRNA, respectively. The ribosomes have d = 20 nm. *Q:* There are millions of ribosomes per cell. *M:* rRNA and the ribosomal proteins.

Schematic representation of a eucaryotic cell



Human Metabolism

11. Hormones

Jens Dilling Lundgren & Per Hellung-Larsen

HORMONES IN GENERAL: Hormones are compounds which are liberated from the endocrine glands, and then transported through the blood, lymph or other extracellular fluids to other cells in the organism, where they exercise a regulatory function. This definition also includes the neurotransmitters, which are not dealt with here due to lack of space. Some compounds act both as hormones and as neurotransmitters (e.g. norepinephrine).

The map reviews the different hormone systems (indicated by the number code at the left side) and gives for each hormone:

1) Location of the synthesis
2) Composition
3) Primary effects
4) Mode of action
5) Factors influencing the secretion.

The feedback regulation of hormones on the secretion of their superior hormones is only mentioned if the concentration is increased – the opposite effect is seen if the concentration is decreased. Some of the information on the map goes beyond general biochemistry, but is fundamental to endocrinology. The map finally shows the cAMP-mechanism through which many hormones exert their effect on the target cell.

ABBREVIATION: AA = amino acid, **CONC** = concentration, **F** = factor, **GL** = gland, **H** = hormone, **IF** = inhibitory factor, **LF** = liberating factor, **LOS** = location of synthesis, **MOA** = mode of action, **RF** = releasing factor.

HYPOTHALAMUS-H's. These H's are called factors. Their secretion is partly influenced by the regulatory compounds and partly by neuronal stimuli. Different F's regulate the secretion of the corresponding H from the anterior lobe of the pituitary gl.

(1) **Corticotropin RF = CRF.** *Composition:* Peptide with 41 aa's. *Secretory inhibitors:* Cortisol, ACTH. *Comments:* Secretion of F is increased neuronally by stress. Secretion of F varies during the day with the highest conc in the morning.

(2) **Follicle stimulating H RF = FSHRF.** *Composition:* Decapeptide. *Secretory inhibitors:* Estrogen, perhaps melatonin. *Comment:* Secretion is inhibited by nursing.

(3) **Luteinizing H RF = LHRF.** *Composition:* Perhaps the same decapeptide as FSHRF. *Moa:* Via cAMP. *Secretory stimulator:* Estrogen (positive feedback mechanism in the middle of the menstruation period). *Secretory inhibitor:* Progesterone, estrogen, androgen, perhaps melatonin. *Comment:* Secretion is inhibited during nursing.

(4) **Melanocyte stimulating H RF = MSHRF and melanocyte stimulating H IF = MSHIF.** *Composition:* Unknown. *Secretory stimulator and secretory inhibitor:* Unknown. *Comment:* The effect of F is established.

(5) **Prolactin IF = PIF.** *Composition:* Unknown. *Comments:* The secretion is inhibited by a neuronal reflex during nursing. Conc is low at birth.

(6) **Thyrotropin RF = TRF.** *Composition:* Tripeptide. *Moa:* Via cAMP. *Secretory inhibitors:* T_3 and T_4 , somatostatin. *Comment:* The secretion of F is decreased neuronally by stress and stimulated by exposure to cold.

(7) **Growth H RF = GHRF and growth H IF = GHIF = somatostatin.** *Composition:* Peptide with about 40 aa's. *Secretory inhibitor:* Growth hormone. *Composition:* Peptide with 14 aa's and one disulfide bond. *Secretory stimulator:* Growth hormone. *Comment:* The secretion of F is increased neuronally by stress.

HORMONES FROM THE ANTERIOR LOBE OF THE PITUITARY GL. This gl contains cell types which can be characterized by staining techniques as well as by the nature of the secretory product.

(1) **Adrenocorticotrophic H = ACTH = Corticotrophin.** *Celltype and composition:* The chromophobic/basophilic corticotrophic cells, peptide with 39 aa's. The N-terminal end is the active part. *Effect:* Increases the production and secretion of glucocorticoids by enhancing the amount of cholesterol in the mitochondria resulting in the synthesis of pregnenolon which diffuses into the cytosol. Stimulates the lipase (enzyme no. 119) in the adipocytes and has diabetogenic effect. *Moa:* Via cAMP. *Secretory inhibitor:* Cortisol. *Secretory stimulator:* CRF. *Comments:* Biological $T_{½}$ = app. 10 min. Secretion of the H varies during the day with the highest conc in the morning.

(2) **Follicle stimulating H = FSH.** *Celltype and composition:* Basophilic, gonadotrophic cells, glycoprotein with two subunits, one of which is identical to that of TSH and LH. *Effect: Women:* Primarily stimulation of the formation of follicles in the ovaries, leading to secretion of estrogen. *Men:* Stimulates the formation of androgen receptors in testicular Sertoli cells, thereby leading to spermatogenesis. *Moa:* Via cAMP. *Secretory inhibitor: Men:* Inhibin (formed in the Sertoli cells). *Secretory stimulator:* FSHRF.

(3) **Luteinizing H = LH.** *Celltype and composition:* Basophilic, gonadotrophic cells, glycoprotein with two subunits, one of which is identical with that of TSH and LH. *Effect: Women:* Stimulates the formation of the mature follicle (following the effect of FSH). Subsequently LH stimulates the ovulation and the formation of corpus luteum, hence stimulating the progesteron synthesis. *Men:* Stimulates the production and secretion of androgens in testicular Leydig cells. *Moa:* Via cAMP (women: increases the vascularity in the follicular theca internal cell layer). *Secretory stimulator:* LHRF.

(4) **Melanocyte stimulating H = MSH.** *Celltype and composition:* Intermediary cells, polypeptide with serveral aa's in the same position as in ACTH. *Effect:* Perhaps stimulates the melanin production in the epidermal melanocytes. *Moa:* Via cAMP. *Secretory inhibitor:* MSHIF. *Secretory stimulator:* MSHRF. *Comment:* H is not secreted by adults.

(5) **Prolactin = lactogenic H = mammotrophin.** *Celltype and composition:* Acidophilic, mammotrophic cells, protein with MW = 3×10^4. *Effect: Women:* Stimulates – as with estrogen and progesterone – the growth of/production of milk in milk producing gl's in mammae during and after pregnancy. *Men:* Unknown. *Moa:* Via cAMP (increases the protein synthesis of the two subunits of enzyme no. 117). *Secretory inhibitor:* PIF. *Secretory stimulators:* Estrogen, T_3 and T_4 . *Comment:* Secretion of H varies during the day with the highest conc during sleep.

(6) **Thyroid stimulating H = thyrotrophin = TSH.** *Celltype and composition:* Basophilic, thyrotrophic cells, glycoprotein with α – and β-subunits, the α-subunit is identical to that of the gonadotrophines (LH and FSH). *Effects:* Stimulates the production of T_3 and T_4 by stimulating the jodide pump activity and pinocytotic activity. Stimulates the lipolysis in adipocytes. Long-term effect after injection: Enhances the vascularity of the thyroid gl. *Moa:* Via cAMP. *Secretory inhibitors:* T_3 , T_4 and glucocorticoids. *Secretory stimulator:* TRF.

(7) **Growth H = somatotrophin.** *Celltype and composition:* Acidophilic, somatotrophic cells, protein with 188 aa's and two disulfide bonds. *Effects:* 1) Increases the transport of aa's into the cells, 2) increases the protein synthesis, 3) increases the β-oxidation of FFA, 4) increases the glycogenolysis in the liver and 5) show a diabetic effect on muscles. *Moa:* Increases the enzyme synthesis, perhaps via a change in the level of cAMP. *Secretory inhibitor:* Somatostatin (GHIF), the H itself, glucose, glucocorticoids and FFA. *Secretory stimulator:* GHRF, increased conc of aa's (especially arginine), glucagon. *Comments:* Biological $T_{½}$ = 20-30 min. The effect is partly modified by the peptide somatomedin. *Gigantism:* Increased secretion of H during infancy. *Acromegaly:* Increased secretion of H after the calcification of the intercalated discs.

HORMONES FROM THE PARS NERVOSA OF THE PITUITARY GL.
The H's are produced in the hypothalamic supraoptic and paraventricular nuclei, but are transported intraaxonally to the pars nervosa.

Antidiuretic H = vasopressin. *Composition:* Nonapeptide with one disulfide bond. *Effect:* Increases the reabsorption of water in the kidneys distal convoluted tubule and the collecting tubules, leading to a decrease in the plasma osmolarity. Acts vasoconstrictorily. *Secretory stimulator:* Increased osmolarity in the plasma or in the cerebrospinal fluid and perhaps decreased blood volume. *Comments:* Absence leads to diabetes insipidus, alcohol decreases the secretion.

Oxytocin. *Composition:* Nonapeptide with one disulfide bond. *Effect: Women:* During and after the pregnancy it stimulates the milk ejection by stimulating the contraction of the myoepithelial cells surrounding the mammary gl. Stimulates the contraction of uterus smooth muscle. *Men:* Unknown. *Secretory stimulus:* Contact with the breast nipples.

STEROID H's. *Synthesis and composition:* See MAIN MAP. *Moa:* 1) H passes the cell membrane due to its lipophilic character 2) H binds to a cytoplasmic receptor, 3) the hormone receptor complex passes the nuclear membrane, 4) the complex stimulates transcription of specific mRNA's.

(3) **Androgens – e.g. testosterone, the male sex H.** *Los.:* The testicular Leydic cells but also in the adrenal cortex. *Effect:* Responsible for the development of the secondary male sex characters. Stimulates the spermatogenesis. Stimulates the protein synthesis and inhibits the gluconeogenesis. *Secretory stimulator:* LH.

(3) **Progesterone.** *Los:* The theca lutein cells of corpus luteum, also in the placenta at pregnancy. *Effects:* Brings the endometrium into the secretory phase after ovulation. A drop in the conc results in menses. Stimulates the formation of a viscous fluid in the cervix of the uterus. *Secretory stimulator:* LH.

(1) **Glucocorticoids – e.g. cortisol and corticosterone.** *Los:* The zona fasciculata of the adrenal cortex. *Effects:* Increases the gluconeogenesis and glycogenesis with glycogenic aa's as substrate. Increases the activity of the lipase in peripheral tissue. Inhibits the immune response, by inhibiting the DNA synthesis in lymphatic tissue. Inhibits the inflammatory response and the formation of eicosanoids. Inhibits enzymes which inactivates catecholamines. *Secretory stimulator:* ACTH. *Comments:* Increased secretion leads to Cushing's disease. Adrenal cortex insufficiency leads to Addison's disease.

Mineralocorticoids – e.g. aldosterone. *Los:* The zona glomerulosa of the adrenal cortex. *Effect:* Increased reabsorption of sodium from the distal tubules of the kidneys. *Secretory stimulator:* Angiotensin II, raise in the conc of potassium in plasma, (ACTH). *Comments:* Primary hyperaldosteroism leads to Conn's disease. Adrenal cortex insufficiency leads to Addison's desease.

(2) **Estrogens – e.g. estradiol and estrone, the female sex H's.** *Los:* The follicles and the corpus luteum's theca interna, also in placenta at pregnancy. *Effects:* Develops the secondary female sex characters, brings the endometrium into the proliferative phase. At pregnancy: Further development of the myometrium. *Secretory stimulator:* FSH.

OTHER HORMONES.

Angiotensin II. *Los:* The capillaries of the lung. *Synthesis:* From angiotensinogen, which is converted to angiotensin I by the enzyme renin. *Composition:* Octapeptide. *Effect:* Increases the secretion of the mineralocorticoids. *Secretory stimulator:* Renin. *Comment:* Biological $T_{½}$ = approx. 2 min.

Calcitonin. *Los:* The thyroid gl's parafollicular cells. *Composition:* Peptide (32 aa's with one disulfide bond). *Effect:* Lowers the plasma conc of Ca^{2+} by reducing the amount and acitivity of osteoclasts.*Moa:* Via cAMP. *Secretory stimulator:* Raise in the plasma conc of Ca^{2+}. *Comment:* Parathyroid H and 1,25-dihydroxycholecalciferol have the reverse effect.

Cholecystokinin = pancreozymin. *Los:* The endocrine cells of the small intestine. *Composition:* Peptide (33 aa's) *Effect:* Stimulates the secretion of the pancreas's enzyme containing exocrine secretion. Stimulates the evacuation of the gall bladder. *Secretory stimulator:* Increased amounts of aa's and FFA's in the intestinal fluid.

1,25-Dihydroxy-cholecalciferol. *Los, synthesis and composition:* See MAIN MAP. *Effect:* Enhances the absorption of Ca^{2+} from the intestine by increasing the synthesis of a calcium binding protein. *Moa:* Like the steroid H's. *Secretory stimulator:* The parathyroid H stimulates the hydroxylation of the C-25 in the kidneys. *Comment:* Parathyroid H has the same effect.

Eicosanoids. *Los:* Probably present in all cells of the organism. *Composition:* C-20 with one cyclopentane ring. *Synthesis:* See the map: OTHER METABOLIC PATHWAYS. *Effect:* Different effects for the different types. Regulates the contraction of the myometrium at delivery, the dilatation of the bronchi, the body temperature and the aggregation of thrombocytes. *Moa:* Partly via cAMP. *Secretory inhibitor:* Glucocorticoids inhibit the release of arachidonic acid from the cell membranes.

Endorphines and enkephalines. *Los:* The brain and perhaps other tissues. *Composition:* Peptides with 5-31 aa's. *Effect:* Reduce pain sensitivity, otherwise unknown. *Comment:* Morphine binds to the same receptors.

Epinephrine. *Los:* The adrenal medulla. (app. 80% of the catecholamine synthesis). *Synthesis and composition:* See MAIN MAP. *Effects:* Through α-receptors: Stimulates vasoconstriction (especially present in skin and intestine). Inhibits the secretion of insulin and glucagon. Stimulates through β_1-receptors: Glycogenolysis, glyconeogenesis, lipase (no 119), the automatism, contractility and rate of the heart beat. Stimulates through β_2-receptors: Vasodilation (especially present in muscles) and bronchodilation. *Moa:* For α-receptors: Increases the cyclic-GMP level. For β-receptors: Via cAMP (see enzyme no. 159 and 160). *Secretory stimulator:* Stress and physical activity mediated through acetylcholine from the sympatic neurosystem preganglionary neurons in the adrenal medulla. *Comments:* Glucocorticoids from the adrenal cortex stimulate the synthesis. Biological $T_{½}$ = 2 min.

Gastrin. *Los:* The endocrine cells in the antrum-pylorus part of the stomach. *Composition:* Peptide with 17 aa's. *Effect:* Increases the secretion of pepsin (no. 143) and activates the H^+-transporting ATP'ase (no. 99) resulting in HCl and instrinsic factor prod. *Secretory stimulators:* Peptides in the nourishment. *Comments:* Biological $T_{½}$ = 2-15 min. The secretion is inhibited at pH < 2 in the stomach.

Glucagon. *Los:* The pancreatic isles of Langerhans' α_2 -cells. Comment: Peptide with 29 aa's. *Effect:* Enhances the plasma glucose conc by stimulating the glucogenolysis and the gluconeogenesis. Activates the lipase (no 119). *Moa:* Via cAMP. *Secretory inhibitor:* Glucose. *Secretory stimulator:* Increased conc of glucogenic aa's in plasma, gastrin and cholecystokinin. *Comment:* Perhaps stimulation of the ketone body synthesis directly. Biological $T_{½}$ = 5-10 min. Insulin has the opposite effect.

Insulin. *Los:* The pancreatic isles of Langerhans' β -cells. *Synthesis:* Made from preproinsulin by removal of 23 aa's and further removal of 31 aa's from proinsulin. *Composition:* Insulin has two chains with 21 and 33 aa's . Linked together with 2 disulfide bonds. *Effects:* Decreases the blood glucose conc by increasing the glucose uptake in muscles and fat cells. Increases the synthesis of glucokinase in the liver, stimulates the glucogenesis by activating the glycogen synthase and inhibiting the activity of glucose-6-phosphatase. Increases the protein synthesis and the amino acid uptake, and lowers the FFA conc by increasing the β-oxidation and inhibiting the lipase (no. 119). *Moa:* Lowers the intracellular cAMP conc, the real mechanism is unknown. *Secretory stimulator:* Increased conc of glucose in the blood, glucagon or cholecystokinin secretion. *Comments:* Decreased secretion leads to diabetes mellitus. Biological $T_{½}$ = 5 min.

Melatonin. *Los:* Mainly Pineal gl. *Synthesis and composition:* See MAIN MAP. *Effect:* Decreases the secretion of FSHRF and LHRF (uncertain).

Norepinephrine. *Los as hormone:* The adrenal medulla. *Los as neurohormone:* At almost all of the transmissions at the postganglionary sympathetic neurones.

Parathyroid H = PTH. *Los:* Parythyroid gl. *Synthesis:* Prepro-PTH (115 aa's is converted to pro-PTH (90 aa's), which splits off 8 aa's). *Composition:* PTH is thereby formed. *Effects:* Increases the plasma conc of Ca^{2+} by stimulating the osteoclast-activity. Increases the phosphate excretion in the kidneys leading to Ca^{2+} reabsorption from the bones. Increases the activation of cholecalciferol. *Moa:* Via cAMP. *Secretory stimulator:* Drop in Ca^{2+} - plasma conc. *Comments:* Calcitonin has the opposite effect. Biological $T_{½}$ = 20 min.

Prostaglandins. See eicosanoids.

Secretin: *Los:* Enteroendocrine cells in the upper part of the small intestine. *Composition:* Peptide (27 aa's). *Effect:* Stimulates the secretion of the exocrine bicarbonate-containing secretion from pancreas. *Moa:* Via cAMP. *Secretory stimulator:* Increased conc of acid.

Serotonin. *Los:* Brain and intestine. *Synthesis and composition:* See MAIN MAP. *Effect:* Vasodilating. *Comment:* Lysergic acid diethylamide (LSD) is an antagonist.

(6) **Tetraiodothyronine = thyroxine = T_4 and triiodothyronine = T_3** . *Los:* The follicular colloid of the thyroid gl. *Synthesis:* Mono- and diidotyrosine (called MIT and DIT) are synthesized after the absorbed iodide ions has been converted to I_2 by the peroxidase catalyzed reaction: $2\ I^- + H_2O_2 + 2H^+ \rightarrow I_2 + 2H_2O$. Final steps in the synthesis: MIT + DIT $\rightarrow$ T_3 + ala, and DIT + DIT $\rightarrow$ T_4 + ala. The reaction takes place bound to the glycoprotein thyroglobulin. *Effects:* Increased metabolism leading to increased O_2 -consumption. Increased absorption of glucose from the intestine. Stimulates the growth in early childhood. Inhibits the production of glucosaminoglycans in the subcutis. *Moa:* Cytosolic receptors upconc the H. Other nuclear receptors bind to the H. The nuclear hormone-receptor-complex increases the transcription of the mRNA for specific enzymes (e.g.: Na^+ -K^+ - ATP'ase). *Secretory stimulator:* TSH. *Comments:* The organism needs about 200 μg iodide per day for normal function. Biological $T_{½}$ = 1.5 day (T_3) and 7 days (T_4). Hyperfunction of the gl leads to hyperthyroidism (e.g. Graves disease). Hypofunction of the gl leads to hypothyroidism (e.g. Myxedema). Congenital hypothyroidism is called cretinism.

SOME HORMONES EXERT THEIR EFFECT VIA CYCLIC AMP.

1) H binds to a specific receptor on the surface of the cell.
2) GTP and perhaps other compounds (eicosanoids) bind to adenylate cyclase.
3) Adenylate cyclase is activated (e.g. no. 9).
4) cAMP activates a protein kinase (no. 166) and perhaps other enzymes (no. 160).
5) Protein kinase (in)activates an enzyme with important metabolic effect by covalent binding (e.g. the lipase, no. 119, is activated by phosphorylation).
6) GTP is hydrolyzed to GDP and P.
7) A phosphodiesterase (no 147) inactivates cAMP.
8) A phosphorylase (in)activates the important enzyme (e.g. the lipase is inactivated by dephosphorylation).