INHERITED METABOLIC DISEASES

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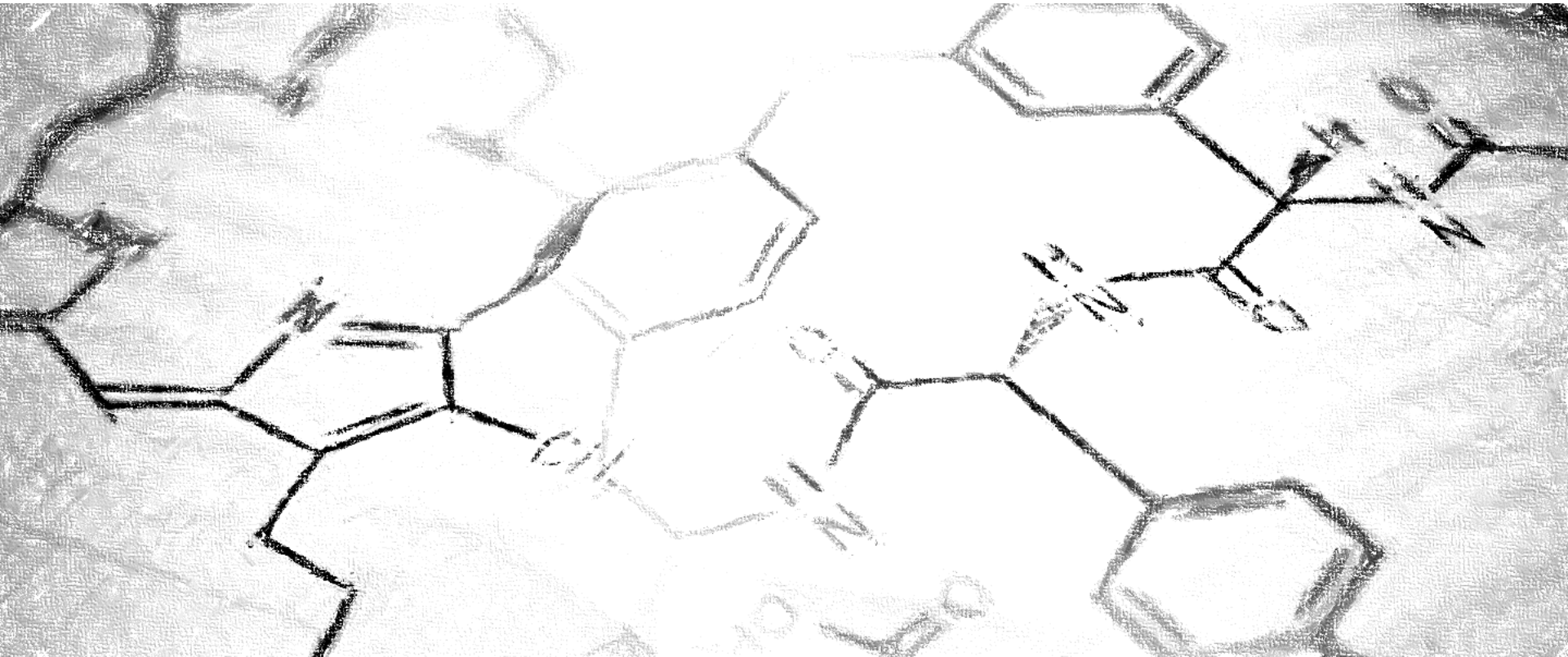


Inherited Metabolic Diseases (IMDs)

- The former term: **Inborn errors of metabolism**
- Definition: **heterogeneous group of diseases, genetically conditioned change of protein**
- In the early 20th century – the conception of IMD was formulated by British physician **sir Archibald Garrod**
- He is known for his work that prefigured the „**one gene-one enzyme“** hypothesis
- He also described the first four IMD: alkaptonuria, albinismus, pentosuria, cystinuria

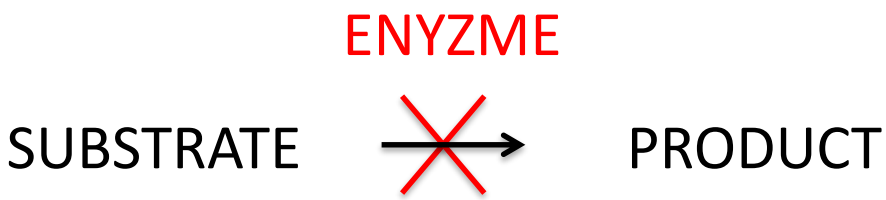
PATHOGENESIS

- IMDs are diseases based on molecular level
- IMDs are **caused by a change in the genetic information**
- Mutation in DNA → fault transcription to

  mRNA → fault syntesis protein → protein with a modified structure
- Mutation → defective transcription → defective translation
- 1 gene encodes synthesis of 1 molecule of protein

FUNCTION OF THE PROTEIN IN THE INTERMEDIARY METABOLISM

- **Enzyme**
- Transport protein
- Structural protein
- Regulatory protein



FORMS OF GENETIC TRANSMISSION

NUCLEAR DNA

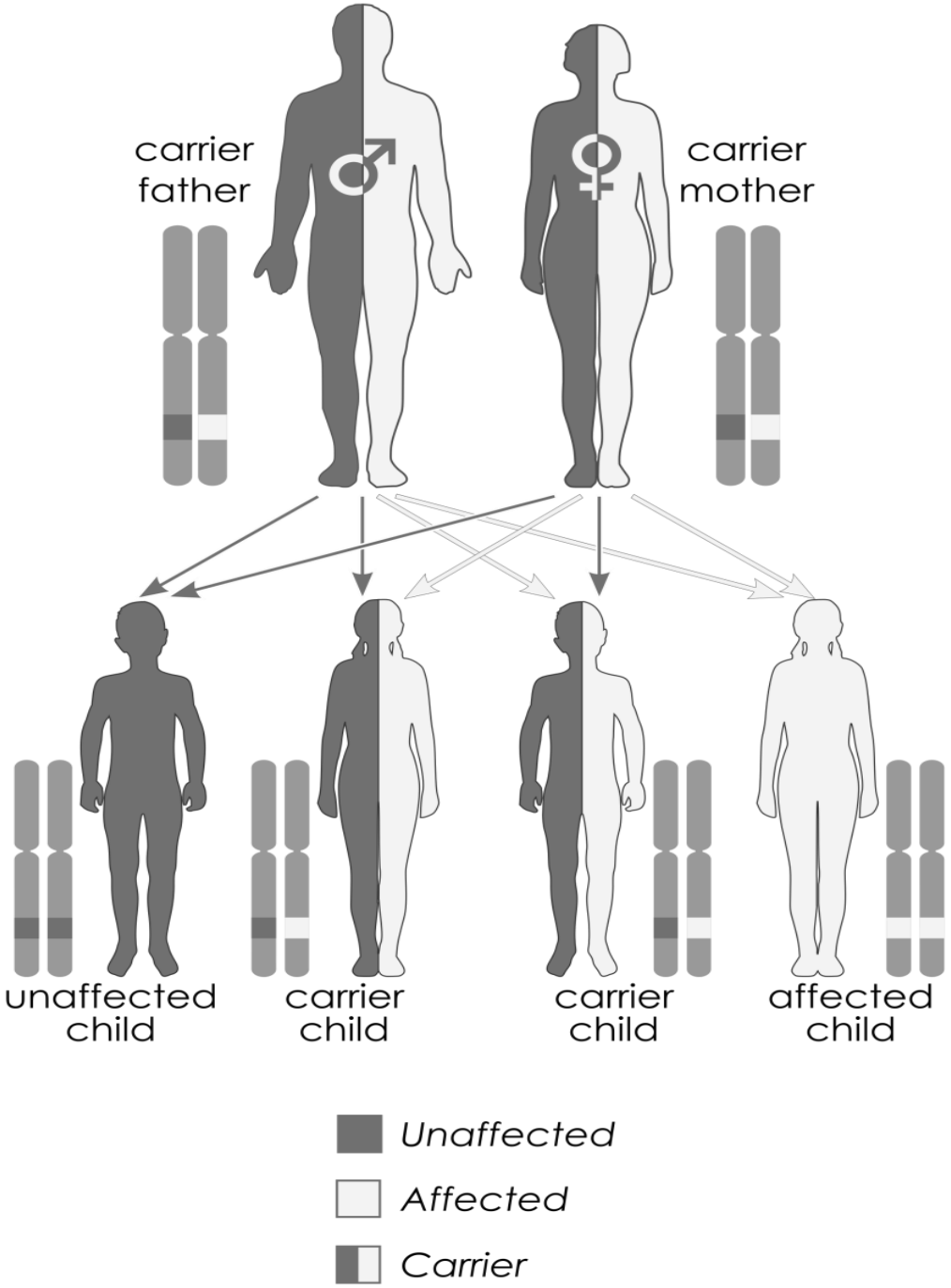
- Autosomal recessive inheritance
- Autosomal dominant inheritance
- Gonosomal dominant inheritance
- Gonosomal recessive inheritance

MITOCHONDRIAL (extranuclear) DNA

- Maternal type inheritance

INHERITANCE AR

- Most IMDs are inherited **autosomal recessive**
- Disease only affects individuals with **two defective copies** of the gene – one from each parent (**recessive homozygotes**)
- Heterozygot is healthy individual, he is only „carrier“ of the defect gene


carrier
father
carrier
mother
unaffected
child
carrier
child
carrier
child
affected
child
Unaffected
Affected
Carrier

INCIDENCE OF IMD

- **Individual** incidence is quite **rare**
  (1:15 000 – 200 000)

- **Collective** – all together is **frequent**
  (1:1000 or higher)

CLASSIFICATION OF IMDs

1. According to the **speed of the onset** of clinical symptoms
2. According to the **metabolic systems**
3. According to the **subcellular localization** of modified protein
4. According to the **analytical method** used for the detection of IMD

1.According to the speed of the onset of clinical symptoms:

- Acute metabolic
- With intermittent course
- Chronically progressive

2. According to the metabolic system

Disorders of:

- **amino acid** metabolism
- **carbohydrate** metabolism
- **organic acid** metabolism
- **storage** diseases

3. According to the subcelullar localization of modified protein:

- cytosolic
- mitochondrial
- lysosomal
- peroxisomal
- Golgi apparatus
- ion channels etc.

MANIFESTATIONS OF IMDs

- Symptoms may appear at any age – from birth to adulthood
- They may be brought on by foods, medications, dehydratation, minor illnesses, or other factors
- Symptoms may come on suddenly or progress slowly
- Severity of the disease depends on the degree of disability

CLINICAL MANIFESTATIONS OF IMD

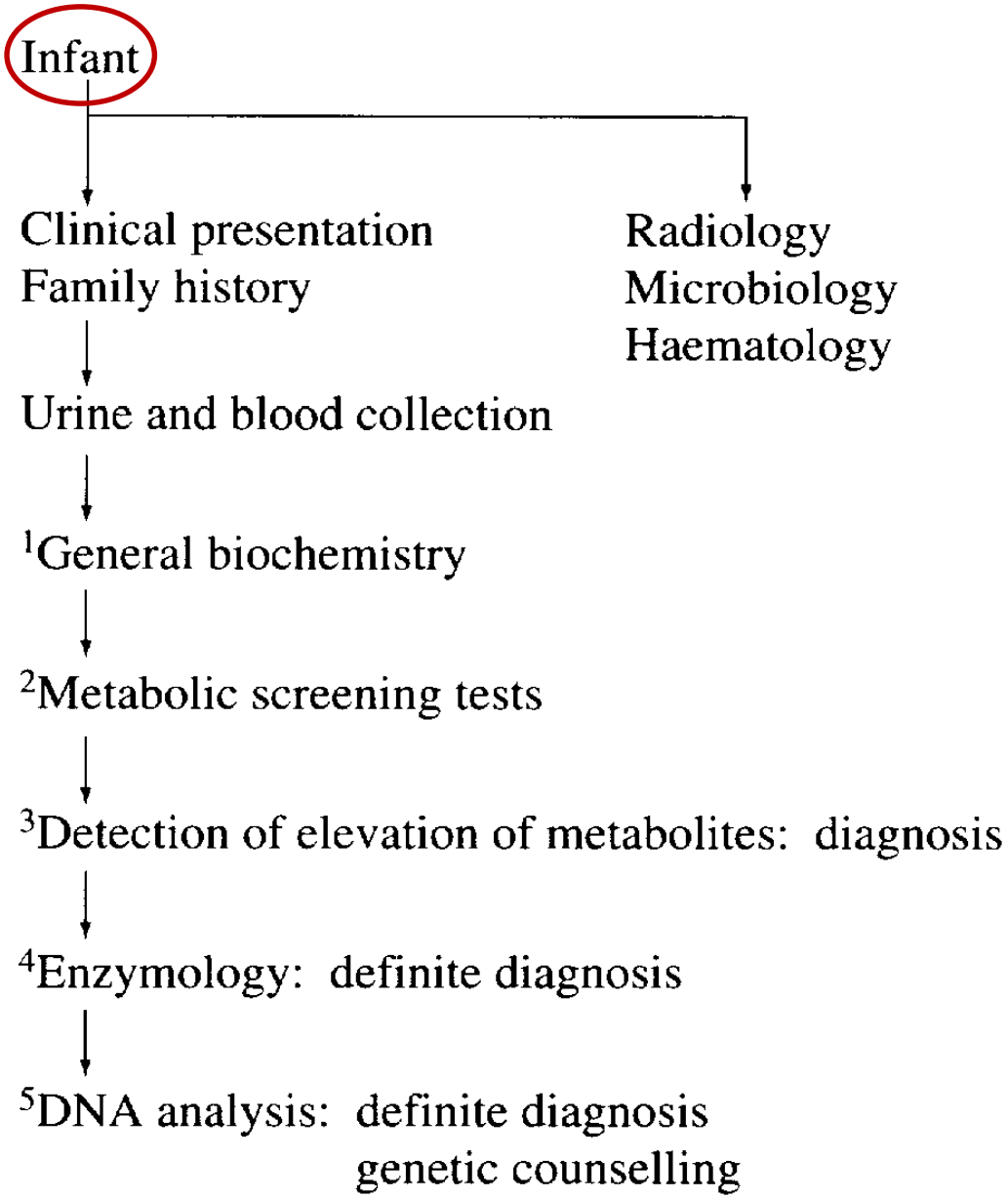
- **Non specific symptoms** – lethargy, coma, muscular hypo or hypertonia, convulsions, poor appetite, vomiting, abdominal pain, weight loss, jaundice, developmental delay…

- **Specific symptoms** – abnormal odor of urine, sweat or saliva…,ectopia of lens,trombembolic events

NONSPECIFIC LABORATORY FINDINGS

- **Acidosis** (for example accumulation of lactic acid – disorders of pyruvate dehydrogenase)
- Alkalosis
- **Hypoglycaemia**
- **Hyperammonaemia** (disorders of urea cycle enzymes)
- Hypoketosis (mitochondrial fatty acid oxidation disorders)
- Hyperketosis (some types of organic aciduria)
- Hypouricemia/hyperuricemia (disorders of purine metabolism)
- Hypocholesterolemia/hypercholesterolemia (7dehydrocholesterol reductase deficiency - Smith-Lemli-Opitz syndrom)

Strategy of the investigation of IMDs



LABORATORY DIAGNOSTICS OF IMD

1. At the level of **metabolites**
2. At the level of **enzymes**
3. At the molecular level (**mutations**)

1. LEVEL OF METABOLITES

- Characteristic: **quantitative measurement** of metabolites such as amino acids, carbohydrates, mucopolysaccharides, purine, pyrimidine, lipids, steroids…or various abnormal metabolites

- Material: serum or plasma, urine, cerebrospinal fluid, whole blood as dry blood spot on the filter paper…

DIAGNOSTICS TECHNIQUES

chromatography - paper
- thin layer
- liquid (ion - exchange, high performance - HPLC)
- gas (with mass spectrometry GC/MS)

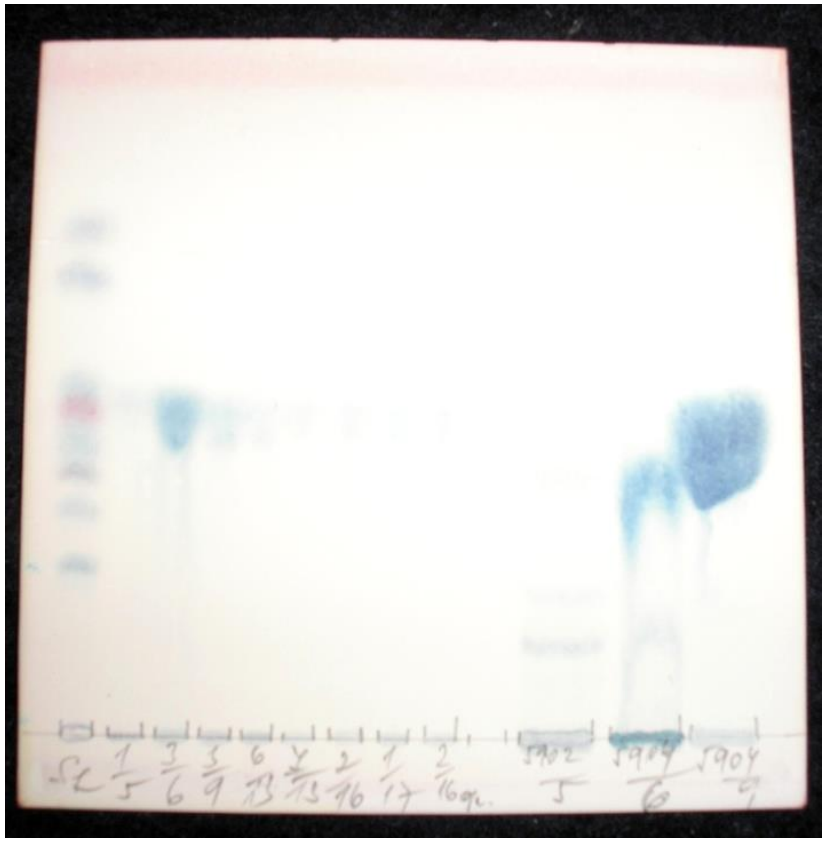
electromigration techniques
- classical electroforesis
- capillary electroforesis

tandem mass spectrometry MS/MS

THIN LAYER CHROMATOGRAPHY

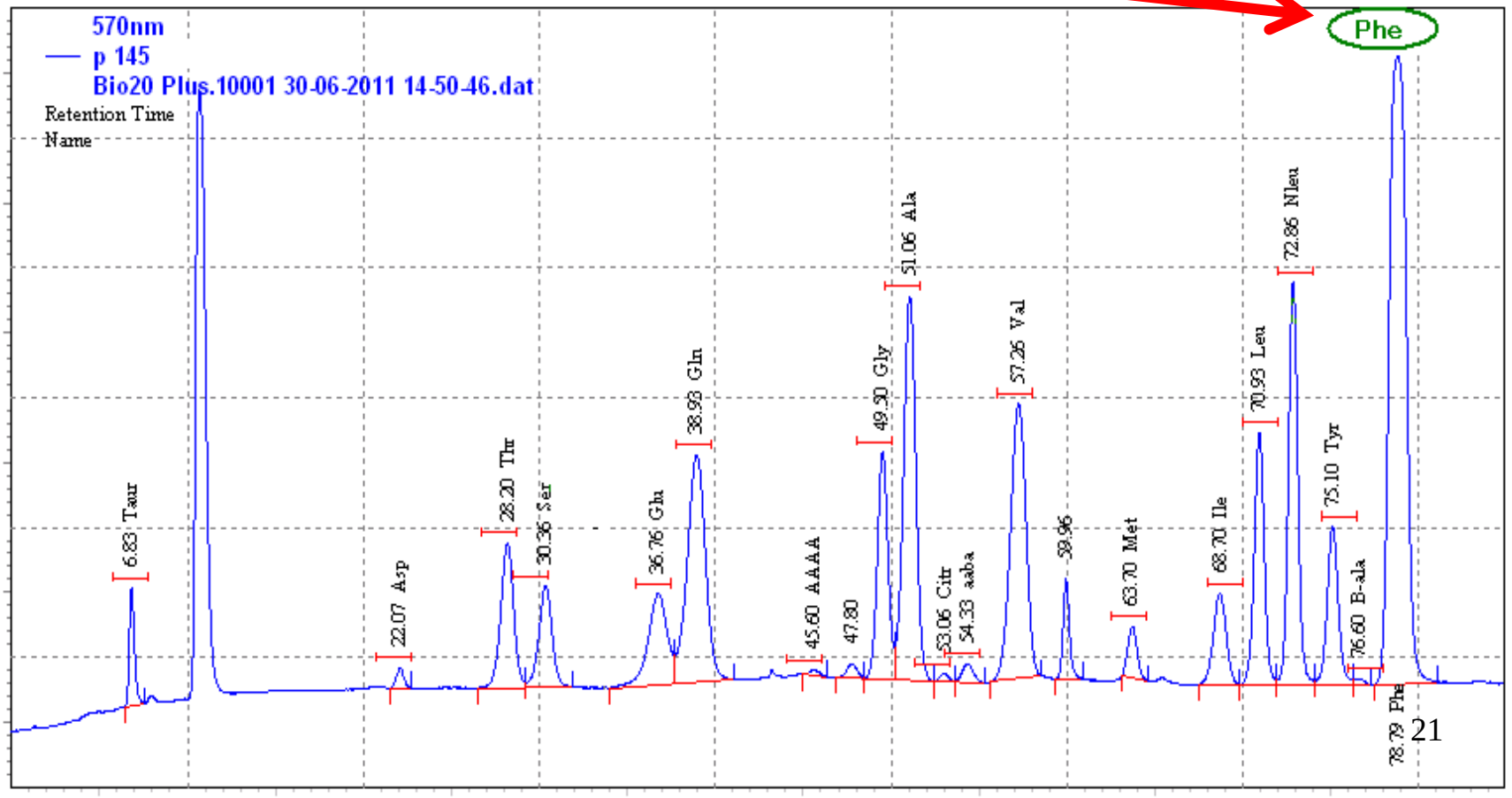
Pozitive result of fructose and galactose in urine

Pozitive result of galactose in serum and urine



LIQUID ION-EXCHANGE CHROMATOGRAPHY

High peak of plasma phenylalanine



2. LEVEL OF ENZYMES

- Characteristic: **measurement of decreased activity of the enzyme**

- Material: leukocytes, erytrocytes or plateles isolated from peripheral blood, serum or plasma, culture of skin fibroblasts, tissue from muscle or liver biopsy

3. MOLECULAR LEVEL

- Characteristic: specific **DNA tests** show defect of gene

- Material: leukocytes of periferal blood, amniotic fluid cells obtained by amniocentesis, chorionic villus cells obtained by biopsy of placenta

TREATMENT OF IMD

1. At the level of **metabolites**
2. At the level of **enzyme**
3. At the **molecular level** (experimental)

- The only causal treatment – at the molecular level
- The symptomatic treatment – reduces symptoms but does not remove the cause.

General principles in the treatment of IMD

- **Reducing or eliminating of any food** that can´t be metabolized properly (special diets)
- **Removing toxic products** of metabolism that accumulate due to the metabolic disorder (for example by dialysis)
- **Replacing the enzyme** that is missing or inactive, where it is possible (ERT)
- **Replacing other supplements** that support metabolism (for example vitamin cofactors)

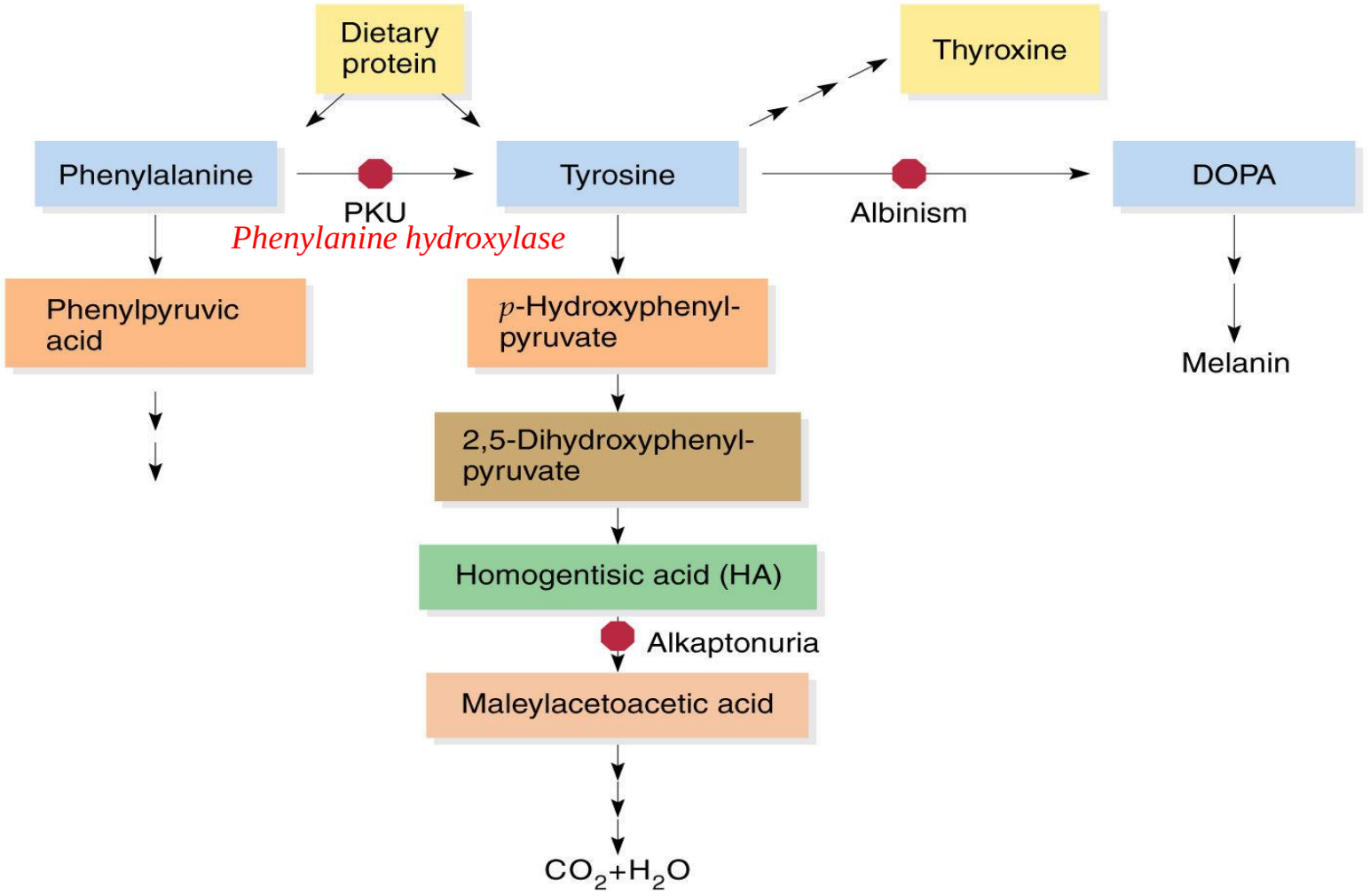
Other treatment options

- Organ transplantation (liver, kidneys, bone marrow)
- Treatment of symptoms and complictions
- Gene transfer – treatment of the future

MAJOR CATEGORIES OF IMDs

- Disorders of **AMINO ACID METABOLISM** (phenylketonuria, maple syrup urine disease…)
- **UREA CYCLE** defects
- Disorders of **CARBOHYDRATE METABOLISM** (galactosemia, glycogen storage diseases…)
- Disorders of **ORGANIC ACID METABOLISM** (metylmalonic and propionic acidemia)
- Disorders of **FATTY ACID OXIDATION** and **MITOCHONDRIAL METABOLISM** (Medium-change acyl-coenzyme A dehydrogenase deficiency…)

Phenylalanine metabolic pathway

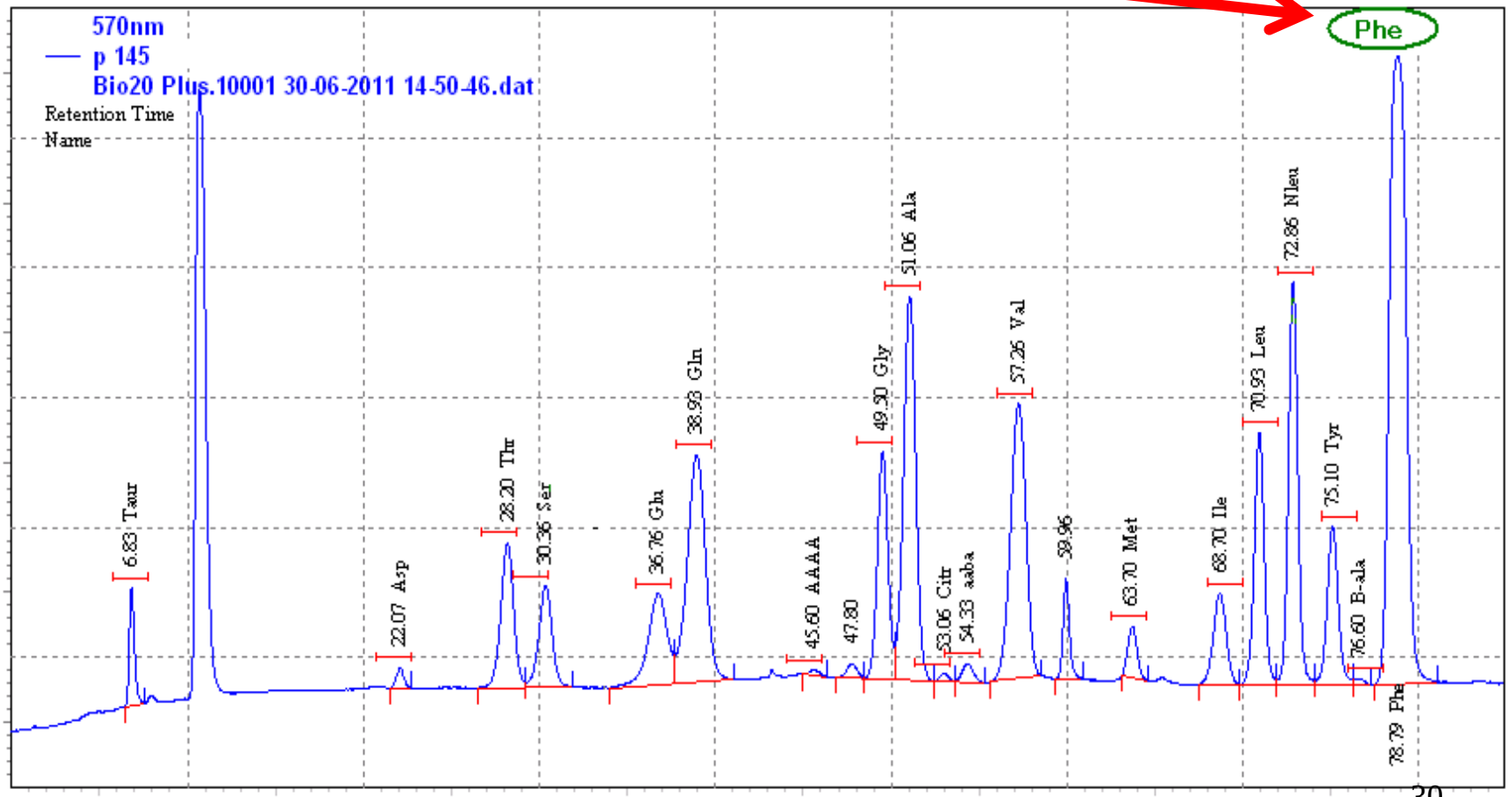


PHENYLKETONURIA (PKU)

- Phenylalanin – aromatic amino acid
- PKU is an IMD due to a **deficiency of hepatic phenylalanin hydroxylase**.
- Deficiency of this enzyme results in **high levels of phenylalanine in the blood**.
- Accumulation of phenylalanin and its metabolites leads to mental retardation, if this condition is not recognized and the strict diet isn´t observed.

1. Case report – baby with PKU

High peak of plasma phenylalanine



1. Case report - phenylketonuria

¶Narozen(a) 25/11/2018
Diagnosa...E70.0 Rodne cislo..[redacted] Vyska... 0
Komentar... Pojistovna...213 Hmotnost 0.0
Odber dne..01/12/2018-09:45

	Nazev vysetreni	Vysledek	Jednotky	Referencni interval		Hodnoceni	
893	S-Fenylalanin	31.6	mg/dl	(0.5...	1.2	VH	(...).<x
894	S-Tyrosin	0.8	mg/dl	(0.5...	2.0		(x..)

* *

¶Narozen(a) 25/11/2018
Diagnosa...Z03.9 Rodne cislo..[redacted] Vyska... 0
Komentar... Pojistovna...213 Hmotnost 0.0
Odber dne..04/12/2018-07:20

	Nazev vysetreni	Vysledek	Jednotky	Referencni interval		Hodnoceni	
893	S-Fenylalanin	20.2	mg/dl	(0.5...	1.2	VH	(...).<x
894	S-Tyrosin	2.3	mg/dl	(0.5...	2.0	H	(...)x
1990	Material S/P:	serum					

* *

1. Case report - PKU

¶Narozen(a) 25/11/2018
Diagnosa...Z03.9 — Rodne cislo..[redacted] — Vyska... 0
Komentar... — Pojistovna...213 — Hmotnost 0.0
Odber dne..06/12/2018-07:10

	Nazev vysetreni	Vysledek	Jednotky	Referencni interval		Hodnoceni	
893	S-Fenylalanin	6.0	mg/dl	(0.5...	1.2	VH	(...).<x
894	S-Tyrosin	1.6	mg/dl	(0.5...	2.0		(.x.)
1990	Material S/P:	serum					

* *

¶Narozen(a) 25/11/2018
Diagnosa...E70.0 — Rodne cislo..[redacted] — Vyska... 0
Komentar... — Pojistovna...213 — Hmotnost 0.0
Odber dne..10/12/2018-07:20

	Nazev vysetreni	Vysledek	Jednotky	Referencni interval		Hodnoceni	
893	S-Fenylalanin	1.2	mg/dl	(0.5...	1.2		(..x)
894	S-Tyrosin	2.1	mg/dl	(0.5...	2.0	H	(...)x
1990	Material S/P:	serum					

* *

2. Case report – argininosuccinic aciduria

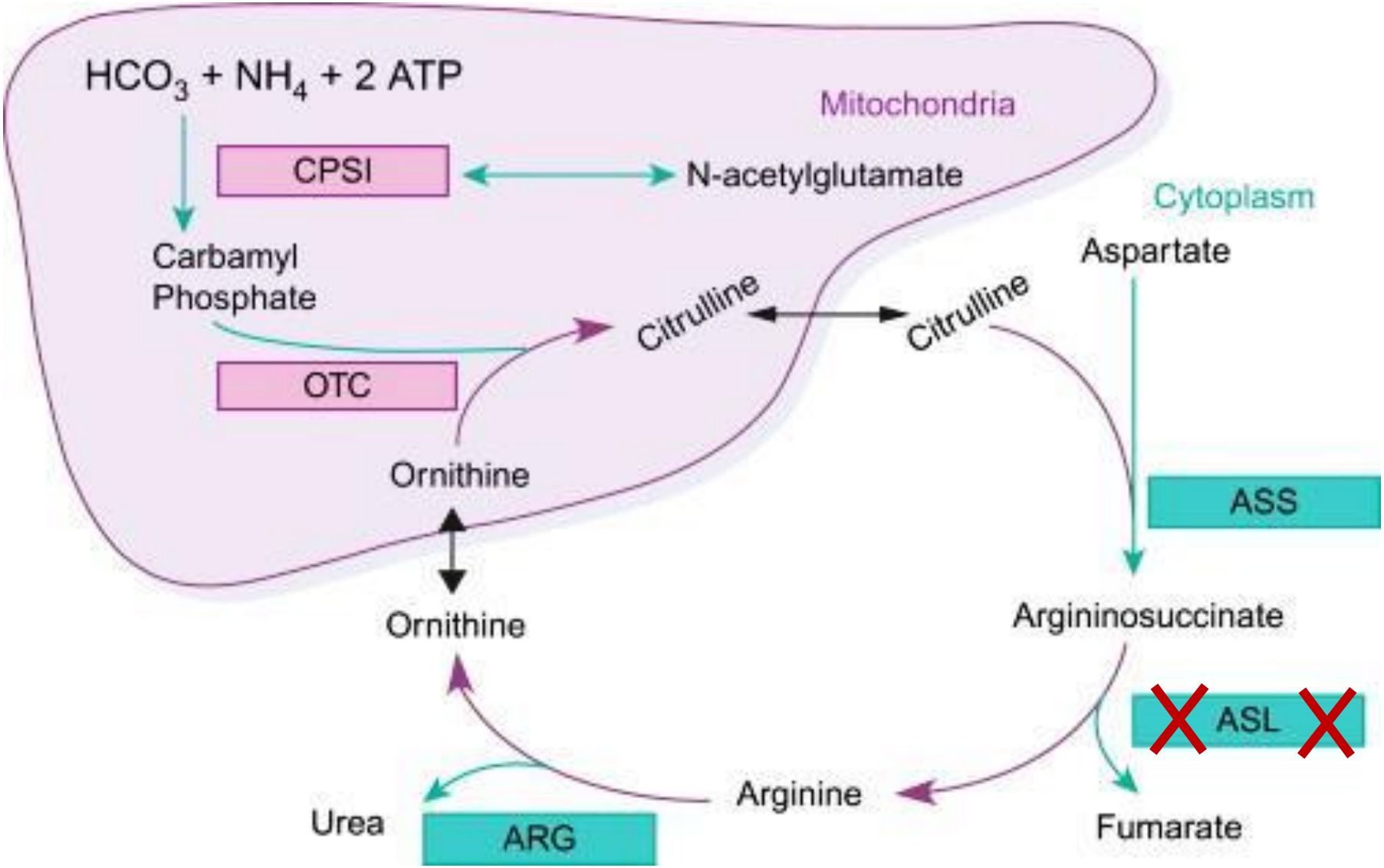
Material cislo 7081 ze dne 19/10/2017-15:04 FN Brno LOKB-PDM 22/10-10:
telefon : 53223 3168

[redacted] STATIM
53312
¶ DN PEK JIP I+II 56 (tel.4406,4458)
¶
JIP-II.cast 72100702/
13692/19
¶Narozen(a) 16/10/2017
Diagnosa...P22.9 Rodne cislo.[redacted] Vyska... 0
Komentar... Pojistovna..[redacted] Hmotnost 0.0
Odber dne..19/10/2017-14:48

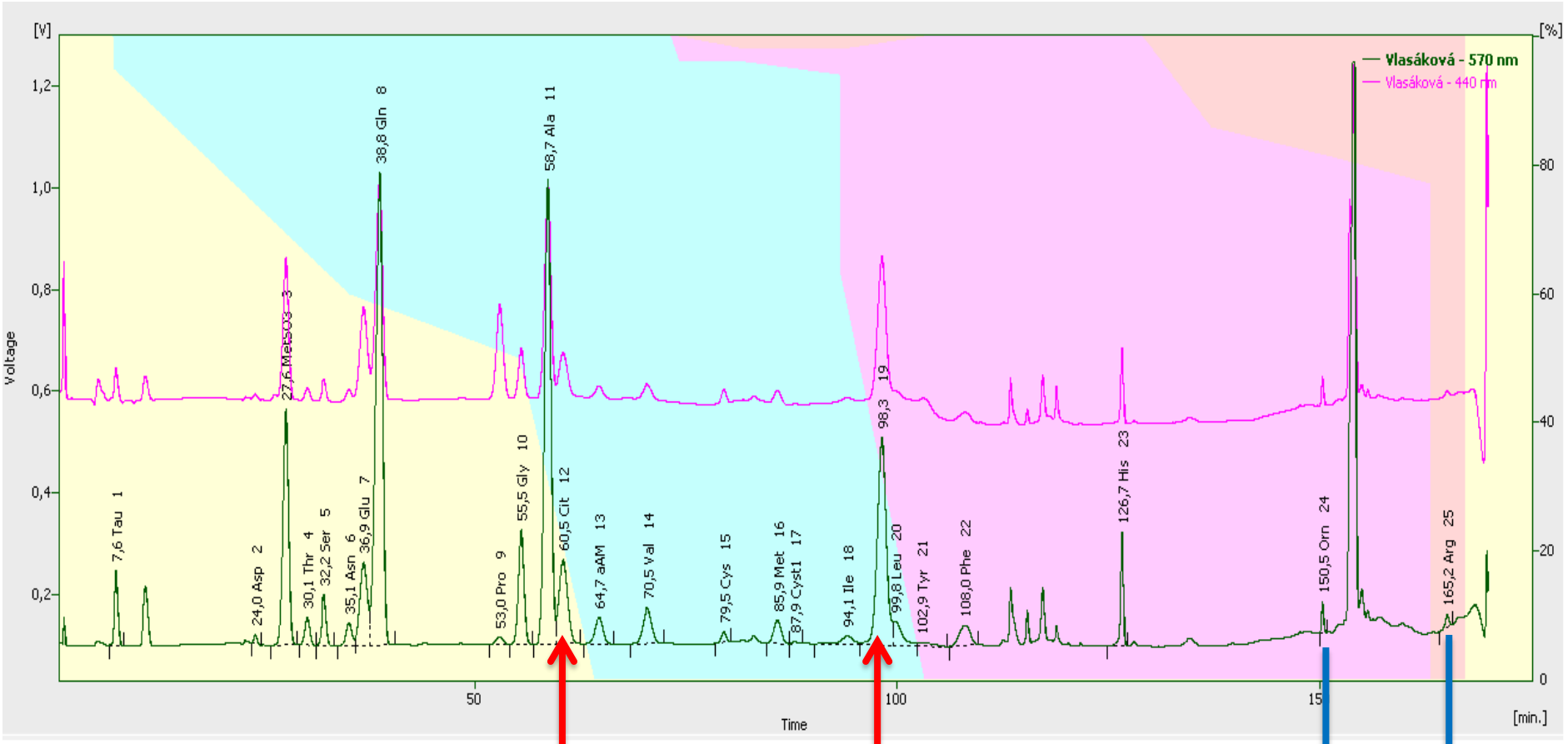
	Nazev vysetreni	Vysledek	Jednotky		Referencni interval		Hodnoceni
1	S/P-Urea	1.5	mmol/l	(	1.4... 4.3		(x..)
2	S/P-Kreatinin	79	umol/l	(	27... 77	H	(...)x
3	S/P-Kys. mocova	532	umol/l	(	140... 340	H	(...)x
41	S/P-Na	152	mmol/l	(	132... 147	VH	(...).<x
42	S/P-K	4.3	mmol/l	(	3.6... 6.1		(.x.)
43	S/P-Cl	115	mmol/l	(	95... 116		(..x)
28	S/P-Ca	1.86	mmol/l	(	1.90... 2.60	L	x(...)
29	S/P-Fosfat anorg	3.47	mmol/l	(	1.45... 2.91	VH	(...).<x
46	S/P-Mg	0.89	mmol/l	(	0.70... 0.95		(.x.)
6	S/P-Bilirub.celk	128.9	umol/l	(			
7	S/P-Bilirub.prim	30.0	umol/l	(			
8	S/P-ALT	1.10	ukat/l	(	0.15... 0.73	H	(...)x
9	S/P-AST	1.13	ukat/l	(	0.38... 1.21		(..x)
10	S/P-GGT	2.58	ukat/l	(	0.37... 3.00		(..x)
12	S/P-LD	9.72	ukat/l	(	3.75... 10.00		(..x)
13	S/P-CK	8.29	ukat/l	(	1.26... 6.66	H	(...)x
16	S/P-Bilkovina c.	56.7	g/l	(	46.0... 70.0		(.x.)
18	S/P-Albumin	38.2	g/l	(	28.0... 44.0		(.x.)
17	S/P-Glukoza	8.5	mmol/l	(	2.8... 4.4	H	(...)x
25	S/P-CRP	< 1.0	mg/l	(	0.0... 5.0		
111	P-Amoniak	viz komentar		(	56... 92		
1990	Material S/P:	plazma					
1991	Hlaseno tel. v	16.15	hod.	(			

Na stanoveno opakovane.
Hodnota amoniaku 1497 umol/l.
Hlaseno na oddel. v 16.15 hod.

Urea cycle


$HCO_3 + NH_4 + 2$ ATP
Mitochondria
CPSI
N-acetylglutamate
Cytoplasm
Carbamyl Phosphate
Aspartate
Citrulline
Citrulline
OTC
Ornithine
ASS
Ornithine
Argininosuccinate
ASL
Arginine
Urea
ARG
Fumarate

Aminogram of serum– report from AAA

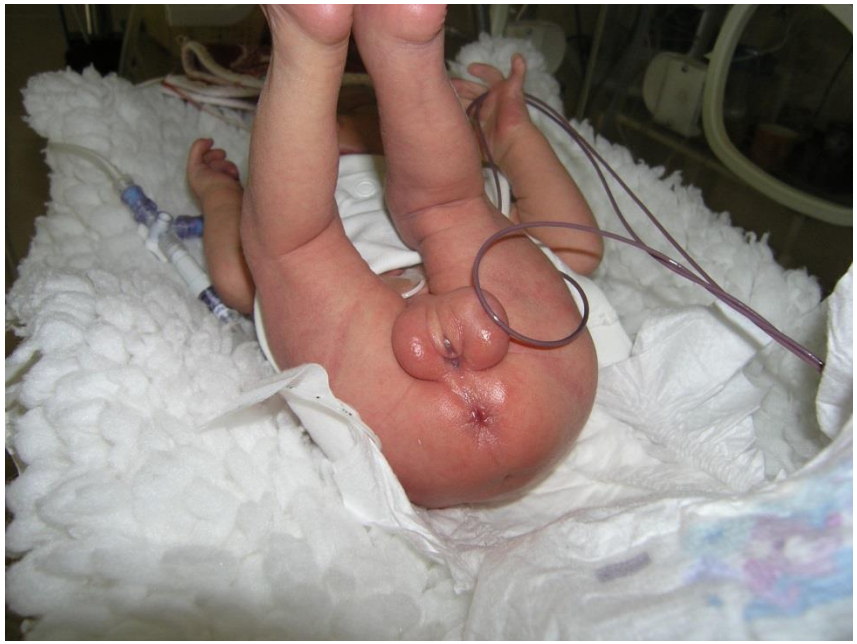


CITRULLINE **ARGININOSUCCCINATE** **ORNITINE** **ARGININE**

3. Case report – SLOS - characteristic physical features

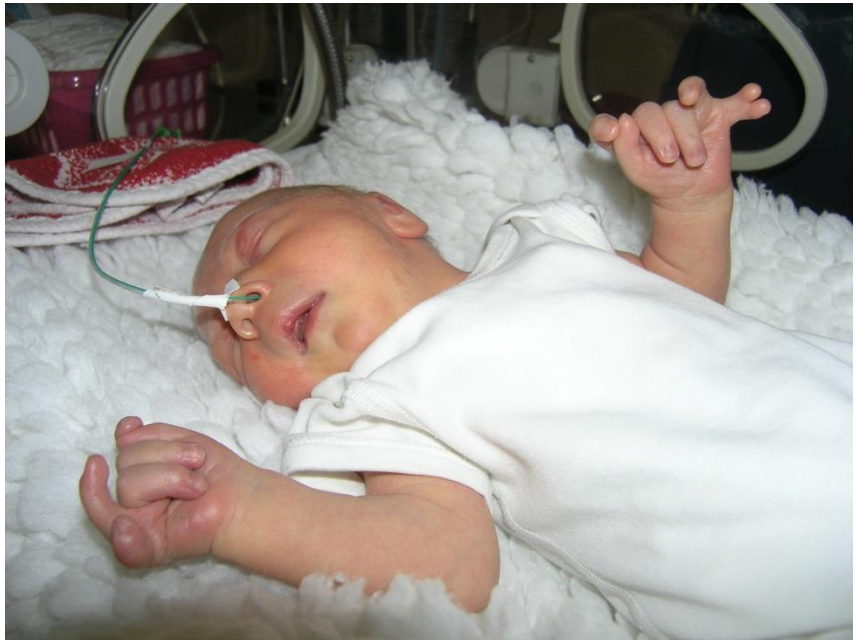
Mandibular hypoplasia

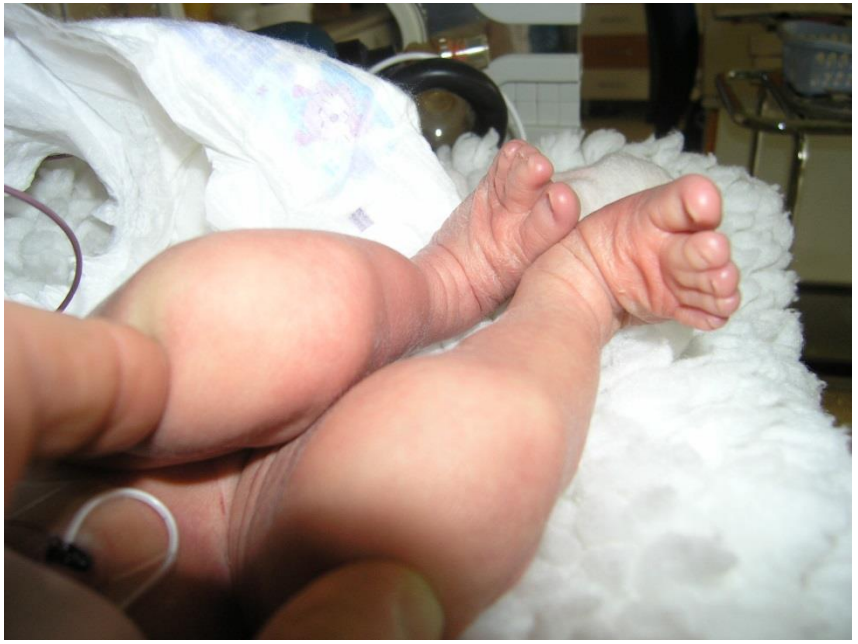
Genital malformations



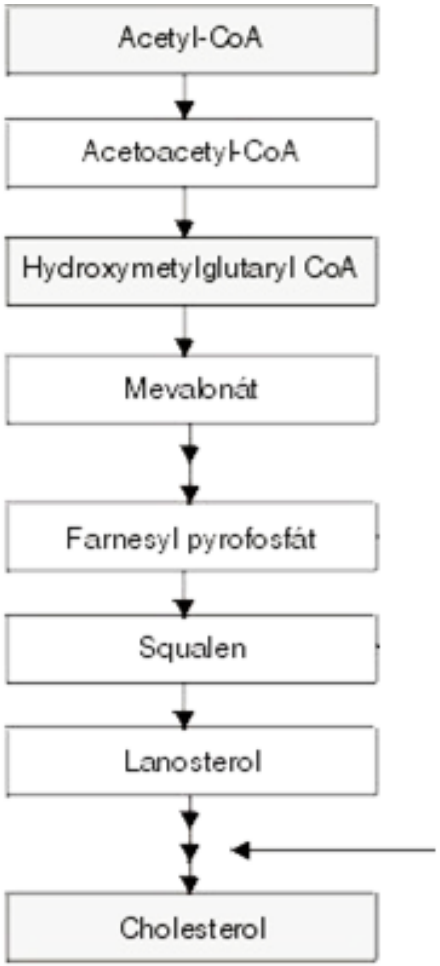
3. Case report – SLOS - characteristic physical features

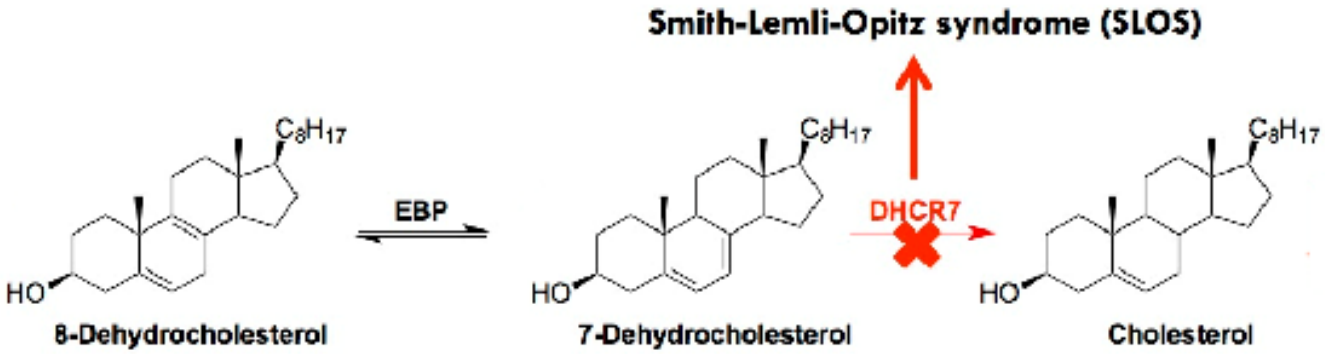
Polydactyly and syndactyly





SLOS - syntesis of cholesterol





3. Case report - SLOS

Material cislo 2290 ze dne 11/05/2017-12:40 FN Brno LOKB-PDM 17/07-10:

telefon : 53223 3168

[redacted] 53312

DN PEK JIP I+II 56 (tel.4406,4458)

JIP-II.cast 72100702/ 13432/11

Narozen(a) 04/04/2017

Diagnosa...Q89.8 Rodne cislo. [redacted] Vyska... 0

Komentar...HEMOLYZA! Pojistovna...205 Hmotnost 0.0

Odber dne..11/05/2017-10:47

	Nazev vysetreni	Vysledek	Jednotky		Referencni interval			Hodnoceni
1	S/P-Urea	4.9	mmol/l	(	1.8...	6.4		(.x.)
2	S/P-Kreatinin	20	umol/l	(	14...	34		(.x.)
29	S/P-Fosfat anorg	1.54	mmol/l	(	1.45...	2.16		(x..)
46	S/P-Mg	0.89	mmol/l	(	0.70...	0.95		(.x.)
8	S/P-ALT	0.46	ukat/l	(	0.15...	0.85		(.x.)
9	S/P-AST	1.01	ukat/l	(	0.27...	0.97	H	(...)x
10	S/P-GGT	0.37	ukat/l	(	0.37...	3.00		(x..)
16	S/P-Bilkovina c.	40.4	g/l	(	56.0...	75.0	L	x(...)
18	S/P-Albumin	22.0	g/l	(	38.0...	54.0	L	x(...)
14	S/P-Cholesterol	0.6	mmol/l	(	2.6...	4.2	VL	x<.(...)
15	S/P-Triacylglyc.	0.96	mmol/l	(	0.40...	1.40		(.x.)
101	S/P-HDLcholest.	nelze stanovit		(	0.9...	1.3		
103	S/P-LDL/chol.vyp	nelze vypocitat		(	1.2...	3.0		
98	S/P-LDL/chol.mer	stanovit nelze		(	1.2...	3.0		
89	Non-HDLchol.vyp.	stanovit nelze		(	0.0...	3.8		
220	S/P-TSH	6.89	mU/l	(	0.27...	4.20	H	(...)x
221	S/P-fT4	13.6	pmol/l	(	12.0...	22.0		(x..)
275	S/P-Kortizol	396.1	nmol/l	(	101.2...	535.7		(.x.)
563	S/P-FSH	0.37	U/l	(	0.00...	10.00		(x..)
564	S/P-LH	0.08	U/l	(	0.00...	6.00		(x..)
565	S/P-Prolaktin	402	mIU/l	(	106...	1270		(.x.)
576	S/P-Testosteron	0.78	nmol/l	(				
1990	Material S/P:	serum						

SCHVALIL MUDr.Vinohradska Hana

3. Case report - SLOS

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‡
Material cislo 7905 ze dne 11/05/2017-12:42          FN Brno LOKB-PDM 17/07-10:
                                                  telefon : 53223 3168
[redacted]                        53312
¶       DN PEK JIP I+II 56 (tel.4406,4458)
¶                                                           JIP-II.cast 72100702/
¶Narozen(a) 04/04/2017
Diagnosa...Q89.8                      Rodne cislo.[redacted]    Vyska...    0
Komentar...                           Pojistovna...205          Hmotnost   0.0
-------------------------------------------------------------------------------
    Nazev vysetreni  Vysledek Jednotky    Referencni interval  Hodnoceni
-------------------------------------------------------------------------------
 860 7-dehydrocholest viz komentar        (
1990 Material S/P:    serum
-------------------------------------------------------------------------------
7-dehydrocholesterol = 287.0 umol/l
Zhodnotila RNDr. A. Mikuskova

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
SCHVALIL MUDr.Vinohradska Hana
‡
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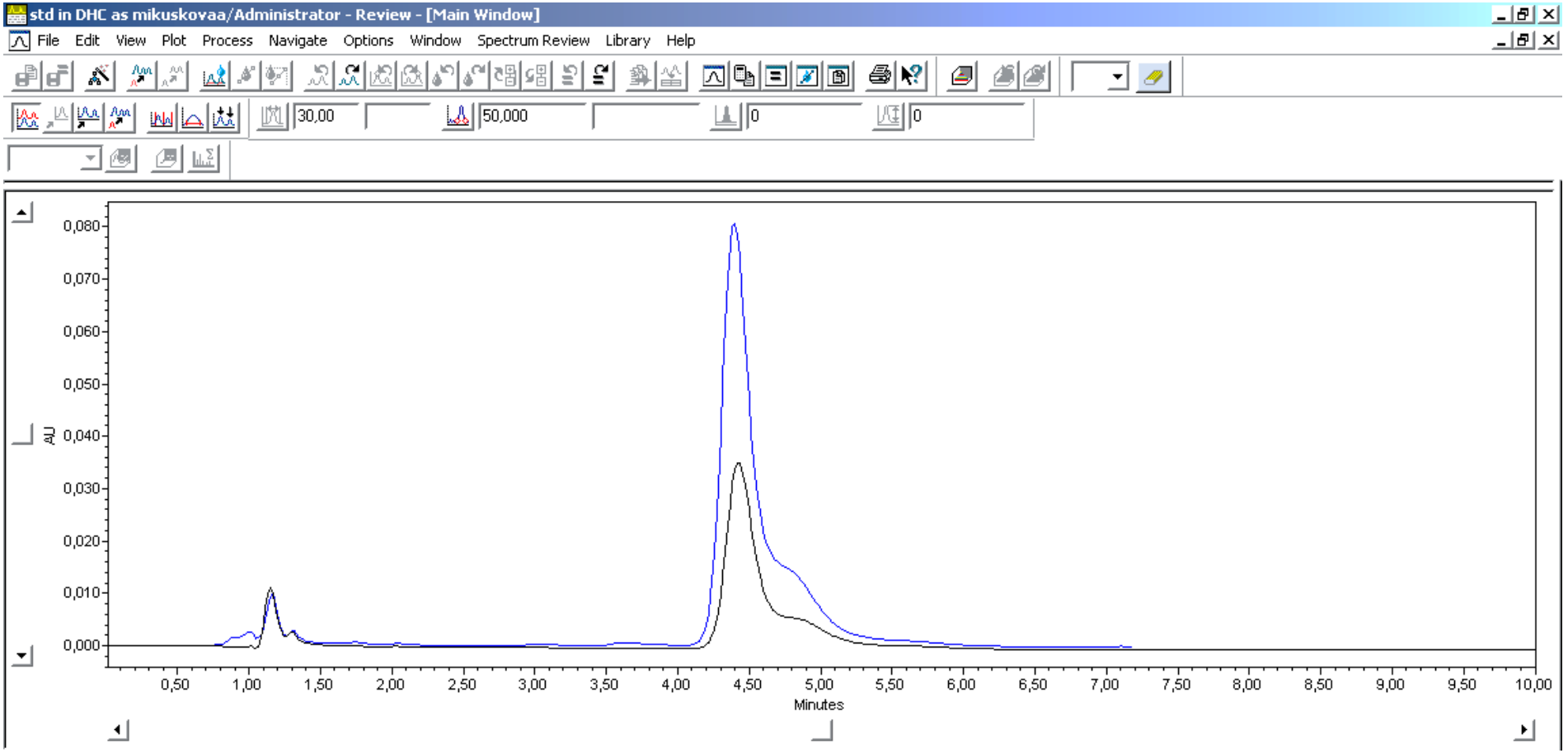
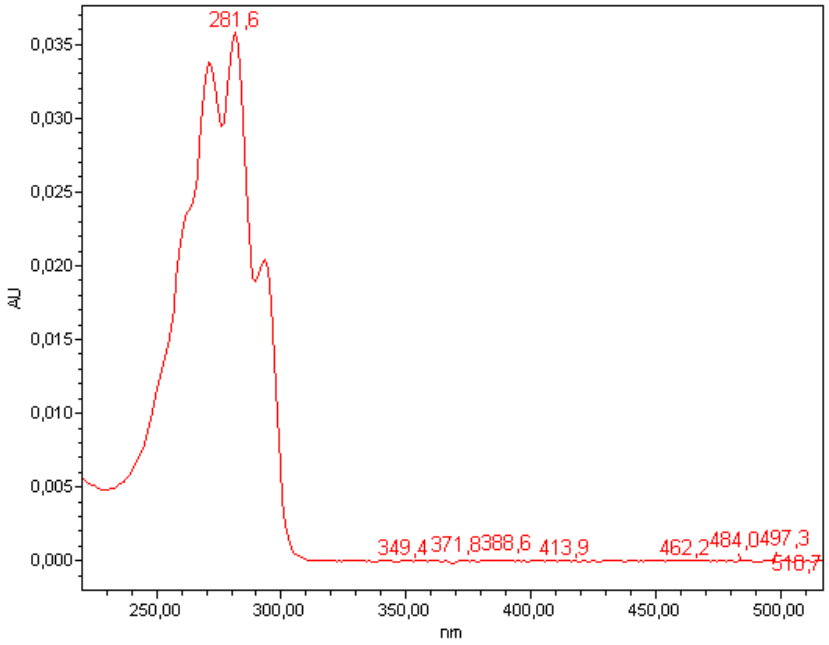
7-dehydrocholesterol – record (graph from HPLC)

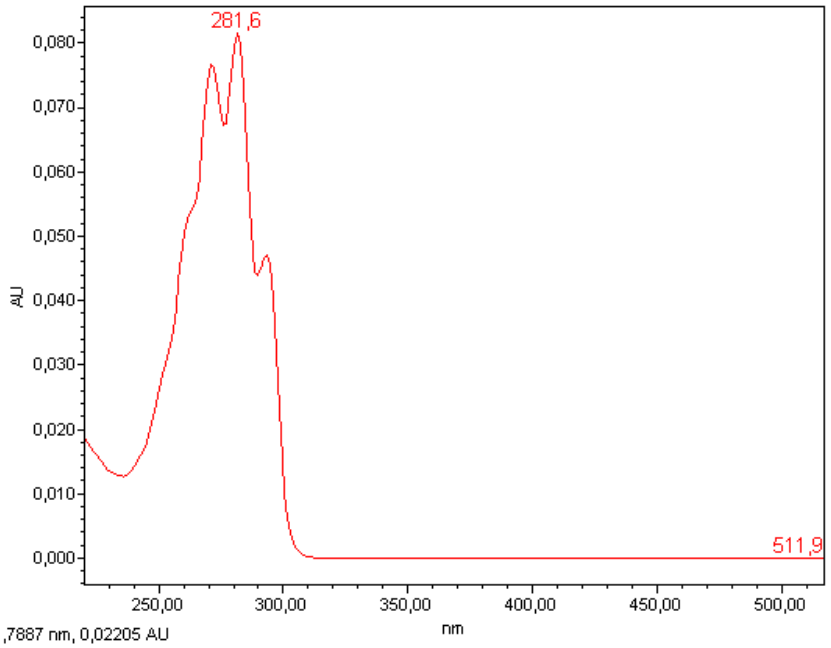


7 dehydrocholesterol – absorption spectrum

Standard



Patient sample



RESOURCES AND REFERENCES

Literature:

- Hoffmann, G.F., Nyhan, W.L. et al., Inherited Metabolic Diseases
- Fernandes,J., Saudubray,J.M., et al., Inborn Metabolic Diseases: Diagnosis and Treatment (2006)
- Scriver Ch.R., Beaudet A.L. et al., The metabolic and molecular bases of inherited disease

Website: www.omim.org