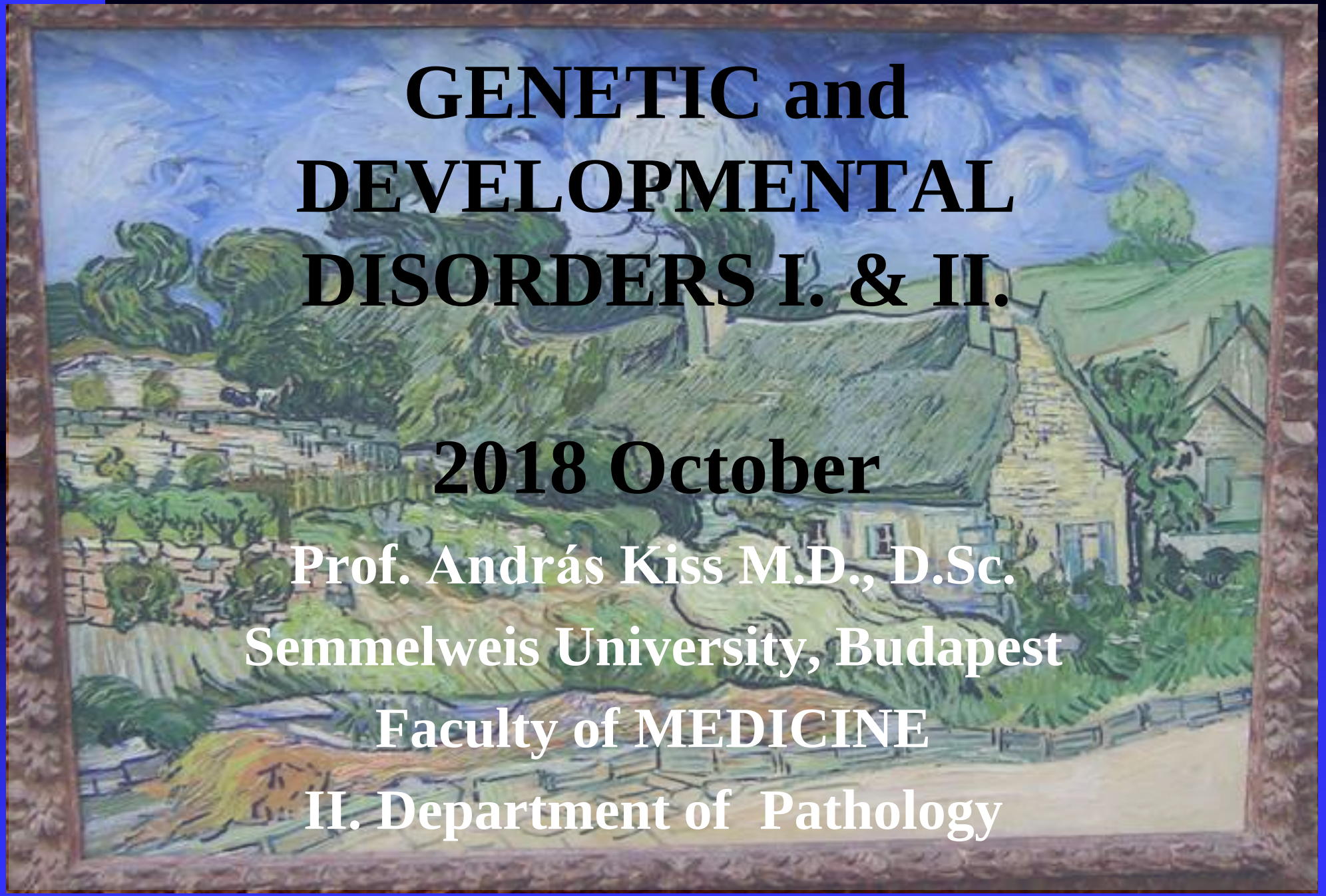


GENETIC and DEVELOPMENTAL DISORDERS I. & II.

2018 October

Prof. András Kiss M.D., D.Sc.

Semmelweis University, Budapest

Faculty of MEDICINE

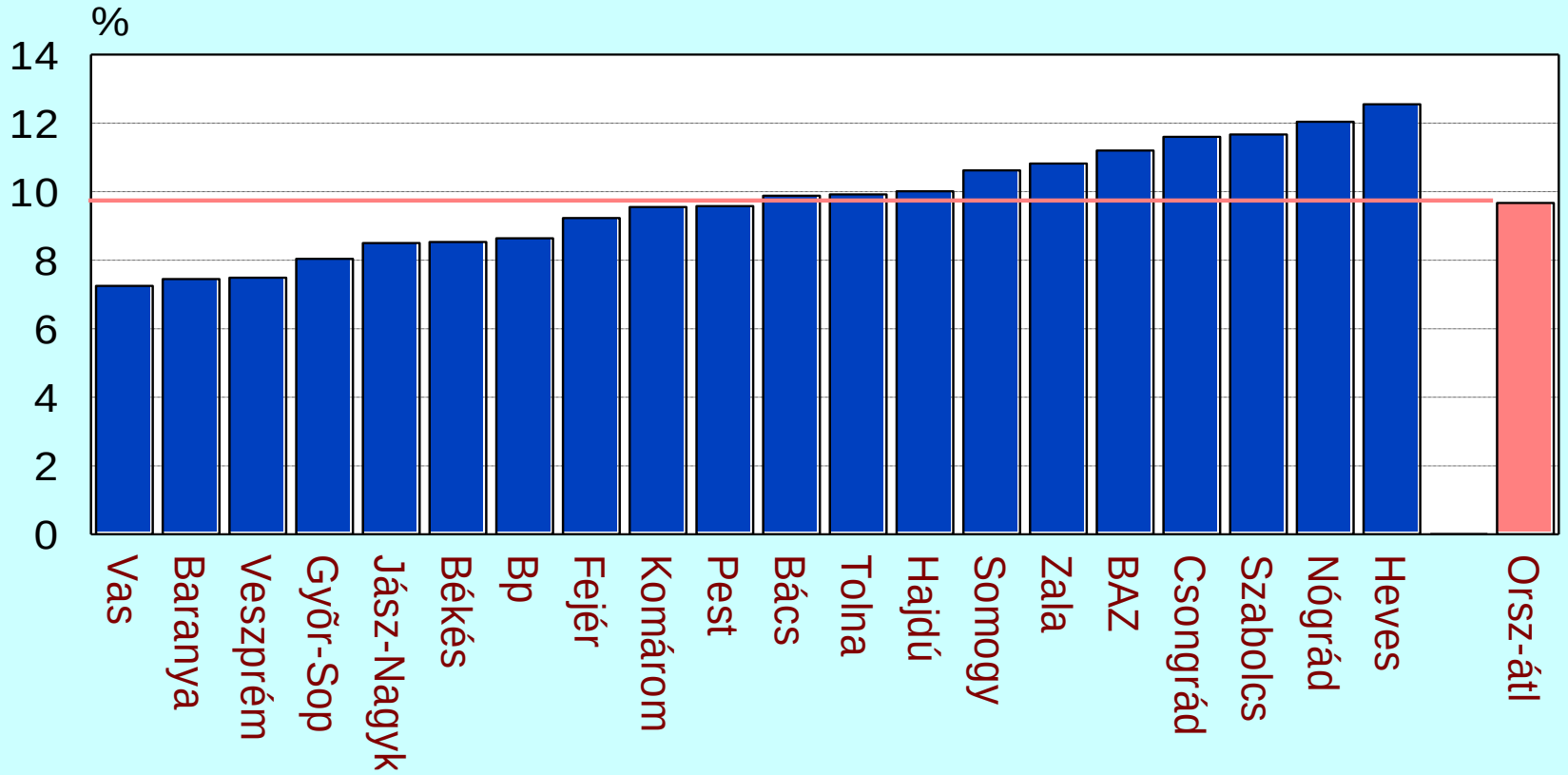
II. Department of Pathology

Importance

- Responsible for the 50 % der spontaneous abortions
- 24% of deaths of newborns and 10% of mortality in childhood are caused by developmental disorders
- Physical and mental disablement of adults

RATE of SMALL FOR BIRTH EVENTS IN HUNGARY

Weight small for birth (≤ 2 500 g)
Frequency in Hungary in 2005



OEP adatok

From Prof. Dr. Paulin Ferenc and Dr. Valent Sándor

Importance

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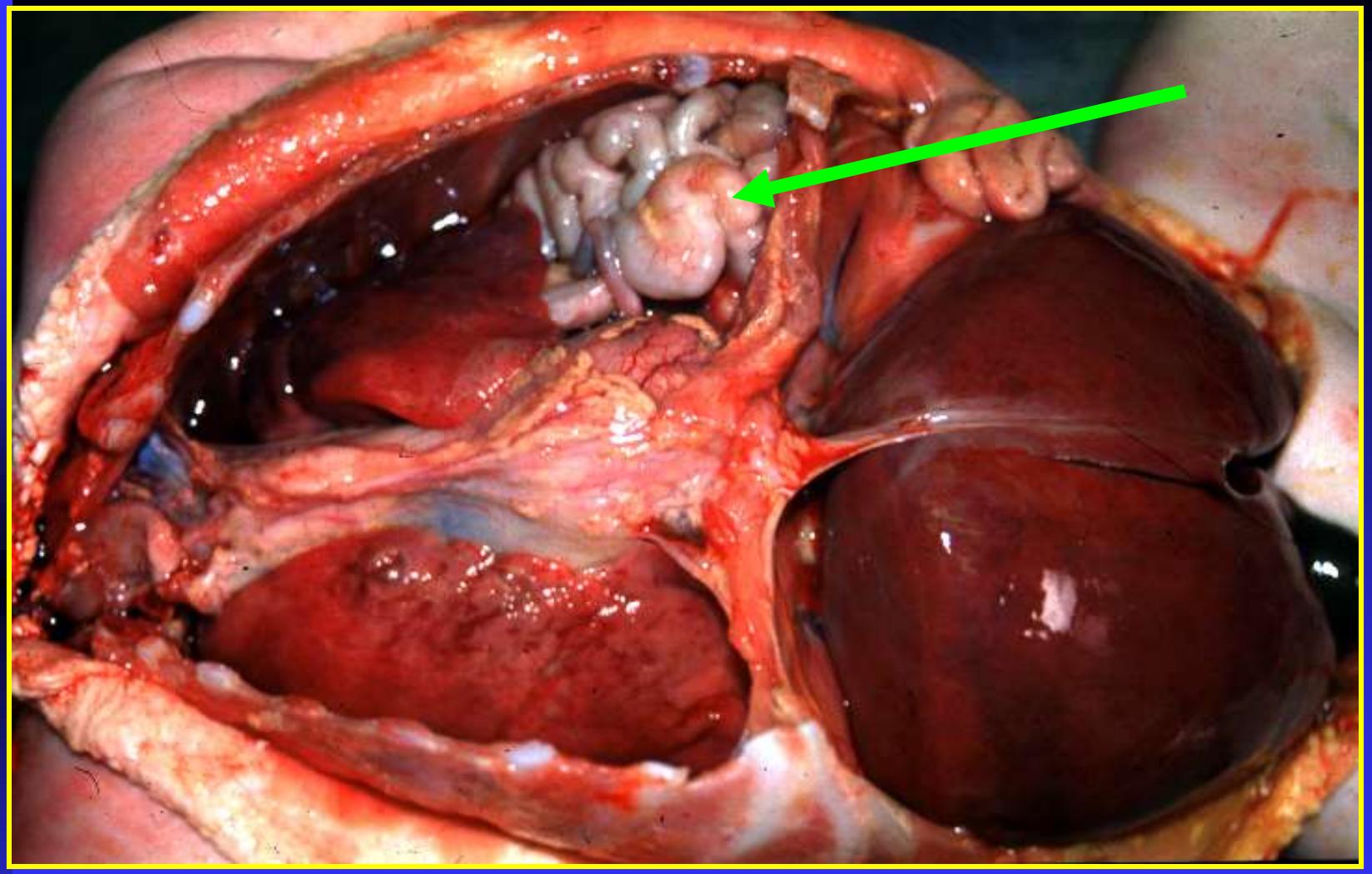
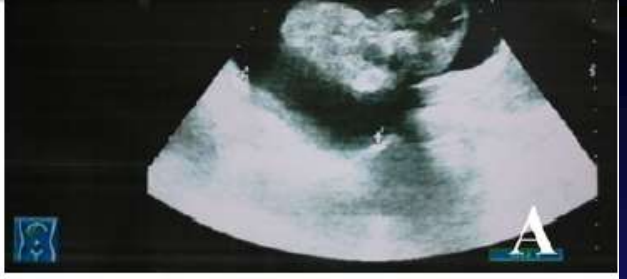
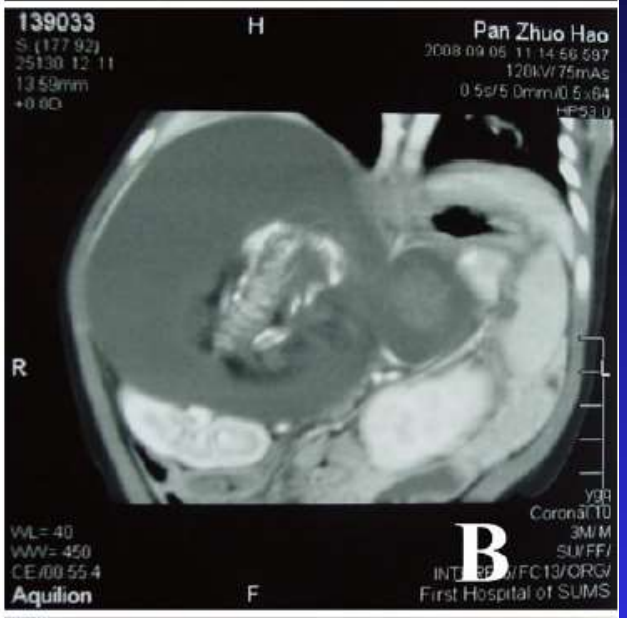
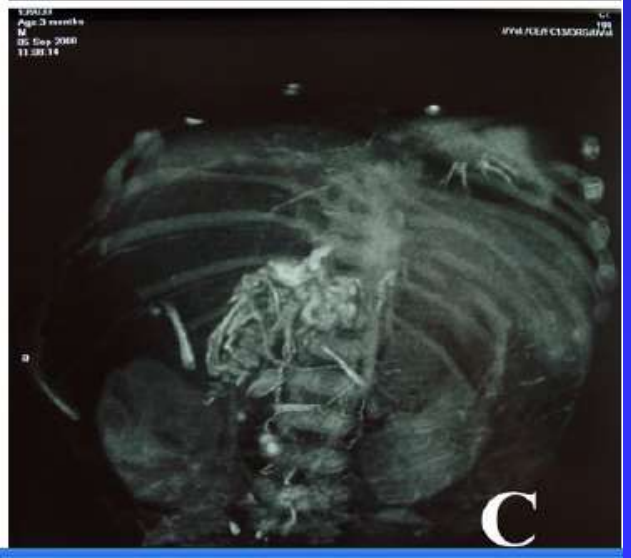








Abdominal Imaging

Abdom Imaging (2011)
DOI: 10.1007/s00261-011-9757-2

Fetus-in-fetu: imaging and pathologic findings

Junjie Sun, Soulithon VongPhet, Zhichong Zhang, Jiacong Mo

Department of Pediatric Surgery, The First Affiliated Hospital, University of Sun Yat-Sen, No. 58 Zhongshan 2nd Road, Guangzhou 510080, China

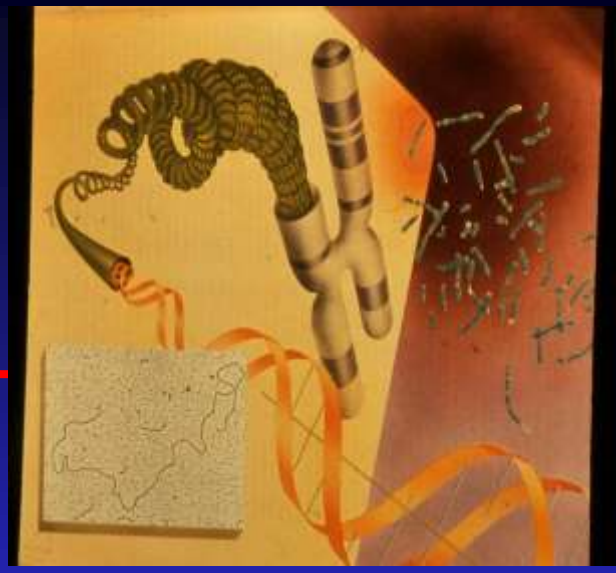
Pathogenesis of Developmental Disorders

- Genetic Diseases
  - Mutations
  - Chromosomal Defects
  - Mitochondrial DNA disorders
  - Multifactorial diseases
- Exogenous Effects
  - Teratogenesis, development of teratoids (monster)

DEFINITION I.

- inherited (Congenital) Diseases
  - genetically determined, inheritable
- innate (Connatal) Diseases
  - exogenous effects (infections, teratogenous chemicals), not inheritable

The human genom



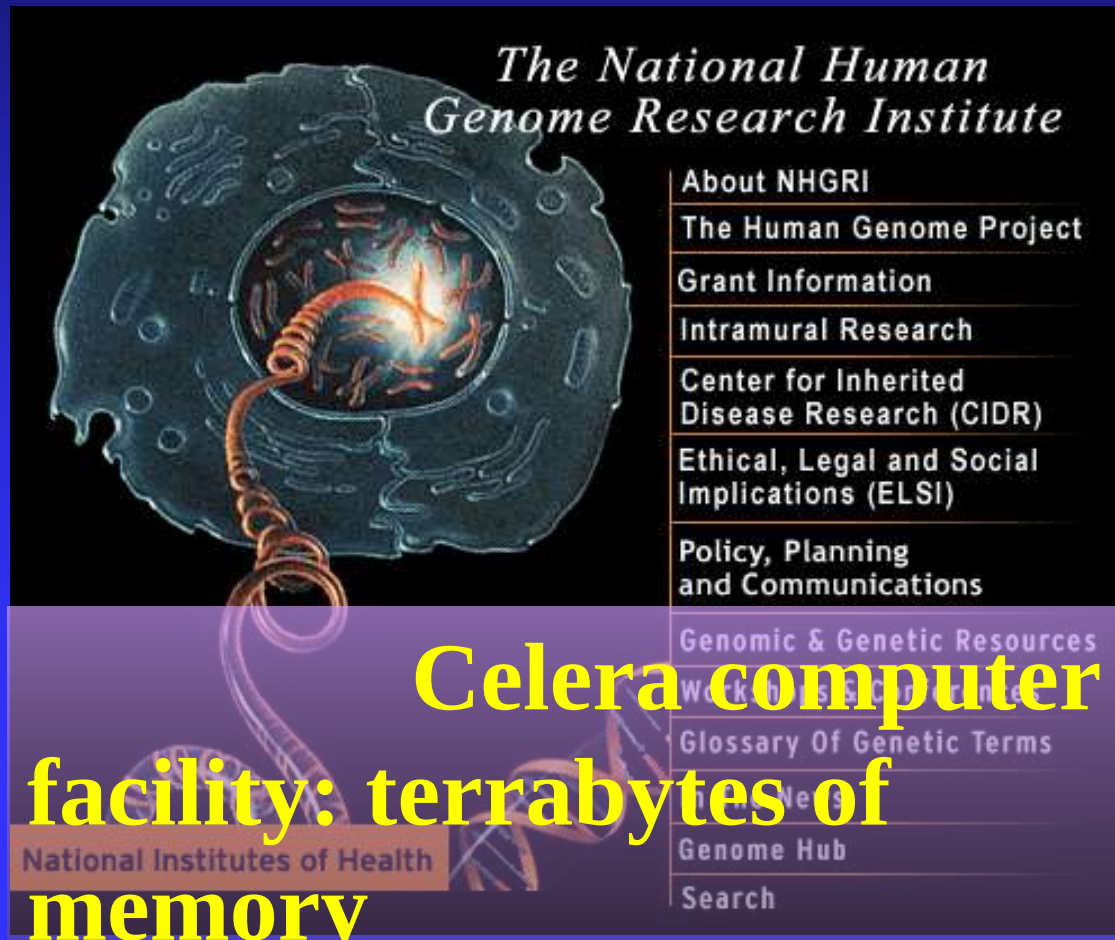
- 1,5 meter DNA pro cell
- 6 milliards- billions of base pairs
- 25-30 000 genes – ~ 100 000 proteins
- 23 pair of chromosomes

Human Genome Project

- (announcement: Bill Clinton és Tony Blair 2000 June 27. !)

Craig Ventner and Sam Broder – Celera Biotech Co. !

Francis Collins - HGRI



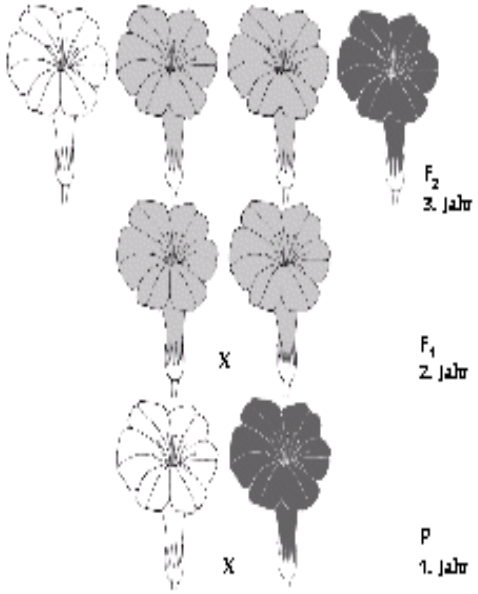
Celera computer facility: terrabytes of memory

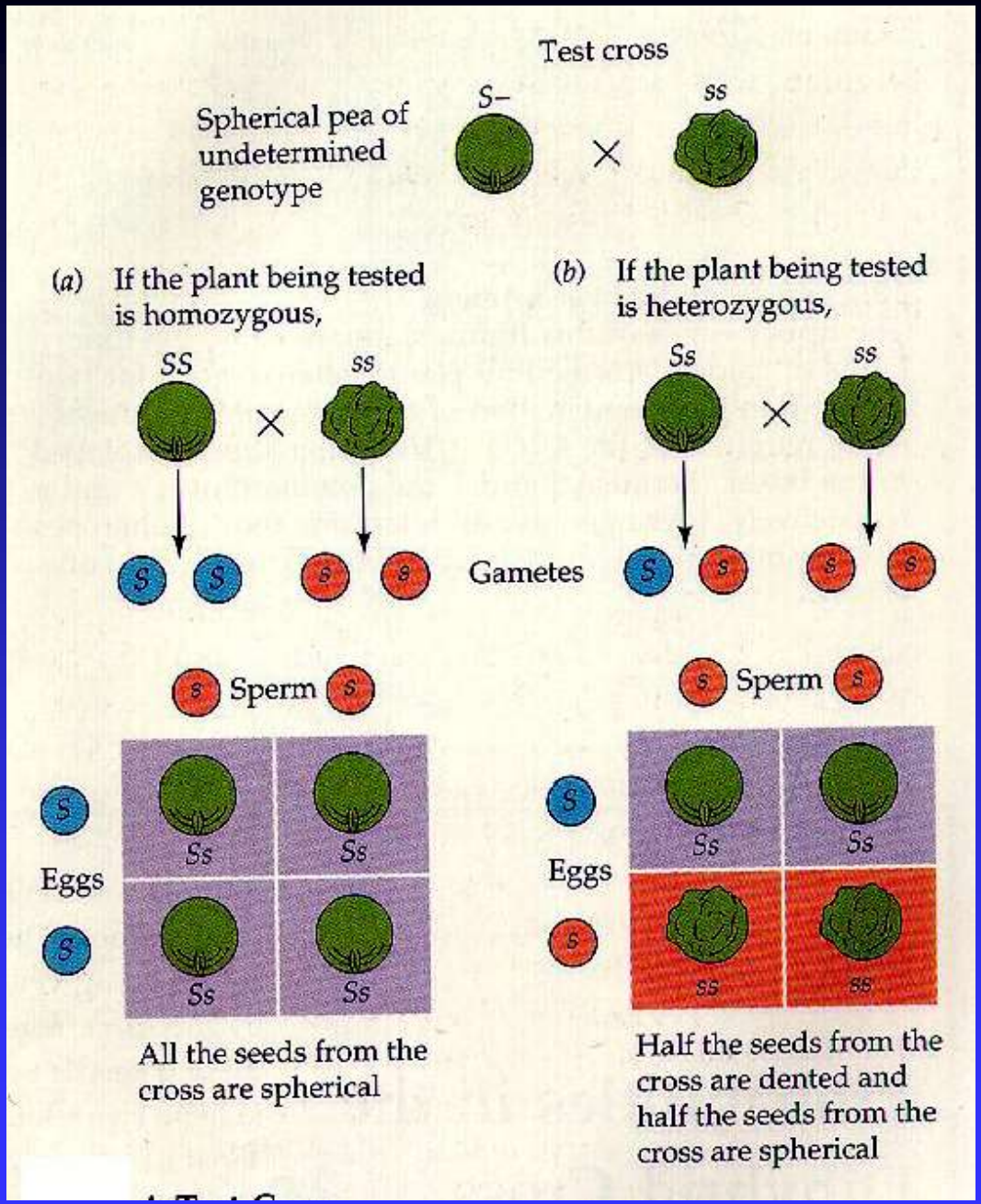
Mendelsche Regel

für intermediäre Vererbung:

Die Merkmale, z.B. die Blütenfarbe weiß und rot, reinerbiger Eltern (P) führen in der F_1-Generation zu einer Mischfarbe (rosa) und spalten sich in der F_2-Generation im Verhältnis 1(weiß) : 2(rosa) : 1(rot) auf.

(Dieses Verhältnis findet man nur bei einer sehr großen Zahl von Versuchspflanzen.)







MORPHOLOGY

!

!

!



DNA – Genes
Expressionsprofile
RNA, Proteins !!!

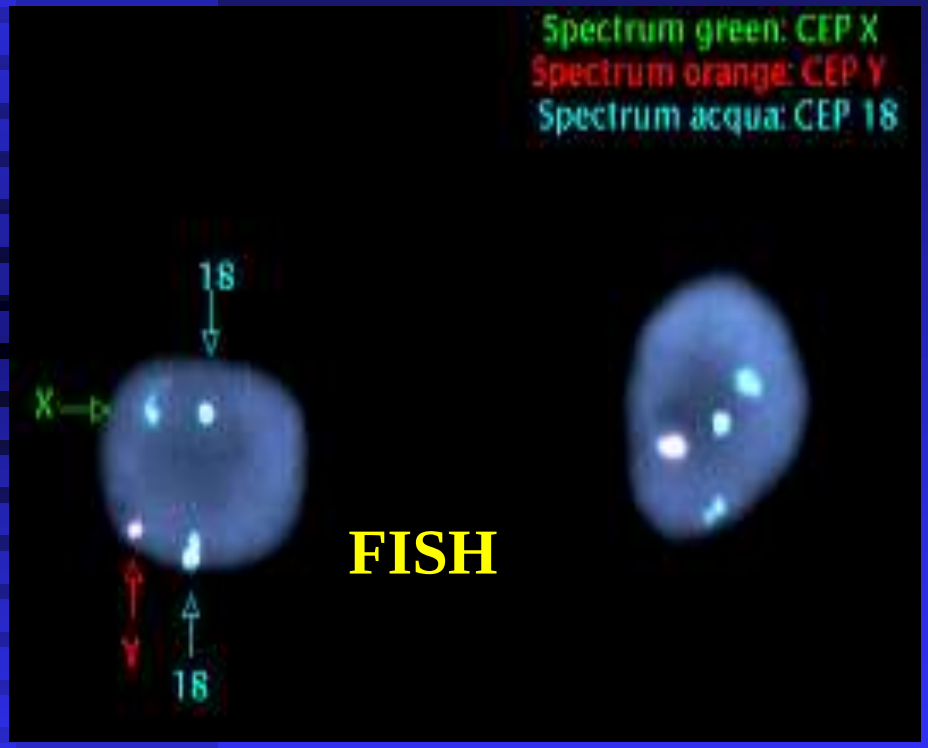




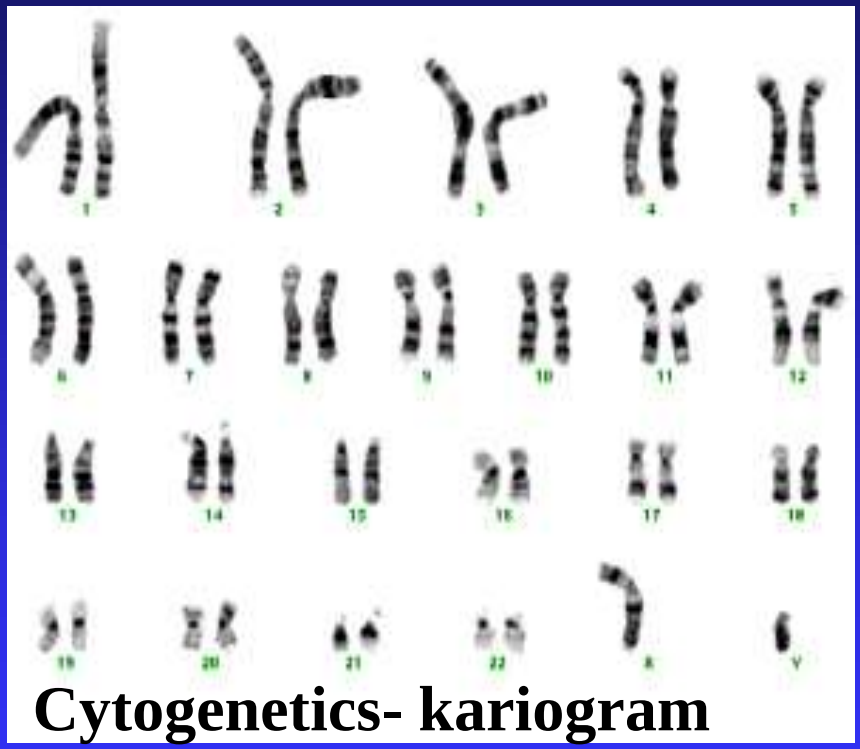
ALTEREGO

MOLECULAR MEDICINE

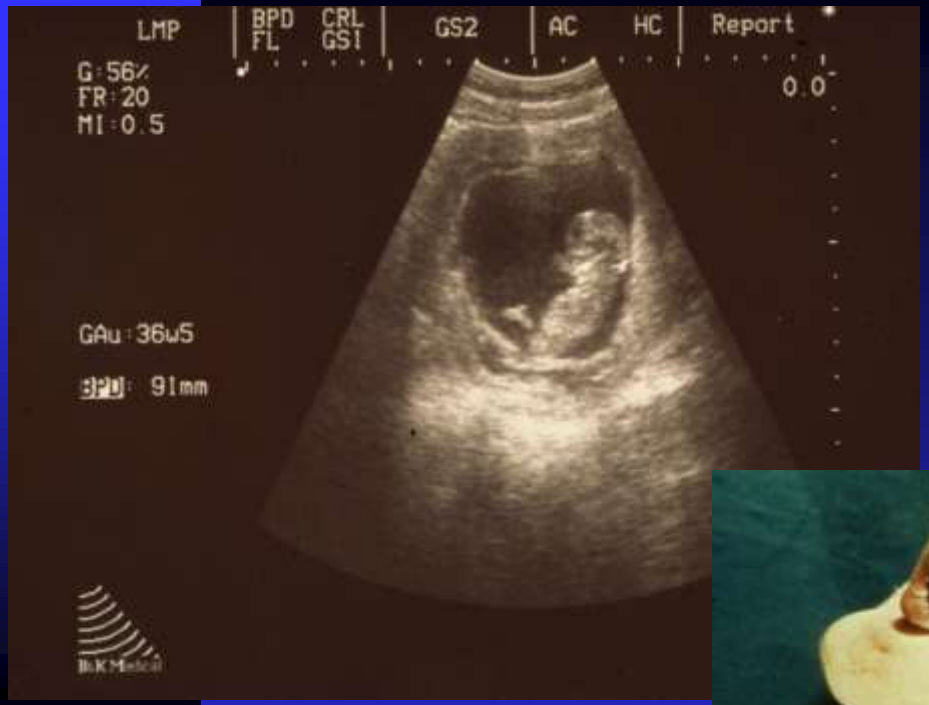
Cytogenetics

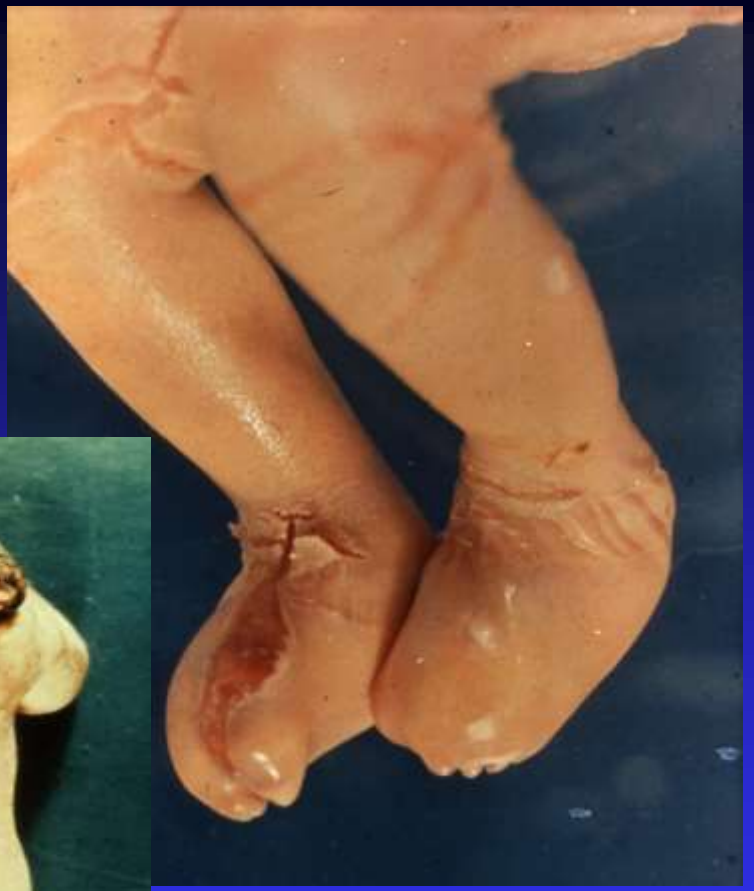


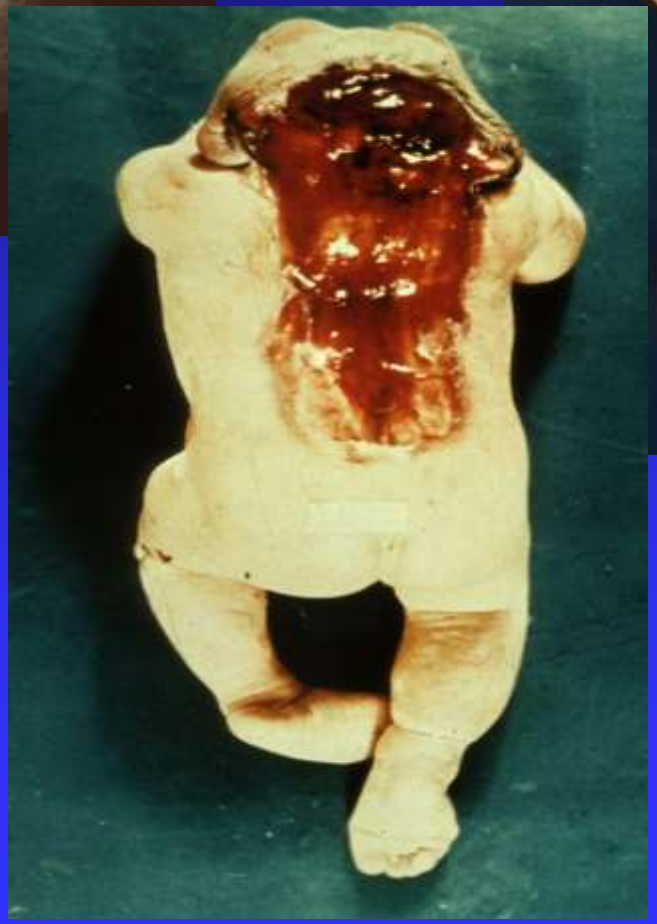
FISH

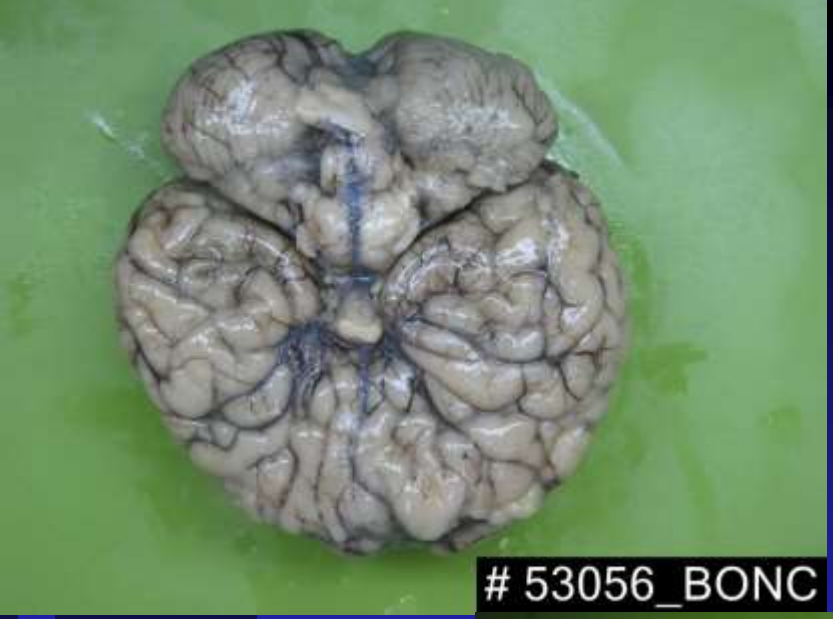


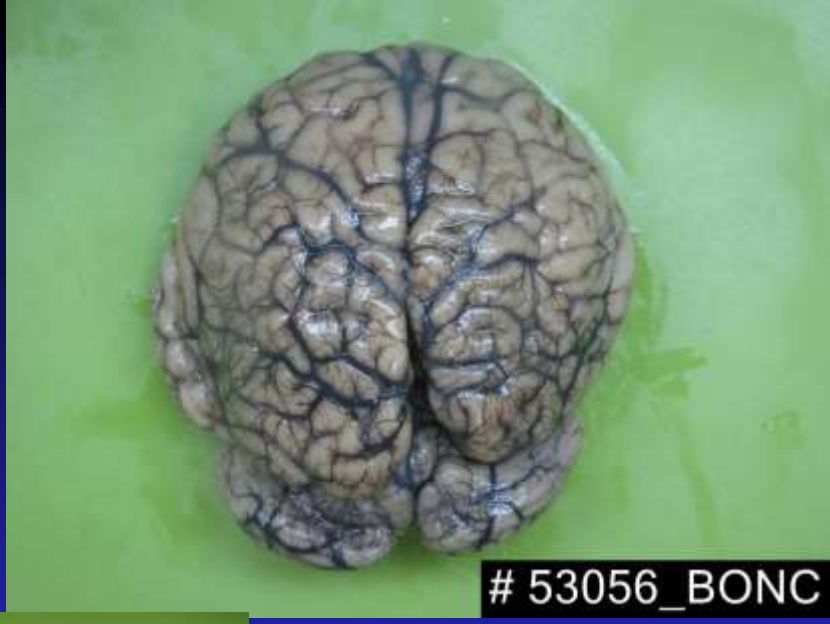
Cytogenetics- kariogram


LMP
BPD
FL
CRL
GS1
GS2
AC
HC
Report
G:56%
FR:20
MI:0.5
0.0
GAu:36w5
BPD 91mm

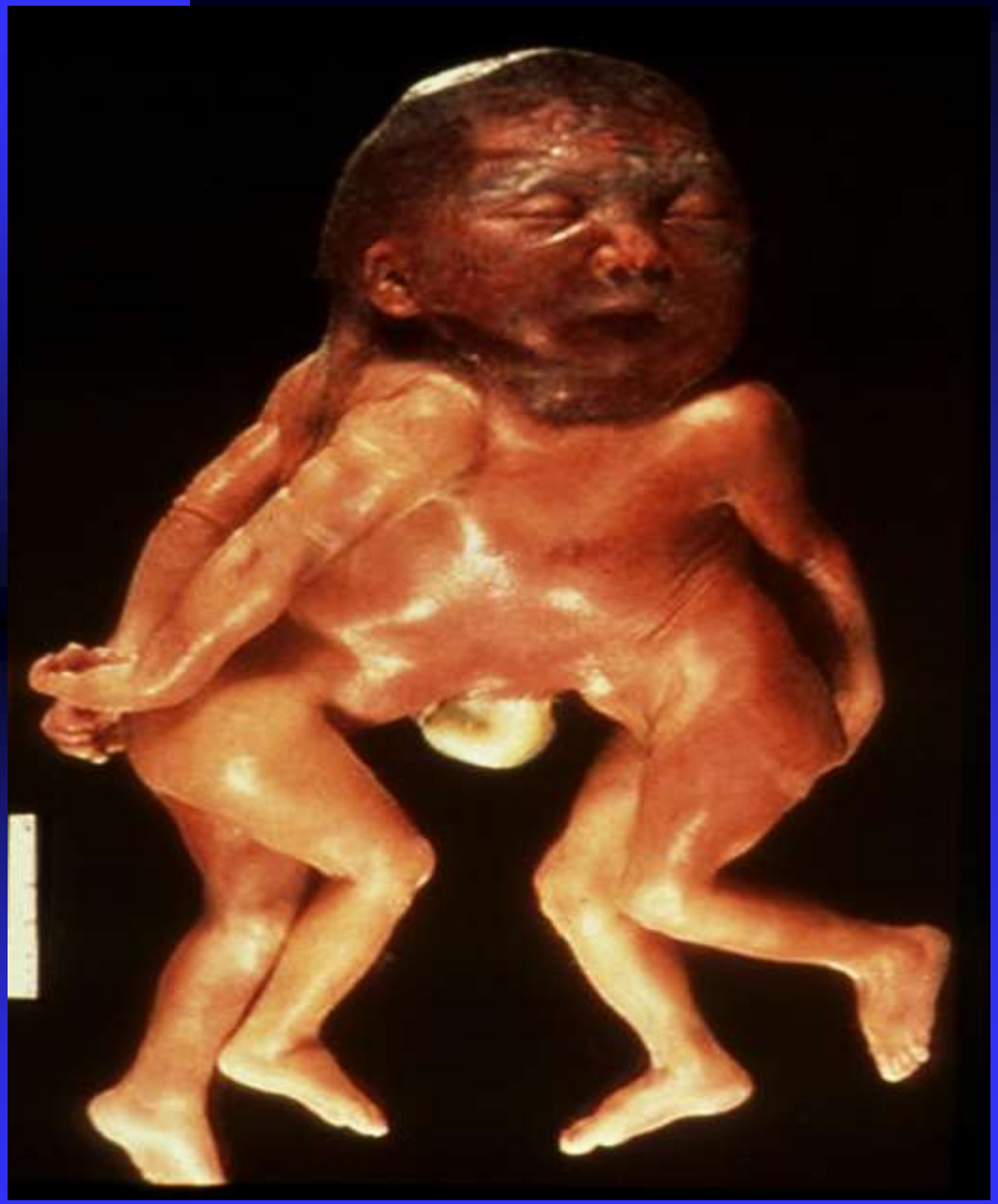








3 years old boy, holoprosencephay of frontal lobe, lateral ventricles are united.



Genetic Diseases

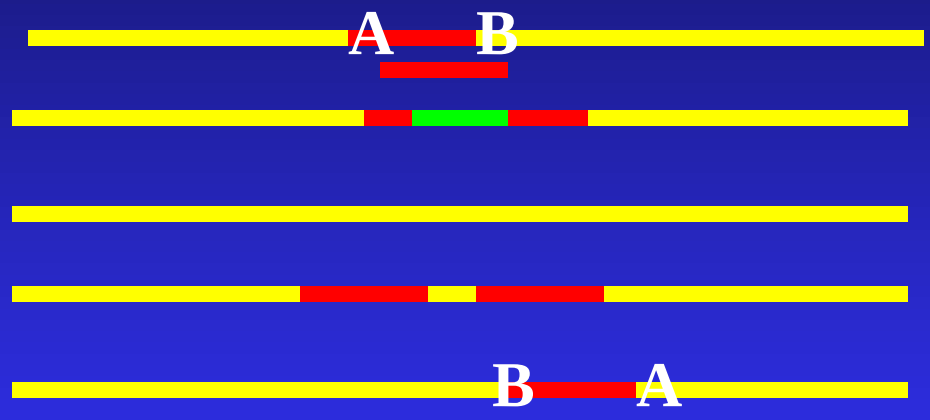
- Diseases with mendelian inheritance
- chromosomal abnormalities
- poligenically inherited diseases
- mitochondrial DNA associated diseases

Diseases with mendelian inheritance

- enzime defects
- receptor defects
- transportprotein-defects
- non-enzymatic protein defects, functional or quantitative abnormalities

Mutations of genes

- Point mutation
  - (missense)
  - (nonsense) mutation
- Frameshift mutation
  - Insertion
  - Deletion
  - Duplication
  - Inversion



- Trinucleotide “repeat” mutation
- Non coding sequence mutation
- Reason: spontaneous, ionizing radiation, mutagenous chemicals, viruses

DEFINITION II.

- ways of inheritance
  - Autosomal
  - sex chromosome bound
  - Dominant
  - Recessive
  - Co-dominant

Penetrance

Genomic imprinting: is a functional haploid state, an epigenetic phenomenon by which certain genes are expressed in a parent-of-origin-specific manner. If the allele inherited from the father is imprinted, it is thereby silenced, and only the allele from the mother is expressed.

Prader-Willie Syndrome (Muscle hypotonia, areflexia, obesity, ment. impairment, behavioral problems, stubborness, compulsive behavior, lack of paternal gene on the chromosome 15.)

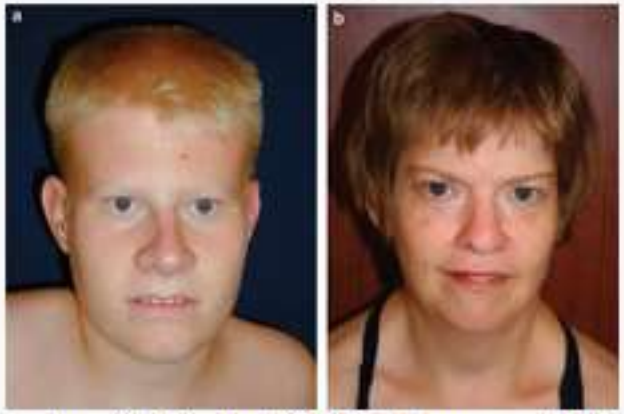
Angelman Syndrome (marionette puppet movements, hypotonia, psychom. disorders, mental disability, tendency to jerky movement, caused by the absence of maternal genes normally present on chromosome 15)

- **Prader-Willi syndrome** is caused by the loss of genes in a specific region of chromosome 15. People normally inherit one copy of this chromosome from each parent. Some genes are turned on (active) only on the copy that is inherited from a person's father (the paternal copy).

- Most cases of Prader-Willi syndrome (about 70 percent) occur when a segment of the paternal chromosome 15 is deleted in each cell. In another 25 percent of cases, a person with Prader-Willi syndrome has two copies of chromosome 15 inherited from his or her mother (maternal copies) instead of one copy from each parent. This phenomenon is called maternal uniparental disomy.

- In infancy, this condition is characterized by weak muscle tone (hypotonia), feeding difficulties, poor growth, and delayed development. Beginning in childhood, some affected individuals develop an insatiable appetite, which leads to chronic overeating (hyperphagia) and obesity. Some people with Prader-Willi syndrome, particularly those with obesity, also develop type 2 diabetes mellitus

Prader-Willi Syndrome



People with Prader-Willi Syndrome, exhibiting characteristic facial appearance including narrow temples, an elongated face, thin upper lip, and a prominent nose.

- **Angelman sydnrome:** maternal deletion in chromosomal region 15q11-13 causing an absence of *UBE3A* expression in the paternally imprinted brain regions. *UBE3A* codes for an E6-AP ubiquitin ligase

- "happy puppet syndrome", developmental delay, functionally severe speech impairment,

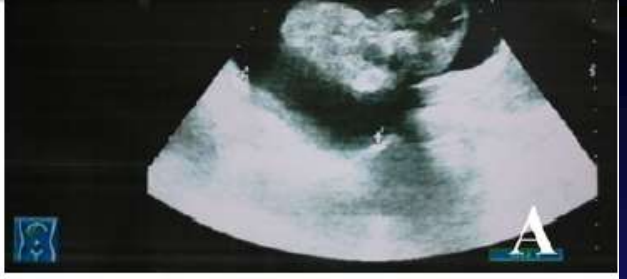
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs

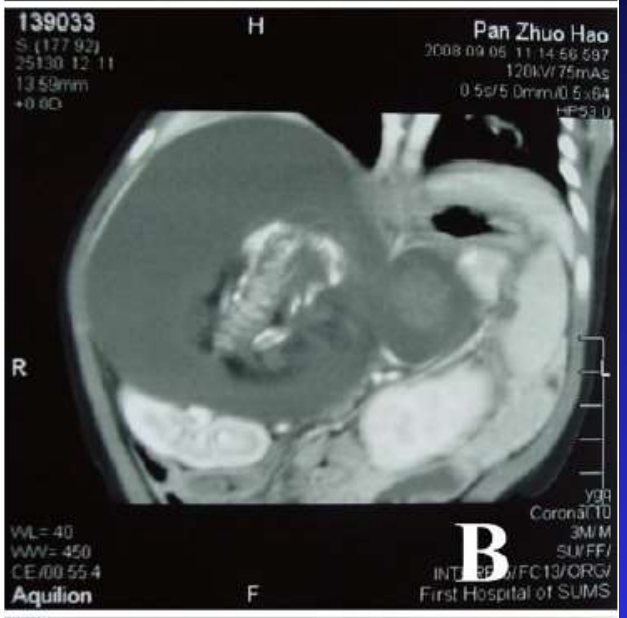
- Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with hand flapping movements; hypermotoric behavior; short attention span

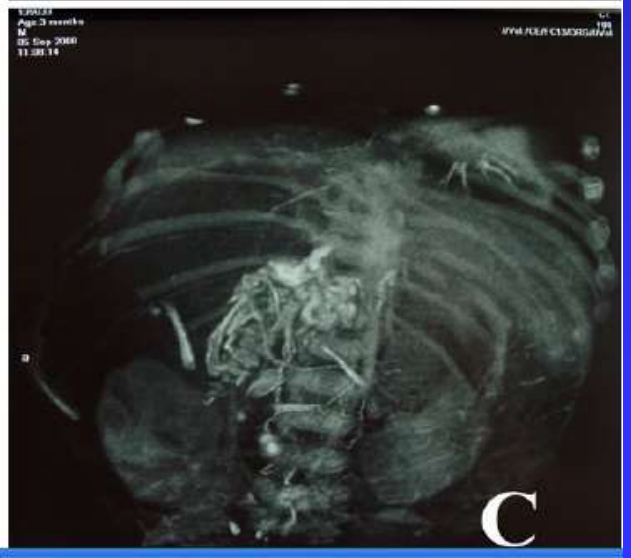
- Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (absolute or relative) by age 2

- Seizures, onset usually < 3 years of age

- Strabismus, hypopigmented skin and eyes







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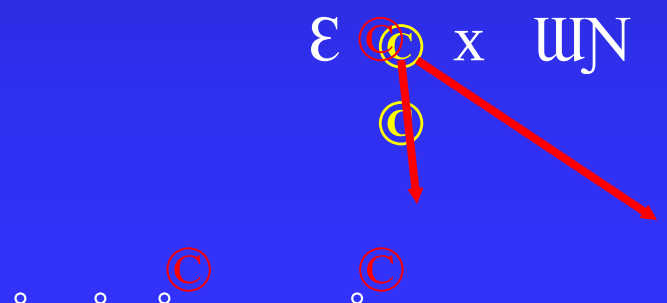
Autosomal-dominant inheritance

- men and women are equally involved
- manifestation in every generation
- manifestation in heterozygous condition
  (depending on penetrance)
- heterozygous carrriers transmit the disease

in 50 % !



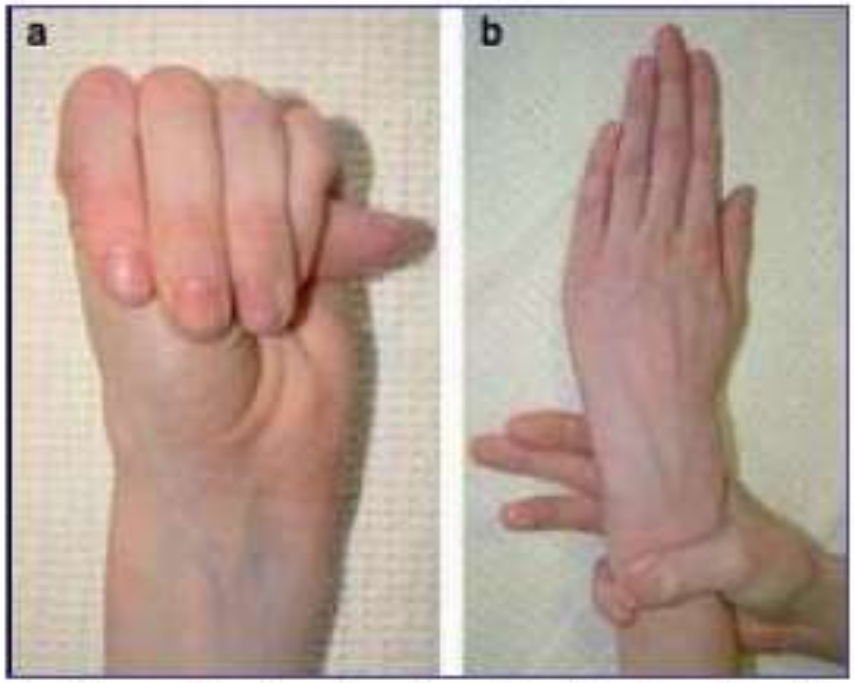
Autosomal-Dominant Diseases

- Marfan Syndrome
- Ehlers-Danlos Syndrome (*)
- Huntington Chorea
- Neurofibromatosis
- Sclerosis tuberosa (Bourneville)
- Polycystic Disease
- sickle cell anemia
- Osteogenesis imperfecta (*)
- Familiary Hypercholesterinemia - LDL receptor defect
- von Willebrand Disease
- acute intermittent porphiria - preuroporfirinogen synthase activity is decreased, cons.: aminoclevunilate synthas activity is increased

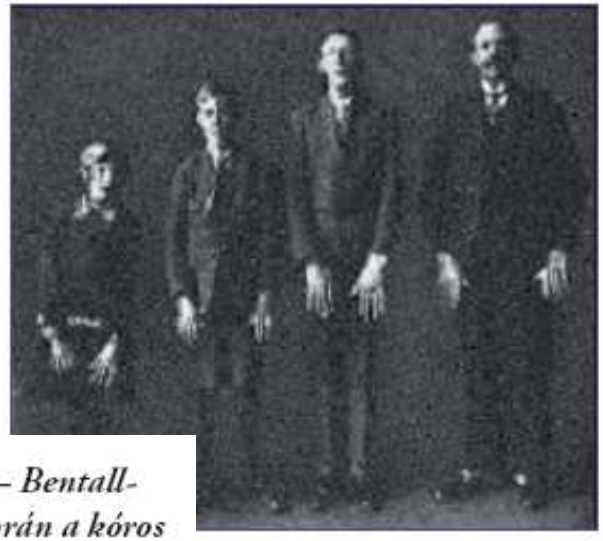
Marfan Syndrome

- **Mutation of Chromosome 15q21**
  - **defect of fibrilline (extracellular matrix protein): '*cutis hyperelastica*'**
- **Rate: 1 : 10 000 - 1 : 20 000**
- **Morphology:**
  - **tall, slim figure, long extremity**
  - **Arachnodactylia – „ spider fingers „**
  - **hyperelastic joints**
  - **mitral prolaps**
  - **cystic medianecrois of Erdheim**
  - **Dissociating aorta aneurysma**

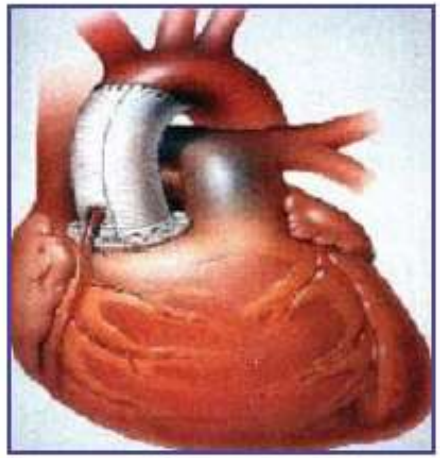
A páciens fizikális vizsgálata során javasolt három, Marfan-szindrómára jellemző tünet megfigyelése. Az első jellegzetesség, hogy a karok fesztávolsága nagyobb, mint a testmagasság: *kartávolság (cm) / testmagasság (cm) > 1,05*. A második típusos tünet, hogy ökölbe szorításkor a hüvelykujj distalis phalanxa teljes egészében túlnyúlik a tenyér ulnaris szélén *(Steinberg-hüvelykujjtünet)*. Végül pedig a hüvelykujj és a kisujj fedik egymást a csukló körbefogásakor *(Walker–Murdoch-csuklótünet)*.



2. ábra – Arachnodactylia: (a) Steinberg-hüvelykujjtünet, (b) Walker–Murdoch-csuklótünet



n-szindrómás család



3. ábra – Bentall-műtét során a kóros aortabillentyű és a tágult felszálló aorta helyére billentyűs érprotézis (composit graft) kerül, melynek műér részébe szájaztatják a coronariákat.

A Marfan szindróma diagnózisa negatív családi anamnézis esetén

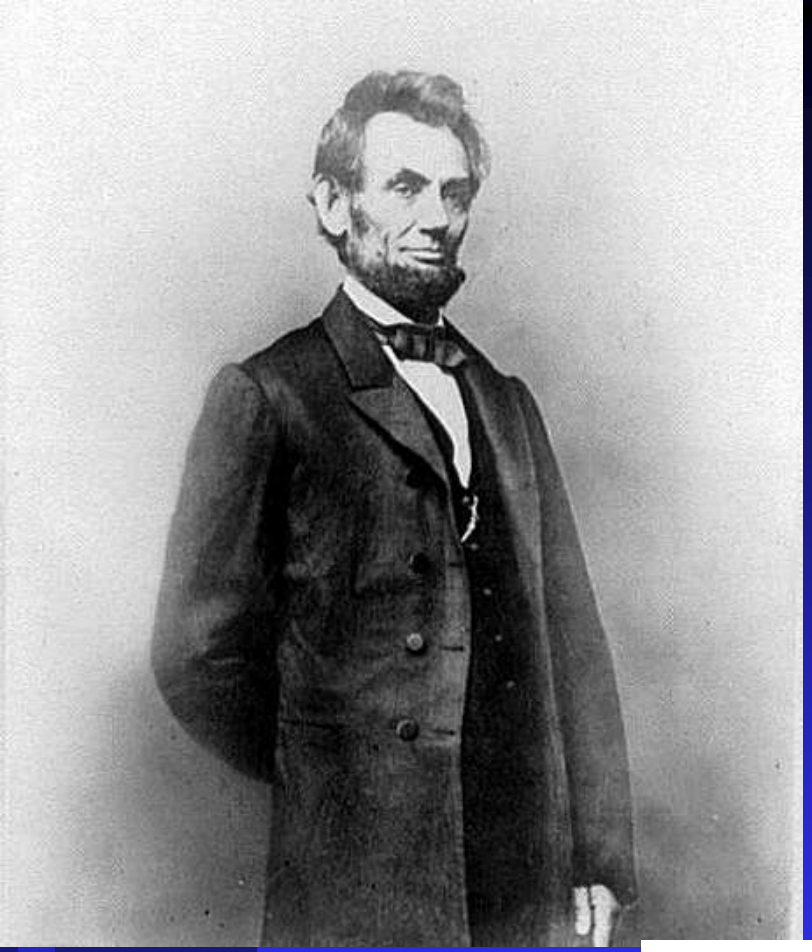
Amennyiben a beteg családjában még nem fordult elő a tünetegyüttes (index case), a módosított Ghent kritériumok értelmében a Marfan szindróma akkor diagnosztizálható, ha a tünetek alábbi négy mintázatának egyike érvényes a vizsgált egyénre:

(1) Az aorta érintettsége ÉS ectopia lentis jelenléte.

(2) Az aorta érintettsége ÉS nagy valószínűséggel Marfan szindrómát okozó fibrillin-1 mutáció megléte.

(3) Az aorta érintettsége ÉS megfelelő szisztémás pontszám alapján megállapított szisztémás érintettség.

(4) Ectopia lentis ÉS a fibrillin-1 bizonyítottan aorta érintettséget okozó mutációjának megléte.



Abraham Lincoln

Marfan -Syndrom

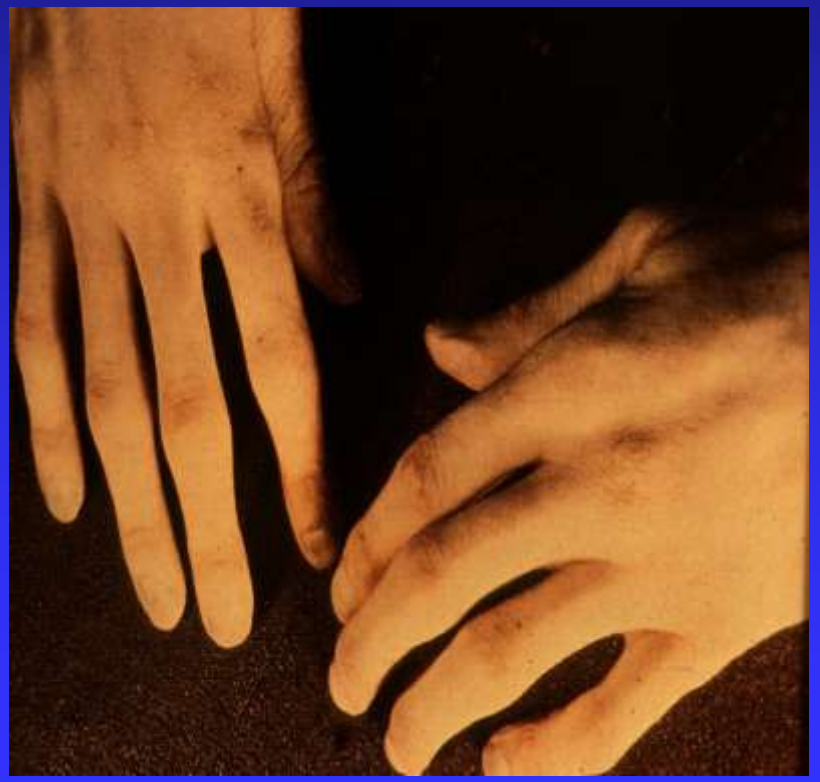
Marfan-szindróma biobankjának létrehozása

A Marfan-szindróma a szervezet kötőszöveti állományát érintő öröklődő betegség, amely Magyarországon hozzávetőleg 2-3000 személyt érint. A betegség manifesztációi multiszisztémásak, ezért a kórismézés sokszor nehézségekbe ütközik. Az "Országos Marfan Regiszter" jelenleg közel 250 Marfan-szindrómában szenvedő beteg adatait tartalmazza, s ez a szám dinamikusan növekszik.

Marfan-szindróma, Marfan Regiszter, biobank, DNS, genetika | Orvosi Hetilap 2012 ;153(8):296-302 Markusovszky Lajos Alapítvány
2012-03-05 07:40:03 | Ágota, A.; Ágg, B.; Benke, K.; Joó, J. G.; Langmár, Z.; Marosi, K.; Lelelovics, Zs.; Deé, K.; Nagy, P.; Köles, B.; Horváth, E.; Crespo, Zs.; Szabolcs, Z.; B. Nagy, Zs.| Marfan-szindróma, Marfan Regiszter, biobank, DNS, genetika

Abraham Lincoln

Marfan -Syndroms



Ehlers-Danlos Syndroms

- clinically and genetically: heterogenous(I.-X.)
  - all three mendelian inheritance pattern
  - disorder of collagene synthesis
- Macroscopic disorders: collagene-rich tissues

Paganini

Skin, Ligaments, Joints

- Skin is vulnerable, elastic
- Flexibility of joints (hyperelastic joints, „snake-acrobats, artists: Paganini !!)
- Rupture of major arteries, rupture of colon, rupture of cornea, hernia of diaphragma (other disorders of collagene synthesis: osteogenesis imperfecta , bullous epidermolysis)

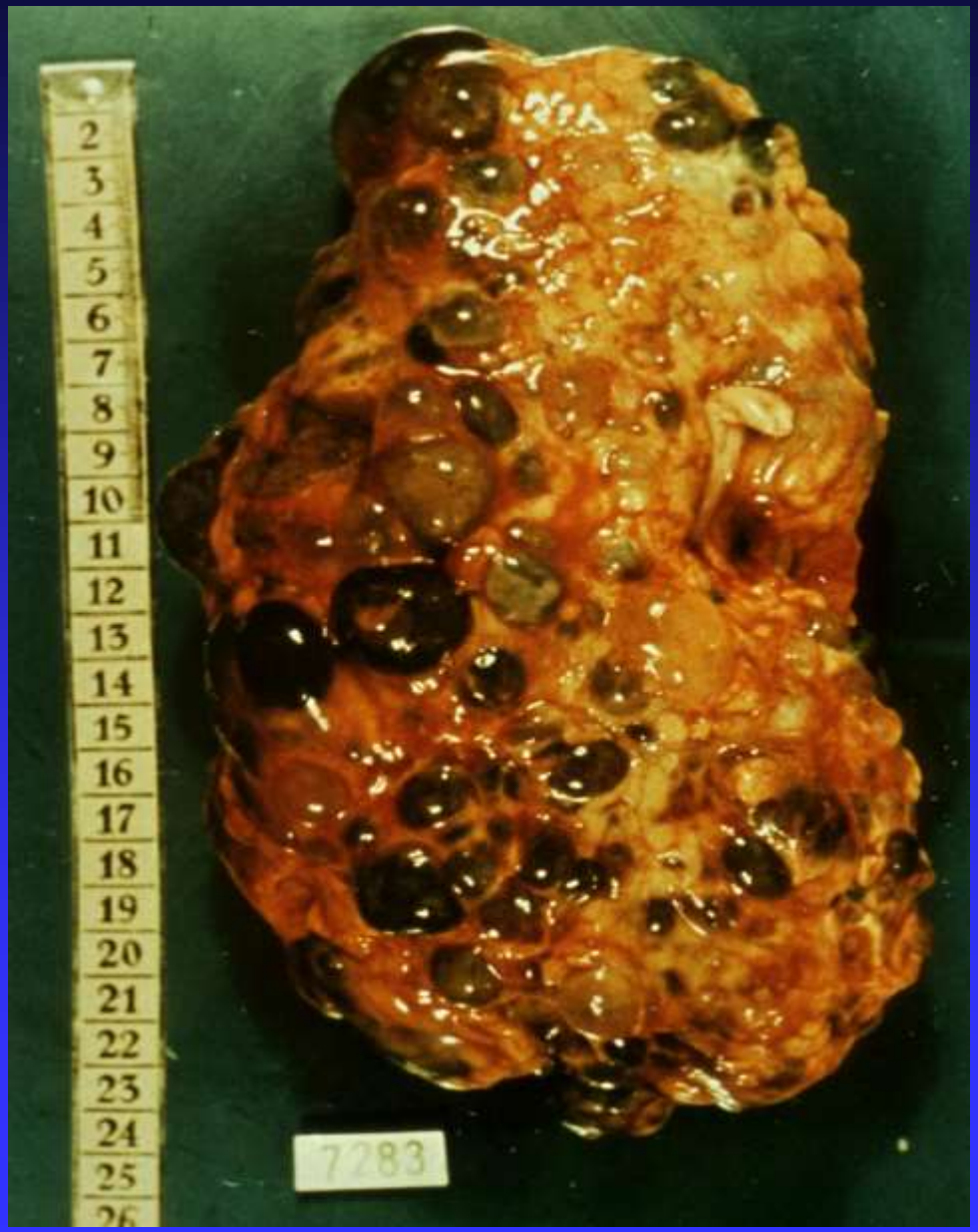
Neurofibromatosis (Recklinghausen's Disease)

- Rate: 1:3000
- Forms:
  - **I.: Neurofibromes on all over the body, café au lait patches**
  - **II.: bilateral acustic Neurinoms, submucous Neurofibroms**

Polycystic Disease

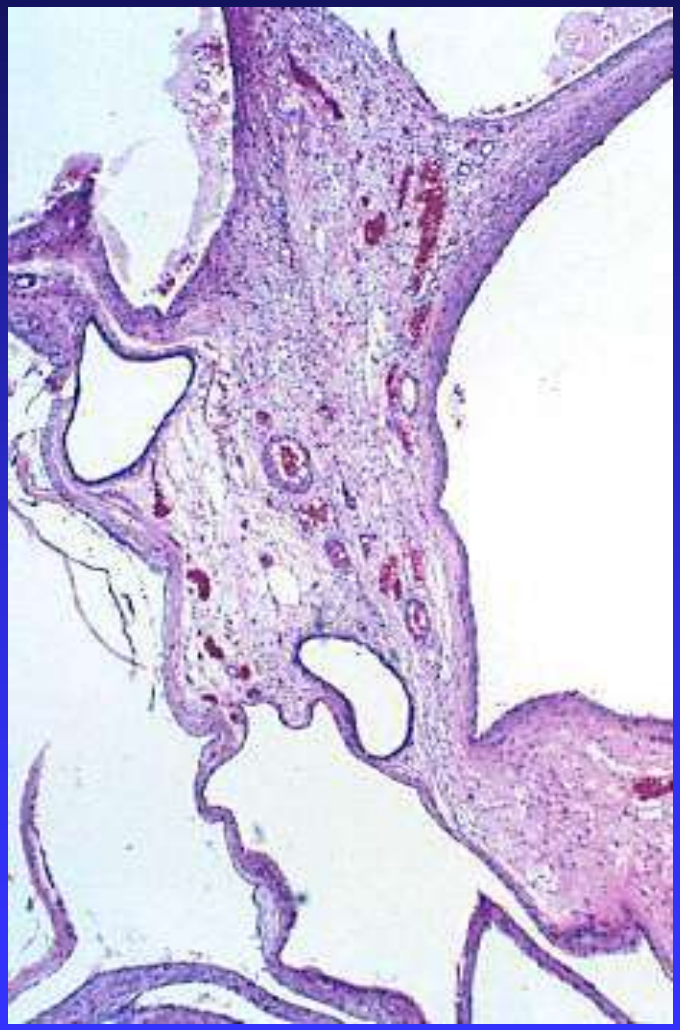
- Polycystic kidneys in adults Polycystic liver
- Polycystic lungs
- **arterious a**neurysms of basilary arteries in the skull

Cystic Kidney Disease I.



Cystic Kidney Disease I.

Autosomal Dominant (Adult Type) Polycystic Kidney Dis.



Cystic Kidney Disease II.

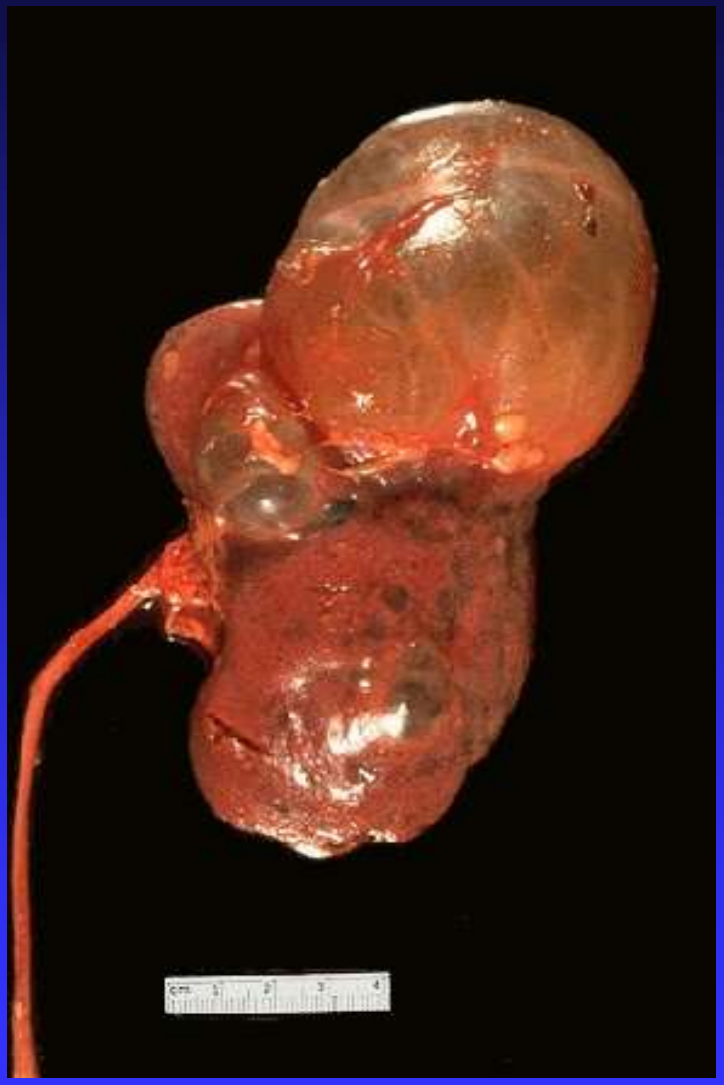
Infantile Polycystic Kidney Dis. (IPKD)

Cystic Kidney Disease

Simple Cyst

No symptoms, this is not a disease

- Bleeding might cause acute pain
- up to 10 cm, transparent, fille with fluid
- lined by one layer of cuboideal or ectropic epithelium
- no treatment is necessary



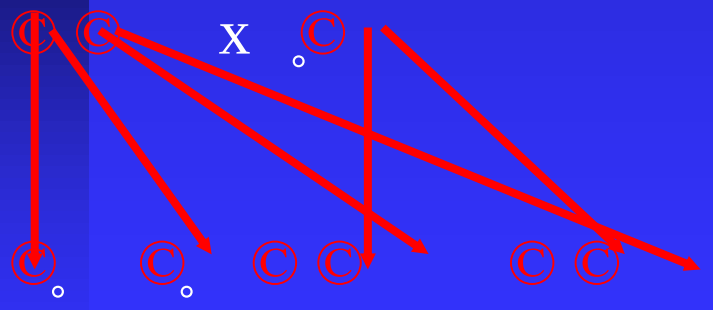
Cystic Kidney Diseases III.

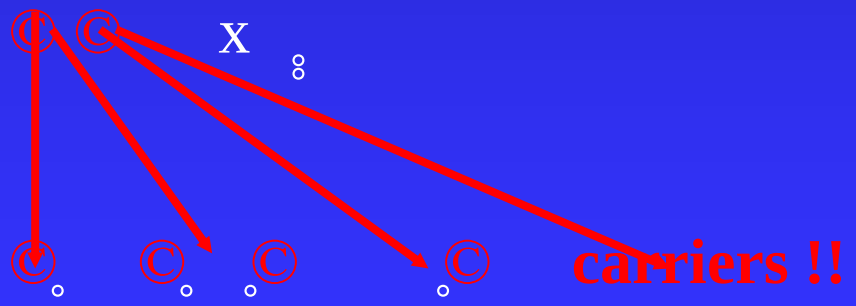
Acquired Cysts

1. 5 years after tranplantation 75 % of patients develops this change
2. Increased risk of renal cell carcinoma (7% 10 years),

Autosomal recessive inheritance

- men and women are equally involved
- the disease “jumps “ generations
- the sick people are always homozygous for the diseased gene
- The children of diseased people are always carriers of the genetic defect





Autosomal recessive diseases

- **cystic fibrosis – mucoviscidosis**
- **Phenylketonuria**
- **Galactosemia**
- **Homocystinuria**
- **Thalassaemias**
- **Hemochromatosis**
- **Wilson's disease**
- **alpha-1 antitripsine deficiency**

STORAGE DISEASES (enzime defects - accumulation of metabolic intermedier products – usually autosomal recessive)

- **Glycogen storage diseases (Liver: von Gierke dis. , , Cori, dis., Andersen dis. ; Muscles: Mc Ardle dis., Pompe dis.)**
  hypoglycemia, hepatomegalia, myopathy

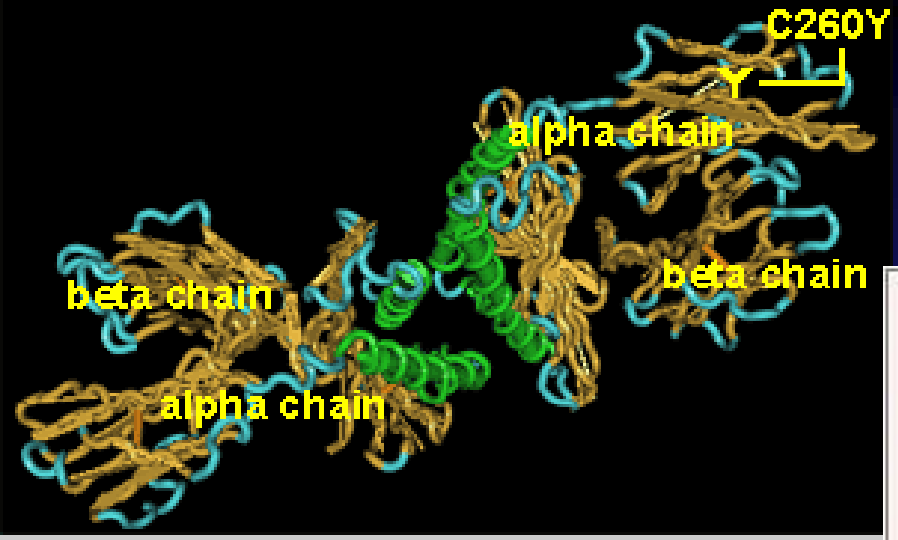
- **Lysosomal storage diseases**
  Lipids/sphyngolipids storage dis. (Gaucher dis. - cerebrozide hidrolaze: spleen/liver/CNS PAS ; Niemann Pick dis.- sphyngomyelinase: spleen/liver/CNS ; Tay-Sachs dis.: CNS)

  Mucopolysacharidoses - GAG (heparane-sulphate, dermatan-sulphate, chondroitin-sulphate, etc.) : connective tissue and neurons - balloon cells
  Hurler dis. - infants – gargoylism, hepatomegalia, mental. ret.
  Hunter dis. - children - hepatomegalia, mental ret.

Cystic fibrosis (Mucoviscidosis)

- most frequent mendelian inherited disease
- Rate: 1:2500 (1:600 - 1:90 000)
- chloride-ion transmembrane channel defect: CF Gene on chromosome 7., long arm 7q
- affected organs:
  - exocrine glands: chronic pancreatitis, liver cirrhosis
  - respiratory tract: infections, bronchiectasia,
  - digestive tract: meconium ileus, malabsorption
  - Gonads: infertility

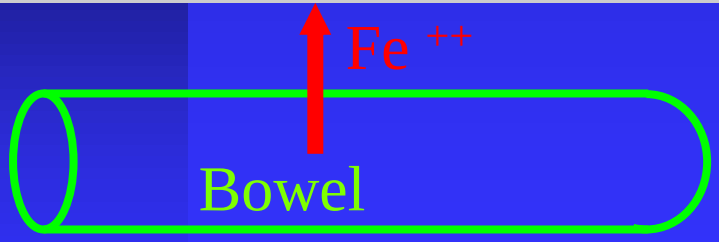
Haemochromatosis (Bronze diabetes)



The HFE protein is similar in structure to MHC class I, consisting of two pairs of alpha and beta chains.
In the mature HFE protein, the mutation is called C260Y. This is because the body's processing of the protein removes 22 amino acids to produce the mature protein.

The C260Y mutation occurs in the alpha 3 domain and disrupts the association between the chains.

Mutant HFE is unable to bind to the iron-loaded transferrin receceptor. Without this interaction, the receptor brings more iron into the cells.



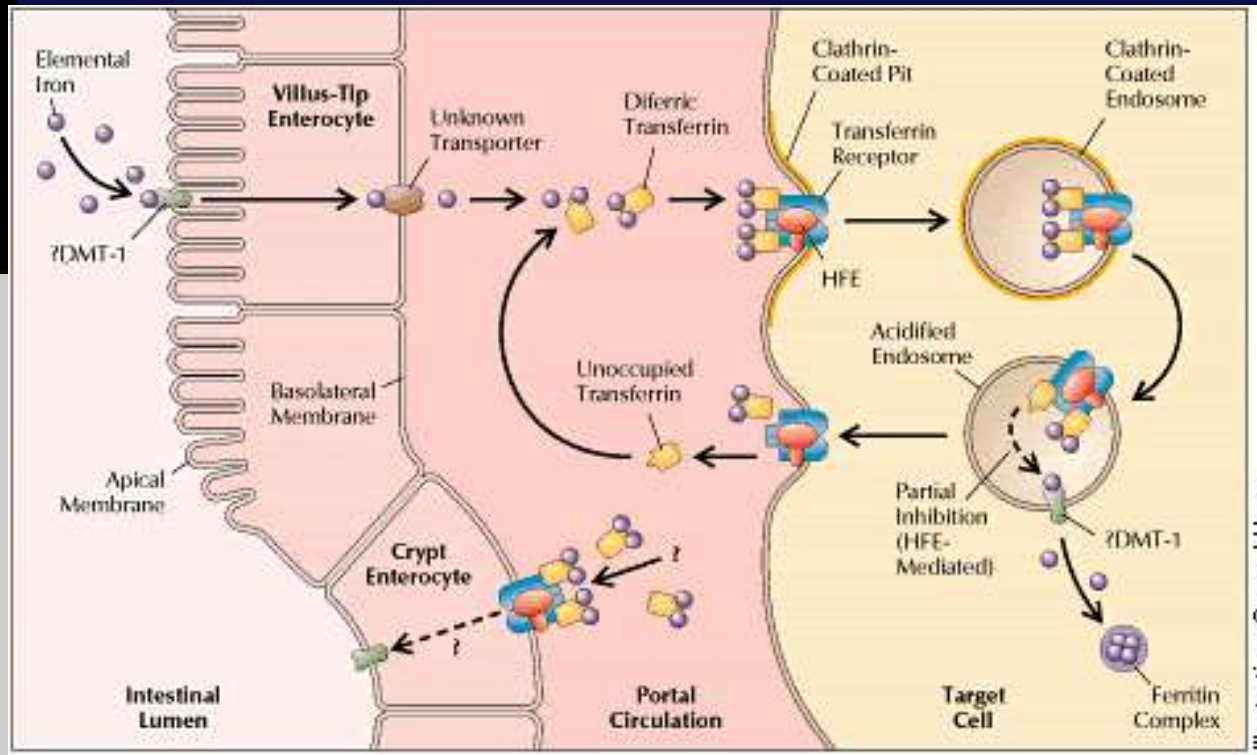


Illustration: Seward Hung

Figure 1. Emerging details of iron metabolism permit at least partial understanding of the function of the HFE protein—and of HFE's absence or dysfunction in causing hereditary hemochromatosis. From the intestinal lumen (left), dietary iron is transported into enterocytes, most likely by the newly described transporter DMT-1. From there iron enters the portal circulation for delivery—by transferrin—to target cells such as hepatocytes and erythroblasts (right). Internalized by endocytosis, the iron is eventually transported from endosomes into the cytoplasm, often for storage in ferritin. Meanwhile, transferrin and its receptor are recycled to the cell surface. HFE binds to the transferrin receptor. Once bound, it inhibits the release of iron, so that an increased fraction of iron-bound transferrin recycles back out of the cell. In the absence of HFE, the cell may become iron-overloaded. A more primary problem may affect the intestinal lining. Here, HFE is hypothesized to act in undifferentiated crypt enterocytes (bottom left), the precursors of villus-tip enterocytes, so as to regulate uptake of plasma iron. Each crypt cell becomes a sensor of the body's iron load, perhaps to program its subsequent expression of DMT-1 (dashed arrow). If HFE function is lost, iron sensing may be disrupted. Falsely sensing low body iron, the crypt cell may overexpress DMT-1, facilitating excessive lumenal iron absorption by mature enterocytes.

Hemochromatosis - Bronzdiabetes

Iron „storage" disease cons. of iron overload of the organismu in the parenchymal organs
Cause: Disability of RHS, to control the iron overload
Forms: *idiopathic* »adult« a. Hemochromatosis is familiary
b) perinatal Form – symptoms after delivery
erythropoetic hemochromatosis by disturbed erythropoesis
iron resorption is increased
Hypersideremia and iron deposition (Siderosis)
Liver cirrhosis (Pigmentcirrhosis)
bronze colored skin
hypofunction or falling out activitiy of endo- and exocrine glands
Hypogonadismus
insulin dependent Diabetes mellitus =
»Bronzediabetes«
Hear insuffitienty – cardiomyopathy
Haar loss

acquired Hemochromatosis e. g. transfusions-hemochromatosis

.

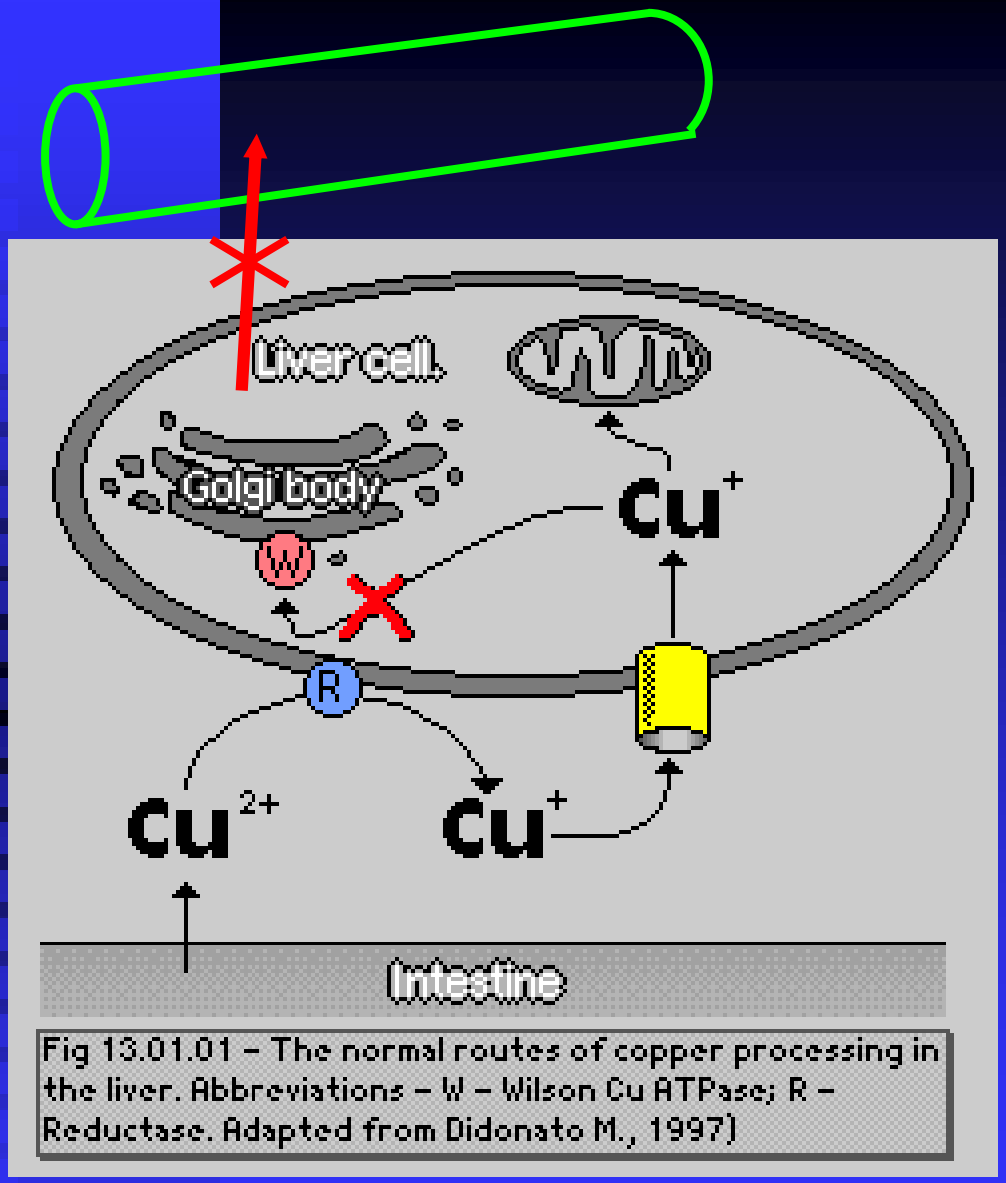
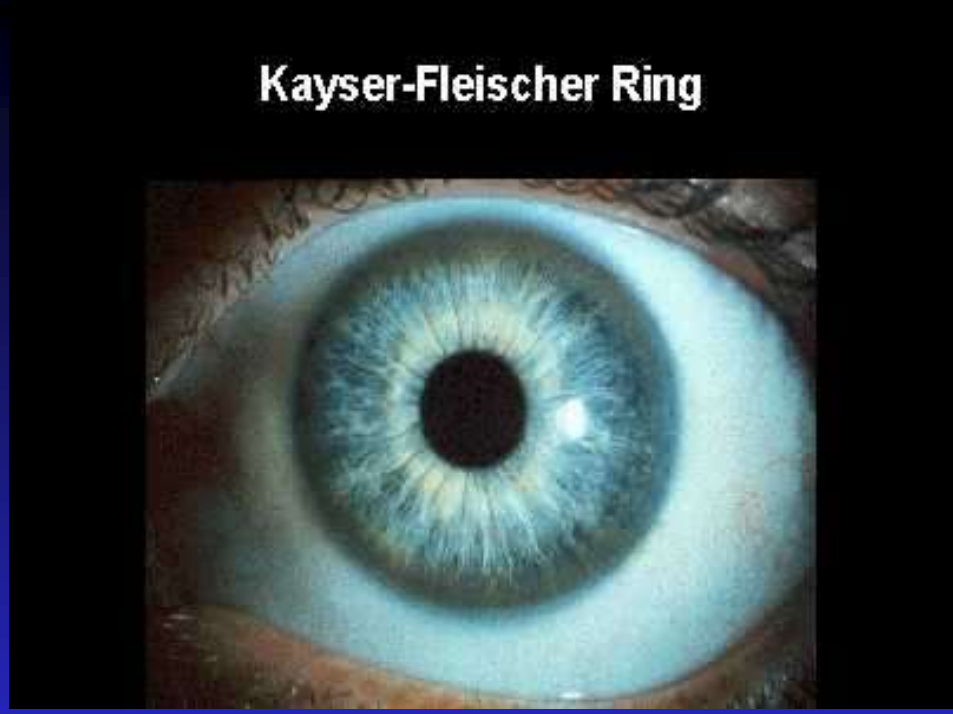


Fig 13.01.01 – The normal routes of copper processing in the liver. Abbreviations – W – Wilson Cu ATPase; R – Reductase. Adapted from Didonato M., 1997)



Wilson disease
(hepatolenticular disease)
(Copper storage disease)

Wilson Disease – hepatolenticular degeneration

autosomal-recessiv - inherited defektparaproteinemia
Disturbed Coeruloplasmin-synthesis
Serum: < 10 mg/100 ml; normal 23-44
Copper enrichment in tissues
Begins at 1.-2. yrs. of age
extrapyramidal symptoms: Tremor, Rigor, Ataxia, Dysarthria, Kontraktures because degeneration of basal ganglia
Pathognomic: Kayser-Fleischer Ring
liver cirrhosis
aminoaciduria – blocked tubulary enzymes by copper
greybrownish colored skin
disturbed carbohydrate metabolism
hyperinsulinismus
intellectual and physical senescene

Kayser-Fleischer Ring

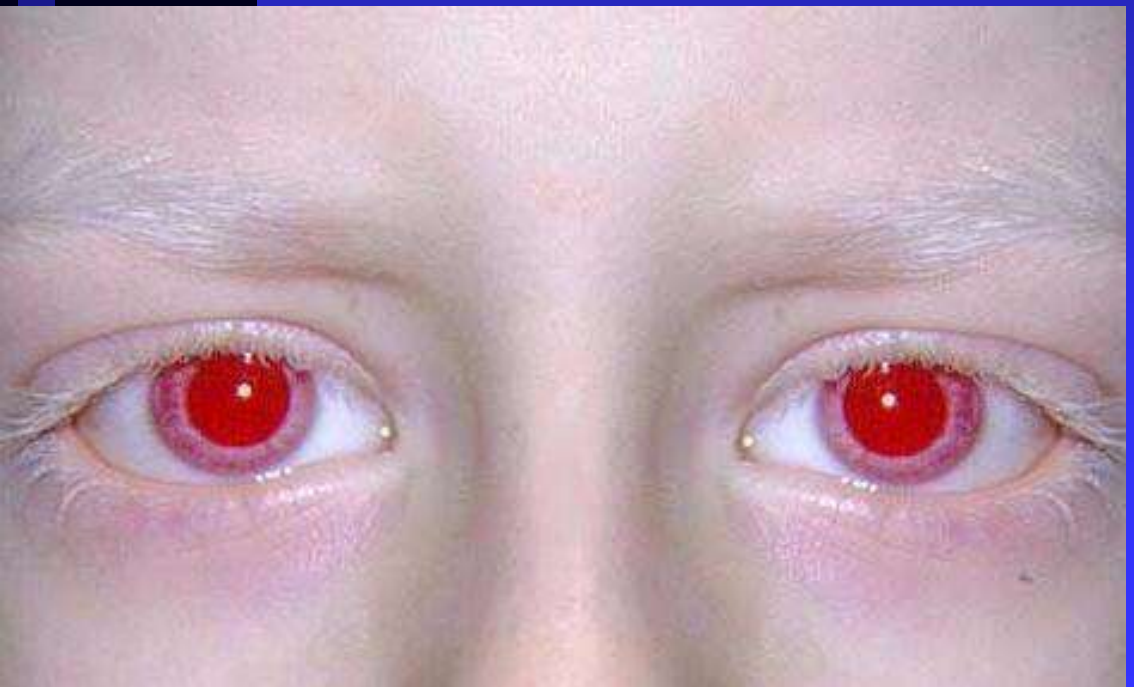
Brownish-greenish limbus-close corneal ring
1-3 mm width
determined by copper deposition

Albinism

- defect of melanin synthesis, **tirosinase defect**

oculocutan forms: autosomal recessive

ocular form: X-bound recessive



albino

Galactosaemia

- defect of **galactose-1 uridil-transferase**
- **sever mental retardation**
- **May be treated with diet on time**
- cirrhosis, mental retardation, catarract

Phenylketonuria

- Rate: 1:20 000
- defect of phenylalanine hydroxilase: on chromosome 12., long arm q
- decreased pigmentation of hair and skin
- severe mental retardation
- Therapy: Diet – beginning in time !

Lysosomal Storage Diseases

- Enzyme defects - accu,ulation of metabolic intermediats
- Forms:
  - Glycogenosis
  - Sphyngolipidosis
  - Sulfatidosis
  - Mucopolysacharidosis
  - Mucolipidosis

Storage diseases:

Glikogenosis (I-VII) (von Gierke I (Liver), IV. Andersen ((Leber – Zirrhose) Mc Ardle V. (muscle) , ! II. Pompe Lysosomal (muscle,) !
Hepatomegalia, Hypotonia

Lipids - sphingolipids(Cerebrozid, gangliozid) - lysosomal

Gaucher dis. - cerebrozid hidrolase - lysosome – liver, spleen – PAS (mental retard., hepatosplenomegalia at young ages)

Niemann Pick: liver, spleen (mental retardation, ataxia and hepatosplenomegalia),

Tay-Sachs: sphyngolipidosis - CNS (mental retard, blindness)

Mucopolisacharidosis - GAG (Heparan Sulfat, dermatan sulfat) - balloon cells, mental retardation and hepatomegaly - lysosomal

Hurler dis. - gargoylism
Hunter dis. – X- recessive

Gierke Disease

Edgar O. C. von Gierke., 1877-1945, Pathologist, Karlsruhe

autosomal-recessive - hepatorenal - Type 1 Glykogenosis

Main symptoms: Hypoglykämien: consequence of decreased levels of Glucose-6-phosphatase

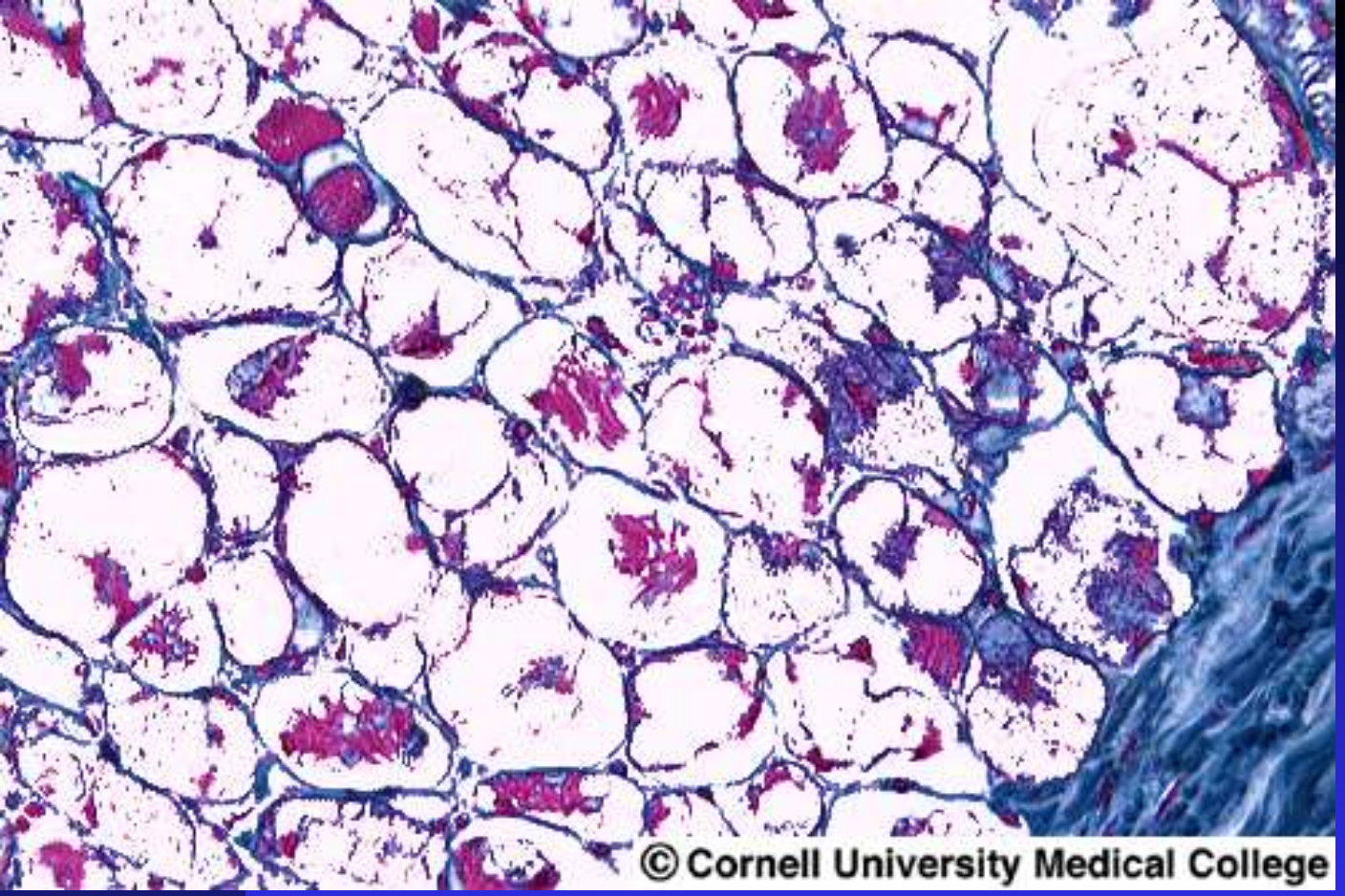
Liver insuffitiency

hämorrhagic diathesis – Thrombozytopathy by glykogene depostition

later emnlarged kidneys (»Nephromegaly«)

Infantilismus - adiposogenital type

sclera dystrophy



Glycogenosis

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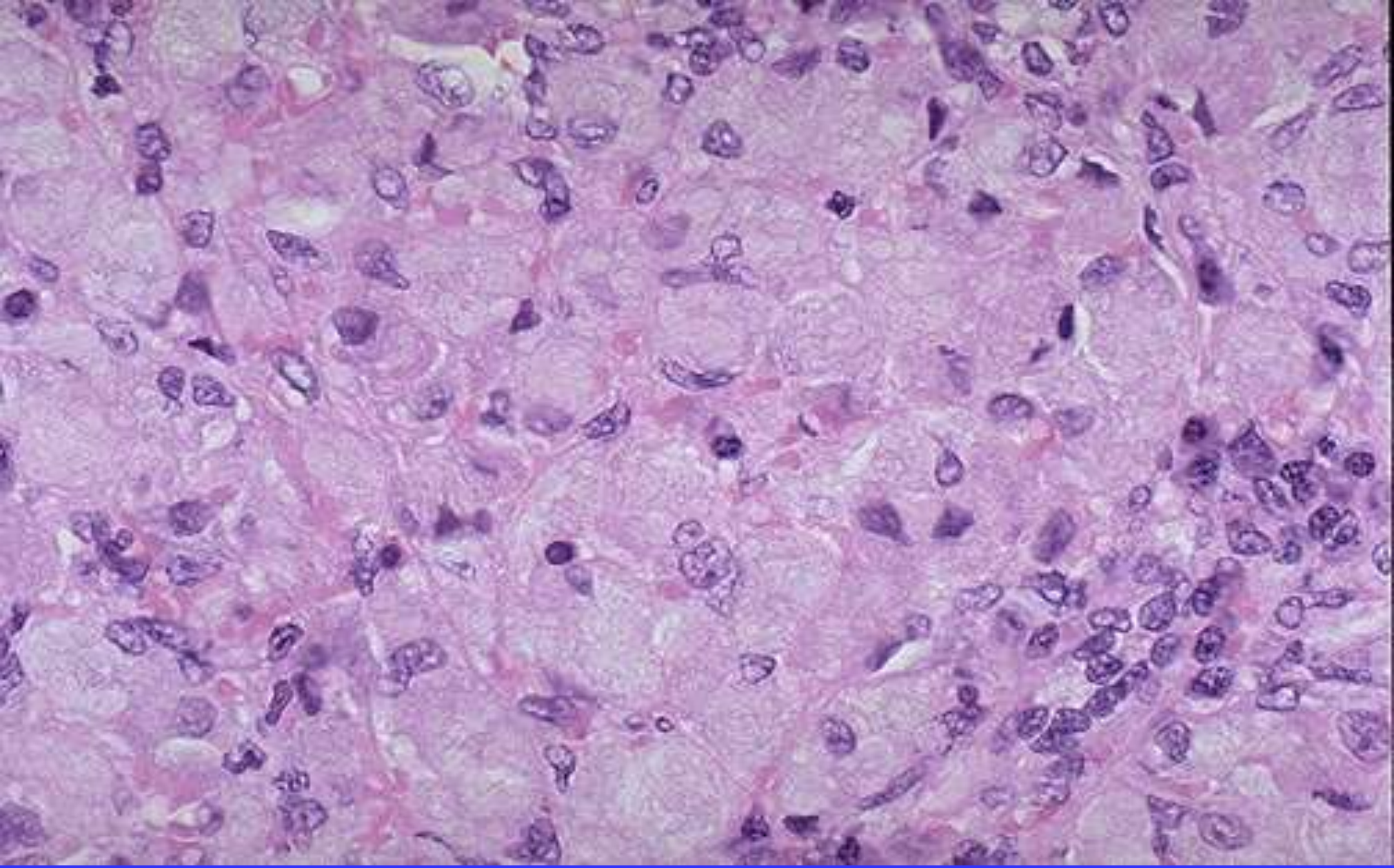
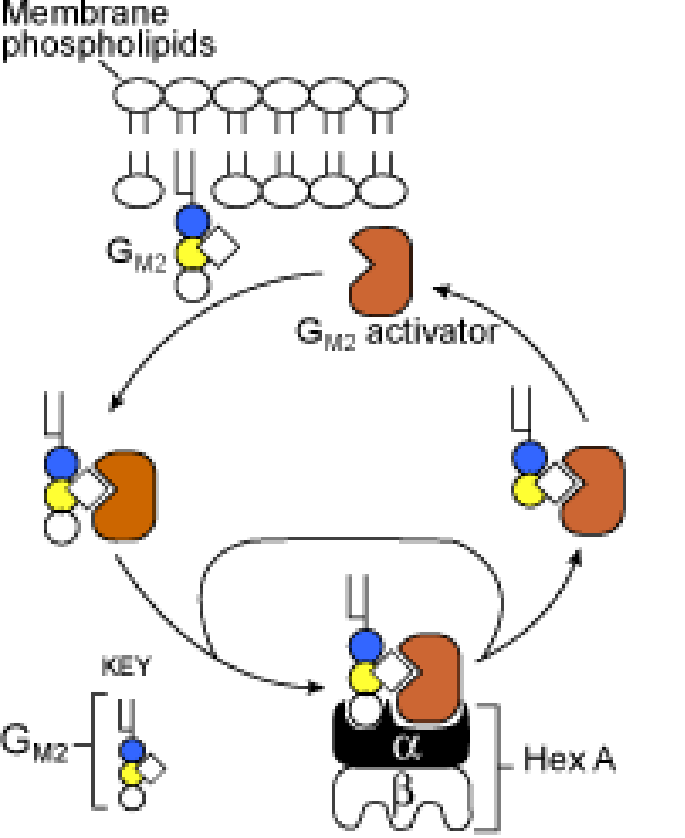
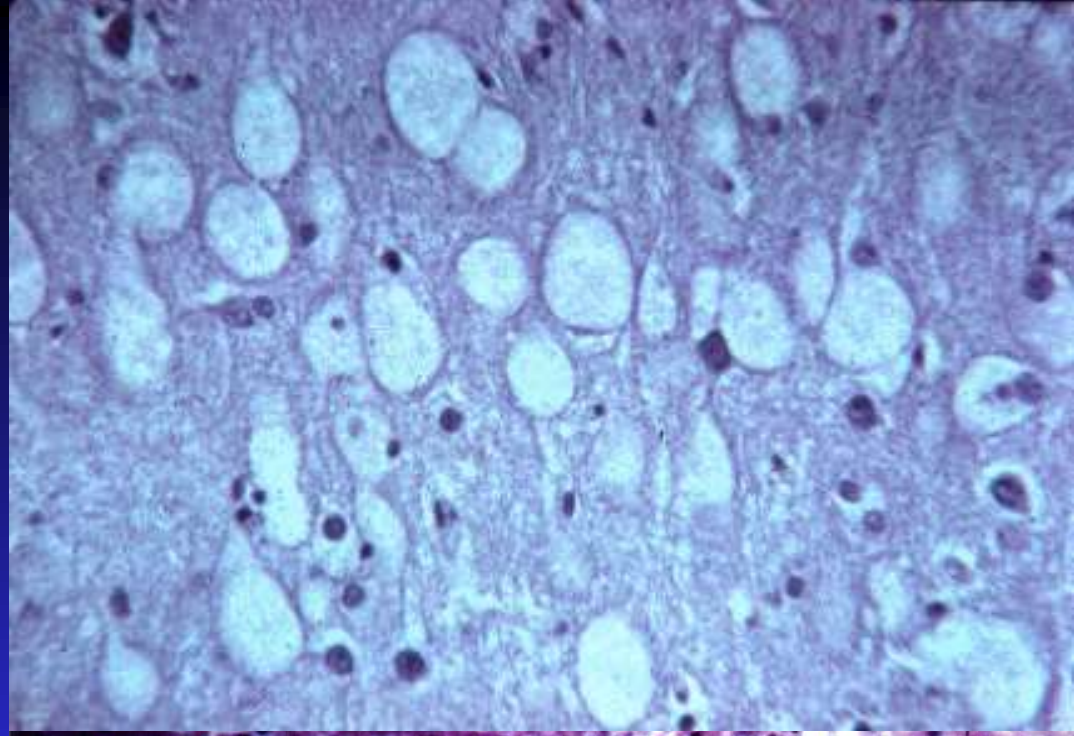


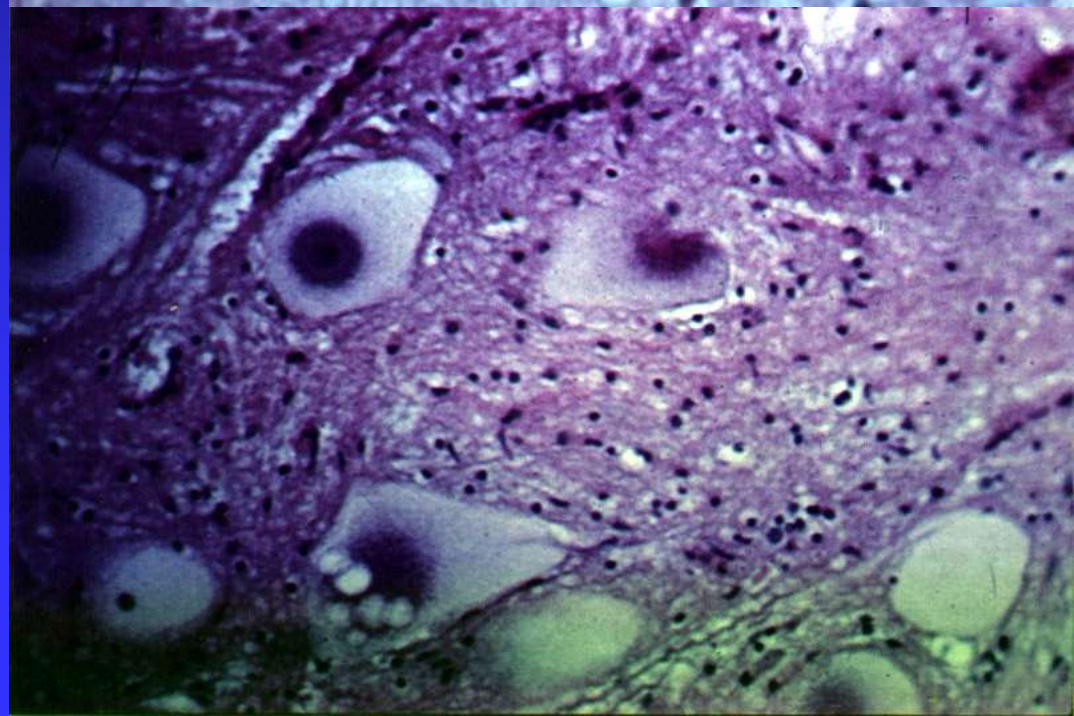
Splenomegalia - morbus Gaucher

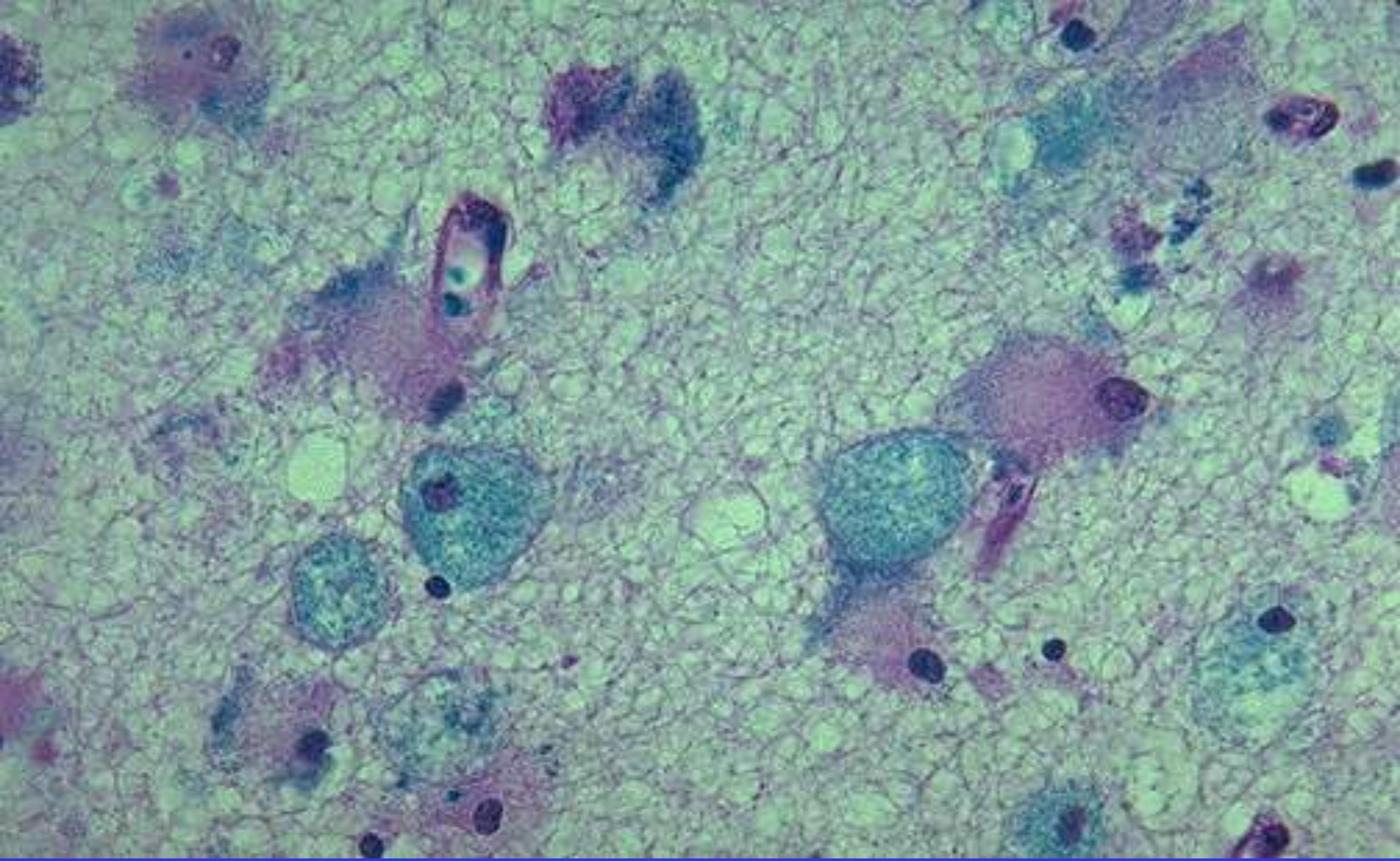
Tay-Sachs Disease



Model for G_{M2} ganglioside metabolism. Under normal conditions, β-hexosaminidase works in the lysosome of nerve cells to breakdown unwanted ganglioside G_{M2}, a component of the nerve cell membrane. This requires three components: an α-subunit, a β-subunit and an activator subunit. In Tay Sachs disease, the alpha subunit of hexosaminidase malfunctions, leading to a toxic build-up of the G_{M2} ganglioside in the lysosyme. [Adapted from: Chavany, C. and Jendoubi, M. (1998) *Mol. Med. Today*, 4: 158-165, with permission.]







Luxol fast blue stain: large swollen neurons in Tay-Sachs disease - Gangliosidosis

Storage diseases:

Glikogenosis (I-VII) (von Gierke I (Liver), IV. Andersen ((Leber – Zirrhose) Mc Ardle V. (muscle) , ! II. Pompe Lysosomal (muscle,) !
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Hurler dis. - gargoylism
Hunter dis. – X- recessive

Mucopolysaccharidosis (Thesaurismosen)

Altered bone - skelet

ZNS
viszeral organs
skind end endokardium

Disturbed degradation of acidic mucopolysaccharids (Glykosaminoglycane) in the lysosomes

4 types of glykosaminoglycanes

Clinical signs: skeletal developmental anomalies with dysmorphy
cornea spots
mental retardation

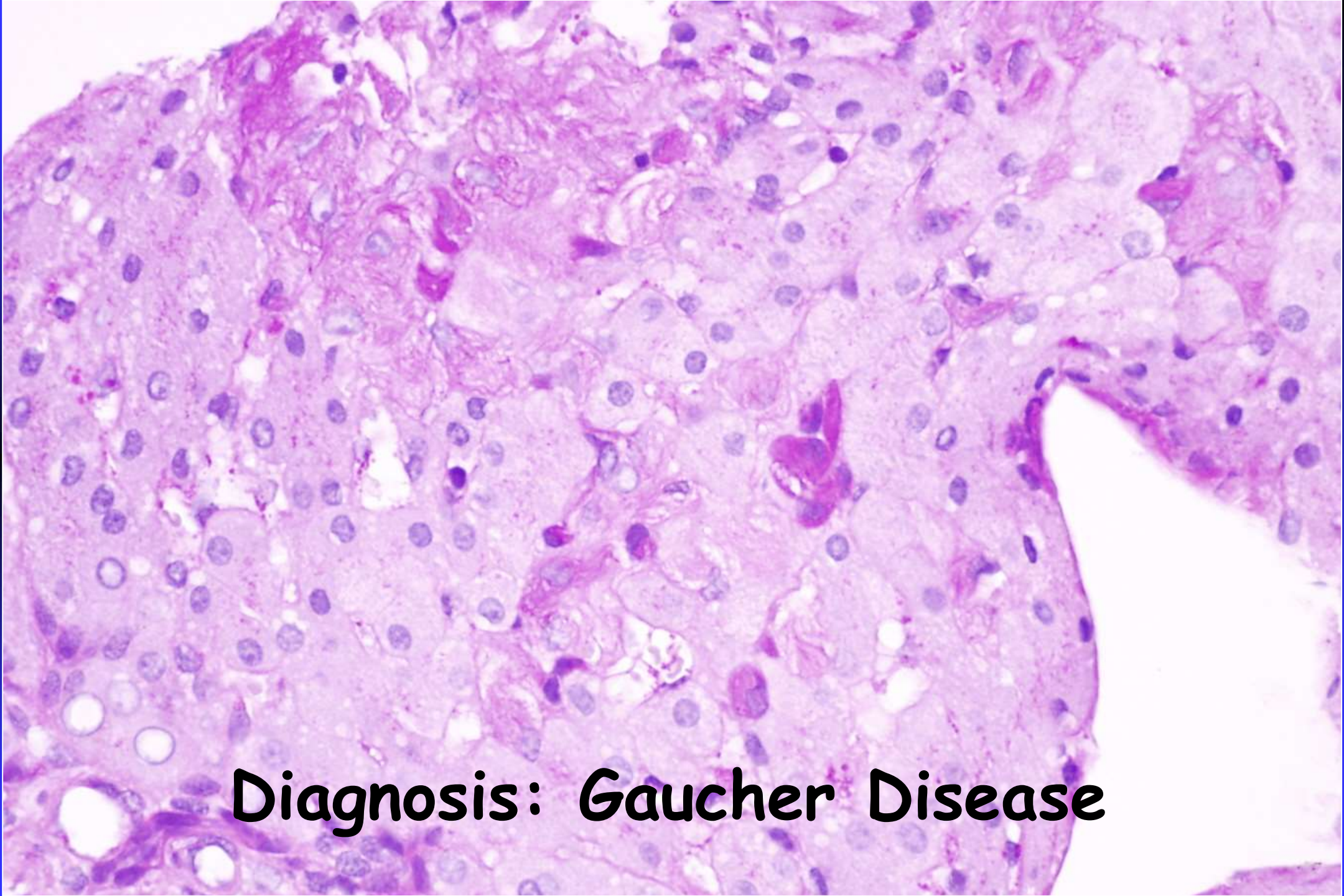
3 years old boy
10695/04

Clinical Data: heavy splenomegaly, Pancytopenia

Virus Serology: negative

Bonemarrow aspiration (in other Institute): negative

Clinical Diagnosis: hematological disease ?


Diagnosis: Gaucher Disease

Sex chromosome related, inherited diseases

- Almost all are X chromosome related
  (Mutations on Y chromosome are lethal)
- all daughter of the diseased father are carriers of the disease
- all sons of the diseased fathers are healthy
- all sons of the carrier mothers are affected

X dominant disease(s)

- women are double frequently involved compared to men
- the disease is more severe in men
- the disease shows manifestation in all generations
  - vitamine D resistent rachitis
  - Melnick-Needles Syndrome (Osteodysplasia, congenital disorders: disproportional dwarfs, decreased intelligence, craniofacial dysmorphy)

X recessive inheritance

- carrier men are sick

  (lethal in homozygous people)
- all daughters of the diseased father are carriers, all sons are healthy
- 50% of the sons of the gene carrier mother are sick, 50% of the daughters are carriers !

X recessive diseases

- Duchenn and Becker type muscle dystrophy
- Haemophilia A and B
- fragile X syndrome ?
- Lesch-Nyhan syndrom (Hyperurikaemia and hyperurikuria, mental retardation)
- chronic granulomatous disease (CGD)
- G6PD deficiency
- Wiscott-Aldrich syndrome (immundeficiency, IgM down, IgA up, thrombocytopenic purpura)

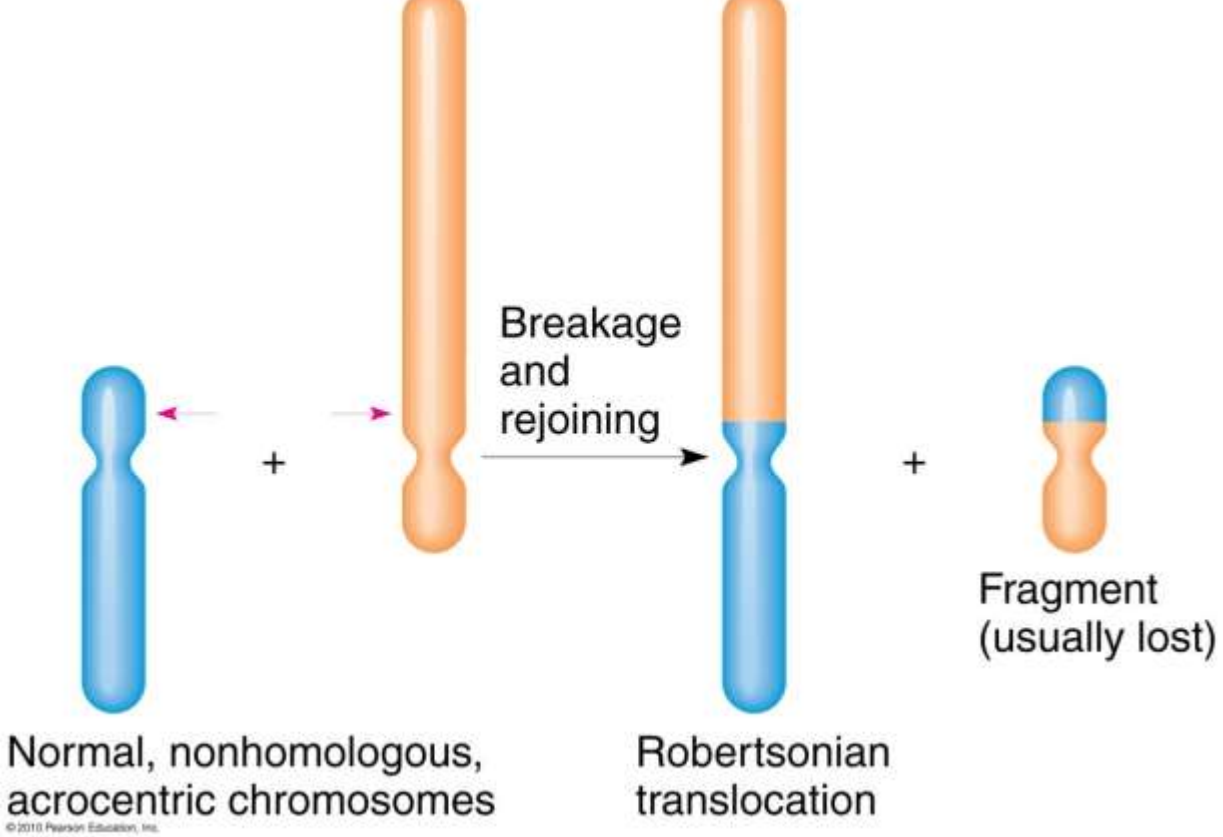
Chromosomal Defects

- **Numeric disorders**
- **Monosomy, Trisomy**

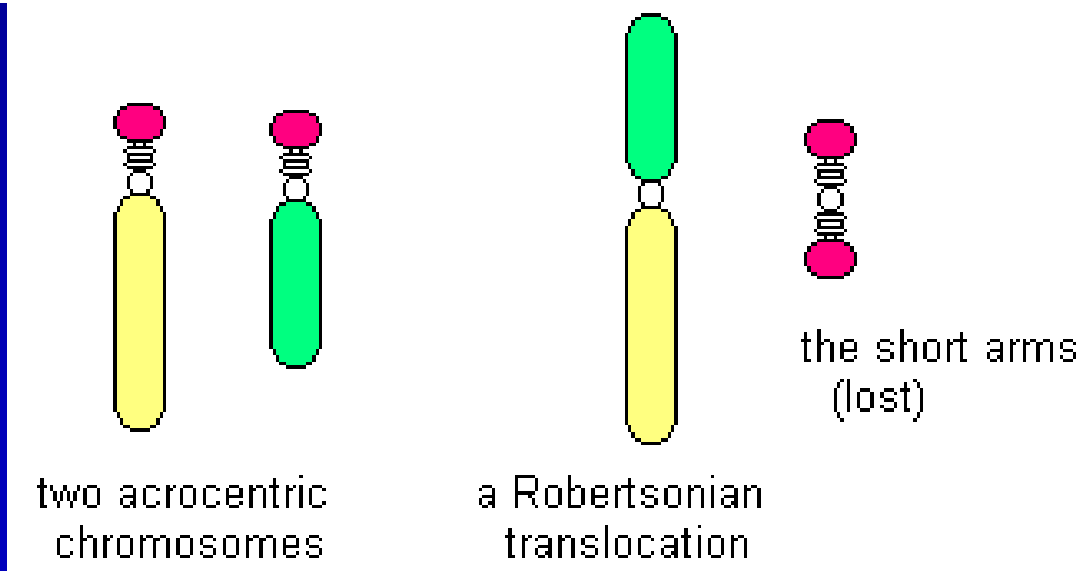
  Cause: no-disjunction, late of the Anaphasis

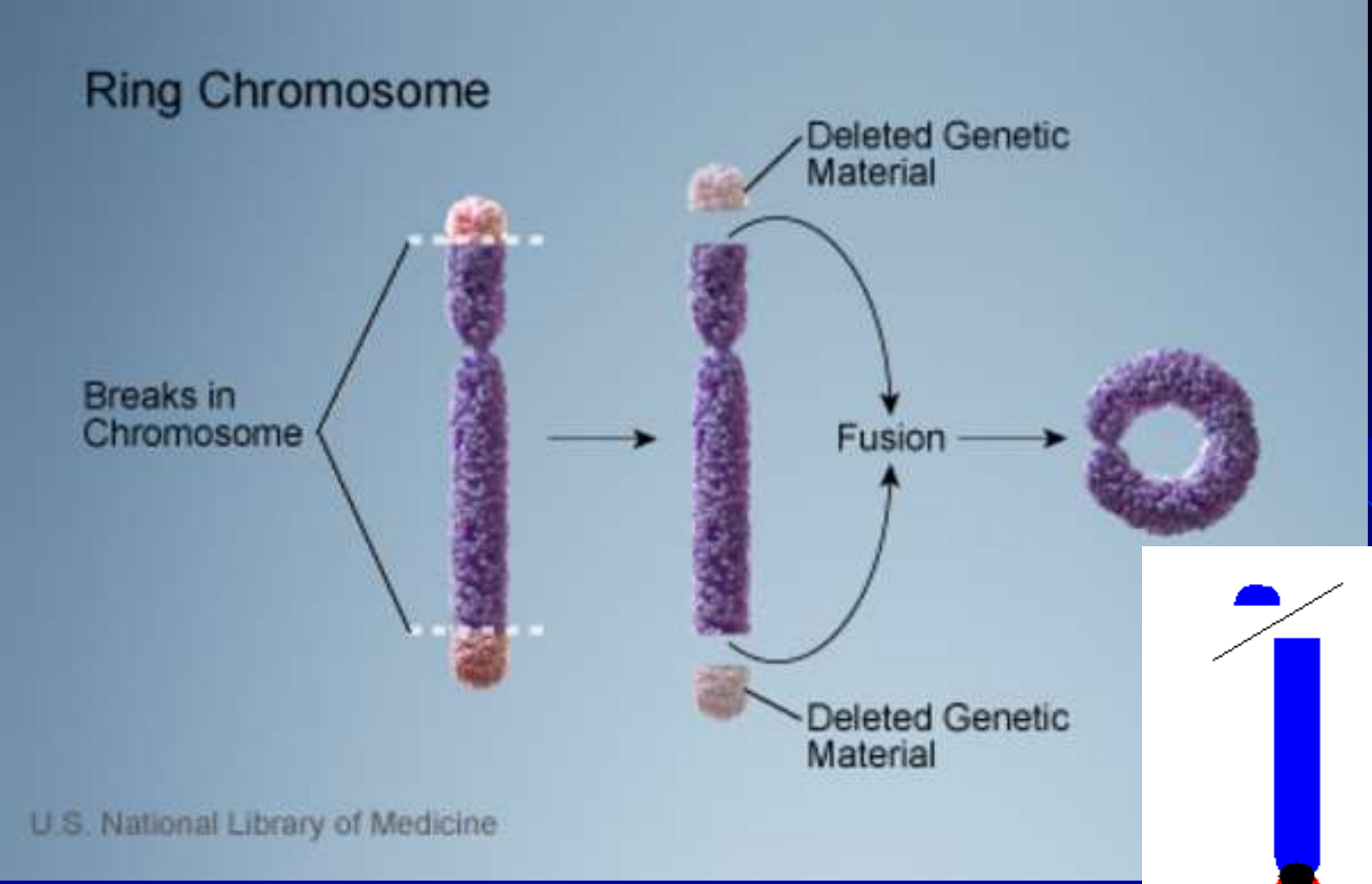
  - **Mosaicism**

    Cause: damage in early embyogenesis
- **Structural Disorders**
  - **Deletion, Addition**
  - **Inversion**
  - **Isochromosom, ringchromosom**

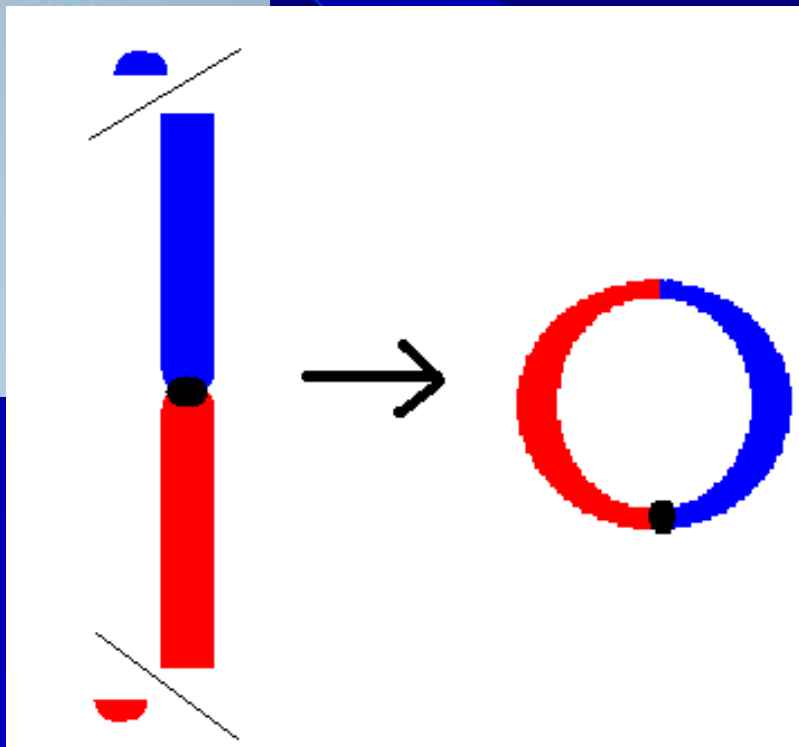


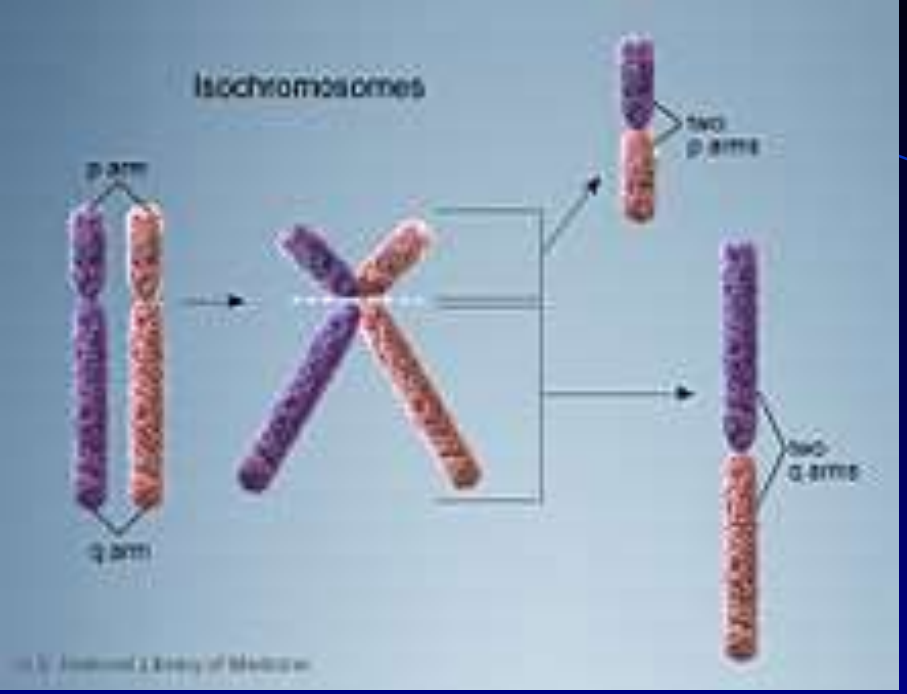
Robertson transzlokáció (akrális fúzió)



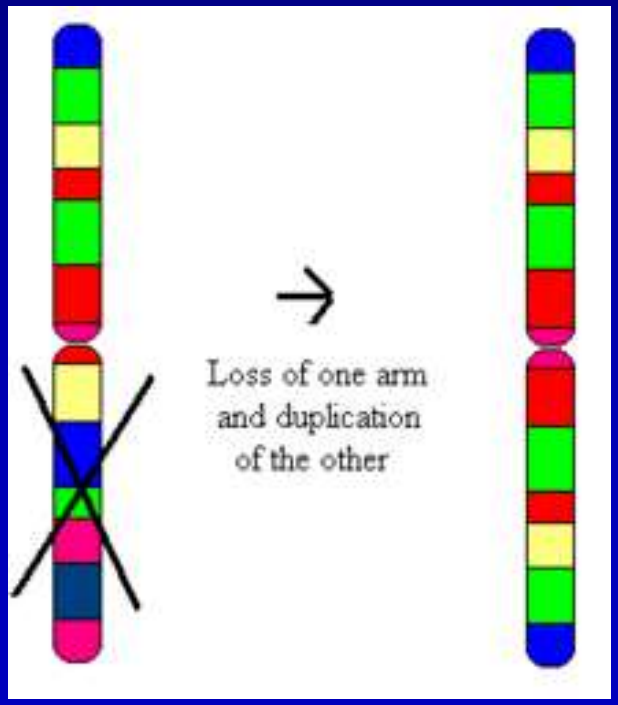


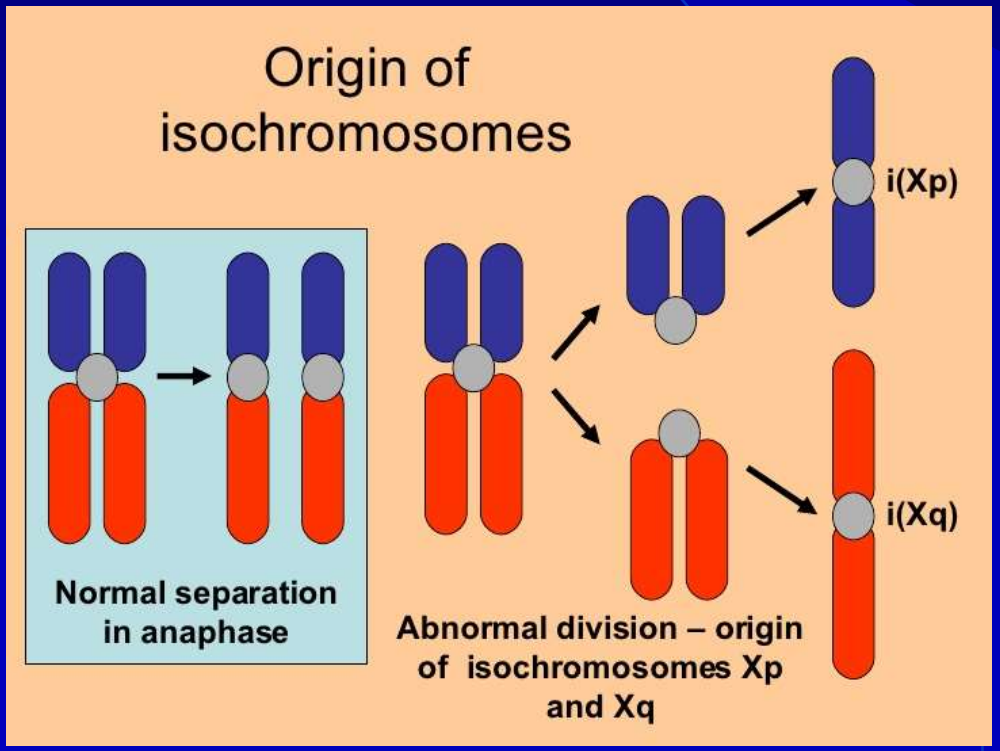
Gyűrű kromoszóma





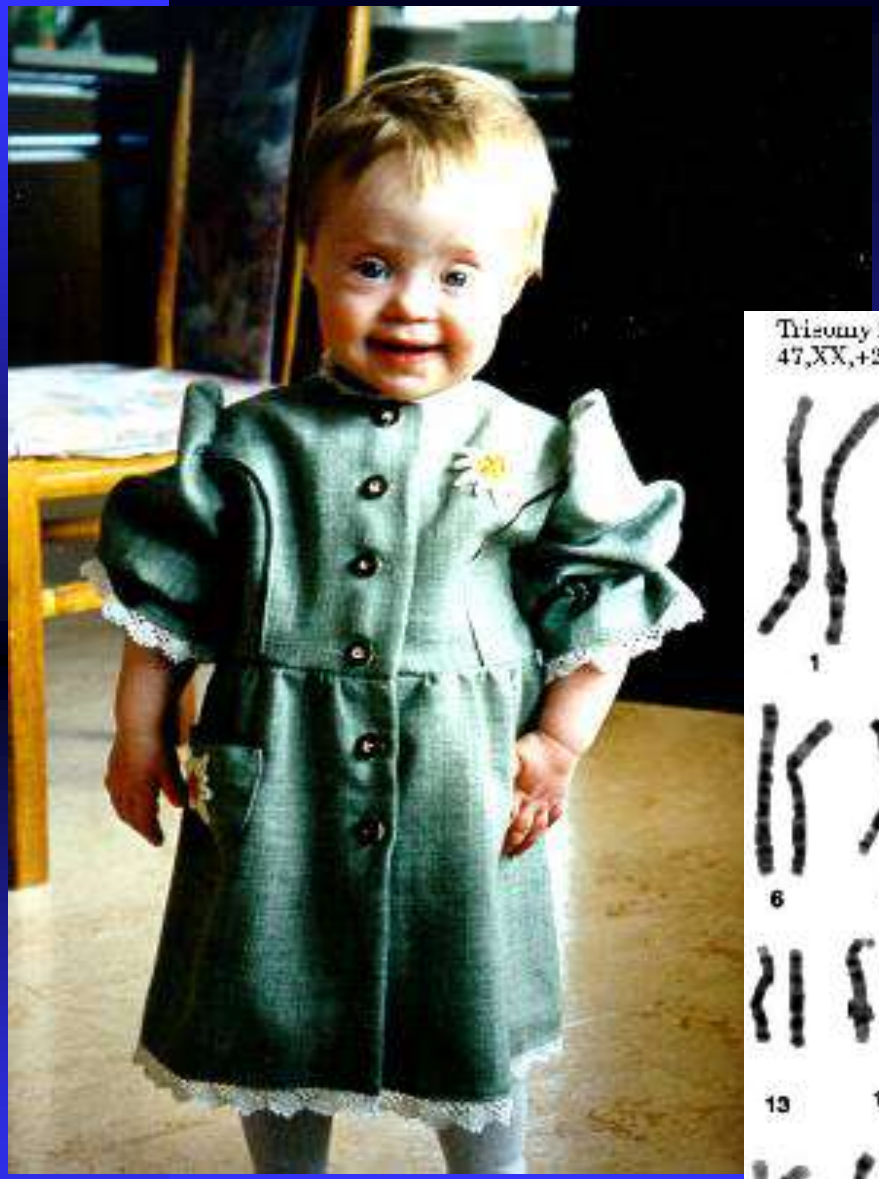
An **isochromosome** is an unbalanced structural abnormality in which the arms of the chromosome are mirror images of each other.[1] The chromosome consists of two copies of either the long (q) arm or the short (p) arm because isochromosome formation is equivalent to a simultaneous duplication and deletion of genetic material. Consequently, there is partial trisomy of the genes present in the isochromosome and partial monosomy of the genes in the lost arm.





Autosomal Defects

- Trisomy:
  - Down syndrom (21 Trisomy)
  - Edwards syndrom (18 Trisomy)
  - Patau syndrom (13 Trisomy)
- Deletions
  - Cri du chat syndrom (5p Deletion)
  - 4p Deletion




Trisomy 21
47,XX,+21
1
2
3
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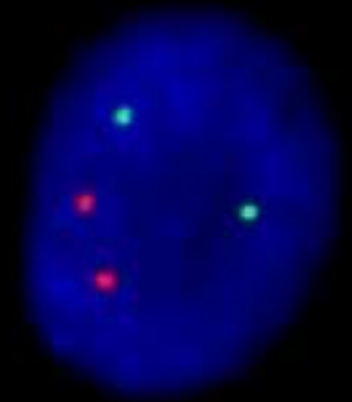
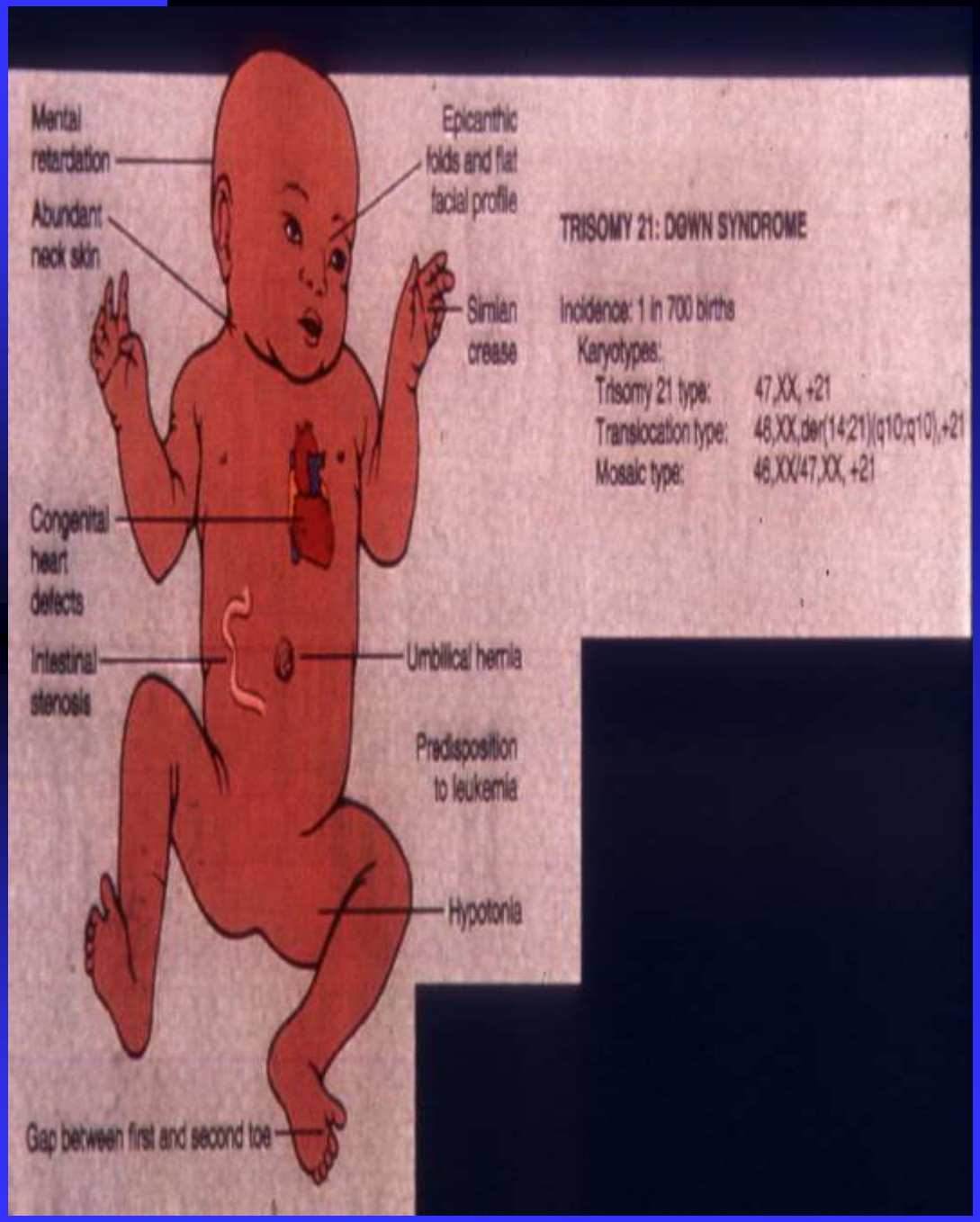
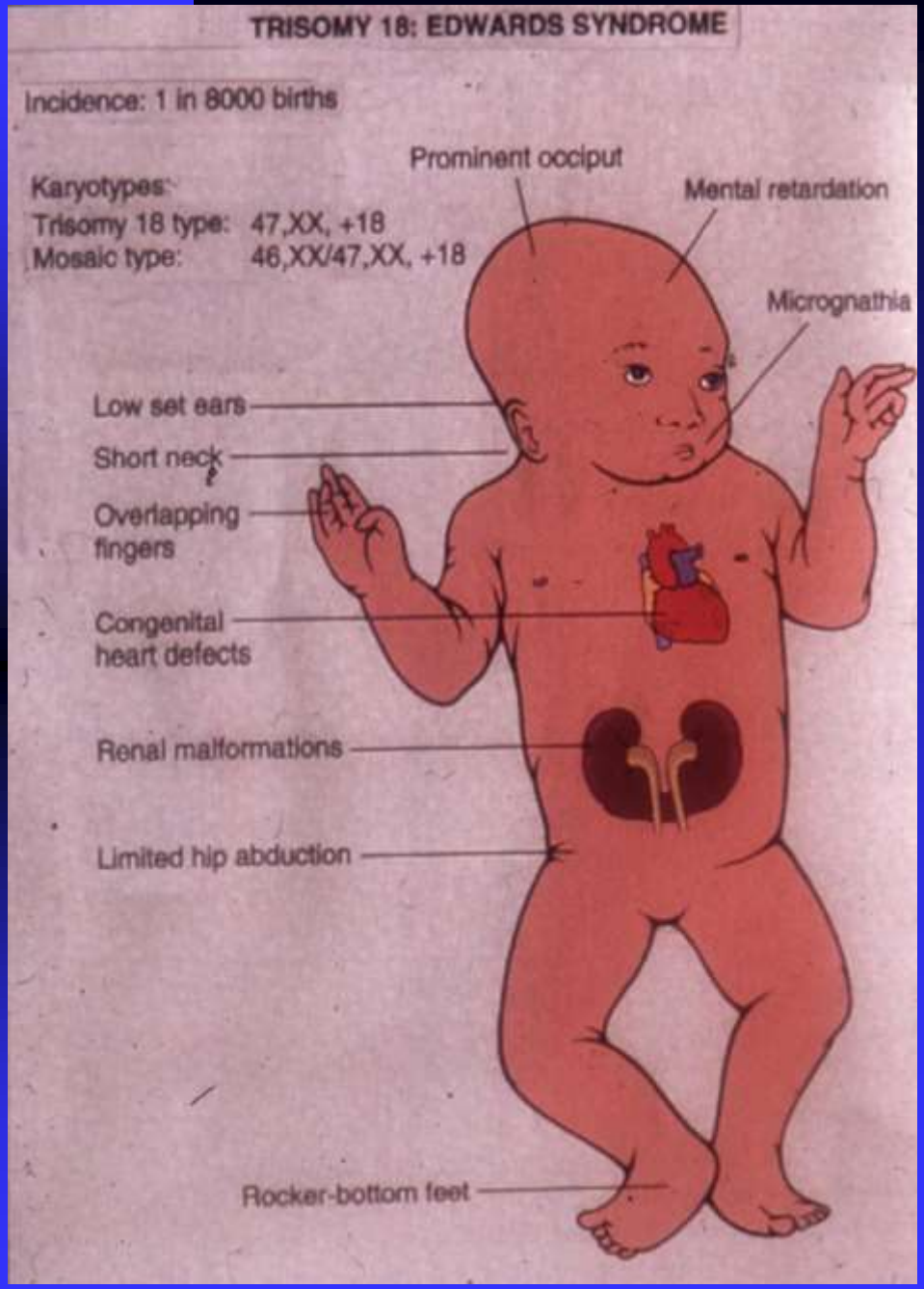
X X



Down syndrom:



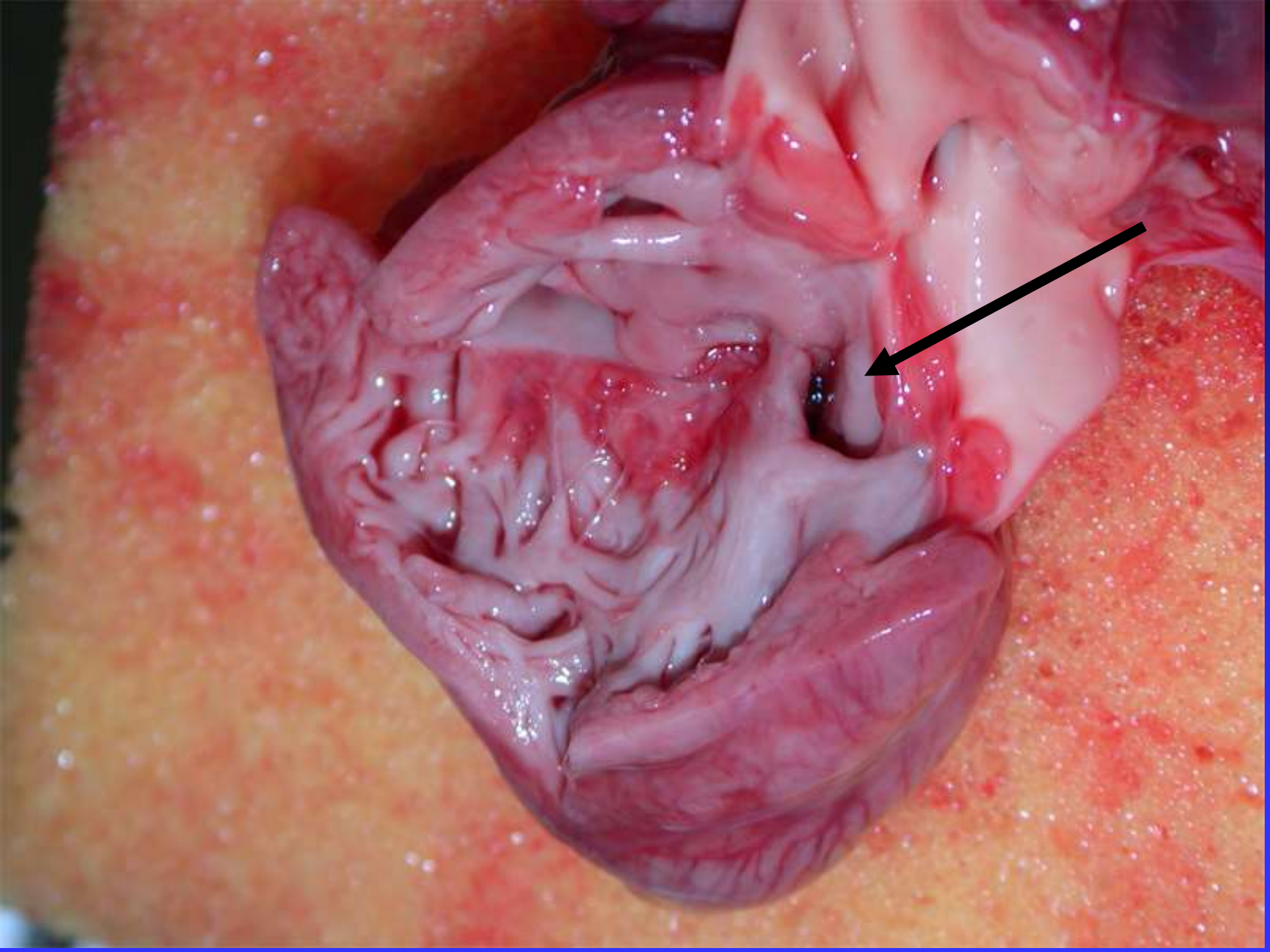


Edwards syndrom:

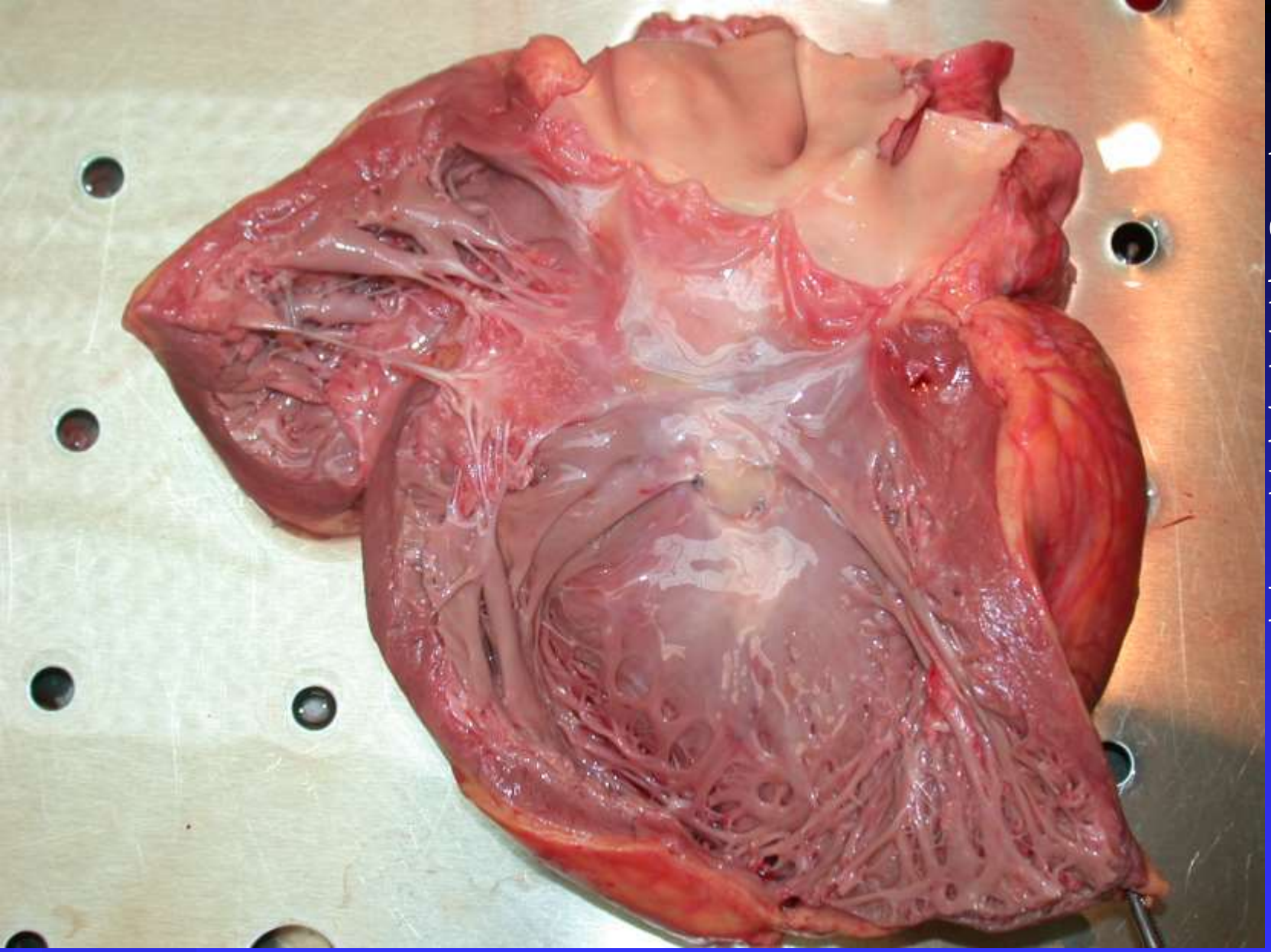
18 chr. trisomy
Mental retardation
short neck
heart defects
horseshoe kidney

Patau syndrom

13 chr. trisomy
Cleft lip and palate
Rocker bottom feet
mental retardation
caridac defects



VSD
(ASD, aorta asc. atresia)



tricusp. insuff.
dilatatio ventr. ,
fixed pulm.
hypertension
progr. circ.
insuffitiency

Exitus: 31 years

Medical history: corrected transpositions of the major arteries
12 years of age: closing of VSD, not attending med. controls after

Defects of the sex chromosoms

- Monosomies:
  - Turner syndrom: 45 X
- Polysomies:
  - Klinefelther syndrom: 47 XXY (48 XXXY, 49 XXXYY, etc.)
  - Superman: 47 XYY (48 XYYY, 49 XYYYY, etc.)

Genetic causes of disturbed sexual Differentiation

TERMS

Sex Reversal: karyotype does not match the genitals (XY female, XX male)

Pseudo-hermafroditism: (male of female) karyotype matches the gonads, bot not the genitals - disagreement between phenotypic and gonadal sex

Hermafroditism: presence of both ovarian and testicular tissue on different sides (contralateral) or combined ovotestis

Ambigous genitals: does not resemble either male or female

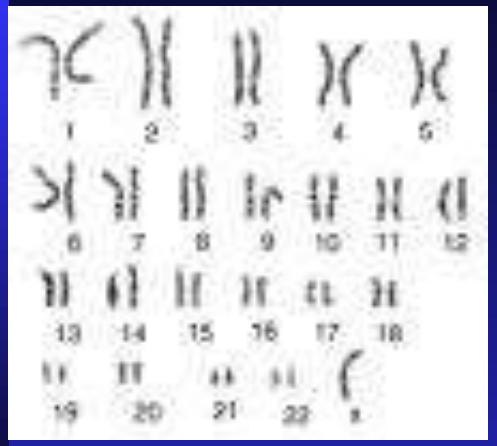
Hermaphroditos was a handsome son of Hermes and Aphrodite.

He was loved by the Nymphe Salmakis who prayed that she could be with him forever.

Some god, on hearing her prayer, merged their two forms into one, to form
a being that was both male and female

(Louvre, Paris)

Turner syndrom: 45 X



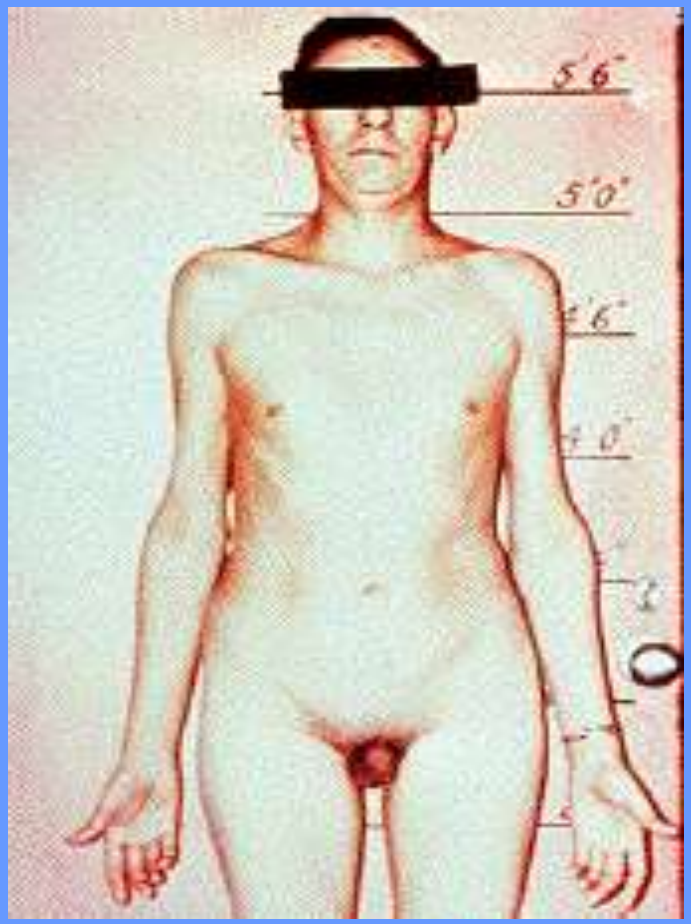
Short stature
Low posterior hairline
webbing of neck
streak ovaries
infertility
amenorrhea
coarctation of the aorta

Klinefelter (XXY) syndrom

Bipotential gonads XX

Testis: small, little amount of SP

Eunuchoid body habitus with abnormnally long legs
infertility
small, atrophic testis
Klinefelter (XXY) syndrom



Pseudo-hermafroditism

karyotype mathces the gonads, external genitalia are ambiguous or female

XY, testes, female or ambiguous genitals

Hormonal:

5-alpha reductase deficiency

Androgen receptor insensivity

(testicular feminization)

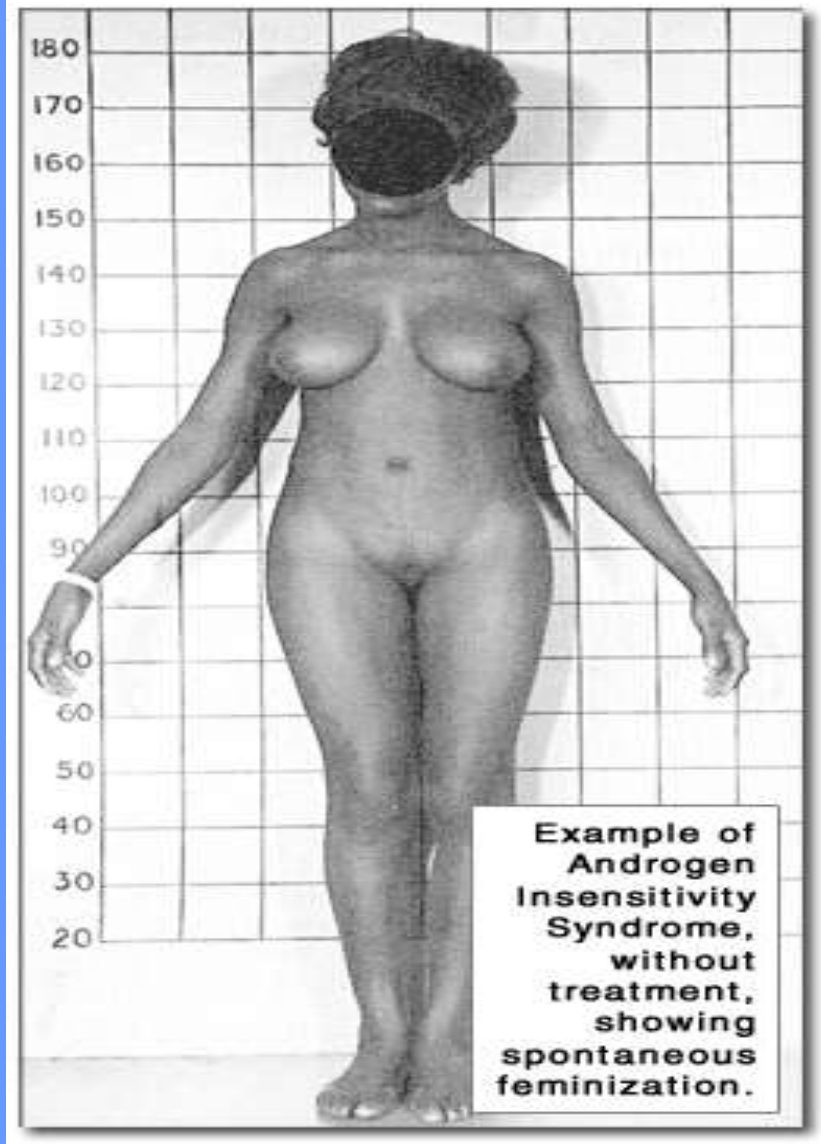
Persistent Mullerian Duct syndrom (I & II)

Leydig cell hypoplasia/agenesy

FTZF1 mutations

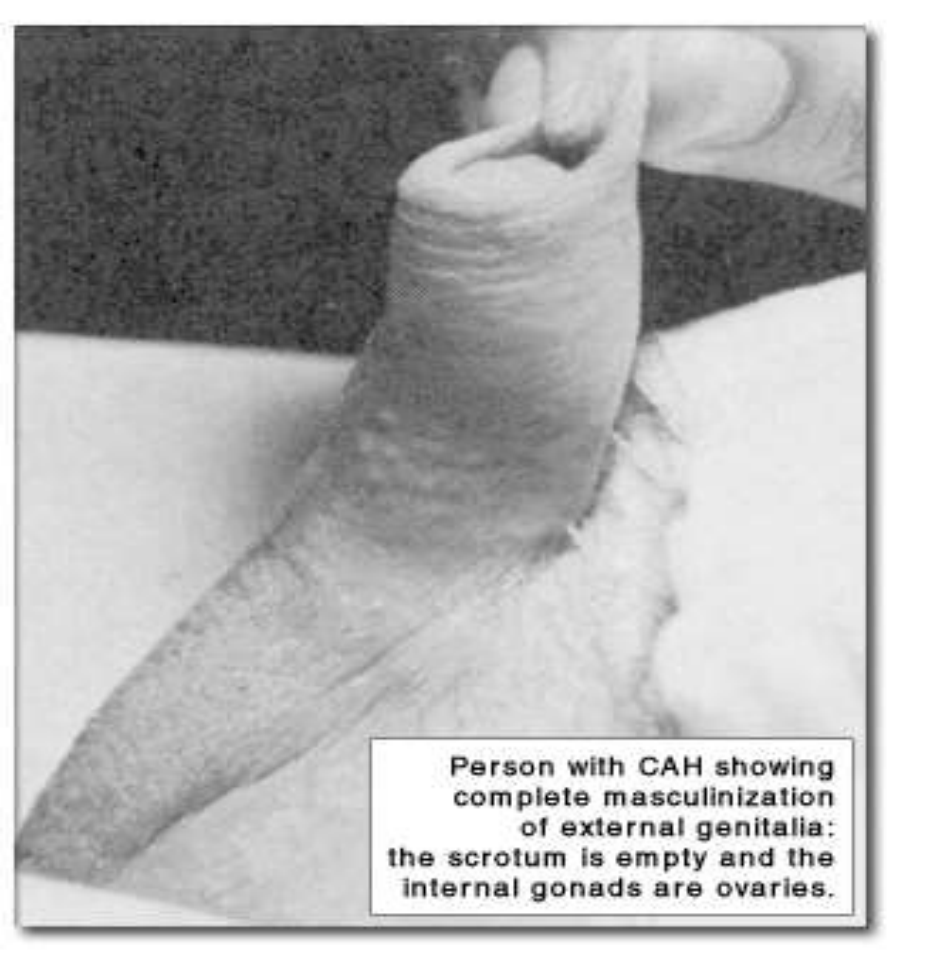
WAGR/Denys-Drash

Smith-Lemli-Opitz syndrom (I & II)



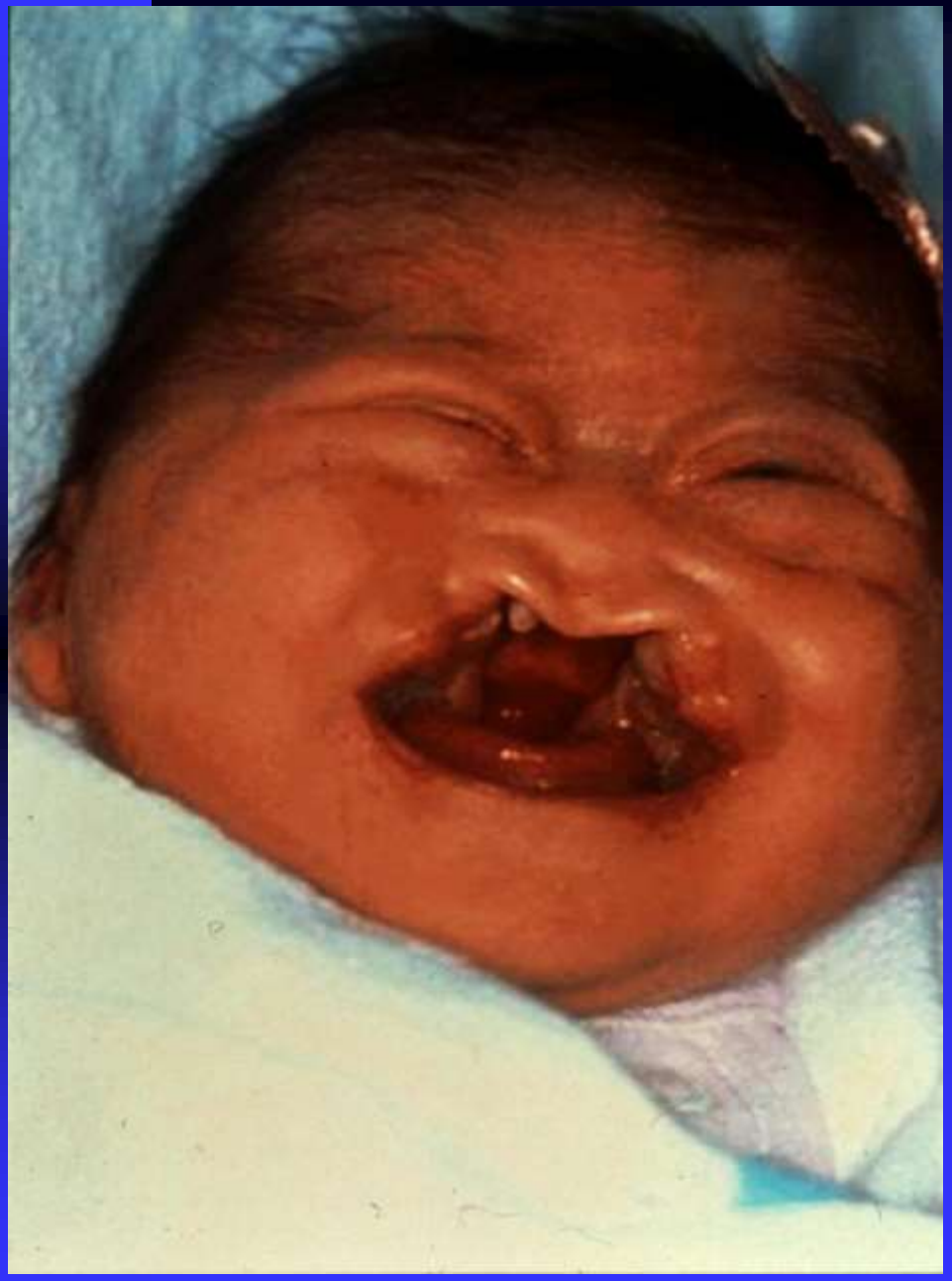
Disturbed synthesis of sex hormons

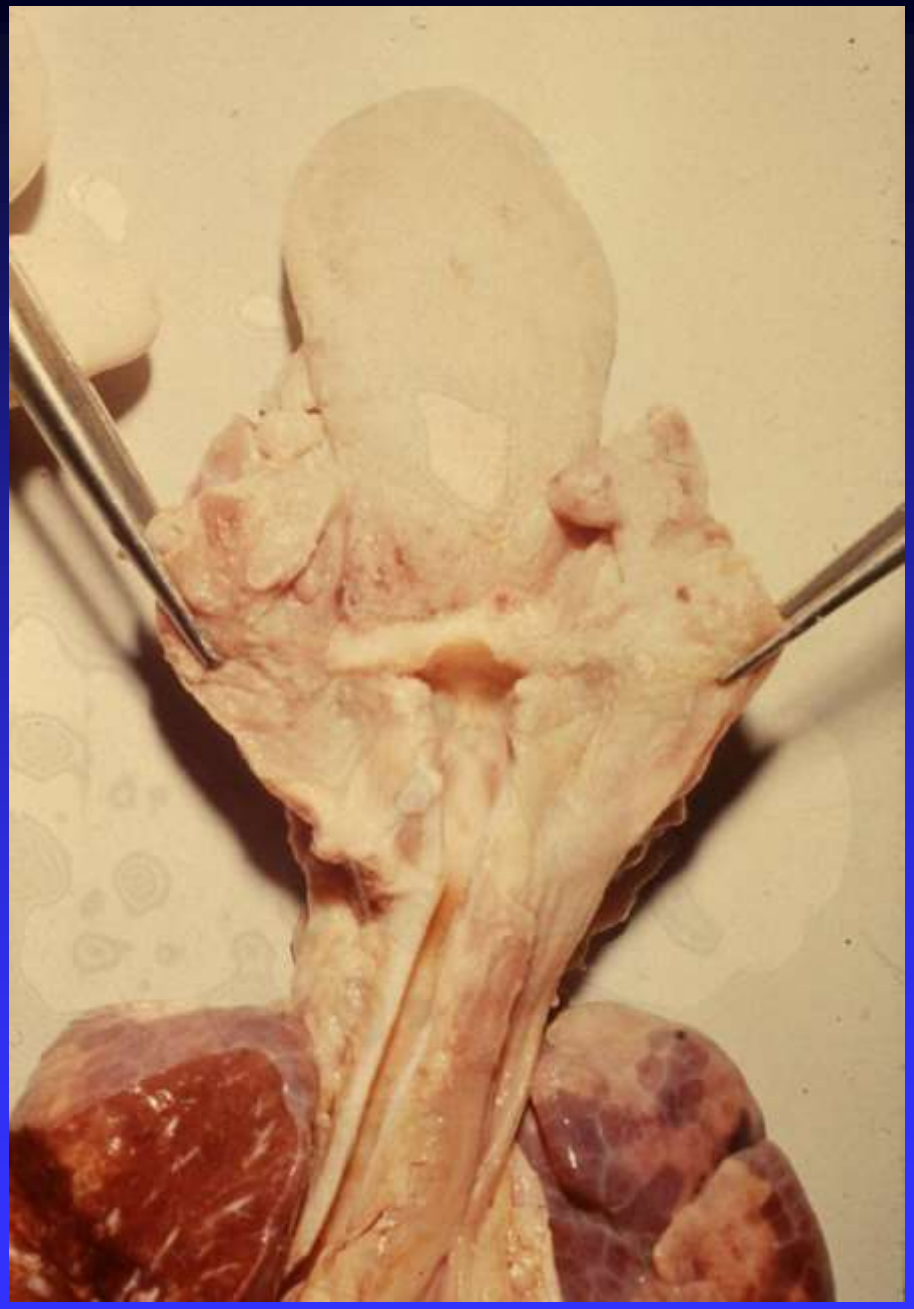
21 hydroxylase deficiency (too much Androgens)

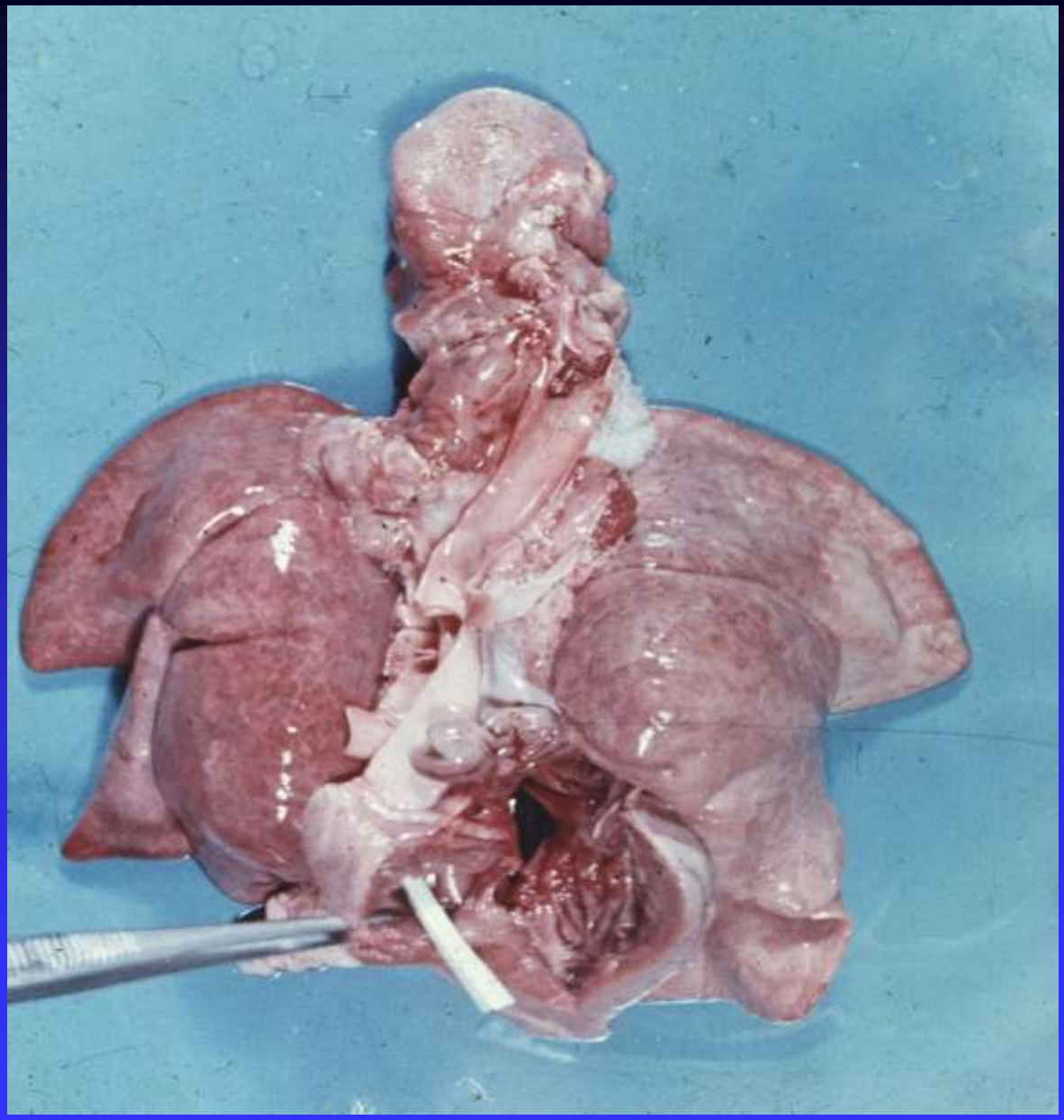


Multifactorial inheritance

- joint effect of several (several hundred) genes (minor genes), together with exogenous faktors
- different appearance in twins
- similar apperance compared to the autosomal diseases with low penetrance







Multifactorially inherited “diseases”

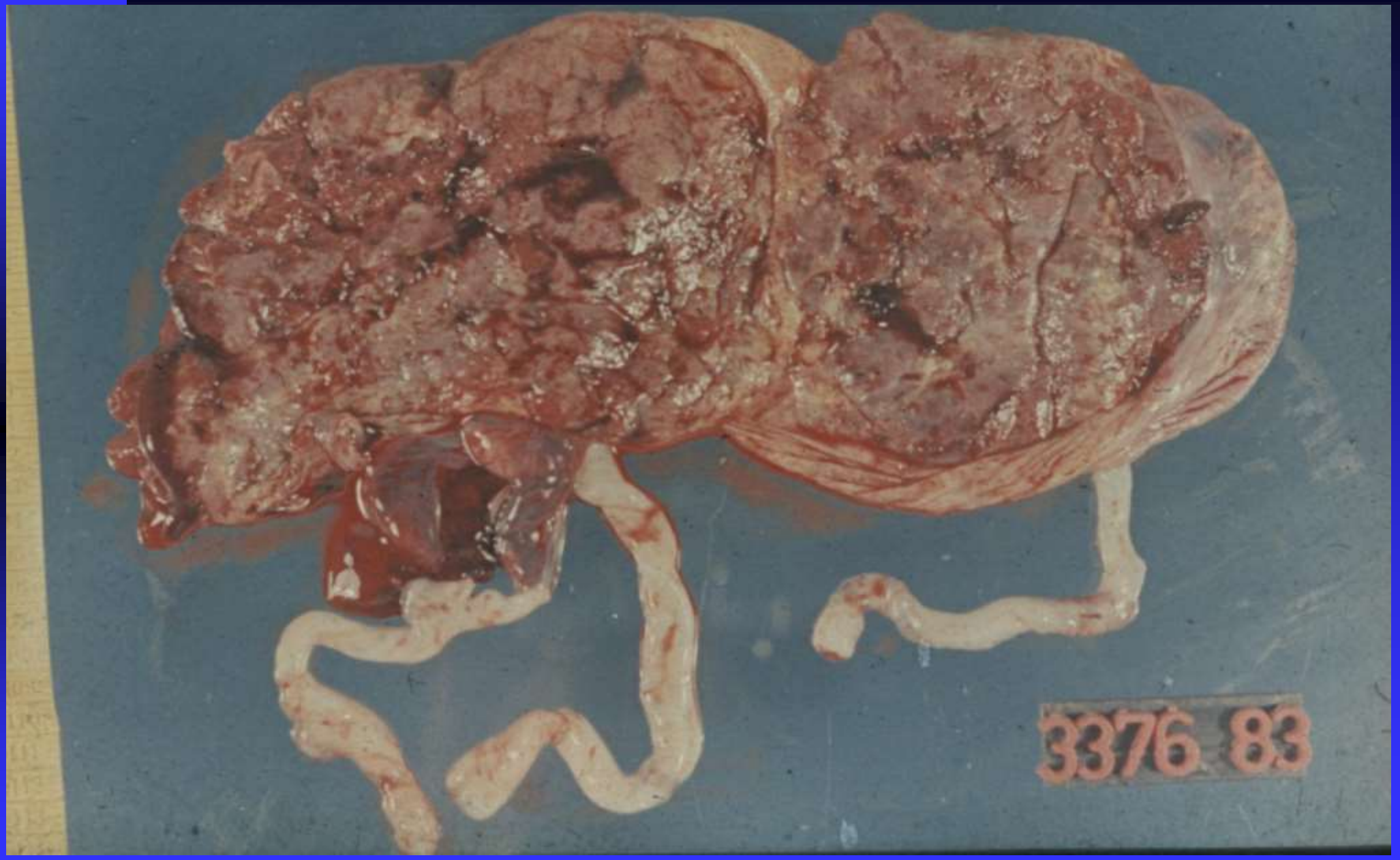
- Figure, color of skin and hair
- blood pressure, arteriosclerosis, diabetes mellitus type II.
- connatal dislocation of the hip, cleft lip (hare-lip), cleft palate, heart septum defects, pylorus stenosis, neurogenous closing defects, club-foot (pes equinovarus)

Diseases associated with mitochondrial DNA

- **Disease is inherited from the mother.**
- **all of the children of the diseased mother are sick, depending on the mitochondrial heterogeneity**
- **a few diseases are known, mostly affecting the eyes, brain and muscles**
  - **Kearns-Sayre syndrome**
  - **Inheritable neuropathy of Leber**

Environmental faktors

- **according to the time of effect:**
  - **Gametopathy: before fertilization**
  - **Blastopathy: 0.-15. days**
  - **Embryopathy: 16.-75. days**
  - **Fetopathy: 75. day-birth**
- **Factors of influence:**
  - **Infection**
  - **chemicals, mutagens**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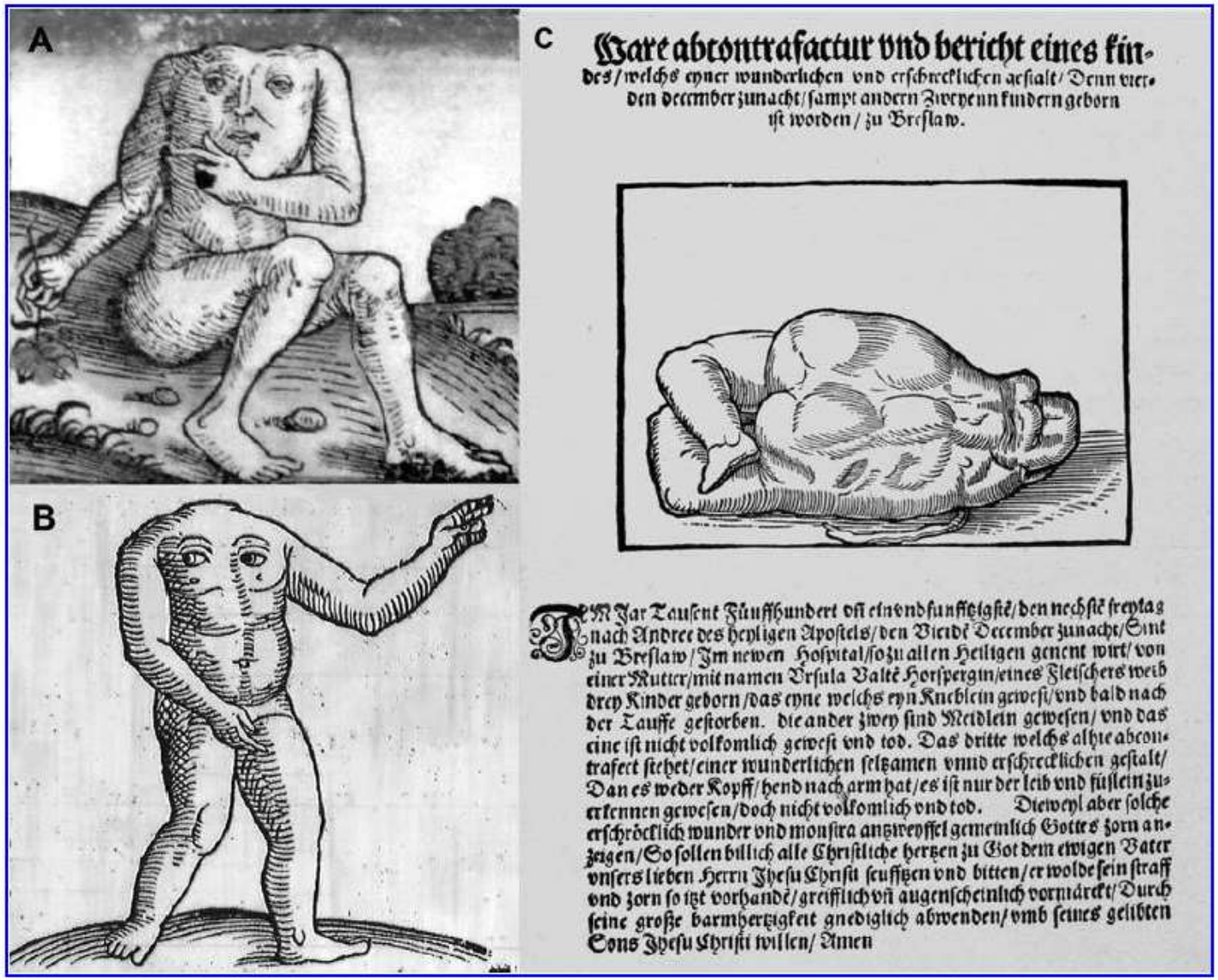


Figure 1 Pre-scientific accounts of acranius as a moral warning. (A) ''Headless blemmye'' from Schedel's Weltchronik 1493 [39]; (B) ''Brustbutzen'' from Lycosthenes' marvelous wonders 1557 [22]; (C) ''Frightening prodigy'' from a Breslau leaflet 1551, see text for details [17].

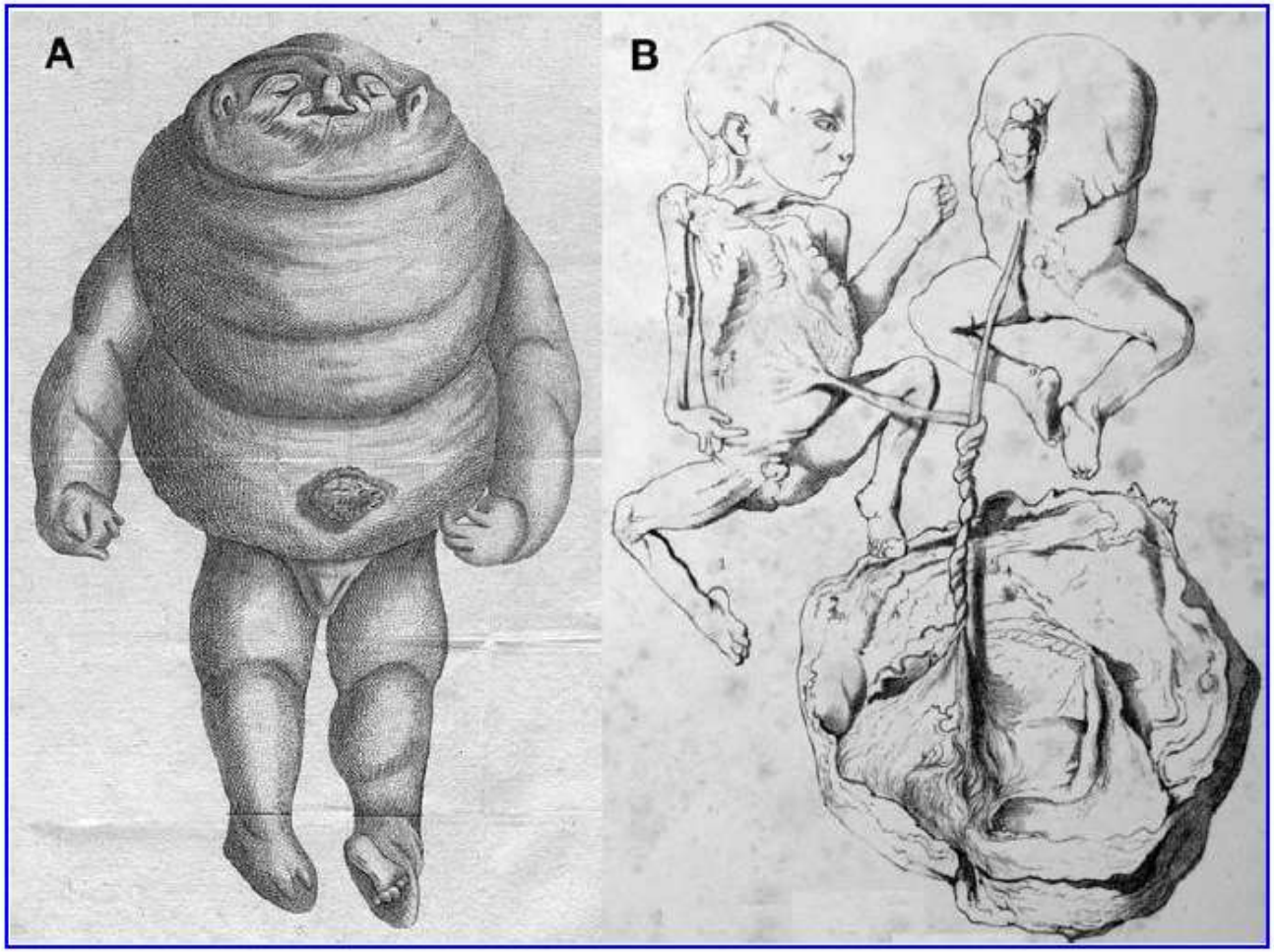


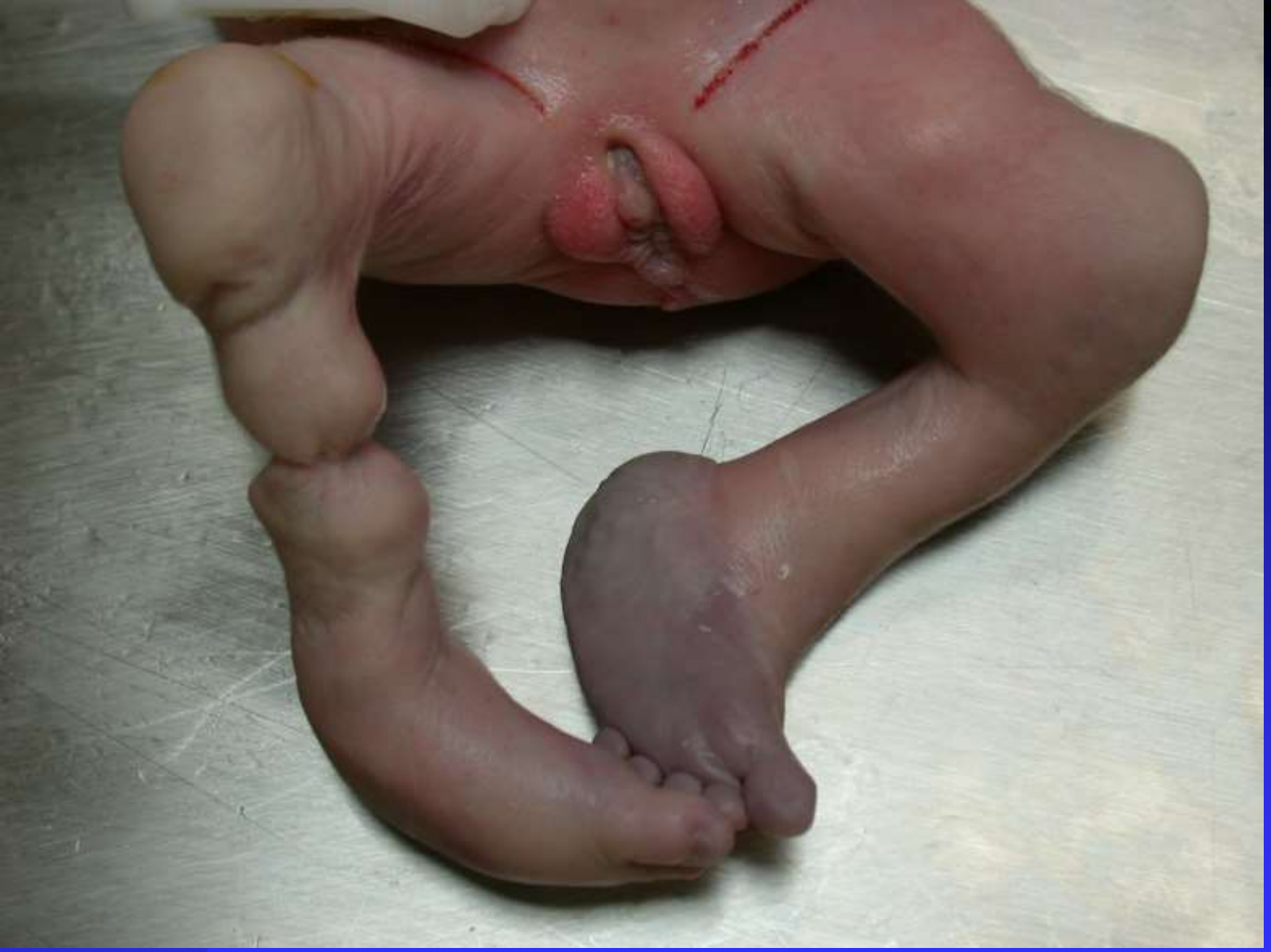
Figure 2 (A) Hydropic acardius anceps ''larger and heavier than the accompanying twins'', described by Kähler 1777 [18], (B) acardius acranius with twisted cord depicted by Ahlfeld 1882 to ''illustrate the connection of the acardiacus with his twin brother and the placenta'' [1].

Teratology- teratogenesis

- **Teratogenesis is a deformed development - resulting teratoids (monstert) because of environmental effects**
- **Forms:**
  - **Isolated deformations (one organcomplex is most frequently affected)**
    - **malformations**
    - **deformations**
    - **dysruptions**
    - **Sequences**
  - **several developmental disorders**

Malformations

- congenital dislocation of the hip
- club-foot (pes equinovarus)
- hare-lip (cheiloschisis)
- cleft-palate (palatoschisis)
- heart septum defects
- congenital pylorus stenosis
- neurogenous closing defects

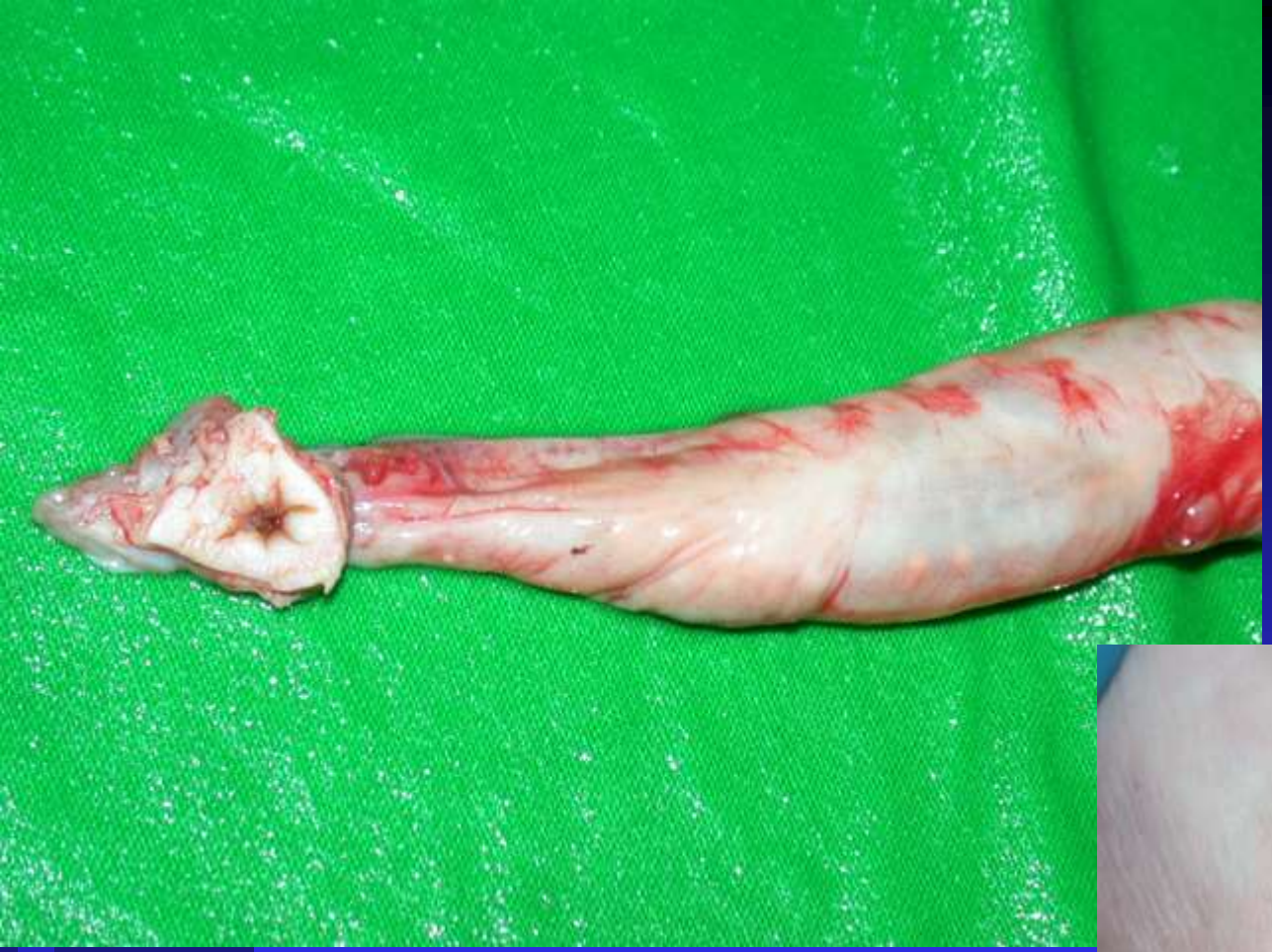


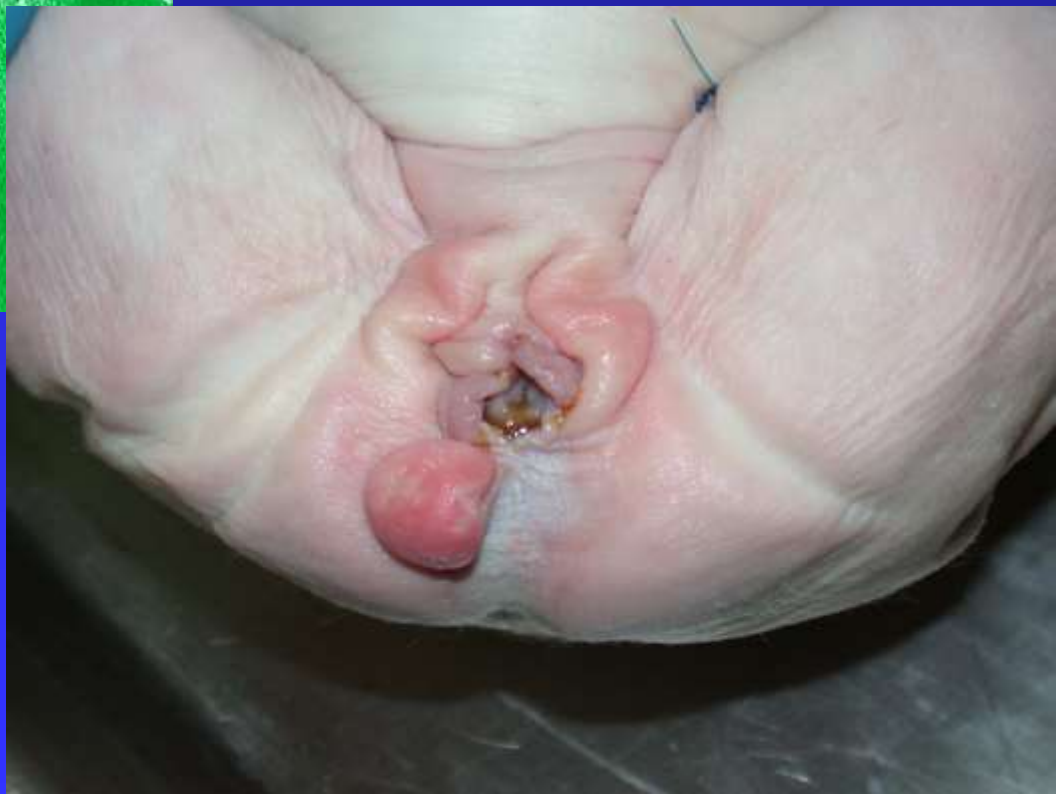
Dongaláb
Anus atresia
Lefűződési barázda

Deformations

- locomotor **apparatus is most frequently involved**
- **Reason:**
  - **disproportion of space (oligohydramnion, twin pregnanc)**
  - **disorders of motoric innervation, central defekts**
  - **inherited dystrophy of the muscles**

anus atresia

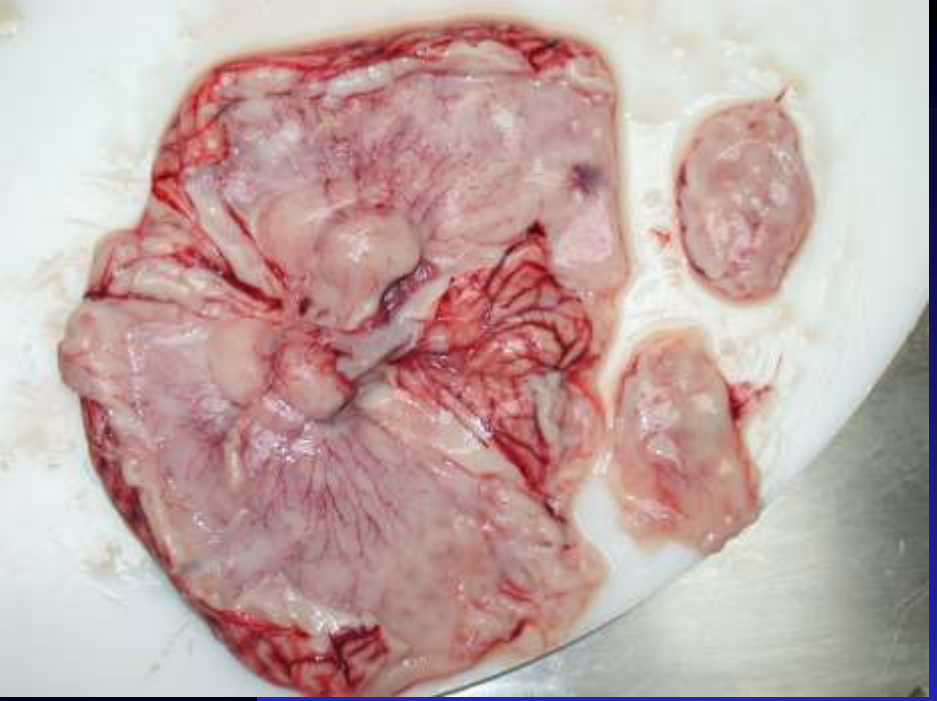




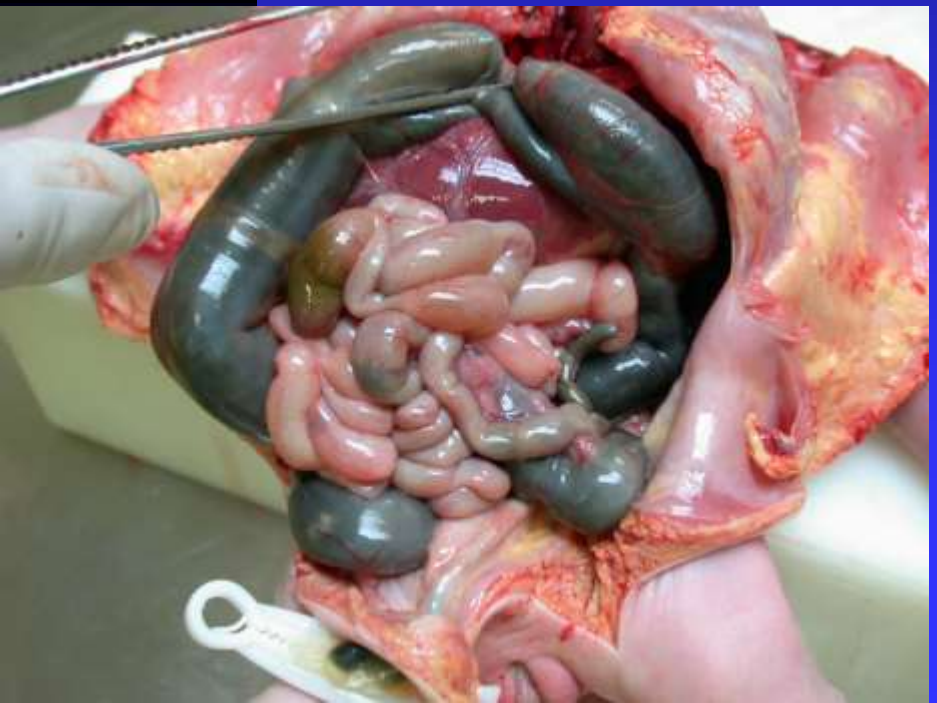
Dysruptions

- **Development of deformity because of total or partial damage of one organ after full development of the organs**
- **Reason:**
  - **compressed by amniotic band**
  - **intrauterine closure of a vessel and following infarction**
    - **atresies, porencephaly**

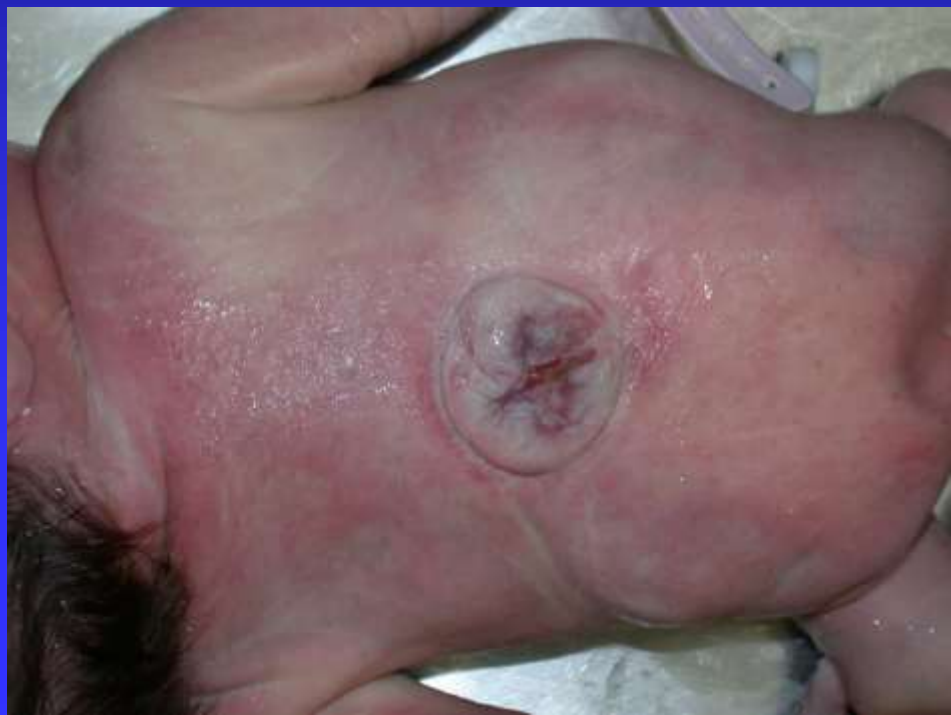
Hydrocephalus internus



Meningocele, spina bifida



atresiák

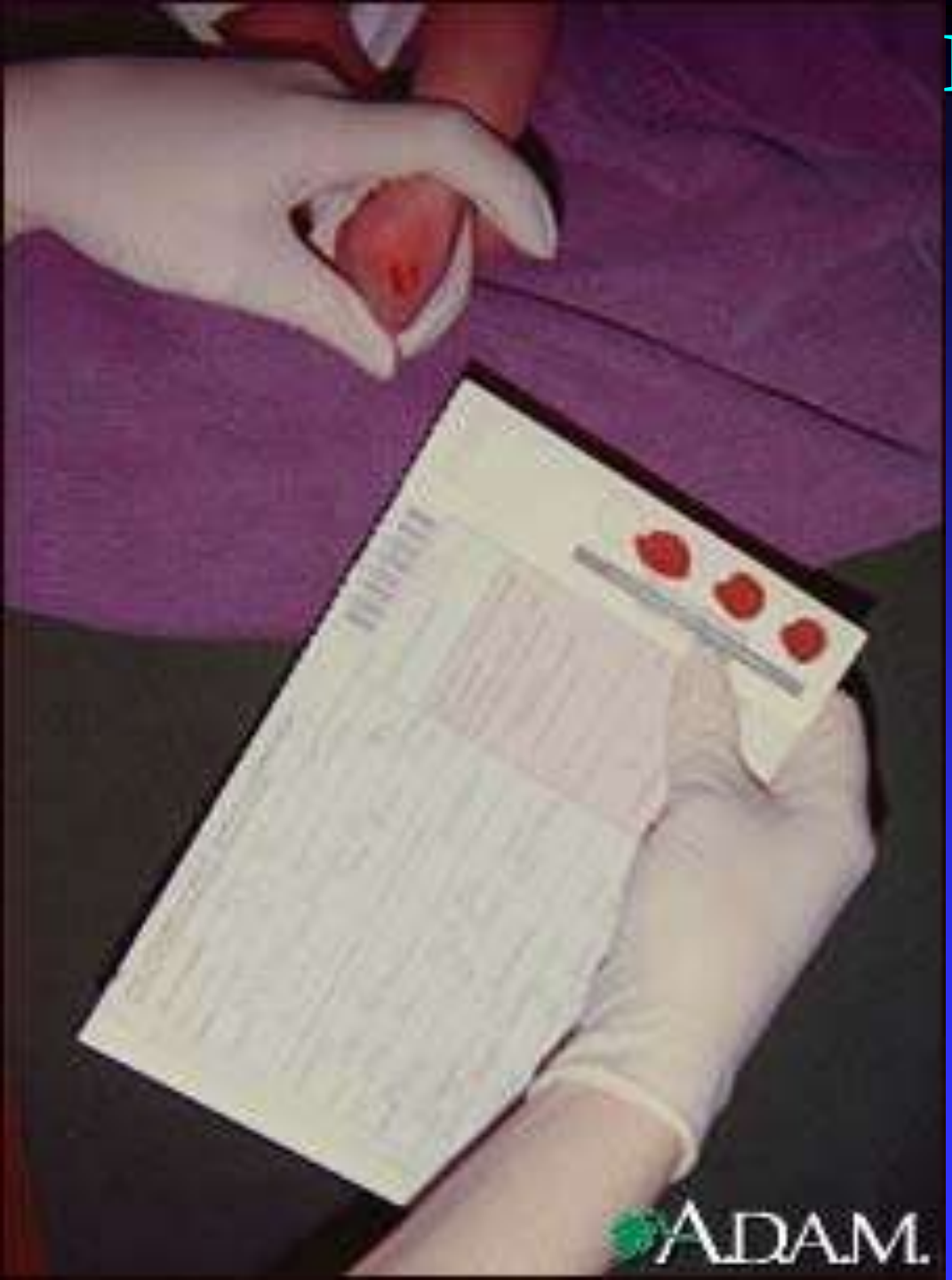


multiple developmental disorders

- two or several ogansystems are involved, the ethiology of the damage is the same
- Reason:
  - Infection (TORCH complex, varicella)
  - Chemicals
  - Aberration of chromosoms
  - e.g.: rubella (German measles) syndrom, fetal alcohol (consumption) syndrom, thalidomide (Contergan)

Diagnosis of the developmental disorders

- **Prenatal Diagnostics - Prevention**
  - **Ultrasonography, AFP, analysis of blood of the mother (non-invasive Methods)**
  - **Definitive genetic diagnosis (invasive Methods)**
    - **Amniocentesis**
    - **Chorion biopsy**
    - **Embryo Skin biopsy**
- **Necessary to perform:**
    - **older mother**
    - **parents are carrier of diseased genes or chromosomes**
    - **previous pregnany with malformations**



Diagnosis

Postnatal screening

Routine tests: cystic fibrosis, phenylketonuria, kretenism, galactosaemia

Diagnosis of developmental disorders

- **Pre und postnatal prevention**
- **Routine clinical tests: Cystic fibrosis, phenylketonuria, cretenism, galactosaemia**
  - **further tests: in case of visible disorders, not explained underdevelopment or mental retardation specific genetic tests are necessary/recommended**

Therapy

- **Prenatal therapy**
  - **abortions, induction of birth**
  - **Intrauterine surgery**
- **Postnatal therapy**
  - **treatment of symptoms**
  - **gene therapy („gene-surgery”)**
    - **– DNA viral or retroviral vectors**