GENETIC and DEVELOPMENTAL DISORDERS I.

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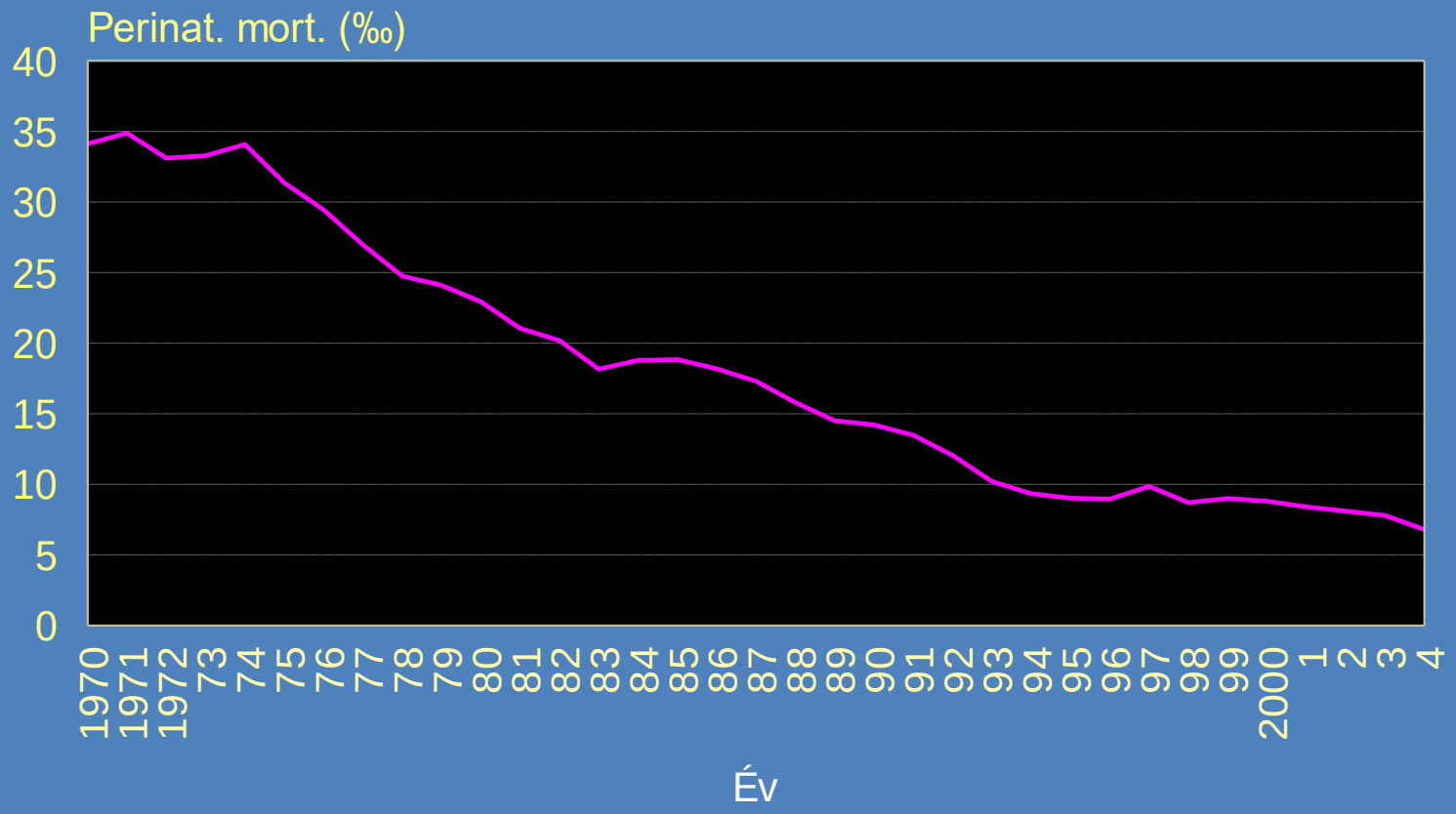
II. Department of Pathology

November, 2021.

250 years of EXCELLENCE in medical education, research & innovation and healthcare

PERINATAL MORTALITY IN HUNGARY

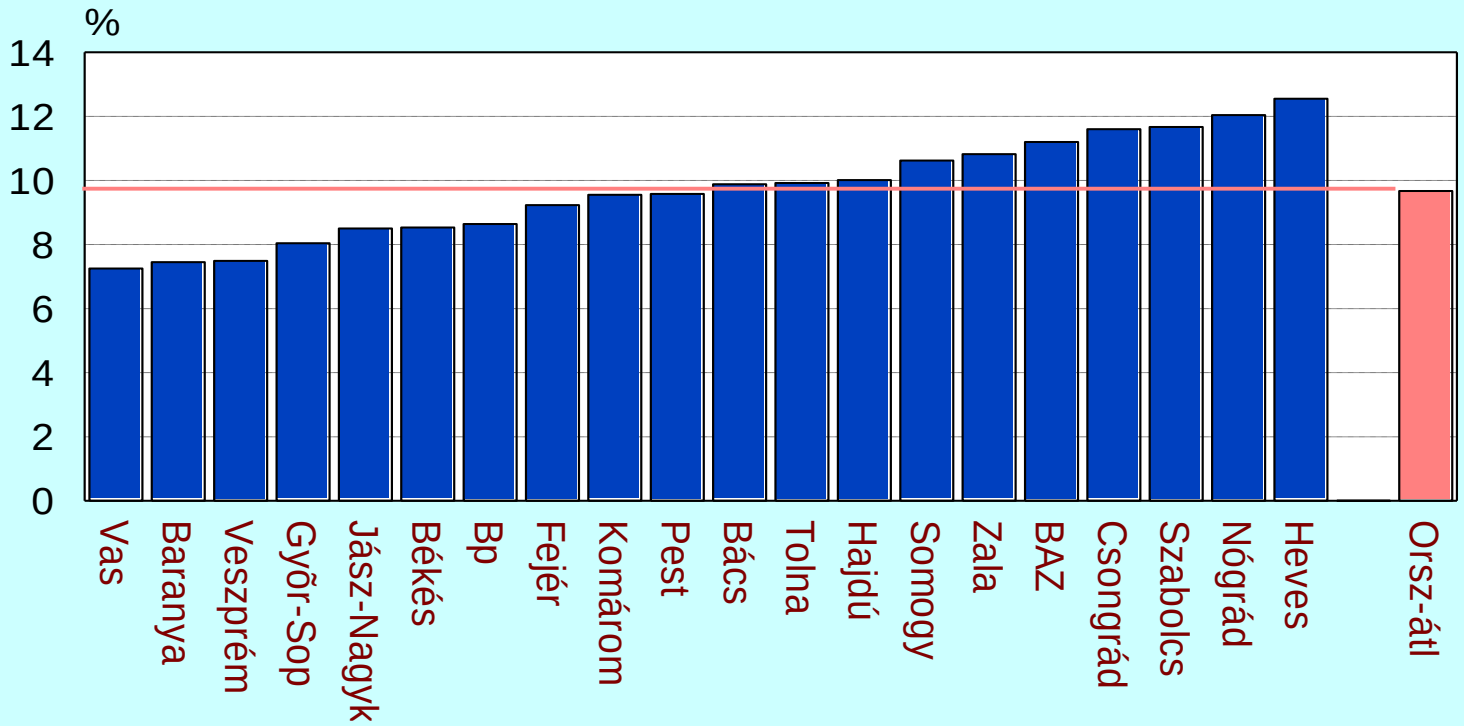
Perinatális mortalitás Magyarországon 1970 és 2004 között (‰)



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

RATE of SMALL FOR BIRTH EVENTS IN HUNGARY

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

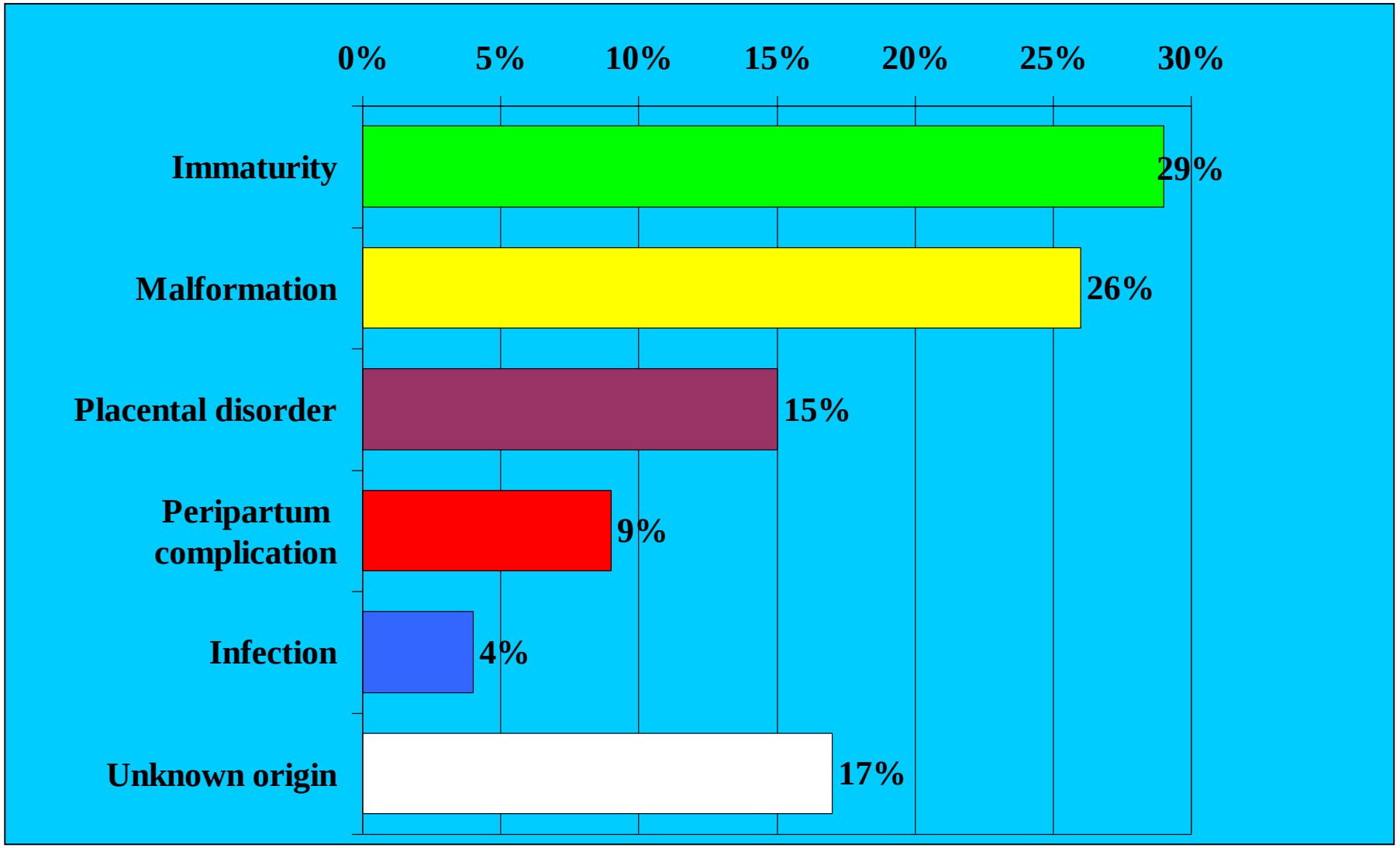


OEP adatok

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

Causes of perinatal deaths

2nd Dept. Of Pathology data 1998-2000



Importance

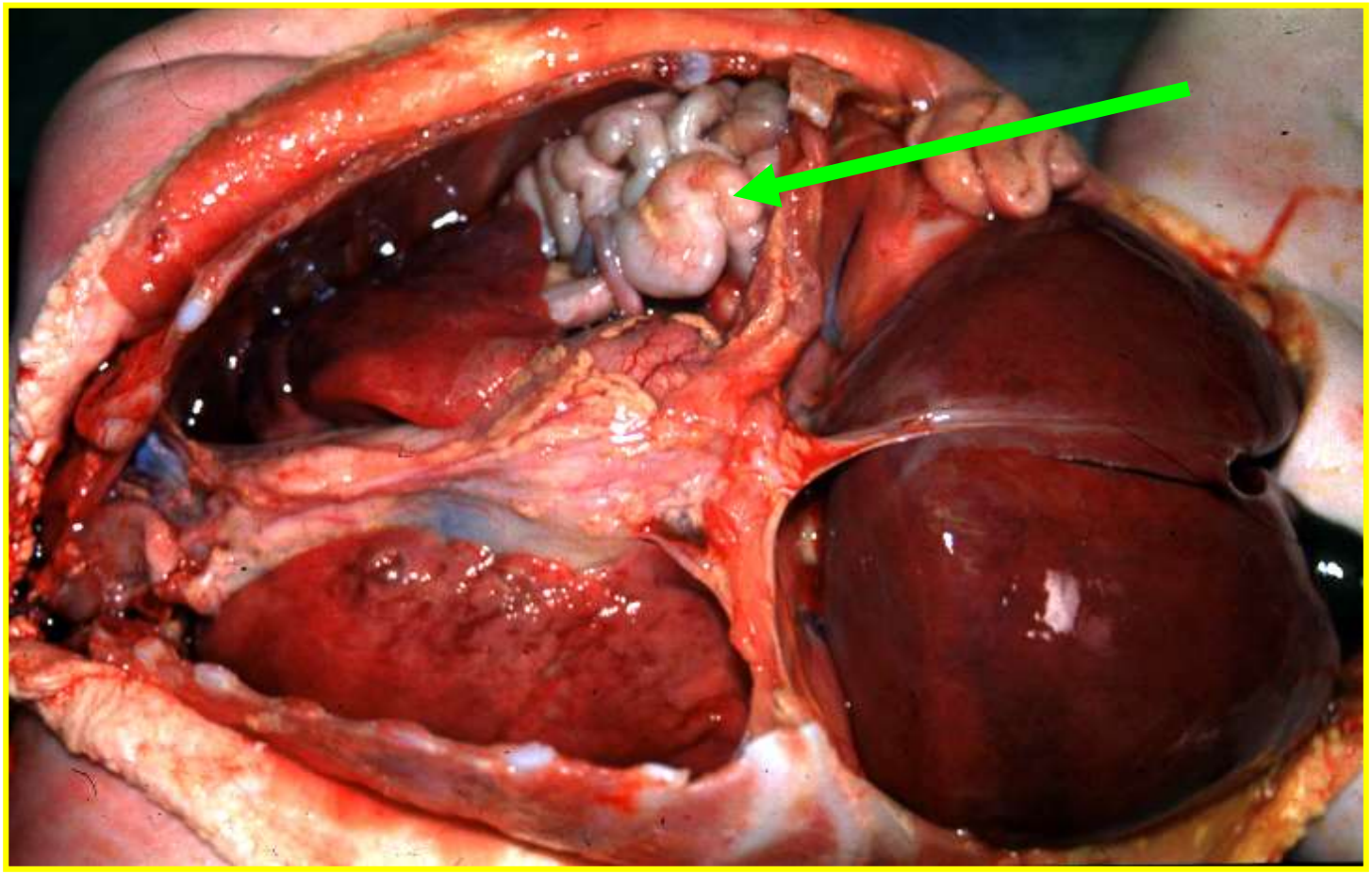
- Responsible for the 50 % der spontaneous abortions
- 24% of deaths of newborns and 10% of mortality in childhood are caused by developmental disorders
- Physical and mental disablement of adults

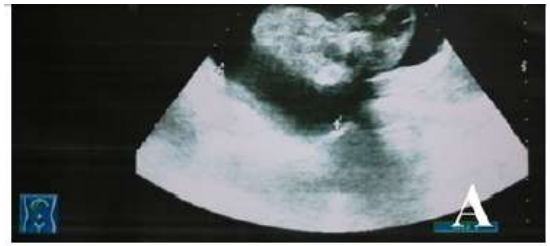
Fetal diseases and *in utero* death

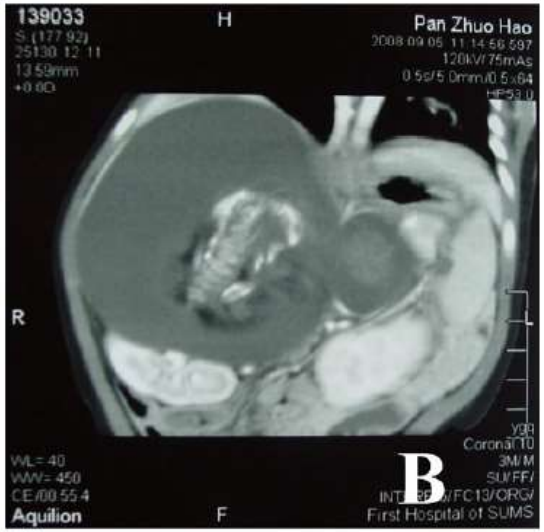
- Major malformation 15-20%
- Feto-maternal bleeding 5%
- Hydrops fetalis
- Fetal arithmia
- Alloimmune thrombocytopenia (stroke)
- Rh isoimmunization

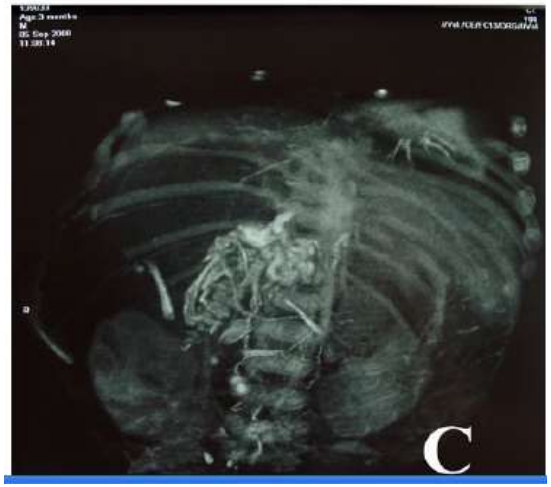
Etiology of death at birth/*in utero* death (2006 – 2008, USA)
in 60,9% probable causes, in 76,2% possible causes

- 29,3% complications at delivery (e.g. preterm delivery)
- 23,6 % Placenta disease (e.g. IUGR)
- 13,7% Genetic/developmental anomaly of the fetus
- 12,9% Maternal or fetal infection
- 10,4% Disoreder of the umbilical cord
- 9,8% Preeclampsia
- 7,8% Other maternal diseases (e.g. autoimmune)









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

Human Genome Project

(announcement: Bill Clinton and Tony Blair

2000 June 27. !)

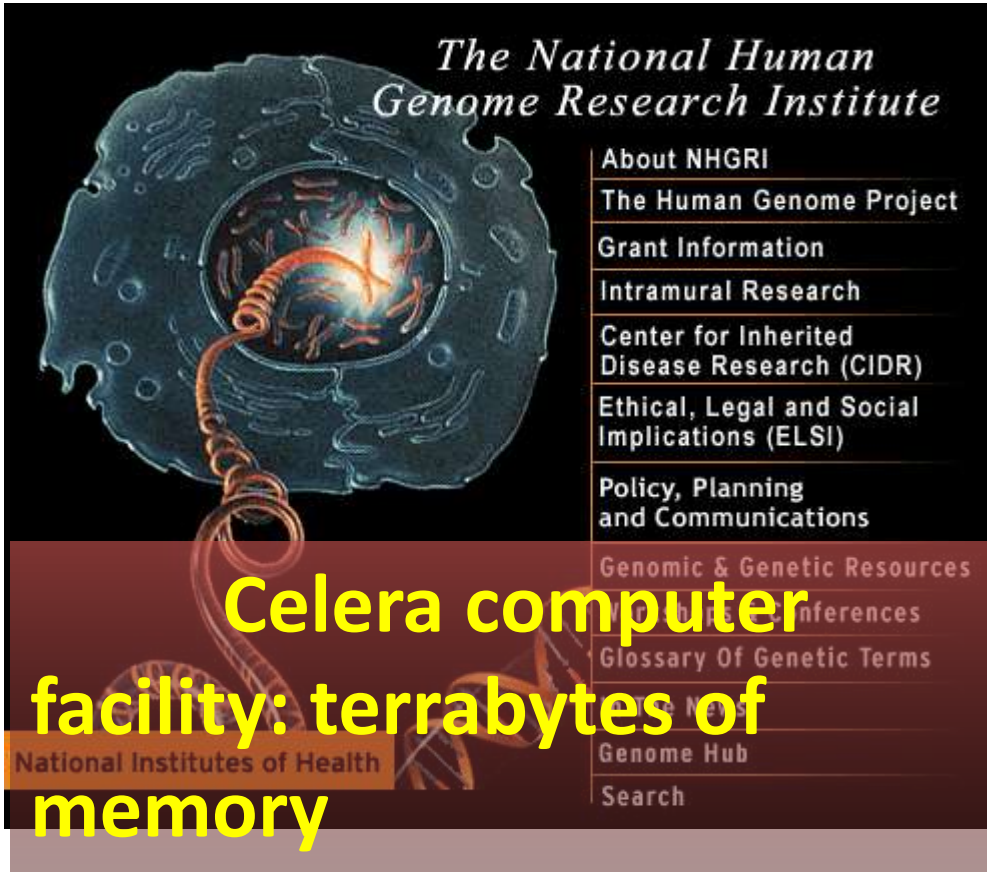
Craig Ventner and

Sam Broder – Celera

Biotech Co. !

Francis Collins -

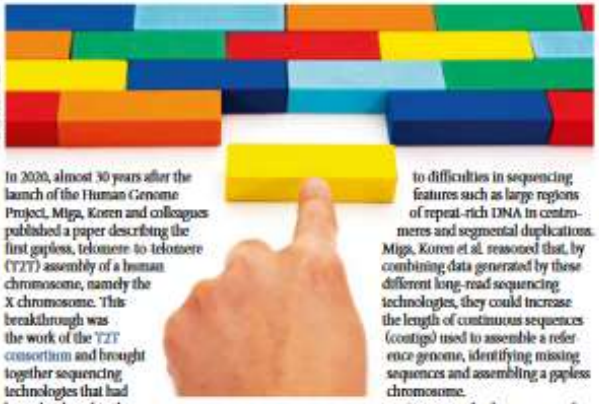
HGRI



Celera computer facility: terrabytes of memory

MILESTONE 17

Filling in the gaps telomere to telomere



In 2020, almost 30 years after the launch of the Human Genome Project, Miga, Koren and colleagues published a paper describing the first gapless, telomere-to-telomere (T2T) assembly of a human chromosome, namely the X chromosome. This breakthrough was the work of the T2T consortium and brought together sequencing technologies that had been developed in the preceding 6 years.

In 2015, Chaisson et al. showed that long-read sequencing technology from Pacific Biosciences (PacBio) could be used to sequence a human genome, specifically that of the complete hydatidiform mole (CHM) cell line CHM1. As CHM cells have a duplicated paternal (but no maternal) genome, bypassing the need to assemble both haplotypes of a diploid genome, they became a key reference genome. Later that year, Berlin, Koren et al. reported the first de novo assembly of a human genome based on PacBio sequencing long reads alone. Then, in 2018, Jain et al. revealed that ultra-long-read nanopore sequencing (from Oxford Nanopore Technologies) could also be used to assemble a human genome de novo (MILESTONE 8). Finally, in 2019, Wenger, Peluso et al. introduced PacBio high-fidelity (HiFi) sequencing, which was 99.8% accurate in sequencing the human genome reference standard HG002 over average read lengths of 13.5 kb.

Although these technological advancements were reported to have closed gaps in the GRCh37 or GRCh38 version of the human reference genome, no chromosome had been sequenced in full owing to difficulties in sequencing features such as large regions of repeat-rich DNA in centromeres and segmental duplications. Miga, Koren et al. reasoned that, by combining data generated by these different long-read sequencing technologies, they could increase the length of continuous sequences (contigs) used to assemble a reference genome, identifying missing sequences and assembling a gapless chromosome.

> “The sequencing of the first two complete chromosomes … suggested that it was technically possible to complete the human genome sequence”

Consequently, they sequenced 155 Gb of DNA from CHM13 cells with nanopore sequencing, using the genome assembly tool Canu to combine these ultra-long reads with data previously generated by PacBio sequencing. Nanopore sequencing, PacBio sequencing and linked-read Illumina sequencing were used to polish their assembly of the CHM13 genome, a 2.94-Gb assembly with a median consensus accuracy of ~99.99% and in which 50% of the genome was within contigs of >70 Mb. The presence of 41 of 46 telomeres at contig ends suggested that CHM13 was a more complete reference genome than GRCh38.

Indeed, Miga, Koren et al. noted that the X chromosome in their CHM13 assembly was broken in just three places. To fill in these gaps, they first mapped ultra-long reads against the assembly, manually identifying reads that joined breaks between contigs; this approach resolved two breaks resulting from segmental duplications. These findings were validated by mapping independent long-read PacBio HiFi data from CHM13 to the X chromosome. To resolve the third break, which was at the centromere, the researchers uniquely tiled ultra-long reads across the repeat-rich centromeric α-satellite array on the X chromosome, confirming the results with long-read PacBio HiFi data and benchmarking and improving the centromere assembly using an automated satellite assembly method (CentroFlye) and evaluation tools (TandemTools). After polishing, the gapless X chromosome assembly was >99.9% accurate and had resolved 29 reference gaps. By precisely mapping long-read data to the finished chromosome, the researchers also produced the first comprehensive, T2T profile of DNA methylation, enhancing our picture of epigenetic regulation over repeat-rich regions.

Sequencing of the X chromosome led the way to the T2T assembly of the first autosome, chromosome 8 from CHM13 cells, as announced by Logsdon et al. later in 2020. Combining nanopore, PacBio and PacBio HiFi sequencing, this work closed up five gaps in chromosome 8 and produced an assembly with an accuracy of >99.99%.

The sequencing of the first two complete chromosomes, 20 years after the release of the first draft human genome (MILESTONE 1), suggested that it was technically possible to complete the human genome sequence. Indeed, in September 2020, the T2T consortium announced that they had filled in all of the gaps, obtaining complete sequences for all the chromosomes in CHM13 cells (apart from the five ribosomal DNA arrays) and thus, outstandingly, a v1.0 assembly of a complete human genome.

Katharine H. Wrighton,
Nature Reviews Cross-Journal Team

ORIGINAL ARTICLE Miga, K. H. et al. Telomere-to-telomere assembly of a complete human X chromosome. Nature 585, 79–84 (2020)
FURTHER READING Berlin, K. et al. Assembling large genomes with single-molecule sequencing and locality-sensitive hashing. Nat. Biotechnol. 33, 623–630 (2015) | Chaisson, M. J. P. et al. Resolving the complexity of the human genome using single-molecule sequencing. Nature 517, 608–611 (2015) | Jain, M. et al. Nanopore sequencing and assembly of a human genome with ultra-long reads. Nat. Biotechnol. 36, 338–345 (2018) | Logsdon, G. A. et al. The structure, function and evolution of a complete human chromosome 8. Preprint at bioRxiv https://doi.org/10.1101/2020.05.26.101253 (2020) | Wenger, A. M. et al. Accurate circular consensus long-read sequencing improves variant detection and assembly of a human genome. Nat. Biotechnol. 37, 1155–1162 (2019) | Jain, M. et al. Linear assembly of a human centromere on the Y chromosome. Nat. Biotechnol. 36, 321–323 (2018) | Kolmogorov, M. et al. Scalable Nanopore sequencing of human genomes provides a comprehensive view of haplotype-resolved variation and high-quality genome assembly. Preprint at bioRxiv https://doi.org/10.1101/2020.07.15.205120 (2020) | Rhie, A. et al. Towards complete and error-free genome assemblies of all vertebrate species. Nature 592, 737–746 (2021)

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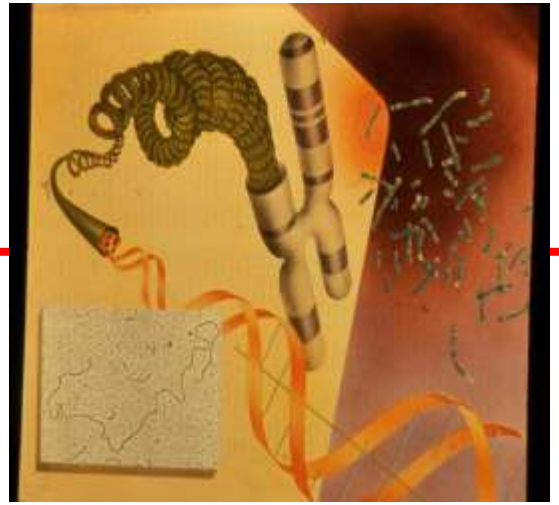
The human genom



- 1,5 meter DNA pro cell
- 6 milliards- billions of base pairs
- ~ 21 000 genes – ~ 100 000 proteins
- 23 pair of chromosomes

ScienceNews

ALL TOPICS LIFE HUMANS EARTH SPACE PHYSI

GENETICS

A recount of human genes ups the number to at least 46,831

The new estimate is based on a broader definition of just what a gene is

By Tina Hesman Saey

SEPTEMBER 17, 2018 AT 7:00 AM

Figuring out how many genes are in the human genetic instruction manual, or genome, isn't as easy as scientists once thought. The very definition of a gene has changed since the completion of the Human Genome Project more than 15 years ago.

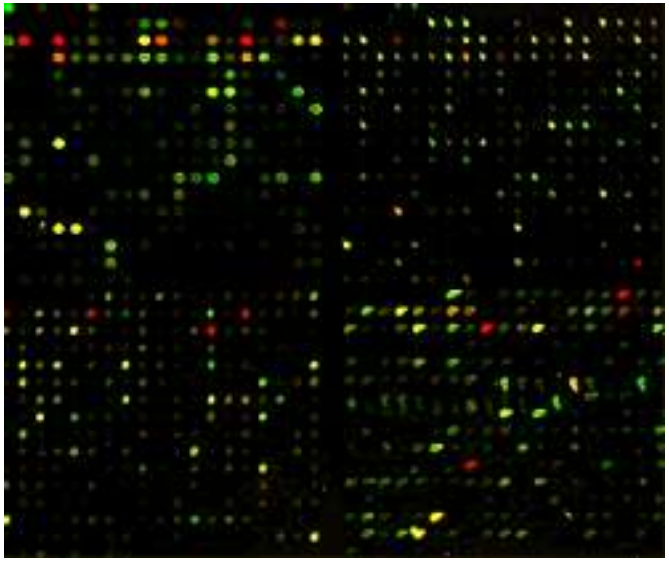
Genes used to be defined as stretches of DNA that contain instructions that are copied into RNA and then turned into proteins. Researchers still don't entirely agree on how many of these protein-coding genes there are. Estimates range from 19,901 to a new count of 21,306 published August 20 in *BMC Biology*.

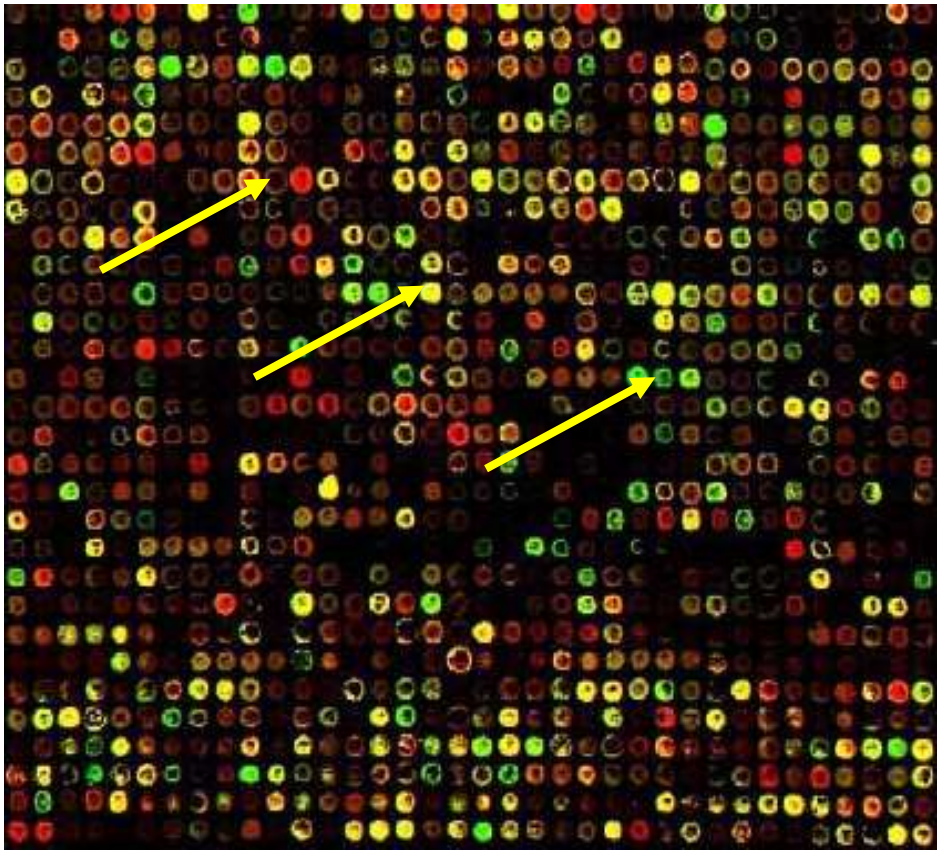
But in the last decade, researchers have learned that not all genes produce proteins. Many scientists have expanded the definition of a gene to include ones that make RNAs that, instead of being turned into proteins, have other functions in the cell.

Numbers of RNA-producing genes (also called noncoding genes) are even more up in the air than protein-coding genes, says Steven Salzberg, a biostatistician at Johns Hopkins University who headed the new count. His team has already found more of these RNA genes — 25,525, including 18,484 long noncoding RNA, or lncRNA genes (*SN: 12/17/11, p. 22*) — than protein-coding ones, and his count doesn't include microRNAs and other recently discovered small RNAs.

Even without the small RNAs, Salzberg's new total of human genes comes to at least 46,831. Other scientists have debated the estimate, and Salzberg says, "I will not be surprised if 10 years from now, we still don't have an agreed-upon number."

MOLECULAR PATHOLOGY
DNA CHIP



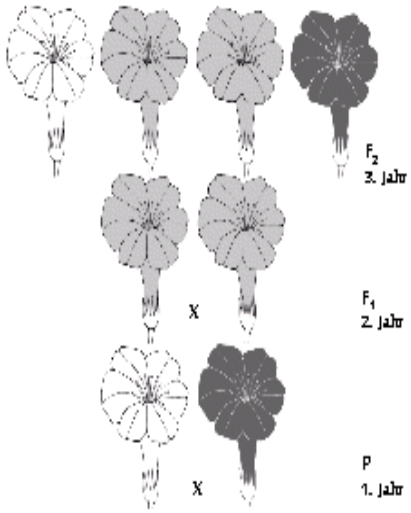


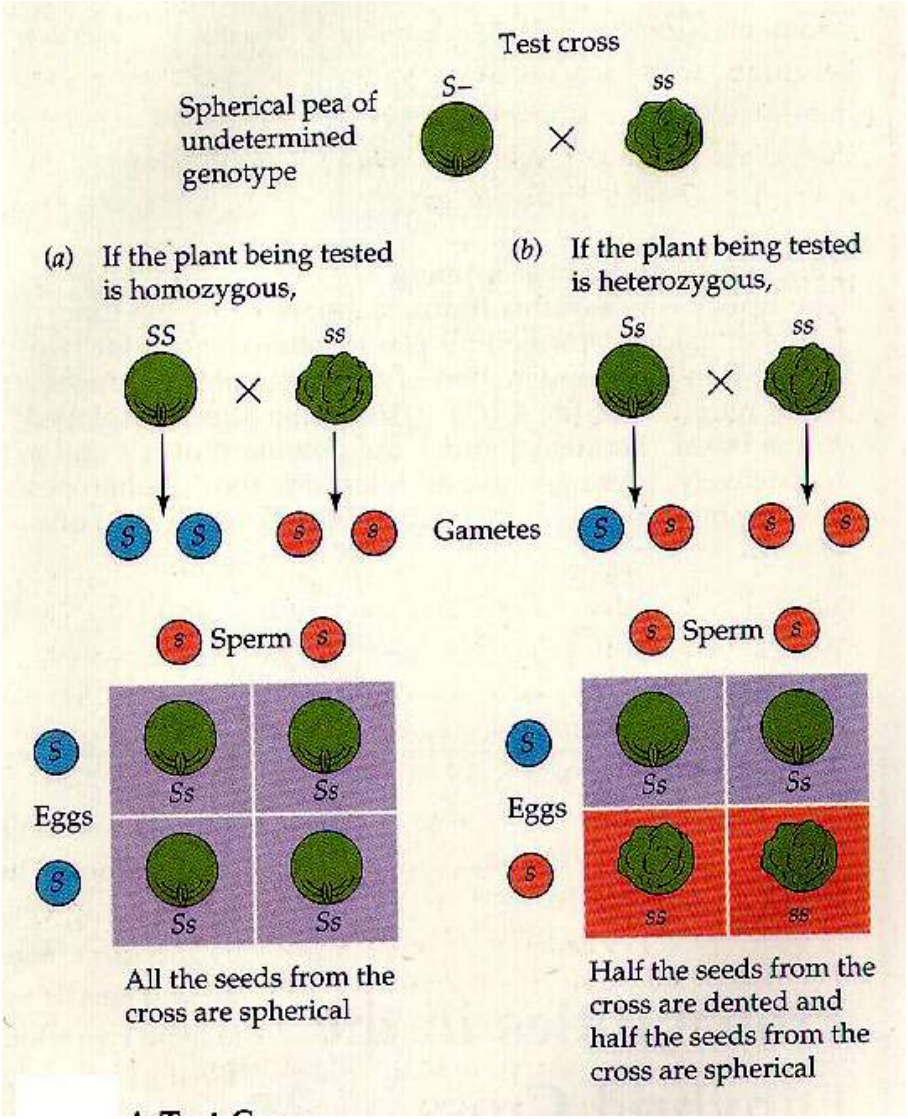
Mendelsche Regel

für intermediäre Vererbung:

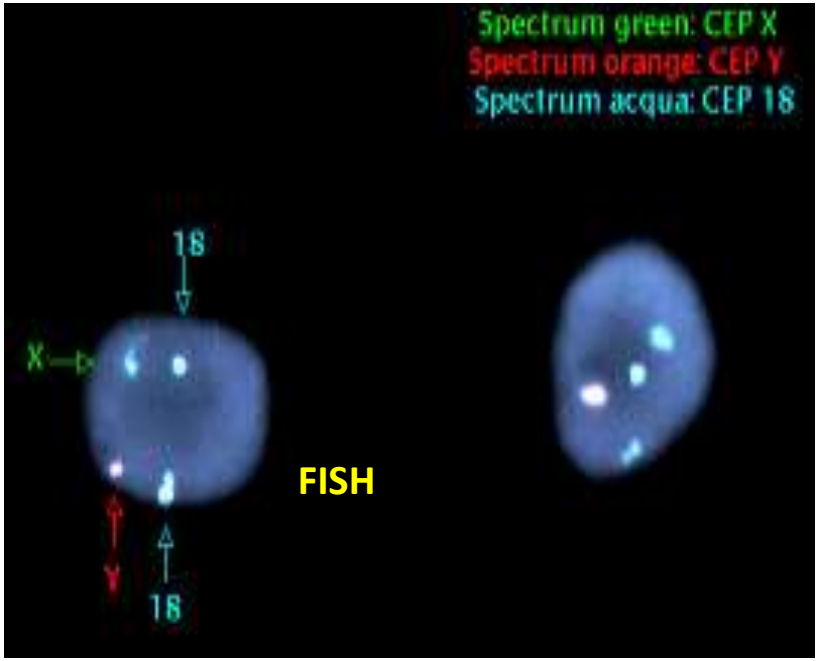
Die Merkmale, z.B. die Blütenfarbe weiß und rot, reinerbiger Eltern (P) führen in der F_1-Generation zu einer Mischfarbe (rosa) und spalten sich in der F_2-Generation im Verhältnis 1(weiß) : 2(rosa) : 1(rot) auf.

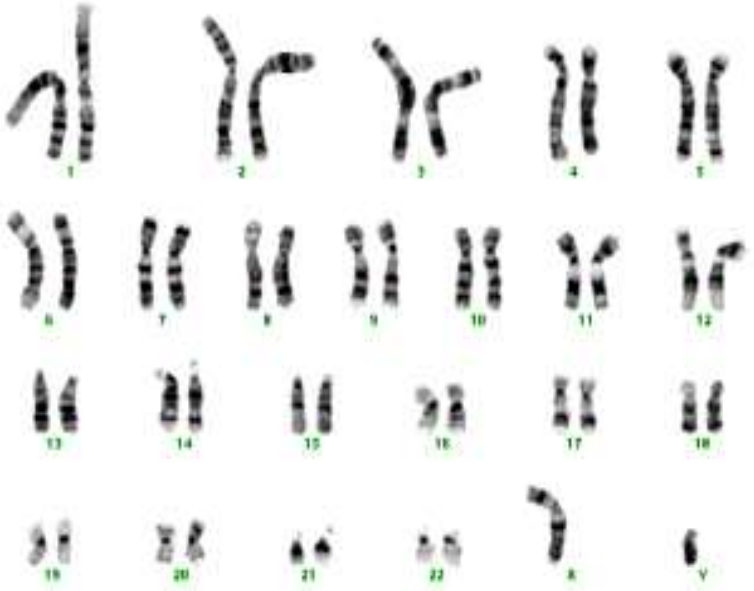
(Dieses Verhältnis findet man nur bei einer sehr großen Zahl von Versuchspflanzen.)





MOLECULAR MEDICINE
Cytogenetics

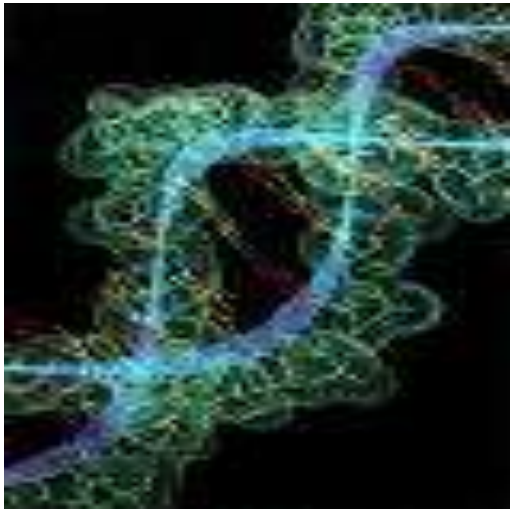
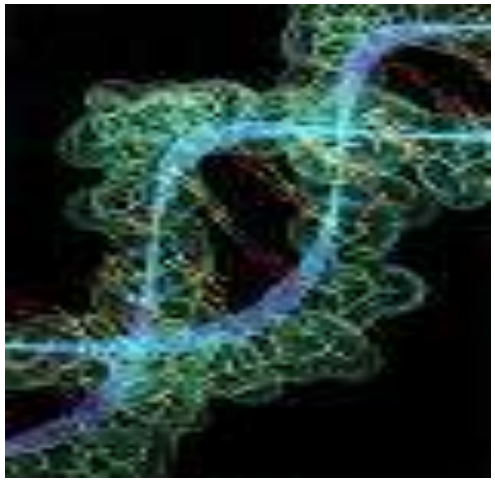




Cytogenetics- kariogram







MORPHOLOGY

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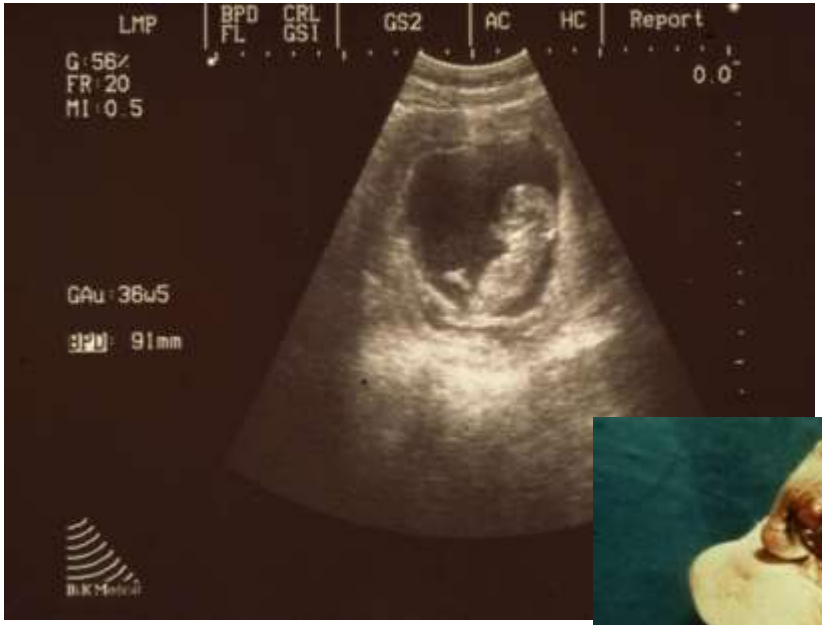
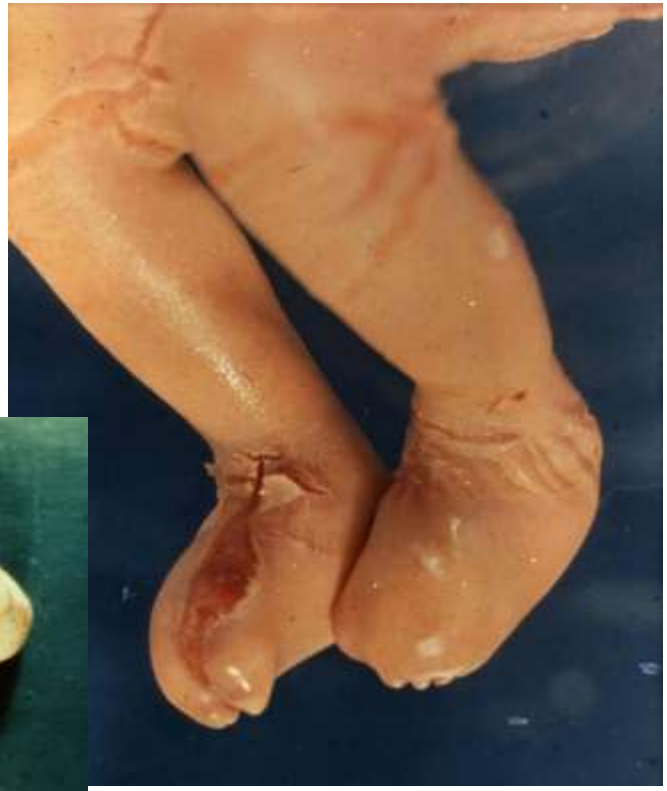
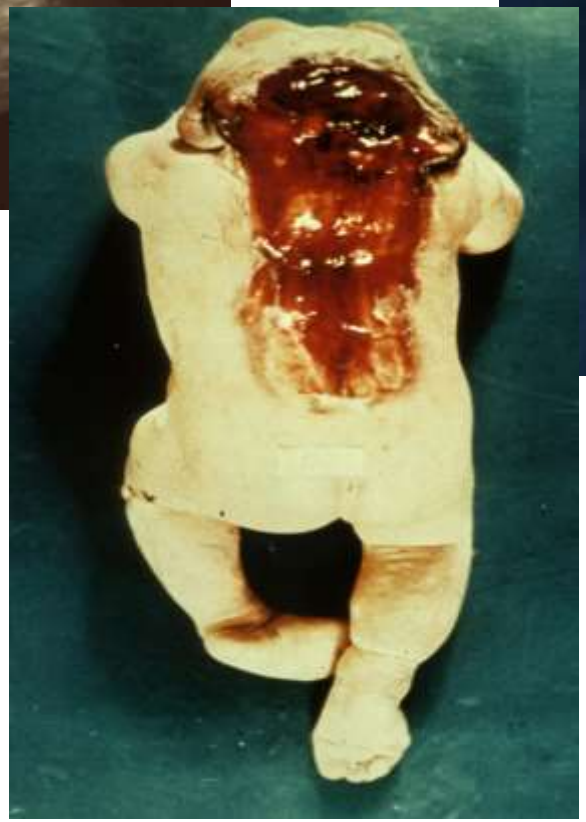
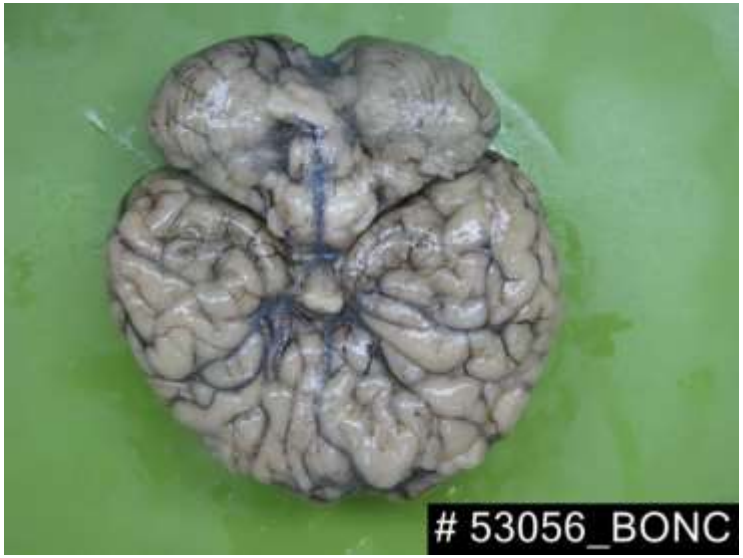
!

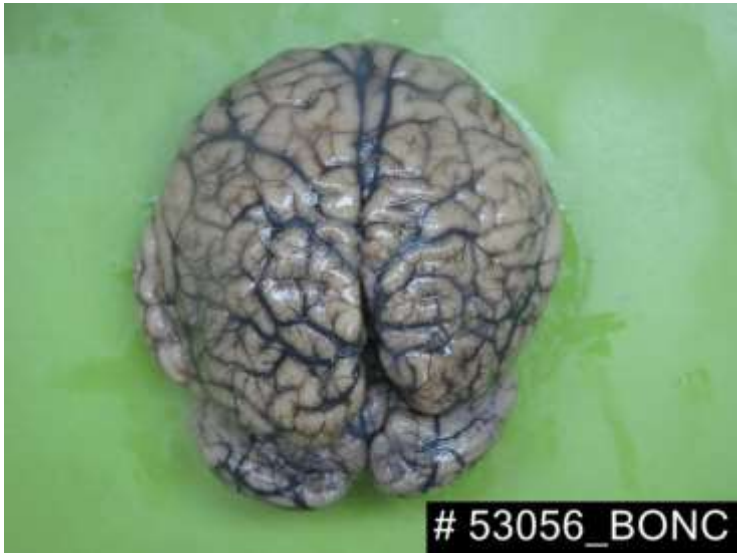
DNA – Genes
Expressionsprofile
RNA, Proteins !!!


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

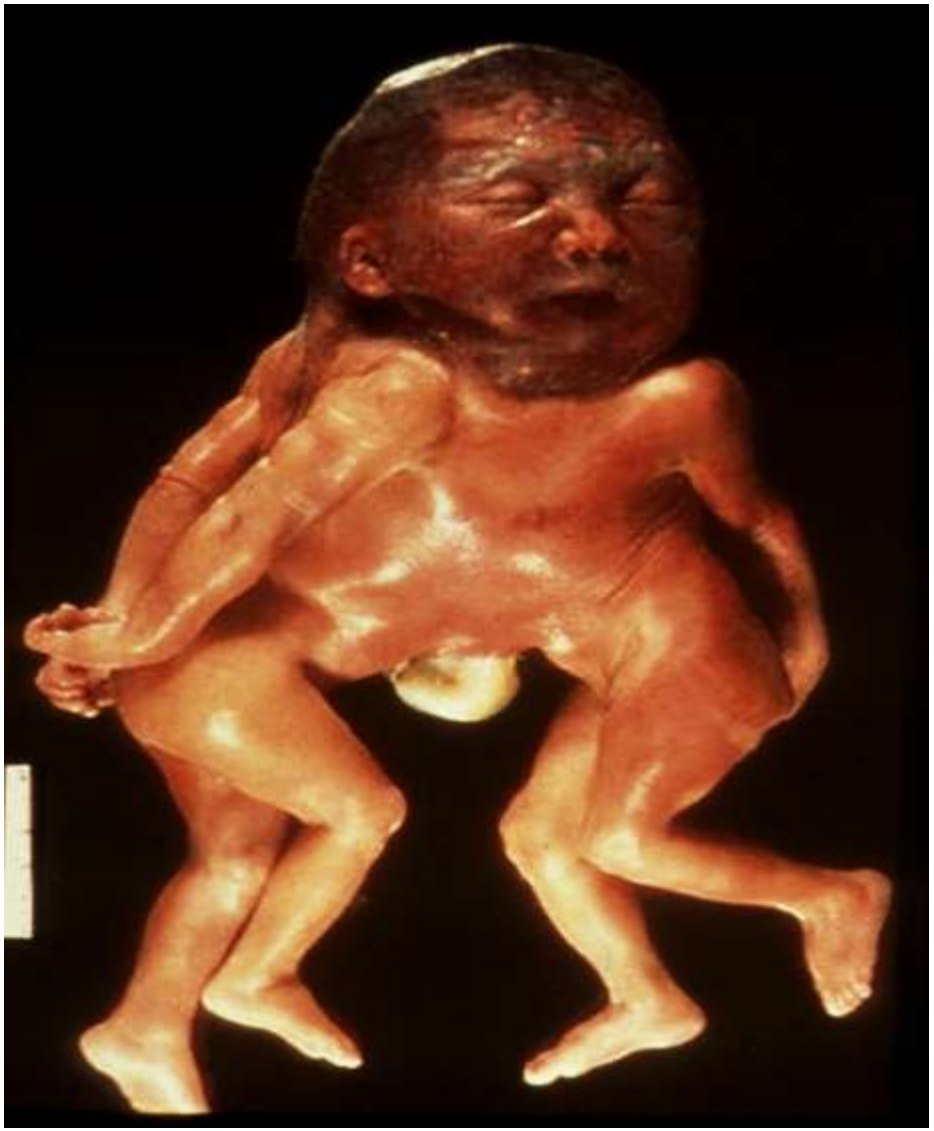


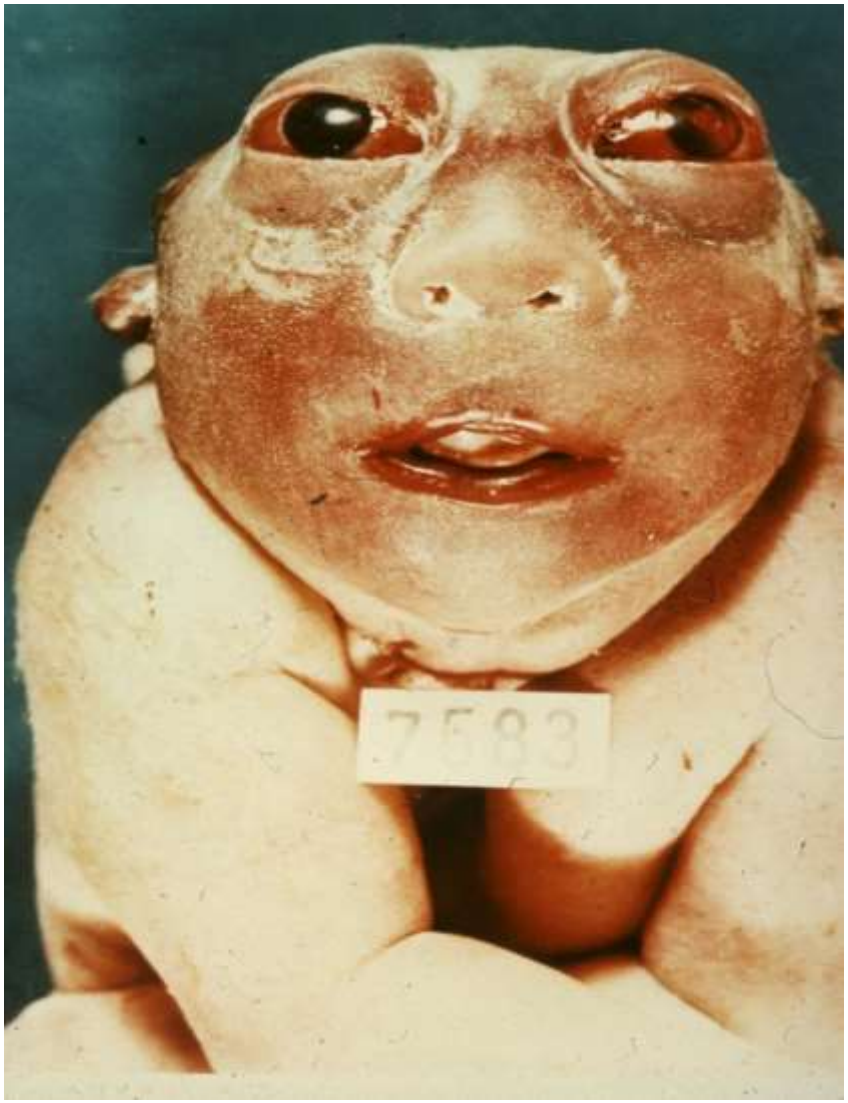






3 years old boy,
holoprosencephay of frontal lobe,
lateral ventricles are united.





Genetic Diseases

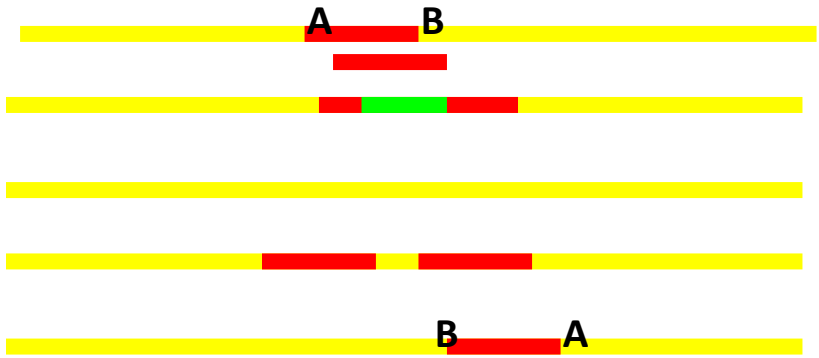
- Diseases with mendelian inheritance
- chromosomal abnormalities
- poligenically inherited diseases
- mitochondrial DNA associated diseases

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.

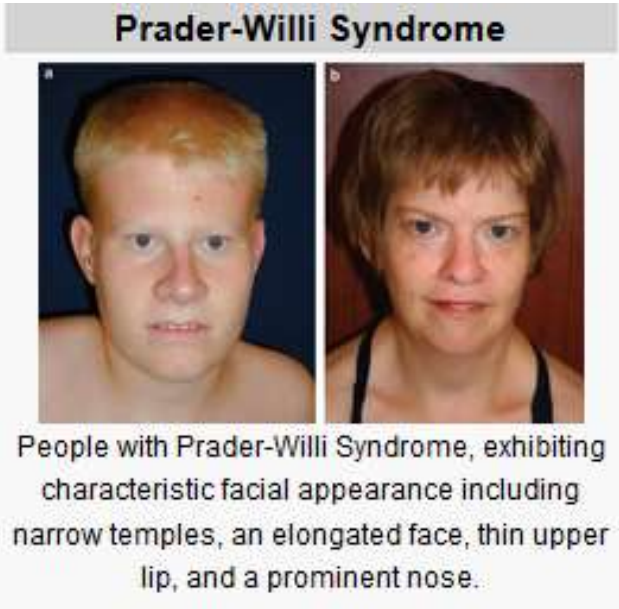
Prader-Willie Syndrome (Muscle hypotonia, areflexia, obesity, ment. impairment, behavioral problems, stubborness, compulsive behavior, lack of paternal gene on the chromosome 15.)

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



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,

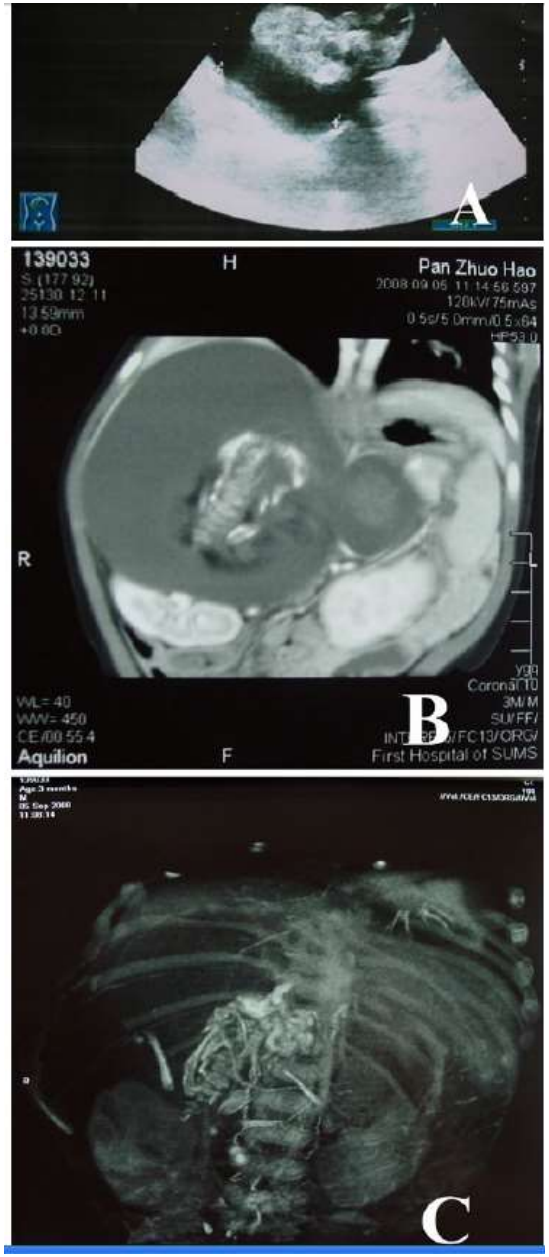
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs

- 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



Abdominal Imaging

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DOI: 10.1007/s00261-011-9757-2

Fetus-in-fetu: imaging and pathologic findings

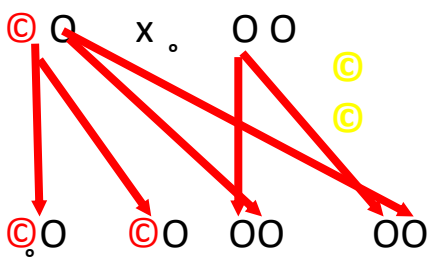
Junjie Sun, Soulithon VongPhet, Zhichong Zhang, Jiacong Mo

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

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 % !

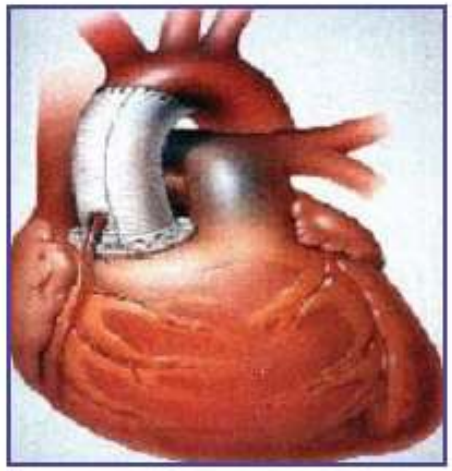


Autosomal-Dominant Diseases

- 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

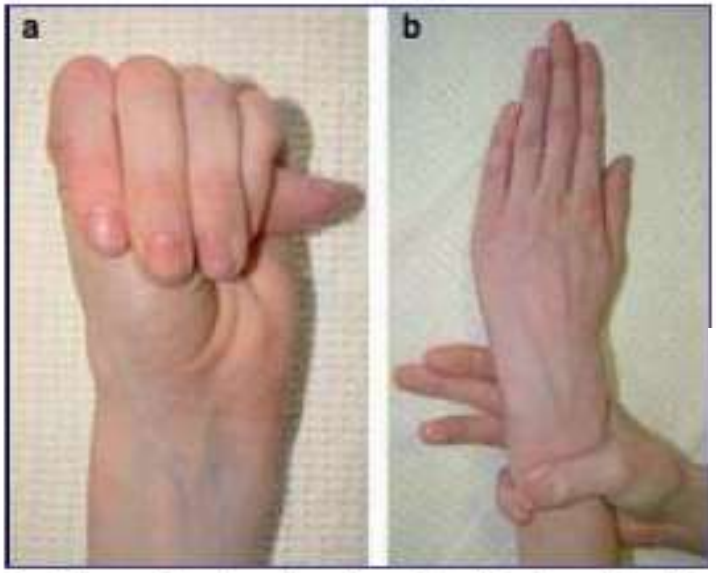
Marfan Syndrome

- 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

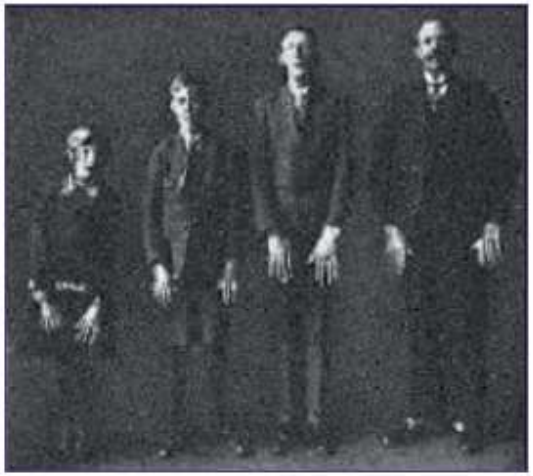


3. ábra – Bentall-műtét során a kóros aortabillentyű és a tágult felszálló aorta helyére billentyűs érprotézis (composit graft) kerül, melynek műér részébe szájaztatják a coronariákat.

A 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



1. ábra – Marfan-szindrómás család

A Marfan szindróma diagnózisa negatív családi anamnézis esetén

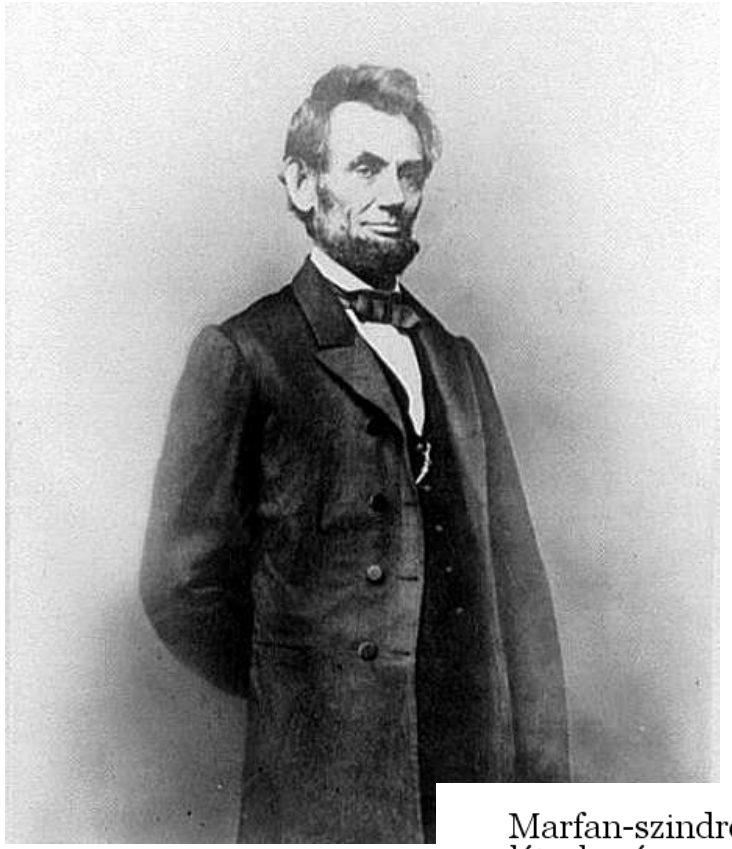
Amennyiben a beteg családjában még nem fordult elő a tünetegyüttes (index case), a módosított Ghent kritériumok értelmében a Marfan szindróma akkor diagnosztizálható, ha a tünetek alábbi négy mintázatának egyike érvényes a vizsgált egyénre:

(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 –syndrom cases

A GYÓGYÍTÁS MŰVÉSZETE

LAM (Lege Artis Medicinæ) LAM

Marfan szindrómás volt Oszama Bin Laden?

Pár nappal azután, hogy egy pakisztáni házban egy amerikai haditengerészeti alakulat, a Navy SEALS rajtaütött Osama Bin Ladenen, máris megindultak a találgatások, miszerint nem is a fejébe küldött golyó, hanem egy rejtélyes betegség, a Marfan szindróma végzett a terrorista vezérrel.

Dr. Steve R. Pieczenik, korábbi állami tisztviselő már évekkel ezelőtt azt nyilatkozta, hogy véleménye szerint Bin Laden már 2001-ben meghalt egy genetikai rendellenesség következtében. A szeptember 11-i terrortámadás után orvos szakértők elemezték ki Bin Laden magasságát, testalkatát, nyurga végtagjait és hosszúkás arcát, melyek mind a Marfan szindróma jellegzetes tünetei. A betegségnek kevésbé látványos velejárói is vannak – például ízületi gondok és szívproblémák -, melyek hirtelen aortaszakadáshoz és ezáltal váratlan halálhoz vezethetnek.

Dr. Richard Devereux csaknem egy évtizeddel ezelőtt szintén így nyilatkozott: „Hosszú ujjai, hosszú karjai vannak, a fejformája is hosszúkás, az arca pedig keskeny. Egészen biztosan Marfan szindrómában szenved."

Dr. Hal Dietz, a John Hopkins Orvosi Egyetem genetikusa azonban nincs erről meggyőződve. „Bin Ladennek nem voltak mélyen ülő szemei, sem koponya deformitása, és szívbetegségéről sem tudunk, továbbá gyermekein sem látszik a betegségnek semmi jele. Ez az egész nem több puszta spekulációnál" – fejtette ki véleményét.

Ehlers-Danlos Syndroms

Paganini

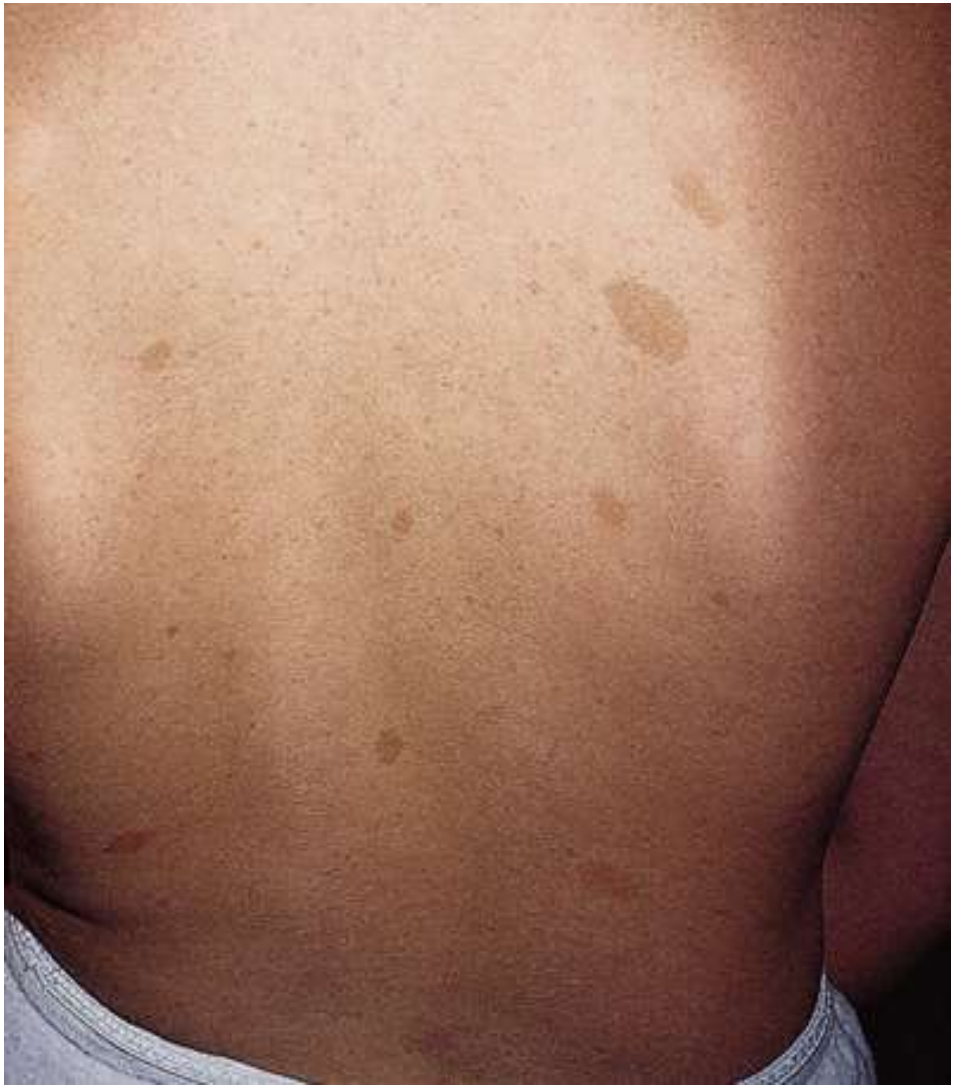
- clinically and genetically: heterogenous(I.-X.)
  - all three mendelian inheritance pattern
  - disorder of collagene synthesis
- Macroscopic disorders: collagene-rich tissues

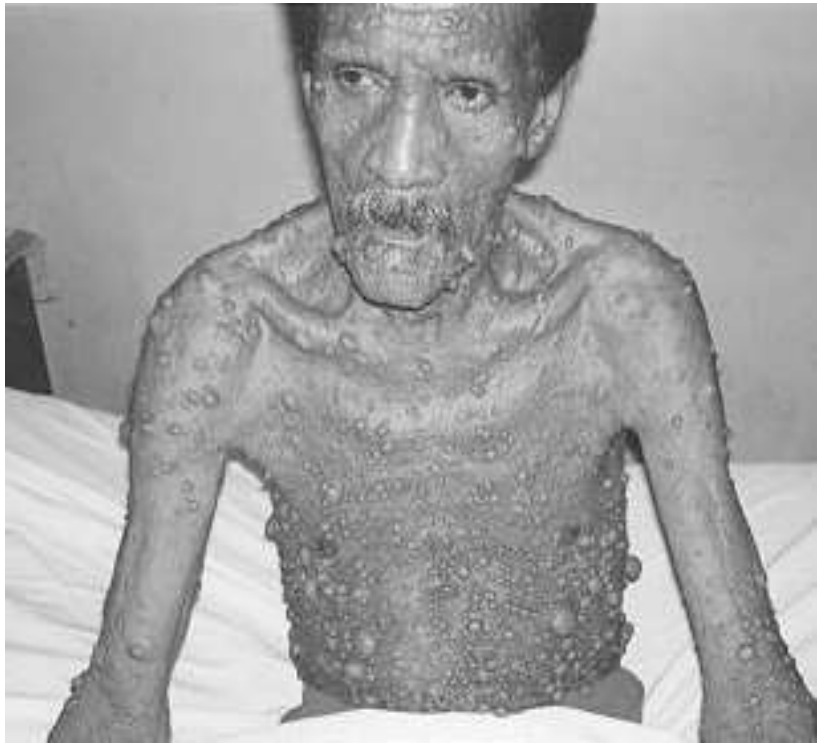
Skin, Ligaments, Joints

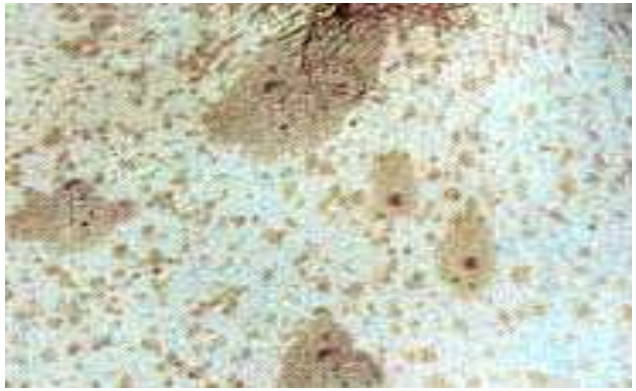
  - Skin is vulnerable, elastic
  - Flexibility of joints (hyperelastic joints, „snake-acrobats, artists: Paganini !!)
  - Rupture of major arteries, rupture of colon, rupture of cornea, hernia of diaphragma (other disorders of collagene synthesis: osteogenesis imperfecta , bullous epidermolysis)

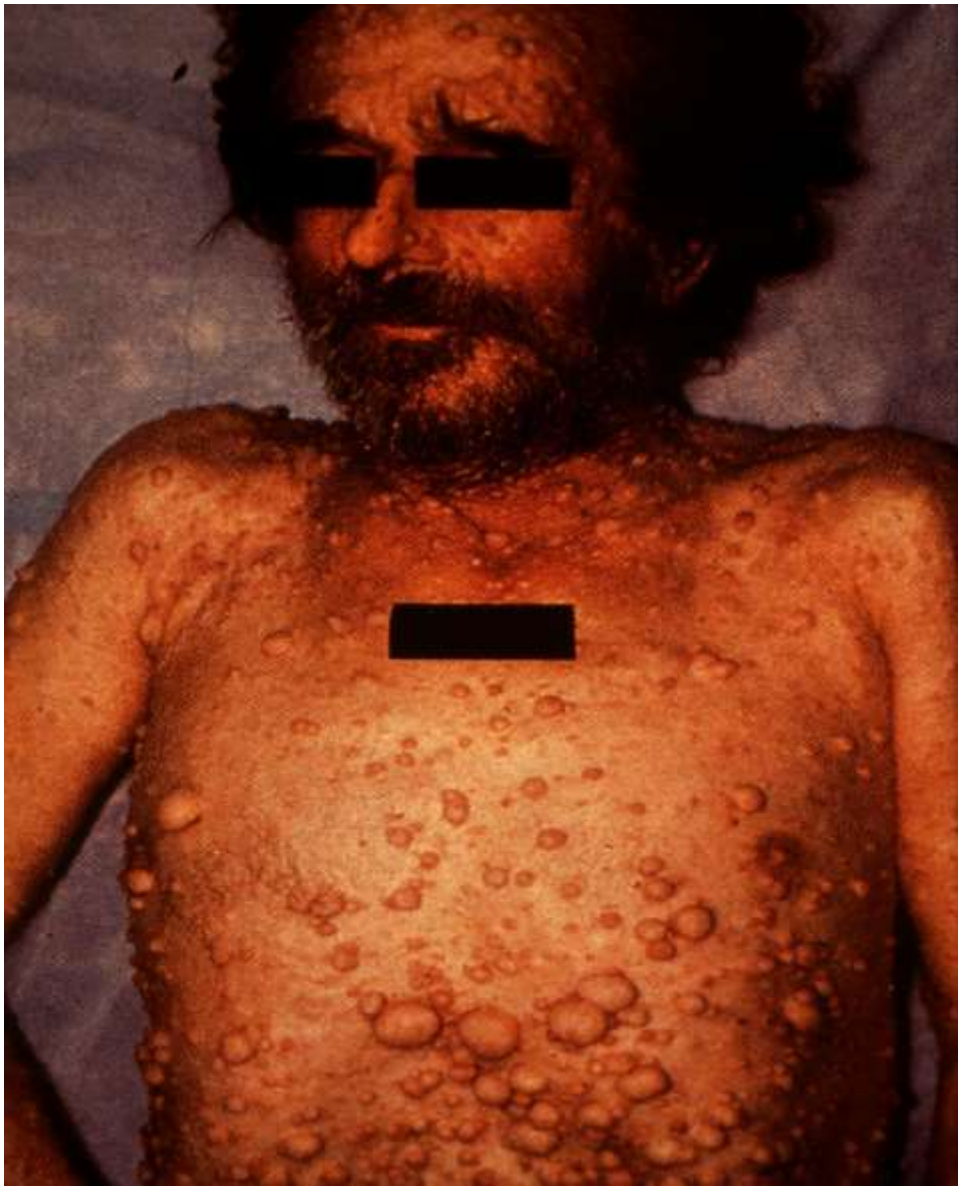
Neurofibromatosis (Recklinghausen's Disease)

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





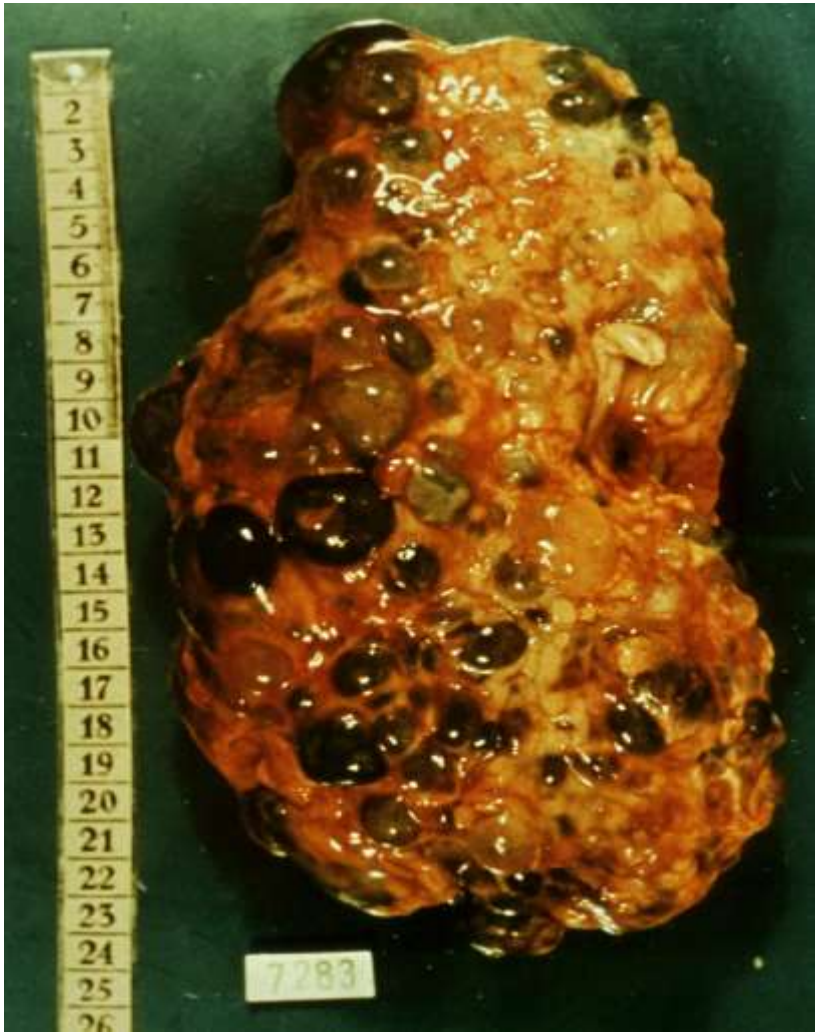




Polycystic Disease

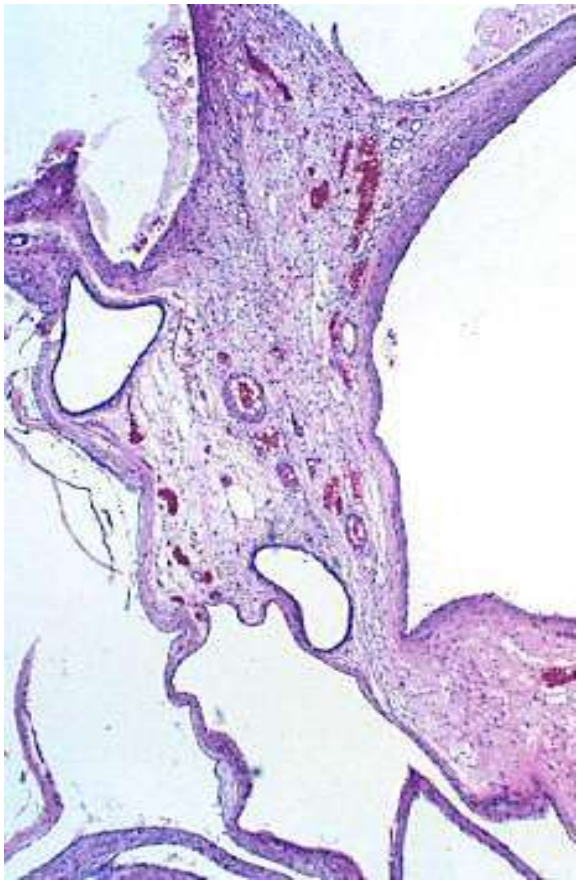
- Polycystic kidneys in adults
  Polycystic liver
- Polycystic lungs
- arterious aneurysms of basilary arteries in the skull

Cystic Kidney Disease I.



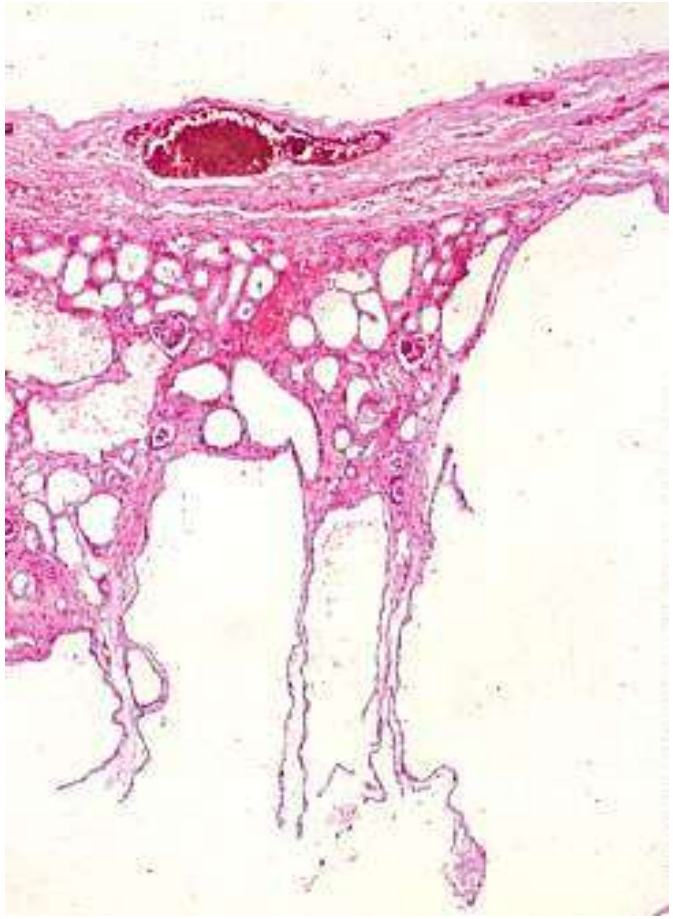
Cystic Kidney Disease I.

Autosomal Dominant (Adult Type) Polycystic Kidney Dis.

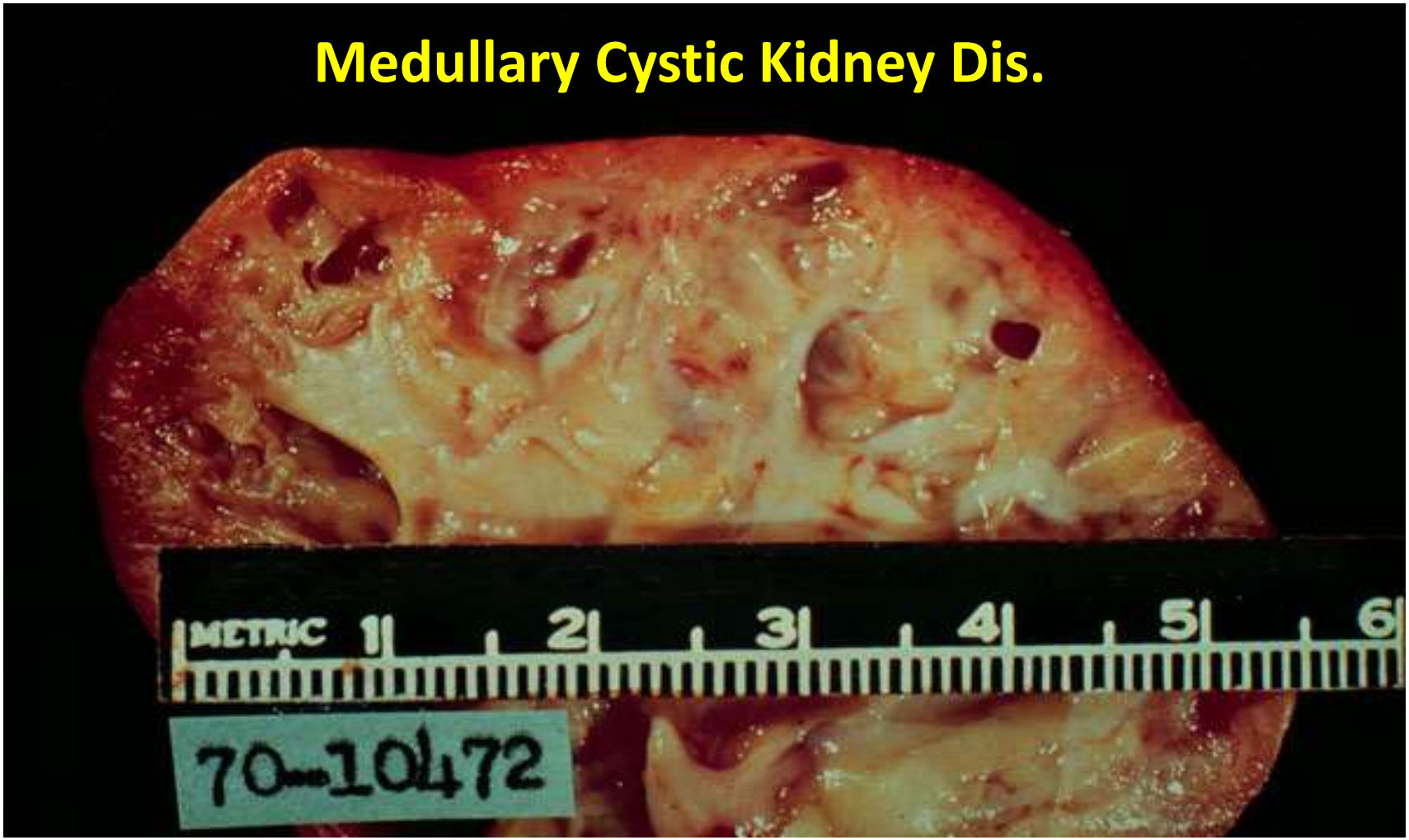


Cystic Kidney Disease II.

Infantile Polycystic Kidney Dis. (IPKD)



Cystic Kidney Disease III.

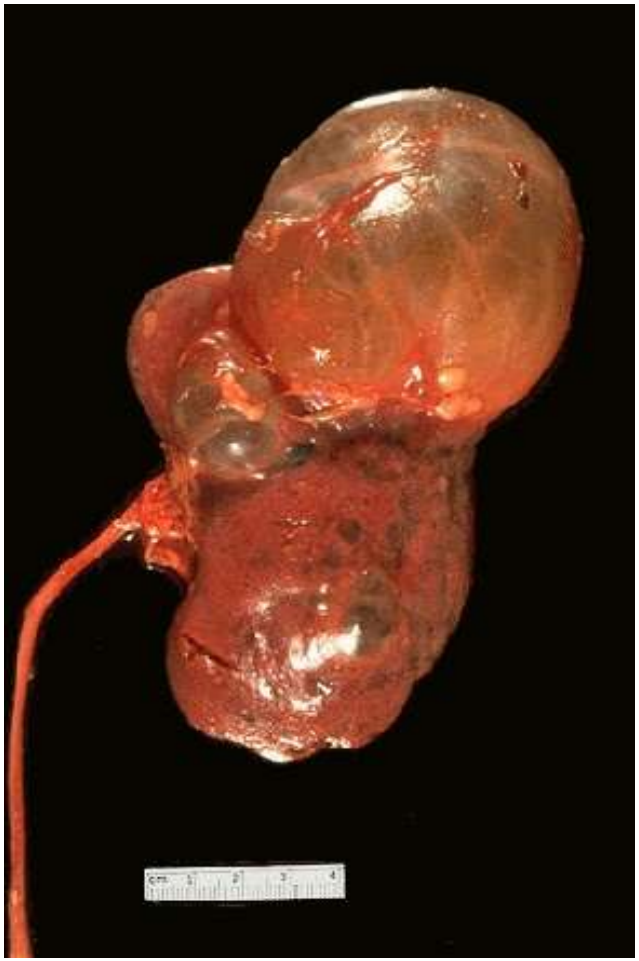


Cystic Kidney Disease

Simple Cyst

No symptoms, this is not a disease

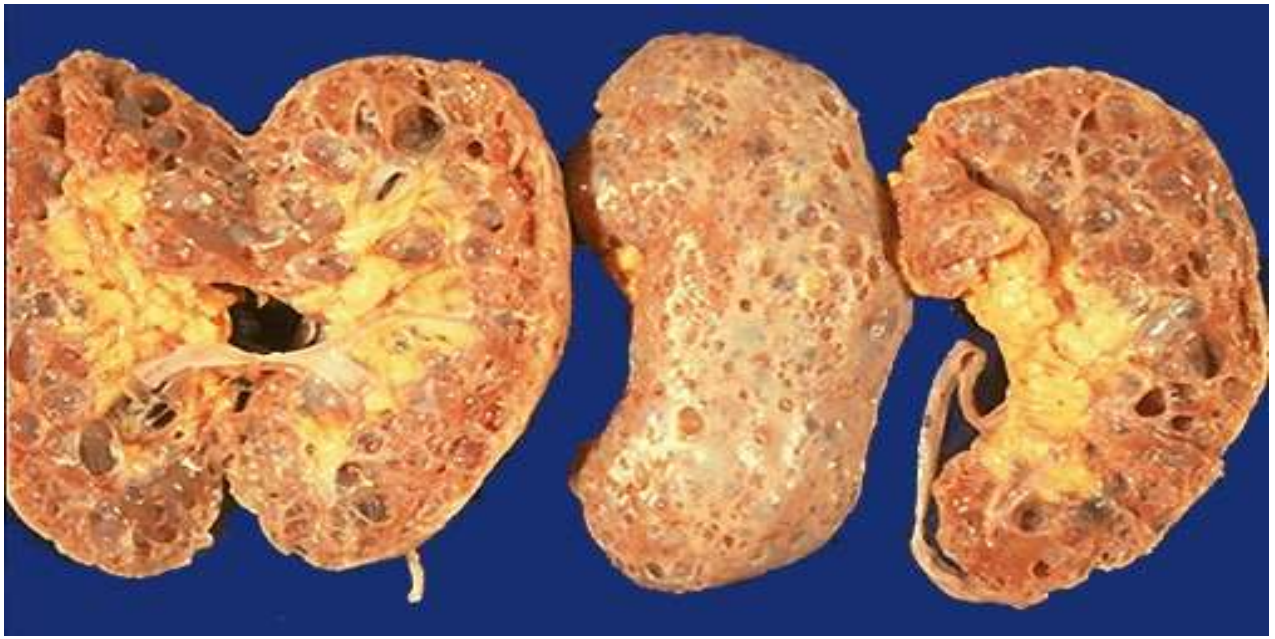
- Bleeding might cause acute pain
- up to 10 cm, transparent, fille with fluid
- lined by one layer of cuboideal or ectropic epithelium
- no treatment is necessary



Cystic Kidney Diseases III.

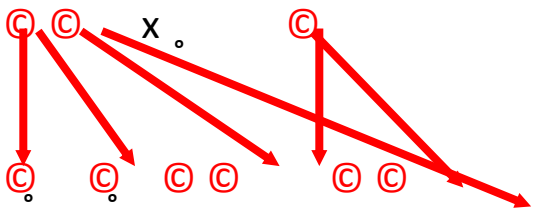
Acquired Cysts

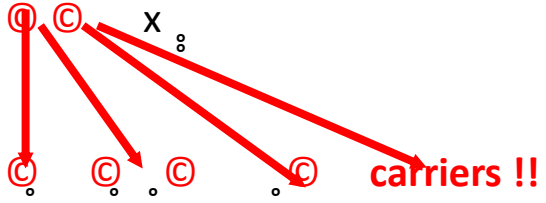
1. 5 years after tranplantation 75 % of patients develops this change
2. Increased risk of renal cell carcinoma (7% 10 years),



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

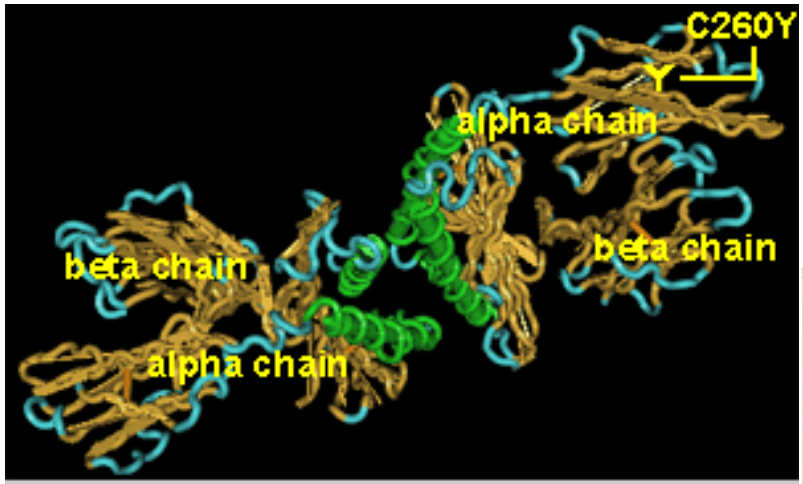
  Hurler dis. - infants – gargoylism, hepatomegalia, mental. ret.

  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

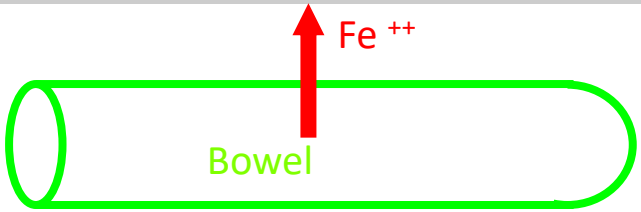
Haemochromatosis (Bronze diabetes)



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.



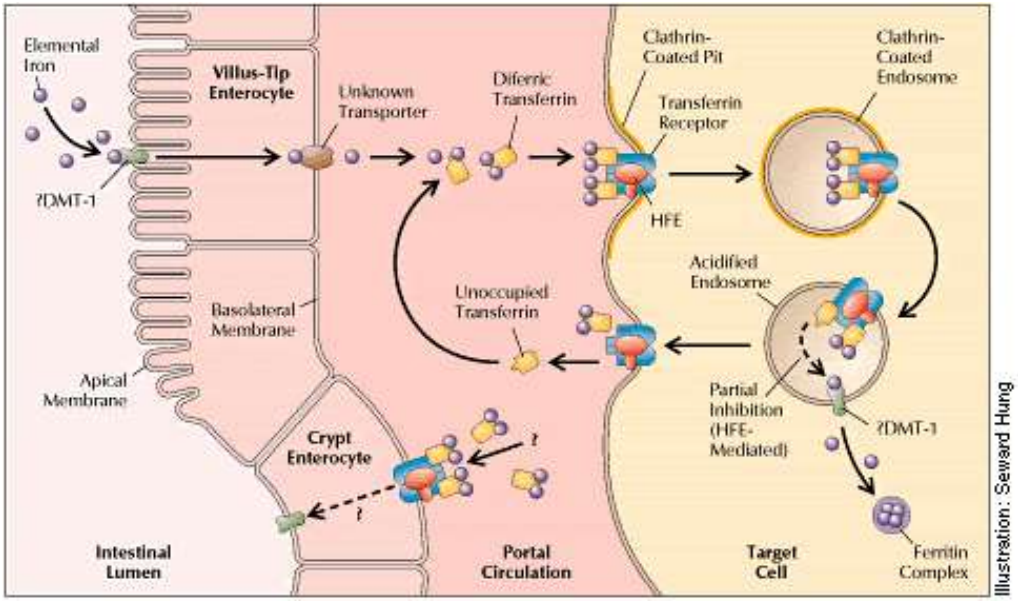


Illustration: Seward Hung

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

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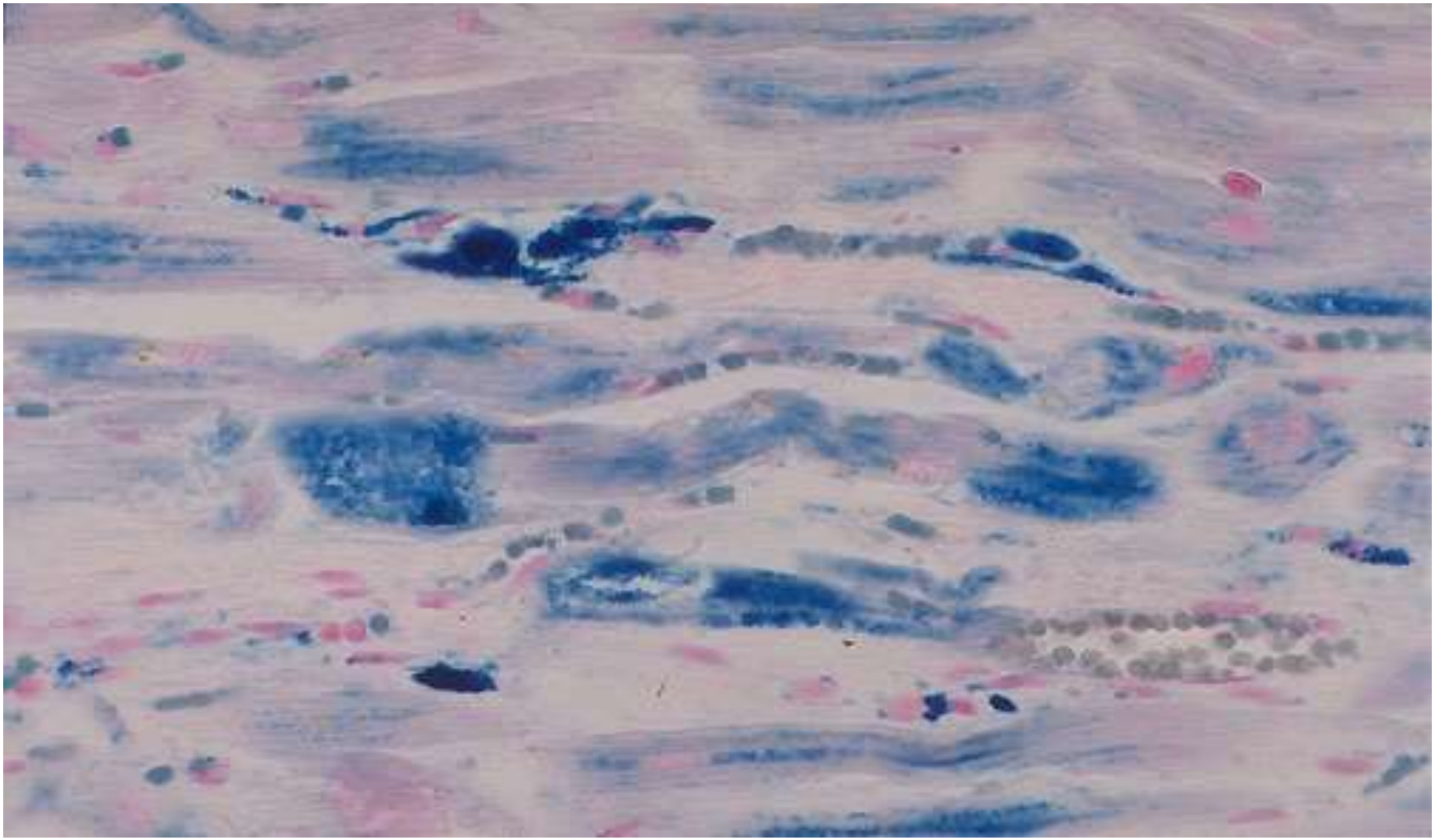


hemochromatosis, with excessive iron deposition - Prussian blue iron stain the excessive deposition of iron leads to heart enlargement and failure

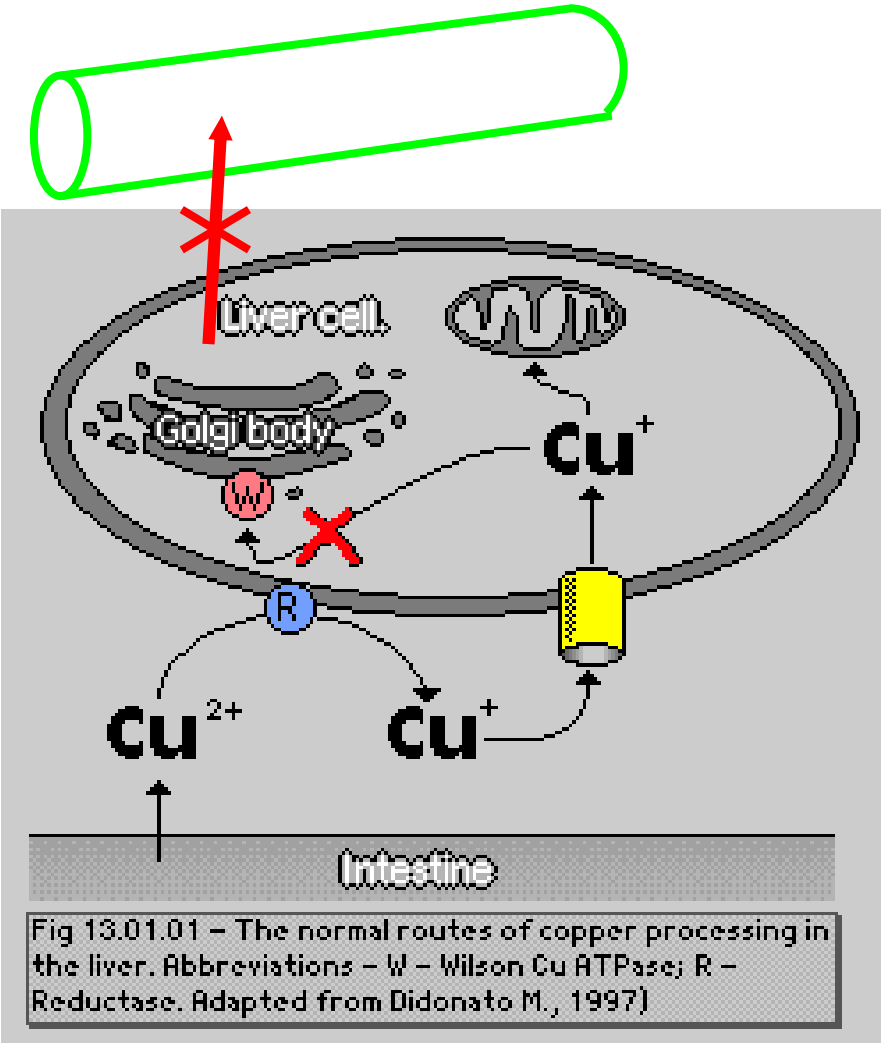


Fig 13.01.01 – The normal routes of copper processing in the liver. Abbreviations – W – Wilson Cu ATPase; R – Reductase. Adapted from Didonato M., 1997)

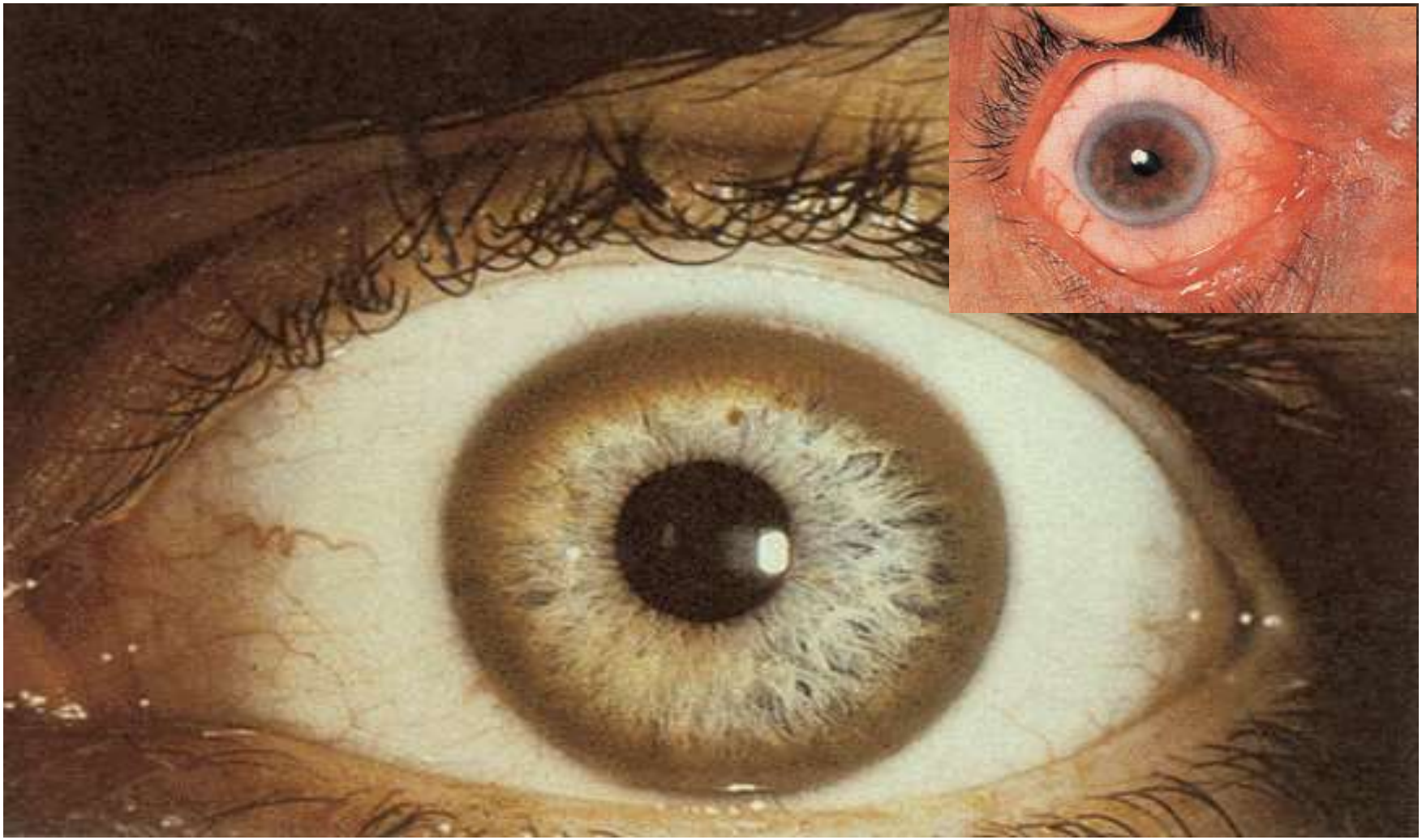
Wilson disease
(hepatolenticular disease)
(Copper storage disease)

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

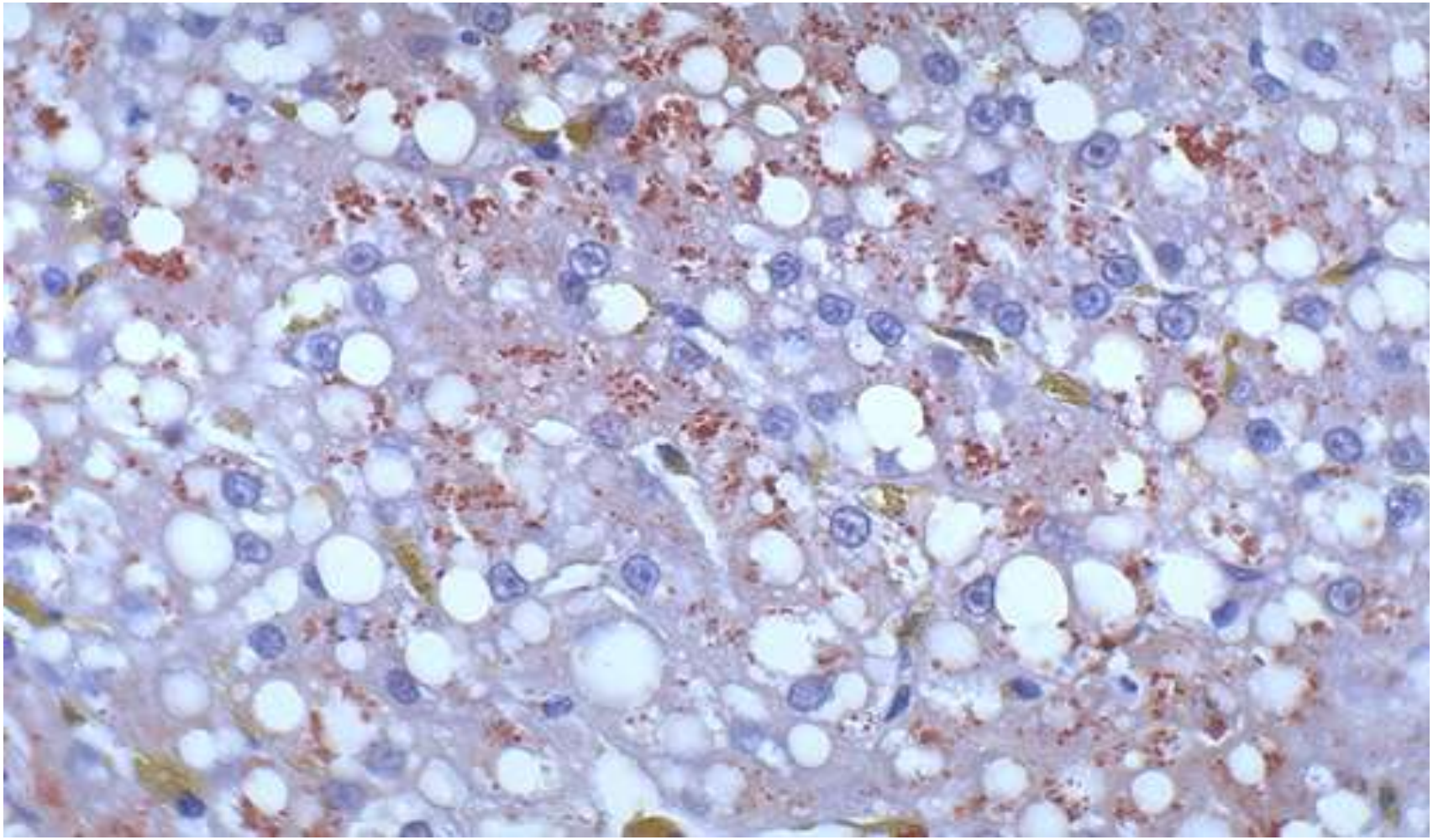
Kayser-Fleischer Ring

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



Kayser-Fleischer Ring

Arcus senilis



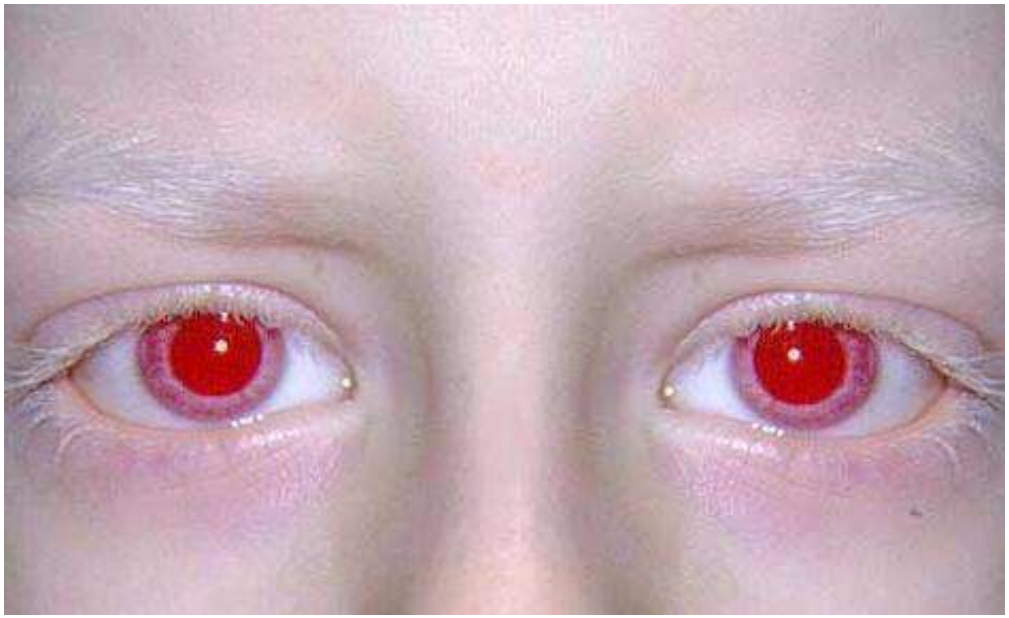
excessive lysosomal copper in a patient with the rare autosomal recessive disorder Wilson's disease

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

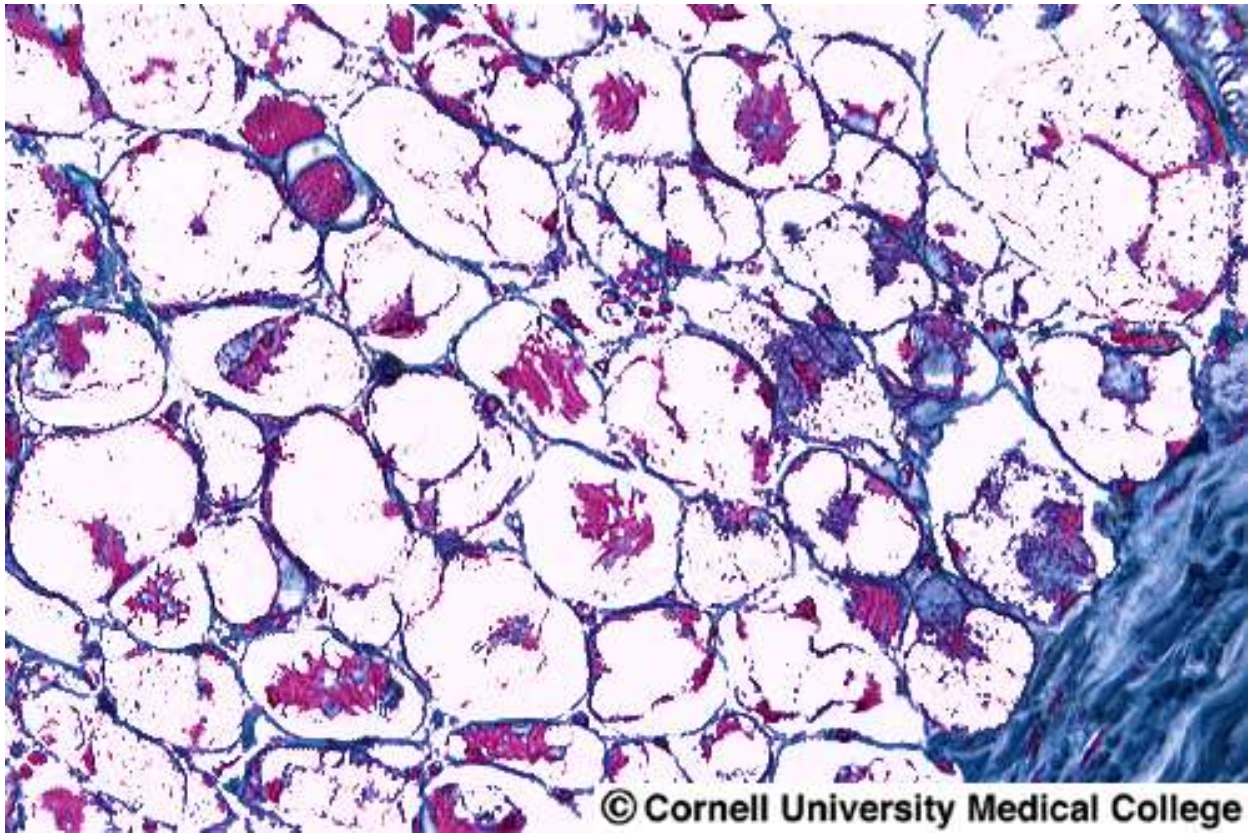
Liver insuffitiency

hämorrhagic diathesis – Thrombozytopathy by glykogene depostition

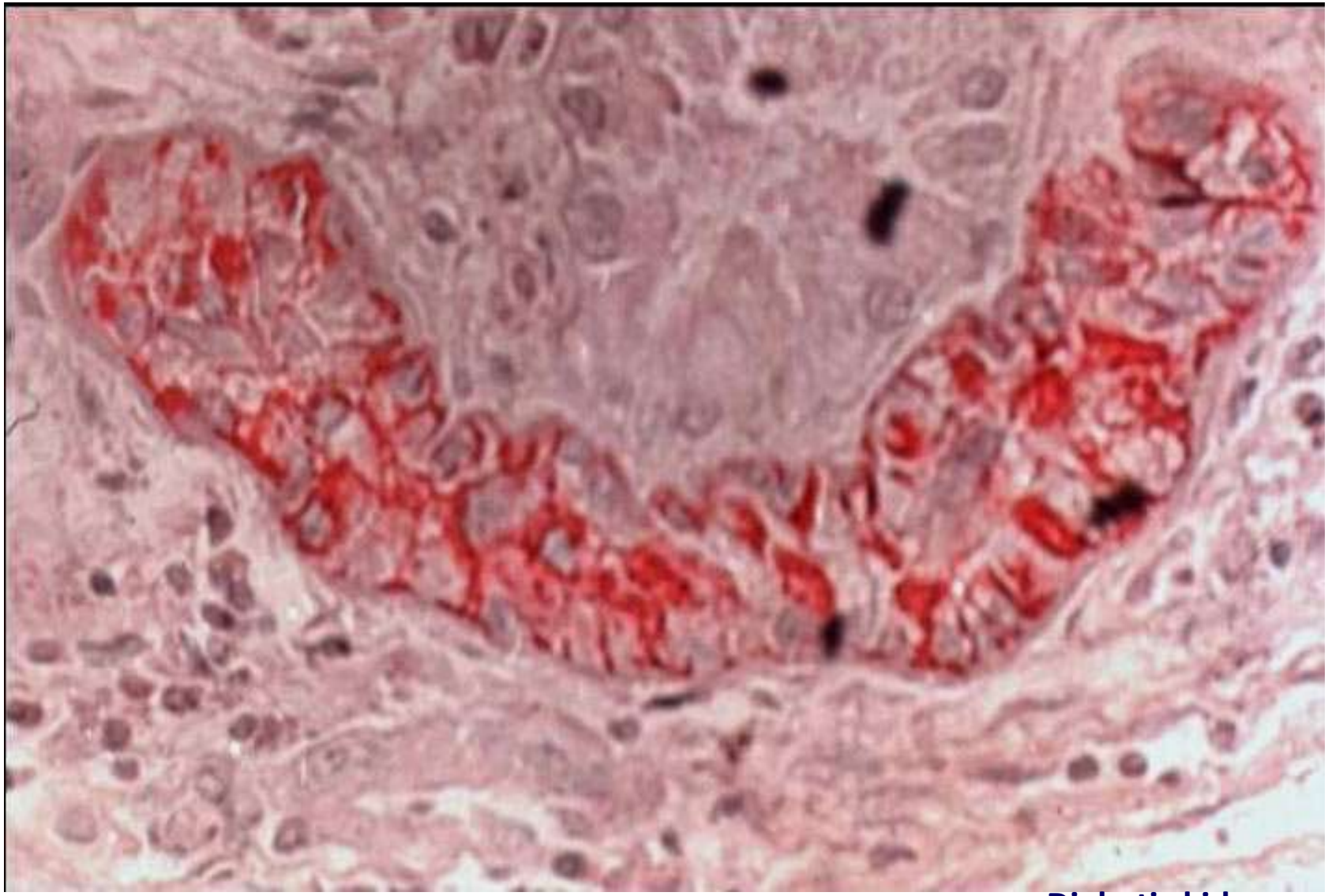
later emnlarged kidneys (»Nephromegaly«)

Infantilismus - adiposogenital type

sclera dystrophy



Glycogenosis



Diabetic kidney

Storage diseases:

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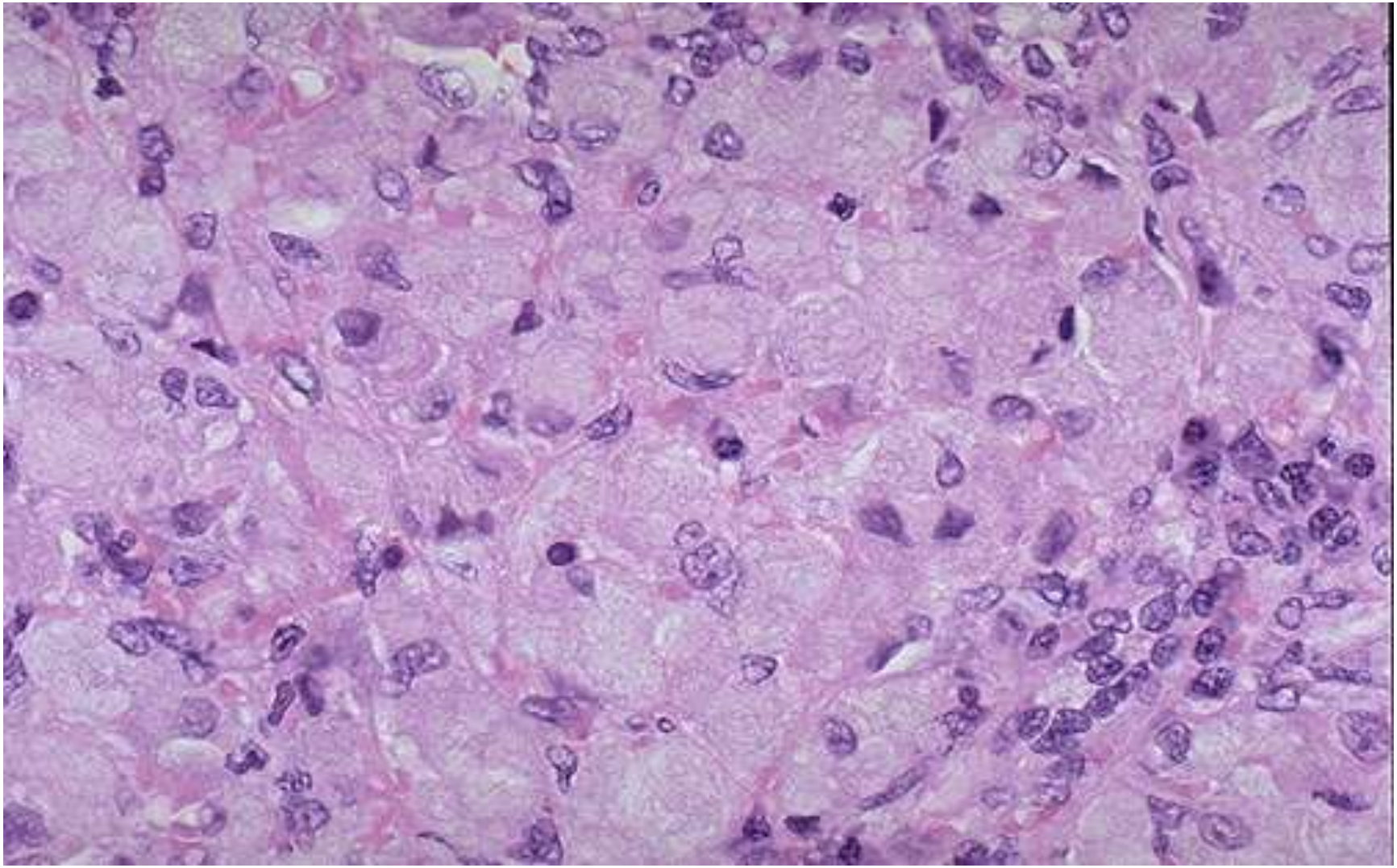
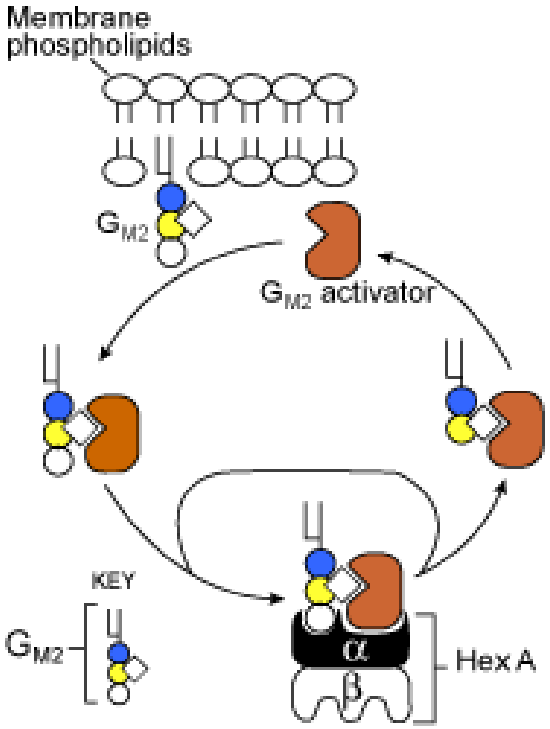
Mucopolisacharidosis - GAG (Heparan Sulfat, dermatan sulfat) - balloon cells, mental retardation and hepatomegaly - lysosomal

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

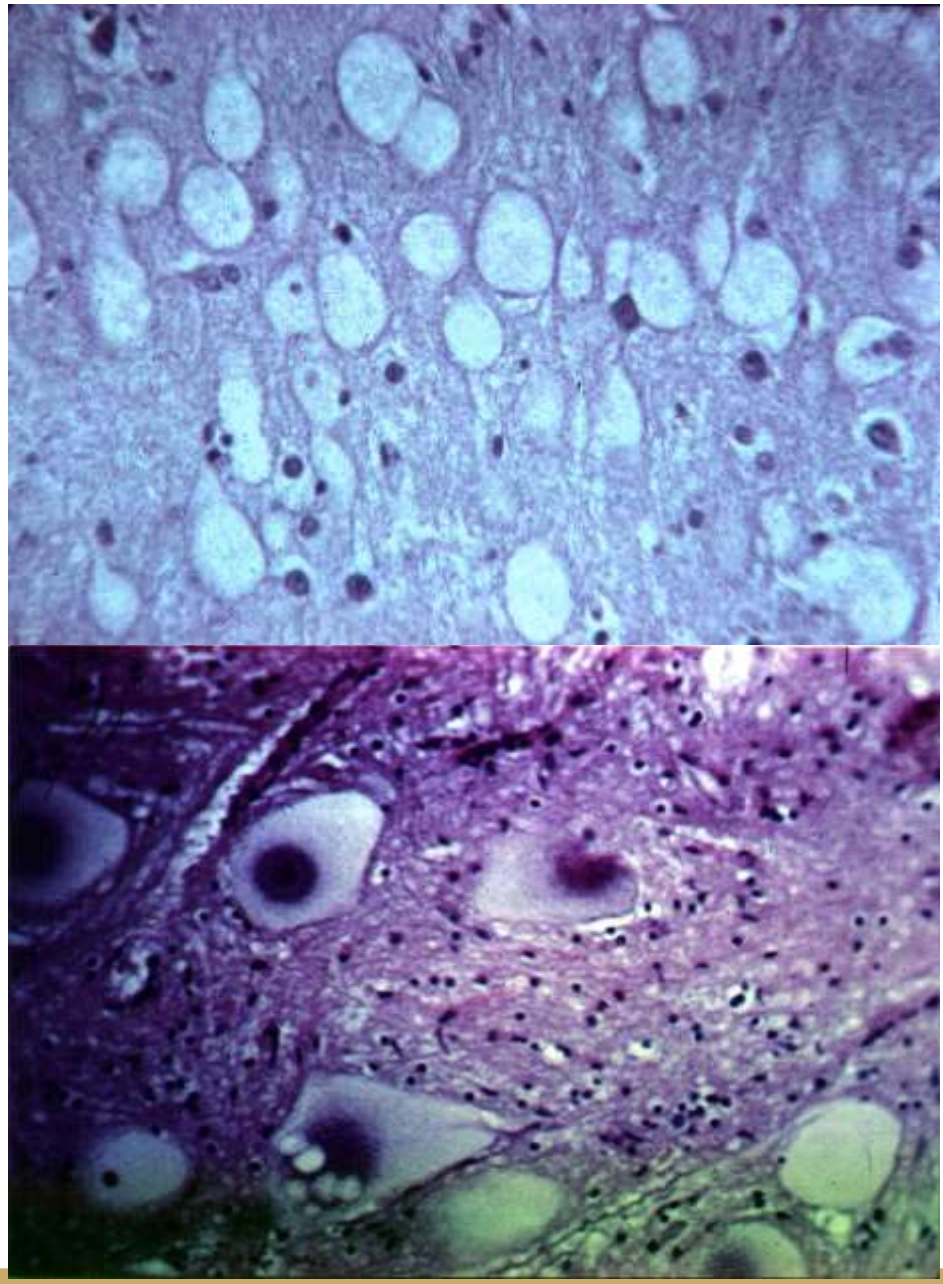


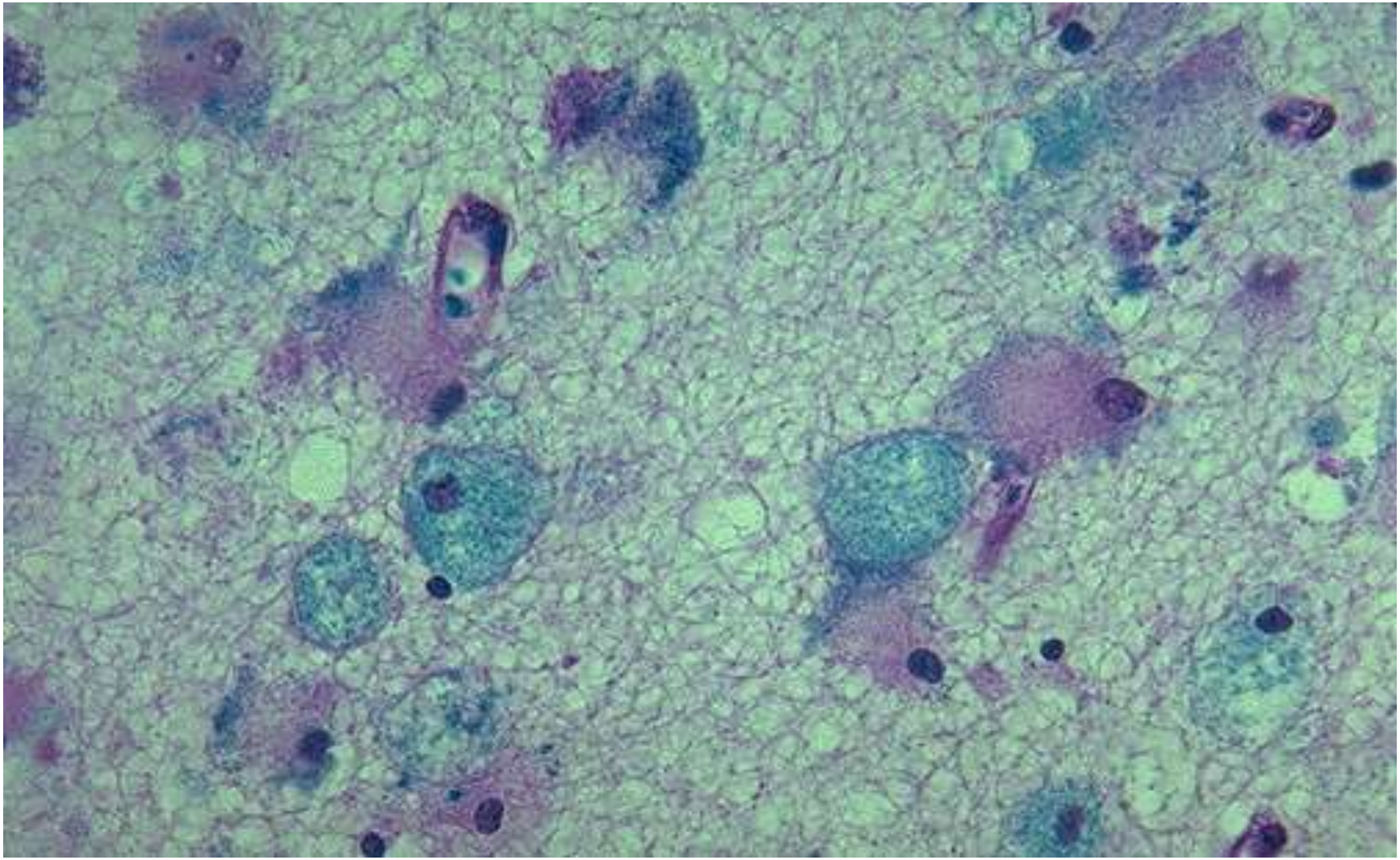
Splenomegalia - morbus Gaucher



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.]

Tay-Sachs Disease





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,) !
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

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

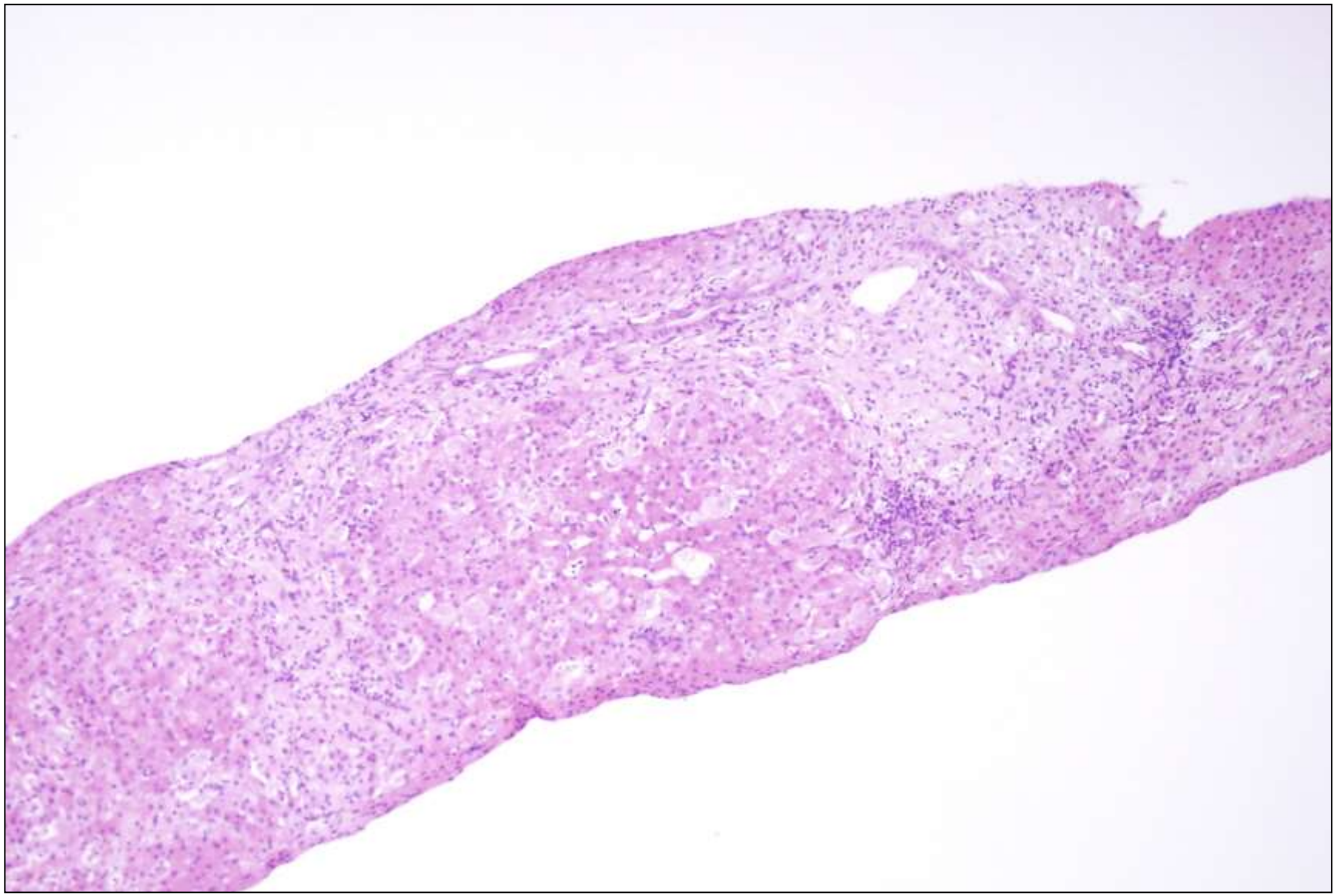
3 years old boy
10695/04

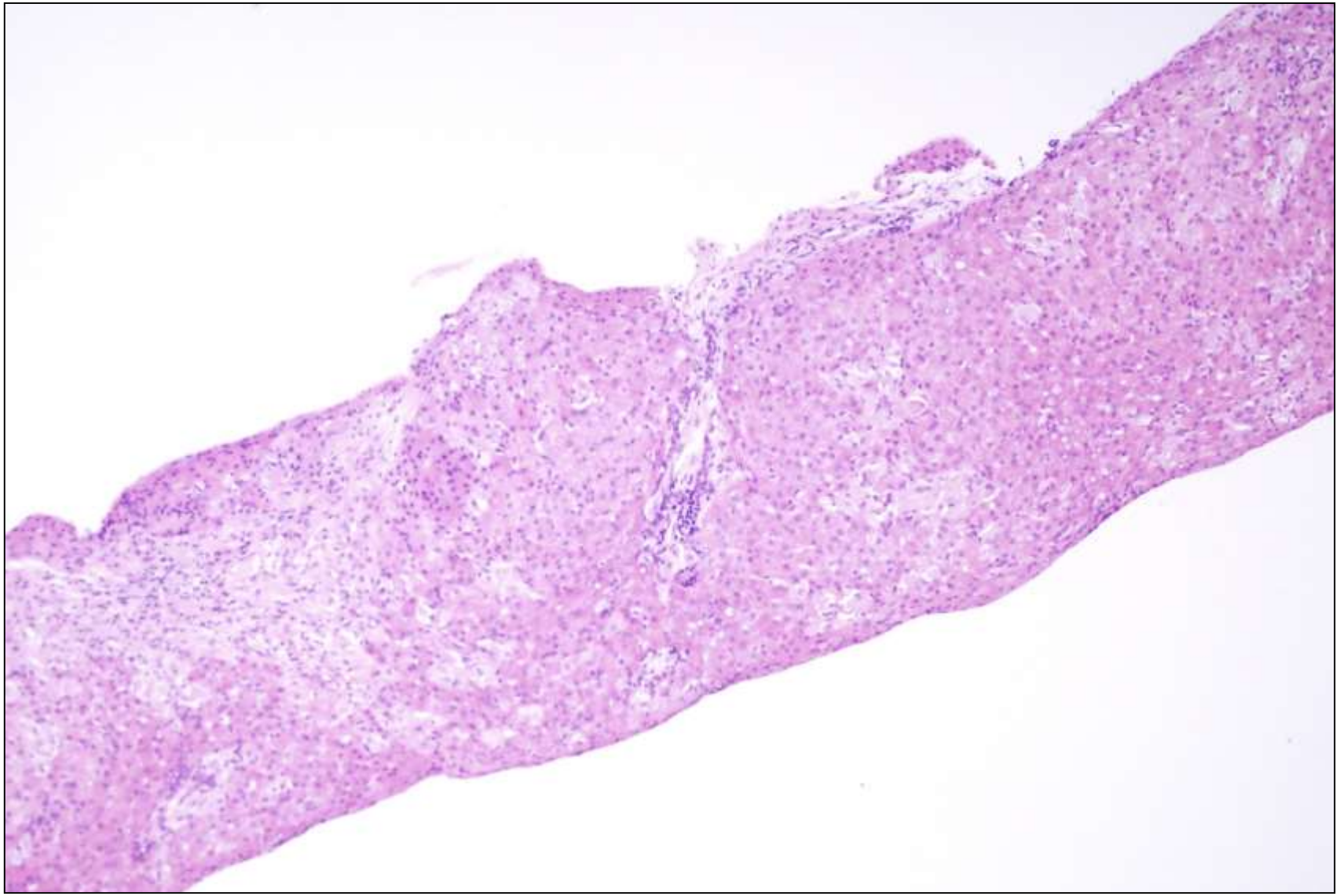
Clinical Data: heavy splenomegaly, Pancytopenia

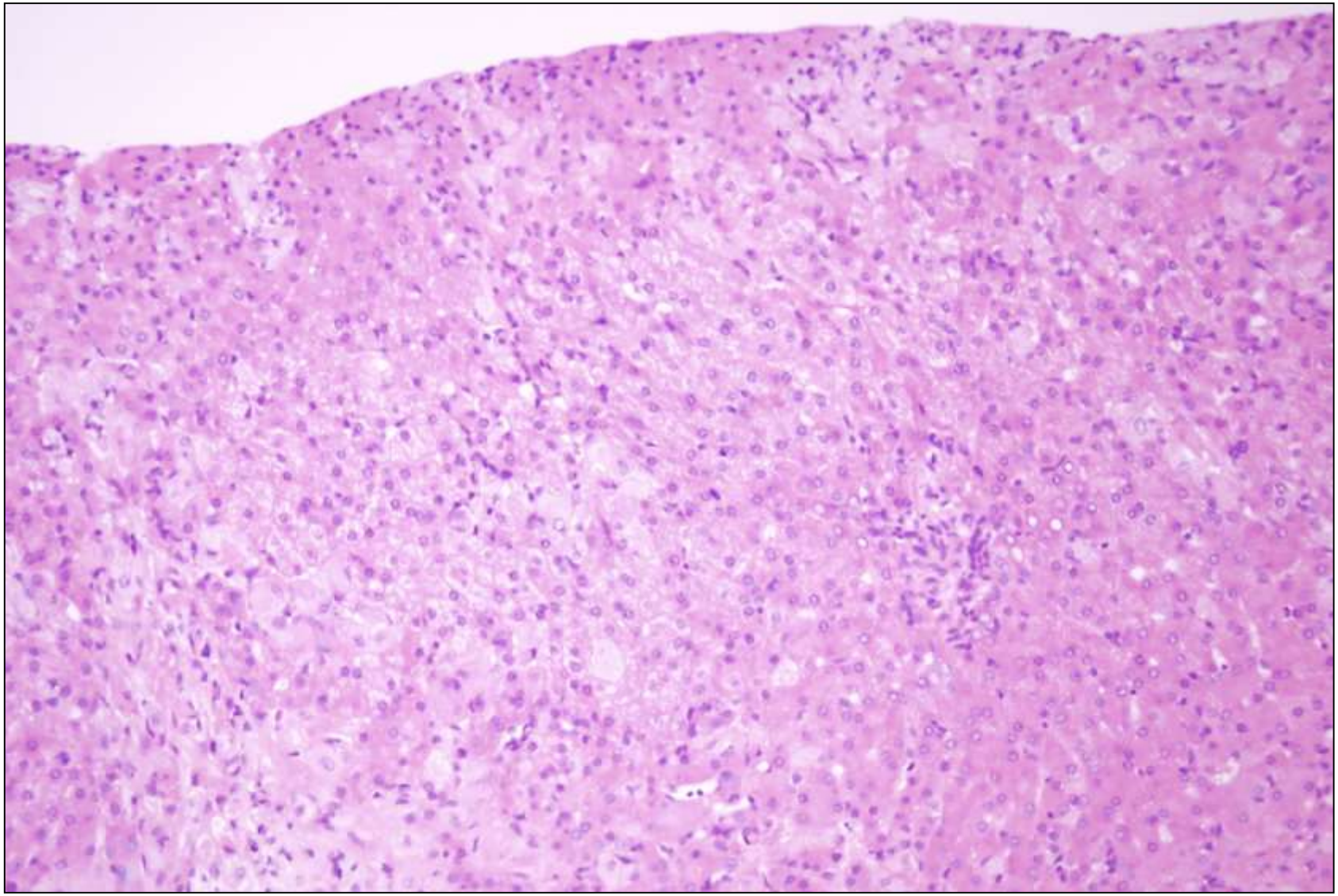
Virus Serology: negative

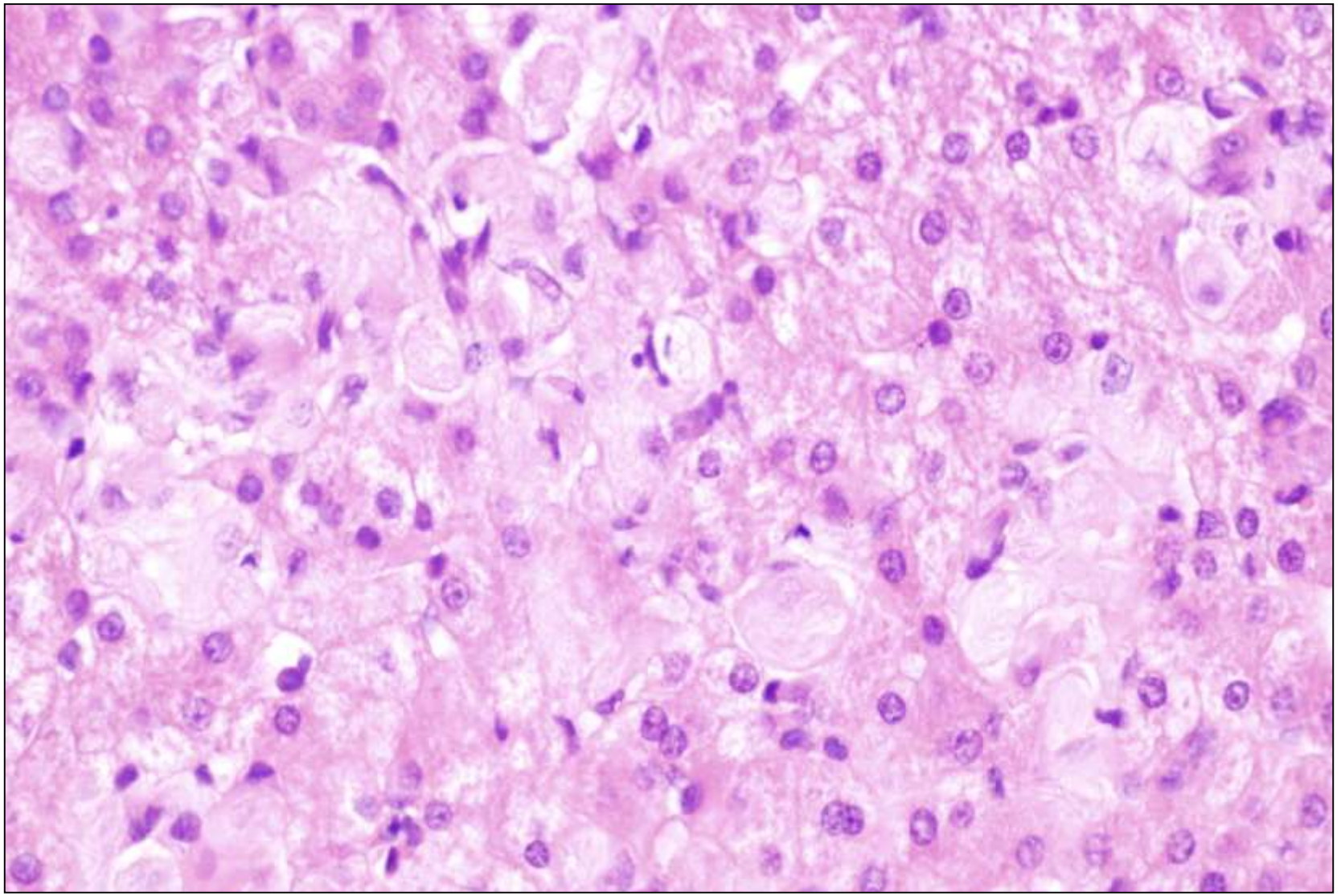
Bonemarrow aspiration (in other Institute): negative

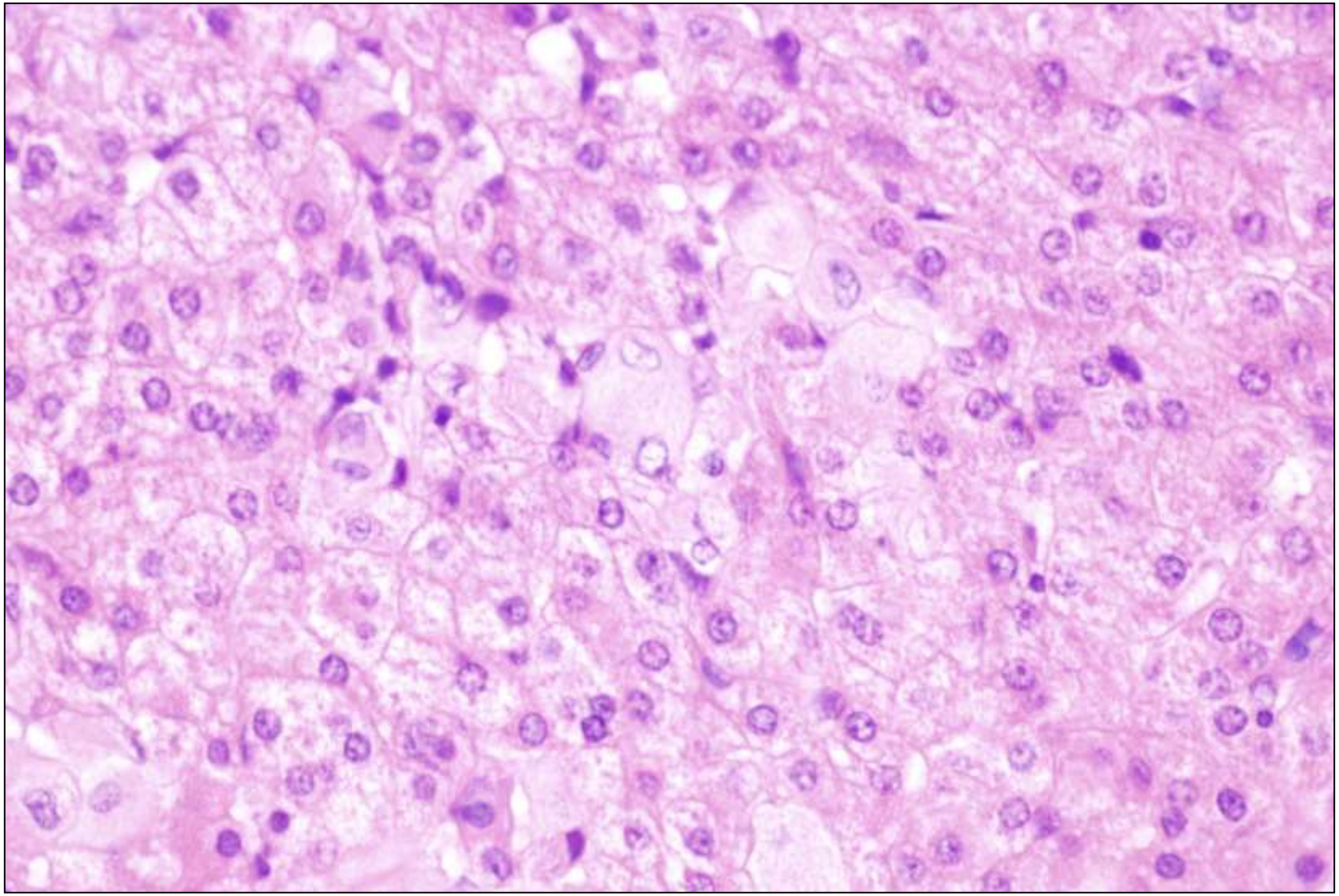
Clinical Diagnosis: hematological disease ?

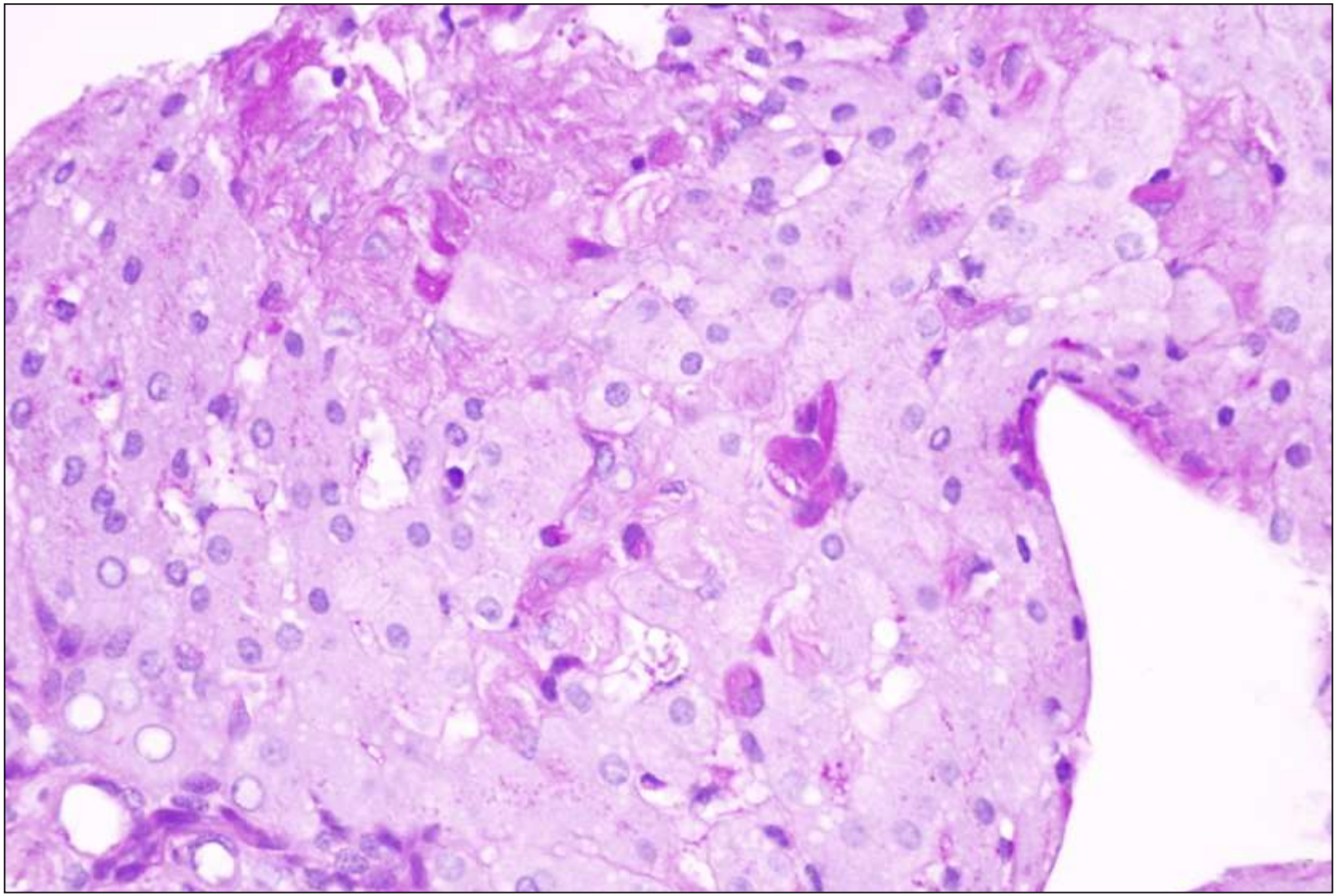


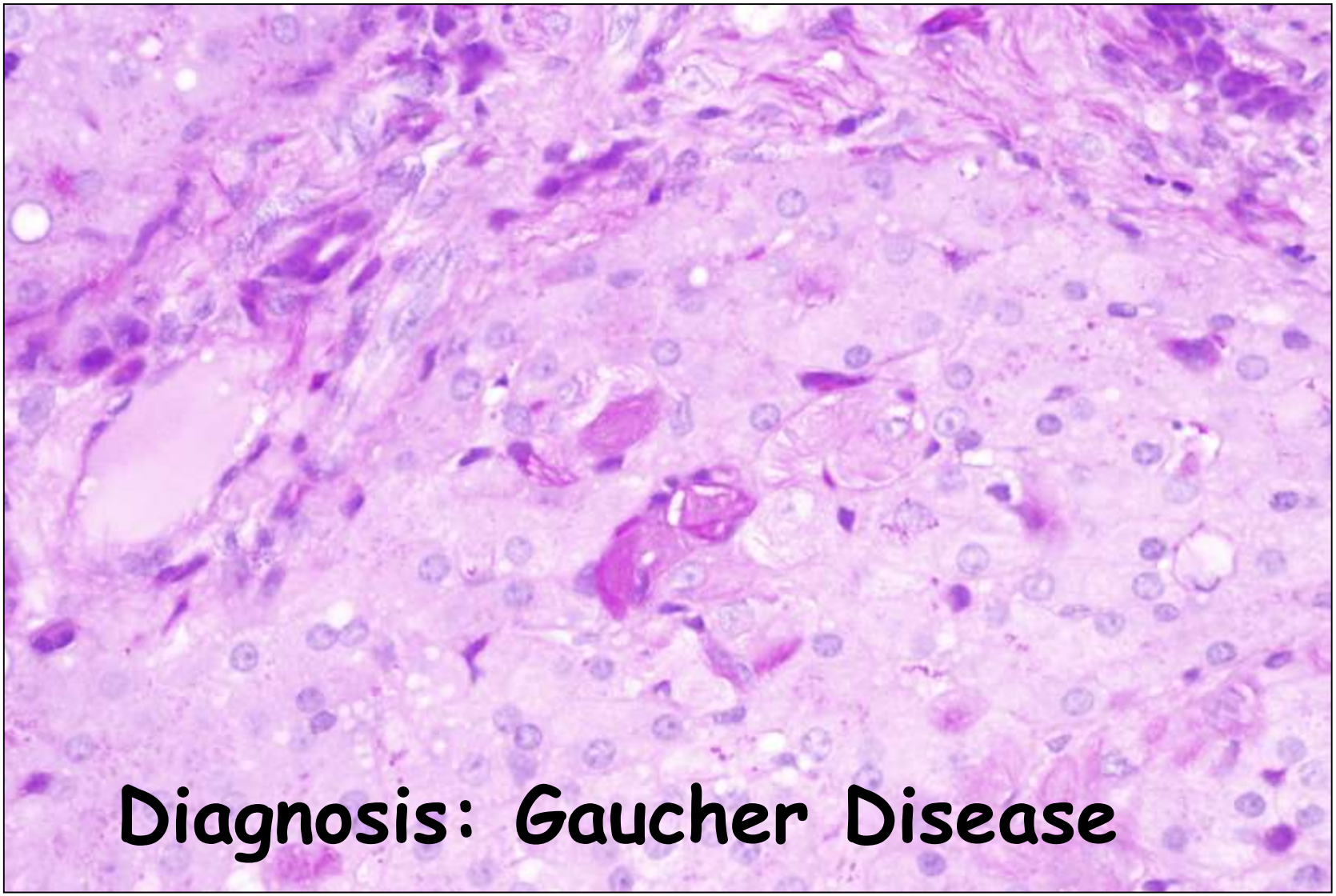












Diagnosis: Gaucher Disease

Tárolási Betegségek Központok

A Tárolási Betegségek Központ feladata a ritka lysosomalis tárolási betegségben, elsősorban Gaucher- és Fabry-kórban szenvedő betegek felkutatása, diagnosztizálása, enzimszubsztitúciós kezelése és gondozása. A Gaucher- és Fabry-kórban szenvedő betegek mutáció analízis vizsgálatát és a családtagok genetikai szűrését is rendszeresen végezzük.

1. **Gaucher Diagnosztikai és Terápiás Központ (GDTK)**
2. **Fabry Diagnosztikai és Terápiás Központ (FDTK)**

Gaucher Diagnosztikai és Terápiás Központ (GDTK)

A Gaucher Diagnosztikai és Terápiás Központ (GDTK) 1991. óta működik Debrecenben, kezdetben a Gyermekimmunológiai Munkacsoport, 1998-tól a Tanszék felügyelete mellett. A Gaucher-kóros betegek komplex gondozásában és ellátásban minden tekintetben elértük a legfejlettebb európai központok szakmai színvonalát. A Debreceni Központ diagnosztikai vizsgáló módszereket állított be (leukocita β-D-glükocerebrozidáz és plazma kitotriozidáz aktivitás mérése, és GBA mutáció analízis) és ezeket a szolgáltatásokat az egész ország, valamint a környező kelet-európai országok betegei számára is biztosítja. A Tanszék szakmai múltja ezen a területen jól ismert és elismert, munkacsoportunk a klinikai betegellátáshoz kapcsolódó kutatásokat is végez. Prof. Maródi László 1997-ben "Gaucher-kóros Betegekért Alapítványt" hozott létre, a betegek folyamatos és színvonalas szakmai ellátásának további segítésére. Jelenleg Magyarország minden részéről Központunkba irányítják a Gaucher-kór miatt kivizsgálásra szoruló betegeket. A Központ a betegek nemzetközi regiszterbe vételéért is felelős.

Fabry Diagnosztikai és Terápiás Központ (FDTK)

A Fabry Diagnosztikai és Terápiás Központ (FDTK) 2003. óta működik a Tanszéken. A Fabry-kór X-kromoszómához kötötten öröklődő lysosomalis tárolási betegség, amely az α-galakozidáz enzim csökkent működését, vagy hiányát okozza. A géndefektus következtében a kis- és nagyerek falában globotriaosylceramid halmozódik fel, amely miatt szívinfarktus, stroke vagy gyors progressziót mutató veseelégtelenség veszélyezteti a beteget. Az érintett férfiak 30-40 éves korra kezelés nélkül életüket veszthetik, a hordozó nőbetegeknél, kb. tíz évvel később manifesztálódnak a szervi eltérések. A betegek komplex gondozása és kezelése tehát több szakma képviselőjéből álló team megszervezését és együttműködését igényli. A korai diagnózis a beteg életét mentheti meg, a családfa analízis és a családtagok szűrővizsgálata pedig segít a betegséget öröklő de még tünetmentes családtagok felkutatásában és kezelésük időben történő megkezdésében. Központunkban az enzimaktivitás mérésre és a genetikai vizsgálatra is lehetőség van.

A Fabry-kóros betegek kezelése 2003. óta Magyarországon is biztosított rekombináns technológiával előállított α-galakozidáz enzim formájában. Magyarországon a SE II. sz. Gyermekgyógyászati Klinikán is működik Fabry Diagnosztikai és Terápiás Központ; a Szent-Györgyi Albert OGyC Neurológiai osztályán, a PE II. sz. Belgyógyászati Klinikán, a Markusovszky Kórház (Szombathely) Neurológiai osztályán és a Szent Erzsébet Kórház (Sopron) Neurológiai osztályán pedig terápiás központok. Tanszékünkön jelenleg 55 beteget tartunk nyilván (21 férfi és 34 nő). A szakorvosok összehangolt tevékenysége elősegíti a betegek szoros követését, a szervi manifesztációk korai diagnosztizálását, szükség esetén speciális kezelését. Kezelő centrumként rendszeresen részt veszünk két nemzetközi Fabry regiszter munkájában és az adatszolgáltatás révén a betegség

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

- only 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 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)