

Types of genetic injury

I. Mutation of one gene

II. Polygenic diseases

III. Aberration of chromosomes: **numerical:** trisomy,
 structural: deletion, inversion, translocation microdeletion,

IV. Single gene disorders with nonclassic inheritance (mitochondrial DNA, imprinting)

Mutation of one gene

point mutation: *indifferent:* changed triplet codes for the same amino acid
 missense: triplet codes for different amino acid : sickle cell anemia
 nonsense: stop
frameshift: insertion, deletion

trinucleotide repeat : expansion of nucleotide triplet:
 polyglutamin diseases CAG repeat (Huntington)
 not CAG repeat : Fragile X syndrome FMRI gene 200-4000
 repeat of CGG

I. Mutation of one gene:

Mendelian inheritance

Mendelian disorders: single gene defect follows mendelian pattern of inheritance

1. Autosomal dominant
2. Autosomal recessive
3. X linked recessive

Single gene mutation many consequence : **pleiotrophy** :Marphan syndrome



Same genetic trait several genetic loci: **genetic heterogeneity**: retinitis pigmentosa

1. Autosomal dominant disorders:

Characteristics:

- Symptoms expressed in heterozygous state
- One parent of index case is affected, they affect males and females equally and both sex can transmit the disease.
- 50% probability to inherit the disease if one parent is affected
- Enzyme proteins are not affected (generally no symptoms). Mutation of receptor or structural proteins.
- Sometimes same disease is due to a new mutation
- Clinical feature is influenced by variable penetrance and expressivity.
- Sometimes onset is in adulthood (Huntington disease Trinucleotide repeat of huntington gene).
- Dominant negative protein product inhibits the function of the normal protein.
- Receptor protein: LDL receptor: familial hypercholesterinaemia
- Structural protein: collagens: Ehler Danlos collagens, Marfan sy.fibrillin

Autosomal dominant diseases:

Nervous system: Huntington disease (CAG trinucleotide repeat), impairment of basal ganglia;
neurofibromatosis, neurofibromin

Urinary: polycystic kidney disease

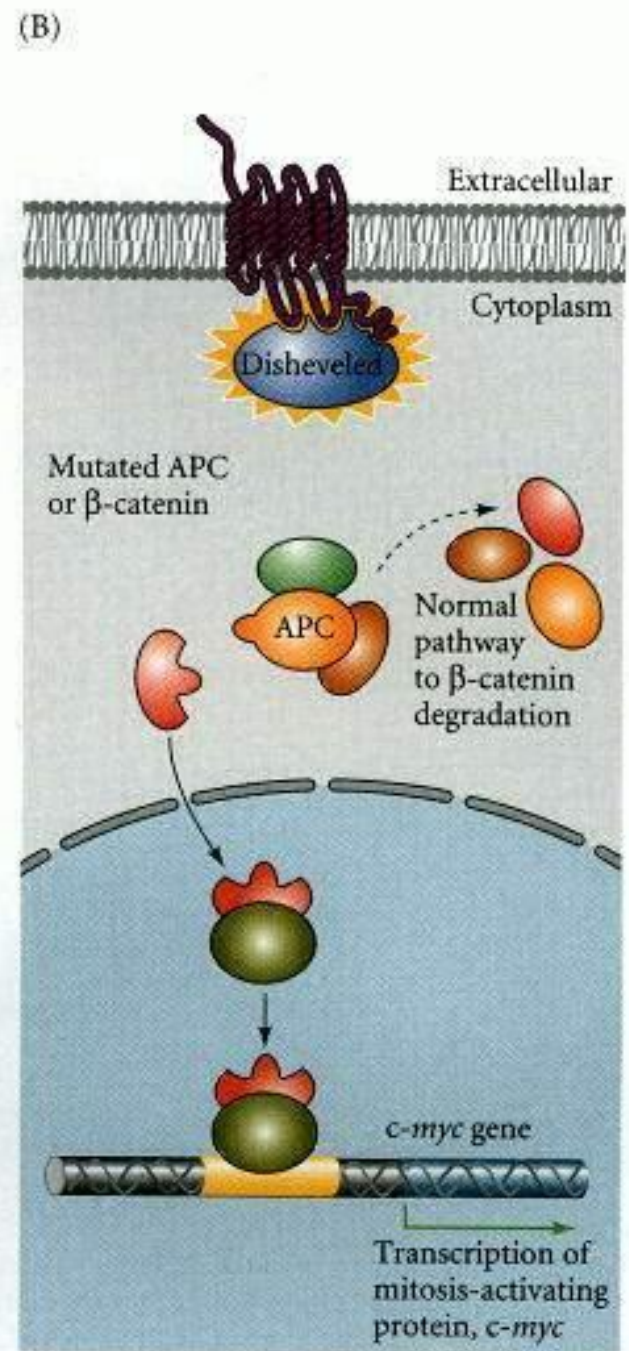
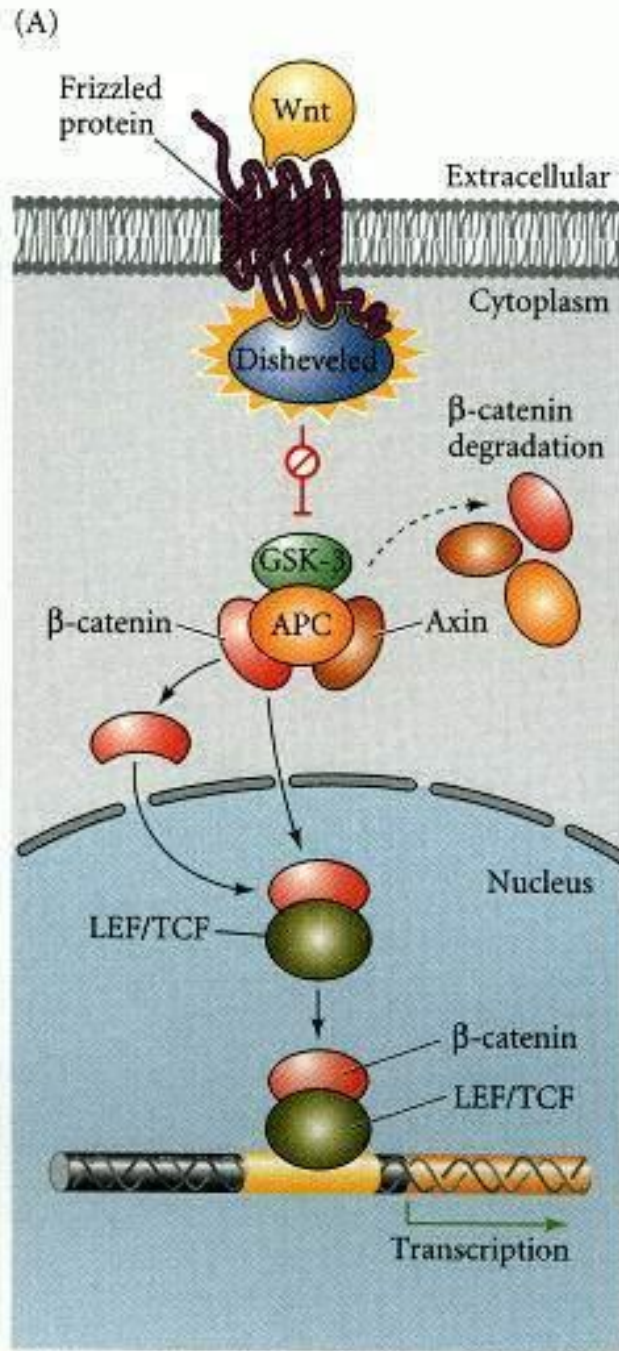
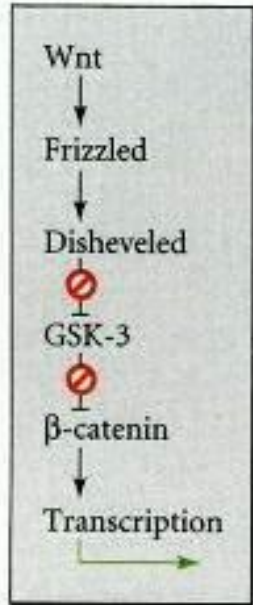
Gastrointestinal: familial polyposis APC gene mutation **Peutz Jeghers syndrome**

Hematopoietic: von Willebrand disease
hereditary spherocytosis

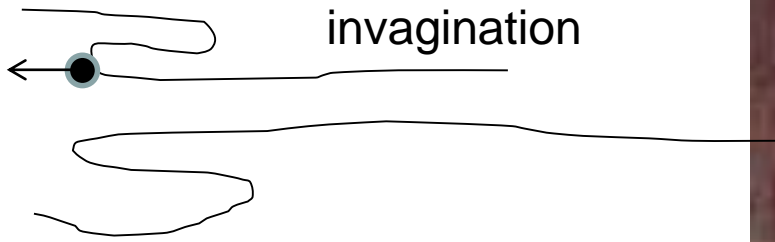
Skeletal: **Marfan syndrome:** fibrillin mutation (protein of elastic fibers)
tall stature- long fingers, subluxation of lens, aortic aneurysm
floppy valves, aortic dissection

Ehlers-Danlos: defect of collagen synthesis (6 variants)
fragile hyperextensible skin, hypermobile joints, rupture of internal organs. Wound healing is poor.

Metabolic: **Familial hypercholesterolemia:** mutation of LDL receptor
hypercholesterolemia, increased risk of arteriosclerosis, coronary artery disease, xanthomas



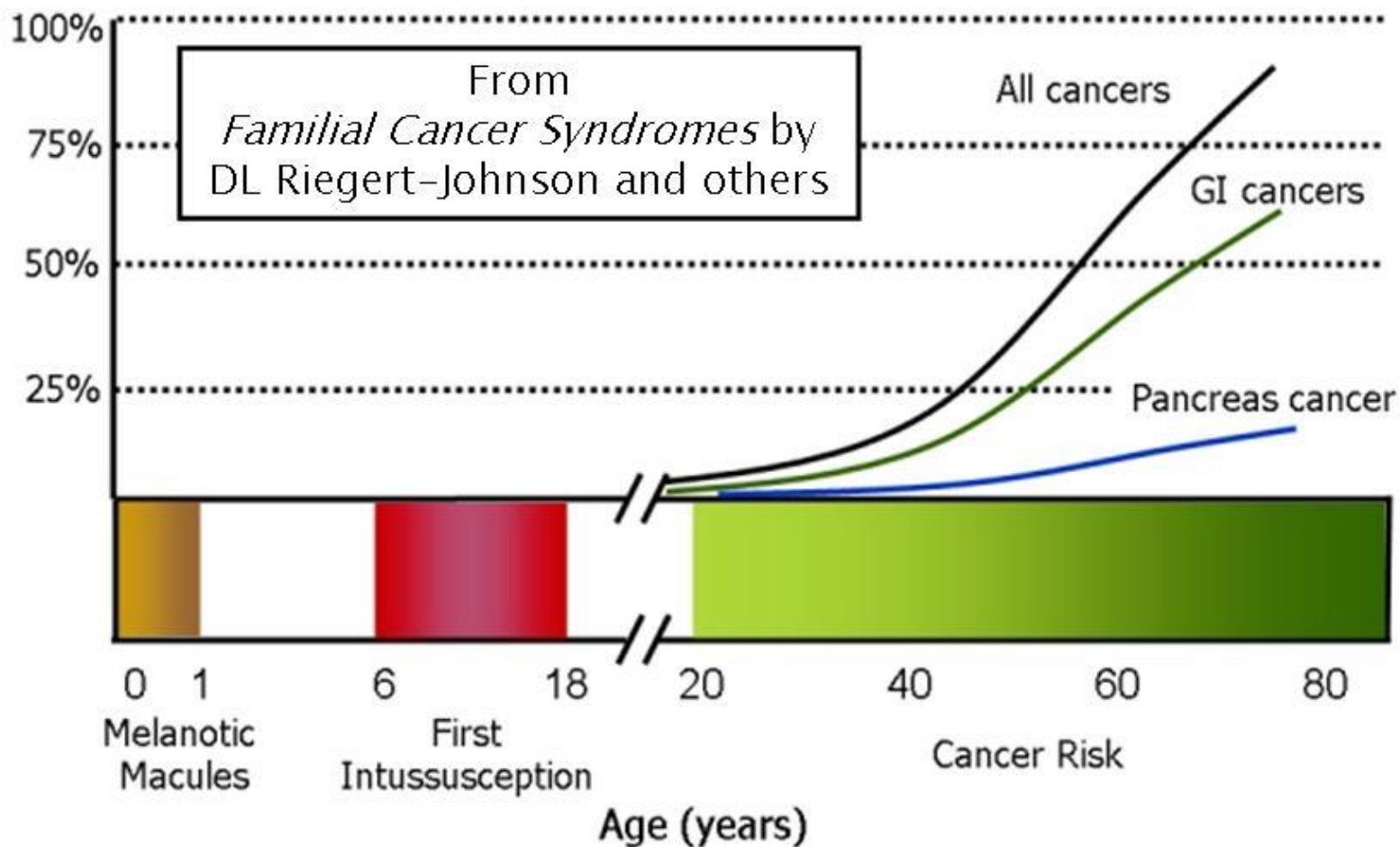
Peutz –Jegher syndrome



Serine/threonine kinase 11 (STK11)

Natural History of Peutz-Jeghers Syndrome

Cumulative Cancer Risk



Pectus excavatum



arachnodactyly

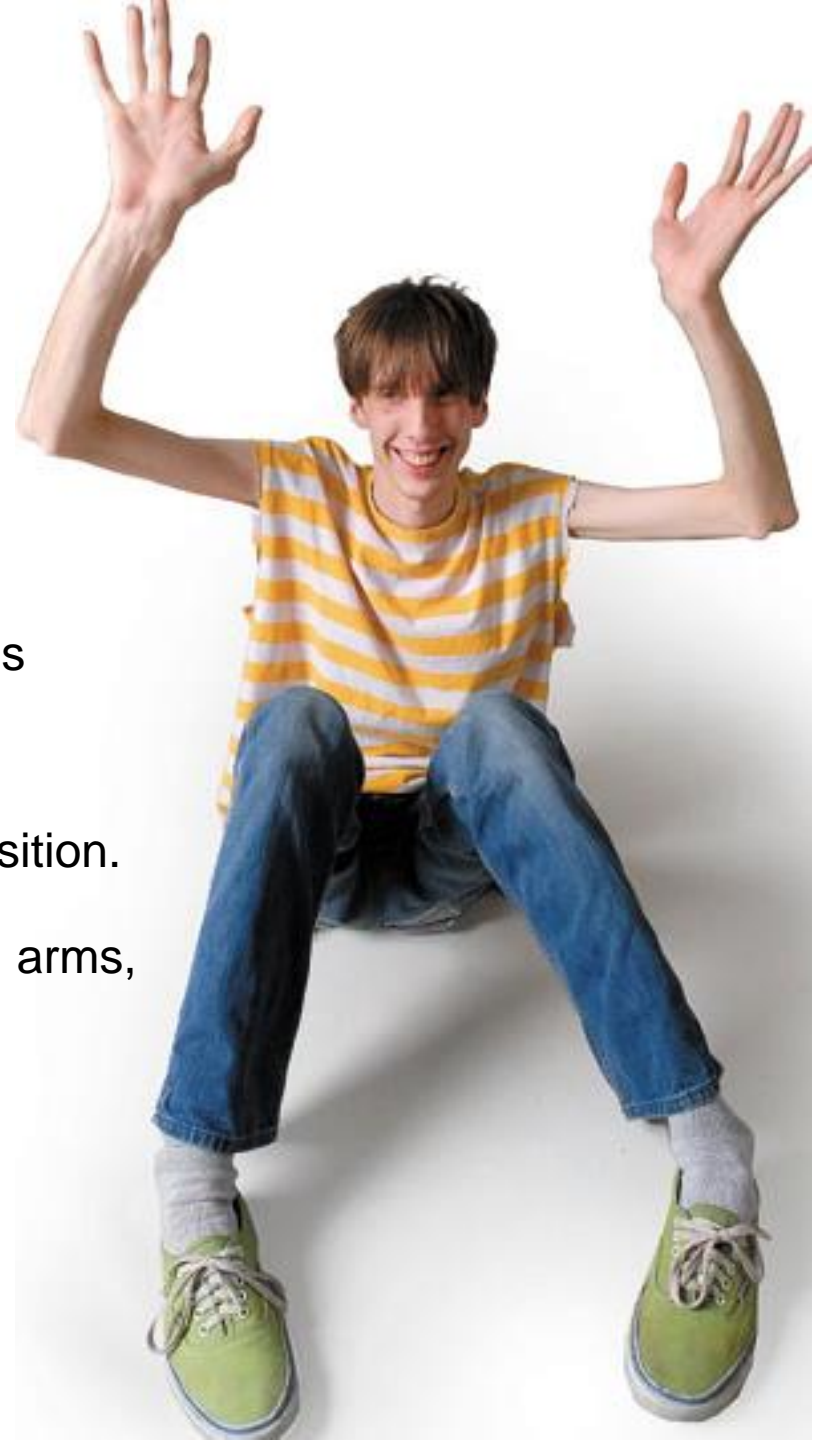


Dilation of aorta



Floppy valves

ADAM.



Fibrillin provide a structure to elastine deposition.

Skeleton: Slender elongated habitus, long legs, arms, long fingers. High, arched palate, Hyperextendibility of joints

Eyes: bilateral dislocation of lens

Cardiovasc: aorta aneurysms, aorta dissection

Dilatation of valves

Ehler-Danlos syndrome



Ehler-Danlos syndrome autosomal dominant or recessive

Defect of collagen synthesis or structure – 30 distinct collagen genes

There are 6 genetic and clinical variants.

Some clinical features are common: skins are hyperextensible, fragile, vulnerable
joints are hypermobile-grotesque contortions
serious internal complications: rupture of colon
diaphragmatic hernia
ocular fragility, rupture of cornea, retinal detachment
Poor wound healing

Types: deficiency of collagen type III synthesis mutation of COL3A1 weakness tissues
collagen type I " " COL1A1
lysyl hydroxylase defect of collagen crosslinking /kyphoscoliosis



Familial hypercholesterinaemia frequency 1:500

Mutation of LDL receptor – most present in the liver

LDL receptor is implicated in the uptake of circulating LDL and IDL.
Mutation of receptor results in increased serum cholesterol level.

In this case circulating acetylated and oxidized LDL binds to scavenger receptors of macrophages. These macrophages are directly related to the development of arteriosclerotic plaques.

LDL receptor mutation heterozygotes 2-3 times increased LDL level

homozygotes 5x

„ xantogranulomas of skin
dies in 15 years .AMI

Types of mutation: Class I: no receptor synthesis

Class II. transport from ER to Golgi is impaired

Class III receptor does not bind LDL

Class IV receptor fails to internalize

Class V receptor-LDL complex can not dissociate, LDL traps in the endosomes.

No LDL receptor LDL is taken up by scavenger receptors- deposition in blood vessels

2.

Autosomal recessive disorders

Characteristic

Both alleles have to be impaired

The trait does not necessarily affect the parents, but sibling may show the disease

Recurrence risk 25% (1 sibling from four)

The expression of the defect is more uniform than in autosomal dominant disorders

Complete penetrance is common

Onset is frequently early

New mutation is rare. Disease may not show up for several generations.

(two heterozygous persons have to marry).

Enzyme proteins are frequently affected

Autosomal recessive disorders

Metabolic

Cystic fibrosis ion transport impaired (chloride ion) 1:2500

mutation in the gene: *cystic fibrosis transmembrane conductance regulator*
Impaired chloride transport resulting in the decreased transport of Na and H₂O- dehydration of mucus –bronchitis-bronchiectasia, pancreatitis, meconium ileus

Phenylketonuria: phenylalanin hydroxylase deficiency 1:12000

hyperphenylalaninaemia-phenylketonuria :hypopigmentation, mental retardation.

Galactosemia: galactose 1 phosphate uridylyltransferase mutation

accumulation of galactose 1-phosphate and its metabolites

vomiting, diarrhea, jaundice, liver injury, cirrhosis, cataracta, impairment of aminoacid transport. Early diagnosis!!!

Lysosomal storage diseases

Glycogen storage diseases

Wilson disease, Hemochromatosis

Hemopoetic

sickle cell anaemia, thalassemia

Skeletal:

Ehler Danlos , Alkaptonuria

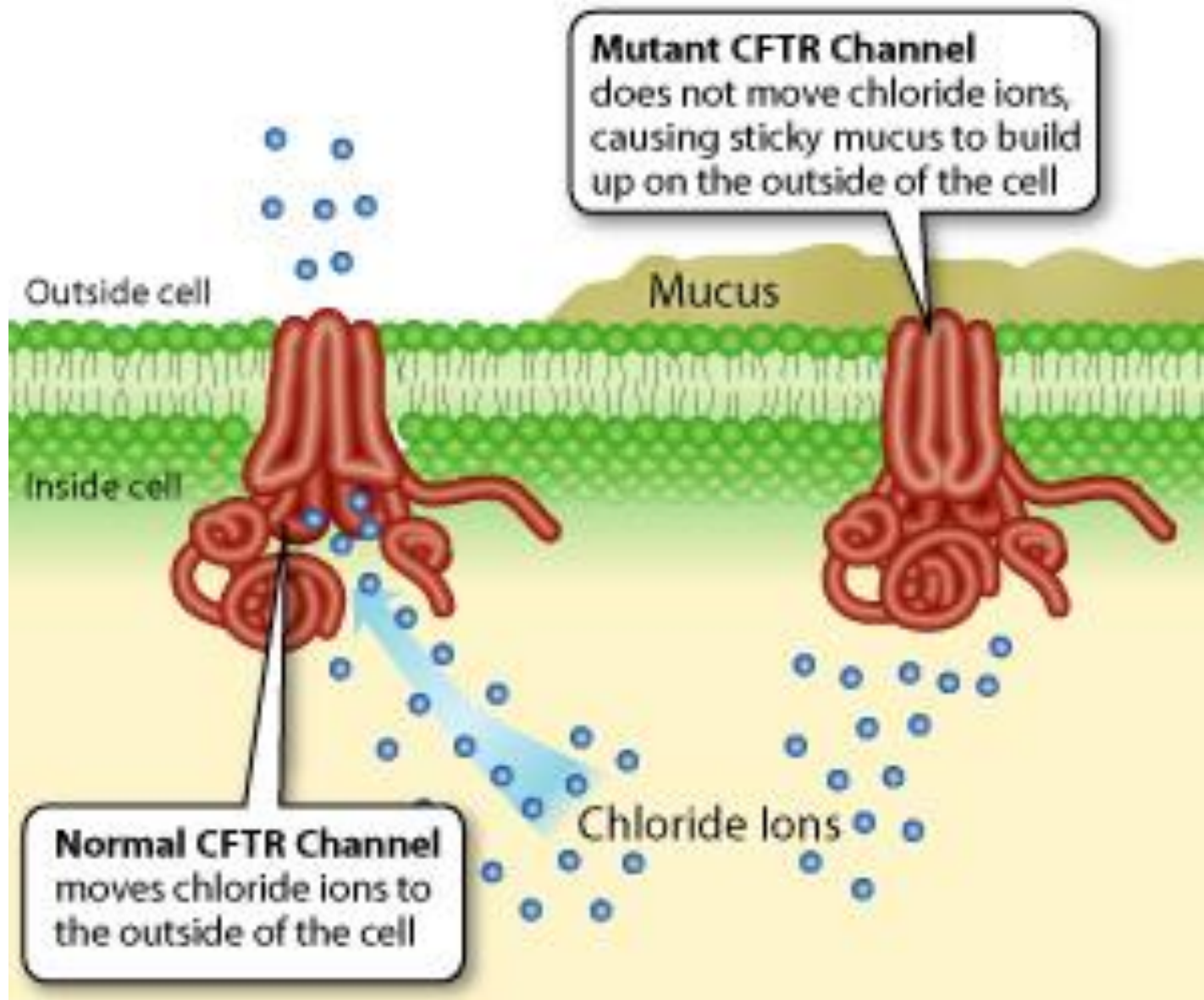
Endocrine: Congenital adrenal hyperplasia (21 hydroxylase deficiency)

Nervous atrophies: Neurogenic muscular atrophy:

Friedreich ataxia GAA trinucleotide repeat >30 impairment of sensory neurons, directing the movement of arms and legs.

Spinal muscular atrophy –motoneurons (first proximal and lung)





Mutant CFTR Channel
does not move chloride ions,
causing sticky mucus to build
up on the outside of the cell

Normal CFTR Channel
moves chloride ions to
the outside of the cell

Chloride ions

A Organs affected by cystic fibrosis

Sinuses:

sinusitis (infection)

Lungs: thick, sticky mucus buildup, bacterial infection, and widened airways

Skin: sweat glands produce salty sweat.

Liver: blocked biliary ducts

Pancreas: blocked pancreatic ducts

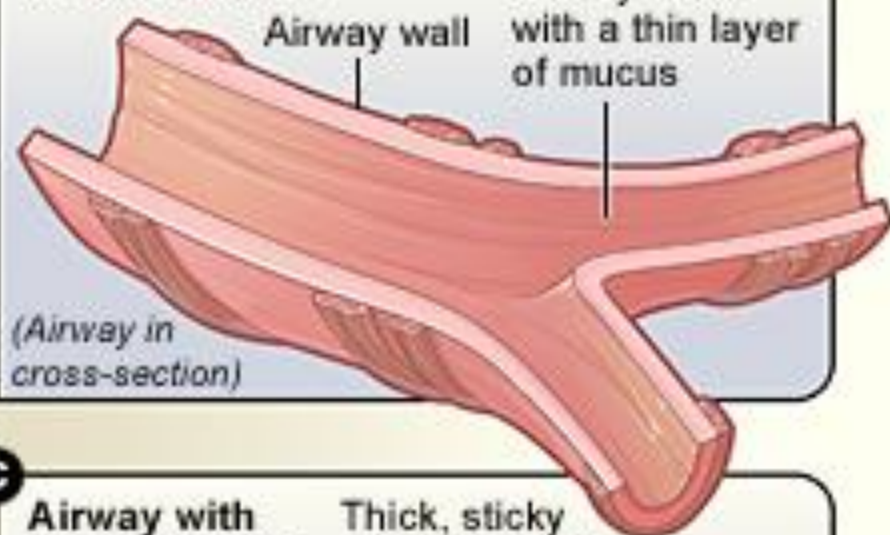
Intestines: cannot fully absorb nutrients

Reproductive organs: (male and female) complications



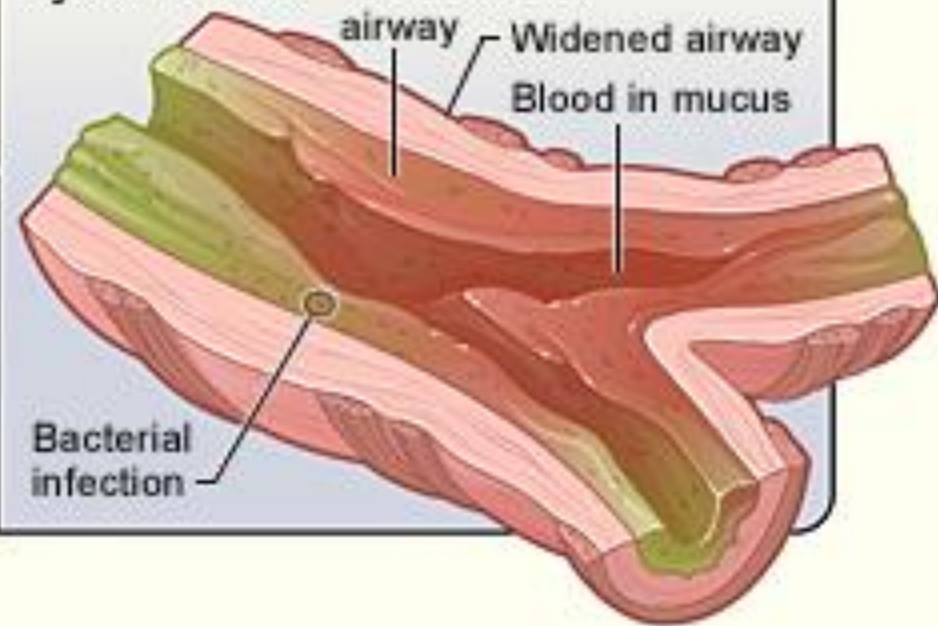
B

Normal airway



C

Airway with cystic fibrosis



Lysosomal storage diseases:

affects infants and children

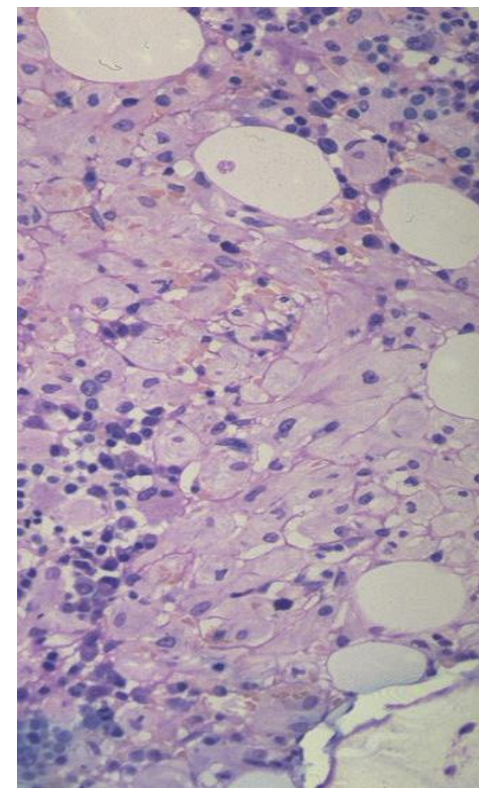
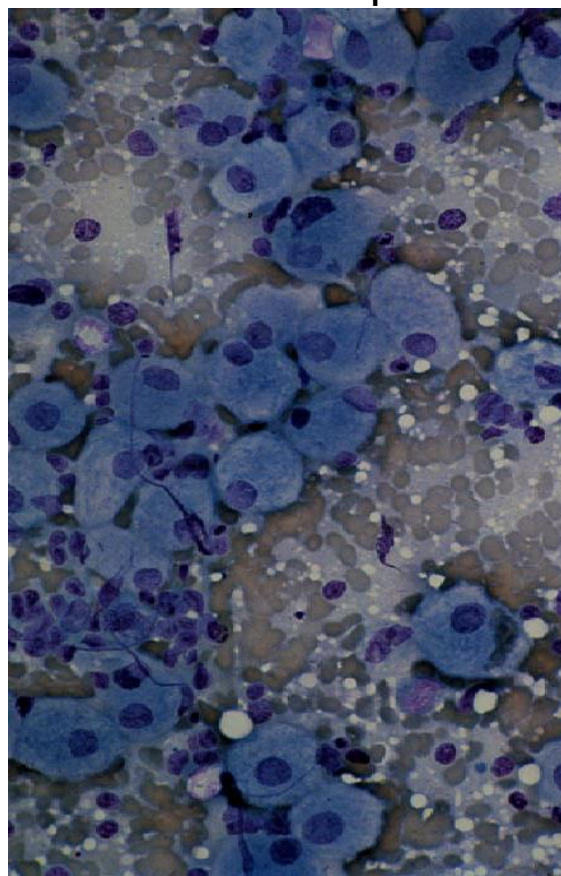
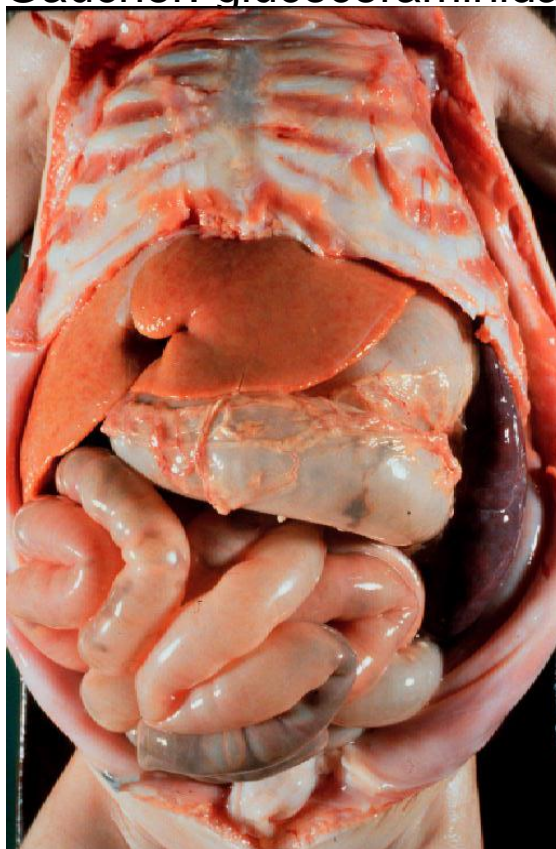
storage of insoluble intermediates in the monocyte-macrophage system

hepatosplenomegaly, mental retardation,

Lipid metabolism:

Impaired degradation of lipids of cell membranes

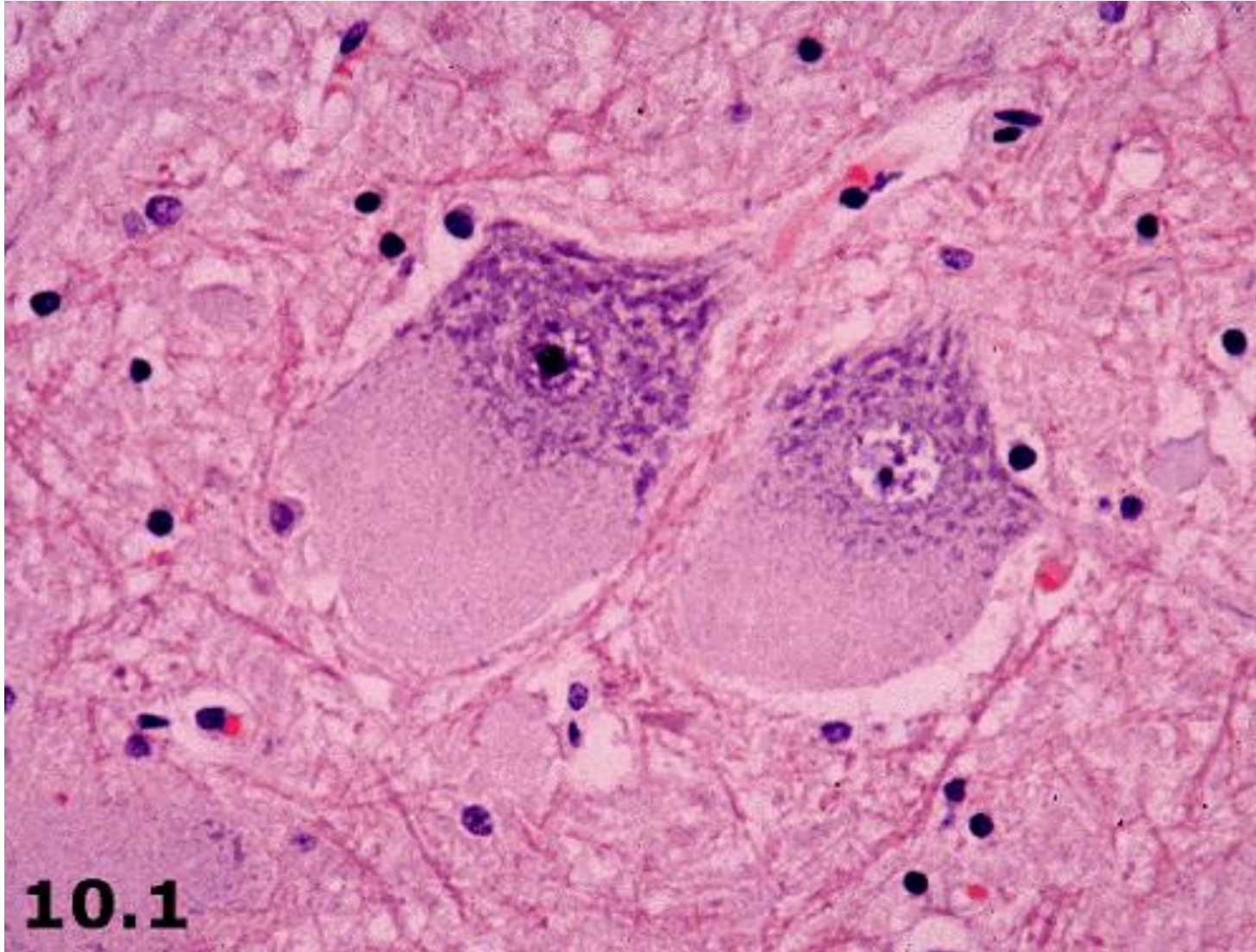
Gaucher: glucocereaminidase: accumulation of lipid in the macrophages No CNS



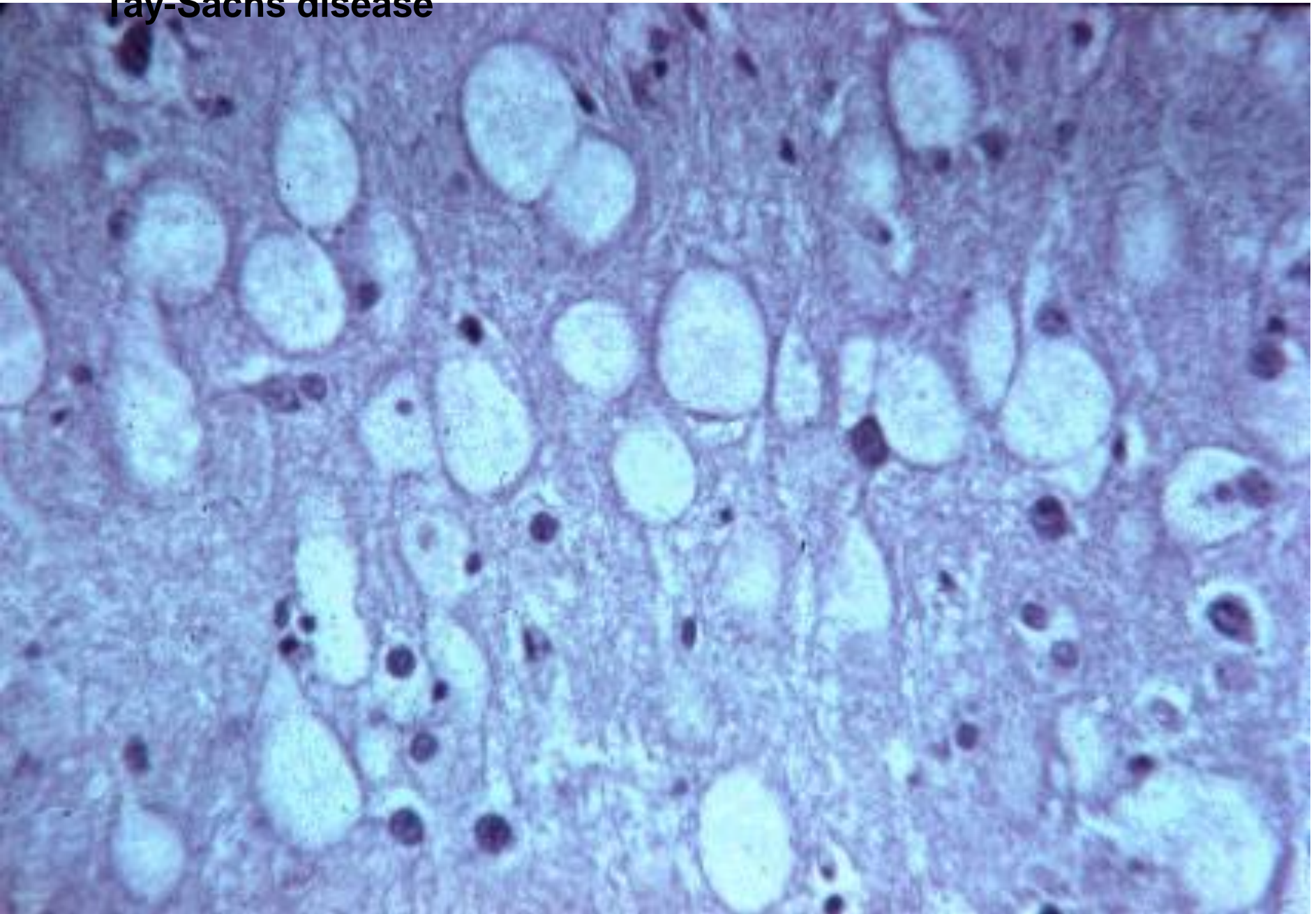
Gaucher disease- glucocereaminidase defficiency

Tay-Sachs disease

Tay –Sachs: mainly CNS: hexosaminidase deficiency, GM2 ganglioside storage. Mental retardation, blindness, convulsion, motor weakness, death.



Tay-Sachs disease



Tay-Sachs disease

Tay –Sachs: mainly CNS: hexosaminidase deficiency, GM2 ganglioside storage

Mental retardation, blindness, convulsion, motor weakness, death.

Tonic phase

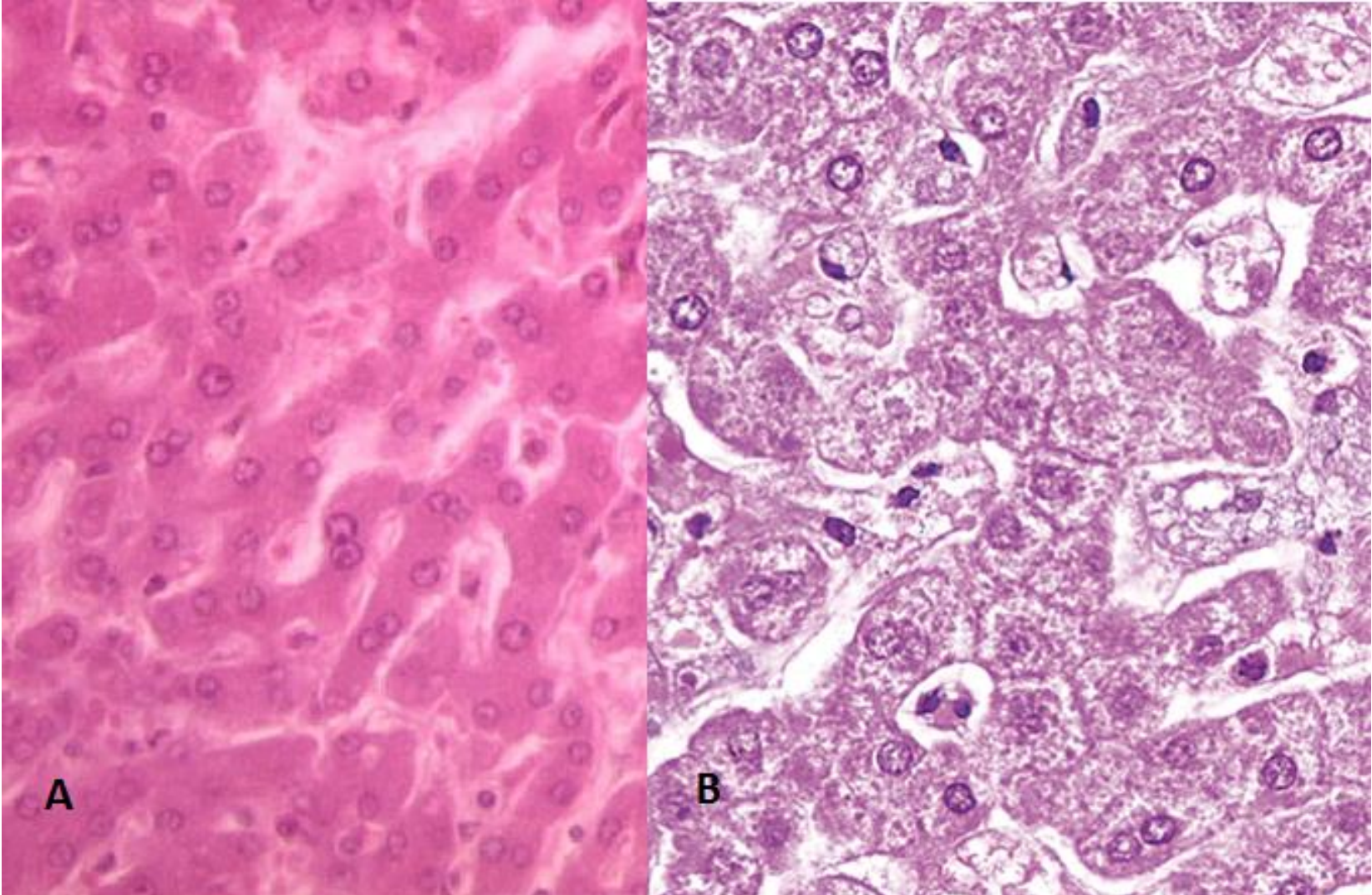


Clonic phase



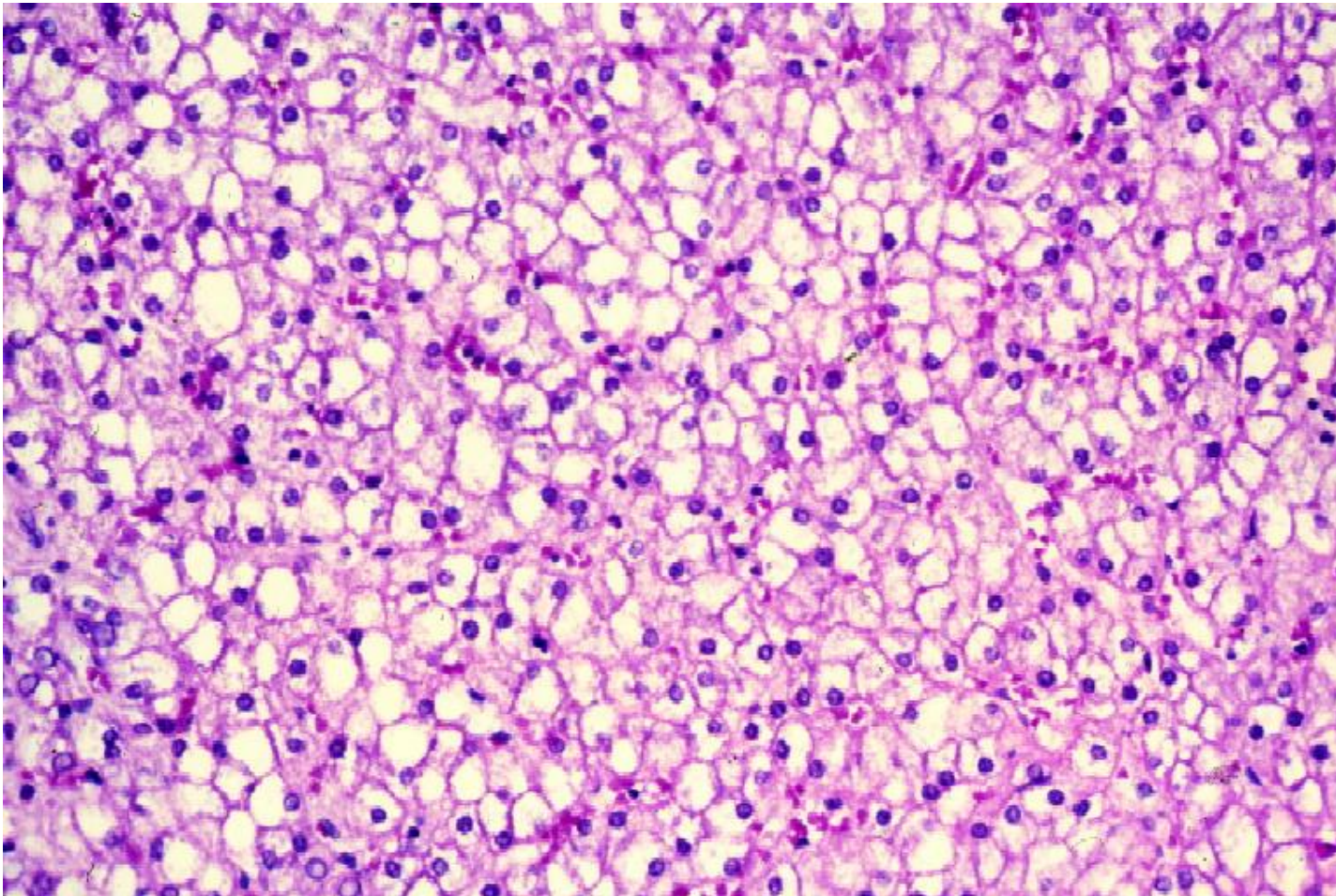
Nieman-Pick

Nieman-Pick: sphingomyelinase deficiency, sphingomyelin storage
Hepatosplenomegaly, mental retardation, seizures, ataxia, dysarthria



Glycosaminoglycans:

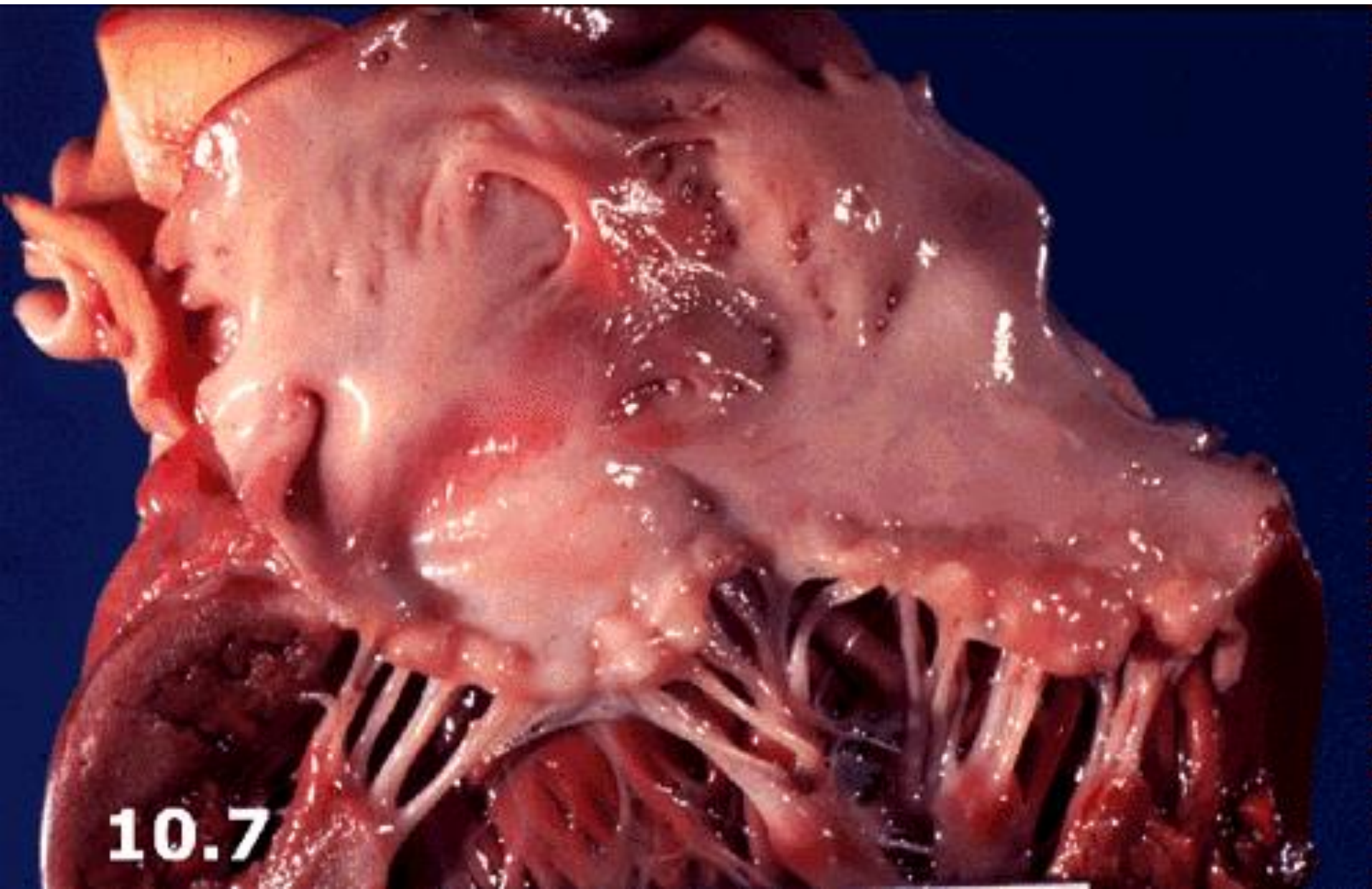
Deposition of heparan and dermatan sulfate in liver, spleen, heart, blood vessels, brain, valves of the heart. . Coarse face gargoylism, skeletal deformities, mental retardation, clouding of cornea





10.6





10.7

mucopolysaccharidosis

Glycogen storage diseases

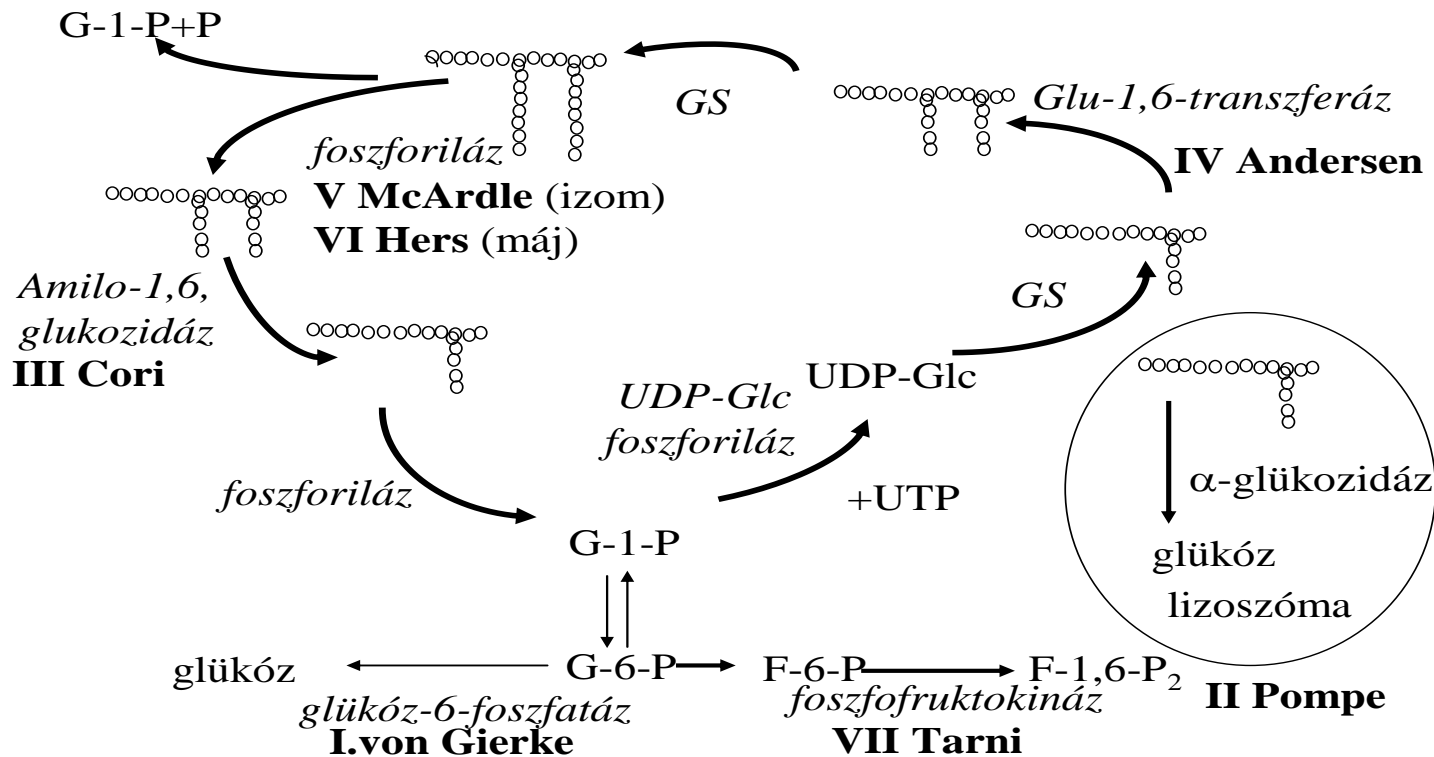
Hepatic type: von Gierke disease-
glucose-6 phosphatase deficiency

Myopathic type: type V

Muscle cramps, weakness myoglobinury

Type II: Pompe: lysosome storage disease
deposition in cardiac muscle

Glikogén tárolás



Wilson disease copper storage : 1:200 deposition of copper in liver-cirrhosis, brain,

Kaiser Fleisher ring., CNS basal ganglia

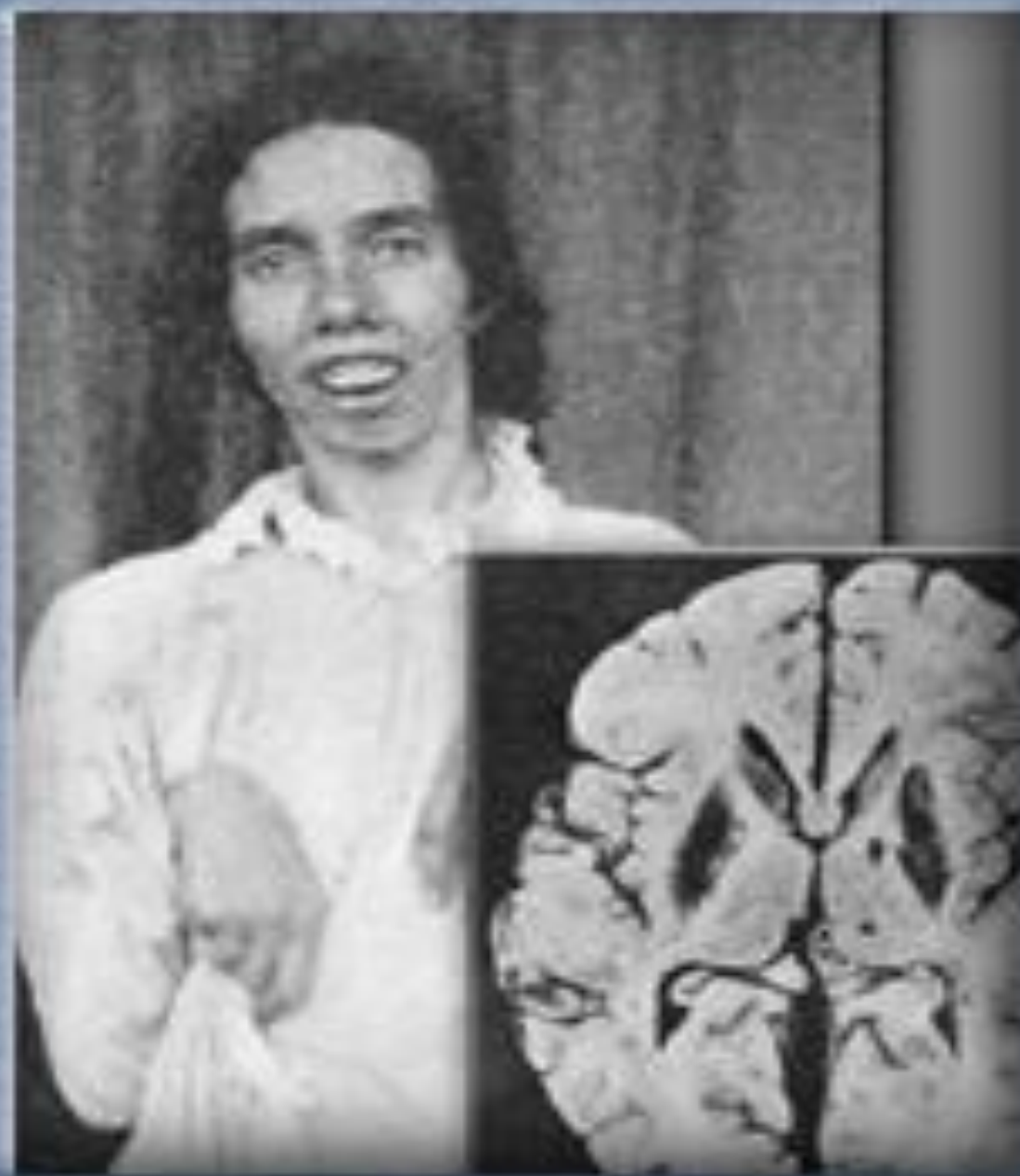
Liver: necrosis, inflammation cirrhosis, neuropsychiatric problems, increased rigidity, ataxia, dystonia

ATP7B insufficiency.

Kayser-Fleischer Ring

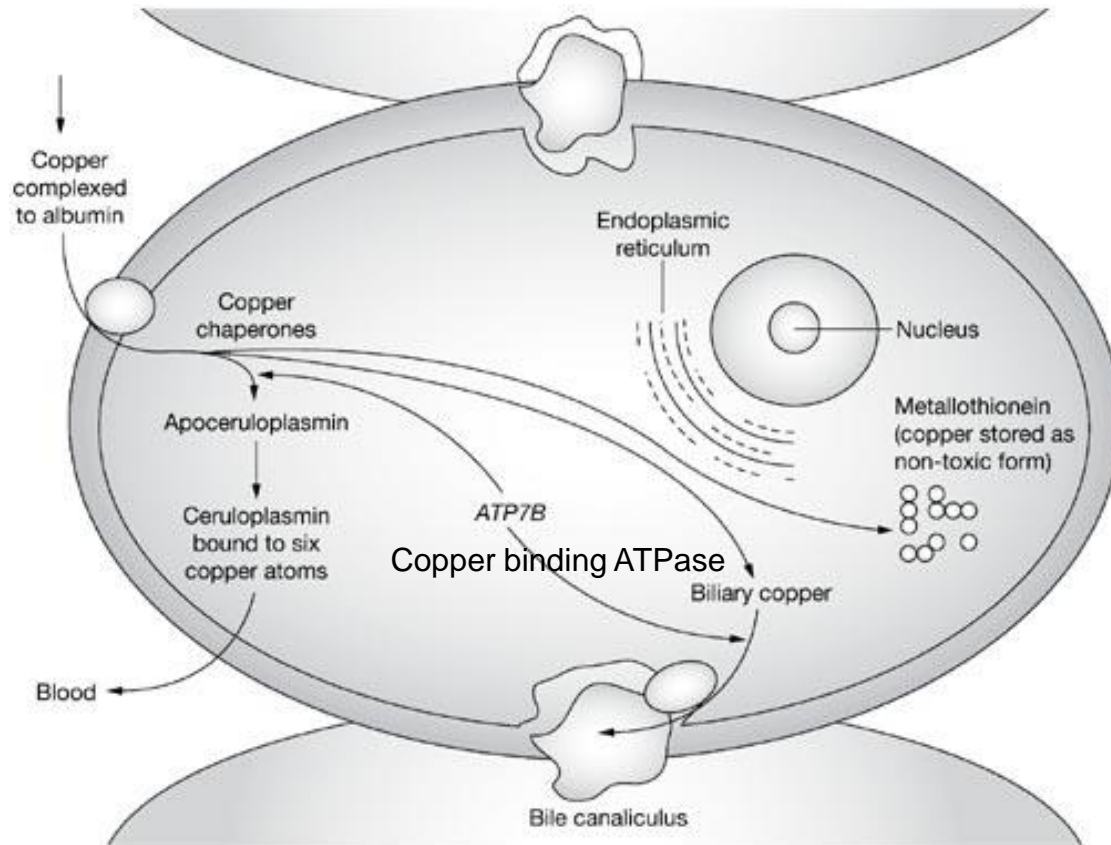


Low level of ceruloplasmin
in the blood



[Click to enlarge](#)

Figure 1 Schematic representation of copper metabolism within a liver cell

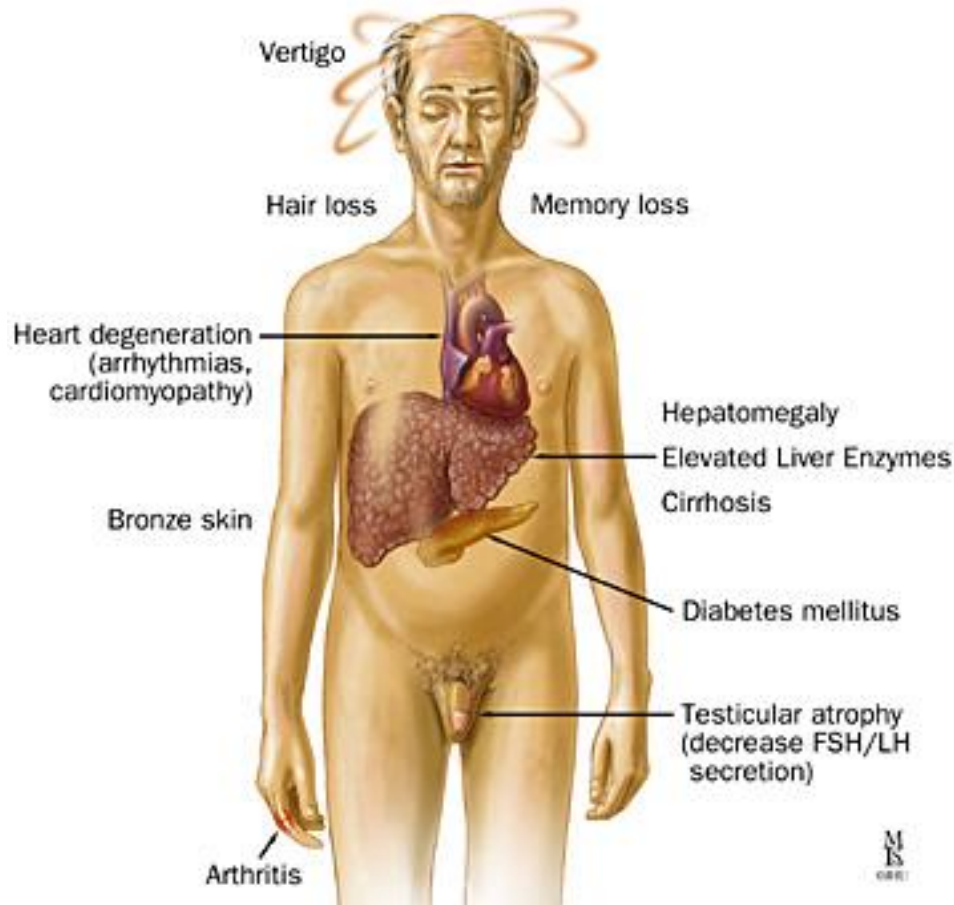


Das SK and Ray K (2006) Wilson's disease: an update
Nat Clin Pract Neurol 2: 482–493 10.1038/ncpneuro0291

Hemochromatosis : broze diabetes :HFE gene mutation- iron absorption is not regulated. Hepcidin.

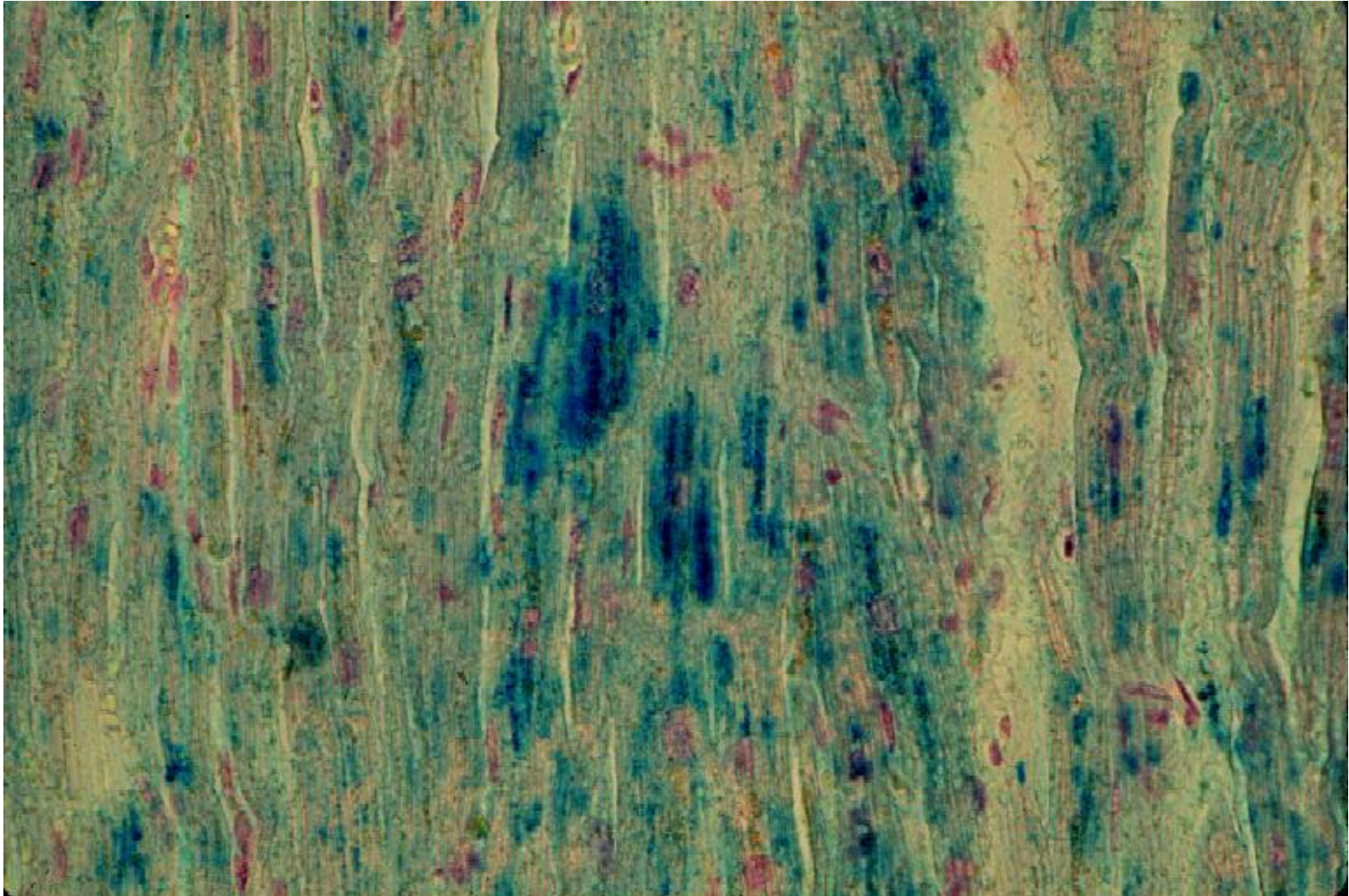
1:300 frequency

Iron deposition in skin, pancreas, liver, heart

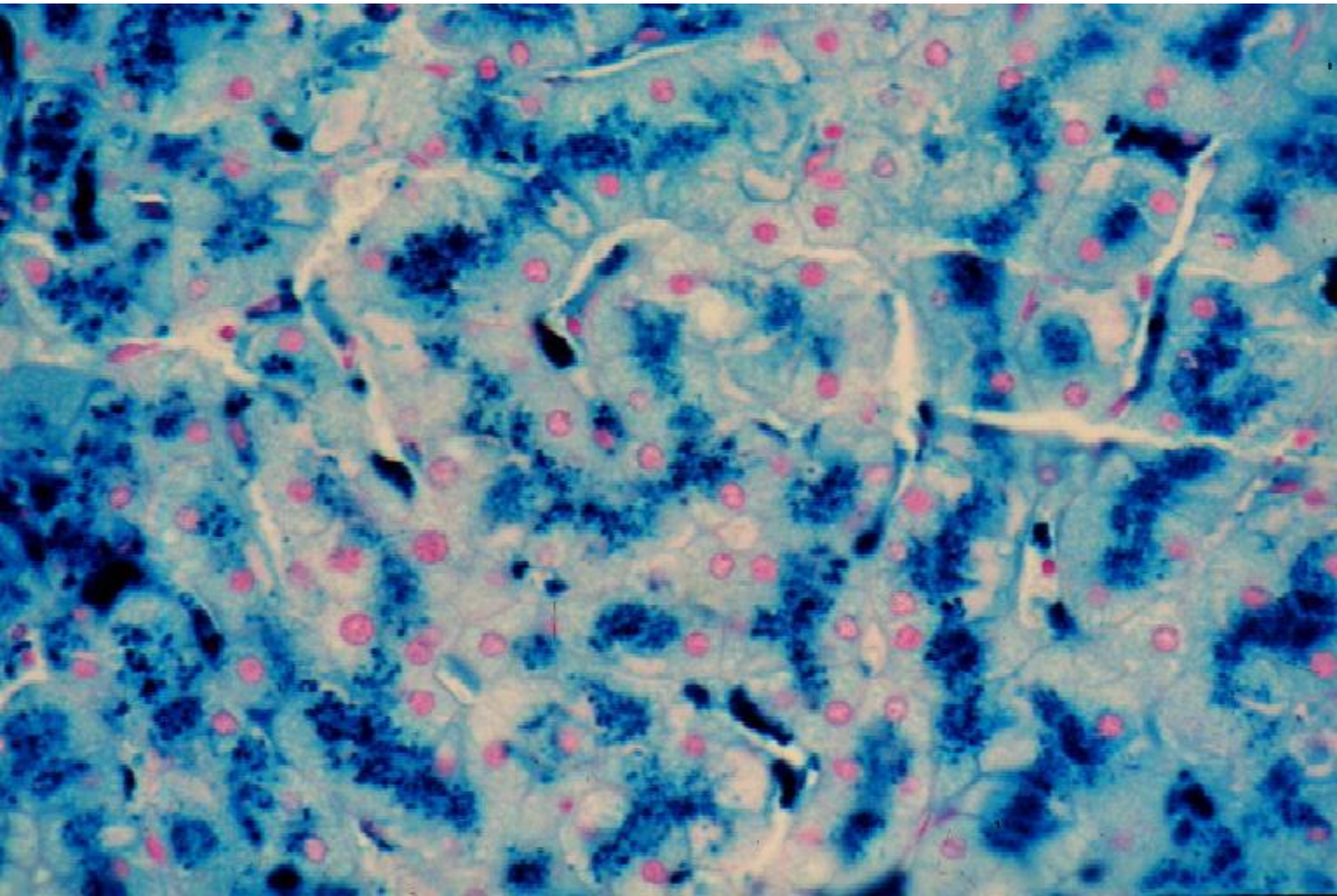


Symptoms and signs of hemochromatosis.

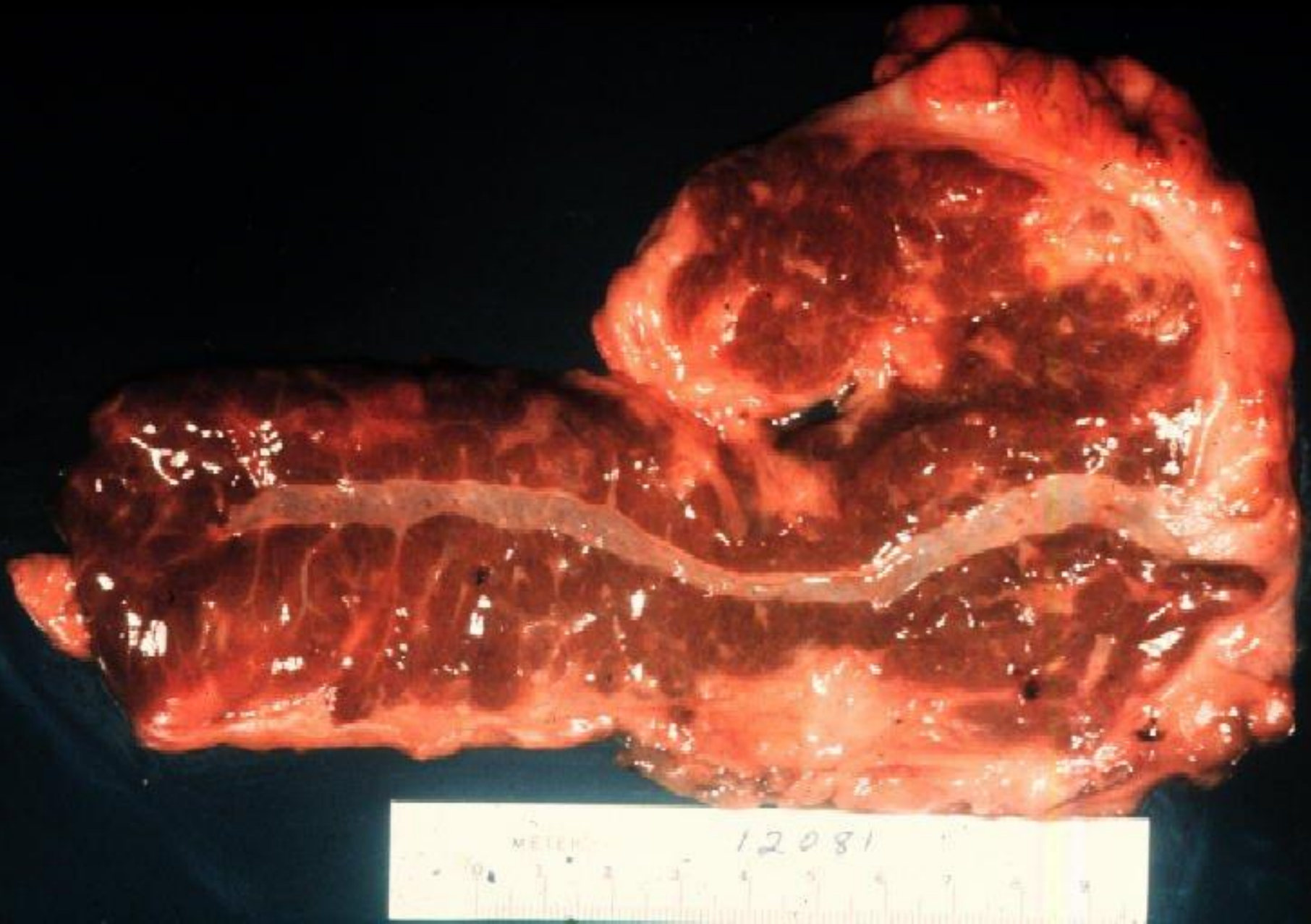
Haemochromatosis in the heart



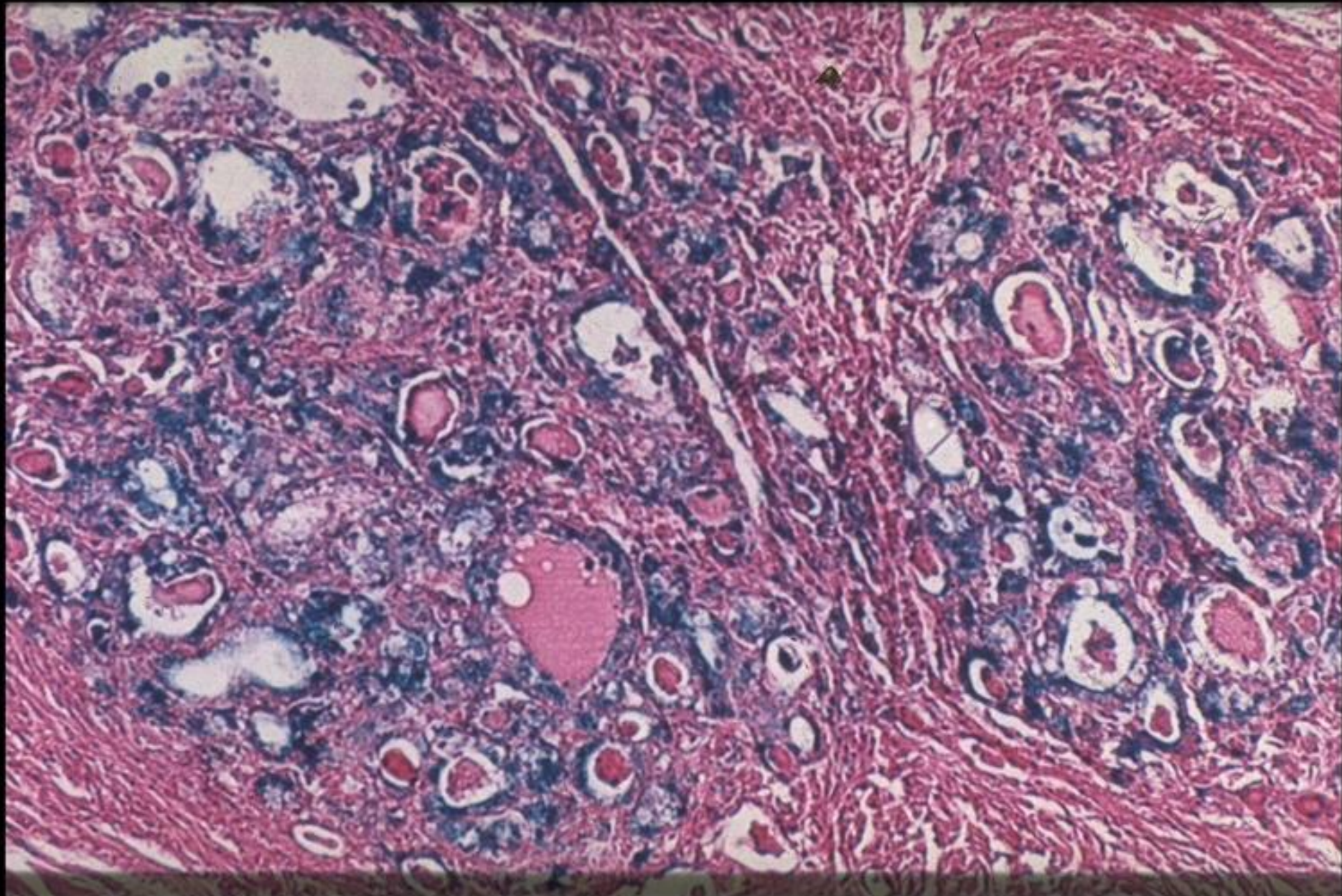
Haemochromatosis a májban



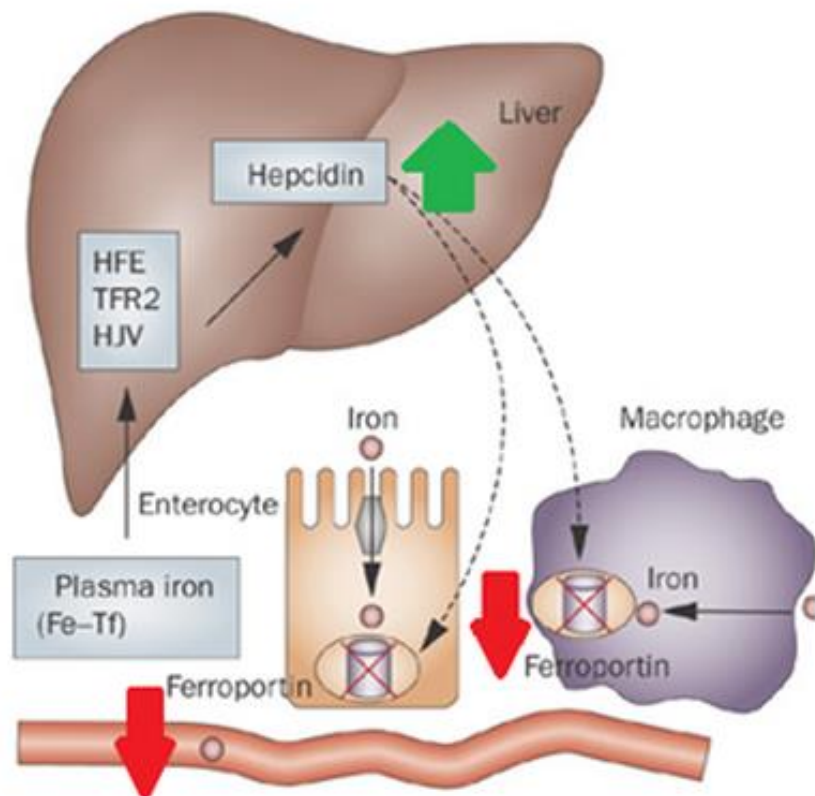
Haemochromatosis pancreas



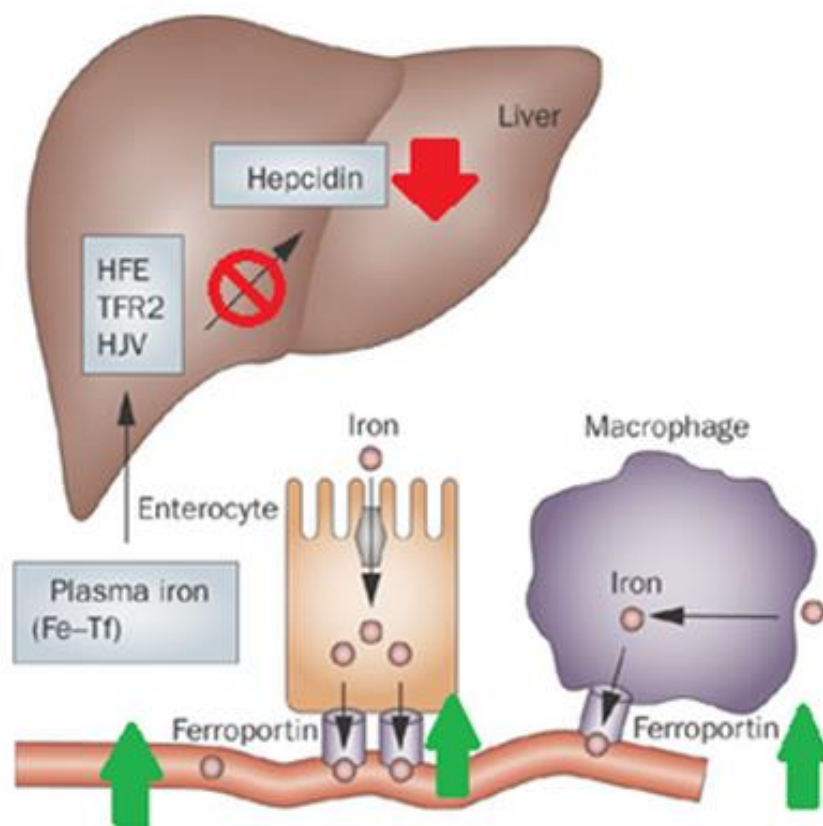
Haemochromatosis a pancreasban



Normal



Hereditary Hemochromatosis



3. X-linked disorders

Characteristic features

Heterozygous female carrier transmit to her sons

Female do not express the phenotype

Affected male do not transmit the disease to males, daughter will be carrier

Diseases:

Musculoskeletal: **Duchenne dystrophy**- dystrophin gene

Blood: **Hemophilia A, B**

Immune: agammaglobulinaemia

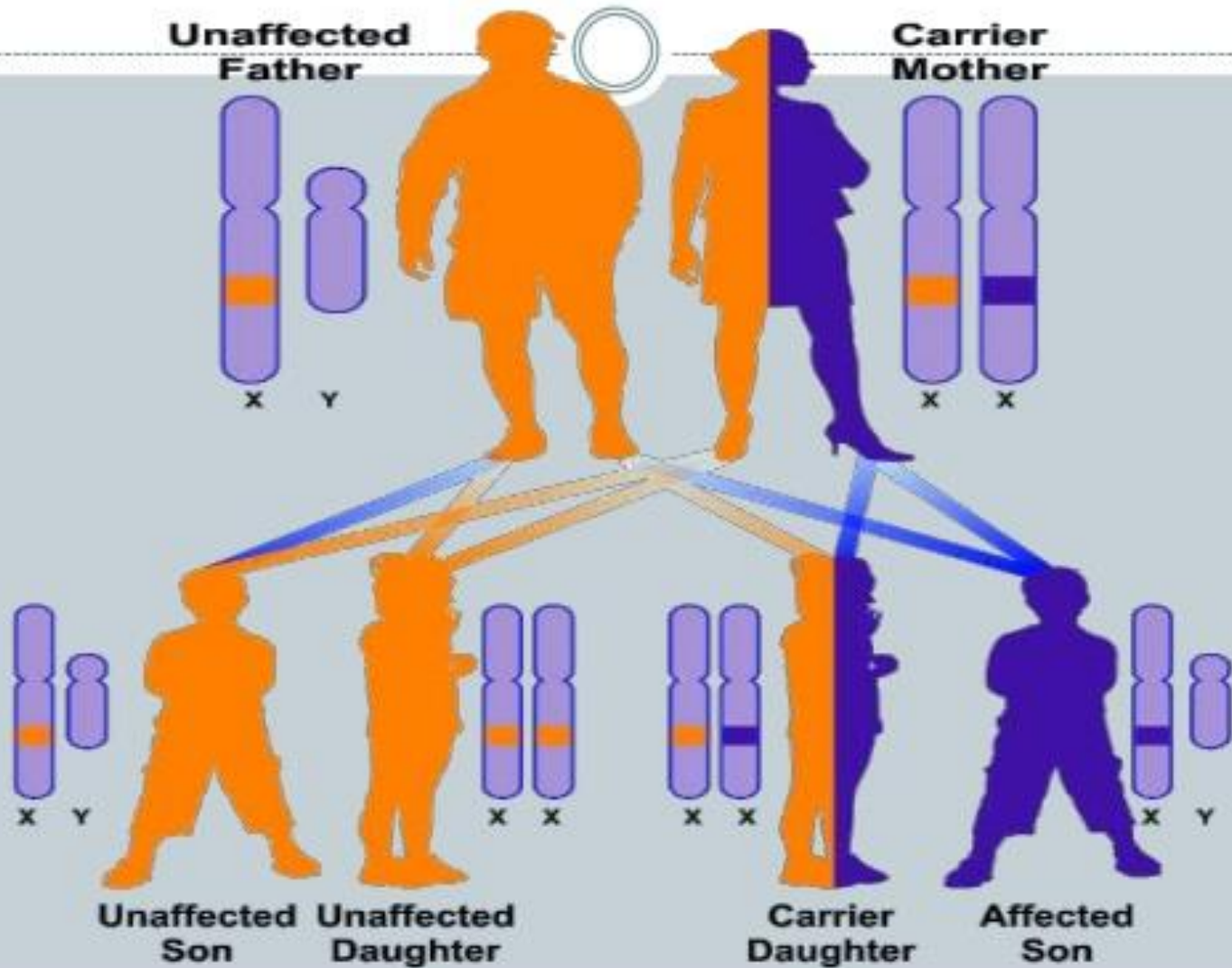
X linked severe combined immunodeficiency

Metabolic: Diabetes insipidus

Lesh Nyhan syndrome hyperuricemia, hyperuricuria, gout, mental retardation, self mutilation (lip and finger biting)

Hypoxanthine-guanine phosphoribosyltransferase

X-linked Recessive, Carrier Mother





Duchenne muscular dystrophy (DMD) 1:3500

3/1

Most common dystrophy

Clinically evident by age 5

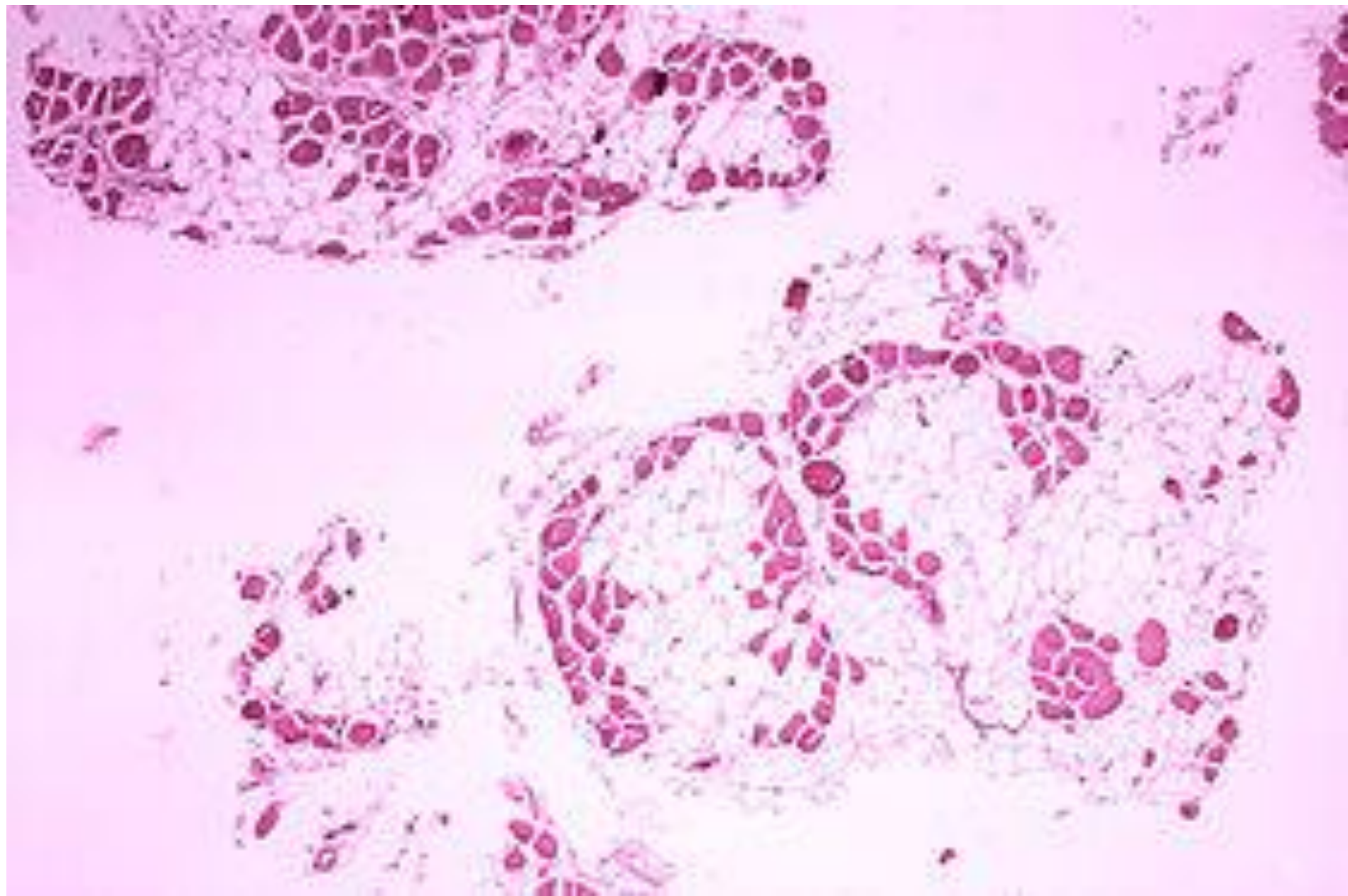
Progressive weakness- wheelchair by age 12
death by age 20

Morphology: marked variation of muscle fiber size
hypertrophy and atrophy of myofibers
degenerative changes-fiber splitting, necrosis

End stage : extensive myofiber loss, adipose infiltrate

Pathomechanisms: deletion of portions of dystrophin gene (Xp21)
dystrophin attaches sarcomere to cell membrane,
maintain structural integrity of muscle cells
Tissue muscle, brain, peripheral nerves

Clinical symptoms: normal birth
delayed walking, weakness starting at pelvic muscles, progress
to shoulders, pseudohypertrophy of calfs (musculus
gastrocnemius), heart failure and arrhythmias may occur.
death? Respiratory insuff. Pulm.infection-



Duchenne dystrophy

3/2

Disorders of clotting factors

Hemophilia A,B

Bleeding after minute injury

Factor VIII is a complex:

FVIII coagulation molecule

von Willebrandt factor

ristocetin cofactor

Hemophilia A: deficiency of FVIII cogulant molecule

X linked recessive trait 75%

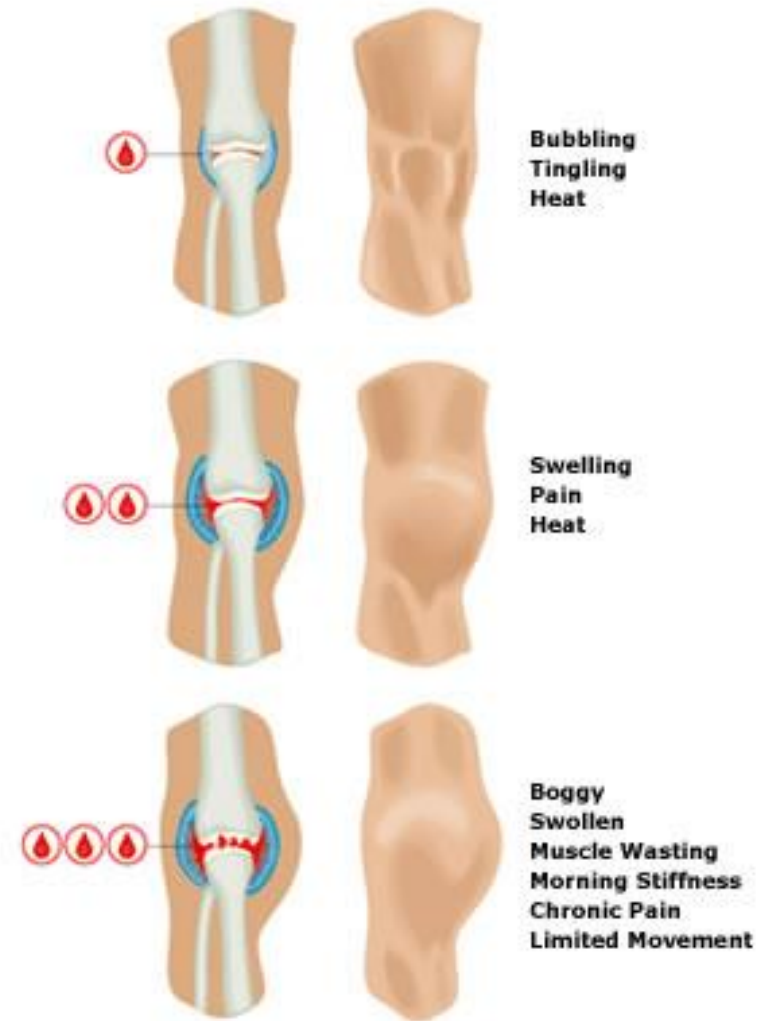
spontan mutation 25%

common in males

Spontaneous bleeding-joints-hemarthros,
joint deformities

Hemophilia B: factor IX deficiency

sex linked, similar to hemophilia A.



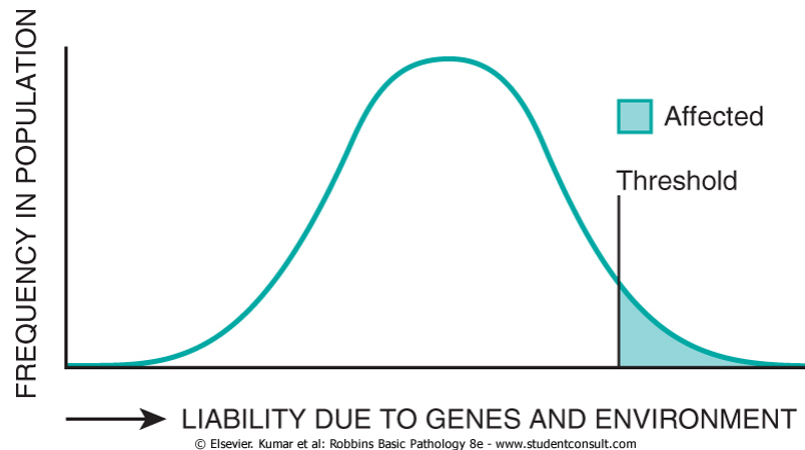


II. Polygenic diseases

Polygenic (Multifactorial) Inheritance

- ❖ More common than monogenic disorders
 - ❖ Abnormalities of complex processes regulated by the protein products of two or more genes
 - ❖ Environmental factors also play an important role in the modulation of the genetic defects
 - 'Normal traits' - height, eye color, intelligence
 - Diabetes mellitus, hypertension, ischemic heart disease, gout, schizophrenia, bipolar disorder, neural tube defects, dwarfism, cleft lip/palate, periodontal disease and some cancers
 - ❖ Risk of occurrence of disease is higher in first-degree relatives and in subsequent pregnancies

II Disorders with multifactorial inheritance (polygenia)



The risk of disease is related the number of affected genes

The risk is higher in children whose both parents are affected

Rate of recurrence is 2-7%

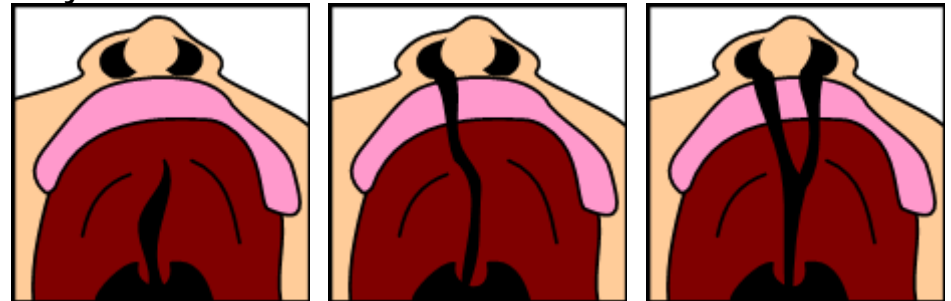
Next child =%

Identical twins: less than 100% (20-40%)

Disorders: Diabetes mellitus, Hypertension, Gout, schizophrenia

Cleft palate

Cleft lip and palate, which can also occur together as **cleft lip and palate**, are variations of a type of clefting congenital deformity caused by abnormal facial development during gestation.. A cleft is a fissure or opening—a gap. It is the non-fusion of the body's natural structures that form before birth. Approximately 1 in 700 children born have a cleft lip and/or a cleft palate. In decades past, the condition was sometimes referred to as **harelip**, based on the similarity to the cleft in the lip of a hare, but that term is now generally considered to be offensive.



ERBB2, CDH2 and IRF6, FGFR
collagen11, glypican3, FGFR2
Sonic hedgehog, etc

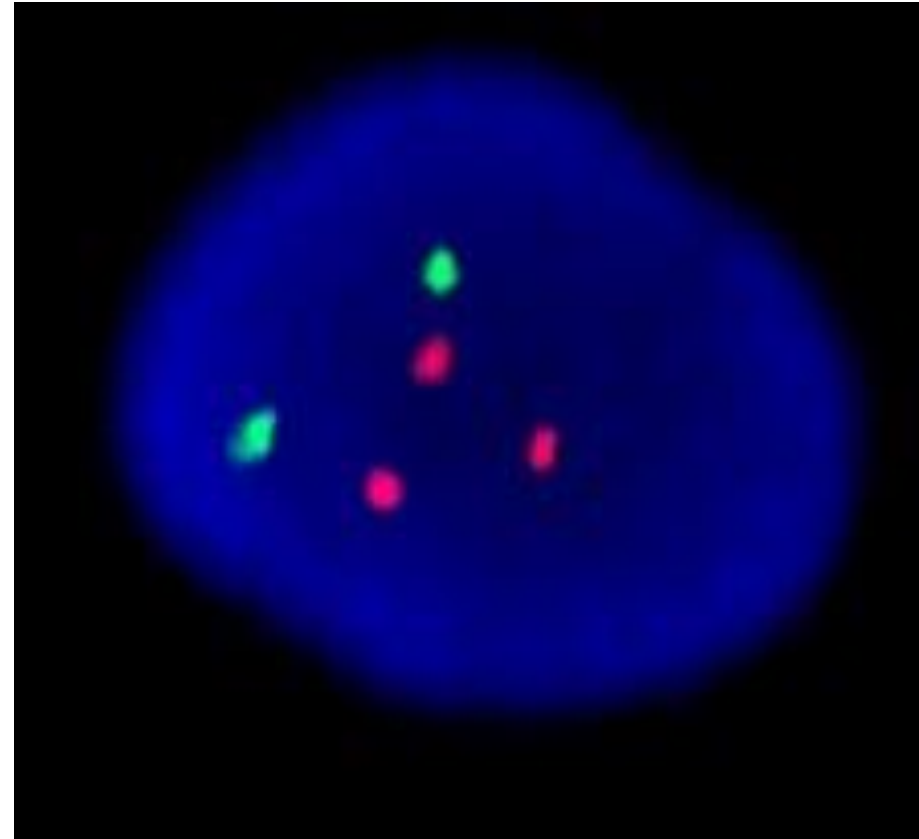
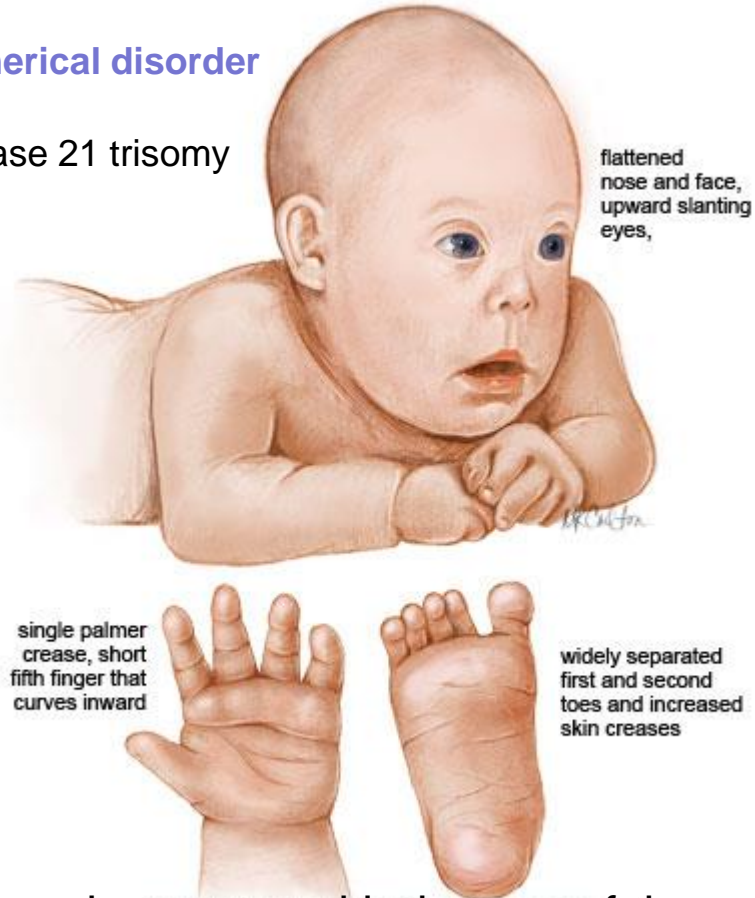
III. Citogenetic disorders

Alteration the number or the structure of chromosomes may affect autosomes:
sex chromosomes

III. a Numerical disorder

Trisomies

Down disease 21 trisomy



Frequency increases with the age of the mother. Abnormal chromosome comes generally from her.

Flat face, epicanthic fold, short neck, congenital heart defect, umbilical hernia, prone for Leukaemia. Mental retardation., Alzheimer disease



III/b Structural abnormalities of chromosomes

Chromosomal breakage, followed by loss of rearranged material

p: short arm, q: long arm numbered from centromere

1. Translocation
2. Isochromosomes
3. Deletion
4. Inversion
5. Ring chromosome

21q deletion syndrome: a spectrum of disorders

heart malformations including outflow tract
facial dysmorphism, developmental delay,
thymic hypoplasia, impaired T cell immunity
parathyroid hypoplasia, hypocalcaemia.

Types: DiGeorge syndrome: Thymus, parathyroid

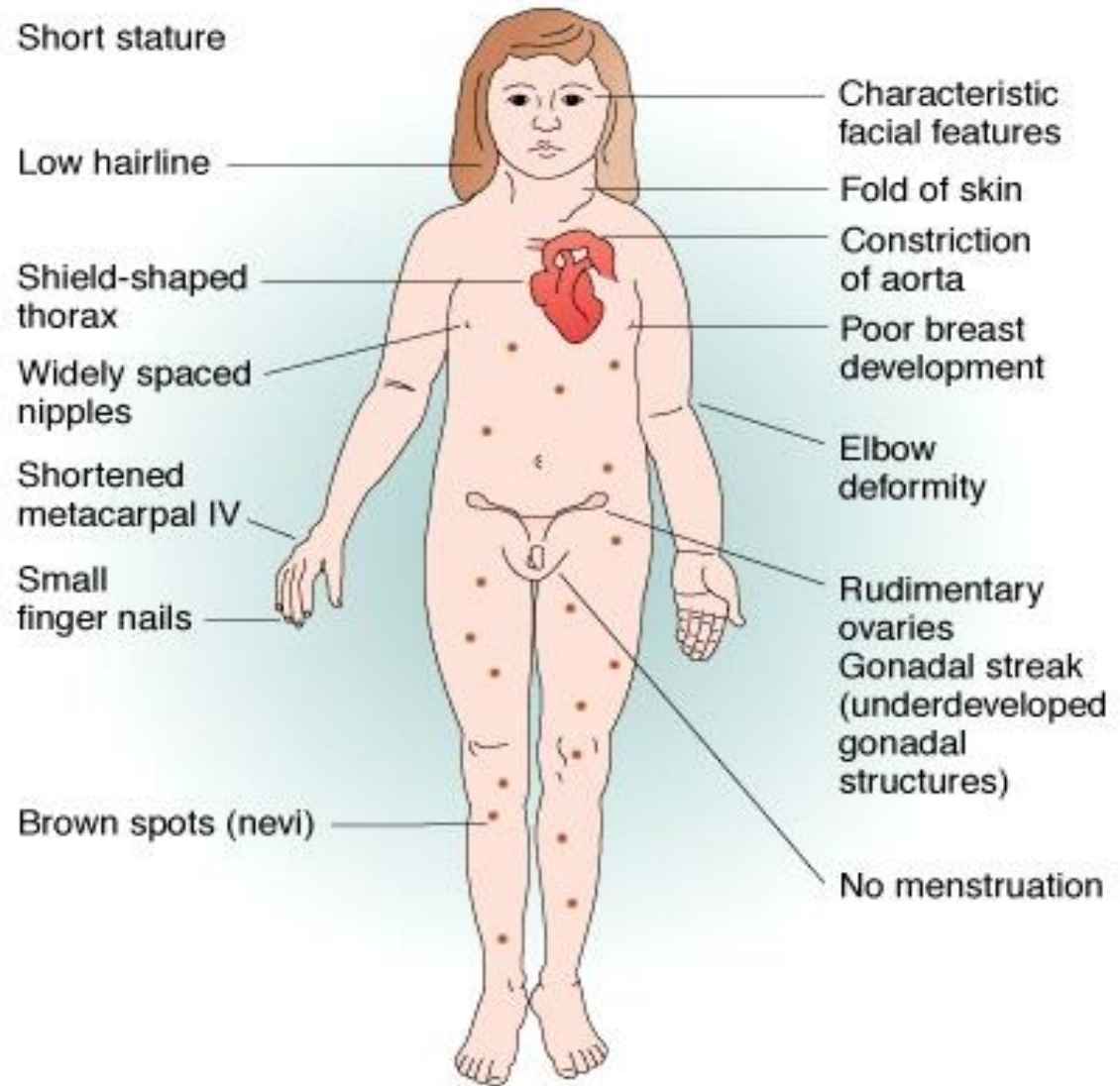
Velocardiofacial syndrome: face, heart

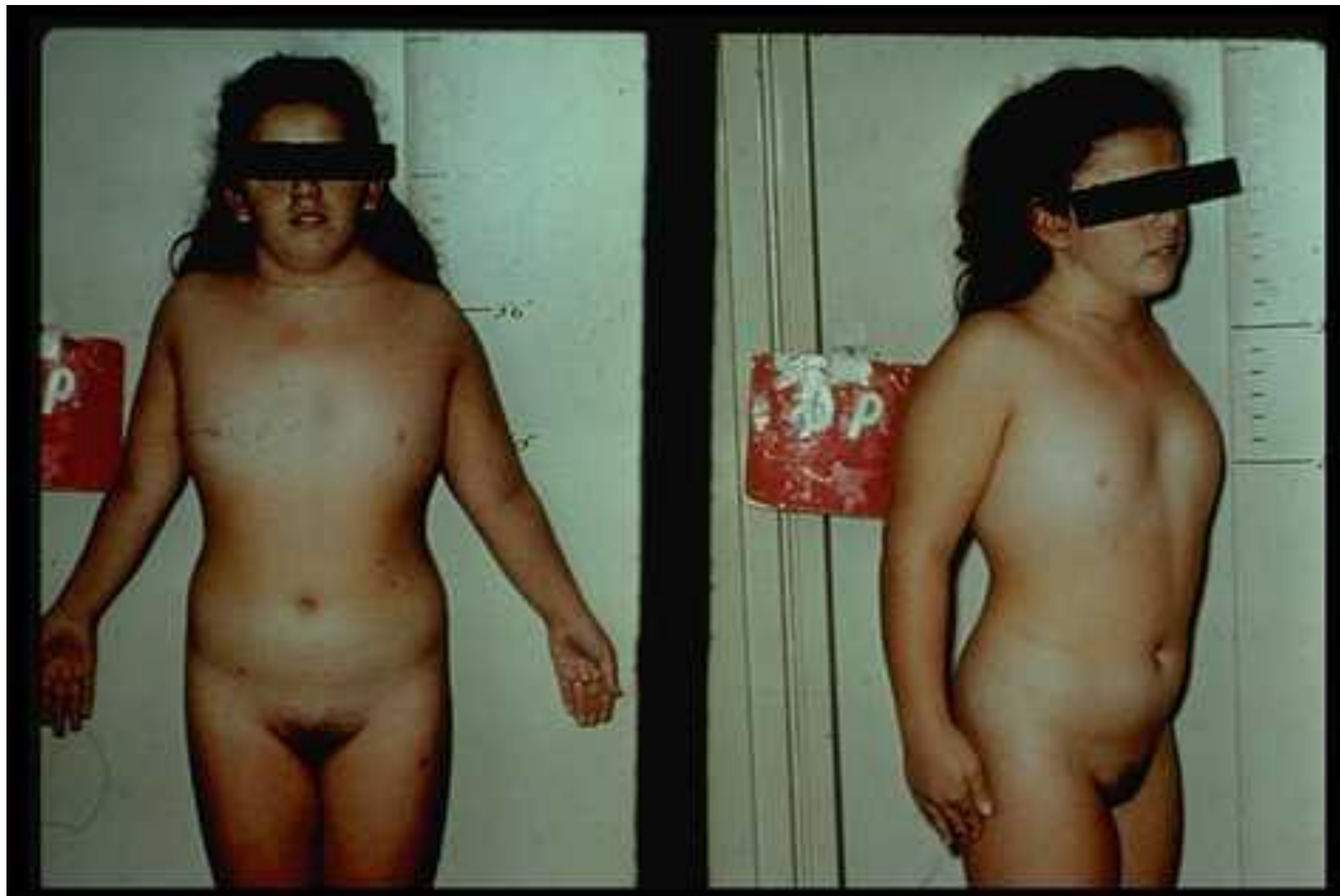
III/c

Cytogenetic disorders of sex chromosomes

Turner syndrome 45X
karyotype
Female phenotype-
hypogonadism

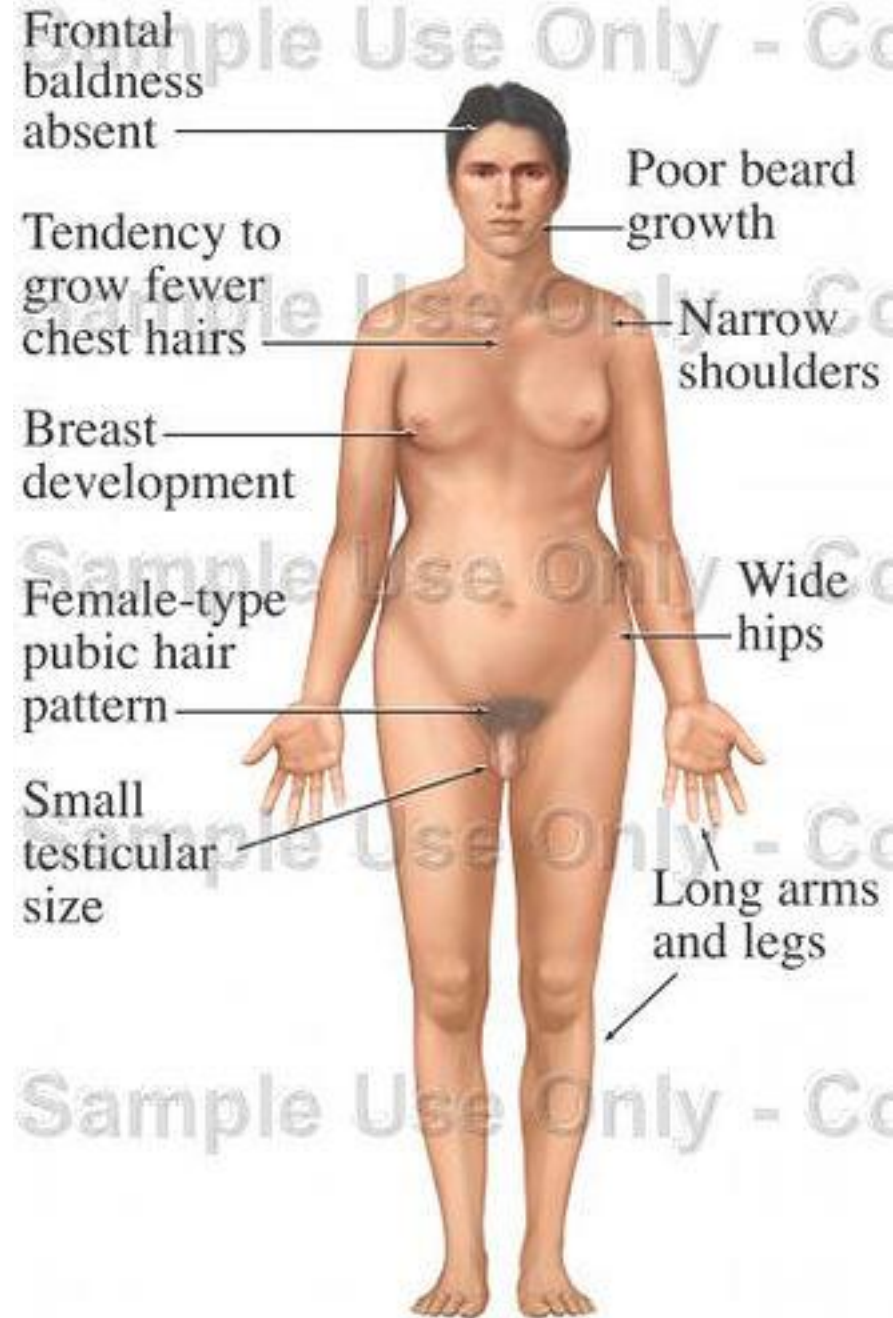
Short stature, webbing neck ,
broad chest, cubitus valgus
Coarctation aortae
Pigmented nevi
Hypofunction of ovaries,
amenorrhea, infertility





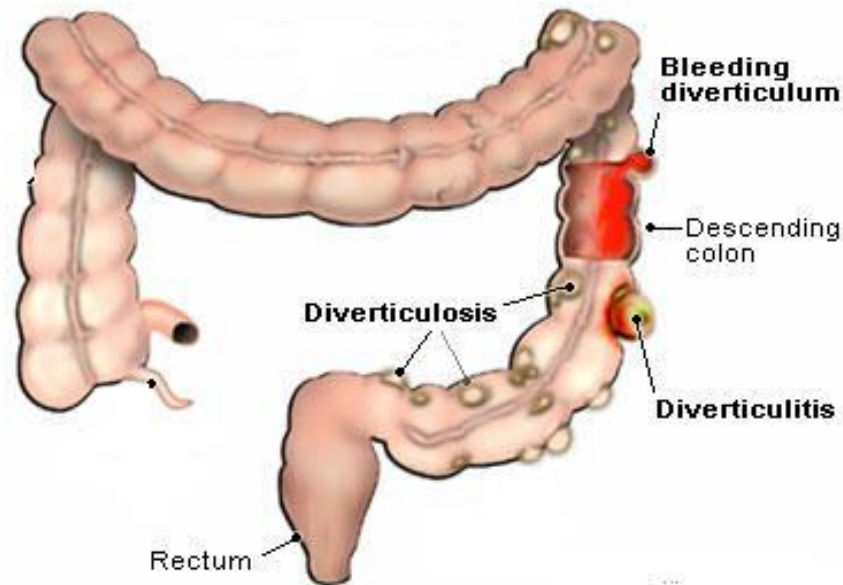
Klinefelter syndrome XXY

Hypogonadism



Diverticulosis is a type of condition in which small sacs (diverticula) form in the [colon](#). Although the exact cause of the condition is not known at this time, it is believed to be linked to a low-fiber diet (which can cause [constipation](#)).

They can cause problems difficult to explain abdominal pain, cramps, anaemia, inflammation, perforation, bleeding.



A **Meckel diverticulum**, a real congenital diverticulum on the ileum. It is the remnant of the omphalomesenteric duct.

Frequency: 2 % and symptoms are more frequent at males. Its length is 3-5 cm and it has a separate blood supply.

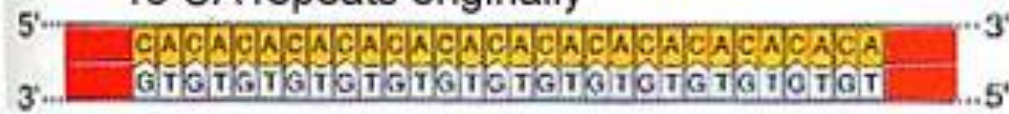
It is named after Johann Friedrich Meckel who recognised its embryonic origin in 1809.

IV Single gene disorders with atypical pattern of inheritance

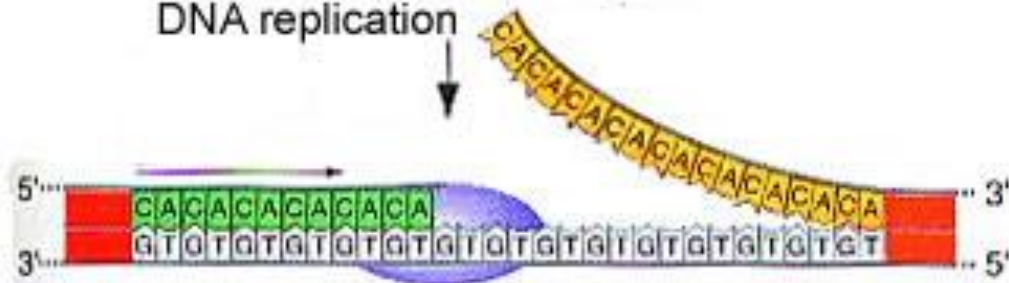
- 1 Triplet repeat mutations (about 30 disease related to 3 repeat disorder, all of them cause neurodegenerative changes)

Fragile X syndrome: familial mental retardation
 long face, large mandibule, large ears, large testis
discontinuity of staining in the long arm of X chromosome, mutation of FMR gene
Xp27.3
20% of males carry the mutation are physically normal.
CGG repeats in normal case : 29
affected individuals 200-400-
Carriers: 52-200 repeat (premutation) conversion to fully mutation in oogenesis.
Symptoms: tremor, ataxia.
Mechanism: repeats on the 5' untranslated region became hypermethylated,
expansion toward promoter region- hypermethylation- silencing of FMR gene
FMR is an mRNA binding protein, carries mRNA to ribosomes in the dendrite and
axons.

15 CA repeats originally

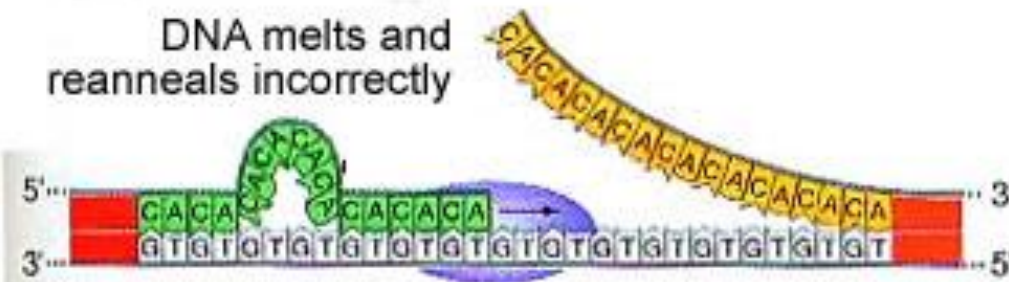


DNA replication

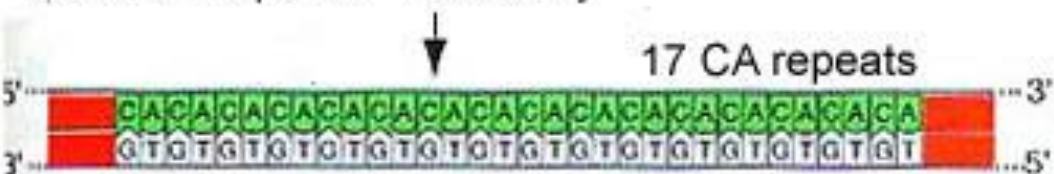


polymerase pauses in CA repeat domain

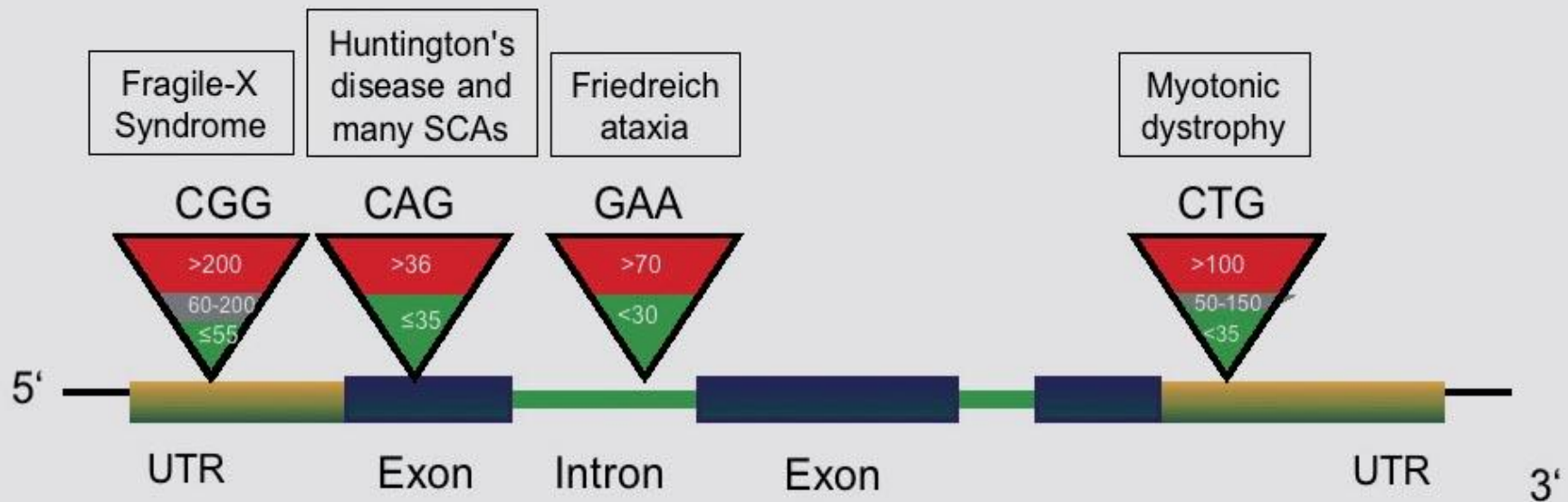
DNA melts and reanneals incorrectly



Mutation 'repaired' incorrectly



Trinucleotide repeat diseases



- Full mutation
- Premutation range (may expand to a full mutation in the next generation)
- Normal alleles

UTR = untranslated region
SCA = spinocerebellar ataxia

2. Mutation of mitochondrial genes : they encode enzymes of oxidative phosphorylation- maternal inheritance- no mitochondria in the sperms
Skeletal muscle, heart and brain is involved.

Leber hereditary optic neuropathy: loss of central vision by age 15.

3. Genomic imprinting

all humans inherit 2 copies of gene (maternal, paternal)

in many gene there are no difference between homologous genes.

In some genes functional differences exists between maternal and paternal gene.

genomic imprinting: genes differentially inactivated

maternal imprinting —————> transcriptional silencing of maternal gene

paternal imprinting —————> transcriptional silencing of paternal gene

Imprinting occurs in ovum and sperm then stably transmitted to all somatic cells.

Del 15(q11;q13)

Prader –Willi syndrome

Paternal chromosome affected

Hypotonia, obesity, mental retardation

hands, hypogonadism

Angelman syndrome

maternal chromosome affected

mental retardation, ataxia, small

inappropriate laughter

„ happy puppet” syndrome



