GENETIC AND PEDIATRIC DISEASES

Marina Kos, Assistant Professor
CONGENITAL ANOMALIES

- STRUCTURAL, FUNCTIONAL, BEHAVIOURAL OR METABOLIC DEFECTS PRESENT AT BIRTH, THAT CAN BECOME CLINICALLY APPARENT YEARS LATER

- ABOUT 3% OF NEWBORNS HAVE A BIRTH DEFECT OF EITHER COSMETIC OR FUNCTIONAL SIGNIFICANCE

- TERATOLOGY – SCIENCE THAT INVESTIGATES THEIR ETIOLOGY
CONGENITAL ANOMALIES

• APPEAR BECAUSE OF THE DERRANGEMENT OF DEVELOPMENTAL PROCESSES

• ONE ORGAN (SYSTEM) OR MORE CAN BE INVOLVED
## CONGENITAL ANOMALIES

<table>
<thead>
<tr>
<th>GENETIC CAUSES</th>
<th>ENVIRONMENTAL INFLUENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CHROMOSOMAL ABERRATIONS</td>
<td>1. MECHANICAL</td>
</tr>
<tr>
<td>2. MENDELIAN INHERITANCE</td>
<td>2. MATERNAL/PLACENTAL INFECTIONS</td>
</tr>
<tr>
<td>3. MULTIFACTORIAL</td>
<td>3. MATERNAL DISEASES</td>
</tr>
<tr>
<td></td>
<td>4. DRUGS AND CHEMICALS</td>
</tr>
<tr>
<td></td>
<td>5. IRRADIATION</td>
</tr>
</tbody>
</table>

40 – 60% UNKNOWN
• The timing of the prenatal teratogenic insult has an important impact on the occurrence and the type of malformation produced.

• BETWEEN the 3rd and the 9th week the embryo is extremely susceptible to teratogenesis.

• The expression of derranged development depends upon the quantity and duration of teratogenic influence.
MINOR MALFORMATIONS - DO NOT AFFECT HEALTH (but are frequently associated with other, more serious malformations)
MAJOR MALFORMATIONS - LETHAL, OR CAUSE SERIOUS DAMAGE OF ORGAN STRUCTURE/FUNCTION
MALFORMATION- primary error of morphogenesis (an intrinsically abnormal developmental process, usually multifactorial)
MALFORMATION - primary error of morphogenesis
DISRUPTION – secondary destruction of an organ or body region that was previously normal in development (an extrinsic disturbance in morphogenesis)

Limb-body wall complex – amniotic bands syndrome
DEFORMATIONS – an extrinsic disturbance of development

clubfeet
SEQUENCE – multiple congenital anomalies that result from secondary effects of a single localized aberration in organogenesis

POTTER sy.

1. RENAL AGENESIS
2. OLIGOHYDRAMNIOIS
3. LUNG HYPOPLASIA
4. POSITIONING DEFECTS
5. TYPICAL FACIAL FEATURES
• MALFORMATION SYNDROME – presence of several defects that cannot be explained on the basis of a single localizing initiating error in morphogenesis (most often caused by a single causative factor – viral infection or a specific chromosomal abnormality that simultaneously affects several tissues)
AGENESIS – complete absence of an organ or its anlage

Renal agenesis

Adrenal glands

Renal agenesis
APLASIA – incomplete development of an organ but the anlage is present
HYPOPLASIA – underdevelopment of an organ
ATRESIA – absence of an opening, usually of a hollow visceral organ or duct (intestines or bile duct)

Atresia of the large bowel

Duodenal atresia
CONGENITAL MALFORMATIONS

INFECTIONS

T OXOPLASMA GONDII
O THER
RUBELLA
C YTOMEGALOVIRUS
H HERPES SIMPLEX VIRUS
Rubella

-The at risk period for rubella infection extends from shortly before conception to the 16th week of gestation.

-The hazard is the greatest in the first 8 weeks.

- CATARACTS
- DEAFNESS
- HEART DEFECTS (persistent ductus arteriosus, pulmonary artery hypoplasia or stenosis, ventricular septal defect, tetralogy of Fallot)
CYTOMEGALOVIRUS (CMV)

- The highest at risk period is the 2nd trimester of pregnancy

- INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM
  - MENTAL RETARDATION, MICROCEPHALY

- BLINDNESS, DEAFNESS

- HEPATOSPLENOMEGALY
TOXOPLASMOsis

- Infection of the mother during the 1st trimester – dissemination and parasitemia

- Encephalitis with destructive lesions of the CNS

- Blindness

- Heart, liver necrosis
CONGENITAL MALFORMATIONS

DRUGS AND CHEMICALS

THALIDOMID

FOLIC ACID ANTAGONISTS

ANTIEPILEPTICS

ANTICOAGULANTS

ISOTRETINOIN

ALCOHOL

SMOKING

HORMONES

RADIATION
CHROMOSOMAL ABNORMALITIES

• IN HUMANS: the normal chromosomal count is 2n (46) - 22 homologous pairs of autosomes (44) + 2 sex chromosomes (XX ili XY)

• CYTOGENETICS- KARYOTYPING

• NUMERIC ABNORMALITIES (non-disjuction)
  – Of autosomes
  – Of sex chromosomes

• STRUCTURAL ABNORMALITIES (deletion, translocation,inversion etc…)  
  – Of autosomes
  – Of sex chromosomes
CHROMOSOMAL ABNORMALITIES

- About 50% of all conceived fetuses are aborted
- 25% of them because of chromosomal disorders (Turner syndrome; triploidy; trisomy 16)

- 10-15% OF LIVEBORN INFANTS SHOW SOME CHROMOSOMAL ABNORMALITY
CHROMOSOMAL ABNORMALITIES

• ABNORMAL NUMBER OF CHROMOSOMES – ANEUPLOIDY (non-disjunction, anaphase lag)
  – Of AUTOSOMES
  – Of SEX CHROMOSOMES

• TRISOMY 21 (DOWN SY.)
• TRISOMY 18 (EDWARDS SY.)
• TRISOMY 13 (PATAU SY.)

• KLINEFELTER SY.
• TURNER SY.
• “TRIPLE X” SY.
EARLY AMNIOCENTESIS, CVS, CORDOCENTESIS

THE FREQUENCY OF ABNORMAL NUMBER OF CHROMOSOMES DEPENDS UPON THE MOTHER’S AGE

THE MOST FREquent ABNORMALITY IS TRISOMY 21 (in the population with 5% of mothers ageing 35 y and more in 1:800)

KARYOTYPING
TRISOMY 21 (DOWN SY.): first time described by Langdon Down in 1866.

MECHANISMS OF DEVELOPMENT:

1. **Meiotic non-disjunction** in the ovum - 95%

2. **Robertsonian translocation** (translocation of the long arm of chromosome 21 to another acrocentric chromosome, usually 22 ili 14 in one of the parental gametes – effect of “triple gene dosage”) - oko 4%

3. **Mitotic non-disjunction** during early embryogenesis - 1% - some cells have 46 and some 47 chromosomes = mosaicism
TRISOMY 21 (DOWN SY.)

Incidence: 1 in 700 births
Karyotypes:
- Trisomy 21 type: 47,XX,+21
- Translocation type: 46,XX,der(14;21)(q10;q10),+21
- Mosaic type: 46,XX/47,XX,+21

Mental retardation
Abundant neck skin
Congenital heart defects
Intestinal stenosis
Umbilical hernia
Predisposition to leukemia
Epicanthic folds and flat facial profile
Simian crease
Hypotonia
Gap between first and second toes
TRISOMY 21 (DOWN SY.)

- Mental retardation
- Abundant neck skin
- Congenital heart defects
- Intestinal stenosis
- Gap between first and second toes
- Epicanthic folds and flat facial profile
- Simian crease
- Umbilical hernia
- Predisposition to leukemia
- Hypotonia

40%
TRISOMY 21 (DOWN SY.)

MENTAL RETARDATION
10-20% greater possibility of ACUTE LEUKEMIA
ABNORMAL IMMUNE RESPONSE
EARLY DEVELOPMENT OF ALZHEIMER’S DISEASE
TRISOMY 18 (EDWARDS SY.)

**TRISOMY 18: EDWARDS SYNDROME**

- Incidence: 1 in 8000 births
- Key features:
  - Trisomy 18 type: 47,XX,+18
  - Mosaic type: 46,XX/47,XX,+18

**Prominent occiput**

- **Mental retardation**
- **Micrognathia**

- **Low set ears**
- **Short neck**
- **Overlapping fingers**
- **Congenital heart defects**
- **Renal malformations**

![Image of a baby with features of Edwards Syndrome]

![Image of kidneys with malformations]
TRISOMY 13 (PATAU SY.)

Incidence: 1 in 15,000 births

Karyotypes:
- Trisomy 13 type: 47,XX,+13
- Translocation type: 46,XX,+13,der(13;14)(q10;q10) 46,XX/47,XX,+13

Microphthalmia
Microcephaly and mental retardation
Cleft lip and palate
Cardiac defects
Umbilical hernia
Renal defects
Rocker-bottom feet
SEX CHROMOSOME DISORDERS

• NUMERICAL DISORDERS (non-disjunction anaphase lag)
• KLINEFELTER sy.
• TURNER sy.
• STRUCTURAL DISORDERS (deletions, microdeletions, increased fragility, genomic imprinting)
• ANGELMAN sy.
• PRADER-WILLI sy.
• FRAGILE X sy.
KLINFEelter Syndrome
(47,XXY)

• Diagnosis at puberty
• Elongated body, long legs, eunuchoid habitus

Small atrophic testes (sterility), small penis, gynecomastia
Lack of secondary male characteristics (deep voice, beard, male distribution of pubic hair)
TURNER SYNDROME (45, X)

Cystic hygroma (cavernous lymphangioma)

Fetal hydrops
TURNER SYNDROME

Karyotype: 45, X (X monosomy)
43% mosaics/structural abnormality of the X chromosome
Short stature
Low posterior hairline
Webbing of the neck
Streak ovaries
Coarctation of the aorta

Accelerated loss of oocytes – complete by the age of 2 years
FRAGILE X SYNDROME

• There is a long repeating sequence of 3 nucleotides
• It is one of the most common causes of familial mental retardation
• Full mutation: 230-4000 CGG repeats (normally average is 29)
• App. 20% of the patients are normal ("carrier males")
• App. 50% of "carrier females" – mental retardation
FRAGILE X SYNDROME

A long face with large mandible

Large everted ears

Large testicles (macro-orchidism)

Mental retardation
PRADER-WILLI SYNDROME – genomic imprinting

• Mental retardation
• Short stature
• Hypotonia
• Obesity
• Small hands and feet
• Hypogonadism

• IN ALL CASES THE DELETION AFFECTS THE PATERNALLY DERIVED CHROMOSOME 15
ANGELMAN SYNDROME – genomic imprinting

• Mental retardation
• Ataxic gait
• Seizures
• Inappropriate laughter (happy puppet syndrome)

• IN ALL CASES THE DELETION AFFECTS THE MATERNALLY DERIVED CHROMOSOME 15
SINGLE GENE DEFECTS (Mendelian disorders)

• about 80-85% are familial, the rest are “de novo” mutations

MUTATIONS INVOLVING SINGLE GENES FOLLOW ONE OF 3 PATTERNS OF INHERITANCE

• AUTOSOMALLY DOMINANT: are manifested in heterozygotes, in many conditions signs and symptoms appear later in life

• AUTOSOMALLY RECESSIVE: the largest group of Mendelian disorders, onset early in life

• X LINKED: are transmitted by heterozygous female carriers, virtually only to sons because they are heterozygous for X chromosome
<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>NERVOUS</td>
<td>Huntingtonon disease</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td></td>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td></td>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td>URINARY</td>
<td>Policystic kidney disease (ADPKD)</td>
</tr>
<tr>
<td>GASTROINTESTINAL</td>
<td>Familial polyposis coli</td>
</tr>
<tr>
<td></td>
<td>Hereditary spherocytosis</td>
</tr>
<tr>
<td></td>
<td>von Willebrandt disease</td>
</tr>
<tr>
<td></td>
<td>Marfan syndrome</td>
</tr>
<tr>
<td>HEMATOPOIETIC</td>
<td>Ehlers-Danlos syndrome (some variants)</td>
</tr>
<tr>
<td></td>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td></td>
<td>Achondroplasia</td>
</tr>
<tr>
<td>SKELETAL</td>
<td>Familial hypercholesterolemia</td>
</tr>
<tr>
<td></td>
<td>Acute intermittent porphiria</td>
</tr>
<tr>
<td>METABOLIC</td>
<td></td>
</tr>
</tbody>
</table>
NEUROFIBROMATOSIS: CAUSED BY MUTATIONS IN PROTEINS THAT REGULATE CELL GROWTH

type 1- von Recklingausen disease - 90%

1. MULTIPLE SUBCUTANEOUS NEUROFIBROMAS OR ANYWHERE INSIDE THE BODY
- 1 to 20 cm, firm or pedunculated
-Malignant Transformation in large plexiform tumors of the head and neck

2. IN MORE THAN 90% OF PATIENTS PIGMENTED SKIN LESIONS (café au lait spots)

3. IN MORE THAN 94% OF THE PATIENTS AGEING MORE THAN 6 years PIGMENTED IRIS HAMARTOMAS (Lisch nodules)
type 2- bilateral acoustic or central neurofibromatosis

- Much rarer than type 1
- Bilateral acoustic schwannomas, multiple meningeomas
- Most patients have “café au lait spots”
- Lisch nodules are absent
MARFAN sy. – caused by mutations in structural proteins

- Mutation of FBN1 gene on chromosome 15 that encodes fibrillin 1 (the major component of microfibrils in the extracellular matrix)
- Over 100 mutations affecting this gene have been found
- The prevalence is 2-3/10 000
- 75% are familial, the rest arise de novo

- Connective tissue of the whole body is affected, but the principal clinical manifestations relate to......
MARFAN sy.

1. **Skeletal abnormalities** – slender, elongated habitus, long legs, arms and fingers (arachnodactily), elongated head (dolichocephaly), spinal and chest deformities, hyperextensible joints

2. **Ocular changes** – bilateral subluxation (dislocation) of the lens because of weak suspensory ligaments
MARFAN sy.

3 cardiovascular changes – fragmentation of elastic fibers in the tunica media of the aorta predisposes to:
- aneurysmal dilatation and aortic dissection
- dilatation of the aortic valve ring and aortic incompetence
- floppy valve syndrome - extremely distensible mitral (tricuspid) valve become incompetent during systole – congestive heart failure
# Autosomal Recessive Disorders

<table>
<thead>
<tr>
<th>System</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic</strong></td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Phenylketonuria</td>
</tr>
<tr>
<td></td>
<td>Galactosemia</td>
</tr>
<tr>
<td></td>
<td>Homocystinuria</td>
</tr>
<tr>
<td></td>
<td>Lysosomal storage diseases</td>
</tr>
<tr>
<td></td>
<td>Alpha-1 antitrypsin deficiency</td>
</tr>
<tr>
<td></td>
<td>Wilson disease, Hemochromatosis</td>
</tr>
<tr>
<td><strong>Hematopoietic</strong></td>
<td>Glycogen storage diseases</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>Sickle cell anemia; Thalassemias</td>
</tr>
<tr>
<td></td>
<td>Congenital adrenal hypoplasia</td>
</tr>
<tr>
<td><strong>Skeletal</strong></td>
<td>Ehlers-Danlos syndrome (some variants)</td>
</tr>
<tr>
<td></td>
<td>Alkaptonuria</td>
</tr>
<tr>
<td><strong>Nervous</strong></td>
<td>Neurogenic muscular atrophies, Spinal muscular atrophy, Friedreich ataxia</td>
</tr>
</tbody>
</table>
PHENYLKETONURIA: inborn error of metabolism due to lack of phenylalanin hydroxilase (PHENYLALANIN IS NOT CONVERTED INTO TYROSINE)

- HYPERPHENYLALANINEMIA DEVELOPS WITHIN FEW WEEKS AFTER BIRTH IMPAIRING BRAIN DEVELOPMENT
- by 6. months – SEVERE MENTAL RETARDATION (immobility, dumbness)
- SEIZURES, NEUROLOGICAL ABNORMALITIES
- DECREASED PIGMENTATION OF HAIR AND SKIN
- DERMATOLOGIC PROBLEMS - ECZEMA
- “MOUSY” ODOR (shunt pathways produce metabolites that are excreted in the urine and sweat)

Phenylalanin free diet!!!
**GALACTOSEMIA**: inborn error in galactose metabolism due to lack of galactose1-phosphate uridylyltransferase

- GALACTOSE-1-PHOSPHATE and other metabolites accumulate in
  - LIVER, SPLEEN, OCULAR LENS, KIDNEY, CEREBRAL CORTEX
- INFANT FAILS TO THRIVE, VOMITS, HAS DIARRHEA
- PERSISTENT JAUNDICE
- HEPATOMEGALY - 1. week of life
- CATARACTS: within few weeks
- MENTAL RETARDATION: within 6-12 months

Removal of galactose form the diet for at least 2 years
LYSOSOMAL STORAGE DISEASES

LYSOSOMAL HYDROLITIC ENZYMES ARE INVOLVED IN THE BREAKDOWN OF MANY COMPLEX SUBSTRATES – IN LSDs THE CATABOLISM OF THE SUBSTRATE REMAINS INCOMPLETE.

PARTIALLY DEGRADED INSOLUBLE METABOLITES ACCUMULATE WITHIN THE LYSOSOMES.
TAY-SACHS DISEASE ($G_{M2}$ GANGLIOSIDOSIS)

- Deficiency of the alpha subunit of the enzyme HEXOSAMINIDASE A, NECESSARY FOR THE DEGRADATION OF $G_{M2}$ in all tissues
- $G_{M2}$ gangliosides accumulate in many tissues (LIVER, HEART, SPLEEN AND MOSTLY CNS, PERIPHERAL NERVES AND AUTONOMIC NERVOUS SYSTEM – within neurons, axon cylinders of nerves and glial cells
- MENTAL RETARDATION, BLINDNESS, SEVERE NEUROLOGIC DYSFUNCTIONS – DEATH WITHIN 2-3 years

"CHERRY RED SPOT" IN RETINA

Swollen, foamy cells
NIEMANN-PICK DISEASE – a group of 3 disorders segregated into 2 categories on the basis of biochemical and molecular criteria

• Types A, B and C
• Type A – sphingomyelinase deficiency
• Sphingomyelin accumulates in ALL PHAGOCYTIC CELLS and NEURONS
• at about 6 months - HEPATOSPLENOMEGALY, SKIN XANTOMAS, NEUROLOGIC DETERIORATION – DEATH WITHIN THE FIRST 3 years

FOAMY PHAGOCYTES (frozen sections – droplets of complex lipid + for lipid dyes - Sudan Black, Oil Red O) in:
SPLEEN (10 times its normal weight)
LIVER, LYMPH NODES, TONSILS, LUNGS
GAUCHER DISEASE

• 3 VARIANTS – deficient activity of a glucocerebrosidase that cleaves glucose residue from ceramide
• Accumulation of glucocerebrosides in THE MONONUCLEAR PHAGOCYTIC CELLS

Type I – 99%
HEPATOSPLENOMEGALY (NO CNS INVOLVEMENT)
(Ashkenazi Jews), shorter life, but not significantly

Type II SEVERE CNS INVOLVEMENT
DOMINATES - lethal early in life

Type III intermediate between types I and II

GAUCHER cells
(“wrinkled paper appearance”)

SPLENOMEGALY (do 10 kg)
LYMPHADENOPATHY
BONE DEFORMATION because of accumulation in the bone marrow
BRAIN: in Virchow-Robinovim spaces
MUCOPOLYSACCHARIDOSES – defective degradation (and storage) of mucopolysaccharides in various tissues

- Mucopolysaccharides that accumulate - DERMATAN SULFATE, HEPARAN S., KERATAN S., CHONDROITIN S.

- Clinical varianta classified numerically from MPS I to MPS VII VII (only HUNTER sy.or MPS II –is inherited as X linked)

- MPSs are progressive disorders that involve multiple organs (LIVER, SPLEEN, HEART AND BLOOD VESSELS)

- Most: COARSE FACIAL FEATURES, CLOUDING OF THE CORNEA, JOINT STIFFNESS, MENTAL RETARDATION

HEPATOSPLENOMEGALY

SUBENDOTHELIAL ACCUMULATION IN HEART AND BRAIN BLOOD VESSELS
- ischemia
- infarction
MUCOPOLYSACCHARIDOSES
COARSE FACIAL FEATURES
IN MPS I – HURLER sy.
GLYCOGEN STORAGE DISEASES - deficiency of any one of the enzymes involved in glycogen synthesis or degradation

• The type of glycogen stored, its intracellular location and the tissue distribution of the affected cells vary depending on the specific enzyme deficiency

• ON THE BASIS OF PATHOPHYSIOLOGY:

1. **HEPATIC FORM** – GLUCOSE-6-PHOSPHATE DEFICIENCY (type I - von GIERKE disease) - HEPATOMEGALY and HYPOGLYCEMIA.

2. **MYOPATHIC FORMS** (type V McARDLE disease) - MUSCLE PHOSPHORYLASE DEFICIENCY - MUSCLE CRAMPS AFTER EXERCISE, NO INCREASE OF BLOOD LACTATE LEVELS)

3. **Type II POMPE disease** – LYSOSOMAL ACID AMYLASE DEFICIENCY – EVERY ORGAN, BUT MOST PROMINENT IS CARDIOMEGALY
<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>METABOLIC</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td></td>
<td>Lesch-Nyhan sy.</td>
</tr>
<tr>
<td>HEMATOPOIETIC</td>
<td>Hemophilias A and B</td>
</tr>
<tr>
<td></td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td></td>
<td>Glucose- 6-phosphate dehydrogenase deficiency</td>
</tr>
<tr>
<td>IMMUNE</td>
<td>Agammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>Wiskott-Aldrich sy.</td>
</tr>
<tr>
<td>NERVOUS</td>
<td>Fragile X syndrome</td>
</tr>
<tr>
<td>MUSKULOSKELETAL</td>
<td>Duchenne muscular dystrophy</td>
</tr>
</tbody>
</table>
DISORDERS WITH MULTIFACTORIAL INHERITANCE

- CLEFT LIP AND/OR PALATE
- DIABETES MELLITUS
- GOUT
- SCHIZOPHRENIA
- HYPERTENSION

MULTIFACTORIAL BECAUSE IS AFFECTED BY

4. PATIENT’S AGE AND THE DURATION OF HYPEURICEMIA
2. GENETIC SUSCEPTIBILITY
3. ALCOHOL CONSUMPTION
4. OBESITY
5. SOME DRUGS - tiazides
6. LEAD TOXICITY
GOUT (URIC DIATHESIS)

• IS A DISORDER OF URIC ACID METABOLISM - HYPERURICEMIA

• IT CAN BE PRIMARY (90%)
  – ENZYME DEFECTS UNKNOWN (85-90% of primary gout)
  – KNOWN ENZYME DEFECT

• AND SECONDARY (10%)
  – INCREASED NUCLEIC ACID TURNOVER (e.g. leukemias)
  – CHRONIC RENAL DISEASE
  – INBORN ERRORS OF METABOLISM (Lesch-Nyhan sy.)
GOUT

• HYPERURICEMIA CAUSED BY OVERPRODUCTION OR UNDEREXCRETION OF URIC ACID OR COMBINATION OF THE TWO

THE INCREASED LEVELS OF URIC ACID IN THE BLOOD AND OTHER BODY FLUIDS (e.g. SYNOVIA) LEAD TO PRECIPITATION OF MONOSODIUM URATE CRYSTALS

CLINICALLY:
4. ACUTE ARTHRITIS,
5. CHRONIC TOPHACEOUS ARTHRITIS
6. SOFT TISSUE TOPHI
7. GOUT NEPHROPATHY
• **ACUTE ARTHRITIS**
  - local congestion, deposition of crystals, synovial edema, neutrophilic inflammatory infiltrate.

Most frequently

- GREAT TOE
- INSTEP
- ANKLE
- HEEL
- WRIST

After recurrent episodes of acute uric arthritis, chronic tophaceous arthritis develops.
• **CHRONIC TOPHACEOUS ARTHRITIS** – large irregular deposits of chalky white sodium urate (TOPHI) on the articular cartilage and adjacent joint capsule

• **Microscopically:** tophi (amorphous or cristallyne urates) surrounded by macrophages, lymphocytes, fibroblasts, foreign body type giant cells
GOUT

- EXCEPT IN THE JOINTS TOPHI CAN FORM IN
  - TENDONS
  - BURSAE
  - CARTILAGE OF THE EAR LOBE, NOSE
  - SUBCUTANEOUS TISSUE ANYWHERE IN THE BODY
  - HEART

- GOUT NEPHROPATY
  - INTRATUBULAR PRECIPITATION AND OBSTRUCTION OF RENAL TUBULES (tumor lysis sy.)
  - DEPOSITION OF CRYSTALS WITHIN THE INTERSTITIUM OF THE RENAL MEDULLA WITH TOPHI FORMATION
  - FORMATION OF URIC RENAL STONES
THE HUNCHBACK OF NOTRE DAME