Congenital anomalies (CA)
Teratology

• Teratology is the study of developmental anomalies (Greek *teraton*, “monster”).

• **Teratogens** are chemical, physical and biological agents that cause developmental anomalies.

• Exposure to a teratogen may result in a malformation, but this is not invariably the case.
Definition

• **Congenital anomalies (malformations)** are persistent morphological changes in the tissue, organ or the whole body, going beyond their normal structure variations.
Etiology of CA

- Errors of morphogenesis
- Chromosomal abnormalities
- Single-gene defects
- Polygenic inherited diseases
Principles of Teratology

• Susceptibility to teratogens is variable.
• Susceptibility to teratogens is specific for each embryologic stage.
• The mechanism of teratogenesis is specific for each agent.
• Teratogenesis is dose dependent.
• Teratogens produce death, growth retardation, malformation or functional impairment.
List of proven teratogens and includes

- cytotoxic drugs,
- alcohol,
- some antiepileptic drugs,
- heavy metals and
- thalidomide
Critical periods

FIGURE 6-2. Sensitivity of specific organs to teratogenic agents at critical stages of human embryogenesis. Exposure to adverse influences in preimplantation and early postimplantation stages of development (far left) leads to prenatal death. Periods of maximal sensitivity to teratogens (horizontal bars) vary for different organ systems but overall are limited to the first 8 weeks of pregnancy.
• Teratogenetic termination period (TTP) - the time limit during which teratogens capable of causing malformations.
Basic cellular mechanisms of teratogenesis

• Cell mechanisms include disturbance of:
  – cell proliferation
  – cell migration
  – cell differentiation

• Tissue mechanisms include:
  – death of individual tissues
  – delay or slowing of the physiological death of tissues, dying in the normal embryogenesis
  – violation of tissue adhesion
Errors of Morphogenesis

- Most complex developmental abnormalities affecting several organ systems are due to injuries that occur between implantation of the blastocyst and early organogenesis. This period is characterized by rapid cell division, cell differentiation and formation of so-called developmental fields, in which cells interact and determine each other’s developmental fate.
Errors of Morphogenesis

• *The stage of embryonic development most susceptible to teratogenesis is formation of primordial organ systems, and many major developmental abnormalities are probably due to faulty gene activity or the effects of exogenous toxins.*

• Disorganized or disrupted morphogenesis may have minor or major consequences at the level of (1) cells and tissues, (2) organs or organ systems and (3) anatomic regions.
Terminology
Agenesis

• **Agenesis** is the complete absence of an organ primordium.

• It may manifest as
  
  (1) total lack of an organ (e.g., unilateral or bilateral renal agenesis);

  (2) absence of part of an organ, as in agenesis of the corpus callosum of the brain; or

  (3) lack of tissue or cells in an organ, as in the absence of testicular germ cells in congenital infertility ("Sertoli cell only" syndrome).
Aplasia

- **Aplasia** is the persistence of an organ anlage or rudiment, without the mature organ. Thus, in aplasia of the lung the main bronchus ends blindly in nondescript tissue composed of rudimentary ducts and connective tissue.
Hypoplasia

- **Hypoplasia** means reduced size due to incomplete development of all or part of an organ. Micrognathia (small jaw) and microcephaly (small brain and head) are common examples.
Dysraphic anomalies

- **Dysraphic anomalies** are defects caused by failure of apposed structures to fuse. In spina bifida, the spinal canal does not close completely, and overlying bone and skin do not fuse, leaving a midline defect.
Division failures

- **Division failures** are caused by incomplete cleavage of embryonic tissues, when that process depends on programmed cell death. Fingers and toes are formed at the distal end of the limb bud by the loss of cells between the cartilage-containing primordia. If these cells do not undergo apoptosis, the fingers will be conjoined or incompletely separated (syndactyly).
Atresia

- **Atresia** reflects incomplete formation of a lumen. Many hollow organs originate as cell strands and cords whose centers are programmed to die, to yield a central cavity or lumen. Esophageal atresia is characterized by partial occlusion of the lumen, which was not fully established in embryogenesis.
Dysplasia

• **Dysplasia** is caused by abnormal organization of cells in tissues, which causes abnormal histogenesis. (This is different from the “dysplasia” of precancerous epithelial lesions.) Tuberous sclerosis is characterized by abnormal development of the brain, in which aggregates of normally developed cells are arranged into grossly visible “tubers.”
Ectopia

• **Ectopia, or heterotopia,** denotes a normally formed organ that is outside its normal anatomic location. Thus, an ectopic heart is not in the thorax. Heterotopic parathyroid glands can be within the thymus in the anterior mediastinum.
Dystopia

- **Dystopia** refers to inadequate migration of an organ that remains where it was during development, rather than migrating to its proper site. Thus, the kidneys originate in the pelvis, then move cephalad out of the pelvis. Dystopic kidneys remain in the pelvis. Dystopic testes remain in the inguinal canal and do not descend into the scrotum (cryptorchidism).
Multiple congenital anomalies

Developmental anomalies caused by interference with morphogenesis are often multiple:

- A polytopic effect occurs when a noxious stimulus affects several organs that are simultaneously in critical stages of development.
- A monotopic effect refers to a single localized anomaly that results in a cascade of pathogenetic events.
- A developmental sequence anomaly (anomalad or complex anomaly) is a pattern of defects related to a single anomaly or pathogenetic mechanism: different factors lead to the same consequences through a common pathway.
Multiple congenital anomalies

A developmental syndrome refers to multiple pathogenetically related anomalies. The term syndrome implies a single cause for anomalies in diverse organs that have been damaged by the same polytopic effect during a critical developmental period. Many such syndromes reflect chromosomal abnormalities or single-gene defects.
# Chromosomal Abnormalities

## Clinical Features of the Autosomal Chromosomal Syndromes*

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Features</th>
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</thead>
<tbody>
<tr>
<td><strong>Trisomic Syndromes</strong></td>
<td></td>
</tr>
<tr>
<td>Chromosome 21 (Down syndrome 47,XX or XY, +21: 1/800)</td>
<td>Epicanthic folds, speckled irides, flat nasal bridge, congenital heart disease, simian crease of palms, Hirschsprung disease, increased risk of leukemia</td>
</tr>
<tr>
<td>Chromosome 18 (47,XX or XY, +18: 1/8000)</td>
<td>Female preponderance, micrognathia, congenital heart disease, horseshoe kidney, deformed fingers</td>
</tr>
<tr>
<td>Chromosome 13 (47,XX or XY, +13: 1/20,000)</td>
<td>Persistent fetal hemoglobin, microcephaly, congenital heart disease, polycystic kidneys, polydactyly, simian crease</td>
</tr>
<tr>
<td><strong>Deletion Syndromes</strong></td>
<td></td>
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<tr>
<td>5p− syndrome (cri du chat 46,XX or XY, 5p−)</td>
<td>Cat-like cry, low birth weight, microcephaly, epicanthic folds, congenital heart disease, short hands and feet, simian crease</td>
</tr>
<tr>
<td>11p− syndrome (46,XX or XY, 11p−)</td>
<td>Aniridia, Wilms tumor, gonadoblastoma, male genital ambiguity</td>
</tr>
<tr>
<td>13q− syndrome (46,XX or XY, 13q−)</td>
<td>Low birth weight, microcephaly, retinoblastoma, congenital heart disease</td>
</tr>
</tbody>
</table>

*All of these syndromes are associated with mental retardation.
Trisomy 21 (Down Syndrome)

- *Trisomy 21 is the most common cause of mental retardation.*

- Liveborn infants are only a fraction of all conceptuses with this defect. Two thirds abort spontaneously or die in utero. Life expectancy is also reduced. Advances in treating infections, congenital heart defects and leukemia—the leading causes of death with Down syndrome—have increased life expectancy.
Trisomy 21 (Down Syndrome)

**FIGURE 6-10.** Incidence of Down syndrome in relation to maternal age. A conspicuous increase in the frequency of this disorder is seen over the age of 35 years.
Trisomy 21 (Down Syndrome)

- Growth failure
- Mental retardation
- Flat occiput
- Congenital heart disease
- Megacolon
- Slanted eyes
- Epicanthal fold
- Brushfield spots
- Dysplastic ears
- Protruding, big, wrinkled tongue
- Short, broad hands with simian crease
- Acute lymphoblastic leukemia
- Wide gap between 1st and 2nd toes
Trisomy 21 (Down Syndrome)

- **Mental status:** Children with Down syndrome are invariably mentally retarded. Their IQs decline relentlessly and progressively with age. Mean IQs are 70 below the age of 1 year, and decline during the first decade of life to a mean of 30.

- **Life expectancy:** During the first decade of life, the presence or absence of congenital heart disease largely determines survival in Down syndrome. Only about 5% of those whose hearts are normal die before age 10, but about 25% with heart disease die by then. If patients reach age 10, the age at death is about 55, which is 20 years or more lower than that of the general population. Only 10% reach age 70.
Trisomies of Chromosomes 18, 13 and 22

• **Trisomy 18 (Edwards syndrome),** at 1 in 8000 live births, is the second most common autosomal syndrome. It results in mental retardation and affects females four times as often as males. Virtually all infants with trisomy 18 have congenital heart disease and die in the first 3 months of life.

• **Trisomies 13 (Patau syndrome) and 22** are rare and both are associated with mental retardation, congenital heart disease and other abnormalities. Syndromes associated with trisomies of chromosomes 8 and 9 have also been described.
Congenital craniofacial anomalies (CFA)
• Approximately 1% of these newborns have syndromes or multiple anomalies; CFA are often a component part.

• Isolated cleft palate (CP) is more frequently associated with congenital malformations (up to 50%), than CL/P (approximately 5 to 10%).
Oral clefts (OC)

• The most widely known and common CFA, occurring in approximately 1 in every 700 live births.

• CFA, other than cleft lip and palate, occur in 1 in every 1600 newborns and include:
  – jaw deformities,
  – malformed or missing teeth,
  – defects in the ossification of facial or cranial bones,
  – facial asymmetries.
Oral clefts (OC) are dysraphic anomalies

- Cleft lip, with or without cleft palate (CL/P)
- Cleft palate (CP)
Cleft lip, with or without cleft palate (CL/P)

- The lip forms between the fourth and seventh weeks of pregnancy.
- A cleft lip happens if the tissue that makes up the lip does not join completely before birth. This results in an opening in the upper lip. The opening in the lip can be a small slit or it can be a large opening that goes through the lip into the nose. A cleft lip can be on one (incomplete) or both sides (complete) of the lip or in the middle of the lip, which occurs very rarely.
- Children with a cleft lip also can have a cleft palate.
Cleft palate

- is a treatable birth defect.
- It happens when the roof of the baby's mouth (palate) doesn't develop normally during pregnancy, leaving an opening (cleft) in the palate that may go through to the nasal cavity.
- A cleft can form on any part of the palate, including the front part of the roof of the mouth (hard palate) or the small flap of tissue that hangs down from the soft palate.
Congenital teeth anomalies
Hypodontia, Oligodontia and Hyperdontia

• Glossary:
  – Anodontia: failure of teeth to develop (same as agenesis of teeth)
  – Hypodontia: having less than 6 congenitally missing teeth (partial anodontia).
  – Oligodontia: having 6 or more congenitally missing teeth.
  – Hyperdontia: extra teeth, same as supernumerary teeth, may be single or multiple as in cleidocranial dysplasia.
• Supernumerary teeth
  extra incisor

• Hyperdontia and Cleidocranial Dysplasia

On the slide - more than 50 teeth. This patient has cleidocranial dysplasia (CCD). This is inherited as an autosomal dominant trait, the gene maps to chromosome #6.
Taurodontism

- A morphologic abnormality of teeth called taurodontism (bull teeth) is seen in slide #12.
Dentinogenesis Imperfecta (DI)

- also known as opalescent dentin
- This is an autosomal dominant condition affecting both deciduous and permanent teeth. Affected teeth are gray to yellow-brown and have broad crowns with constriction of the cervical area resulting in a “tulip” shape. Radiographically, the teeth appear solid, lacking pulp chambers and root canals. Enamel is easily broken leading to exposure of dentin that undergoes accelerated attrition. The gene maps to chromosome #4. It encodes a protein called dentin sialophosphoprotein (DSPP). This protein constitutes about 50% of the noncollagenous component of dentin matrix.
Congenital enamel hypoplasia or Amelogenesis Imperfecta

is a genetic disorder in which there is underdevelopment of tooth enamel causing it to be unusually thin, discoloured, pitted and fragile. Rarely, it may be associated with abnormally enlarged gums which make oral hygiene difficult.
jaw bones malformations

- is disorder in the formation or shape of the jaw
  - Micrognathism
  - Prognathism
  - Retrognathism
  - Pierre Robin syndrome
Retrognathism

- abnormal posterior positioning of the maxilla or mandible, particularly the mandible, relative to the facial skeleton and soft tissues.
Micrognathism

- also called micrognathia, strawberry chin, hypognathia or hypognathism, is a condition where the jaw is undersized.
Prognathism

- an abnormal facial configuration in which one or both jaws project forward.
Anomalies of pharyngeal (branchial) arches and pouches

• Pouch anomalies:
  – cyst: no internal or external communication
  – fistula: communicates both internally and externally
  – sinus: incomplete tract
• Arch anomalies
Figure 6: Bilateral branchial cyst.

Figure 7: Saliva coming out of third branchial fistula.
1st Arch Anomalies

• Involves malformations of eyes, ears, palate, and mandible

• 2 main manifestations of “First Arch Syndrome”
  – Treacher Collins Syndrome
  – Pierre Robin Syndrome
Treacher Collins Syndrome

• Mandibulofacial dysostosis
  – Inherited autosomal dominant
  – Features:
    • Midface and mandibular hypoplasia
    • Ear anomalies: microtia, anotia, malformation of malleus and incus
    • Eye anomalies: coloboma of lower lids, downsloping palpebral fissures
    • Cleft palate
Pierre Robin syndrome (or sequence) is a condition present at birth, in which the infant has a smaller-than-normal lower jaw, a tongue that falls back in the throat, and difficulty breathing.

Pierre Robin Sequence is not a syndrome, it’s a sequence. While it is a collection of features, one happens because of the one that came before.

Pierre Robin Sequence is associated with cleft palate (50% of children with the sequence have cleft palate).

The features are:
- Retrognathia/micrognathia (posterior mandible or very small mandible)
- Glossoptosis (downwards/posterior displacement of the tongue due to the small mandible)
- Airway obstruction (because the tongue is in the way)