1.3.2 congenital abnormalities
1.3.2 congenital abnormalities:
- principles,
- patterns of anomalies,
- maternal illness,
- drug abuse,
- medications,
- infectious agents,
- malnutrition
Malformation - definition

- Congenital malformation are structural defects present at birth.
- They may be gross or microscopic, on the surface of the body or within it, familiar or sporadic, hereditary or nonhereditary, single or multiple.
- A major congenital anomaly is one that is incompatible with survival, is life-threatening, or seriously compromises an individual’s capacity to function normally in society.
- **Malformation** is a primary structural defect resulting from a localized error of morphogenesis.
- **Disruption** is a specific abnormality that results from disruption of normal developmental processes. It depends on time, not on agent.
- **Deformation** is an alteration in shape/structure of previously normally formed part.
- **Syndrome** is a recognized pattern of malformations with a given etiology.
Birth defects

- 3% of all live-born infants have an major anomaly
- Additional anomalies are detected during postnatal live – about 6% at 2 year-olds, 8% in 5-year-olds, other 2% later
- Single minor anomalies are present in about 14% of newborns
Birth defects

- Major anomalies are more common in early embryos (up to 15%) than they are in newborns (3%).
- Most severely malformed embryos are spontaneously aborted during first 6 to 8 weeks.
Causes of congenital anomalies

Figure 9–1. Graphic illustration of the causes of human congenital anomalies. Note that the causes of most anomalies are unknown and that 20 to 25% of them are caused by a combination of genetic and environmental factors (multifactorial inheritance).
Figure 3.9 Sources of Congenital Defects

- Inherited defects
  - Chromosomal abnormalities
    - Too many or too few chromosomes
    - Broken or damaged chromosomes
  - Genetic abnormalities
    - Recessive genes for a disorder
    - Dominant genes for a disorder
  - Complications of the birth process
  - Prenatal exposure to damaging effects

- Environmental defects

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Inherited defects may be due to

• 1 Chromosomal Abnormalities may be due to a change in chromosome number i.e. too many or too few chromosomes

• 2 Chromosomal Abnormalities may be due to a change in chromosome structure i.e. broken or damaged chromosomes

• 3 Genetic abnormalities

• Recessive genes for a disorder

• Dominant genes for a disorder

• 4 Genetic mutations
Anomalies caused by genetic factors

- Chromosomal aberrations are common and are present in 6 to 7% of zygotes – (result = abort)
- **Numerical chromosomal abnormalities** – usually non-disjunction- error in cell division
  - Down syndrom (21) Edwards (18) Patau (13)
  - Turner (X0), Klinenfelter (XXY)
- **Structural chromosomal abnormalities** – chromosome breaks = translocation, deletion (cri du chat syndrome), duplication, inversion.
- **Mutant genes** – achondroplasia, fragile-X syndrome
<table>
<thead>
<tr>
<th>Disorder or Abnormality</th>
<th>Main Symptoms</th>
<th>Disorder or Abnormality</th>
<th>Main Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal Recessive Inheritance</strong></td>
<td></td>
<td><strong>X-Linked Recessive Inheritance</strong></td>
<td></td>
</tr>
<tr>
<td>Albinism</td>
<td>Absence of pigmentation</td>
<td>Androgen insensitivity syndrome</td>
<td>XY individual but having some female traits; sterility</td>
</tr>
<tr>
<td>Hereditary methemoglobinemia</td>
<td>Blue skin coloration</td>
<td>Red–green color blindness</td>
<td>Inability to distinguish among some or all shades of red and green</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Abnormal glandular secretions leading to tissue, organ damage</td>
<td>Fragile X syndrome</td>
<td>Mental impairment</td>
</tr>
<tr>
<td>Ellis–van Creveld syndrome</td>
<td>Dwarfism, heart defects, polydactyly</td>
<td>Hemophilia</td>
<td>Impaired blood clotting ability</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>Physical abnormalities, bone marrow failure</td>
<td>Muscular dystrophies</td>
<td>Progressive loss of muscle function</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>Brain, liver, eye damage</td>
<td>X-linked anhidrotic dysplasia</td>
<td>Mosaic skin (patches with or without sweat glands); other effects</td>
</tr>
<tr>
<td>Phenylketonuria (PKU)</td>
<td>Mental impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle-cell anemia</td>
<td>Adverse pleiotropic effects on organs throughout body</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Autosomal Dominant Inheritance</strong></td>
<td></td>
<td><strong>Changes in Chromosome Structure</strong></td>
<td></td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>One form of dwarfism</td>
<td>Chronic myelogenous leukemia (CML)</td>
<td>Overproduction of white blood cells in bone marrow; organ malfunctions</td>
</tr>
<tr>
<td>Camptodactyly</td>
<td>Rigid, bent fingers</td>
<td>Cri-du-chat syndrome</td>
<td>Mental impairment; abnormally shaped larynx</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>High cholesterol levels in blood; eventually clogged arteries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Nervous system degenerates progressively, irreversibly</td>
<td></td>
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</tr>
<tr>
<td>Marfan syndrome</td>
<td>Abnormal or no connective tissue</td>
<td></td>
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<tr>
<td>Polydactyly</td>
<td>Extra fingers, toes, or both</td>
<td></td>
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<tr>
<td>Progeria</td>
<td>Drastic premature aging</td>
<td></td>
<td></td>
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<tr>
<td>Neurofibromatosis</td>
<td>Tumors of nervous system, skin</td>
<td></td>
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</tbody>
</table>
• ALL OF THE CONDITIONS THAT WE WILL BRIEFLY MENTION IN THIS INTRODUCTORY SESSION WILL BE DISCUSSED IN SOME DETAIL IN SUBSEQUENT SESSIONS IN THIS COURSE.

• BUT WE WILL SAY A FEW WORDS TODAY ABOUT SOME OF THESE MALADIES
Chromosomal Abnormalities

– may be too many or too few chromosomes
Chromosomal & Genetic Factors

- **Numerical Abnormalities**
  - Trisomy 21 (Down syndrome)
  - Trisomy 18
  - Trisomy 13
  - Klinefelter Syndrome
  - Turner Syndrome
  - Triple X Syndrome

- **Structural Abnormalities**

- **Mutant Genes**
Chromosomal Abnormalities

• May be numerical or structural
• Important causes of congenital malformations & spontaneous abortions
• Estimated that 50% of all conceptions end in spontaneous abortion & 50% of these have major chromosome abnormalities
• Most common chromosome abnormalities in aborted fetuses is:
  – Turner syndrome (45,X)
  – triploidy
  – trisomy 16
Numerical Abnormalities

• Normal gametes are haploid (n = 23)
• Normal human somatic cell contains 46 chromosomes; Diploid (2n = 46)
• Euploid-Exact multiple of n
• Aneuploid-Any chromosome # that is noneuploid
  – Additional chromosome
  – Missing chromosome
• Most common cause is nondisjunction during either meiosis to mitosis
  – Risk of meiotic nondisjunction with maternal age
Changes in Chromosome Structure or Number

• On rare occasions, a chromosome may undergo a large-scale, permanent change in its structure, or the number of autosomes or sex chromosomes may change.

• In humans, such changes usually result in a genetic disorder.
Heritable Changes in the Chromosome Number

• Occasionally, new individuals end up with the wrong chromosome number
  – Consequences range from minor to lethal

• **Euploids**
  – Normal number of chromosomes

• **Aneuploidy**
  – Too many or too few copies of one chromosome
  – Extra or missing chromosomes

• **Polyploidy**
  – Extra sets of chromosomes (triploids, tetraploids)
  – Three or more copies of each chromosome
  – Spindle fails during mitosis
- Organisms with more than two complete sets of chromosomes, have undergone **polypoidy**.

- This may occur when a normal gamete fertilizes another gamete in which there has been nondisjunction of all its chromosomes.
  - The resulting zygote would be *triploid* (3n).

- Alternatively, if a 2n zygote failed to divide after replicating its chromosomes, a *tetraploid* (4n) embryo would result from subsequent successful cycles of mitosis.
• Polyploids are more nearly normal in phenotype than aneuploids.
• One extra or missing chromosome apparently upsets the genetic balance during development more than does an entire extra set of chromosomes.
Aneuploids

• Abnormalities usually prevent embryo development

• Exception in humans is Down syndrome
  – Three copies of chromosome 21 (trisomy 21)
  – Physical and learning difficulties
  – Frequency of nondisjunction increases as women age
Aneuploidy of Sex Chromosomes

Nondisjunction

Fertilization by normal sperm

Resulting zygotes

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### Aneuploidy of Sex Chromosomes

**Table 13.1** Effects of Unusual Combinations of Sex Chromosomes in Humans

<table>
<thead>
<tr>
<th>Combination of Sex Chromosomes</th>
<th>Approximate Frequency</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>XO</td>
<td>1 in 5000 births</td>
<td>Turner syndrome: females with underdeveloped ovaries; sterile; intelligence and external genitalia are normal; typically, individuals are short in stature with underdeveloped breasts</td>
</tr>
<tr>
<td>XXY</td>
<td>1 in 2000 births</td>
<td>Klinefelter syndrome: male external genitalia with very small and underdeveloped testes; sterile; intelligence usually normal; sparse body hair and some development of the breasts; similar characteristics in XXXY and XXXXY individuals</td>
</tr>
<tr>
<td>XYY</td>
<td>1 in 1000 births</td>
<td>XYY syndrome: apparently normal males but often taller than average</td>
</tr>
<tr>
<td>XXX</td>
<td>1 in 1000 births</td>
<td>Triple-X syndrome: apparently normal female with normal or slightly retarded mental and physical development</td>
</tr>
</tbody>
</table>

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**Notes:**
- Turner syndrome affects females and is characterized by underdeveloped ovaries, internal organs, and secondary sex characteristics.
- Klinefelter syndrome affects males and is characterized by small testes, underdeveloped secondary sex characteristics, and intellectual disability.
- Triple-X syndrome affects females and is characterized by normal development.
Polyploids

- Uncommon in animals
  - Usually has lethal effects during embryonic development
Numerical abnormalities

- **euploidy** - normal 46 (2n)
- **polyploidy** (3n or 4n) - spontaneous abortion
- **aneuploidy**
- **trisomy (2n+1) - 47** - compatible with life
- **monosomy (2n-1)** - autosomal - incompatible with life
- - sex chromosomal - compatible with life
Alterations of chromosome number or structure cause some genetic disorders

- **Nondisjunction** occurs when problems with the meiotic spindle cause errors in daughter cells.
  - This may occur if tetrad chromosomes do not separate properly during meiosis I.
  - Alternatively, sister chromatids may fail to separate during meiosis II.
As a consequence of nondisjunction, some gametes receive two of the same type of chromosome and another gamete receives no copy.

Offspring results from fertilization of a normal gamete with one after nondisjunction will have an abnormal chromosome number or aneuploidy.

- **Trisomic** cells have three copies of a particular chromosome type and have $2n + 1$ total chromosomes.

- **Monosomic** cells have only one copy of a particular chromosome type and have $2n - 1$ chromosomes.

If the organism survives, aneuploidy typically leads to a distinct phenotype.
Nondisjunction

• Changes in chromosome number can be caused by **nondisjunction**, when a pair of chromosomes fails to separate properly during mitosis or meiosis

• Affects the chromosome number at fertilization
  – Monosomy ($n-1$ gamete)
  – Trisomy ($n+1$ gamete)
Nondisjunction

1. Chromosome alignments at metaphase I
2. Nondisjunction at anaphase I
3. Alignments at metaphase II
4. Anaphase II
5. Chromosome number in gametes

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Nondisjunction (1)

- Failure of homologous pair separation during Meiosis I

Nondisjunction during the first meiotic division causes both chromosomes of one pair to be delivered to the same pole of the spindle. The nondisjunction produces two gametes with an extra chromosome and two with a missing chromosome.
Nondisjunction (2)

• Failure of chromatid separation during Meiosis II

Nondisjunction during the second meiotic division produces two normal gametes, one gamete with an extra chromosome and one gamete with a missing chromosome.
Autosomal Change and Down Syndrome

• Only trisomy 21 (Down syndrome) allows survival to adulthood
  – Characteristics include physical appearance, mental impairment, and heart defects

• Incidence of nondisjunction increases with maternal age

• Can be detected through prenatal diagnosis
Trisomy 21
Fig. 12-13b, p. 194

chromosome alignments at metaphase I

NONDISJUNCTION AT ANAPHASE I

alignments at metaphase II

anaphase II

CHROMOSOME NUMBER IN GAMETES

$n + 1$

$n - 1$
• (a) A case of nondisjunction. This karyotype reveals the trisomic 21 condition of a human female.

• (b) One example of how nondisjunction arises.

• Of the two pairs of homologous chromosomes shown here, one fails to separate during anaphase I of meiosis.

• The chromosome number is altered in the gametes that form after meiosis.
Down's Syndrome

• Caused by non-disjunction of the 21st chromosome.

• This means that the individual has a trisomy (3 – 21st chromosomes).
Down’s Syndrome
or Trisomy 21
Down Syndrome and Maternal Age
Down Syndrome

a. Chromosome diagram showing an extra chromosome 21.

b. Graph showing the incidence of Down syndrome per 1000 births versus mother’s age.
Change in Sex Chromosome Number

• Changes in sex chromosome number may impair learning or motor skills, or be undetected

• Female sex chromosome abnormalities
  – Turner syndrome (XO)
  – XXX syndrome (three or more X chromosomes)

• Male sex chromosome abnormalities
  – Klinefelter syndrome (XXY)
  – XYY syndrome
Kleinfelter’s syndrome
(or Klinefleter’s)

• Disorder occurring due to nondisjunction of the X chromosome.
• The Sperm containing both X and Y combines with an egg containing the X, results in a male child.
• The egg may contribute the extra X chromosome.
• Klinefleter's
Turner Syndrome

• XO (one unpaired X chromosome)
  – Usually caused by nondisjunction in the father
  – Results in females with undeveloped ovaries
Broken or damaged chromosomes
Structural abnormalities

- breakage followed by loss or rearrangement
- deletion, translocation

**Generally:**
- loss of chromosomal material is more dangerous than gain
- abnormalities of sex chromosomes are better tolerated than autosomal
- abnormalities of sex chromosomes sometimes symptomatic in adult age (e.g. infertility)
- usually origin de novo (both parents and siblings are normal)
Heritable Changes in Chromosome Structure

- On rare occasions, a chromosome’s structure changes; such changes are usually harmful or lethal, rarely neutral or beneficial.

- A segment of a chromosome may be duplicated, deleted, inverted, or translocated.
Chromosomal Alterations

- **Deletion**: broken segment lost from chromosome
- **Duplication**: broken segment inserted into homologous chromosome
• Breakage of a chromosome can lead to four types of changes in chromosome structure.

• **A deletion** occurs when a chromosome fragment lacking a centromere is lost during cell division.
  – This chromosome will be missing certain genes.

• **A duplication** occurs when a fragment becomes attached as an extra segment to a
**Chromosomal Alterations (2)**

- **Translocation**: broken segment attached to nonhomologous chromosome

- **Inversion**: broken segment reattached in reversed orientation
• **An inversion** occurs when a chromosomal fragment reattaches to the original chromosome but in the reverse orientation.

• **In translocation**, a chromosomal fragment joins a nonhomologous chromosome.
  – Some translocations are reciprocal, others are not.

---

(c) An inversion reverses a segment within a chromosome.

(d) A translocation moves a segment from one chromosome to another, non-homologous one.
Deletion

- Loss of some portion of a chromosome; usually causes serious or lethal disorders

![Diagram showing deletion of segment C](image-url)
Deletions

- When homozygous, most deletions are lethal, because most genes are necessary for life and a homozygous deletion would have zero copies of some genes.
- When heterozygous, the genes on the normal homologue are hemizygous: there is only 1 copy of those genes, and thus they are expressed even if recessive (like genes on the X in male mammals).
- Heterozygous deletions are aneuploid, because the genes in the deleted region are present in only 1 copy instead of the normal two copies. Some genes need to be present in two copies, so heterozygous deletions sometimes give rise to defects in the affected individual, especially if the deletions are large.
Cri du chat syndrome

• also known as chromosome 5p deletion syndrome, 5p minus syndrome or Lejeune’s syndrome, is a rare genetic disorder due to a missing part of chromosome 5.

• Its name is a French term (cat-cry or call of the cat) referring to the characteristic cat-like cry of affected children.
Deletion: Cri-du-chat

Infant

4 years old
For most genes it is a reasonable assumption that a specific allele will have the same effect regardless of whether it was inherited from the mother or father.

However, for some traits in mammals, it does depend on which parent passed along the alleles for those traits.

- The genes involved may or may not lie on the X chromosome.
- Involves “essential” silencing of one allele during gamete formation.

The phenotypic effects of some mammalian genes depend on whether they were inherited from the mother or the father (genomic imprinting).
Two disorders, Prader-Willi syndrome and Angelman syndrome, with different phenotypic effects are due to the same cause, a deletion of a specific segment of chromosome 15.

- Individuals with Prader-Willi syndrome are characterized by mental retardation, obesity, short stature, and unusually small hands and feet.
- These individuals inherit the abnormal chromosome from their father.
- Individuals with Angelman syndrome exhibit spontaneous laughter, jerky movements, and other motor and mental symptoms.
- This is inherited from the mother.
Duplication

- DNA sequences are repeated two or more times; may be caused by unequal crossovers in prophase I
Duplications

• Genes are duplicated if there is more than one copy present in the haploid genome.

• Some duplications are “dispersed”, found in very different locations from each other.

• Other duplications are “tandem”, found next to each other.
Translocation

- Typically, two broken chromosomes exchange parts (reciprocal translocation)
Translocations

- In a translocation, two different, non-homologous chromosomes are broken and rejoined to each other. All the genes are present, so an individual with a translocation can be completely normal. However, an individual who is heterozygous for a translocation and a set of normal chromosomes can have fertility problems.

- The problem occurs during meiosis 1, as the result of confusion about how the chromosomes should segregate to opposite poles.

- During prophase and metaphase of M1, the homologous chromosomes pair up. Because translocations have pieces of two different chromosomes attached together, they pair up in a cross-shaped configuration, so all the pieces have a partner. This structure is three-dimensional, not flat, and there is ambiguity about which centromeres are attached to which pole of the spindle.

- When anaphase occurs, two main possibilities exist: alternate segregation, where centromeres on opposite sides of the cross go to the same pole, and adjacent segregation, where centromeres on the same side of the cross go to the same pole.
Translocational Down Syndrome

• Most cases of Down syndrome, trisomy-21, are spontaneous. They are caused by non-disjunction which gives an egg or sperm with two copies of chromosome 21.

• However, about 5% of Down’s cases are caused by a translocation between chromosome 21 and chromosome 14. These translocational Down’s cases are heritable: several children in the same family can have the disease.

• Both chromosome 14 and chromosome 21 are acrocentric, and the short arms contain no essential genes.

• Sometimes a translocation occurs that joins the long arms together on one centromere and the short arms on another centromere. In this case the short arm chromosome is usually lost. The individual thus has a normal chromosome 14, a normal chromosome 21, and a translocation chromosome, called t(14;21).

• During meiosis, one possible gamete that occurs has both the normal 21 and the t(14;21) in it. When fertilized, the resulting zygote has 2 copies of the important parts of chromosome 14, but 3 copies of chromosome 21: 2 normal copies plus the long arm on the translocation. This zygote develops into a person with Down syndrome.
Inversion

• Part of the sequence of DNA becomes oriented in the reverse direction, with no molecular loss.
Inversions

• An inversion is when a segment of a chromosome is removed and then replaced backwards.
• The problem with inversions occurs in meiosis, when a chromosome containing an inversion is heterozygous with a normal chromosome. A crossover within the inverted region results in aneuploidy and death of the resulting embryo.
• One consequence of this is that crossing over is apparently suppressed.
• Inversions can be either paracentric, where the centromere is NOT in the inverted region, or pericentric, where the inversion is in the inverted region.
Genetic abnormalities

Recessive genes for a disorder
Dominant genes for a disorder
Medical Genetics

When studying rare disorders, 6 general patterns of inheritance are observed:

• Autosomal recessive
• Autosomal dominant
• X-linked recessive
• X-linked dominant
• Codominant
• Mitochondrial
Autosomal recessive

• The disease appears in male and female children of unaffected parents.
• e.g., cystic fibrosis
Autosomal dominant

- Affected males and females appear in each generation of the pedigree.
- Affected mothers and fathers transmit the phenotype to both sons and daughters.
- e.g., Huntington disease.
X-linked recessive

- Many more males than females show the disorder.
- All the daughters of an affected male are “carriers”.
- None of the sons of an affected male show the disorder or are carriers.
- e.g., hemophilia
Medical Genetics (cont.)

X-linked dominant

- Affected males pass the disorder to all daughters but to none of their sons.
- Affected heterozygous females married to unaffected males pass the condition to half their sons and daughters.
- e.g. fragile X syndrome
Codominant inheritance

- Two different versions (alleles) of a gene can be expressed, and each version makes a slightly different protein.
- Both alleles influence the genetic trait or determine the characteristics of the genetic condition.
- E.g. ABO locus
Mitochondrial inheritance

- This type of inheritance applies to genes in mitochondrial DNA
- Mitochondrial disorders can appear in every generation of a family and can affect both males and females, but fathers do not pass mitochondrial traits to their children.
- E.g. Leber's hereditary optic neuropathy (LHON)
Genetic mutations
• Genetic Abnormalities
  – Many passed to children by parents who are carriers of recessive alleles
  – Some are caused by dominant alleles
  – Some result from mutations – changes in structure of one or more genes
    • Spontaneous
    • Environmental hazards
Defining Genetic Disorders and Abnormalities

- **Genetic abnormality**
  - A rare or uncommon version of a trait; not inherently life threatening

- **Genetic disorder**
  - An inherited condition that causes mild to severe medical problems, characterized by a specific set of symptoms (a syndrome)
Recurring Genetic Disorders

• Mutations that cause genetic disorders are rare and put their bearers at risk

• Such mutations survive in populations for several reasons
  – Reintroduction by new mutations
  – Recessive alleles are masked in heterozygotes
  – Heterozygotes may have an advantage in a specific environment
Mutations

- Gene mutations can be either inherited from a parent or acquired.
- A hereditary mutation is a mistake that is present in the DNA of virtually all body cells.
- Hereditary mutations are also called germ line mutations because the gene change exists in the reproductive cells and can be passed from generation to generation, from parent to newborn. Moreover, the mutation is copied every time body cells divide.
• Mutations occur all the time in every cell in the body.

• Each cell, however, has the remarkable ability to recognize mistakes and fix them before it passes them along to its descendants. But a cell's DNA repair mechanisms can fail, or be overwhelmed, or become less efficient with age. Over time, mistakes can accumulate.
# Disease Mutations

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single mutations</td>
<td>Fragile X</td>
</tr>
<tr>
<td></td>
<td>Sickle Cell Anemia</td>
</tr>
<tr>
<td>Common mutations</td>
<td>Deafness</td>
</tr>
<tr>
<td></td>
<td>Hemochromatosis</td>
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<tr>
<td>Panel of mutations</td>
<td>Cystic Fibrosis</td>
</tr>
<tr>
<td>Private mutations</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer</td>
</tr>
</tbody>
</table>
Mutations

A mutation may be defined as a permanent change in the DNA.

Mutations that affect the germ cells are transmitted to the progeny and may give rise to inherited diseases.

Mutations that arise in somatic cells are important in the genesis of cancers and some congenital malformations.
Mutations may be classified into three categories:

*Genome mutations* – involve loss or gain of whole chromosomes (giving rise to monosomy or trisomy)

*Chromosome mutations* – result from rearrangement of genetic material and give rise to visible structural changes in the chromosome.

*Gene mutations* – may result in partial or complete deletion of a gene or, more often, affect a single base. For example, a single nucleotide base may be substituted by a different base, resulting in a point mutation.
Autosomal dominant disorders  (neurofibromatosis, tuberous sclerosis, polycystic kidney disease, familial polyposis coli, hereditary spherocytosis, Marfan syndrome, osteogenesis imperfecta, achondroplasia, familial hypercholesterolemia)

Autosomal recessive disorders  (cystic fibrosis, phenylketonuria, homocystinuria, hemochromatosis, sickle cell anemia, thalassemias, alkaptonuria, neurogenic muscular atrophies)

X-linked disorders  (glucose-6-phosphate dehydrogenase deficiency)
Biochemical and molecular basis of single-gene disorders

1) Enzyme defects and their consequences

2) Defects in receptors and transport systems

3) Alterations in structure, function or quantity of nonenzyme proteins

4) Genetically determined adverse reactions to drugs.
1-Disorders associated with defects in structural proteins

Marfan syndrome

A disorder of the connective tissues of the body, manifested principally by changes in the skeleton, eyes, and cardiovascular system.

Ehlers-Danlos syndromes

A clinically and genetically heterogeneous group of disorders that result from some defect in collagen synthesis or structure (other disorders resulting from mutations affecting collagen synthesis include osteogenesis imperfecta, Alport syndrome, epidermolysis bullosa)
2- Disorders associated with defects in receptor proteins

Familiar hypercholesterolemia
A disease that is the consequence of a mutation in the gene encoding the receptor for low-density lipoprotein (LDL), which is involved in the transport and metabolism of cholesterol. More than 150 mutations, including insertions, deletions, and missense and nonsense mutations, involving the LDL receptor gene have been identified.
• These can be classified into five groups: Class I mutations - uncommon, they lead to a complete failure of synthesis of the receptor protein.
• Class II mutations - common, they encode receptor proteins that accumulate in the endoplasmic reticulum because they cannot be transported to the Golgi complex.
• Class III mutations - affect the LDL-binding domain of the receptor.
• Class IV mutations - encode proteins that are synthesized and transported to the cell surface efficiently, they bind LDH normally, but the bound LDL is not internalized.
• Class V mutations - encode proteins that are expressed on the cell surface, can bind LDL, and can be internalized, however, the acid-dependent dissociation of the receptor and the bound LDL fails to occur.
3-Disorders associated with defects in enzymes

**Lysosomal storage diseases:** Lysosomes contain different types of hydrolytic enzymes, which can cleave various substrates in the acid milieu and can be secreted.

With an inherited deficiency of a functional lysosomal enzyme, catabolism of its substrate remains incomplete, leading to the accumulation of the partially degraded insoluble metabolite within the lysosomes.

These organells become large and numerous giving rise to the lysosomal storage disorders.

These disorders result exclusively from mutations that lead to reduced synthesis of lysosomal enzymes.
• There are also other defects: Synthesis of a catalytically inactive proteins that cross-react immunologically with normal enzymes, so the enzyme level appear to be normal.,., defects in post-translational processing of enzymes (example is a failure of mannose-6-phosphate receptor), lack of an enzyme activator or protector protein, lack of a substrate activator protein, lack of transport protein.
The lysosomal storage disorders can be divided into:

1. Glycogenoses,
2. Sphingolipidoses (lipidoses),
3. Mucopolysaccharidoses, and

Examples follow:
Disorders associated with defects in enzymes

*Tay-Sachs disease* – GM2 gangliosidosis, hexosaminidase $\alpha$-subunit deficiency, GM2 ganglioside accumulates in heart, liver, spleen etc., destruction of neurons, proliferation of microglia and accumulation of lipids in phagocytes within the brain.

*Niemann-Pick disease* – types A and B, two related disorders with lysosomal accumulation of sphingomyelin, deficiency of sphingomyelinase, 80% of all cases represents type A – the severe infantile form with neurologic involvement, visceral accumulation of sphingomyelin and early death within the first 3 years of life.

*Gaucher disease* – a cluster of autosomal recessive disorders resulting from mutations in the gene encoding glucocerebrosidase, the most common lysosomal storage disorder, accumulation of glucocerebrosides, types I-III, the glucocerebrosides accumulate within phagocytes (Gaucher cells) throughout the body – spleen, liver, bone marrow, lymph nodes, tonsils thymus etc.
Disorders associated with defects in enzymes

**Mucopolysaccharidoses (MPS)** – the deficiencies of lysosomal enzymes involved in the degradation of mucopolysaccharides (glycosaminoglycans), several clinical variants classified from MPS I (Hurler syndrome) to MPS VII, each resulting from the deficiency of one specific enzyme, all the MPS except one are autosomal recessive disorders, the exception (Hynter syndrome) is an X-linked recessive disorder, involvement of multiple organs including liver, spleen, heart, blood vessels, joint stiffness, mental retardation.

**Glycogen storage diseases** – resulting from a hereditary deficiency of one of the enzymes involved in the synthesis or sequential degradation of glycogen, 3 forms: hepatic, myopathic, miscellaneous (deficiency of α-glucosidase and lack of branching enzymes, type II – Pompe disease and type IV, death early in life.
Disorders associated with defects in enzymes

Alkaptonuria (Ochronosis) – an autosomal recessive disorder in which the lack of homogentisic oxidase blocks the metabolism of phenylalanine-tyrosine at the level of homogentisic acid, homogentisic acid accumulates in the body, it selectively binds to collagen in connective tissues, tendons, and cartilage, these tissues have a blue-black pigmentation (ochronosis) most evident in the ears, nose, and cheeks, the deposits of the pigment in the articular cartilages cause the cartilage to lose its normal structure and function resulting in osteoarthritis.
Disorders associated with defects in proteins that regulate cell growth

**Neurofibromatosis:** *types 1 and 2* – two autosomal dominant disorders, neurofibromatosis type 1 previously called von Recklinghausen disease, neurofibromatosis type 2 previously called acoustic neurofibromatosis. Although there is some overlap in clinical features, these two entities are genetically distinct.
Disorders associated with defects in proteins that regulate cell growth

**Neurofibromatosis-1:** The neurofibromatosis 1 gene (NF-1) has been mapped to chromosome 17q11.2. It encodes a protein called neurofibromin, which down-regulates the function of the p21ras oncoprotein. NF-1 therefore belongs to the family of tumor-suppressor genes. Three major features of disorder – multiple neural tumors (neurofibromas) dispersed anywhere on or in the body, numerous pigmented skin lesions, and pigmented iris hamartomas, also called Lisch nodules. A wide range of associated abnormalities has been reported in these patients – skeletal lesions like erosive defects, scoliosis, intraosseous cystic lesions, subperiosteal bone cysts, pseudoarthrosis of the tibia. Patients have also a twofold to fourfold greater risk of developing other tumors (Wilm´s tumor, rhabdomyosarkoma, meningioma, optic glioma, pheochromocytoma, chronic myeloid leukemia). There is also tendency for reduced intelligence. Whem neurofibromas arise within gastrointestinal tract, intestinal obstruction or bleeding may occur. A frequency about 1 in 3000.
Disorders associated with defects in proteins that regulate cell growth

Neurofibromatosis-2: an autosomal dominant disorder in which patients develop a range of tumors – bilateral acoustic schwannomas, multiple meningiomas, gliomas, ependymomas of the spinal cord, and/or non-neoplastic lesions – nodular ingrowth of Schwann’s cells into the spinal cors, meningiomatosis, glial hamartia. Pigmented (café au lait) spots like NF-1 are present, but Lisch nodules are not found. The NF-2 gene, located on chromosome 22q12, is also a tumor-suppressor gene, the product of this gene called merlin shows structural similarity to a series of cytoskeletal proteins, but is function remains uncertain. An frequency about 1 in 45,000.
5 Disorders with multifactorial inheritance

**Down syndrome (trisomy 21):** The incidence in newborns is about 1 in 700, the most common cause is meiotic nondisjunction of genetic material, symptoms: the mental retardation (IQ of 25 to 50), 40% congenital heart malformations, atresias of esophagus and small bowel, 10-fold to 20-fold increased risk of developing acute leukemia, 100% patients after 40 years of age haveneuropathologic changes, Alzheimer disease, a degenerative changes of brain, abnormal immune responses.

**Edwards syndrome** (trisomy 18), **Patau syndrome** (trisomy 13): like Down sy., however, the malformations are much more severe and wide-ranging. These infants only rarely survive beyond the first year of life.

**DiGeorge syndrome (chromosome 22q11 deletion** – a small deletion of band 11 on the long arm of chromosome 22): Thymic hypoplasia, congenital heart defects, abnormalities of the palate, facial dysmorphism, developmental delay, and variable degrees of T-cell immunodeficiency and hypocalcemia. The molecular basis of this syndrome is not known. The similar clinical and cytogenetic feature has **velocardiofacial syndrome,** which includes facial dysmorphism (prominet nose, retrognathia), cleft palate, cardiovascular anomalies, and learning disabilities, the immunodeficiency is less frequent.
Disorders with multifactorial inheritance

*Klinefelter syndrome* (2 or more X chromosomes and 1 or more Y chromosomes): male hypogonandism, eunuchoid body habitus, infertility, cryptorchidism, hypospadias, skeletal changes.

*XYY syndrome*: Individuals are excessively tall, may be susceptible to severe acne, the intelligence is in the normal range, only 1-2% of individuals exhibit deviant behavior.

*Turner syndrome (complete or partial monosomy of the X chromosome)*: hypogonandism with female phenotype, short body, webbing of neck, heart anomalies, infertility, amenorrhea, pigmented nevi, peripheral lymphedema at birth.
6- Single-gene disorders with nonclassic inheritance

Diseases caused by triplet-repeat mutations (fragile X chromosome syndrome): The mutation which is characterized by a long repeating sequence of three nucleotides CGG. It is the second most common genetic cause of mental retardation after Down sy. The affected males are mentally retarded (IQ 20-60) with a long face and large mandibule, large everted ears, and large testicles (macro-orchidism). 50% of affected females have mental retardation.

Diseases caused by mutations in mitochondrial genes (leber hereditary optic neuropathy)

Diseases associated with genomic imprinting (Prader-Willi syndrome)

Diseases associated with gonadal mosaicism (germ line mosaicism, gonadal mosaicism)
Congenital Malformations/abnormalities

• Causes
  – Genetic/chromosomal
  – Environmental

• Incidence
  – 2-3% of newborn (4-6% by age 5)
  – In 40-60% of all birth defects cause is unknown
    • Genetic/chromosomal
      – 10%-15%
    • Environmental
      – 10%
    • Multifactorial (genetic & environmental)
      – 20%-25%
Types of Anomalies

- **Malformations**
  - Occur during formation of structures
    - Complete or partial absence
    - Alterations of its normal configuration

- **Disruptions**
  - Morphological alterations of structures after formation
    - Due to destructive processes
      - Vascular accidents! bowel atresias
Types of Anomalies (cont.)

• **Deformations**
  - Due to mechanical forces that mold a part of fetus over a prolonged period of time
    - Clubfeet due to compression in the amniotic cavity
    - Often involve the musculoskeletal system & may be reversible postnatally

• **Syndromes**
  - Group of anomalies occurring together with a specific common etiology
    - Diagnosis made & risk of recurrence is known
Syndrome examples

- **CHARGE**
  - Colobomas
  - Heart defects
  - Atresia of the choanae
  - Retarded growth
  - Genital anomalies
  - Ear anomalies

- **VACTERLI**
  - Verterbral anomalies (A)
  - Anal A
  - Cardiac A
  - Tracheoesophageal A
  - Renal A
  - Limb A
• 1.3.2 congenital abnormalities:
• principles,
• patterns of anomalies,
• maternal illness,
• drug abuse, ----chemical agents, hormones
• medications,
• infectious agents,
• malnutrition/nutritional deficiencies
Congenital malformations

- structural defects present at birth - some may become apparent later!
- etiology is either genetic or environmental
- viral infections (rubella, CMV) - during first 3M
- other infectious (toxoplasmosis, syphilis, HIV)
- drugs (thalidomide, alcohol, cytostatics)
- irradiation
- in 40-60% is the cause unknown!
Anomalies caused by environmental factors

- **Teratogens** are exogeneous agents that may cause developmental defects:
  - **Drugs** (warfarin, valproic acid, phenytoin, vitamin A, thalidomide, cytostatic drugs – cyclophosphamide, lithium carbonate)
  - **Chemicals** (PCBs, methylmercury, alcohols)
  - **Infections** (rubella, cytomegalovirus, herpes, toxoplasma, syphilis)
  - **Ionizing radiation** (RTG)
  - **Maternal factors** (diabetes mellitus, hyperthermia, phenylketonuria, hyper-/hypo-thyreosis)
Perinatal infections

- **ascending (transcervical)** - in utero or during birth (HSV, HIV)
- **transplacental** - syphilis, toxoplasmosis, rubella, CMV
Maternal Disease

• Disturbances in CHO metabolism (diabetic mothers)
  – High incidence of stillbirth, neonatal deaths
  – Abnormally large infants
  – Congenital malformations
    – Risk 3-4X
  • Cardiac, Skeletal, CNS Anomalies
  • Caudal dysgenesis
    – Partial or complete agenesis of sacral vertebrae in conjunction with hindlimb hypoplasia
  – Hypoglycemic episodes! teratogenic (why?)
  – Oral hypoglycemic agents! maybe teratogenic
Maternal Disease (cont.)

- Phenylketonuria (PKU)
  - Enzyme phenylalanine hydroxylase is deficient! phenylalanine (PA) concentrations
    - Mental retardation
    - Microcephaly
  - Risk can be! with low PA diet
Chemical agents/Drugs

• Role of chemical agents & drugs in production of anomalies is difficult to assess
  – Most studies are retrospective
    • Relying on mother’s memory
  – Large # of pharmaceutical drugs used by pregnant women
    • NIH study – 900 drugs taken by pregnant women
      – Average of 4/woman during pregnancy
      – Only 20% of women use no drugs during pregnancy
  – Very few drugs have been positively identified as being teratogenic
Recreational drugs

• PCP angel dust
  – Possible malformations & behavioral disturbances

• Cocaine-vasoconstrictor ! hypoxia
  – Spontaneous abortion
  – Growth retardation
  – Microcephaly
  – Behavioral problems
  – Urogenital anomalies
  – gastroschisis
Alcohol

• Relationship between alcohol consumption & congenital abnormalities

• Fetal alcohol syndrome
  – Craniofacial abnormalities
    • Short palpebral fissures
    • Hypoplasia of the maxilla
  – Limb deformities
    • Altered joint mobility & position
  – Cardiovascular defects
    • Ventricular septal abnormalities
  – Mental retardation
  – Growth deficiency
Alcohol (Ethanol)

Ethanol is the causative agent of Fetal Alcohol Syndrome (FAS). FAS is seen in approximately 2 in 1000 live births, depending upon culture and socioeconomic status. For instance, there is an occurrences of FAS in 19.5:1000 live births in American Native Indian culture verses a rate of 1.9:1000 in middle class Caucasian families. **FAS does seem to be dose dependant in that greater amounts of alcohol consumed increases the chances of having an FAS child.**
Fetal alcohol syndrome
FAS was formally defined in 1970 as containing a combination of the malformations seen below:

<table>
<thead>
<tr>
<th>Growth deficiencies</th>
<th>Maxillary hypoplasia</th>
<th>Decreased philtrum size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microphthalmia</td>
<td>Microcephally</td>
<td>Narrow upper lip</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>Short palpebral fissures</td>
<td>Low nose bridge</td>
</tr>
<tr>
<td>Small brain size</td>
<td></td>
<td></td>
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</tbody>
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**Fetal alcohol effects (FAE)**
Neural crest cells are particularly sensitive to alcohol-induced injury and cell death.

Alcohol interferes with the development of neurotransmitter systems.
Fatal alcohol syndrome

Due to high level of alcohol intake during early pregnancy

Thin upper lip, Flat nasal bridge, Short nose, microcephaly

Elongated and poorly formed philtrum (vertical groove in median part of upper lip)

Mental retardation
Cigarette Smoking

• Has **not** been linked to major birth defects
  – Smoking does contribute to intrauterine growth retardation & premature delivery
  – Some evidence that is causes behavioral disturbances
Drugs

• **Thalidomide**
  – Antinauseant & sleeping pill
  – Found to cause amelia & meromelia
    • Total or partial absence of the extremities
  – Intestinal atresia
  – Cardiac abnormalities
  – Many women had taken thalidomide early in pregnancy (in Germany in 1961)
Amelia and meromelia

A) Quadruple amelia (complete absence of the upper and lower limbs).

B, C) Meromelia (partial absence) of the upper limb.

due to thalidomide.

caused by thalidomide.
Various types of meromelia

Partial absence of limbs (disturbance of growth of limb)

A) absence of hands and most of fore-arms
B) absence of the digits
C) absence of the hand
D) absence of the fourth and fifth digits, syndactyly of the second and third digit
E) absence of third digit, cleft hand
F) absence of second and third toes, syndactyly of fourth and fifth toes
Meromelia

Limb reduction

Caused by thalidomide ingested during critical period of limb development
Drugs (cont.)

• Aminopterin
  – Antagonist of Folic Acid
  – Antineoplastic agent which inhibits mitosis
  – Defects
    • Anencephaly
    • Meningocele
    • Hydrocephalus
    • Cleft lip & palate
Aminopterin-induced abnormalities

Is an anti-metabolite drug

A) meroanencephaly (partial absence of the brain)

B) intrauterine growth retardation, large head, small mandibles, deformed ears, clubhands and clubfoots
Drugs (cont.)

- **Anticonvulsants (to treat epilepsy)**
  - Diphenylhydantoin (phenytoin)
    - Craniofacial defects
    - Nail & digital hypoplasia
    - Growth abnormalities
    - Mental deficiency
    - The above pattern is known as “fetal hydantoin syndrome”
  - Valproic acid
    - Neural tube defects
    - Heart defects
    - Craniofacial & limb anomalies
• **Trimethadione (syndrome)**
  – Malformed ears
  – Cleft palate
  – Cardiac defects
  – Urogenital anomalies
  – Skeletal anomalies
Drugs (cont.)

- Antipsychotic drugs (major tranquilizers)
  - Phenothiazine & lithium
    - Suspected teratogenic agents
- Antianxiety drugs (minor tranquilizers)
  - Meprobamate, chlordiazepoxide,
    - Severe anomalies in 11-12% of offspring where mothers were treated with the above compared to 2.6% of controls
  - Diazepam (valium)
    - Fourfold in cleft lip with or without cleft palate
Drugs (cont.)

• **Anticoagulants**
  – Warfarin (A.K.A cumadin or cumarol)
    • Teratogenic
    • Hypoplasia of nasal cartilage
    • Chondrodysplasia
    • Central nervous system defects
      – Mental retardation
      – Atrophy of the optic nerves

• **Antihypertensive agents**
  – angiotensin converting enzyme (ACE) inhibitor
    • Growth dysfunction, renal dysfunction, oligohydramnios, fetal death
Drugs (cont)

• Propylthiouracil
  – Goiter
  – Mental retardation

• Potassium iodide
  – Goiter
  – Mental retardation

• Streptomycin
  – Deafness

• Sulfonamides
  – Kernicterus

• Imipramine (antidepr.)
  – Limb deformities

• Tetracyclines
  – Bone & tooth anomalies

• Amphetamines
  – Oral clefts
  – CV abnormalities

• Quinine
  – Deafness

• Aspirin
  – Potentially harmful in large doses
Drugs (cont.)

• **Isotretinoin (13-cis-retinoic acid)**
  – Analogue of vitamin A
  – Drug is prescribed for treatment of cystic acne & other chronic dermatoses
  – Highly teratogenic
    • Reduced & abnormal ear development
    • Flat nasal bridge
    • Cleft palate
    • Hydrocephaly
    • Neural tube defects
    • Heart anomalies
Hormones

• **Androgenic Agents**
  – Synthetic progestins were used frequently to prevent abortion
    • Ethisterone & norethisterone
      – Have considerable androgenic activity
        » Masculinization of female genitalia

• **Diethylstilbesterol**
  – Commonly used in the 1940’s & 1950’s to prevent abortion; in 1971 determined that DES caused increased incidence of vaginal & cervical cancer in women who had been exposed to DES in utero
  – In addition high % suffered from reproductive dysfunction

• **Oral Contraceptives**
  – Low teratogenic potential, discontinue if pregnancy suspected

• **Cortisone**-cleft palate in mice (not humans)
Infectious Agents

• Rubella (German Measles)
  – Malformations of the eye
    • Cataract (6\textsuperscript{th} week)
    • Microphthalmia
  – Malformations of the ear (9\textsuperscript{th} week)
    • Congenital deafness
      – Due to destruction of cochlea
  – Malformations of the heart (5\textsuperscript{th} -10\textsuperscript{th} week)
    • Patent ductus arteriosus
    • Atrial septal defects
    • Ventricular septal defects
Infectious Agents (cont.)

• **Rubella (German measles)**
  – May be responsible for some brain abnormalities
    • Mental retardation
  – Intrauterine growth retardation
  – Myocardial damage
  – Vascular abnormalities

– Incidence
  • 47% - during 1st four weeks
  • 22% - 5th – 8th weeks
  • 13% - 9th – 16th week
Infectious Agents (cont.)

• Rubella (cont.)
  – Lab tests permit detection of virus
  – Antibody levels can be determined
  – In one study 85% of women tested were immune (n = 600)
  – Virus infects fetus via the placenta
    • Infection of the child may persist after birth for a number of years
      – Infection can be transmitted to hospital personnel
  – Vaccines are considered safe & effective
Cataract and glaucoma

A) bilateral cataract caused by Rubella virus also have cardiac defect and deafness.

B) congenital glaucoma caused by Rubella virus with enlarged corneal diameter.
Infectious Agents (cont.)

- **Cytomegalovirus**
  - Disease is often fatal early on
  - **Malformations**
    - Microcephaly
  - **Cerebral calcifications**
  - **Blindness**
    - Chorioretinitis
  - **Kernicterus** (a form of jaundice)
    - multiple petechiae of skin
  - **Hepatosplenomegaly**
  - Mother asymptomatic
Infectious Agents (cont.)

• **Herpes Simplex Virus**
  – Intrauterine infection of fetus occasionally occurs
  – Usually infection is transmitted close to time of delivery
  – Abnormalities (rare)
    • Microcephaly
    • Microphthalmos
    • Retinal dysplasia
    • Hepatosplenomegaly
    • Mental retardation
  – Usually child infected by mother at birth
    • Inflammatory reactions during first few weeks
Infectious Agents (cont.)

• **Varicella (chickenpox)**
  – Congenital anomalies
    • 20% incidence following infection in 1\textsuperscript{st} trimester
    • Limb hypoplasia
    • Mental retardation
    • Muscle atrophy

• **HIV/AIDS**
  – Microcephaly
  – Growth retardation
  – Abnormal facies (expression or appearance of the face)
Infectious Agents (cont.)

• **Toxoplasmosis**
  – Protozoa parasite (*Toxoplasma gondii*)
    • Sources
      – Poorly cooked meat
      – Domestic animals (cats)
      – Contaminated soil with feces

• **Syphilis**
  – Congenital deafness
  – Mental retardation
  – Diffuse fibrosis of organs (eg. liver & lungs)

• In general most infections are pyrogenic
  – Hyperthemia can be teratogenic
    • Fever
    • Hot tubs & Saunas
TORCHS Infections

- **Toxoplasmosis**
  - Rash, seizures, microcephaly/microphthalmia

- **Rubella**
  - Heart defects, deafness, neurologic abnormalities

- **Cytomegalovirus**
  - IUGR, purpura, chorioretinitis, microcephaly

- **Herpes simplex virus**
  - Disseminated or localized HSV (CNS, skin, eye)

- **Syphilis**
  - "Snuffles," rash of trunk, palm and soles
Environmental factors

- Radiation
- Hypoxia
Radiation

- Teratogenic effect of ionizing radiation well established
  - Microcephaly
  - Skull defects
  - Spina bifida
  - Blindness cleft palate
  - Extremity defects

- Direct effects on fetus or indirect effects on germ cells

- May effect succeeding generations

- Avoid X-raying pregnant women
Radiation

- Studies of offspring of Japanese women who were pregnant at the time of the atomic bomb explosions over Hiroshima & Nagasaki who survived the blast
  - 28% aborted
  - 25% gave birth to children who did not survive their first year
  - 25% of the surviving children had abnormalities of CNS
    - e.g. Microcephaly & mental retardation
Hypoxia

• Associated with congenital malformations in a great variety of experimental animals
  – In humans ???
    • Maybe smaller babies e.g. offspring at high altitude
Environmental Chemicals

• **Mercury**
  – Fish, seed corn sprayed with mercury containing fungicide
    • Multiple neurological symptoms

• **Lead**
  ! ! abortions
  – Growth retardation
  – Neurological disorders
Prevention of birth defects

• Good prenatal care
• Iodine supplementation eliminates mental retardation & bone deformities
  – Prevent cretinism
• Folate/Folic Acid supplementation
  ! ! incidence of neural tube defects
• Avoidance of alcohol & other drugs during all stages of pregnancy
  ! ! incidence of birth defects
• REVIEW IN YOUR EMBRYOLOGY TEXTS
  THE TOPIC  TERATOLOGY

• Note the maternal illness, drug abuse, chemical agents, hormones, medications, infectious agents, malnutrition/nutritional deficiencies that cause congenital abnormalities.