Chapter 5

Genetics and Teratology

CONTENTS:

HUMAN GENETICS

Human genetics deals with the variations between humans. These variations are, in part, reflections of differences that exist at the DNA level.

Chromosome features:

(a) Chromatids. Metaphase chromosomes are divided longitudinally into two sister chromatids

(b) Centromere. The chromatids are held together at the centromere, or primary constriction, which delineates the chromosome into a short arm (p) and a long arm (q).

(c) Centromere position**.** Chromosomes are divided into three groups based on centromere location.

1) Metacentric chromosomes: (such as chromosome 1), have a central centromere.

2) Submetacentric chromosomes: (such as chromosome 6), have a centromere that is displaced from the center.

3) Acrocentric chromosomes: (such as chromosome 13), have a centromere near one end.

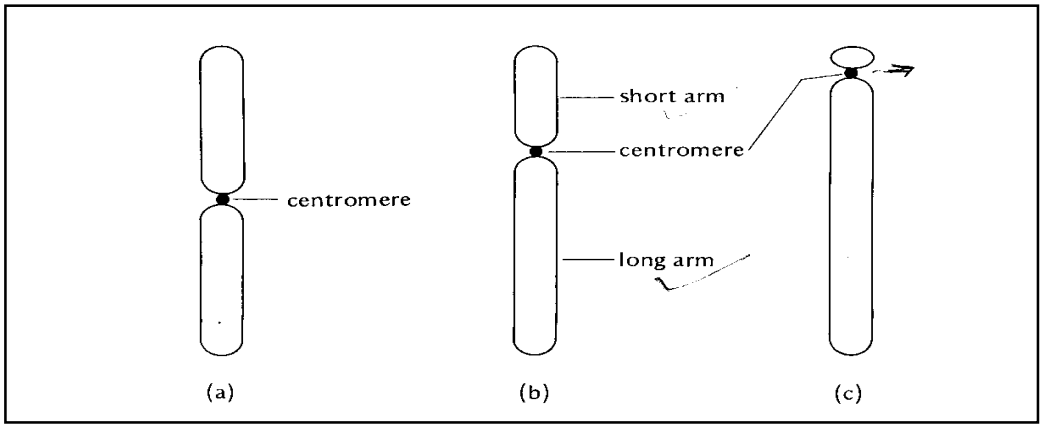


Fig. 1: Types of chromosomes according to the position of centromere. (a) Metacentric (b) Submetacentric (c) Acrocentric

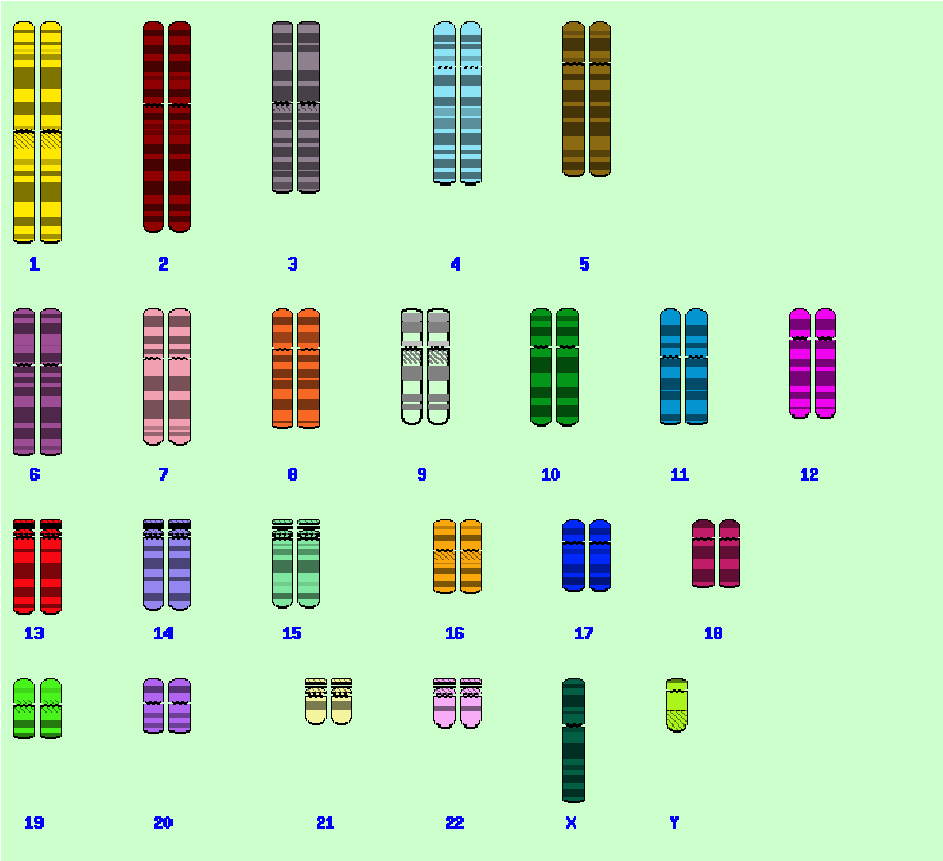


Fig. 2: Normal human karyotype

The normal human karyotype ;(fig.2)

Itconsists of 23 pairs of chromosomes: 22 homologous pairs of autosomes and one pair of sex chromosomes.

The autosomes, by convention, are divided into seven groups:

A (chromosomes I to 3),

B (chromosomes 4 and 5),

C (chromosomes 6 to 12),

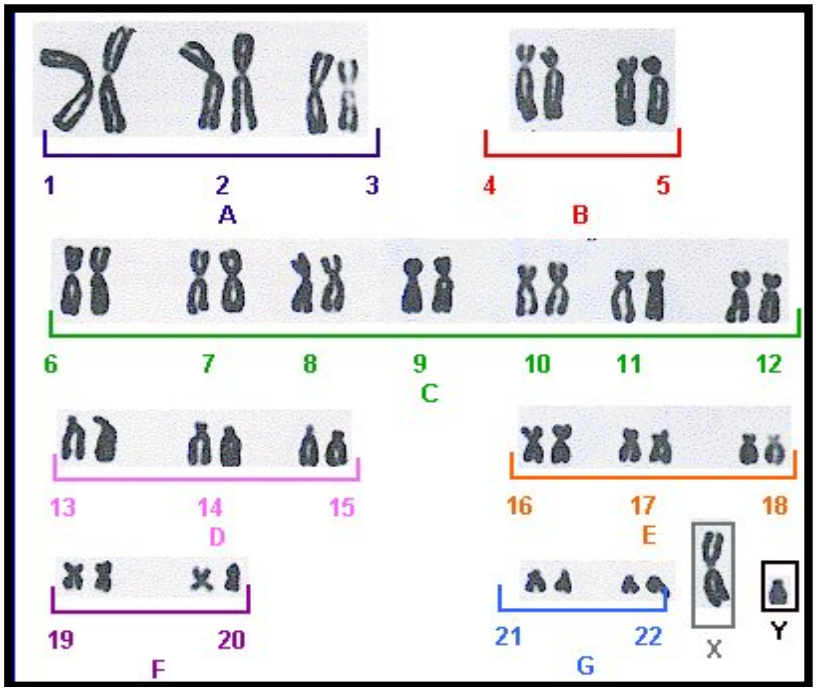
D (chromosomes 13 to 15),

E (chromosomes 16 to 18),

F (chromosomes 19 and 20),

G (chromosomes 21 and 22).

The sex chromosomes are **XX** or **XY**.



Diagnostic cytogenetic analysis can be performed with metaphase or prometaphase chromosomes obtained from rapidly dividing cells in tissue culture, or, in some cases, directly from tissues with high mitotic activity.

Genetic Defects and Mode of Inheritance

- The genetic diseases may range from loss or gain of entire chromosomes or large chromosome segments **(Chromosomal abnormalities)** to just change of a single base pair within a gene **(single gene mutations).**
- A third type of genetic diseases is a process in which a disorder results of interaction between one or more abnormal genes and environmental factors **(Multifactorial inheritance).**

I - Single Mutant Gene:

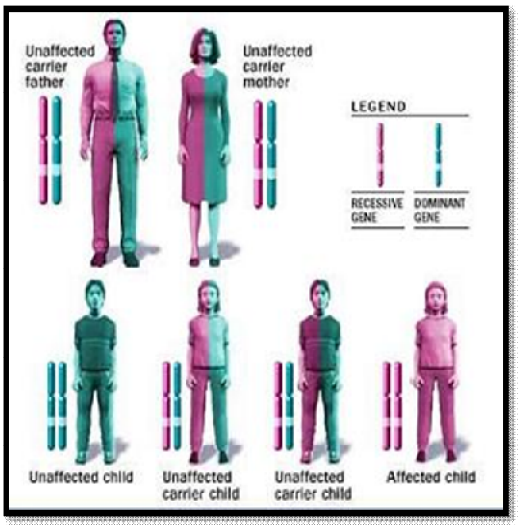
- Each single mutant gene will exhibit one of 4 patterns of Mendelian inheritance:

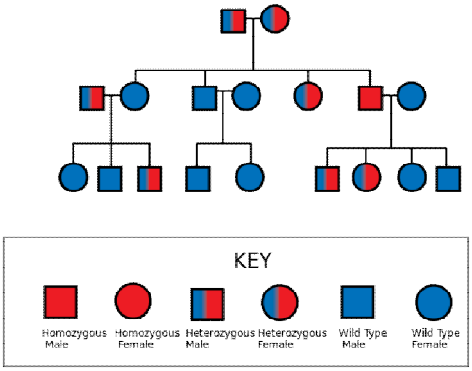
Autosomal recessive	X - linked recessive
Autosomal dominant	X - linked dominant

- Disease is said to be autosomal or X-linked depending on whether the mutant gene is located on an autosome or X chromosome.

- Also, it is classified as recessive when the one mutant gene cannot express the disease, while dominant when only one mutant gene is sufficient to express the disease.

I - Autosomal recessive inheritance:

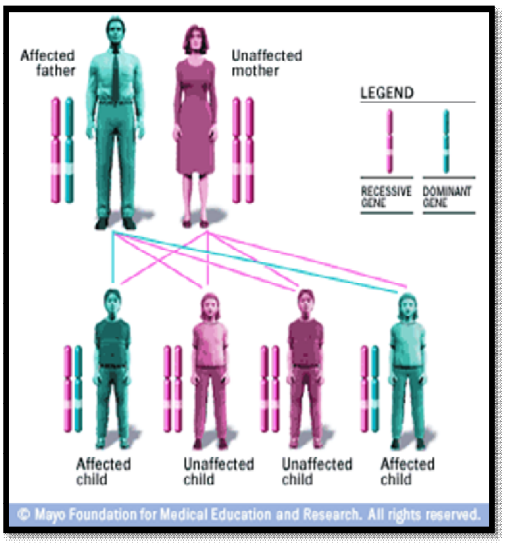


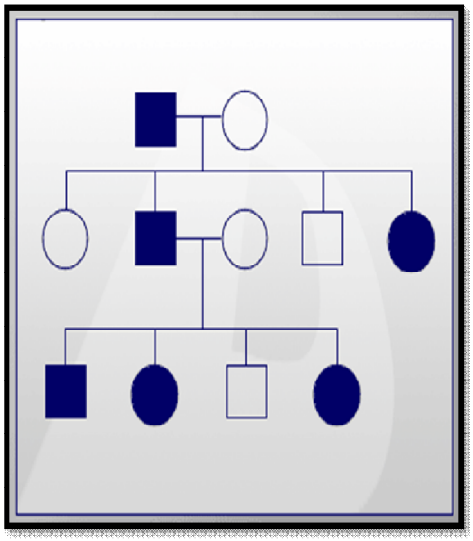


- It has the following characteristics:

- **The parents:** Phenotype: usually normal.
- **Genotype:** It is always heterozygous for this abnormal gene i.e., carrier for the disease. They usually related to each other (high incidence of consanguinity).
- **The risk of occurrence and recurrence:** The child of 2 heterozygous parents has a 25% chance of being homozygous. Males and females are affected with equal frequency.
- **The pedigree:** It usually "horizontal" i.e. affected individual are in the same generations.
- **The most common diseases:** Thalassemia, sickle cell disease, and glycogen storage disease.

2 - Autosomal Dominant Inheritance:

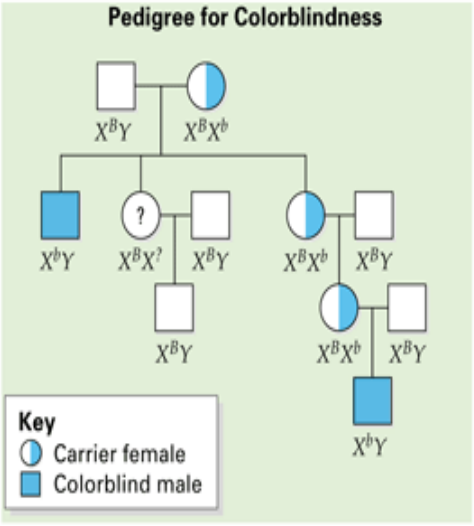


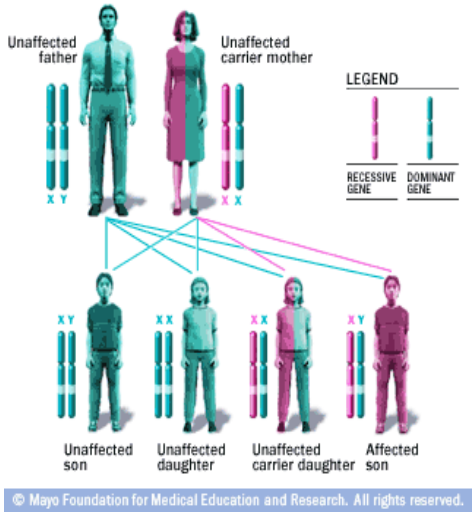


- It has the following characteristics:

- **The parents**: One only (paternal or maternal) has a one dominant mutant gene i.e. genotype abnormal and also phenotype express the disease. The other is normal as regard to genotype and phenotype. There is no relation between consanguinity and this disease.
- **The risk of occurrence and recurrence:** The child of one affected parent has a 50% chance of being affected.
- Males and females are affected with equal frequency.
- **The pedigree:** It tends to be "vertical" i.e. there are affected individuals in several generations.
- **The most common diseases are:** Hereditary spherocytosis, Huntington chorea, and achondroplasia.

3 – Sex- linked recessive inheritance





- It has the following characteristics:
- **The parents:** The mother is genotypic carrier and phenotypic normal. The father is genotypic and phenotypic normal. There is no relation between consanguinity and this disease.
- **The risk of occurrence and recurrence:**Fifty % of a carrier mother's sons will be diseased and 50% of a carrier mother's daughters will be carriers.
- **The pedigree:** It tends to be "oblique" i.e. the affected individuals usually are carrier mother's brothers and carrier mother's sons.
- **The most common diseases are:** Glucose - 6 - phosphate dehydrogenase deficiency, hemophilia A and B, and Duchenne muscular dystrophy.

4 - Sex - Linked Dominant Inheritance:

It is a rare pattern of inheritance.

The example of this mode is vitamin D-resistant rickets.

II - Multifactorial Inheritance:

The points that characterize this pattern are:

- There is a similar rate of recurrence (2-10%) among all 1st degree relatives. The risk of recurrence is related to the incidence of the disease.
- Some disorders have a sex predilection.
- The likelihood that both identical twins will be affected is less than 100%.
- The risk of recurrence is increased when multiple family members are affected.
- The risk of recurrence may be greater when the disorder is more severe.
- The most common diseases are: allergic diseases, pyloric stenosis, and developmental dislocation of the hips.

III - Chromosomal Abnormalities:

These disorders are an important cause of mental retardation and congenital anomalies. They include abnormalities of either chromosome number or structure.

1 - Abnormalities of chromosome number

Human cell, in which number of chromosomes is 23, is called haploid cell. When the number of chromosomes is multiple of haploid (i.e. 46), the cell is called euploid.

Cell deviation from these is called aneuploid i.e. it has either extra chromosome (trisomies i.e., 47 chromosomes) or loss of chromosome (monosomies i.e., 45 chromosomes).

The most common example of abnormalities of chromosomal number is:

- Trisomy 21, Down syndrome (47 +21)
- Monosomy, Turner syndrome (45, X.)

2 - Abnormalities of chromosome structure

When a piece of a chromosome is missing, this is called "deletion", while "translocation" means transfer of chromosomal material from one chromosome to another.

The most common example of chromosomal structure abnormalities is:

- Translocation, Down syndrome {46^{+} t (14q –21q)}.
- Deletion, Cri du chat {46, (5p-)}.

Genetic Counseling

- **Genetic counseling (G.C.)** is defined as " an educational process that seeks to assist affected and/or at risk individuals to understand the nature of a genetic disorder, its transmission and the options available to them in management and family planning.
- G. C is an important form of preventive medicine. It is expensive but it is an effective way of diminishing society burden of chronic disease, which is far more expensive.

I - Premarital G.C.

1 - General advice

The chance of both parents carrying the same rare recessive gene is greater if they are related. The likelihood of the patient's disease being recessively inherited is thus increased in the presence of consanguinity.

2 - Specific advice:

Premarital screening carrier cases of some common recessive disorder e.g. thalassemia, is an important task. A premarital advice for those carriers may lead to prevention of such incurable diseases.

II - Preconception G.C.

1 - General advice:

The increasing risk of trisomy with increasing parental age must be put in mind.

2 - Specific advice:

Parents with previous baby with definite genetic disorder must be informed about the nature of this disease, the risk of recurrence and the available options, e.g. family planning if already have children (in the case of autosomal recessive disorder).

III – Post conception G.C.

1 - General advice:

Avoidance of any teratogens e.g., radiation, drugs and infections during pregnancy.

2 - Special advice:

- Pregnancy at risk of genetic disorder gets benefit of prenatal diagnosis. This may include ultrasound, amniocentesis and chorionic villus sampling and fetal blood sampling.
- After a definite diagnosis of a genetic disorder, some disease may get benefit from intrauterine treatment e.g. hydrocephalus.
- On the other hand genetic indication for interrupting pregnancy is still controversial (for religious causes) e.g. trisomy.

IV - Neonatal Screening

1 - General advice

Universal neonatal screening is helpful for detection of common genetic disorder in which early detection is mandatory e.g. hypothyroidism.

2 - Specific advice

The high-risk newborn infant for specific genetic disease must be screened early for this disease, e.g. developmental dislocation of the hip.

Prenatal Diagnosis

Definition

1. Prenatal diagnosis is the process that aims at reaching a diagnosis regarding the presence or absence as well as the nature of a possible genetic or dysmorphic disorder present in a fetus.
2. Prenatal diagnosis allows the detection of birth defects and genetic disorders before delivery giving the parents the option of pregnancy termination or additional time for emotional adjustment.

Indications

1. **Prenatal diagnosis is indicated in cases with increased risk of birth defect or genetic disease such as:**
    1. Women >35 years (risk of Down syndrome)
    2. Elevated maternal serum alpha fetoprotein (risk of open defect, e.g. neural tube defects)
    3. Low maternal serum alpha fetoprotein (risk of Down syndrome)
    4. Prior history of autosomal trisomy (risk of trisomy)
    5. Parents with balanced chromosomal translocation (risk of unbalanced karyotype). Balanced translocation means translocation of a part of a chromosome to another chromosome within the same cell so that the genetic material of the whole cell is not changed.
    6. Family history of genetic disorder or carrier parent (risk of specific disorder in family)
    7. Family history of isolated structural defect (risk of same structural defect).

Techniques used in prenatal diagnosis

1-Maternal serum alpha fetoprotein (AFP)

2-Fetal ultrasound

3-Amniocentesis

4-Chorionic villus sampling (CVS)

5-Percutaneous umbilical blood sampling (PUBS)

6-Fetoscopy

Trisomy 21

(Down syndrome)

Down syndrome (DS), has a consistent and specific phenotype (mental retardation and mongoloid facies) and constant genotype (presence of three copies of chromosome 21).

Incidence:

Down syndrome occurs in approximately 1 in 600 births but the chance of occurrence varies with the mother's age.

The sex ratio at birth is 1.24 males to 1.0 female.

Genotypes of Down syndrome:

1 - Meiotic non-disjunction Trisomy 21:

- All the cells show an additional No. 21 chromosome, i.e. 47, XX, +21. This type is resulting frommeiotic non-disjunction.
- Approximately 95% of all Down syndrome are of this type.
- About 70% of trisomy 21 is born to mothers over 30 years.
- However, both parents are usually normal as regards to phenotypes as well as genotypes.

2 - Translocation Trisomy 21:

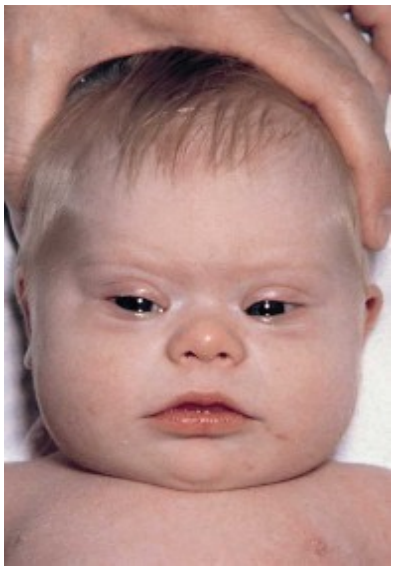
- All cells show normal number of chromosomes (46), however an extra-chromosome 21 is attached to another one (13,14, 15 or 21) i.e. 46, XX, +t (14q 21q).
- Approximately 4% of Down syndrome is of this type.
- The 2 underlying mechanisms of translocation are:

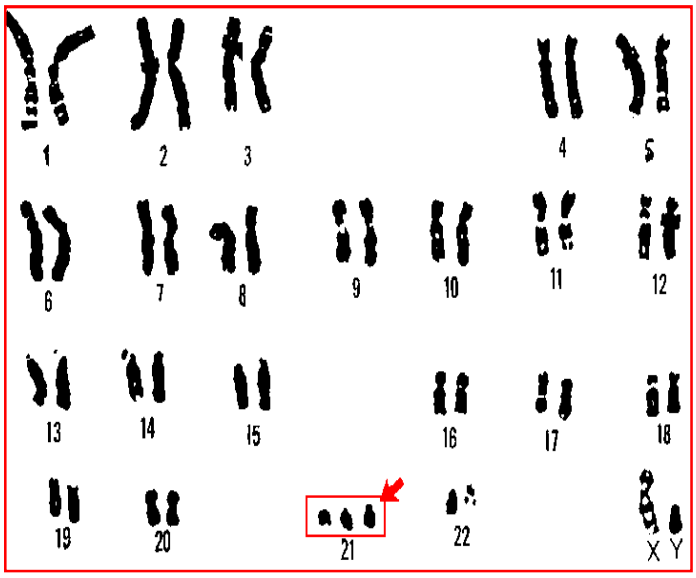
  a) Sporadic type: half of translocated Down syndrome arise de novo in the affected individual. Both parents are usually normal.

  b) Inherited type: another half inherited the disease from a translocation carrier parents i.e. 46, XX, t (14q 21q).

3 - Mosiacism:

- The incidence of this is about 1% of Down syndrome. They have various proportions of trisomy 21 (47, XX, + 21) and normal cells (46, XX) resulting from mitotic non-disjunction. This group may be of normal intelligence, depending on the number of trisomic cells present.
- The parents are usually normal, however, parental mosiacism had been discovered in some cases.





Clinical Manifestations:

1 - Early presentations:

- There is an increased frequency of prematurity, and birth weight is usually somewhat decreased.
- Prolonged physiological jaundice may be present.

2 - General manifestations:

- The head: It tends to be brachycephalic (occipital flattening). Head circumference is likewise smaller than average. The fontanels may be late in closing. The hair is often fine and soft and may be sparse. The face is usually rounded with a flat profile.
- The eyes: They have many characteristic signs. The palpebral fissures slant upward and outward, and epicanthic folds are often present. The epicanthic folds and flat nasal bridge may give the appearance of hypertelorism, but interorbital distance is usually not increased. Small white spots, referred to as Brushfield spots, may be visible on the iris.
- Ears: They tend to be small and ear canals may be atretic.
- Mouth cavity: High arched palate may be present. In older children the tongue is often protuberant due to narrow oral cavity. Eruption of the teeth is frequently delayed and the positioning irregular. The neck short, and the nuchal skin excessive.
- Hands are short, and there is often a single transverse palmar crease (simian crease) and incurved fifth finger (clinodactyly). A single fifth finger crease is common. There is often a wide gap between the first and second fingers and toes. The dermal ridge patterns provide valuable diagnostic evidence.

3 - CNS manifestations:

- During the first years of life profound hypotonia and laxity of joints are often evident but lessen, as the child grows older.
- The most significant feature of Down syndrome is varying degrees of mental retardation. The milestones including speech, locomotion and social behavior are all decayed. The intelligent quotient (I.Q.) ranges from 20 to 75 with a mean of 50.

Complications of Down syndrome:

1 - Congenital heart diseases (CHD): At least 40% have CHD, of which the most characteristic are endocardial cushion defects, followed by ventricular or atrial septal defects.

2 - Gastrointestinal malformation: These include duodenal stenosis or atresia, esophageal atresia, anal atresia, and megacolon.

3 - Intercurrent infection: Frequent respiratory, eyes and skin infections. Serous otitis media may end by hearing loss. Down syndrome has a decreased immune defense mechanism.

4 - Oncology: There is a 10 to 30 fold increased risk of acute lymphoblastic leukemia compared with the general population.

5 - Sexual development: Males may be infertile owing to interstitial fibrosis of the testes and hypoplasia of semeniferous tubules.

6 - Neurological complications: In about 10 - 15% of Down syndrome has unstable atlanto-axial joint with subsequent dislocation and neurological complications.

7 - Congenital hypothyroidism may coexist and requires thyroid replacement.

8 - Ophthalmic complications: refractive errors and keratoconus.

Investigations:

1 - Cytogenetic studies:

- Although the clinical picture of DS is often straight forward, cytogenetic analysis should always be obtained.
- This test provides confirmation of the diagnosis as well as determine the genotypes of DS for accurate genetic counseling.
- Chromosomal study can be obtained from any dividing nucleated cell. Because blood is easy to obtain, cytogenetic studies are usually done on lymphocytes. If there is a suspicion of mosiacism, fibroblast cytogenetic studies must be considered.
- Karyotyping must be done for diseased infant and for parents.

2 - Laboratory findings:

- Polycythemia in the first days of life has been noted, as well as transient congenital leukemoid reaction that resolves by age 5 months.
- Complete blood pictures and bone marrow examinations are mandatory when leukemia is suspected.

3 - Imaging studies:

- Pelvis X-ray may reveal flattening of the inner edges of the ileum and widening of the iliac wings.
- The secondphalanx of the little finger is often small or absent.
- Screening lateral cervical radiograph has been recommended at about age 6 years to diagnose unstable atlanto-axial joint.
- Echo-Doppler evaluation is mandatory for all cases even if there are no clinical cardiac abnormalities

4. Genetic counseling:

i – Preconception:

Advise the mother not to be pregnant in advanced ages to prevent the occurrence of DS and other genetic disorders.

ii - Prenatal:

Pregnant women with the risk of having DS (old age, translocated carrier) may get benefit from prenatal diagnosis. This procedure can be achieved by:

a. **Screening tests:** decreased maternal serum alpha - fetoprotein and unconjugated estriol while increased human chorionic gonadotropin.

b. **Confirmation test:** amniocentesis or chorionic - villus sampling for chromosomal analysis.

c. After definite prenatal diagnosis medical abortion may be indicated in some countries.

iii - Postnatal:

Family with DS must be aware of the nature of the disease and recurrence risk (RR), which depends upon cytogenetic analysis of infant and parents.

Recurrence risk

Recurrence risk of Down syndrome due to various cytogenetic patterns:

Infant	Parents	Recurrence risk
Trisomy 21:	Normal Mosiac (M or F)	1-2% Depends upon degree of mosiacism
Translocation: 14/21 14/21 14/21 21/21	 Normal Carrier (mother) Carrier (father) Carrier (M or F)	 Slightly increased 10- 15% 3-5 % 100%
Mosiac:	Normal Mosiac (M or F)	Slightly increased Depends upon degree of mosiacism

Teratogenesis and Mutagenesis

- **Both teratogens and mutagens** can cause alterations in the structure and functioning of the body, but the mechanisms differ.
- **Teratogens** cause damage by altering embryonic or fetal development directly. **Mutagens** cause changes within the genetic material that may lead to inherited disease if the germ cells are affected or to cancer if somatic cells are involved.

TERATOGENESIS

- A teratogen is an agent that can produce a permanent alteration of structure or function in an organism after exposure during embryonic or fetal life.
- Teratogens include environmental factors, medications, drugs of abuse, and occupational chemicals.

Clinical teratology is concerned with the following:

1. The relationship between the anomalies in a child and teratogenic exposure.

2. The risk of anomalies for a child of a woman who has been exposed to a teratogen.

3. The risks to a pregnant woman of treatment or exposure to a given agent.

Principles of clinical teratology:

Teratogens act at vulnerable periods of embryogenesis and fetal development.

a. **In general,** the embryo is most sensitive to damage between 2 and 10 weeks after conception (4 to 12 weeks after the beginning of the last menstrual period). During this time, most structures and organs are differentiating and forming. Each structure has its own period of greatest sensitivity within this time.

b. **The first 2 weeks after conception** is generally considered to be a period that is resistant to the induction of malformations by teratogens. At this point, the embryo consists of few cells, and damage is usually either repaired completely or results in death of the embryo.

c. **By 10 weeks after conception,** most structures in the embryo have been formed, so malformations are unlikely to be produced by subsequent exposures.

Teratogenic factors are thought to be responsible for about **10%** of all congenital anomalies.

These factors fall into several groups:

1) **Maternal metabolic imbalance:** as children of women with insulin-dependent diabetes mellitus have a risk of congenital anomalies that is two to three times greater than that of the general population.

2**) Infectious agents** can involve the embryo or fetus transplacentally.

For example:

- ✓ Congenital toxoplasmosis (may be asymptornatic or present with a variety of abnormalities. Severely affected infants may exhibit chorioretinitis, hydrocephaly or microcephaly, intracranial calcification, and mental retardation.
- ✓ Rubella (German measles) embryopathy produces fetal growth retardation, hepatosplenomegaly, purpura, jaundice, microcephaly, cataracts, deafness, congenital heart disease, and mental retardation.
- ✓ Congenital cytornegalovirus (CMV) infection may produce fetal growth retardation, hepatosplenornegaly, hemolytic anemia, purpura, jaundice, intracranial calcification, and microcephaly.

3) **Ionizing radiation** causes DNA damage and can injure the developing embryo.

4) Environmental agents and occupational chemicals:

1. Hyperthermia, regardless of cause, that produces sustained elevation of maternal body temperature to levels substantially above normal (e.g., 40 ºC)
2. Lead

5) Drugs of abuse

(1) **Alcohol:** Classic fetal alcohol syndrome occurs among the children of women with chronic, severe alcoholism during pregnancy.

(2) **Cocaine:** Maternal use of cocaine during pregnancy has been associated with placental abruption and the occurrence of vascular disruptions such as encephaloclastic lesions in the fetus.

(3) **Medications:**

1. **Thalidomide** exposure in the first trimester of gestation may produce limb reduction defects, facial malformations, and other congenital anomalies.
2. **Aminopterin** and other **cytotoxic drugs** kill rapidly growing cells in the fetus and cause growth deficiency and a variety of other anomalies.
3. An increased rate of congenital anomalies is observed among the children of epileptic women treated with **anticonvulsant medications** during pregnancy.

MUTAGENESIS

A mutagen is an agent that can alter the DNA or chromosomes.

1. While teratogens act only during embryonic or fetal development, mutagens may act at any time of life. Thus, mutations may occur in the gamete, zygote, embryo, fetus, child, or adult.

2. Teratogens affect the development of a tissue, organ, or structure. In contrast, a mutation always affects a single cell.

a) If this single cell is a germ cell, the mutation may be transmitted to subsequent generations.

b) If a single cell in a very early embryo sustains a mutation, many tissues of the embryo (including the germ cells) may be affected as embryogenesis progresses.

c) If a single cell in an embryo, fetus, child, or adult sustains a mutation; only cells derived from the mutated cell will carry the mutation. Most cells in the individual will not contain the mutation.