Subject: Anthropology
Class notes for - DSC-1B (CC-2)
Topic: Biological Basis of Inheritance
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CHROMOSOMAL ABNORMALITIES

Importance :

The processes of cell division ensure the orderly distribution of chromosome s from one generation of living materials to another. Errors in cell division and changes in the structure of the chromosome do occur, resulting in cells and individuals with abnormal chromosomes or with modified chromosomes. Since the smallest chromosome carries a large number of genes, a change in chromosome number represents a drastic reduction in genetic balance. About 8% of diagnosed pregnancies an embryo that has some major chromosomal abnormality. It is estimated that a visible chromosomal abnormality is present in between 5 and 6 out of every 1000 live births (Jacob et.al. 1974). Hammerton et.al. 1975). The incidence is about 60 times greater than this in aborted specimens, chromosomal abnormalities being present about 35% of spontaeneous abortions (Carr 1969). Since about one out of 7 fertilizations ends in a spontaeneous abortions, at least 5.6% conceptions contain deleterious gross chromosomal abnormalities (not considering still births). (Machin & Crolla, 1974). So, chromosomal abnormalities are significant in developmental disorders, mortality and lethality.

Changes of normal choromosome combinations:

We know, human gametes are haploid (n). They carry on complete set of chromosome consisting of 22 autosomes and one sex chromosome. Somatic cells, by contrast, are diploid (2n), because they carry two haploid sets of chromosomes 46 altogether(Tjio & Levan , 1956). Presence of extra complete sets of chromosome is referred to as a change in *ploidy* (whole set of chromosome) , with an appropriate prefix to indicate the number of cells, the condition of having more than two complete sets of chromosomes is known as *polyploidy*. So, cells that have three haploid sets of chromosome (3n=69) are known as triploids and those with four haploid sets (4n=92) are called tetraploids . Nearly all human ploypoidy observed has been in malignant cells and in spontaeneous abortions, in which it accounts for about 10% of all those which occur during first half of pregnancy. Polyploidy can arise from fertilization involving unreduced gametes (complete non disjunction) , through *dispermy* (fertilization by two

sperm) , or by the failure of duplicated chromosome s to separate into daughter cells during mitosis.

Another type of abnormality in chromosome number involves individual chromosomes instead of entire sets of chromosomes. The term *aneuploidy* is given to variation of this nature and the suffix " *somy*" (number of individual chromosome) is a part of their nomenclature. For example, when one chromosome is missing from the diploid complement, producing a condition known as *monosomy* , symbolized as 2n-1=45 . If there is one extra chromosome present in the diploid complement, producing a condition called *trisomy* , symbolized as 2n+1=47.

Changes in total number of chromosomes most frequently result from the occasional failure of chromosome s to move to opposite poles or Disjoin during anaphase of cell division. Such a failure is called non-disjunction, which is principal cause of *aneuploidy*. Another mechanism is loss of chromosome due to anaphase lagging – during anaphase movement one chromosome may lag behind the others. Meiotic non-disjunction which occurs in a cell with a normal chromosome complement is called "*primary nondisjunction*" . If cells already contain an abnormal chromosome set as the result of a prior nondisjunction, then secondary nondisjunction occurs.

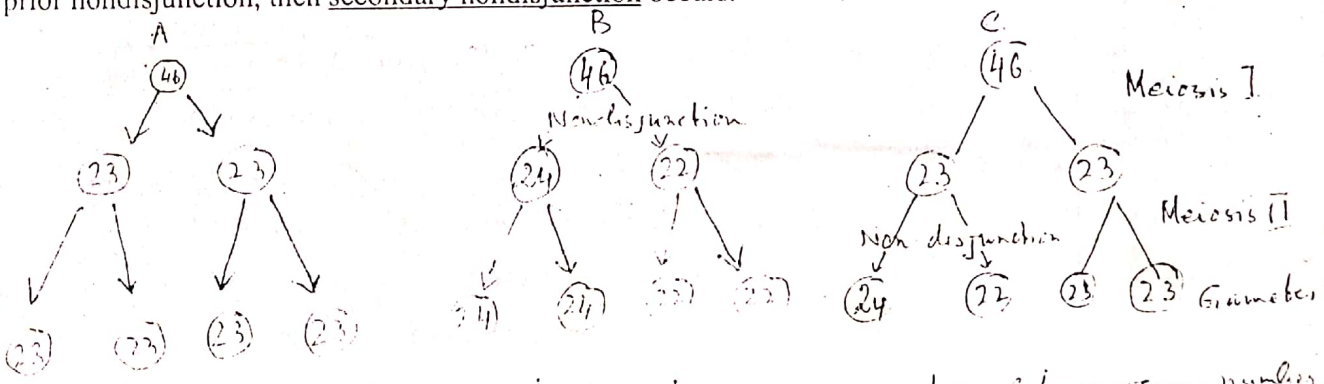


Fig : Effect of meiotic nondisjunction on gamete chromosome number. A: Normal meiosis B Nondisjunction during first meiotic sequence C: Nondisjunction during Second meiotic sequence

Chromosomal abnormalities are mainly two types: I) Changes in the amount of chromosomal material – usually change in chromosome number; II) changes in the arrangement of the chromosome material.

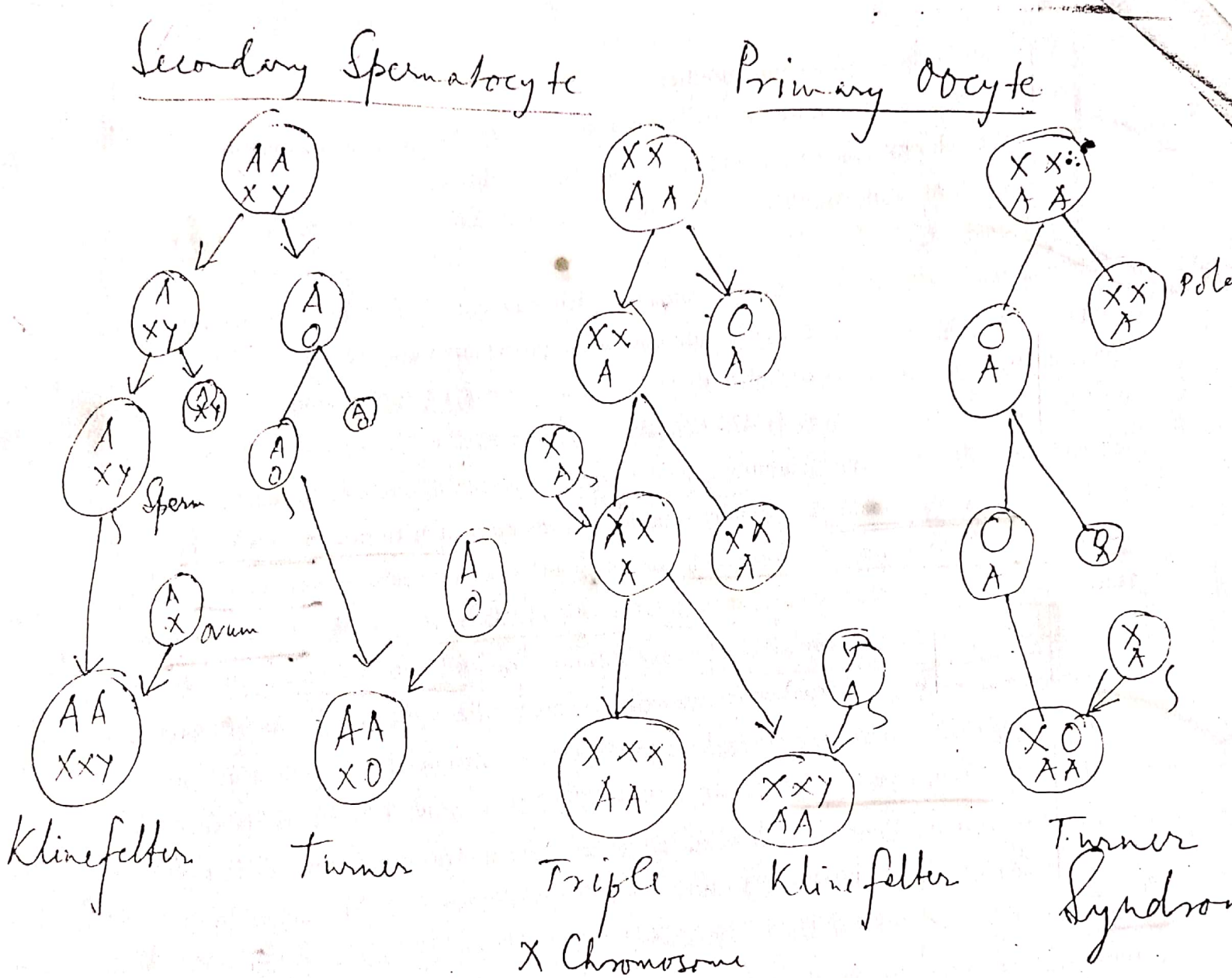
A) Changes in the chromosome number:

Chromosomal abnormalities occurs in autosomes i.e. autosomal abnormalities as well as in sex chromosomes i.e. sex chromosomal abnormalities .

I) Autosomal abnormalities :_The most frequent autosomal abnormalities are mentioned below:

Down's syndrome : Most common autosomal trisomy among live born children is trisomy 21, also known as **Down's syndrome**, after physician Longdon Down. (1866) All the patients with this characteristic phenotype have all or most of chromosome 21 triply rather than doubly. Karyotype is 47, +21: the '+'preceding the '21' denoting an extra chromosome 21. It is most common chromosomal abnormality in live births (1/600 births). Characteristic features: mentally retarded, short, a peculiarity in the folds of the eyelids; stubby hands and feet, swollen tongue, congenital heart disease , many 'loops' in the finger tips, simian crease etc. Life expectancy of patients is reduced. Women over 45 years are about 20 times more likely to give births to a child with Down syndrome. (*Syndrome means a group of symptoms occurring together with sufficient regularity that it can be recognized as a distinct clinical entity*) than are women aged 20.[Mother's Age < 19= 1/1700, <30=1/1400, <35=1/750, >45=1/16 (L.S Penrose)] There is indirect evidence that the nondisjunction may occur either in the ovum during meiosis or in the cleavage stages of the zygote. Translocation involving chromosome 21 and either 14 or 15 is another mechanism for Down syndrome. Such patients are found to have 46 chromosomes with two normal chromosomes 21 , one normal chromosome 14 or 15 and an unpaired large chromosome which is interpreted as a fusion of the long arms of chromosome 21 and 14 or 15. Persons with translocation Down syndrome are phenotypically indistinguishable from those of the more usual 21.

Trisomy 18: It is also known as Edwards' syndrome (1960) . It is about eight times less than Down syndrome. Normal karyotype is 47, +18. Clinical features are: growth failure ; mental and physical retardation ; elongated skull with low set, malformed ears ; jaw and oral cavity are small ; congenital heart disease etc. Incidence of trisomy 18 increases with age of mother . The life expectancy of males is about three months ; in affected females , it is about 9 months. Its frequency is 1/6500 live born.



Mechanism by which aneuploidy of Sex Chromosome might developed.

Trisomy 13 : It is also known as Patau's syndrome (Patau et.al. 1960) . It is equally severe as trisomy 18. Karyotype is 47, +13. Clinical features are : growth failure , mental retardation , malformed thumb and extra digits , harelip and cleft palate , small skull and eyes , malformed ears and deafness , congenital heart disease etc. Its frequency is 1/5000 live born.

II) Sex chromosomal abnormalities: The most frequent sex chromosomal abnormalities are mentioned below:

Trisomy X : Women with this syndrome have 47 chromosomes , including three X chromosomes (XXX) denoting (47,XXX). XXX females are physically quite normal and usually able to bear children, but some have menstrual irregularities and an early onset of menopause. The most striking feature is mental retardation , which is something severe. Incidence is about 1 per 950 new live babies.

Klinefelter's syndrome : Abnormal males possessing an extra chromosome (XXY) have a karyotype with 47, XXY . They are called Klinefelter males (after Harry Klinefelter, who first discovered). Clinical features are: male external genitalia but testis consistently small , body hair sparse , sterile, gynecomastia – female like breast development , mental retardation , long legged. Occurrence is about 1 per 1000 new live babies. Approximately two thirds of these arise from primary nondisjunction in the mother , leading to an egg carrying two X chromosome and there is a slightly enhanced risk of the condition among sons of older mothers.

Turner syndrome: Aneuploid females with only one X chromosome. Chromosomal constitution: 45, XO. Characteristic features of Turner (after Harry Turner , 1959) syndrome : female external genitalia , short stature , webbed neck , low set ears, broad shield like chest with widely spaced nipples , under developed breasts , small uterus , ovaries represented by only fibrous steaks. Occurrence is about 1 per 5000 new live babies. More than 1% of all recognized pregnancies in humans involves an embryo that is chromosomally XO , and approximately three fourth of these are caused by abnormal sperm that lack a sex chromosome.

Autosomal vs sex chromosomal abnormalities :

It is observed that chromosomal abnormalities involving the autosomes have more severe phenotypic effects than these involving the sex chromosome. Possible reasons are twofold: Firstly , abnormal gene dosage of the Y chromosome has a milder effect than that of an autosome because Y chromosome seems to carry few genes beyond those responsible for the development of maleness . Secondly, an abnormal number of X chromosomes is rendered less harmful than in abnormal number of autosomes because of dosage compensation involving the single active X principle.

B) Changes in the chromosome structure:

Structural abnormalities refer to abnormal structure in the chromosome due to breakage and reunion, loss, a portion represented twice . The most important reason for the origin of abnormal chromosome is chromosome breakage. Chromosomes are fragile objects and they sometimes break spontaeneously. The incidence of chromosome breakage is greatly increased by exposure of the chromosomes to a wide variety of agents, including X rays and certain chemicals. Broken chromosomes also tend to 'heal' – to undergo restitution. The broken ends behave as if they are 'sticky' (they come together and fuse) and the restitution probably involves particular enzymes that aid in their repair process. Most of the time broken chromosomes restitute correctly and broken ends rejoin at the point of fracture. But sometimes they are not restituted correctly and chromosomal abnormalities result.

Structural abnormalities of chromosome, which are of greatest importance in human genetics, are as follows:

Deletion: A deletion is the loss of a portion of a chromosome and in effect, represents partial monosomy. A piece of chromosome that is broken off and lacking a centromere is easily lost during cell division.

The most frequently observed deletion is one that occurs in the short arm of chromosome 5 . The most striking feature of the deletion 5 syndrome is the characteristic baby's cry like that of cat's cry ; hence **cri-du- chat** (cry of the cat) by French discoverer Lejeune . The physical anomalies are low birth weight , round face , moon faces , low set

ears , short neck , microcephaly , broad based nose and mental retardation. I.Q range is 20.

Deletion of part of the long arm of chromosome 22 produces an abnormality known as Philadelphia chromosome (as it was discovered in Philadelphia) . It is found in the bone marrow in approximately 90% of patients with chronic myelocytic leukemia (a kind of cancer). Usually the missing piece of chromosome 22 can be found translocated to one of the larger autosomes (frequently chromosome 9).

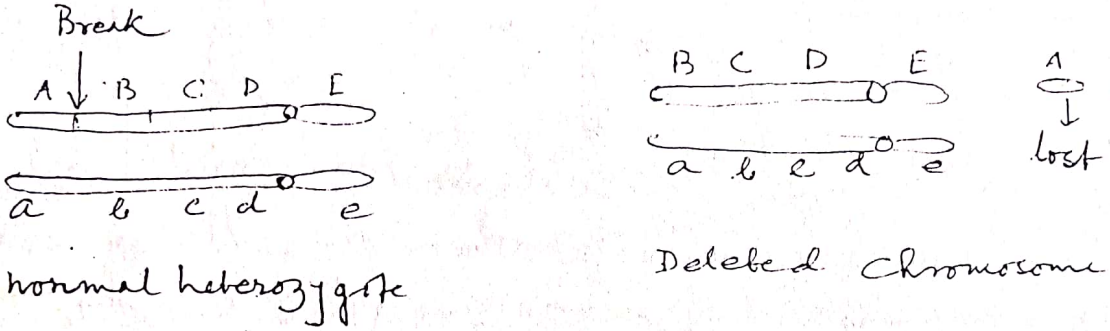


Fig: Diagrammatic interpretation for the formation of deletion chromosome.

Translocation: It is the displacement of part or all of one chromosome to another. Translocation involves the transfer of a portion of a one chromosome to another usually non-homologous chromosome. This requires a break in each of the chromosomes involved, followed by exchanged of the broken portions during repair. This is known as reciprocal translocation. The result is two abnormal chromosomes but no change in the chromosomal number. A modified form of translocation is centric fusion which involves two acrocentric chromosome s in which the breaks occur in the extremely short arms at or near centromere, followed by rejoining of the two large portions and the loss of two small fragments of the short arms.

The most important translocation is D/G centric fusion, especially between chromosome 15 and 21. The presence of translocation does not lead to an abnormal phenotype. For example , if an individual possesses a 15/21 centric fusion in which only a small amount of satellite material was lost from each chromosome during translocation , this one chromosome will be genetically equivalent to one number 15 and one number

21 . If this individual also possesses one normal number 15 and one normal number 21 chromosome, he or she will be phenotypically normal but will possess a total of only 45 chromosomes.

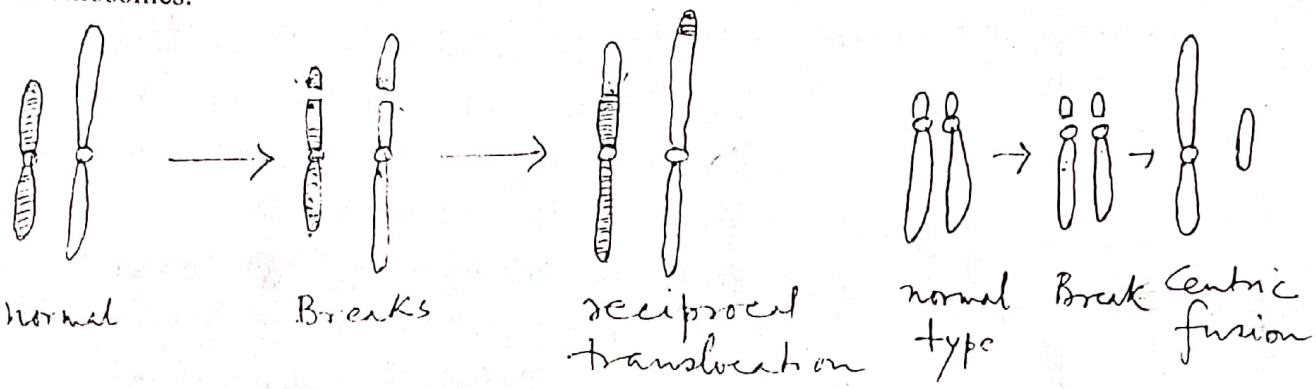
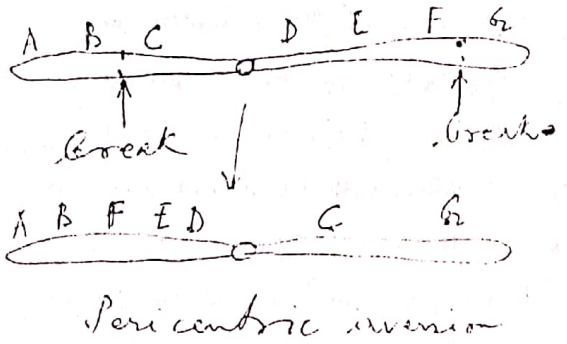


Fig: Diagrammetic interpretation of the formation of translocation

Inversion: An inversion involves two breaks in a chromosome followed by a reinsertion of a segment in a reversed order. No genes are lost or added, an individual with the inversion is usually phenotypically normal. Two kinds of inversions are distinguished:

a) Paracentric inversion : when the inversion takes place without centromere.

b) Pericentric inversion : when the inversion takes place with centromere;



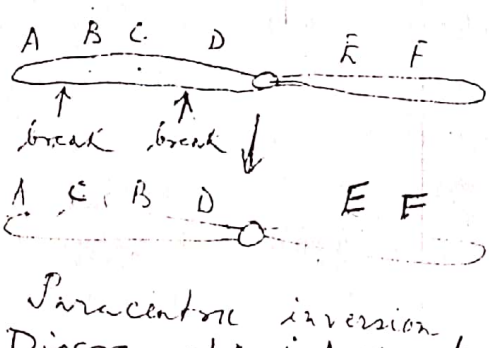


Fig: Diagrammetic interpretation of the formation of inversions

Ring chromosome: If breaks occur at each end of a chromosome, the broken ends may become joined to form a ring chromosome.

fig: Diagrammetic interpretation of the formation of ring chromosome.

Isochromosome : It arise during cell division when centromere splits transversely rather than longitudinal splitting . An isochromosome of the long arm of the X chromosome has been observed in some cases of chromatin positive Turner syndrome. An isochromosome of the long arm of chromosome 21 has been found in some cases of Down's syndrome.

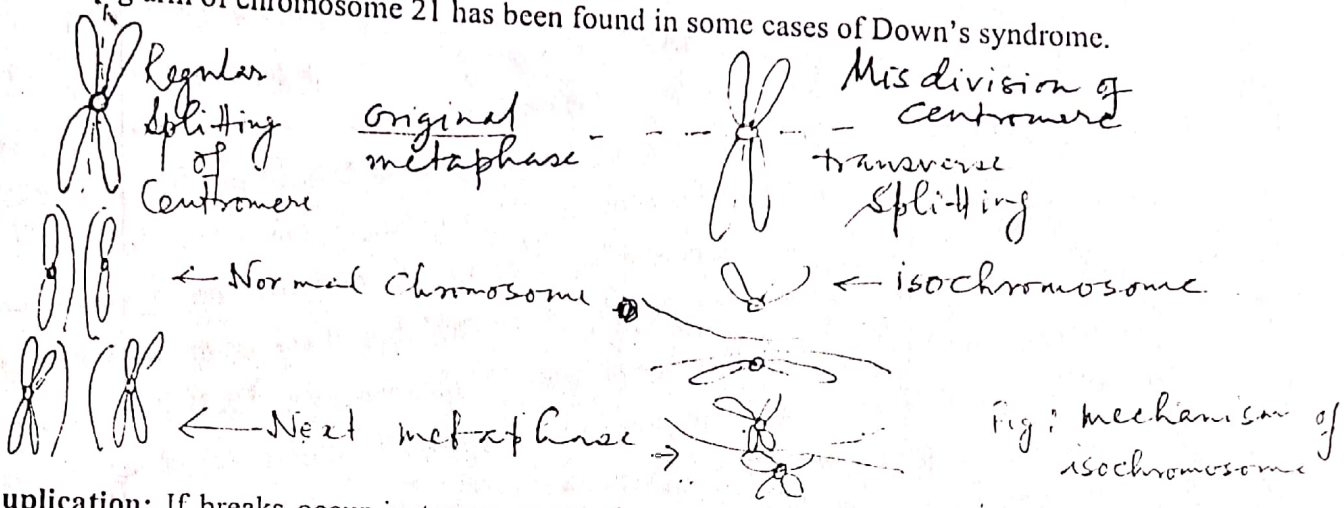
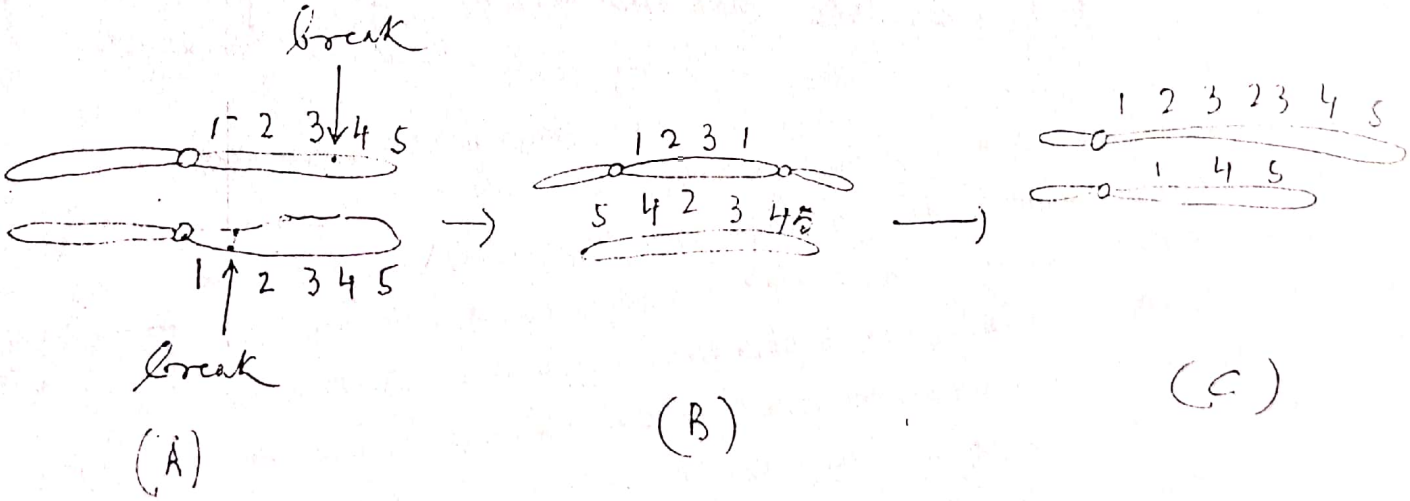


Fig : mechanism of isochromosome

Duplication: If breaks occur in two separate chromosomes, more genetic newness mat result. (fig. A) . If two homologous chromosome s break at different places , reunion of four fragments may lead to formation of a chromosome with two kinetochores and a fragment without one (Fig B). Such recombination chromosome s may result in a breakage –fusion – bridge cycle or reunion of the fragments may result in an exchange of nonidentical parts and the creation of two new stable chromosomes , one without middle section , the other with this section duplicated (Fig C).A cell that contains both chromosome s retains the normal number of all alleles , but when the two chromosome segregate into different gametes , during meiosis , these gamete possess either deficiency or a duplication and will produce zygotes with new phenotypes.



Duplication:

A duplication is the presence of an extra copy of a piece of chromosomal material. The duplication may be a result of unequal crossing over; such a crossover would result in one chromosome with a duplication and one with a deficiency.

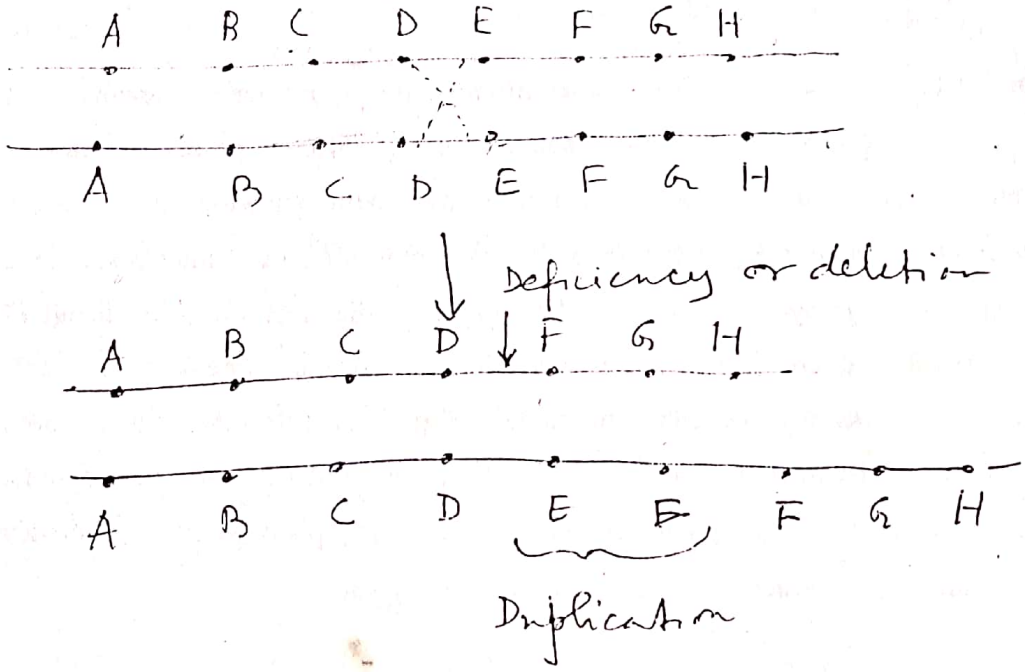


Fig: A possible mechanism of duplication

Sex Determination in Man :

Various mechanisms have developed in different groups of plants and animals for sex determination and sexual development. Sexual differentiation is genetically controlled by the sex chromosome (X and Y) in human. A normal female possesses 2X chromosome and a normal male has 1X chromosome and 1 Y chromosome as his sex chromosome constitution in addition to 22 pairs of autosomes . As female possesses 2X chromosome, they usually produce only X -bearing gametes while XY male is expected to produce half X-bearing and half Y – bearing sperm from normal spermatogenesis. It is found that Y-chromosome of a male always comes from his father; if the egg is fertilized by an X-bearing sperm , a female will developed. The combined action of genes on both X chromosome is apparently necessary to produce a fertile female. An individual with only a single X – chromosome (XO) will develop toward femaleness but will be sterile . Whereas an individual with chromosome complement XXY (Klinefelter syndrome) produces male phenotype. So, in human genes on the Y-chromosomes are required for the development of maleness, particularly development of testes. Even in cases of abnormal numbers of the sex chromosome s , individuals with XO, XXX, XXXX or XXXXX develop toward femaleness and persons with XXXY , XXXXY develop towards maleness. The gonads do not usually develop normally in individuals with abnormal sex chromosome complements and nearly all are sterile. So male sex phenotype is precisely correlated with the presence of a Y chromosome. In the absence of a Y chromosome, the sex phenotype develops along female lines regardless of the number of Y chromosome present.

Barr body and Lyon hypothesis :

In 1949 Murray Barr discovered a difference in the interphase somatic nuclei of males and females: a chromatin mass called the sex chromatin or Barr body, is present in the normal female but not in the normal male which is first discovered in the neurons of the cat. The Barr body or sex chromatin, can be recognized very easily in certain kinds of cells , such as epithelial cells of the buccal mucosa which lines the mouth cavity. It is found that the maximum number of Barr bodies in any one cell is one less than the number of X chromosome s present. Barr body is derived from one X- chromosome is

provided by two observations: I) Cells in an early phase of mitotic division show that one X chromosome of the female stains differently from the other X and from the autosomes ; this X chromosome is said to be heterochromatic; II) In cultures of cells from the female , thymidine labeled with tritium (H3) can be added. The thymidine becomes incorporated into newly synthesized DNA of such cells. Asynchrony of DNA synthesis by the two X chromosomes can be observed by means of autoradiographs made of cells dividing in these cultures. The heterochromatic X chromosome synthesizes DNA late in the process of mitosis and is the X chromosome that constitutes the Barr body. This statement is based on the fact that the cells of persons with three X chromosomes , two late labeling X chromosomes , and two Barr bodies ; persons with four X chromosome s have three and so on.

The Lyon hypothesis (after Dr. Mary Lyon of England) proposes that the Barr body is related to dosage compensation in man and other mammals, that is , that it provides an explanation why the normal female with a double dose of X chromosome genes show no greater effects than the normal male with a single dose. The hypothesis states that after a time early in embryogenesis one X chromosome becomes genetically inactive and forms Barr body of interphase nuclei. It further suggests I) that it is a random matter as to which X chromosome in any single cell – whether the one derived from the father or the one from the mother is the inactive one; and II) that once the differentiation of the chromosomes has occurred in a given cell, with one X chromosome assuming an inactive role, then the same X chromosome remains inactive in all descendants of the cell.