UNIT - I

GENE INTERACTION

- *The expression of a single character by the interaction of more than one pair of genes is called* **genic interaction** *or* **interaction of genes.** *It includes several deviations from the usual mendelian inheritance.*

- **Bateson** *and* **Punnet** *proposed* **factor hypothesis** *to explain genic interaction. According to this hypothesis, some characters are produced by the interaction of two or more pairs of factors (genes).*

- The genic interaction is of two types, namely
  - *Non-allelic gene interaction.*
  - *Allelic gene interaction.*

- *The genic interaction occurring between genes located in different locus of the same chromosome or different chromosomes is known as* **non-allelic gene interactions.**

- *The genic interaction between the two alleles of a single locus is known as* **allelic gene interaction.**

Some of the important forms of genic interactions are as follows:-

- ✓ Complementary genes
- ✓ *Supplementary genes*
- ✓ *Epistasis*
- ✓ *Co-dominance*
- ✓ *Pleiotropism*
- ✓ *Penetrance*
- ✓ *Expressivity*

Epistasis

- ✓ **Epistasis** *is* the prevention of the expression of one gene by another *non-allelic gene. Epistasis means* **stopping** *or* **inhibiting**
- ✓ The inhibiting gene is called **epistaticgene.** The inhibited gene is called **hypostatic gene**
- ✓ *Epistasis is of two types, namely* dominant epistasis *and* recessive epistasis

Dominant Epistasis

- ✓ The prevention of the expression of a gene by a dominant non-allelic gene *is called* **dominant epistasis.** *Eg.* White and colour feather in fowls
- ✓ Epistasis is a **non-allelic gene interaction.** In epistasis, a single character is controlled by the interaction of two or more non-allelic genes
- ✓ Here gene located on one locus interacts with another gene located in another locus. So, it is a **non-allelic gene interaction**

1. Inheritance of Colour Pattern in Poultry

- Inheritance of **colour pattern** in poultry is a case of **dominant epistasis**
- The coloured birds are due to a dominant gene **C** which produces colour pigment. When this gene is recessive **c,** the bird cannot produce colour pigment and the bird is white
- Further, the dominant gene **C** is inhibited by another dominant gene **I** located in another locus. When **I** is present along with **C**, the bird cannot produce colour pigment and hence the bird is white. The recessive gene ***i*** cannot inhibit **C.** Thus the colour pattern in white leghorn occurs as follows:

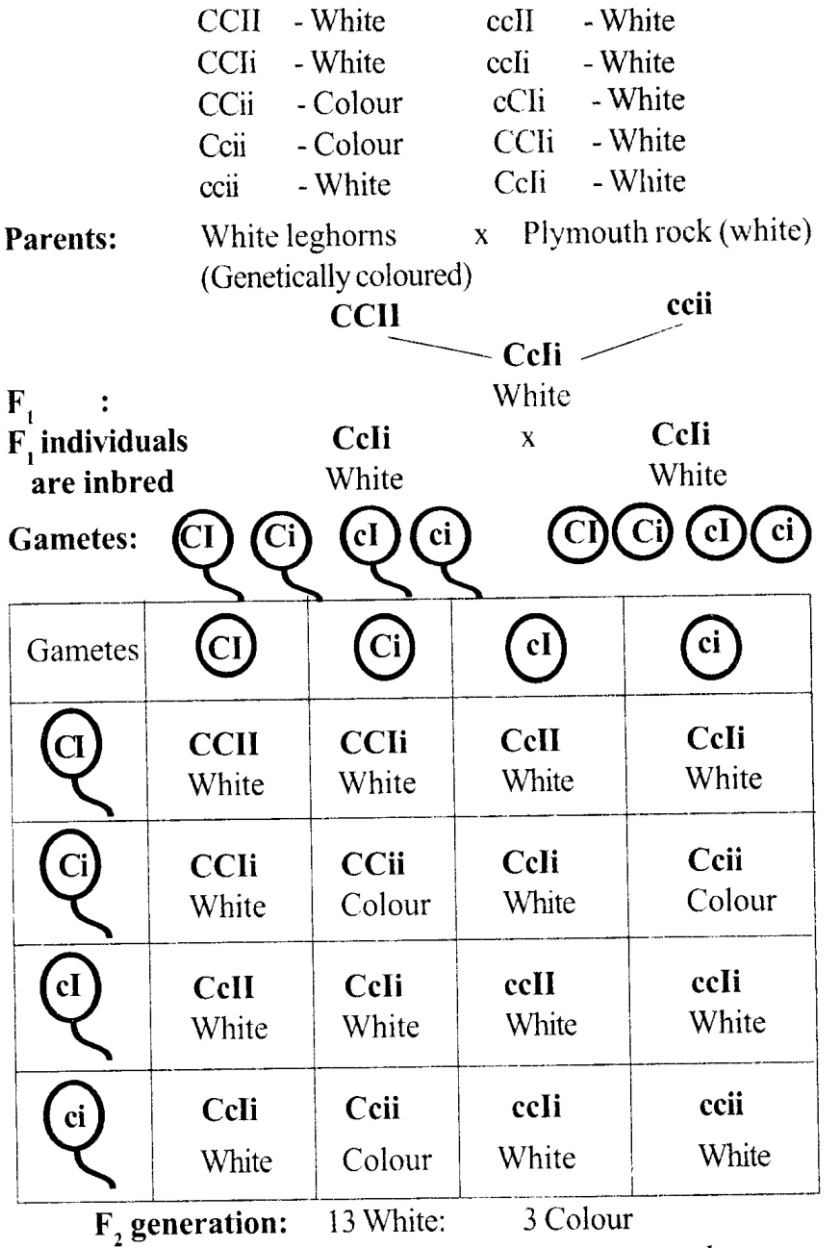
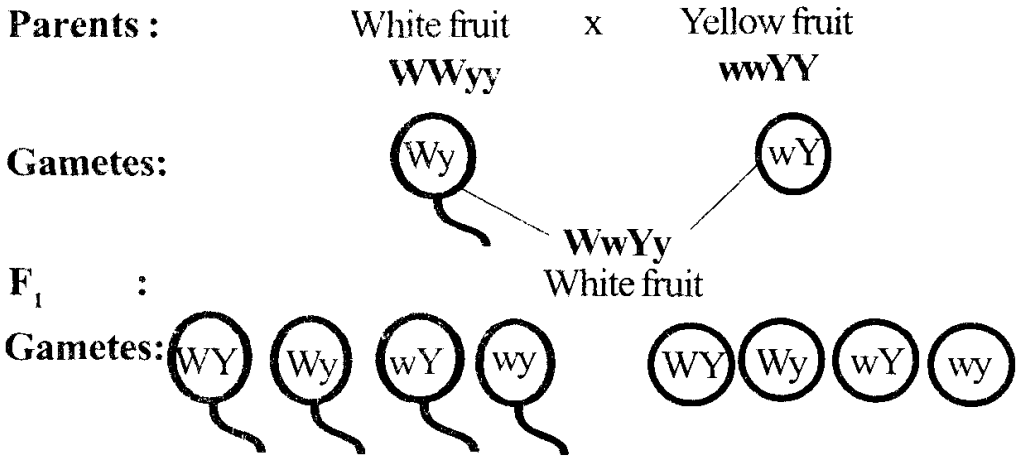


Fig.: Inheritance of colour pattern in poultry

- In **plymouth rock,** the coloured bird is due to a dominant gene **C** and white bird is due to a recessive gene **c.** Here also the **I** gene inhibits the **C**.
- When white leghorn and plymouth rock are crossed, the F_1 birds are all white. When the F_1 birds are crossed, in the F_2 generation, white and colour birds appear in the ratio **13:3**.

2. Inheritance of Fruit Colour in *Cucurbita*

- In summer squash **(*Cucurbita pepo*),** the gene **Y** is dominant over **y** and is responsible for **yellow fruit colour.** Similarly, the gene **W** is dominant over **w** and is responsible for **white fruit colour.** The dominant gene **W** is epistatic over **Y** and masks the expression of yellow fruit colour. Since one dominant gene masks the expression of another dominant gene, it is said to be a **dominant epistasis**
- A summer squash plant producing white fruits (**WWyy)** is crossed with another variety with yellow fruit colour **(wwYY)** to get F1 plants. The F1 plants are all white fruit producing plants **(WwYy**). When the F1 plants are crossed together, the F2 plants with fruits colour **white, yellow** and **green** in the ratio of 12:3:1



♀ \ ♂	WY	Wy	wY	wy
WY	WWYY White	WWYy White	WwYY White	WwYy White
Wy	WWYy White	WWyy White	WwYy White	Wwyy White
wY	WwYY White	WwYy White	wwYY Yellow	wwYy Yellow
wy	WwYy White	Wwyy White	wwYy Yellow	wwyy Green

White 12 : Yellow 3: Green 1

Fig.: Inheritance of fruit colour in Cucurbita pepo

- In 12/16 individuals, the gene **W** is present so that expression of **Y** gene is stopped. Hence, they are all white fruit producing plants. In 3/16 individuals, the gene **W** is absent but **Y** is present and hence they produce yellow fruits. In the remaining 1/16 individuals, neither **W** nor **Y** is present so that they produce **green fruits**.

PLEIOTROPISM

- ✓ The production of many characters by a single pair of genes *is* called **pleiotropism**
- ✓ It is the **multiple effect** of a pair of genes
- ✓ It is the antithesis of Mendel who said that a single character is controlled by a pair of genes. In pleiotropism, a single pair of genes controls many characters
- ✓ The genes **pp** for **phenylketonuria** produce the accumulation of phenylalanine in the blood. In addition, it produces many other characters such as **mental retardation, widely spaced incisors**, **pigmented patches on skin, excessive sweating, non-pigmented hairs** and **eyes,** etc.
- ✓ **Similarly, the** potato mutant gene **suppresses the growth of** meristematic tissue, axillary shoot **and** petals. **It produces** apocarpous pistil **and *d***ilatory anthers

PENETRANCE

- ✓ The percentage of individuals expressing the character for a particular genotype ***is called*** **penetrance**
- ✓ The penetrance is of two types, namely **complete penetrance** and **incomplete penetrance**
- ✓ If all the individuals express the character for a particular genotype, the penetrance is called **complete penetrance.**
- ✓ In complete penetrance, the character is expressed in 100% individuals. Eg. Mendel's tall and dwarf plants
- ✓ If a few individuals do not express the character even though they contain the necessary genes, the penetrance is called **incomplete penetrance.** Eg. *Blue eyes*
- ✓ In Mendel's pea plants, all the plants containing the genotype **TT** produce tall character. Similarly, all the plants, containing **Tt,** produce tall character; all the plant, containing **tt,** produce dwarf character. Thus, in pea plants there is 100% penetrance
- ✓ The genes for blue eyes **BB** produce blue eyes only in 90% human beings. About 10% people have white eyes even though they contain the genes **BB** for blue eyes. So, eye colour in man has only 90% penetrance
- ✓ Penetrance is influenced by **environmental factors** such as food, light, temperature, etc.

EXPRESSIVITY

- ✓ The variation in the degree of expression of a particular gene ***is called*** **expressivity**
- ✓ A particular gene may produce varying degrees of expression in different individuals
- ✓ Expressivity is due to the influence of **environmental factors** on the genes
- ✓ A very good example for the expressivity is the **vestigial** wing ***in*** Drosophila
- ✓ The vestigial wing is controlled by a pair of recessive genes **vv.**
- ✓ The vestigial wing develops in all recessive flies (complete penetrance)
- ✓ But it shows variation in the degree of expression
- ✓ When the flies are grown in normal room temperature **(72°F),** all the flies develop **typical vestigial wings**
- ✓ When they are grown at **80°F,** the wings are slightly longer.
  When they are grown at **88°F,** the wings are still longer extending upto the tip of abdomen

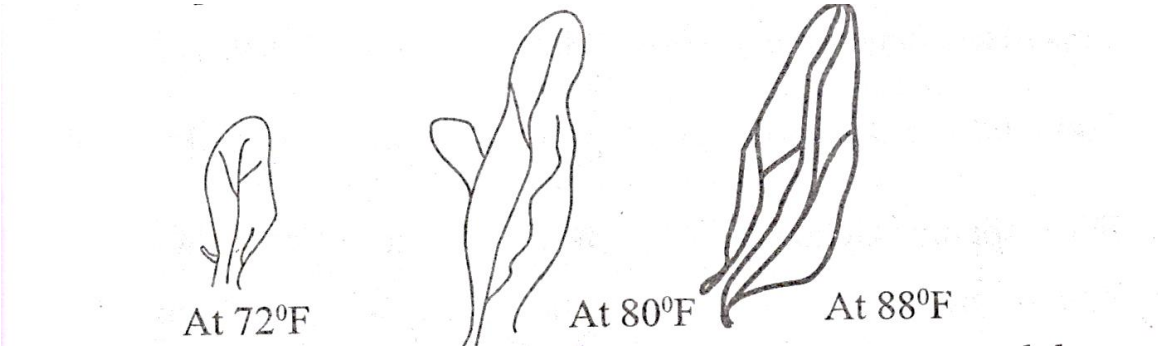


Fig.: *Expressivity in vestigial wing of Drosophila*

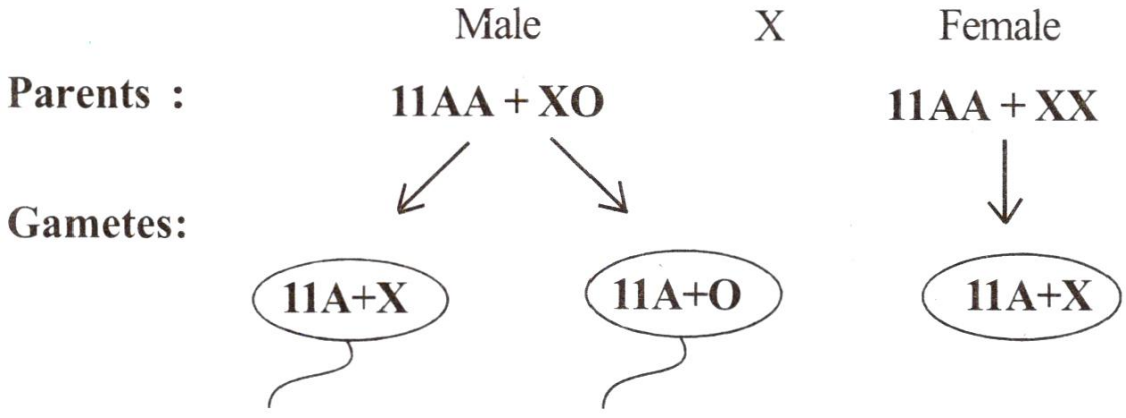
UNIT – III

SEX DETERMINATION

- ✓ The development of a zygote into male or female is called sex determination
- ✓ Sex is a character. It has two alternatives, namely maleness and femaleness. The male produces the sperm and the female produces the egg
- ✓ Sex is determined by the following factors
    - Chromosomes
    - Environment
    - Hormones
    - Metabolism
    - Parasites

Sex Determination in Grasshopper

- ✓ In grasshopper, sex is determined by XO chromosomes. The male is heterogametic and the female is homogametic
- ✓ In grasshopper, the females have 11 pairs of autosomes and one pair of X chromosomes (11AA+XX). The males have 11 pairs of autosomes and only one X chromosome (11AA +XO). It is said to be evolved by the loss of Y chromosome
- ✓ In grasshopper, males are heterogametic and females are homogametic
- ✓ The female produce only one type of egg which carries 11 autosomes and one X (11A +X). But the male produces two types of sperms, one carrying 11 autosomes and one X chromosome (11A +X) and the other type carries only the autosomes (11A + O).
- ✓ Fertilization by a sperm of the first type (11A +X) results in a female and by a sperm of the second type (11A+0) results in a male



Sex Determination in *Bonellia*

- ✓ In *Bonellia*, sex is determined by environmental factors.
- ✓ *Bonellia* is a marine echiuroid worm. It exhibits sexual dimorphism.
- ✓ The female is very large and is about 8cm with a proboscis of about one metre long. The male is very small and is about 1 to 3mm
- ✓ The female lives in a burrow at the sea bottom. The male lives as a parasite in the uterus of the adult female
- ✓ The larvae of *Bonellia* are alike and they have potentialities to develop into any sex. A larva settled on the proboscis of the female develops into male. A larva settled in the mud develops into a female
- ✓ If the larva is detached from the proboscis of female before the completion of development, the larva develops into an intersex
- ✓ CO_2 is the sex determining factor in *Bonellia*.
- ✓ In the proboscis of female, the amount of CO_2, is high because some amount of CO_2, is released in respiration.
- ✓ In sea water, comparatively the CO_2, content is less. So higher CO_2, content determines the maleness and lower CO_2, content determines the femaleness

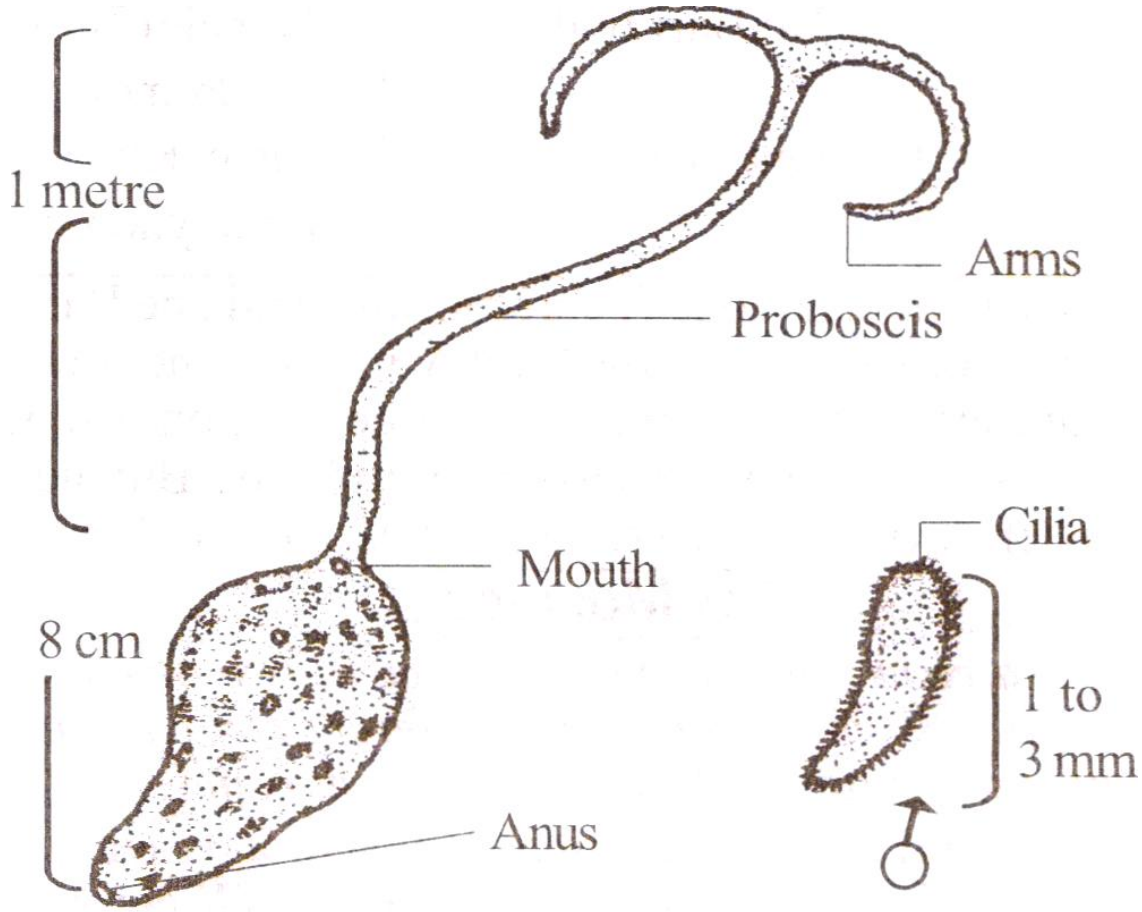


Fig. : Bonellia.

Sex Determination in Free-martin *(Cattle)*

- ✓ In cattle, when twins of opposite sex (one female and other male) are born, the male is normal but the female is sterile with many male characteristics.
- ✓ Such sterile females are called free martins
- ✓ In cattle, twins occur frequently.
- ✓ If both the young ones are zygotically of the same sex, they develop normally; if however, one member is a male and the other female, then the development of the female is not normal
- ✓ During development both the twins are connected by a common umbilical cord.
- ✓ The gonads of the male develop earlier than those of the female.
- ✓ So the male gonads produce male hormones earlier in development.
- ✓ These male hormones reach the female embryo and influence the development of male sex in the female embryo.
- ✓ This results in a sterile intersex having female phenotype with sterile male
  gonads

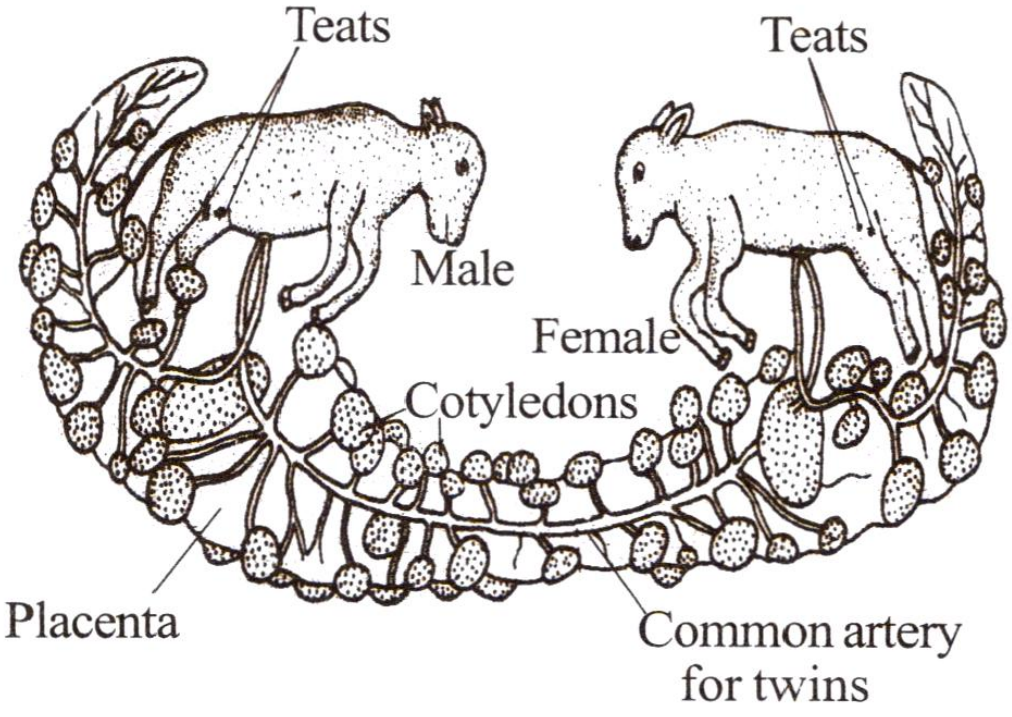


Fig. : Free martin.

Sex Determination in *Pigeon*

- ✓ According to Dr. Oscar Riddle, the degree of metabolism plays an important role in sex determination.
- ✓ Normally the metabolic rate is higher in males than that of females
- ✓ Pigeons produce two types of eggs which are differentiated by their yolk content.
- ✓ An egg which develops into male has small amount of yolk than the egg which develops into female.
- ✓ An increased rate of oxidation, larger water content and less protein storage in development lead to the production of more males.
- ✓ At the same time the low rate of oxidation, smaller water content and higher protein storage in development influence the production of more females

Sex Determination in *Sacculina*

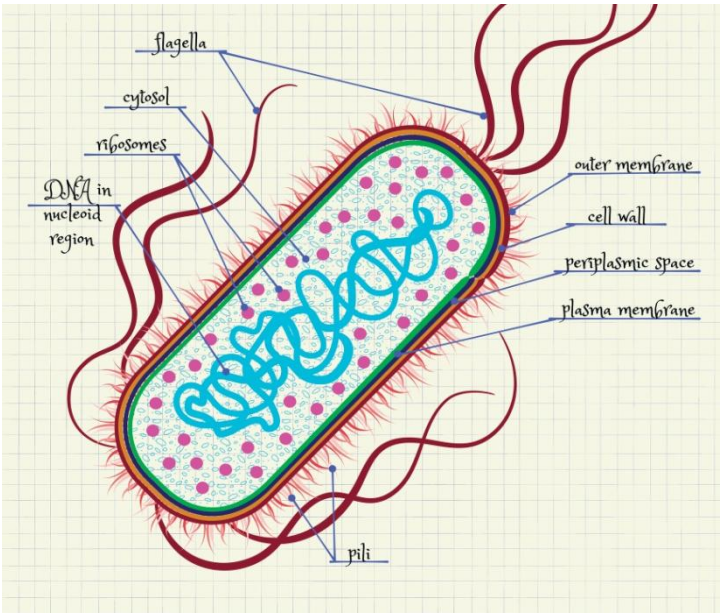
- ✓ Endoparasites of some animal change the sex of their host.
- ✓ In the case of crabs *(Inachus),* if a crustacean parasite called *Sacculina* is present in a male, it is changed into a female in course of time.
- ✓ This may be due to the physiological disturbances caused by the presence of parasites inside the host.

MICROBIAL GENETICS -METHODS OF GENE TRANSFER

- The progress in modem genetics is mainly by the experiments done in microbial organisms like bacteria and virus.
- In these organisms, the nucleus is not separated from the cytoplasm.
- They have only haploid number of chromosomes.
- Hence each character is controlled by only one allele

Bacteria

- Bacteria are aptly described as the work-house of the modern genetical world.
- Bacteria are Prokaryotes.
- The most commonly used bacterium for genetical work is *Escherichia coli* living in the colon of man.



- It is microscopic, unicellular and rod shaped.
- It is covered by two layers, namely an outer cell wall and an inner plasma membrane.
- Many flagella arise from the body.
- The cytoplasm is colloidal in nature and contains granules of glycogen, proteins and lipids.
- Endoplasmic reticulum, Golgi complex, lysosomes, mitochondria, etc. are absent.
- Ribosomes are present. They are smaller than eukaryotic ribosomes.
- Genetic information is carried by a single circular DNA present in the cytoplasm. This is called bacterial chromosome and it represents the Nucleoid

Recombination

- Recombination is the rearrangement and reshuffling of genes resulting in new genotypes.
- Bacterial recombination is brought about by the transfer of genetic materials from one bacterium to other.
- The bacterium which donates the genetic material is called donor and the bacterium which receives it is called recipient
- It occurs in four methods. They are
    1. Transformation
    2. Conjugation
    3. Sexduction
    4. Transduction

1. Transformation

- In this method, the donor bacterium liberates the DNA by the dissolution of the cell and the DNA is absorbed from the medium by the recipient bacterium.
- Hence the recipient bacterium is transformed into another strain. This is called transformation. Transformation is described by Griffith (1928) in *Pneumococcus pneumonia*
- Griffith in 1928 carried out a series of experiments with *Pneumococcus*.
- There are two types of *Pneumococcus* bacteria, namely virulent and avirulent
- Virulent strains have smooth carbohydrate capsules and give smooth colonies, Avirulent strains have no capsules and give rough colonies.
- These two strains also differ in their antigenic properties and virulence for the disease pneumonia. Virulence is determined by genetic factors.
- When virulent strains are injected into mice, they kill them with pneumococcal infection.
- When mice are inoculated with avirulent bacteria there was no ill effect.
- Then mice are injected with virulent bacteria after killing with heat. In this case, no ill-effect is produced and the mice survive.
- Finally, mice are injected with a mixture of avirulent and heat-killed virulent bacteria. In this experiment the mice die due to pneumococcal infection.
- The analysis of dead mice shows that it contains virulent bacteria.
- The heat killed virulent bacteria are responsible for the transformation of avirulent bacteria into virulent smooth bacteria.

- Something from the heat killed (dead) virulent bacteria was apparently transferred to the live avirulent bacteria. This phenomenon is known as Griffith effect or Bacterial transformation

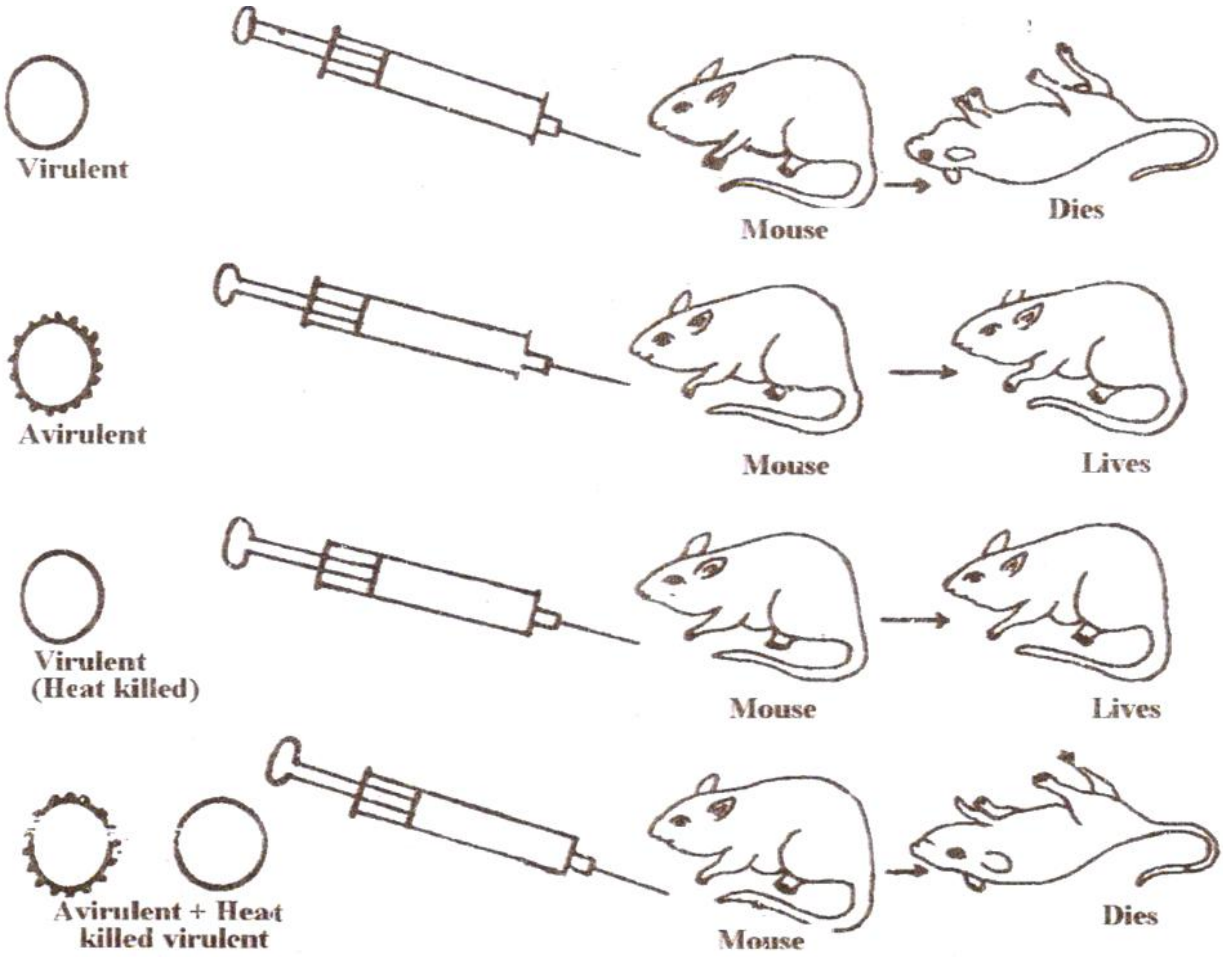


Fig. Griffith's experiment to explain bacterial transformation

2. Conjugation

- In this method, two bacteria join together and a portion of DNA of donor is transferred to the recipient
- F+ and F^- cells join together and a conjugation tube is formed.
- Now a nick is made in one strand of the plasmid of F+ cell.
- The 5' end of the broken strand is inserted into the F^- cell through the conjugation tube and in a few minutes the complete strand is transferred to the F^-cell.
- The single strands of F+ and F^- cells now synthesize a complementary strand producing a double stranded circular plasmid. After this, the conjugants separate.
- Now each exconjugant is provided with a plasmid. Thus the F^- cell is transformed into F+ cell by conjugation
- Conjugation also occurs between Hfr cells and F^- cells.
- In Hfr (high-frequency recombination) cells, the plasmid remains integrated with the bacterial chromosome
- During conjugation, the Hfr cell transfers the plasmid or the plasmid with a portion of bacterial chromosome.
- The F^- cells receives not only the genes present in the plasmid, but also a set of chromosomal genes

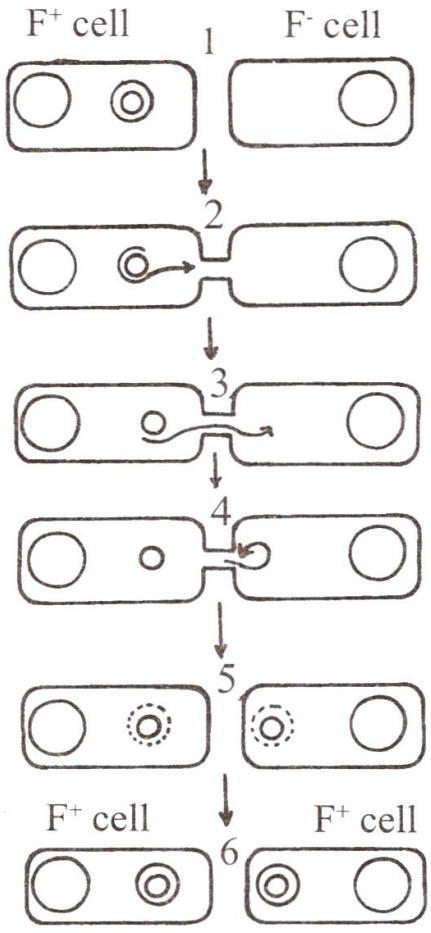


Fig. Conjugation

3. Sexduction

- The transfer of chromosomal genes through plasmid from one bacterium to another is called sexduction.
- In the Hfr cell, sometimes, the plasmid is deintegrated from the chromosome.
- During deintegration a part of the bacterial chromosome is included into the plasmid.
- Now the plasmid is called F_1 element and the cell is called F_1 cell.
- When conjugation occurs between F_1 cell and F^- cell the plasmid is transferred along with some genes of chromosomes

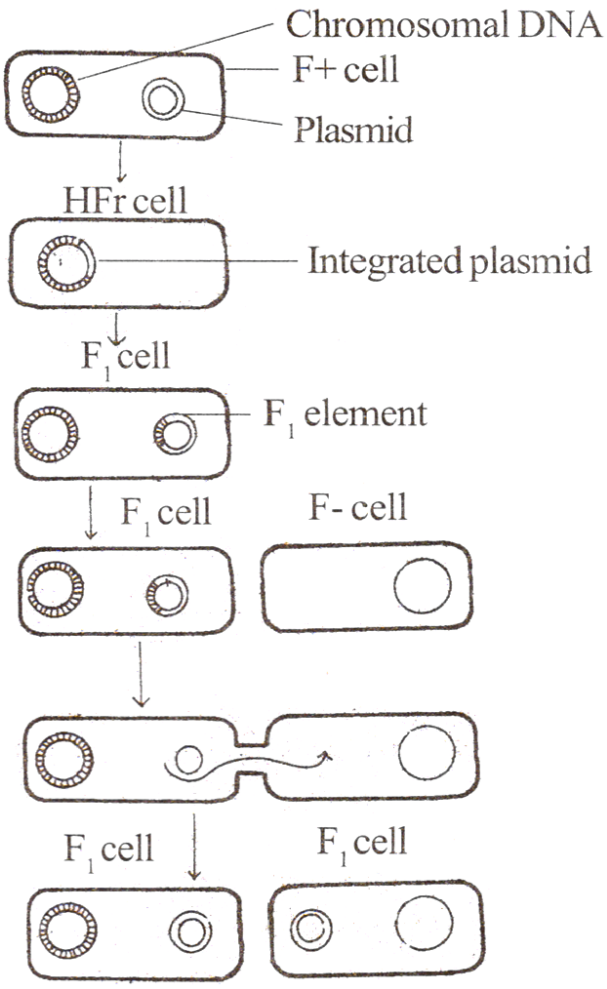


Fig. sexduction

4. Transduction

- Transfer of genetic material from one bacterium to another through bacteriophages is called transduction.
- As in the lysogenic cycle, the viral DNA gets integrated with the bacterial chromosome to become prophage.
- Then the prophage DNA deintegrates.
- During the process, the prophage DNA gets a fragment of bacterial DNA.
- This phage DNA replicates several times to produce many viral particles. These are released by the rupture of bacterial cells.
- These phages containing a portion of bacterial DNA are called transducing phages.
- These phages now infect new hosts and the DNA is integrated with the bacterial chromosome.
- When the viral DNA, deintegrates from the bacterial DNA, it leaves the bacterial DNA drawn from the first bacterium.
- Thus the bacterium gets a fragment of DNA from the previous bacterium through bacteriophages

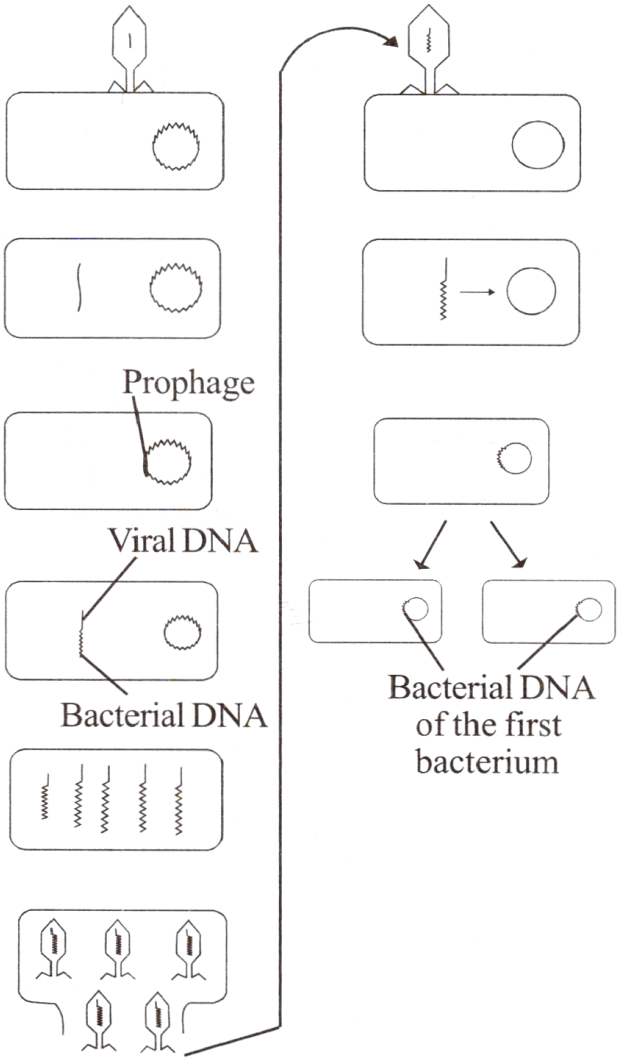


Fig. Transduction

UNIT-IV
Mutation

- Mutation is a sudden change of a gene or chromosome from one form to another. It produces an alteration in the character under its control. Dobzhansky stated that mutation is a mistake or misprint in cell division.
- The term **mutation** was introduced by **De Vries.**
- Mutations may occur at **chromosomal level** or **gene level.**

Chromosomal mutations (Genome mutations)

- ***The changes in the structure and number of chromosomes (genome) are called chromosomal mutations.***
- ***Since these mutations occur at the chromosomal level, they are also called chromosomal aberrations.***
- The **genome** is defined as the total genetic material contained within the chromosomes of an organism.
- Humans have 46 chromosomes. Our 46 chromosomes represent our genome. Genomic mutations take place due to abnormalities in cell divisions.
- They may occur due to change in structure of chromosomes or due to change in the chromosome number.
- Any change in individual genes has not been considered in genome mutations. Genomic mutations are analyzed with cytological investigations of cells.

Types chromosomal mutation

Genome mutation is of two types, namely

I. Changes in the structure of chromosomes.
II. Changes in the number of chromosomes.

I. Changes in the structure of chromosomes.

The change in the structure of chromosome there are of 4 types, namely

1. Deletion; 2. Duplication; 3. Inversion; 4. Translocation

1. Deletion

- ***Deletion is a chromosomal aberration where a segment of the chromosome is lost. Here some genes are lost.***
- Deletion is of two types, namely **terminal deletion** and **intercalary deletion.**
- In **terminal deletion**, a terminal segment is lost.
- In **intercalary deletion**, an intermediate segment of the chromosome is lost

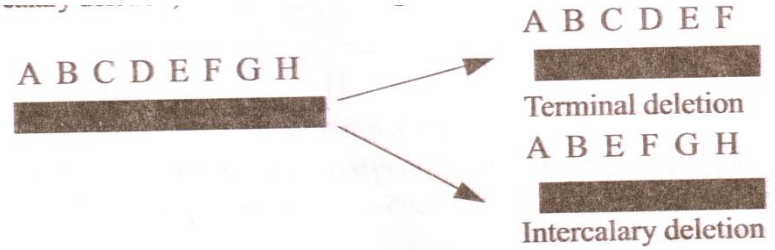


Fig. Deletion

- In human babies, deletion of a segment of chromosome number 5 causes a disease called **cridu chat syndrome.**
- The baby cries like a cat; it is mentally retarded with small head.

2. Duplication

- Duplication is a chromosomal aberration where a segment is repeated.
- Hence a set of genes is present in double doses.

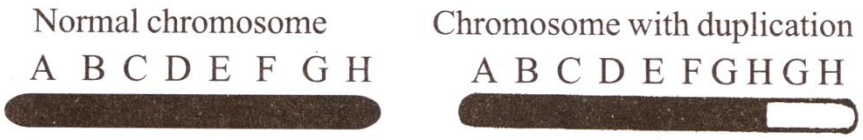


Fig. Duplication

- During meiosis, the duplicated segment forms a **loop.**
- In **Drosophila, bar eye** is due to duplication

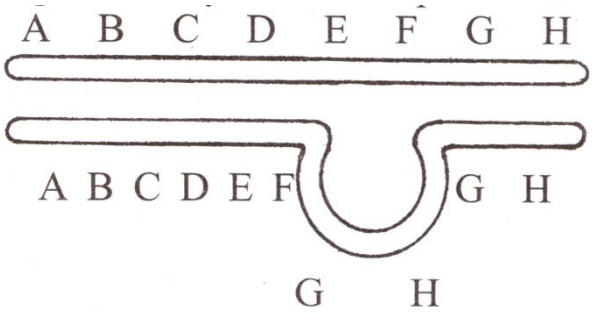
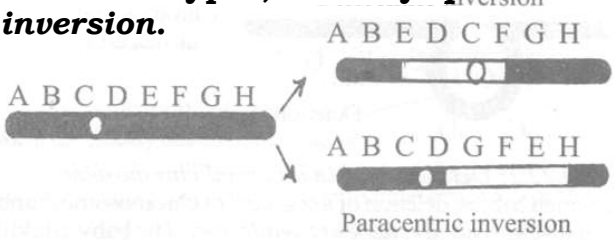


Fig. Duplication loop

3. Inversion

- Inversion *is* a chromosomal aberration where a segment of chromosome breaks and reunites in the reverse order.
- In inversion, there is no loss or gain of genes. But the genes are rearranged in reverse order.
- **Inversion is of two types, namely *pericentric inversion* and *paracentric inversion.***



- In **pericentric inversion,** the centromere is included in the inverted segment.
- In **paracentric inversion,** the centromere is not included in the inverted segment.
- The chromosome with the inverted segment produces an inversion loop.
- Inversion prevents crossing over.

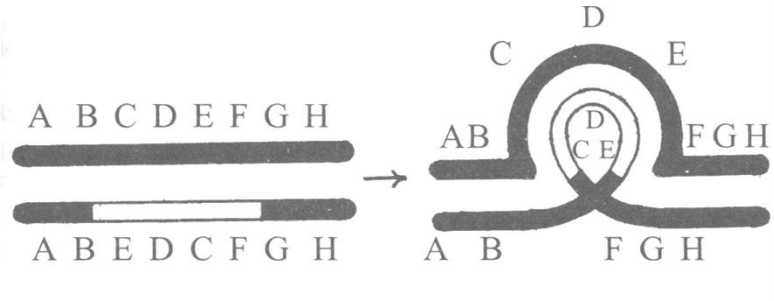


Fig. Inversion loop

- Inversion produces variation and speciation

4. Translocation

- ***Translocation is*** a chromosomal aberration where non- homologous chromosomes exchange segments.

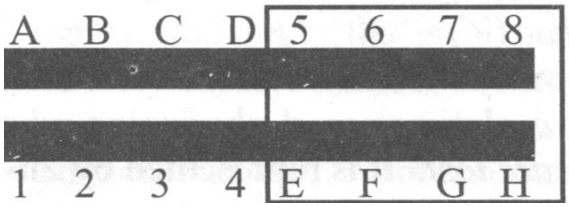


Fig. Translocation

- Translocation produces a **cross-shaped** structure during pairing.
- Translocation causes **position effect.**
- Translocation alters the **linkage groups.**

II. Change in the Number of Chromosomes

- Change in the number of chromosomes *is called* ploidy.
- ***Ploidy may be due to a loss or gain of a chromosome of a set or changes in the number of chromosome sets.***
- ***Based on this, there are two kinds of ploidy, namely***

1. Aneuploidy
2. Euploidy

1. *Aneuploidy*

- ***Aneuploidy is*** a chromosomal aberration where there is a gain or loss of one or more chromosomes in a set.
- ***Aneuploidy is caused by non-disjunction of chromosomes.***
- ***It is of three types, namely***
  - **1.** Monosomy
  - **2.** Nullisomy
  - **3.** Trisomy

1. Monosomy

- **Monosomy *is* a chromosomal aberration where one chromosome is lost from a pair.**
- ***It is represented by 2n-1.***
- ***The monosomic individual has one chromosome less from the normal number of chromosomes.***
- ***A monosomic* Drosophila *has 8-1=7 chromosomes.***
- ***A monosomic man has 46-1=45 chromosomes.***
- ***It is an*** aneuploidy.
- ***It is produced in woman when an egg without an X chromosome fuses with a sperm containing, an X chromosome.***
- ***It causes a syndrome called*** Turner's syndrome**.**

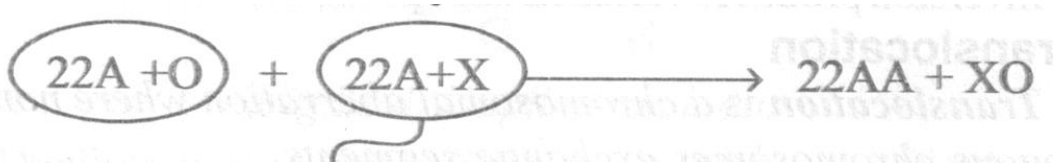


Fig. Monosomy with the loss of one X chromosome.

2. Nullisomy

- *Nullisomy is a chromosomal aberration where both chromosomes of a pair are lost.*
- *It is represented by 2n-2.*
- **It is an** aneuploidy.
- A nullisomy is produced by the fusion of gametes having one chromosome less.

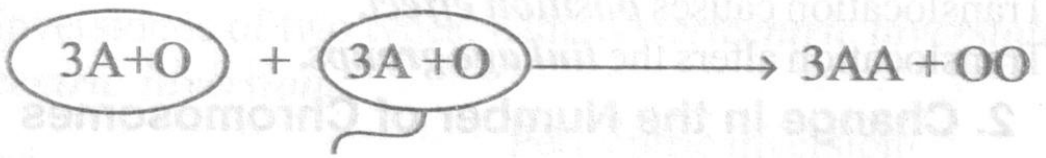


Fig. Nullisomy with the loss of a pair of chromosomes.

- *Nullisomic individuals cannot survive.*

3. Trisomy

- **Trisomy *is* a chromosomal aberration where one chromosome is added to a pair.**
- ***It is represented by 2n+l.***
- ***A trisomic individual has an additional chromosome from the normal number.***
- ***Thus a trisomic* Drosophila *has 8+1=9 chromosomes.***
- ***A trisomic man has 46+1=47 chromosomes.***
- ***It is an aneuploidy.***

- ***Trisomy is caused by* non-disjunction.**
- ***There are two types of trisomy, namely* trisomy of autosomes and *trisomy of sex* chromosomes.**
- Trisomy of autosome is due to the addition of one chromosome to any one homologous pair of autosome.
- When a chromosome is added to 21[a] pair of autosome, it is called **trisomy-21.**
- Trisomy-21 in man causes a syndrome called **Down's syndrome** (Mongolism).
- A trisomic man has 47 chromosomes instead of 46. They are mentally retarded. They have broad face and flat stubby nose.
- Trisomy of sex chromosome is due to the addition of one sex chromosome. When an X chromosome is added to a man, he has 47 chromosomes, 22AA+XXY.
- It causes a syndrome called **Klinefelter's syndrome.**

2. Euploidy

- *Euploidy* ***is*** *a chromosomal aberration involving change in the number of chromosome sets.* ***It is of two types, namely***
  1. *Haploidy*
  2. *Polyploidy*

1. Haploidy or Monoploidy

- The basic set of chromosome in any species is haploid; each chromosome is represented singly; that is (N) number.
- The gametes carry haploid number of chromosomes. During fertilization the parental chromosomes unite together by the fusion of gametes forming diploid number (2N) of chromosomes.
- Sometimes in the life of an animal a set of chromosomes will be lost and this leads to haploidy. So some characters which are present in any parent, will be lost from the resulting individual.

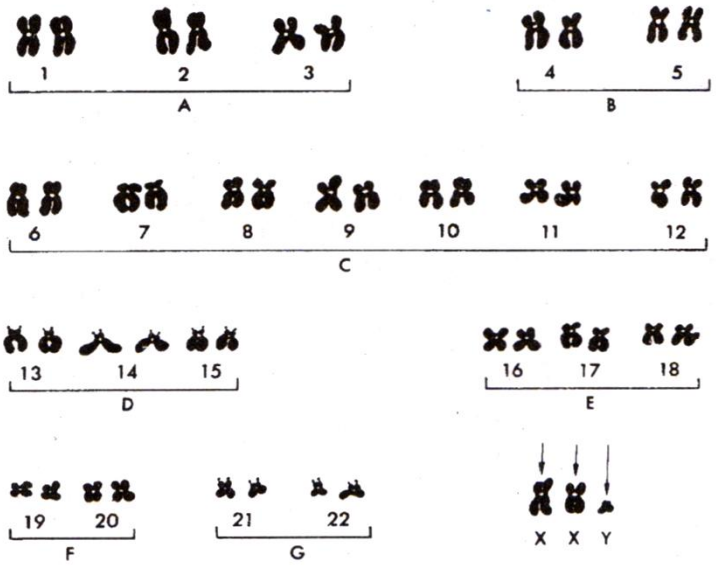
2. Polyploidy

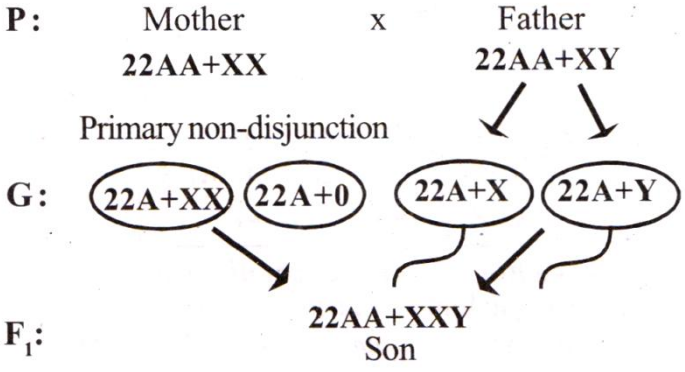
- Polyploidy is the condition in which an organism contains more than the usual two sets of chromosomes. Such animals are said to be **polyploid.**
- Polyploid organisms may have three, four or more sets of chromosomes and they are called **triploids (3N); tetraploids (4N); pentaploids (5N); hexaploids (6N) hectaploids (7N); octoploids(8N); nanaploids (9N); decaploids (10N)** and so on.
- Polyploidy may be **autopolyploidy** or **allopolyploidy.**
- In autopolyploidy, the chromosome sets are derived from the same species so no addition of new genes occurs but in allopolyploidy the chromosome sets are derived from distinct species it involves the addition
  of new genes hence much variations occur in organisms.
- These variations are inherited by the offspring which seem to be different from their parents.

KLINEFELTER'S SYNDROME

(22AA+XXY) = 47

- *Klinefelter's syndrome is a genetical disease caused by an additional X chromosome in human male*
- *It is a sexual abnormality in males discovered first by Harry (1942)*
- *It is caused by chromosomal aberration*
- *It is caused by trisomy (aneuploidy) where one chromosome is added to a set (2n +1)*
- *This abnormality is due to the presence of 47 chromosomes instead of 46.*
- *The victims possess an additional X chromosome with XY. So the chromosomal make up is 22AA +XXY*
- *It is caused by non-disjunction of XX chromosomes. When an abnormal egg with XX chromosomes is fertilized with a sperm with Y chromosome, the resulting baby contains XXY*
- *They are sterile males; the testes are small; there is no spermatogenesis*
- *Male sex glands are poorly developed; the breasts are enlarged*
- *Amount of male hormone is low*
- *They are mentally affected; they are tall*

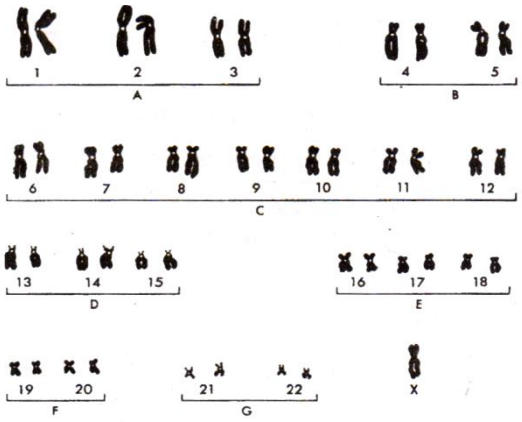


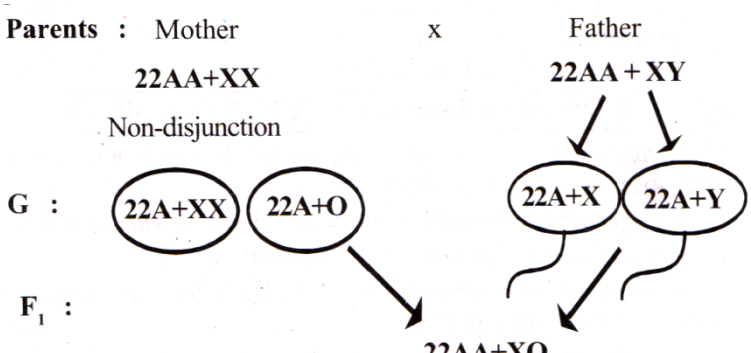


TURNER'S SYNDROME

(22AA+X) = 45

- *Turner's syndrome is a genetical disease in human female caused by the absence of one X chromosome*
- *It is a sexual abnormality in female discovered by Turner in 1938*
- *It is caused by a chromosomal aberration*
- *It is caused by monosomy (aneuploidy) where one chromosome is lost from one pair (2n-1)*
- *This abnormality is due to 45 chromosomes instead of 46.*
- *The missing chromosome is one X chromosome. Hence the chromosomal make up is 22AA + XO= 45*
- *It is caused by non-disjunction of XX chromosomes. When an abnormal egg without any X chromosome is fertilized by a sperm with X chromosome, the resulting baby contains XO chromosomes*
- *The baby develops into a sterile female. She has female phenotypes. But there is no menstruation*
- *Ovaries are represented by ridge of whitish tissue called streak gonad*
- *Female hormones are low. The chest is broad. Breasts are poorly developed. They are dwarf and mentally retarded*





EDWARD'S SYNDROME

(trisomy 18)

- *Edwards syndrome, also known as trisomy 18*
- *In 1980, Edward discovered a new syndrome associated with the presence of an extra group E chromosome, here considered to be a No. 18 chromosome*
- *Nondisjunction during anaphase of mitotic or meiotic nondisjunction or nondisjunction in zygote lead to the mosaicism*
- *In 90% of cases death occurs within the first six months.*
- *But Hook (1965) recorded a mentally retarded female who was living at 15 years of age.*
- *The ratio of affected females to males is 3 to 1.*
- *The abnormal finding is an extra chromosome number 18, giving a total chromosome count of 47.*
- *If there is only a small additional part of the 18 chromosome, then the effect on the phenotype might be a modified trisomy syndrome.*
- Children born with Edwards syndrome may have some or all of these characteristics: kidney malformations, structural heart defects at birth, intestines protruding outside the body, esophageal atresia, intellectual disability, developmental delays, growth deficiency, feeding difficulties, breathing difficulties, and arthrogryposis.
- Some physical malformations associated with Edwards syndrome include small head (microcephaly) accompanied by a prominent back portion of the head (occiput), low-set, malformed ears, abnormally small jaw (micrognathia), cleft lip/cleft palate, upturned nose, narrow eyelid folds (palpebral fissures), widely spaced eyes (ocular hypertelorism), a short breast bone, clenched hands, underdeveloped thumbs and/or nails, clubfoot or rocker bottom feet, and in males, undescended testicles.

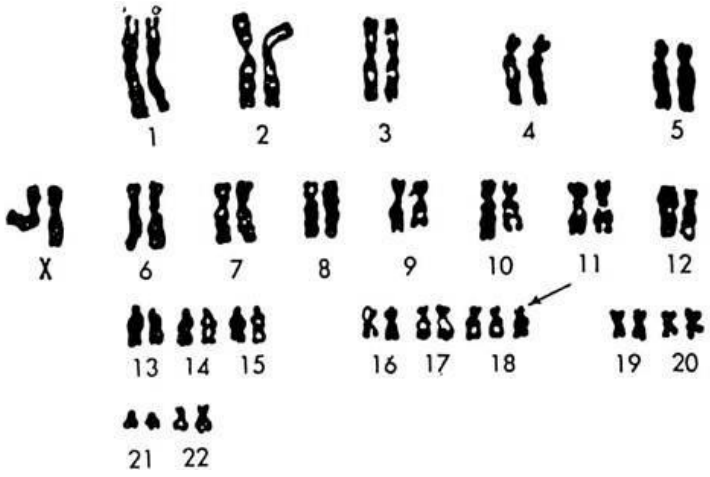
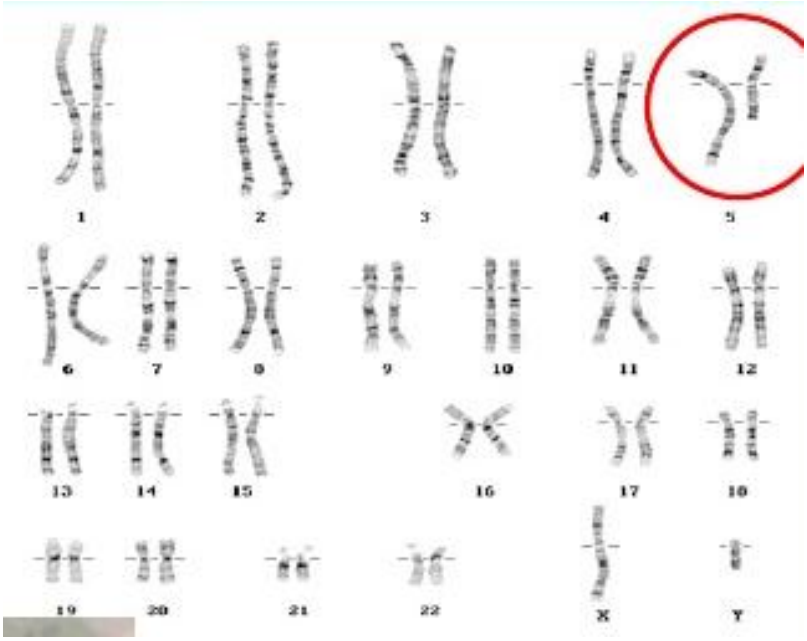


Fig. Karyogram of Edward syndrome

CRI DU CHAT SYNDROME

- Cri-du-chat syndrome is an autosomal deletion syndrome caused by a partial deletion of chromosome 5p
- and is characterized by a distinctive, high-pitched, catlike cry in infancy with growth failure, microcephaly, facial abnormalities, andmental retardation throughout life. See the images below
- It is a rare genetic disorder due to chromosome deletion on 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.
- It was first described by Jérôme Lejeune in 1963.
- The condition affects an estimated 1 in 50,000 live births across all ethnicities and is more common in females by a 4:3 ratio
- The syndrome gets its name from the characteristic cry of affected infants, which is similar to that of a meowing kitten, due to problems with the larynx and nervous system.
- Other symptoms of cri du chat syndrome may include:
    - feeding problems because of difficulty in swallowing and sucking;
    - low birth weight and poor growth;
    - behavioral problems such as hyperactivity, aggression, outbursts and repetitive movements;
    - unusual facial features, which may change over time;
    - excessive drooling;
    - small head (microcephaly) and jaw (micrognathism);
    - widely-spaced eyes (hypertelorism);
    - skin tags in front of eyes.



Molecular Basis of Gene Mutations

- The change in the base sequence of genes is called gene mutation.
- Mutation produces an altered gene.
- The organism carrying the altered gene is called a mutant.
- The organism carrying the normal (unaltered) gene is called wild type.

The process of producing mutation is called mutagenesis.

Mutation is classified into the following types:

1. Spontaneous Mutation

- The mutation occurring naturally is called spontaneous mutation.
- It is due to normal cellular operations or due to random interactions with the environment.

2. Induced Mutation

- Artificially produced mutations are called induced mutations.
- They are caused by certain factors called mutagens.
- Mutagens may be physical or chemical factors. Eg. X-rays, nitrous acid, etc.

3. Point Mutation

- When a single base pair is altered, the mutation is called point mutation.
- A point mutation is classified into three types, namely

a. Base Substitution: In base substitution, a base is replaced by another base.

b. Base Insertion: In base insertion, a new base is inserted.
c. Base Deletion: In base deletion, a base is missing.
d. Base Inversion: In base inversion, the base sequence is reversed.

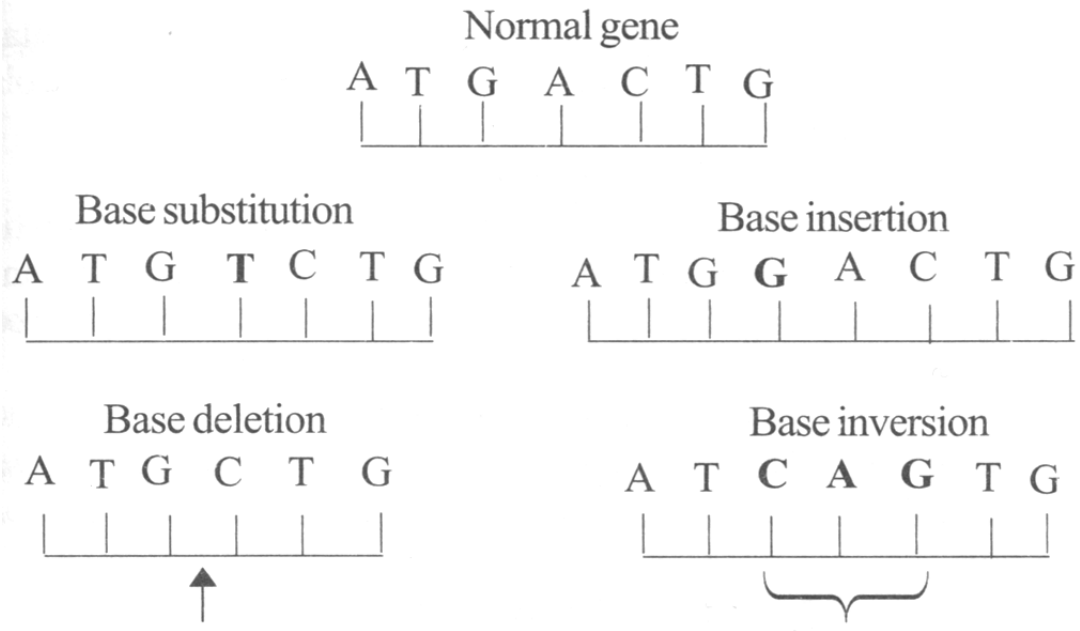


Fig.22.9: Point mutations.

4. Missense Mutation

Sometimes in a polypeptide chain, an amino acid is substituted by another amino acid. This is due to substitution of three bases (a codon) in the DNA. This mutatic alled **missense mutation.**

5. Non-sense Mutation

Sometimes mutation produces a base sequence that does not code for any amino acid (non-sense codon). In such cases, termination of the synthesis of protein occurs at this point. This mutation is called **non-sense mutation** or **chain termination mutation.**

6. Transition

Transition is a point mutation where one purine base is substituted by another purine or one pyrimidine base is substituted by another pyrimidine. Eg. G-C pair is exchanged with an A-T pair or vice versa.

(Purines and Pyrimidines are nitrogenous bases that make up the two different kinds of nucleotide bases in DNA and RNA.

The two-carbon nitrogen ring bases (adenine and guanine) are purines, while the one-carbon nitrogen ring bases (thymine and cytosine) are pyrimidines.)

7. Transversion

Transversion is a point mutation where a purine is replaced by a pyrimidine or vice versa. Eg. *An* **A-T** *pair is replaced by a* **T-A** *or C-G pair*

8. Base-analogue Mutation

Certain chemicals are similar to the bases of DNA. These chemicals are called **base- analogues.** The base-analogue has the ability to pair with a base of the DNA causing an alteration in the gene. *The mutation caused by the pairing of a base-analogue with a base of the DNA* is called **base-analogue mutation.**

The base *5-bromouracil (BU)* is an analogue of thymine. Hence BU functions like thymine and can easily pair with adenine causing base-analogue mutation.

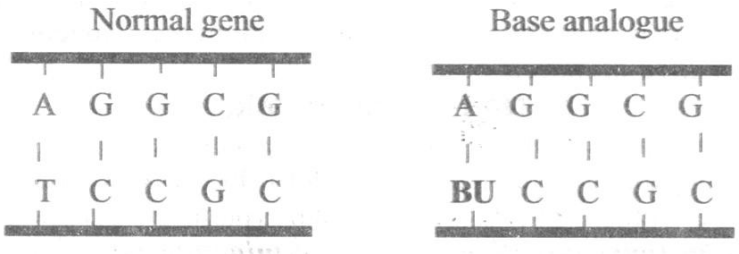


Fig. Base-analogue mutation by BU.

9. Frameshift Mutation

A mutation that inserts or deletes a single base will change the reading frame for the entire subsequent sequence. **A change of reading frame** *is called* **frameshift mutation.**

When the genetic code is read in non-overlapping triplets, there are three possible ways of translating a nucleotide sequence into protein, depending on the starting point These are called *reading frames.*

For example, the following sequence has three reading flames:

DNA sequence

ACG ACG ACG ACG ACG ACG ACG

Reading frames

ACG ACG ACG ACG ACG ACG ACG
CGA CGA CGA CGA CGA CGA CGA
GAC GAC GAC GAC GAC GAC GAC

Fig. Three possible reading frames of a DNA sequence

- As the sequence of the new reading flame is completely different from the old one, the entire amino acid sequence of the protein is altered beyond the site of mutation. Thus the function of the protein is altered.

Tyrosine, Glutamate, Tyrosine, Glycine, Isoleucine

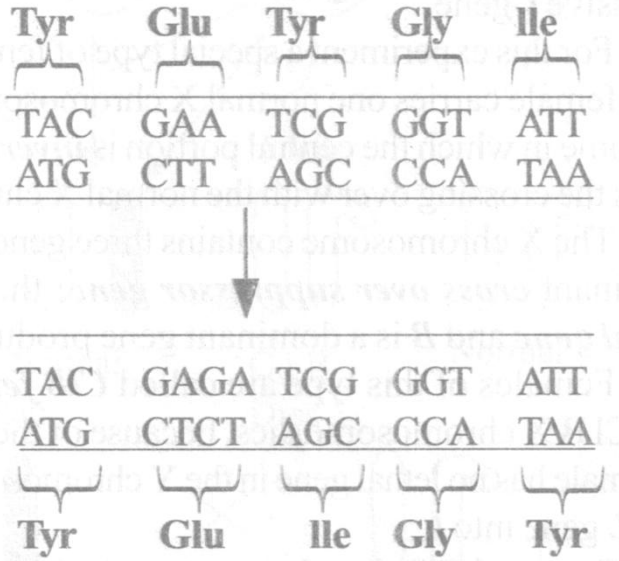


Fig. Frame shift mutation. The addition of a new base results in the change in the sequence of amino acids

- The base shift mutation is induced by acridine compounds that bind to DNA and distort the structure of the double helix causing additional bases to be incorporated or omitted during replication.

Mutagens

- Mutagens are agents that cause changes in genetic code which are then passed to future generations.
- The changes caused in the genetic code are called mutations.
- The formation of mutations is called mutagenesis.
- A mutation changes the activity of a gene.
- The activity of a gene is expressed in the form of a protein.
- A protein is composed of a chain of amino acids.

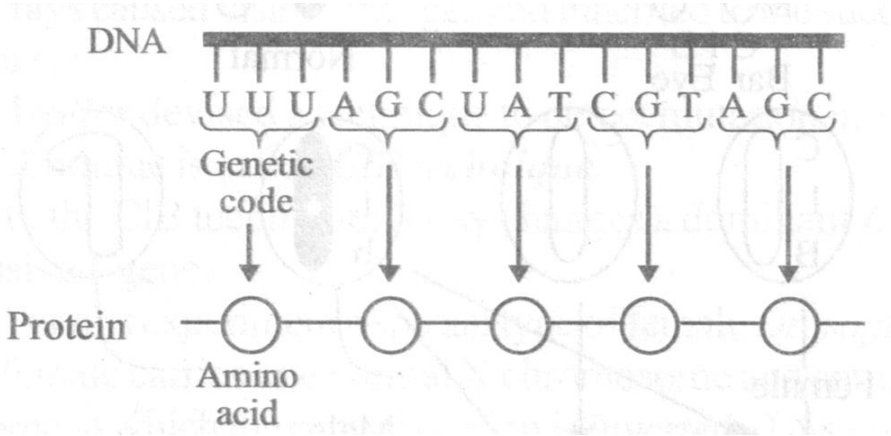


Fig. The genetic codes specify the type and sequence of amino acids in a protein molecules

Each amino acid of a protein is specified by a genetic code of three bases. For example, the codon **UUU** specifies the amino acid **phenylalanine.** When the third base is replaced by another base A, the resulting code **UUA** specifies another amino acid **leucine** instead of phenylalanine. This results in a new protein. This is caused by mutation of genetic code.

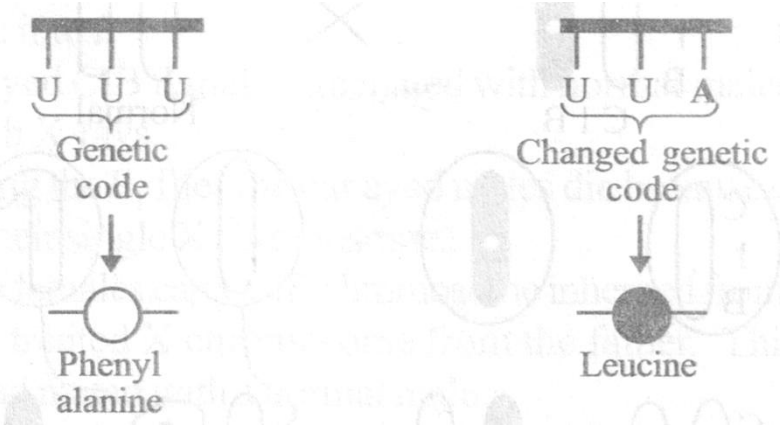


Fig. A mutation; the base U is replaced by A. The amino acid is also changed

Mutagens cause mutation by several mechanisms such as

- Replacement of base by another base
- Addition of a new base
- Deletion of a base
- Insertion of a base
- Deamination of a base (the removal of an amino group from an amino acid or other compound.)
- Incorporation of base analogues.
- Tautomerization of a base (**Tautomers** are constitutional isomers of organic compounds that readily interconvert. This reaction commonly results in the relocation of a proton. ... The chemical reaction interconverting the two is called **tautomerization**.)

- Many mutagens are carcinogenic also. But not all mutagens are carcinogenic.

Mode of action of mutation mutagens

- The mutagens are mutation causing agents.
- The mutagens may be physical or chemical agents.
- The chemical mutagens include

Mustard gas	Formaldehyde
Nitrous acid	Peroxides
Nitrogen mustard	Caffeine

- The physical agents include radiation, temperature, light, etc.
- The radiations include

X-rays	Beta rays
Gamma rays	Ultraviolet rays
Alpha rays	Infra red rays

1. Mode of action of chemical mutagens

- Based on the mode of action, the chemical mutagens are classified into the following types

  - *Alkylating agents*
  - *Base analogues*
  - *Acridines*
  - *Deaminating agents*

- The **alkylating mutagens** donate alkyl groups (methyl or ethyl) to the DNA bases resulting in altered base pairing.
- The alkylating agents include **mustard gas, methyl methyl sulphonate** and **ethyl methyl sulphonate.**
- Some alkylating agents produce **cross links** in DNA strands causing chromosome breaks.
- **Base analogues** are bases similar to DNA bases.
- **5-Bromouracil** (5-Bu) is a base similar to thymine. Hence 5-Bu is a base analogue. It is a mutagenic agent.

- The 5-Bu can substitute thymine during the replication of DNA.

Fig. During replication of DNA, thymine of DNA is substituted by the mutagenic agent 5-bromouracil

- Frequently 5-Bu changes into tautomeric form (enol form).
- In such a state 5-Bu pairs with **guanine.**
- Hence A-T pair may be converted into G-C pair which is a mutant caused by 5-Bu.

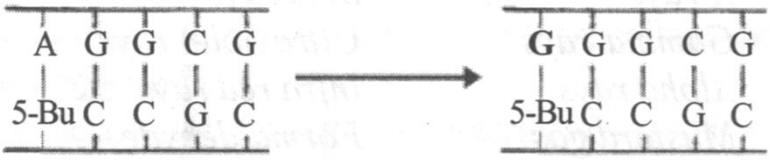


Fig. 5-Bu base pairs with guanine

2. Mode of action of radiation

- Radiations act as mutagens.
- The mutagenic radiations include X-rays, alpha rays, beta rays, gamma rays, UV rays, infra red rays, etc.
- Among radiations, the **ionizing radiations** are high energy radiations.
- They are powerful mutagenic agents.
- The **non-ionizing** radiations (UV rays) are low energy radiations.
- They are weak mutagenic agents.

- The ionizing radiations have high penetrating power. So they penetrate through the body coverings, cell wall, cell membrane, cytoplasm, nuclear membrane, nucleoplasm, etc. and attack the DNA itself. This mode of action of radiations directly on the DNA is called **direct hit.**

- The non-ionizing radiations (UV rays) have low penetrating power. So they do not reach the DNA and do not attack the DNA directly. They attack the molecules of cytoplasm which in turn brings about changes in the DNA. This indirect effect of radiations on DNA is called **indirect hit.**

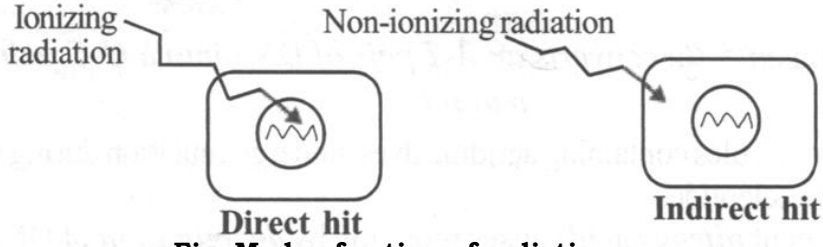


Fig. Mode of action of radiation

DNA REPAIR MECHANISM

- Restoring the damaged part of DNA is called *DNA repair.*
- DNA is a fragile molecule that can be easily damaged. It is prone to damage due to replication and mutagenic agents.
- The following damages are caused to DNA
    - Insertion of a **wrong base** during replication. Eg. ***Conversion of* cytosine *to* uracil** (found only in RNA).
    - Loss of a **purine** base.
    - **Alteration** of bases. Eg. ***UV rays alter bases.*** Loss of an amino group (deamination) converts **C** to **U.**
    - Breakage of DNA strands. It may be single stranded break (SSB) or double stranded break (DSB).
    - **Covalent** linkages between bases. It may be on the same strand (intrastrand) or between strands (interstrand).
    - Mismatches of the normal bases. Eg. Incorporation of **U (found** only in RNA) instead of **T.**
- The following agents cause damage to DNA:
    - **Radiation -** UV rays, X rays, gamma rays ,etc.
    - Highly reactive **oxygen** - **radicals** produced during normal cellular respiration.
    - Chemicals in the **environment (Hydrocarbons)** including those found in **cigarette smoke.**
    - Plant and microbial products **Aflatoxins.**
    - Chemicals used in chemotherapy especially **chemotherapy** of **cancer.**
- If the DNA damage is not repaired, it will lead to **mutation.** Thus DNA damage may cause mutation; if not corrected. **A failure to repair DNA produces mutation.**
- The following are the DNA repair mechanisms seen in living cells:
    - Direct repair
    - Excision repair
    - Mismatch repair
    - Recombinational repair

Direct Repair

- In direct repair mechanism, the changes introduced in the bases within a DNA are corrected directly without breaking the DNA.
- Here the repair is done without breaking the backbone of DNA.
- It is carried out by only one enzyme.
- Ultraviolet rays cause **thymine dimers** resulting in the linking of intrastrand thymines.
- It is corrected by direct repair
- The thymine dimers are corrected by the process of photoreactivation.
- **Photoreactivation** is the reversal of DNA damages caused by UV rays by the visible light.
- The repair is carried out by the enzyme **DNA photolyase**

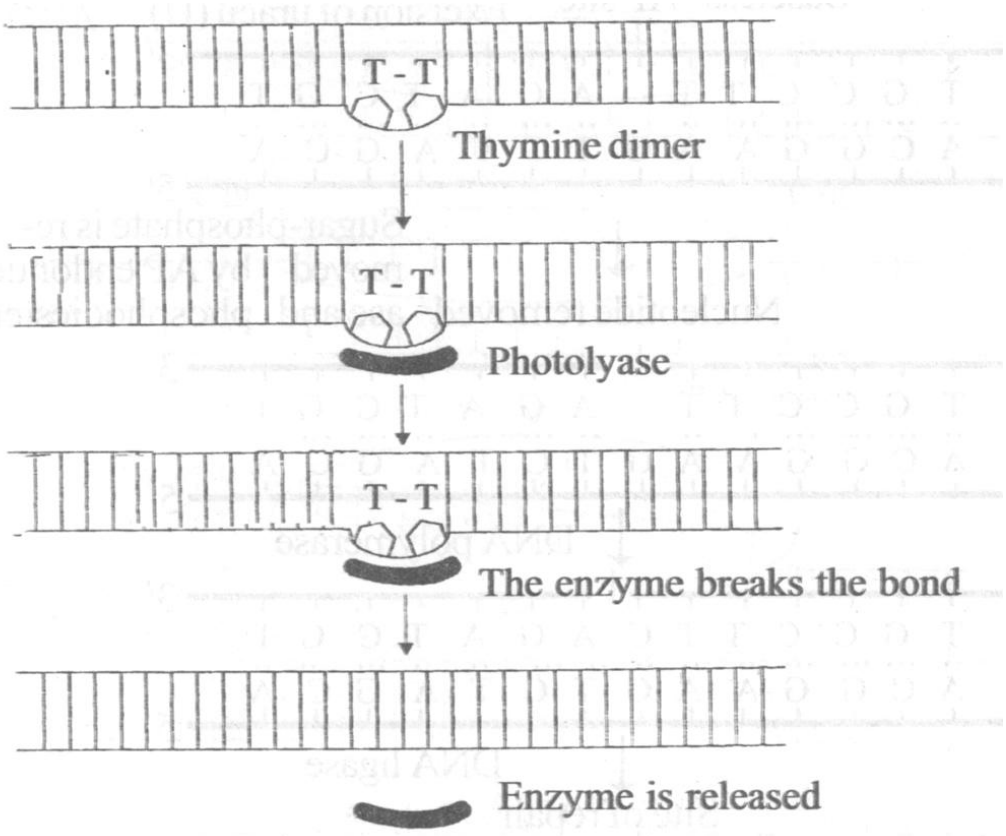


Fig.: Photo reactivation

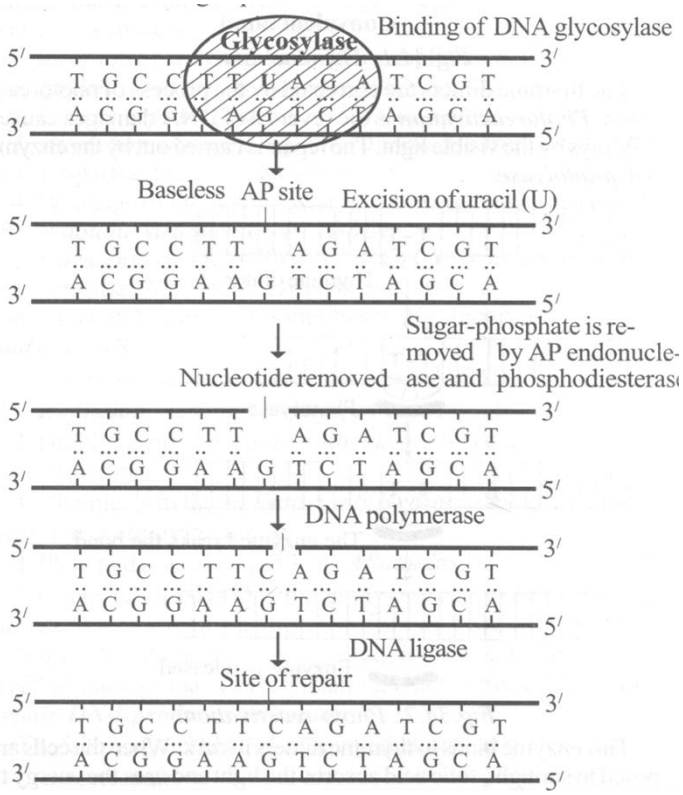
- This enzyme binds to thymine dimers in dark. When the cells are exposed to sunlight, folic acid absorbs the light and uses the energy to break the intrastrand linkages of thymine dimer

Excision Repair

- The damaged base or bases of DNA are excised and the gap is filled with the correct base or bases.
- Excision repair is a dark repair and is independent of light. It requires a set of three or four enzymes.
- The excision repair is of two types. They are the following:
    - Nucleotide excision repair
    - Nucleotide stretch excision repair

Nucleotide excision Repair

- In nucleotide excision repair, single damaged base is removed with the backbone of DNA and is replaced by a correct one.



Apurinic/apyrimidinic (AP) endonuclease is enzyme that is involved in the DNA base excision repair pathway (BER).

Fig.: Repair of DNA by base excision pathway

- It involves the following steps:
    - The enzyme **glycosylase** recognizes the damaged base (deamination) and binds to it on the DNA strand
    - It **hydrolyzes** the **N-glycosyl** bond linking the base to the sugar-phosphate backbone. The damaged base is excised and removed. This creates a baseless site in the DNA strand
    - Then an **endonuclease** and **phosphodiesterase** hydrolyze the **phosphodiester bond** so that the sugar and phosphate are removed
    - Then DNA polymerace fills up the missing nucleotide. The **DNA ligase** seals the nick

Nucleotide Stretch Excision Repair

- In nucleotide excision repair, a damaged segment of DNA is excised and replaced by the correct segment.

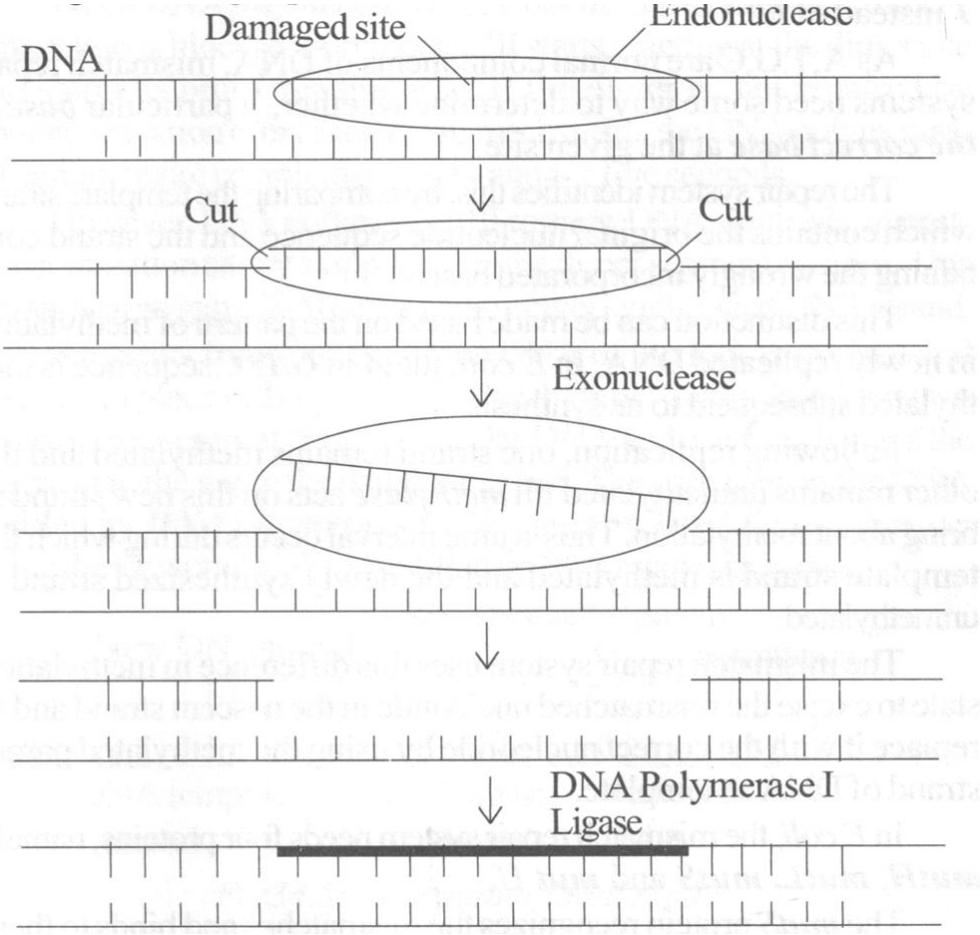


Fig.: Nucleotide stretch excision repair

- It involves the following steps
  - The enzyme **endonuclease** is attached to the damaged site. Then the enzyme cuts the polynucleotide on either sides of the damaged site resulting in the excision of a segment of 12 nucleotides including the damaged part.
  - The enzyme **5'-3' exonuclease** removes the excised segment by breaking the bond attaching it to the complementary strand
  - The gap is filled by **DNA polymerase I.**
  - The nick is closed by a **phosphodiester bond** formed by *DNA ligase.*

Mismatch Repair

- Mismatch is a wrong incorporation of nucleotide in the newly synthesized strand.
- It is an error in replication Mismatch repair is an excision repair independent of light.
- It is a **dark process.** It is a **post replicative** repair
- During replication, the nucleotides of DNA are copied in the daughter strand in 100% accuracy.
- However very rarely an incorrect nucleotide is incorporated as a result of a shift in the electronic state of the nitrogen base of an incoming nucleotide or of the template nucleotide.
- As a result, **A** may pair with **C** instead of T or may pair with **T** instead of **C.**
- As A,T,G,C are normal components of DNA, mismatch repair systems need some way to determine whether, a particular **base is the correct base** at the given site
- The repair system identifies this, by comparing the template strand which contains die original nucleotide sequence and the strand containing the wrongly incorporated base
- This distinction can be made based on the pattern of methylation in newly replicated DNA. In **E.coli**, **GATC** sequence is methylated subsequent to its synthesis
- Following replication, one strand remains methylated and the other remains unmethylated till **methylase** acts on this new strand to bring about methylation.
- Thus a time interval occurs during which the template strand is methylated and the newly synthesized strand is unmethylated
- The mismatch repair system uses this difference in methylation state to excise the mismatched nucleotide in the nascent strand and to replace it with the correct nucleotide by using the methylated parent strand of DNA as template
- In **E.coli,** the mismatch repair system needs four proteins, namely **mutH, mutL, mutS** and **mut U**
- The **mutS** protein recognizes the mismatches and binds to them to initiate the repair process; **mutH** and **mutL** proteins join with **mutS**

Recombinational Repair

- *In recombinational repair, the damaged part of a DNA is replaced by a part of another DNA molecule. This repair mechanism is found in E.coli and virus*
- Recombinational repair requires the presence of an identical sequence similar to the damaged sequences.
- The enzymatic machinery responsible for this repair process is nearly identical to the machinery responsible for chromosomal **cross over** during **meiosis**
- *It is a post-replicative repair mechanism*
- DNA dimers, caused by UV rays, are repaired by **photoreactivation** or **excision repair mechanism**
- When **DNA pelymerase-III** reaches the dimer (thymine dimer), replication is blocked. Polymerase III starts reacting at the dimer site and starts its proof reading role.
- If the dimer is not repaired by photoreactivation orexcision repair mechanism, die DNA polymerase III cannot make complementary strand for five seconds
- However, DNA polymerase-III restarts DNA synthesis, in post dimer initiation site by skipping over the dimer segment (lesion).
- This leaves a large gap of800 bases in the newly synthesized DNA strand
- An error- free segment of the DNA of the fork is excised and inserted in place of the gap created by thymine dimer.
- **RecB** cuts out an error free segment from the similar DNA and **recA** exchanges the segment to the gap in the daughter strand.
- The gap if any in the DNA is filled by **DNA pilymerase I** and joined by **DNA ligase.**
- The gap in the donor strand is likewise filled up by the same enzymes

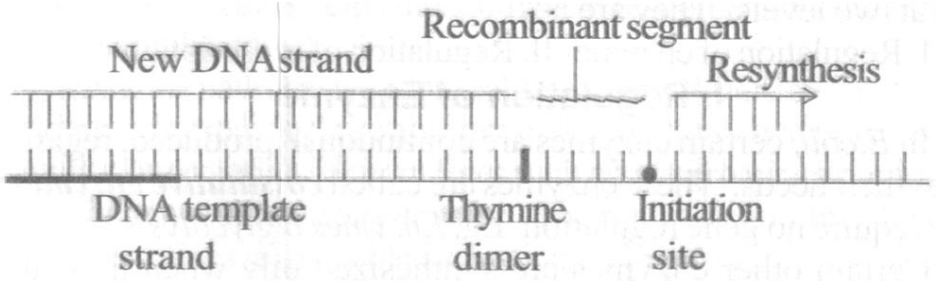


Fig.: Recombinational Repair