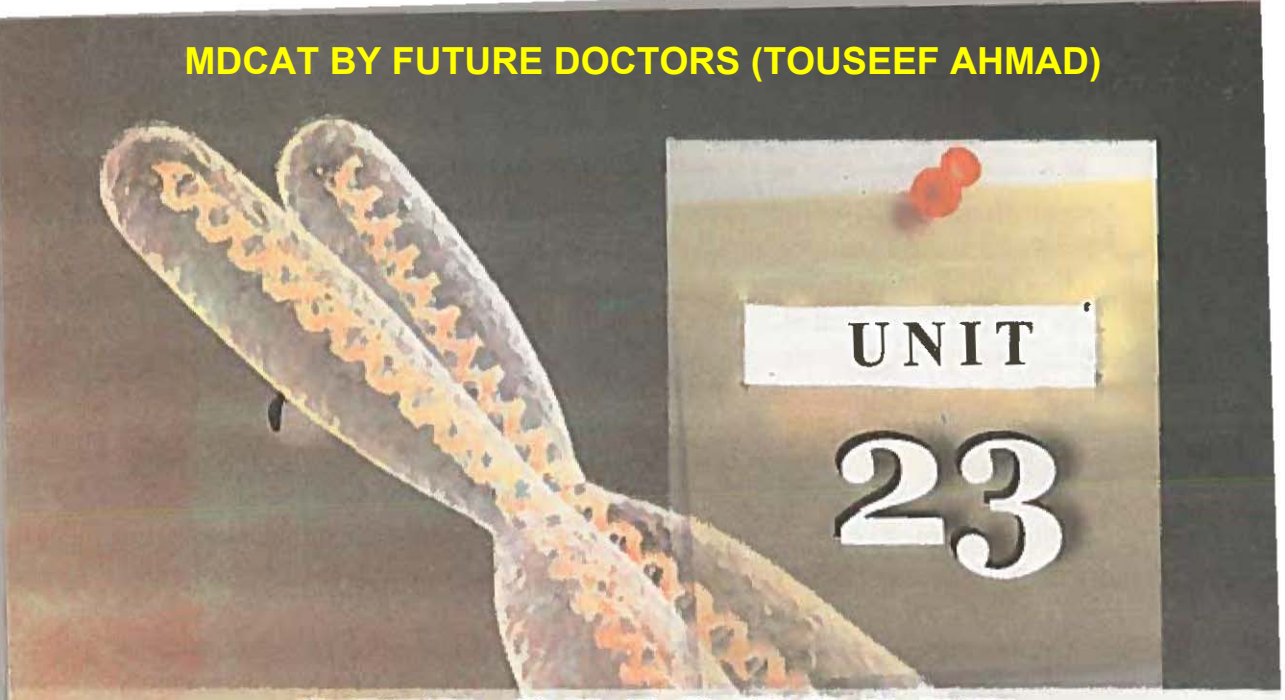


UNIT

23

CHROMOSOME AND DNA

KEY CONCEPTS

Gregor Mendel's "hereditary factors" were purely an abstract concept when he proposed their existence in 1865. At that time, no cellular structures were known that could house for these imaginary units. Today we can show that genes - Mendel's "factors" are located along chromosome and we can see the locations of a particular gene by tagging chromosome with a florescent dye that highlights that gene.

23.1 CHROMOSOMES

Chromosomes are thick thread like structures that appear in nucleus during cell division. In an interphase cell chromosome become uncondensed and look like very fine network called chromatin network.

Chromosomes were first observed by German embryologist Walther Fleming in 1882, when he was examining the rapidly dividing cells of salamander larvae. The term **"chromosome"** was proposed by Waldeyer, which literally means coloured bodies. Since their discovery, chromosomes have been found in the cells of all eukaryotes. However, in prokaryotic cell, its single DNA molecule is also referred as chromosome.

23.1.1 Number of chromosome:

The number of chromosome varies from species to species and usually it is a characteristic feature of many species. ***Penicillium***, a fungus, has only one pair of chromosome, while some ferns have more than 500 pairs. Many species have two sets of chromosomes in their somatic cells, hence called **diploid**, while some may have more than two sets of chromosomes; they are called polyploids (tetraploid, hexaploid). The term **"haploid"** is referred to the number of chromosome exactly half than the somatic number of chromosome. Gametes and spores are usually haploid cells. A haploid cell may be monoploid (one set), diploid (two sets), triploid (three sets), and etc.

Table: 23.1 Number of chromosomes in human and wheat.

Name of Species	Somatic Number	Haploid	Monoploid (n)
Human	46(2n)	23(n)	23
Wheat	42 (6n)	21(3n)	7

23.1.2 Structure of chromosome:

A typical chromosome consists of two strands called **chromatids**; each is made up of a long DNA molecule which is highly coiled along with histone proteins. Generally both chromatids are attached with each other at a point known as

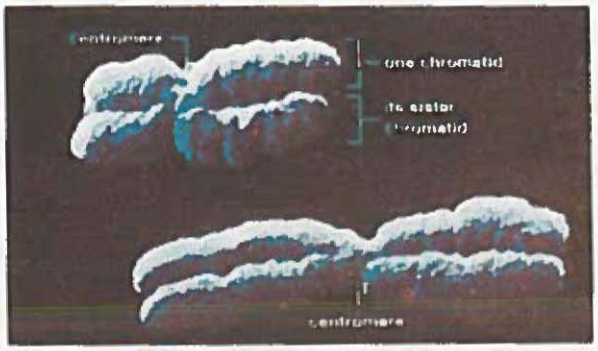


Fig: 23.1 Chromosomes showing chromatids and centromere.

centromere or **primary constriction**, so each chromosome shows two **arms** (region from centromere to an end). Some chromosomes may have another point of union along the length of chromatids, called **secondary constriction** or **nucleolar organizer**. It gives rise to nucleoli during interphase.

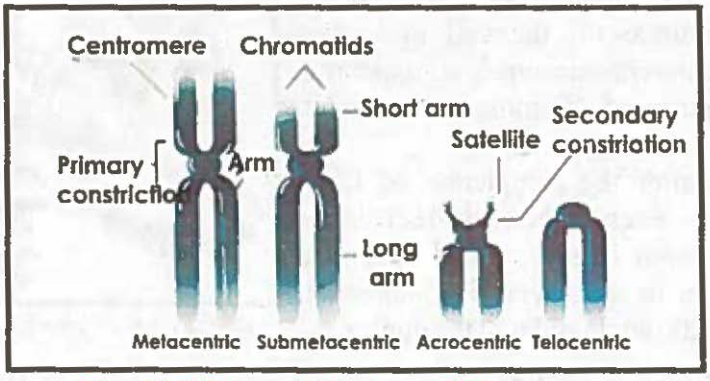


Fig: 23.2 General structure of Chromosome.

At least one pair of homologous chromosomes possesses nucleolar organizer region. Beside secondary constriction the end becomes a knob like structure called **satellite**. This region has a useless sequence of DNA called **junk DNA**. The terminal ends of chromosomes are called **telomeres** which prevent the two chromosomes to attach with each other from their ends.

On the basis of position of centromere along the length, a chromosome may be called **metacentric** (centromere located in the center), **submetacentric** (centromere located slightly away from the center), **acrocentric** (centromere located near the end), and **telocentric** (centromere located at an end).

23.1.3 Composition and organization of chromosome:

Generally a chromosome is made up of 40% DNA and 60% protein. In the cell, which is ready to divide, the chromosome has two identical DNA molecules i.e. each chromatid has one DNA molecule.An average sized human chromosome has approximately 5 cm long DNA which consist of about 140 million nucleotides. So can you imagine how such a huge molecule fit into a tiny chromosome? DNA is a negatively charged molecule because of phosphate groups; therefore it has strong affinity to histone proteins, which are positively charged unlike many other proteins due to the abundance of some basic amino acid such as arginine and lysine. There are five types of histone proteins (H_1, H_2A, H_2B, H_3, and H_4) found in the chromosome.

During S phase of cell cycle DNA and histones are completely disorganized from each other, but after DNA is replicated, both DNA and histones begin to organize again and the process of condensation remains continue till the cell undergoes division and the chromosome's are appeared. The organization of chromosomes occurs in four levels:

Just after the completion of DNA replication, each DNA molecule of enormous length begins to coil around a histones core. In this level of organization about every 200 nucleotides of the duplex

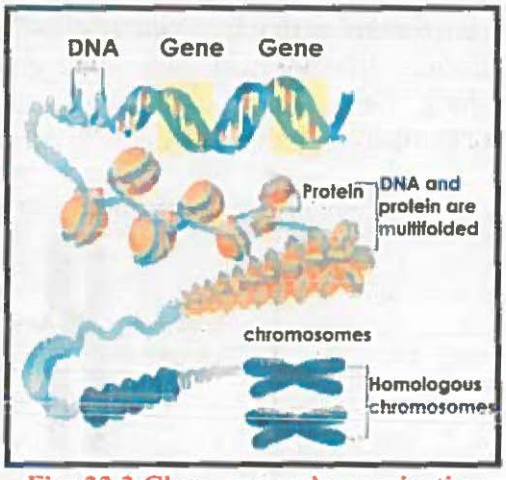


Fig: 23.3 Chromosomal organization.

DNA wrap twice around the core of eight histones (two of each H_2A, H_2B, H_3, and H_4), thus forming a complex known as nucleosome, while H_1 is associated with a small segment of DNA (linker DNA) between every two nucleosome. In this way the whole DNA (2nm thick) is turned to a chain of beads like appearance called nucleosome string (10 nm thick).

Immediately the nucleosome string begins to coil again about its axis to form yet another thick fiber of 30 nm, called chromatin fiber or solenoid. During G_1 and G_2 phases, chromosomes are found in this level of organization. The chromatin fiber shows two regions i.e. heterochromatin and euchromatin. Heterochromatin is highly condensed and unexpressed region while euchromatin is non-condensed and the genes of this region are also expressed. When cell undergoes division, euchromatin is also condensed so that a uniform chromatin fiber is established.

When cell division begins, the higher order coiling of chromatin fiber gives rise supercoil which has diameter of 200 nm. Immediately supercoil establish into the chromatid of 700nm as result of further coiling around itself.

23.2 CONCEPT OF GENE

23.2.1 Historical Background:

Charles Darwin first conceived the idea of hereditary units when he published his theory of **pangenesis** in 1868. In this model, circulating units called **gemmules** are accumulated in the gonads and transmitted to the off-spring. This theory was discredited by experimental tests performed by Francis Galton in the 1870s. Galton used blood transfusions in rabbits to show that the alleged gemmules in one rabbit's blood did not alter the heredity of the recipient rabbit's blood. In the 1890s **Hugo de Vries** took the term "pangenesis" and trimmed it to **"pangene"** for the assumed units of inheritance. He argued that pangenes remained inside the cell and did not migrate. It was this theory of intracellular pangenesis that led de Vries to independently find what **Gregor Mendel** had discovered thirty years earlier in his work with contrasting traits in garden peas—there are units of inheritance that are transmitted by reproduction. **Wilhelm Johansson** introduced the term **"gene"** to replace several contending and misleading terms for the basic unit of heredity in 1909. The term **"genetics"** came earlier, when **William Bateson** coined the word in 1906 to represent the new field that studied heredity, variation, and evolution.

23.2.2 Modern concept of gene:

It is believed that the modern concept of gene was given by the Mendel while his experimentation on pea plant. *According to the Mendel, each trait in the pea plant is controlled by the discrete units,* what he referred as **elementen** or **factors**. In modern terminology Mendel's factors are called **genes**. Since the rediscovery of Mendelian work in 1900, the nature and expression of gene is being explored by various geneticists in all over the world and this job is still continued. But now we know that ***a gene is composed of nucleotide sequence of a short segment of DNA which encodes the sequence of amino acid of a particular polypeptide.***

23.2.3 Where do genes reside?

These genes are found in the chromosome. The position on a chromosome where a gene is located is often referred to as a **locus**. Most genes exist in alternative versions, or **alleles**, with differences at one or more nucleotide positions in the DNA. The alleles related to the same trait are occupied on the same locus. For example, gene of ABO blood group i.e. *"I"* exist in three different alleles *(I^A, I^B, i)* that are found on the same locus at chromosome 9.

23.2.4 Structure of a gene:

We have already discussed that a gene is a particular segment of DNA in which nucleotide sequence determines the sequence of amino acid of a polypeptide. A gene usually has regulatory regions and a structural region. The regulatory region located to the 5' end of coding strand of the gene is called **promoter** that controls the binding RNA polymerase during transcription. Other regulatory region, the **terminator**, is located to the 3' end of coding strand of the gene. The terminator region causes RNA polymerase to stop transcription. The region between promoter and terminator is **structural region** of the gene that comprises information (genetic code) for a particular polypeptide or functional RNA. In eukaryotic genes the information of structural region is interrupted by the non-functional sequences called **introns** whereas the functional sequences are called **exons**. There is no such pattern of introns and exons in prokaryotic DNA. In prokaryotes many adjacent structural gene that synthesize different polypeptides are regulated by same promoter and terminator regions. Such a group of genes is called **operon.**

23.3 CHROMOSOME THEORY OF INHERITANCE

The chromosomal theory of inheritance is the idea that genes, the units of inheritance, which are physical in nature, are found in the chromosomes, so chromosomes act as carriers of heredity.

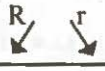
First time this idea was put forward in 1900 by a German geneticist Karl Correns, in one of the paper announcing the rediscovery of Mendel's work, but he had no supportive evidences for this idea. Therefore, actual credit of this theory goes to both Walter Sutton (an American who at that time was a graduate student) and Theodor Boveri (a German biologist). In 1902, these scientists recognized independently that the behavior of Mendel's factors (genes) is parallel to the behavior of chromosome at meiosis, which is pointed out in the following table:

In addition to the above evidences based on parallel behavior between genes and chromosome during meiosis, we can also analyze the mechanism of sexual reproduction, which involves the initial union of two cells, egg and sperm. If Mendel's model is correct, then these two gametes must make equal hereditary contributions.

Sperm, however, contains little cytoplasm and during fertilization it only contribute nucleus to the zygote. Therefore the hereditary units must reside within the nucleus of the gametes, whereas, chromosomes are also found in the nucleus. Beside above mentioned parallel behavior between genes and chromosome during meiosis, this observation also indicates that genes would be present in chromosomes.

Many investigators of that time pointed out a serious objection on Sutton's theory. According to that, let we accept that Mendelian traits are determined by the factors / genes located on chromosome, and if the genes are segregated due to segregation of chromosome and independent assortment of genes is reflected by the independent assortment of chromosome in meiosis, why is it that number of genes that assort independently of one another in a given kind of organism is often much greater than the number of chromosome pairs that the organism possesses. But later on this objection was cleared after the discovery of linkage by the historical experimentation of **T. H. Morgan** in 1910 on *Drosophila*.

Parallel behavior of genes and chromosomes during meiosis.

Behavior of chromosomes	Behavior of genes
1. Diploid cells (before meiosis) have two copies of each chromosome (homologous pairs) while gametes (after meiosis) have only one. e.g. In pea plant diploid cells have 7 pairs of homologous chromosomes while gametes have single 7 chromosomes.	1. According to the Mendel, diploid cells have two copies of each gene (pair of alleles) while gametes have only one, e.g. In pea plat, diploid cells have a pairs of alleles for each gene like *Rr, Yy,* and *Tt,* while gametes have single *R* or *r*, *Y* or *y* and *T* or *t*.
2. Homologous pairs of chromosomes segregate during meiosis.	2. According to the Mendel, pair of gene for each trait also segregates form each other during meiosis, e.g. Rr 
3. During meiosis, each pair of homologous chromosomes orient on the metaphase plate independently of any other pair so that in anaphase each pair assort independently of the other.	3. According to the Mendel, alleles of one gene pair also assort independently to the alleles of other gene pair during meiosis, e.g. RrYy genotype as a result of independent assortment can form four type of gametes i.e. RY, rY, and ry.

Morgan's work with respect to the gene linkage and inheritance of eye color in drosophila, you have already been studied in the previous chapter.

23.4 DNA AS HEREDITY MATERIAL

When the chromosome theory of inheritance was confirmed in 1910, geneticist started think over the issue that, in which form, the heredity units are found in the chromosome. It was known that chromosomes contain both DNA and protein.

On which of these was the heredity information written? Over a period of 30 years, starting in the late 1920s, a series of investigators addressed this issue, resolving it clearly. Here, we are going to learn three experiments, each of which yields a clear answer in a simple and elegant manner.

23.4.1 Griffith's Experiment:

In 1928, British microbiologist Fredrick Griffith made a series of unexpected observations while experimenting with *Streptococcus pneumonae* which are found in two types. One of its types has a polysaccharide capsule, its colony appears as smooth or shiny, and hence it is called S-type. The other type forms a rough colony due to the absence of polysaccharide capsule; this is referred as R-type.When Griffith injected healthy mice with a strain of S-type, all the mice died, but when he injected similar mice with a strain of R-type, the mice showed no ill effect. On the basis of these observation, Griffith made a hypothesis that virulent effect of S-type might be associated with polysaccharide capsule as the R-type that lack a capsule, appeared non virulent.

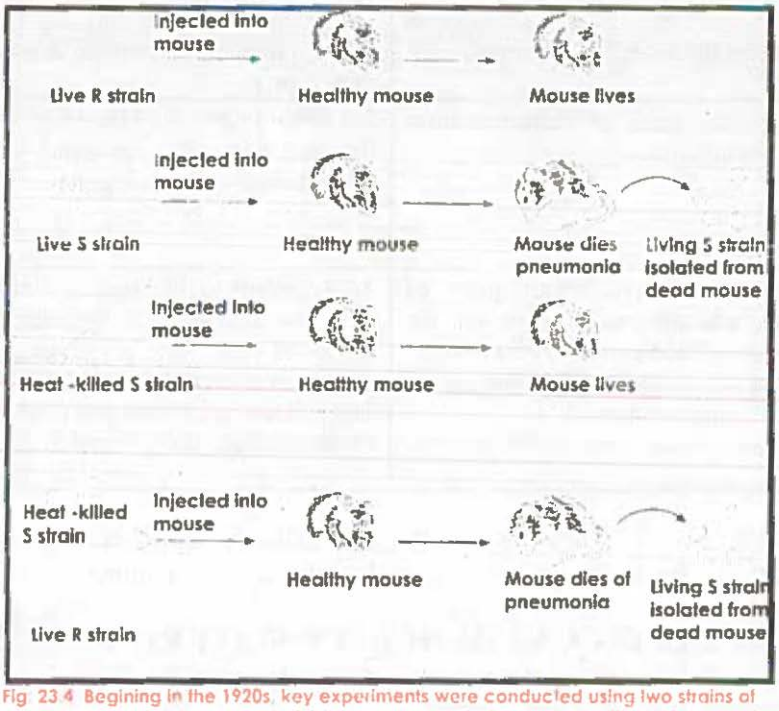


Fig. 23.4 Begining in the 1920s, key experiments were conducted using two strains of *Diplococcus* bacteria, a smooth (S) from and a rough (R) form. In Griffith's first experiment, mice were injected with either the S or R *Diplococcus*. Those injected with the R strain were unaffected, but those receiving the S strain died of pneumonia. In later experiments, mice injected with heat killed S bacteria lived, however, if those S form were first mixed with live R bacteria and then injected into a mouse, it died and was found to contain live S forms.

As a final control, he blended living R-type with heat killed S-type, both of these strains were already confirmed as non-virulent. When he injected this mixture into the healthy mice, unexpectedly, the injected mice developed disease symptoms and many of them died. The blood of the dead mice was found to contain large number of living S-type virulent bacteria.

On the basis of these unexpected observations, Griffith concluded that somehow the information specifying the polysaccharide capsule and virulence had passed from the heat killed S-type bacteria to the live R-type once in the control mixture, transforming them into live S-type virulent bacteria that killed the mice. This transfer of genetic material from one organism to another, by which genetic make-up of recepient is altered, is called **transformation.**

23.4.2 Avery's Experiment:

The agent responsible for transforming R-type to S-type went undiscovered until 1944. In a classic series of experiments, Oswald Avery along with Colin Macleod and Maclyn McCarty characterized what they referred to as the "transforming principle". They first prepared mixture of dead S-type and live R-type *Streptococcus pneumonae* that Griffith had used in his last experiment. Then they removed as much of the protein as they could from the preparation by treating it with protease enzyme, eventually achieving 99.98% purity. Despite removal of nearly all protein, the transforming activity was not reduced. In the second attempt, all the RNA contents were removed with the help of RNAase enzyme, but transformation remained continue. Finally, when, mixture was treated with DNAase enzyme in order to remove DNA contents of S-type. The mice injected with such a mixture in which DNA contents of S-type had removed, developed no ill effect because no transformation occurs. In this way it was confirmed that the transforming agent in the Griffith's experiment was DNA.

23.4.3 Hershey & Chase Experiment:

Soon after the Avery's results, another very convincing experiment on bacteriophages was performed by Alfred Hershey and Martha Chase in 1952, which was difficult to ignore.

Bacteriophages are the viruses that attack upon bacteria, their body consists of DNA and protein, during infection they multiply in the host and their many copies emerged within 20-25 minutes. It was not known till 1952 that either DNA or protein which possesses hereditary information of bacteriophages. Even, scientists were not sure that during infection, the whole viral particle entered the host body or only its DNA or protein get entry.

In 1952, Hershey and Chase set out an experiment to identify the viral part that is injected into the host body at the start of infection. For this purpose they labeled the DNA of bacteriophages with a radioactive isotope of phosphorus, ^{32}P, and also labeled their protein coats with radioactive isotope of sulfur, ^{35}S. The labeled viruses were permitted to infect bacteria. Soon after the infection bacterial cells were separated from media contents with the help of centrifugation technique. Then media contents and bacterial cells were analyzed for the activity of ^{32}P and ^{35}S. In this analysis, ^{32}P was found in the bacterial cells while ^{35}S was found in the medium. These observations clearly showed that during infection, ^{32}P labeled DNA of bacteriophage was injected into the bacterial cell while its ^{35}S labeled protein coat remained outside. Subsequently, many viral particles released outside the host. Based on these observations, Hershey & Chase claimed that the virus DNA, not the virus protein, was responsible for directing the production of new viruses.

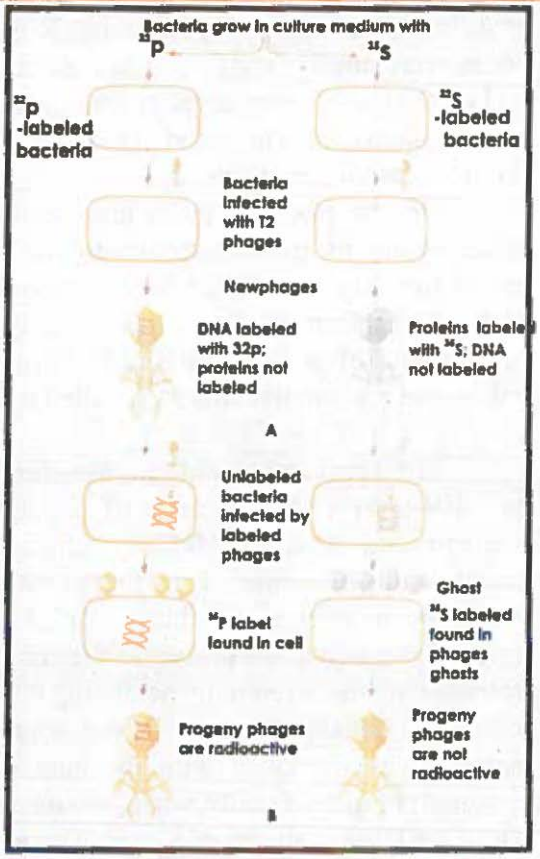


Fig: 23.5 Hershey and Chase famous phage experiment finally settled the question of whether protein or DNA was the genetic material

23.5 DNA REPLICATION

The process of self-synthesis of DNA molecule is called DNA replication. This process occurs only once in S-phase during the life cycle of a cell. The molecule of DNA which is replicated is called parent DNA, while the molecules, produced in this process are called daughter DNA. A parent DNA molecule after replication gives rise two daughter DNA molecule. How duplex DNA can replicate? Scientists started struggle to find the answer of this by the discovery of DNA structure.

Over all three different models to explain the replication process were come forward:

23.5.1 Semi-conservative Model:

This model was given by the Watson and Crick, who also proposed that structure of DNA. According to this model the parent DNA molecule becomes unwind and lost its base pairs (unzipping), both strands act as template that allow the formation of new strands, as a result two daughter DNA molecules are formed with one old and one new strand (hybrid DNA). In this way the parental strands are partially conserved in both daughter DNA molecules.

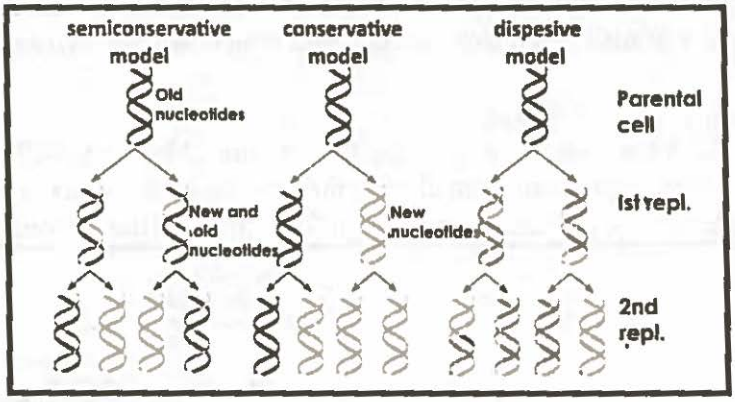


Fig: 23.6 Replication models of DNA.

23.5.2 Conservative Model:

According to this model the parental DNA remains intact in its duplex state, while a daughter DNA molecule with both new strands is established. In this way the parental DNA is fully conserved in the next generation.

23.5.3 Dispersive Model:

This model predicted that the parental DNA would become completely dispersed into fragments, which will be mixed with new nucleotide fragments.

In this way the daughter DNA molecules would be mixture of old and new fragments.

23.5.4 Meselson-Stahl Experiment:

The three models of DNA replication were evaluated by Mathew Meselson and Franklin Stahl of the California Institute of technology in 1958. In this experiment, it was concluded finally that the replication of DNA occurs according to semi-conservative model.

Culturing of bacteria

They grew bacteria in a medium containing heavy isotope of nitrogen, ^{15}N, which became incorporated into the bases of bacterial DNA. After several generations, the bacteria were shifted to three separate plates, which were already contained ^{14}N medium.

Sampling of DNA

Three DNA samples were taken from bacteria shifted from ^{15}N medium to the ^{14}N medium. First sample was obtained from first plate just after the transfer of culture; called sample at 0 minute, the second sample was taken from second plate after 20 minutes, called sample at 20 minutes, and third sample was taken from third plate after another 20 minute, called sample at 40 minute. In addition to these, a control sample was also taken from the bacteria which were grown separately in ^{14}N medium.

Centrifugation of DNA samples:

The DNA samples were dissolved in cesium chloride (CsCl) solution and then spun at a very high speed in an ultra-centrifuge for many hours. The cesium and chloride ions tend to be pushed by centrifugal force towards the bottom of the tube.

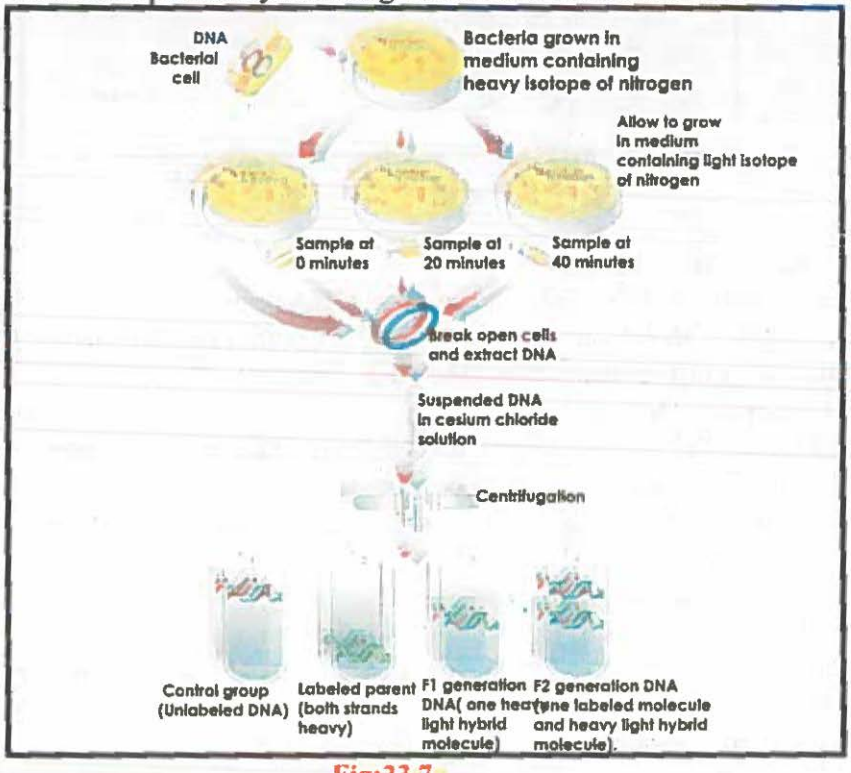


Fig:23.7

Results of centrifugation:

DNA of control sample was appeared lightest as formed sediment at the top of test tube, while DNA of sample at 0 minute was appeared heaviest as it formed sediment at the bottom of test tube. The DNA of sample at 20 minute formed sediment intermediate level to that of control sample and sample at 0 minute whereas sample at 40 minute had two sediments, one at the top and other at intermediate level.

Interpretations of results:

Meselson-Stahl interpreted their results as follows: the DNA of control sample appeared lightest because it had both strands of ^{14}N, whereas DNA of sample at 0 minute appeared heaviest because it had both strand of ^{15}N, but after first round of replication each daughter duplex was a hybrid possessing one strand of ^{14}N and one of ^{15}N, so it formed sediment at intermediate level.

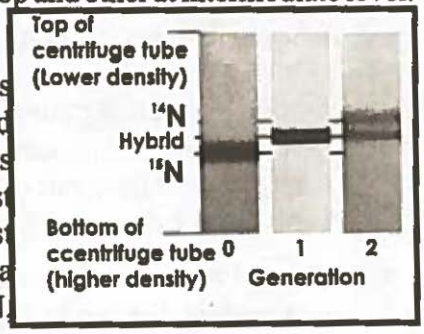


Fig: 23.8

When this hybrid duplex replicated in second round of replication, it contributed ^{15}N strand to form another hybrid duplex and ^{14}N strand to form a light duplex containing both ^{14}N strands that is why this sample formed two sediments. On the basis of above mentioned results, they claimed that the DNA replication is sem iconservative.

23.5.5 Process of DNA replication:

Although DNA replication is a continuous process but here we are going to discuss it in different phases for our convenience.

Initiation phase:

The initiation phase is characterized by the formation of replication bubble and replication fork, which are formed at a particular site, called **origin of replication** site. It is a specific sequence of nucleotides along the length of DNA from where process of replication begins. In eukaryotic DNA there may be more than one origin of replication sites but in prokaryotic DNA there is only one origin of replication.Replication bubble is formed when **DNA gyrase (topoisomerase)** and **DNA helicase** enzymes work at origin of replication. DNA gyrase opens the turns of DNA duplex so the DNA is converted from spiral ladder like form to straight ladder like form. At the same time DNA helicase breaks down the base pairs of DNA so the two strands gradually separate from each other and give a bubble like appearance at origin of replication.

After the breakdown of base pairs, the single strands of DNA are prevented to pair up again by specific proteins called **single stranded binding (SSB)**

proteins. Both single strands of DNA will act as template strand in the next phase and direct the synthesis of daughter strands along themselves. Each side of replication bubble is now termed as **replication fork.**

Extension / Polymerization phase:

Extension or polymerization is referred to the formation of daughter strands (leading or lagging strands) along the template strands. The daughter strands are actually synthesized by **DNA polymerase** enzyme but this enzyme cannot work unless some nucleotides are arranged on template. For this purpose **primase** enzyme is involved to arrange some nucleotides on template stands. Such short fragments of few nucleotides are called **primers**. Each primer is short oligonucleotide strand of RNA, acts as start site for the activity of DNA polymerase.

After the establishment of primers, synthesis of daughter strands begins by the DNA polymerase enzyme. There are three different forms of this enzyme:

- **DNA polymerase-I:** it performs an important role in termination phase of replication so it provides a support to the DNA polymerase-III in the main replication process.
- **DNA polymerase-II:** it involves in the repairing process of DNA damages during the life time of a cell.
- **DNA polymerase-III:** it is the main enzyme that synthesizes both daughter strands along the template during replication process.

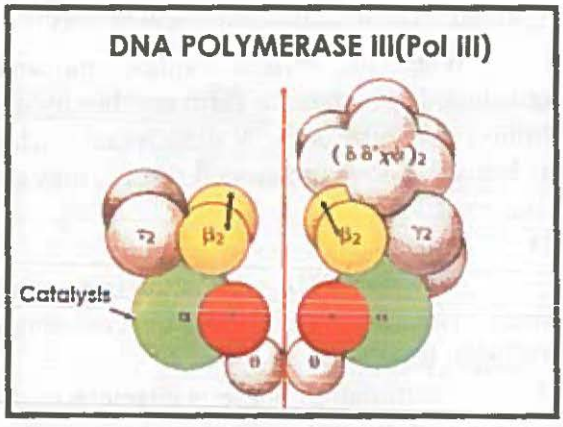


Fig: 23.9

Mechanism of DNA polymerase-III activity:

This enzyme is a huge dimer molecule i.e. it consists of two units that further consist of several sub units. DNA polymerase-III cannot initiates replication process, it can add a nucleotide onto only a preexisting 3'-OH group, and, therefore, needs a primer to perform its polymerase activity. It always adds nucleotide at 3' end of primer so the direction of replication becomes 5' to 3' end. One of its subunit also possesses ability to remove wrong nucleotide if it is added mistakenly. This ability is called proofreading.

Both units of DNA polymerase-III are interlinked by a small polypeptide chain, first unit work on one template and continuously synthesize a daughter strand towards replication fork, this continuously growing daughter strand is called **leading strand,** while the second unit work on other template and synthesize another daughter strand away from replication fork. As the two units are interlinked so the second unit is allowed to polymerize daughter

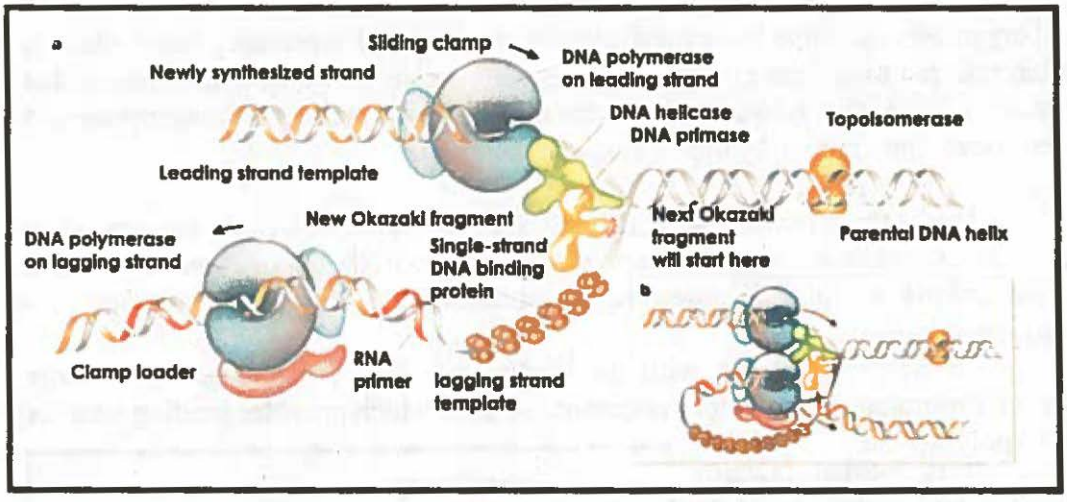


Fig: 23.10 Mechanism of DNA replication.

strand up to a specific length then it has to jump back (100 to 200 nucleotides in prokaryotes and 1000 to 2000 nucleotides in eukaryotes) to a new primer to perform polymerization again. Therefore, this daughter strand grows discontinuously away from the replication fork by forming short fragments interrupted by primers, called **Okazaki' fragments.** This discontinuously growing strand is called **lagging strand.**

Termination phase:

Termination phase is characterized by the replacement of primers by DNA nucleotides and joining of Okazaki's fragments in lagging strand to form a continuous strand.

The replacement of primers by DNA nucleotides is carried out by **DNA polymerase-I** that has dual function i.e. beside **polymerase** it also acts as **exonuclease.** It is attached to the 3' end of Okazaki's fragment where it adds DNA nucleotide so that it can extend while on the other hand it cleaves nucleotide from 5' end of primer. In this way primers are removed and each Okazaki's fragment is extended up to the next Okazaki's fragment but they do not join together.

The joining of Okazaki's fragments is carried out by **DNA ligase** enzyme that finally constructs phosphodiester bonds between Okazaki's fragments so a continuous strand is formed.

23.6 GENE EXPRESSION

23.6.1 Central Dogma of gene expression:

All organisms use same basic mechanism of reading and expressing genes which is often referred to as central dogma. In this mechanism the genetic information that resides in DNA, first flows down into the mRNA by the process of transcription and then convert into protein by the process of translation.

23.6.2 Transcription:

This is the process in which an mRNA copy of the DNA sequence encoding the gene is produced with the help of an enzyme, RNA polymerase. Process of transcription is completed in three phases: initiation, elongation and termination.

Initiation phase:

Transcription begins with the binding of RNA polymerase at promoter region. Promoter is a regulatory region of the gene which provides binding sites for RNA polymerase.

It is located towards the 5' end of coding strand. In prokaryotes, there are two binding sites are located in promoter i.e. TATAAT also called -10 sequence and TTGACA also called -35 sequence, whereas in eukaryotes, TATA (TATA box) also called -25 sequence and CAAT (CAAT box) also called -70 sequence. Names of these sequences (-10, -35 or -25, -70) refer to position that these sequences are located before the initiation site of structural region of the gene.

RNA polymerase consists of four subunits:

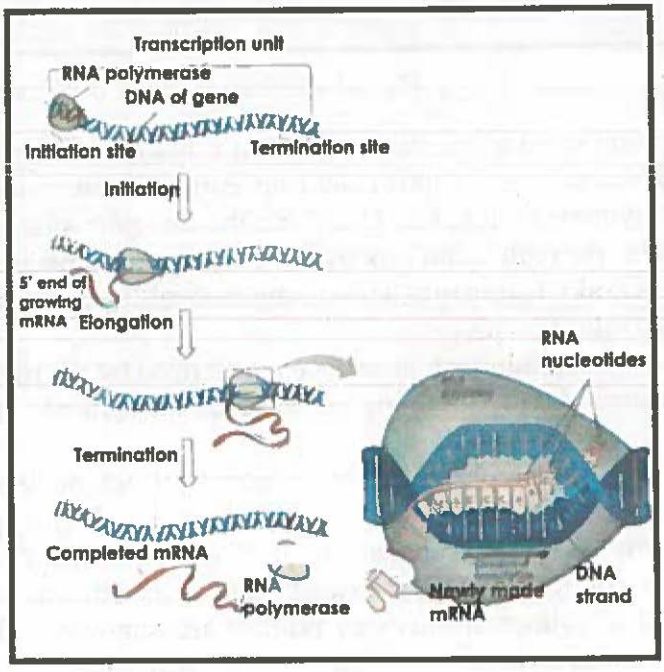


Fig: 23. 11 Transcription Process

beta, beta' and sigma; only the first three subunits are required for polymerase activity and are considered the core enzyme while the sigma factor is required for RNA polymerase to bind to the promoter. It is similar to the DNA polymerase in that it also adds nucleotides to the 3' end of the growing polypeptide chain but unlike DNA polymerase it does not require primer to perform polymerase activity.

In prokaryotes, only one type of RNA polymerase is found while in eukaryotes, there three types of RNA namely RNA polymerase-I, which synthesize rRNA, RNA polymerase-II, which synthesize mRNA, RNA polymerase-III which synthesize tRNA.

As the RNA polymerase binds to the promoter, DNA duplex become unwind, base pairs are broken down, and a bubble like structure, the transcription bubble is appeared.

Elongation phase:

As the RNA polymerase binds to promoter, sigma factor is released and remaining core enzyme extends the polymerization of ribonucleoside triphosphates (rNTP). It does not require primer to initiate polymerization. One of the two strand of the gene acts as template for transcription. This template strand is also called antisense because mRNA is complementary to this strand. The other strand of the gene is called coding or sense strand. In elongation phase RNA polymerase keep on moving from 5' to 3' direction towards the terminator region, beside it transcription bubble also moves along the DNA, leaving the growing RNA strand protruding from the bubble. This event continues till the RNA polymerase reaches the terminator region of the gene.

Termination phase:

The sequence of terminator region of the gene stops the synthesis of mRNA. The terminator region consists of a series of GC base pairs followed by a series of AT base pairs. The part of mRNA which is transcribed in this region, project to form a loop likes structure called GC hairpin followed by a small tail of AU nucleotides. The GC hairpin causes the RNA polymerase to stop the synthesis of RNA.

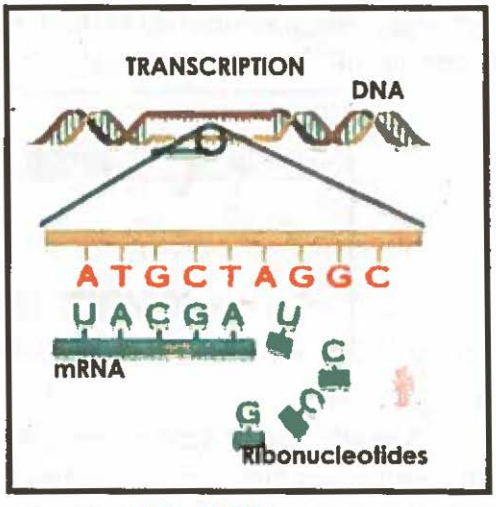


Fig: 23.12

23.6.3 Post Transcriptional Modifications of mRNA:

Post-transcriptional modification is a process by which primary mRNA transcript is converted into mature RNA or functional RNA.

This process is only associated with eukaryotic transcription because in prokaryotes, the mRNA that is synthesized during transcription is ready for translation into a protein due to the absence of a definite nucleus. On the other hand eukaryotic mRNA is produced inside the nucleus, is not immediately ready for translation because it has to pass comparatively long distance to reach ribosomes in the cytoplasm. During this journey, some enzymes like **phosphatases** and **nucleases** can degrade mRNA before its translation.

Another problem is that a newly formed eukaryotic mRNA comprises many non-protein coding sequences. As described earlier in this chapter that eukaryotic genes have a pattern of **exons** (protein coding sequence) and **introns** (non-protein coding sequence). So these non-protein coding sequences from a primary mRNA transcript are to be removed. Post transcriptional modification is therefore involved two events, addition of a cap and tail to protect it from degradation and RNA splicing to remove non-protein coding sequences.

Addition of Cap and Tail:

A cap and a tail are added to both ends of primary mRNA so that the molecule may remain stable and cannot be degraded by phosphatases and nucleases during long journey to ribosome. A cap is in the form of **7-methyl GTP**, which is liked from its 5′ to the 5′ end of mRNA. A modification also takes place at the opposite end of the RNA transcript in the form of a small chain of 30-500 adenine nucleotides, called poly-A tail, which is attached to the 3' end of the mRNA. These two modifications prevent the mRNA to be degraded by phosphatases and nucleases.

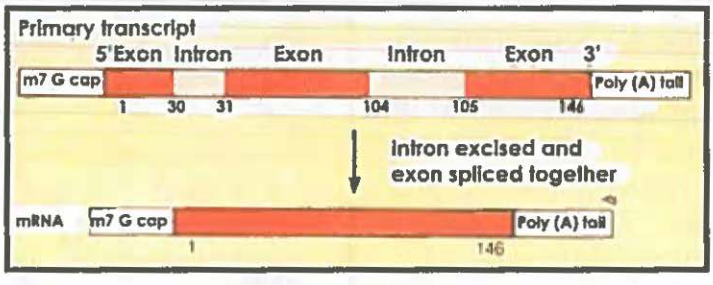


Fig: 23.13

RNA Splicing:

A newly emerged eukaryotic mRNA is very long as it contains both exon and intron sequences. Introns are non-protein coding sequences, which are to be removed form primary mRNA before its translation on ribosome.

This removal of introns and maturation of primary mRNA to secondary or functional mRNA is called **RNA splicing.**

23.6.4 Genetic Code:

The sequence of nucleotides in DNA or RNA that determines the specific amino acid sequences of the proteins is called genetic code. It is the biochemical basis of heredity and nearly universal in all organisms. The Genetic Code is stored on one of the two strands (the coding or sense strand) of a DNA molecules as a linear, non-overlapping sequence of the nucleotides.

The genetic code is a coded language, which is based on an "alphabet" consisting of only four types of nucleotides Adenine (A), Guanine (G), Cytosine (C) and Thymine (T), which are variously arrange to form code words called **codons.** Usually, a codon specifies an amino acid so the order in which codons are arranged in mRNA, determines the order in which the amino acids are arranged in a protein

Each code word (codon) is a unique combination of three letters that will eventually be interpreted as a single amino acid in a polypeptide chain. There are 64 code words possible from an 'alphabet' of four letters.

One of these code words, the start codon (AUG) begins all the sequences that code for amino acid chains. Three of these code words act as stop codons (UGA, UAG, and UAA) that indicate that the message is over. Since, these three codons do not encode any amino acid, hence called non sense codon, while all the other sequences that encode specific amino acids are called sense codons.

Second letter

First letter	U	C	A	G	
U	UUU, UUC: Phenyl-alanine UUA, UUG: Leucine	UCU, UCC, UCA, UCG: Serine	UAU, UAC: Tyrosine UAA: Stop codon UAG: Stop codon	UGU, UGC: Cytosine UGA: Stop codon UGG: Tryptophan	U C A G
C	CUU, CUC, CUA, CUG: Leucine	CCU, CCC, CCA, CCG: Proline	CAU, CAC: Histidine CAA, CAG: Glutamine	CGU, CGC, CGA, CGG: Arginine	U C A G
A	AUU, AUC, AUA: Isoleucine AUG: Methionine	ACU, ACC, ACA, ACG: Threonine	AAU, AAC: Asparagine AAA, AAg: Lysine	AGU, AGC: Serine AGA, AGG: Arginine	U C A G
G	GUU, GUC, GUA, GUG: Valine	GCU, GCC, GCA, GCG: Alanine	GAU, GAC: Aspartic acid GAA, GAG: Glutamic acid	GGU, GGC, GGA, GGG: Glycine	U C A G

Some amino acids are only coded for by a single codon; while some others are coded for by up to four codons and amino acids leucine and serine are encoded by six codons.

Degeneracy of the genetic code is an important characteristic which refers that an amino acid can be encoded by more than one codons but a particular codon does not specify more than one amino acid. So the genetic code has redundancy but no ambiguity. For example, although codons GAA and GAG both specify glutamic acid (redundancy), neither of them specifies any other amino acid (no ambiguity).

The genetic code is universal. It is the same in almost all the organisms. For example AGA specifies arginine in bacteria, in humans and all other organisms whose genetic code has been studied. Because of the universality of codon the genes can be transferred from one organism to another and be successfully transcribed and translated in their new host.

The study of genetic code of mitochondrial DNA however, showed that genetic code is not that universal. For example:

Codon	Nuclear DNA	Mitochondrial DNA
UGA	Stop codon	Tryptophan
AUA	Iso leucine	Methionine
AGA & AGG	Arginine	Stop Codon

Thus it appears that genetic code is not quite universal.

23.6.5 Translation:

Translation is the second stage of protein synthesis (gene expression). In translation, messenger RNA (mRNA) produced by transcription is decoded by the ribosome to produce a specific amino acid chain, or polypeptide, that will later fold into an active protein. In Bacteria, translation occurs in the cell's cytoplasm, where the large and small subunits of the ribosome are located, and bind to the mRNA. In Eukaryotes, translation occurs across the membrane of the endoplasmic reticulum.

Although translation is a continuous process but for convenience we will discuss it in four phases: activation, initiation, elongation and termination. After that the product of translation in the form of amino acid chain, or polypeptide is formed.

I. Activation of amino acids:

Activation of amino acids refers to the binding of free amino acids dispersed in cytoplasm to the 3' end of particular tRNA molecules, in this way a complex is formed called aminocyl tRNA complex is formed. This binding is catalyzed by aminocyl tRNA synthase (activation enzyme). Various amino acids that are to be take part in polypeptide formation have been continuously activated throughout the process of translation.

ii. Formation of initiation complex:

Process of translation actually begins with the formation of initiation complex. It is formed by the combination of ribosomal subunits, mRNA and first aminocyl tRNA complex. First a tRNA molecule carrying a chemically modified methionine (called N-formyl methionine) binds to the smaller ribosomal subunit. This binding is controlled by an enzyme called initiation factor. At the same time 5′ end of mRNA molecule also binds to the ribosome with the help of another initiation factor. Initiation complex is completed when larger subunit of ribosome is also placed upon smaller subunit.

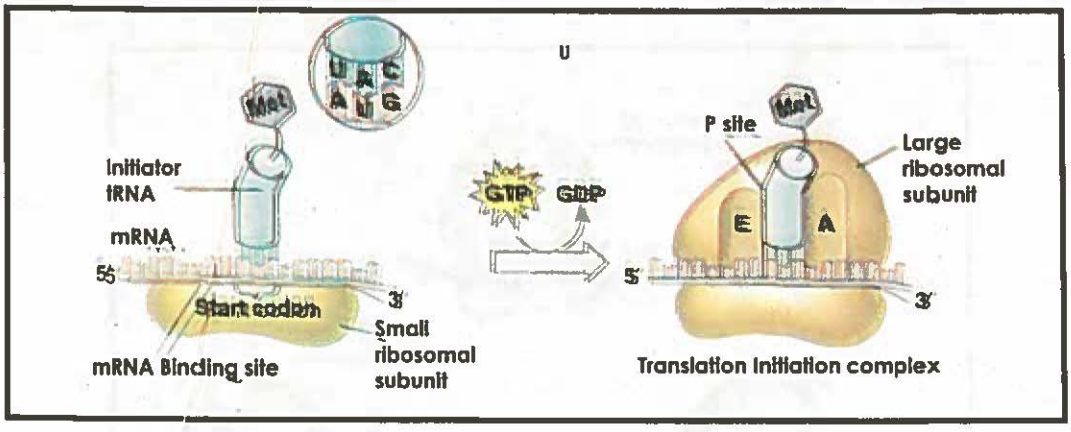


Fig: 23.14 Translation Process

The region of smaller ribosomal subunit where first aminocyl tRNA complex is attached is called P site (peptidyl site), here peptide bonds will be formed between successive amino acids during elongation phase. Nearby two other sites are also established. A site (aminocyl site) where successive tRNAs bearing amino acids will be attached and E site (exit site) where empty tRNAs will leave ribosome during elongation phase.

iii. Polypeptide elongation:

In this phase ribosomal units move along mRNA, amino acids are brought by tRNAs, which are joined together to form a polypeptide chain. This is accomplished by three steps which are repeated again and again throughout this phase.

- Whichever codon of mRNA is exposed at A site, its anticodon bearing aminocyl tRNA complex binds to it with the help of an enzyme, the elongation factor.

- Then an enzyme peptidyl transferase is emerged from P site. It removes the amino acid (may be a chain) from tRNA present on P site and binds it to the newly coming amino acid with the help of peptide bond.
- Then ribosomal sub units slightly move along mRNA from 5′ to 3′ direction so that a new codon is exposed at A site. This movement is called translocation. As a result, the empty tRNA is reached at E site to leave the ribosome, while the other tRNA bearing a chain of amino acid is shifted from A site to P site, and another codon is exposed to A site.
- These three steps are repeated again and again until the stop codon is reached at A site.

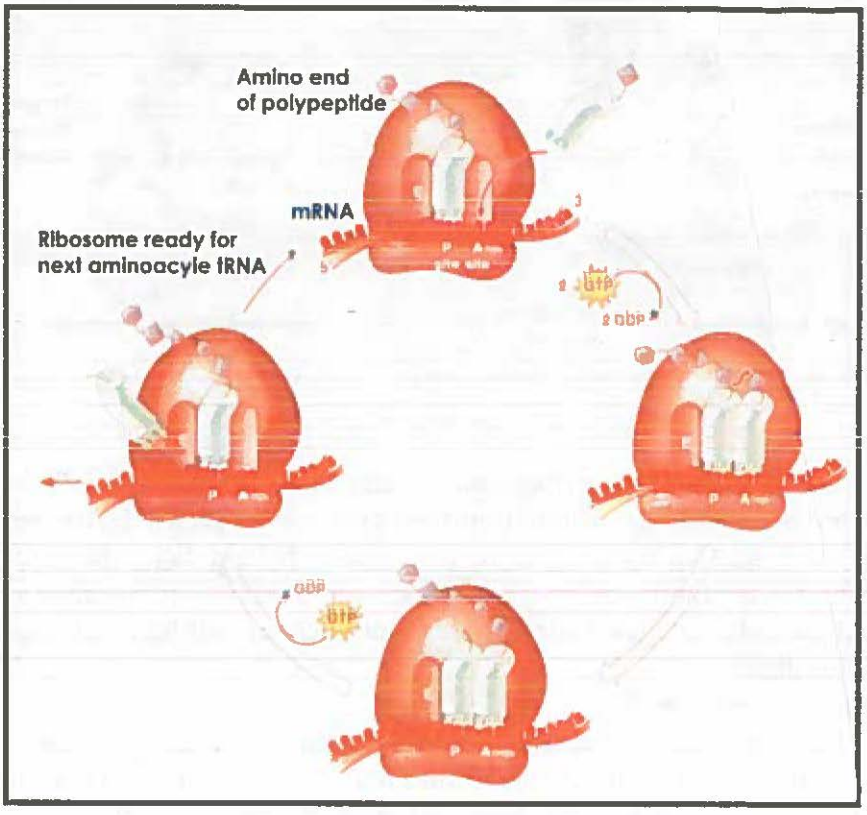


Fig: 23.15

iii. Termination:

Elongation continues in this fashion until a chain-terminating non sense codon is exposed at A site.

Non sense codons do not bind to any tRNA, but they recognize by release factors that terminate the process of translation and the polypeptide is released from the tRNA, the tRNA is released from the ribosome, and the two ribosomal subunits separate from the mRNA.

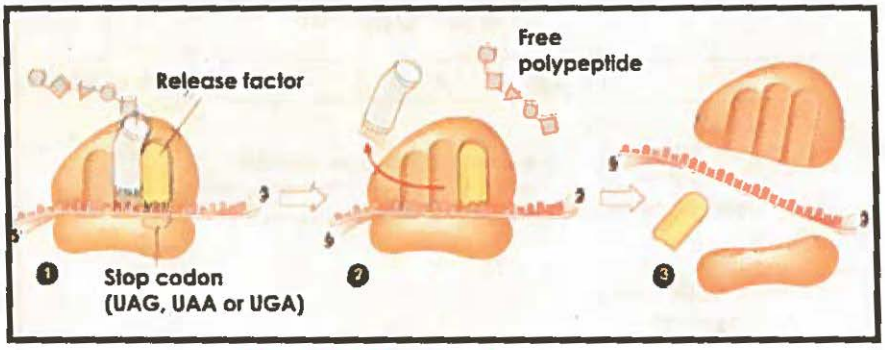


Fig: 23.16 Termination process.

23.7 REGULATION OF GENE EXPRESSION

23.7.1 Importance of gene regulation:

Regulation of gene expression (or gene regulation) is essential for prokaryotes and eukaryotes as it increases the versatility and adaptability of an organism by allowing the cell to express protein when needed. Furthermore, gene regulation drives the processes of cellular differentiation and morphogenesis, leading to the creation of different cell types in multicellular organisms where the different types of cells may possess different gene expression profiles though they all possess the same genome sequence.

23.7.2 Methods of gene regulation:

There are two possible ways of regulation of gene expression, positive regulation and negative regulation. When the expression of genes is quantitatively increased by the presence of specific regulatory protein (**the activator**) is called **positive gene regulation**. Whereas, when the expression of genes is diminished by the presence of specific regulatory protein (**the repressor**) is called **negative gene regulation**.

23.7.3 *Lac* Operon (Dual Positive and Negative Control of gene expression):

A classic example of a positive regulation in bacteria is the *lac* operon, responsible for obtaining energy from β-galactosides such as lactose.

In bacteria, genes are clustered into operons which are gene clusters that encode the proteins necessary to perform coordinated function, such as catabolism of a substrate obtained from outside (***lac* operon**) or biosynthesis of a given amino acid (***trp* operon**).

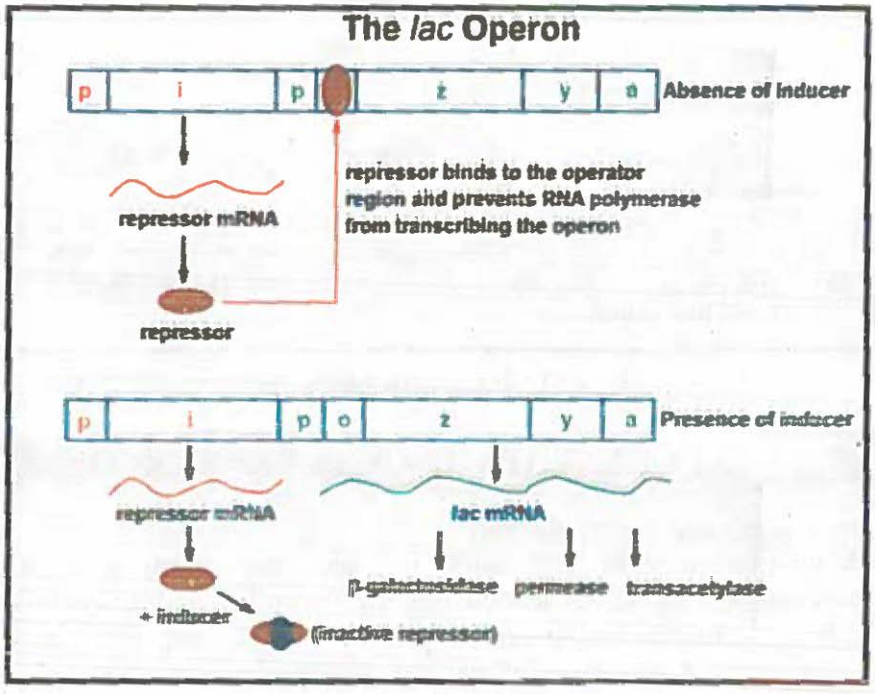


Fig: 23.17

RNA that is transcribed from prokaryotic operons is **polycistronic** a term implying that multiple proteins are encoded in a single transcript.

The *lac* operon (see diagram below) consists of one regulatory gene (the *i* gene) and three structural genes (*z*, *y*, and *a*). The *i* gene codes for the repressor of the *lac* operon. The *z* gene codes for **β-galactosidase (β-gal),** which is primarily responsible for the hydrolysis of the disaccharide, lactose into its monomeric units, galactose and glucose. The *y* gene codes for **permease,** which increases permeability of the cell to β-galactosides. The *a* gene encodes a **transacetylase,** an enzyme that transfers an acetyl group from acetyl-CoA to β-galactosides. Its precise function as part of the *lac* operon is not understood currently.

23.8 MUTATION

A gene mutation is a permanent change in the DNA sequence that makes up a new allele in the population. Mutations range in size from change in a single DNA nucleotide to a large segment of a chromosome or whole chromosome or some times changes in the number of chromosome. Mutations are caused by radiation, viruses, transposons and mutagenic chemicals, as well as errors that occur during meiosis or DNA replication. These agents that cause mutations are called **mutagens** while the organism in which mutation is occurred is called **mutant.**

Some mutations are very rare; others are common in the population. Mutations that occur in more than one percent of the population are called **polymorphisms**. They are common enough to be considered a normal variation in the DNA. Polymorphisms are responsible for many of the normal differences between people such as eye color, hair color, and blood type. Although many polymorphisms have no negative effects on a person's health, some of these variations may influence the risk of developing certain disorders.

23.8.1 Origin of Mutation:

Gene mutations occur in two ways: they can be inherited from a parent or acquired during a person's lifetime. Mutations that are passed from parent to child are called **hereditary mutations** or **germ line mutations** (because they are present in the egg and sperm cells, which are also called germ cells). This type of mutation is present throughout a person's life in virtually every cell in the body.

Mutations that occur only in an egg or sperm cell, or those that occur just after fertilization, are called **new (de novo) mutations**. De novo mutations may explain genetic disorders in which an affected child has a mutation in every cell, but has no family history of the disorder.

Acquired (or somatic) mutations occur in the DNA of individual cells at some time during a person's life. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if a mistake is made as DNA copies itself during cell division. Acquired mutations in somatic cells (cells other than sperm and egg cells) cannot be passed on to the next generation.

23.8.2 Types of mutation:

Mutations are of two types on the basis of how mutation occurs in cells. The mutations which occur naturally and automatically due to internal factors are called **spontaneous mutations**, whereas the mutations which are produced by external factors are called **induced mutations.**

Mutations are of two types on the basis of where the mutations occur and to what extent. A mutation that causes change of single or few nucleotides in the DNA is called **point mutation,** whereas the mutation that causes change in the structure or number of chromosome is called **chromosomal mutation or aberration.**

Point mutations involve a sudden change in the sequence of nucleotides of a gene that causes change in the phenotype of an organism. Such mutations occur in following ways:

- **Deletion:** It is the removal of one or few nucleotide from a particular segment of DNA. For example:

ATTAGCCTTAGAACT

↓ Deletion

ATTAGCCTAGAACT

- **Insertion:** It is the addition of one or few nucleotide in a particular segment of DNA. For example:

ATTAGCCTTAGAACT

↓ Insertion

ATTAGCC AA TTAGAACT

- **Base substitution:** It is the replacement of one or few nucleotide in a particular segment of DNA. For example:

ATTAGCCTTAGAACT

↓ Base substitution

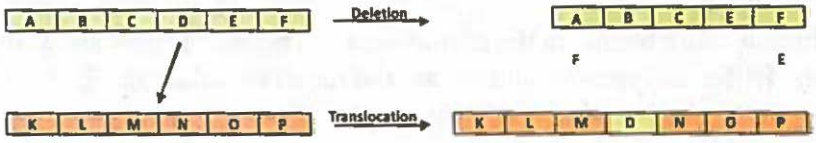
ATTAGCC A TAGAACT

Structural changes in chromosome are the type of chromosomal mutations or aberrations. Such changes in chromosomes take place during meiosis when due to certain mutagen chromosome is split down into several fragments but later on when these fragments reunite, its new pattern become changed from original one . Structural changes in chromosome are of following type:

Deletion: It is the removal of a segment of chromosome comprising single of few genes. For example:

Inversion: In this case a portion of a chromosome breaks off, turns around and joins again in such a way that the sequence of genes gets reversed. For example:

Translocation: It involves shifting of a segment of one chromosome to another non homologous chromosome. Thus both the chromosomes are affected. The donor chromosome suffers a deletion, while the recepient chromosome becomes longer than normal. For example:



Duplication: It is the repetition of one or few genes in the same chromosome. For example:

Another aspect of chromosomal aberration is the change in the number of chromosome which occurs due to chromosomal non disjunction during meiosis. Change in the number of chromosome due to addition or loss of one or more chromosome is called **aneuploidy**, whereas change in the number of chromosome due to addition or loss of one or more complete set of chromosome is called **euploidy.** Aneuploidy may be of following type:

- **Monosomy (*2n - 1*):** It is the result of loss of single chromosome from the diploid set.
- **Nullisomy (*2n - 2*):** It is the result of loss of a pair of homologous chromosome from the diploid set.
- **Trisomy (*2n + 1*):** It is the result of addition of single chromosome in the diploid set. For example: Down's syndrome and Klinfelter's syndrome.
- **Tetrasomy (*2n + 2*):** It is the result of addition of a pair of homologous chromosome in the diploid set.

Euploidy is the state of a cell or organism having an integral multiple of the **monoploid** (single set) number of chromosome. It is also called **polyploidy**. It exist in various forms like **triploidy** (three sets), **tetraploidy** (four sets), **pentaploidy** (five sets), **hexaploidy** (six sets) and so on. As a general rule polyploids can be tolerated in plants, but are rarely found in animals. One reason is that the sex balance is important in animals and variation from the diploid number results in sterility.

23.8.3 Types of Mutagens:

Mutations can be artificially produced (induced mutation) by certain agents called mutagens or mutagenic agents. Following are two major types of mutagens.

Physical Mutagens:

Short wave radiations are the most important physical mutagens. H. J. Muller was the first to induce mutations using X rays in drosophila. Other than X rays, gamma rays and ultra violet radiation can be used to induce mutations. The main source of spontaneous mutations is the natural radiations coming from cosmic rays of the sun. They occur in small amounts in the environment and are known as background radiations.

Radiation cause breaks in the chromosome. These cells then show abnormal cell divisions. Different types of cancers are the result of radiations. UV rays affect the structure of DNA helix and also affect the replication process.

Chemical Mutagens:

A number of chemicals act as mutagens such as nitrous acid, formaldehyde, mustard gas, 5-bromouracil; acridines etc. chemicals such as colchicine induce polyploidy in cells. Caffeine, nicotine, food preservatives and pesticides are also mutagenic. The first chemical mutagen discovered was mustard gas that was used as chemical weapon during 1st world war.

23.8 DISEASES INDUCED BY MUTATION

23.8.4 Sickle Cell Anemia (Drepanocytosis):

Sickle-cell anaemia is an autosomal recessive genetic blood disorder characterized by abnormal, rigid, sickle shape red blood cells. Sickle shape decreases the cells' flexibility due to which they can also get stuck more easily in small blood vessels, and break into pieces that interrupt healthy blood flow.

Signs and Symptoms:

Signs and symptoms of sickle cell disease usually begin in early childhood. Characteristic features of this disorder include a low number of red blood cells (anemia), repeated infections, and periodic episodes of pain. Anemia can cause shortness of breath, fatigue, and delayed growth and development in children. The rapid breakdown of red blood cells may also cause yellowing of the eyes and skin, which are signs of jaundice. Almost all patients with sickle cell anemia have painful episodes (called crises), which can last from hours to days. These crises can affect the bones of the back, the long bones, and the chest.

Cause & Risk Factor:

Sickle cell anemia is caused by a recessive allele *HbS* which encode defective β globin chain as a result abnormal haemoglobin is formed called **haemoglobin S**. HbS is originated from HbA (normal haemoglobin gene) due to a point mutation. The patients inherit two such alleles from both parents. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Sickle cell disease is much more common in people of African and Mediterranean descent. It is also seen in people from South and Central America, the Caribbean, and the Middle East.

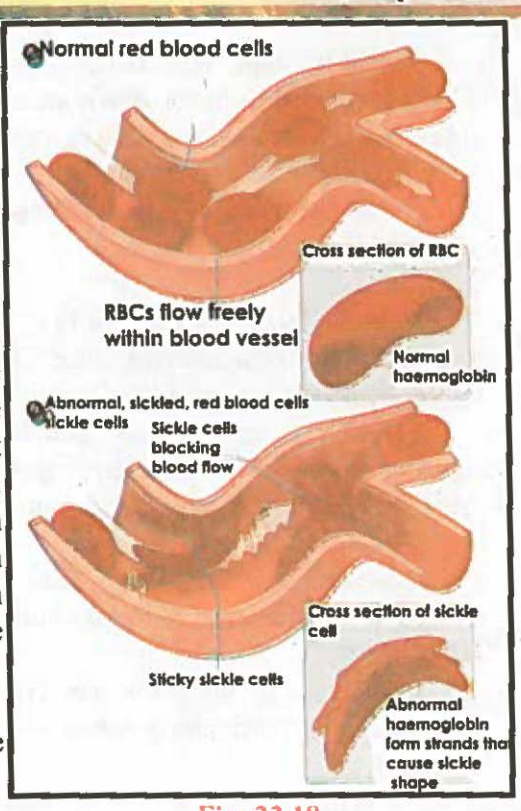


Fig: 23.18

Treatment:

The goal of treatment is to manage and control symptoms, and to limit the number of crises. Folic acid supplements should be taken. Folic acid is needed to make red blood cells.

Treatment for a sickle cell crisis includes: blood transfusions (may also be given regularly to prevent stroke), pain medicines, plenty of fluids

Other treatments for sickle cell anemia may include: hydroxyurea (Hydrea), a medicine that may help reduce the number of pain episodes (including chest pain and difficulty breathing) in some people, antibiotics to prevent bacterial infections, which are common in children with sickle cell disease.

23.8.5 Phenylketonuria:

Phenylketonuria (PKU) is a rare condition in which a baby is born without the ability to properly break down an amino acid called **phenylalanine**.

Causes, incidence, and risk factors:

Phenylketonuria (PKU) is inherited, which means it is passed down through families. Both parents must pass on the defective gene in order for a baby to have the condition. This is called an autosomal recessive trait.

Babies with PKU are missing an enzyme called ***phenylalanine hydroxylase***, which is needed to break down an essential amino acid called phenylalanine. The substance is found in foods that contain protein.

Without the enzyme, levels of phenylalanine and two closely-related substances build up in the body. These substances are harmful to the central nervous system and cause brain damage.

Symptoms:

Phenylalanine plays a role in the body's production of melanin, the pigment responsible for skin and hair color. Therefore, infants with the condition often have lighter skin, hair, and eyes than brothers or sisters without the disease.

Other symptoms may include: delayed mental and social skills, head size significantly below normal, hyperactivity, jerking movements of the arms or legs, mental retardation, skin rashes, tremors, and unusual positioning of hands.

If the condition is untreated or foods containing phenylalanine are not avoided, a "mousy" or "musty" odor may be detected on the breath and skin and in urine. The unusual odor is due to a buildup of phenylalanine substances in the body.

Treatment:

PKU is a treatable disease. Treatment involves a diet that is extremely low in phenylalanine, particularly when the child is growing. The diet must be strictly followed.

Phenylalanine occurs in significant amounts in milk, eggs, and other common foods. The artificial sweetener Nutra Sweet (aspartame) also contains phenylalanine. Any products containing aspartame should be avoided.

A special infant formula called Lofenalac is made for infants with PKU. It can be used throughout life as a protein source that is extremely low in phenylalanine and balanced for the remaining essential amino acids.

23.8.6 Down syndrome:

Down syndrome (also called trisomy 21) is a chromosomal condition characterized by the presence of an extra copy of 21st chromosome, either in whole or part (such as due to translocations). So these individuals generally have 47 chromosomes (2n + 1).

Sign and Symptoms:

Although the severity of Down syndrome ranges from mild to severe, most individuals with Down syndrome have widely recognizable physical characteristics. These include:

Fig: 23.19

- α flattened face and nose, a short neck, a small mouth sometimes with a large, protruding tongue, small ears, upward slanting eyes that may have small skin folds at the inner corner (epicanthic fold) and inner corner of the eyes may be rounded instead of pointed;
- white spots (also known as Brushfield spots) may be present on the colored part of the eye (iris);
- the hands are short and broad with short fingers, and with a single crease in the palm;
- poor muscle tone and loose ligaments are also common; and
- development and growth is usually delayed and often average height and developmental milestones are not reached

For Your Information

Down syndrome is named after **Doctor Langdon Down**, a British physician, who in 1866 first described the syndrome as a disorder. Although Doctor Down made some important observations about Down syndrome, he did not correctly identify what causes the disorder. It wasn't until 1959 that **Dr. Jérôme Lejeune** discovered the genetic origin of Down syndrome

Causes & risk factor:

It is the consequence of **autosomal non-disjunction** during which 21st chromosome fail to segregate, resulting gamete with 24 chromosomes. This gamete fertilizes normal gamete the new individual will have 47 ($2n + 1$) chromosomes.

The incidence of Down syndrome is estimated 1 per 800 births before the age of 30, although it is statistically more common with older parents (especially mothers), for example, a woman has risk of Down syndrome up to about 1 in 350 by age 35. By 40 the risk rises to about 1 in 100.

For Your Information

The average IQ of children with Down syndrome is around 50, compared to normal children with an IQ of 100. A small number have a severe to high degree of intellectual disability.

Treatment:

Although the genetic cause of Down syndrome is known, there is no specific treatment available currently. But it can be managed to some extent by taking few measures like:

- Corrective surgery for heart defects, gastrointestinal irregularities, and other health issues is necessary for some individuals.
- Regular health checkups should be scheduled to screen for other conditions such as visual impairments, ear infections, hearing loss, hypothyroidism, obesity, and other medical conditions.
- Individuals with Down syndrome should be fully included in family and community life because many children with Down syndrome who have received family support, enrichment therapies, and tutoring have been known to graduate from high school and college, and enjoy employment in the work force.

23.8.7 Klinefelter's Syndrome:

Klinefelter syndrome (also called XXY syndrome) is a condition in which human males have an extra X chromosome. Klinefelter syndrome is named after **Dr. Henry Klinefelter**, who in 1942, first described a group of symptoms found in some men. In 1959, these men with Klinefelter syndrome were discovered to have an extra sex chromosome (XXY) instead of the usual male sex complement (XY).

Signs & Symptoms:

All affected males with the condition do not have the same symptoms or to the same degree.

- As babies, many XXY males have weak muscles and reduced strength. They may sit up, crawl, and walk later than other infants.
- As XXY males enter puberty, they often don't make as much testosterone as other boys. This can lead to a taller, less muscular body, less facial and body hair, and broader hips than other boys.
- As teens, XXY males may have larger breasts, weaker bones, and a lower energy level than other boys. They tend to be quiet and shy meaning they may have more trouble "fitting in" with other kids
- By adulthood, XXY males look similar to males without the condition, although they are often taller. XXY males can have normal sex lives, but they usually make little or no sperm. Between 95 percent and 99 percent of XXY males are infertile
- They may have some kind of trouble using language to express thoughts and needs, problems reading, and trouble processing what they hear.

Cause & Risk:

Klinefelter's syndrome is caused by non-disjunction of sex chromosome during oogenesis in mothers. These persons inherit two X chromosome from mother and a Y chromosome from father, so they have sex chromosome trisomy (XXY).

Klinefelter's syndrome affects 1 in 500 to 1,000 males. Most variants of Klinefelter syndrome are much rarer, occurring in 1 in 50,000 or fewer male births. Klinefelter syndrome does not occur in females.

Treatment:

The XXY chromosome pattern cannot be changed. But, there are a variety of ways to treat the symptoms of the XXY condition.

Testosterone replacement therapy (TRT) can greatly help XXY males get their testosterone levels into normal range to develop more masculine appearance and identity. Having a more normal testosterone level can help develop bigger muscles, deepen the voice, and grow facial and body hair. With treatment, most boys grow up to have normal sex lives, successful careers and normal social relationships. Educational services and physical, speech and occupational therapy may also increase their confidence level.

23.8.8 Turner's syndrome:

Turner's syndrome is chromosomal disorder which is characterize by the missing of one X chromosome (44 + X). In 1938, Henry Turner first described Turner syndrome. Since these persons do not have Y chromosome so they always develop as female.

Signs & Symptoms:

- More than 95% of adult women with Turner syndrome exhibit short stature.
- They have non-functioning ovaries which do not produce sex hormones (estrogen and progesterone) so they do not start menstruation or dev elop breasts without hormone treatment at the age of puberty.
- Even though many women who have Turner have non-functioning ovaries and are infertile, their other genitalia are totally normal so pregnancy with donor embryos may be possible.
- In early childhood, these girls may have frequent middle ear infections. Recurrent infections can lead to hearing loss in some cases.
- These girls have normal intelligence with good verbal skills and reading skills. Some girls, however, have problems with mathematics, memory skills and fine-finger movements.

Cause and Risk:

Turner's syndrome is caused by sex chromosomal non-disjunction that may occur during oogenesis in mother. As a result mother produces an egg lacking X chromosome (nullo gamete). When such egg is fertilized by an X chromosome containing sperm, the female baby is developed with 44 autosomes and one X chromosome (monosomy). This condition occurs in about 1 in 2,500 female births worldwide, but is much more common among pregnancies that do not survive to term (miscarriages and stillbirths).

Treatment:

Having appropriate medical treatment and support allows a woman with Turner syndrome to lead a normal, healthy and happy life. Treatments include:

- Growth hormone injections are beneficial to increase final adult height by a few inches.
- Estrogen & progesterone replacement therapy can help in breast development and start of menstruation which is necessary to keep the womb healthy; it also prevents osteoporosis.

KEY POINTS

- All animals and plant cells have nuclei.
- Nucleus contains chromosomes.
- Chromosomes are composed of DNA and protein.
- The number, shape and size of chromosomes is same for a particular species.
- DNA is stable molecule and capable of self-duplication with full conservation of its specificity.
- DNA is polynucleotide chain of four different kinds of nucleotide. The difference in the type of nucleotide lies in the type of nitrogen bases, adenine, guanine called purine and cytosine, thymine called pyrimidine.
- Two strands of double helix molecule of DNA are formed of sugar and phosphate group bounded in linear sequence and held together by hydrogen bonds between specific kinds of bases.
- Two strands of DNA molecule separate from each other during DNA replication, each serving as a model for the synthesis of new complimentary strand
- Sometime errors occur in replication resulting in alteration in base sequence along DNA molecule.
- Change in the base sequence result in mutation.
- Proteins are long polypeptide chains of amino acids.
- Each gene directs the synthesis of a particular polypeptide chain.
- Three kinds of RNA take part in the synthesis of protein and these are mRNA, tRNA, rRNA.
- Code lying in chromosomal DNA is transcribed in mRNA, which is translated by tRNA in ribosome into polypeptide chain.
- Change at gene level or change in the structure or number of chromosomes result in mutation.

EXERCISE

1- Multiple Choice Questions

(i) ***A chromosome with unequal length of its arms is called:***

(a) Metacentric (b) Sub metacentric
(c) Acrocentric (d) Telocentric

(ii) ***In Hershey & Chase experiment, ^{32}P labeled bacteriophages allowed to infect the bacteria. During analysis ^{32}P activity was detected:***

(a) In culture medium
(b) On the surface of bacterial cell
(c) Inside the bacterial cell
(d) Both a & b

(iii) ***In Meselson & Stahl experiment, the DNA from sample at 20 minutes, after centrifugation it made sediments at the:***

(a) Top (b) Bottom
(c) Intermediate (d) Top & intermediate

(iv) ***Which of the following act as a stop codon?***

(a) UGG (b) UGC
(c) UAG (d) UGU

(v) ***In mitochondria UGA codon act to specify ------- instead stop codon:***

(a) Argenine (b) Valine
(c) Glutamic acid (d) Trytophan

(vi) ***If the amount of adenine in DNA of a bacterial cell is 36% of the total nitrogenous bases, what will be the amount of guanine in the DNA of a cell in next generation:***

(a) 14% (b) 28%
(c) 36% (d) 64%

(vii) ***If an mRNA is synthesized with all the different codons, what is the minimum number of amino acids in the protein that is formed by mRNA:***

(a) 64 Amino acids (b) 62 Amino acids
(c) 60 Amino acids (d) None of them

(viii) ***In eukaryotic mRNA molecule there are 90 nucleotide involved in translation process. What is the number of amino acid in the protein formed by this mRNA molecule?***

(a) 29 amino acids (b) 30 amino acids
(c) 45 amino acids (d) 90 amino acids

EXERCISE

(ix) In Griffith experiment mice developed pneumonia when they were injected with:

(a) R-type bacteria
(b) heat killed S-type bacteria
(c) heat killed R-type bases
(d) heat killed S-type bacteria along with live R-type bacteria.

(x) If the codon consisted of only two nucleotides, there would be how many possible codons?

(a) 4 (b) 8
(c) 20 (d) 16

2- Short Questions

(i) Differentiate the concept of monoploid and haploid.
(ii) List are the types and role of histone proteins in chromosome?
(iii) Give any two evidences provided by Sutton in favour of chromosome theory of inheritance.
(iv) What was the conclusion of Avery's experiment?
(v) Differentiate between conservative and semiconservative models of DNA replication.
(vi) Give a brief comparison between RNA polymerase and DNA polymerase.
(vii) "Genetic codes are universal but not quite universal". Analyze this statement.
(viii) Summarize the structure of a eukaryotic gene?
(ix) Define RNA splicing?
(x) What is the structure of *Lac* Operon?

3- Long Questions

(i) Critically analyze the history of chromosome theory of inheritance.
(ii) Prove that an evidence of DNA as heredity material.
(iii) Eloborate the work of Meselson & Stahl to justify the semi conservative replication as a correct model of replication.
(iv) Describe the events of the process of DNA replication.
(v) Describe post transcriptional modification of mRNA.
(vi) Explain the process of translation of mRNA into polypeptide.
(vii) Discuss the regulation of gene expression with help of *lac* operon model.
(viii) Describe cause, symptoms, and treatment of Down's syndrome.

EXERCISE

4- Analyzing and Interpreting

- Interpret an experiment in which a radio isotope labeled DNA can be traced in the progeny of an organism.
- Interpret how DNA conserves one strand during replication.
- Interpret that how many types of tRNA molecules are necessary for a living cell, if the genetic code is a triplet code.

5- Initiating and Planning

- Make a list of all the proteins that have been studied or referred to till now.
- Make list of some commonly occurring minor mutation in human.
- Justify why mutations prevail in a population and are inherited.

6- Science, Technology, and Society Connections

- Describe the paradoxical nature of DNA, as a tool of geneticists and forensics
- Describe how various scientists in the field of biotechnology and genetic engineering have used the DNA replication.
- Suggest possible ways to solve lives or treat genetic diseases (like diabetes) through the knowledge gained under this heading.
- Explain how harmful mutations have been eradicated by nature.

7- Online Learning

- www.johnkyrk.com/DNAreplication
- www.genome.wellcome.ac.uk
- www.scienceblogs.com
- www.ghr.nlm.nih.gov
- www.biobase-international.com.