UNIT 23

CHROMOSOME AND DNA

Major Concept

23.1 Chromosomal Theory of Inheritance
23.2 DNA as the Hereditary Material
23.3 DNA Replication
23.4 Gene Expression
23.5 Regulation of Gene Expression
23.6 Mutation

Learning Outcomes

Students will be able to:

- Critically analyze the history of chromosomal theory with reference to Correns' work.
- Critically analyze the experiments of T. H. Morgan in support of the above mentioned theory.
- Annotate the detailed structure of a chromosome.
- Describe the concept of gene and gene locus.
- Explain the concept of alleles as the alternative forms of a gene.
- Narrate the experimental work of Griffith and Hershey-Chase, which proved that DNA is the hereditary material.
- Describe the three models proposed about the mechanism of DNA replication.
- Narrate the work of Meselson and Stahl to justify the semi-conservative replication as the correct method of replication.
- Describe the events of the process of DNA replication.
- Explain DNA stability and variability as two characters of the replicating DNA molecule.
- Describe the central dogma of gene expression.
- Define gene and genetic code.
- Describe the characteristics of genetic code (universal, triplet, non-overlapping, degenerate, punctuated).
- Differentiate between the terms genetic code and codon.
- Explain the mechanism of transcription.
- Explain why the length of transcribed m-RNA molecule (in Eukaryotes) shortens as it enters the cytoplasm for translation.
- Describe the mechanism of protein synthesis.
- State the difference between protein synthesis in prokaryotes and eukaryotes.
- Suggest possible ways in which the synthesized protein can be used within or outside a cell that synthesized it.
- State the importance of the regulation of gene expression.

- Describe the negative control of gene expression by repressor proteins.
- Describe the positive control of gene expression by activator proteins.
- Relate gene expression with introns and exons.
- Define mutation and identify various sources of mutation.
- Differentiate between neutral and induced mutations and mutagens.
- Justify that most mutations are harmful.
- Rationalize that mutations might be a contributing factor towards evolution.
- Describe the symptoms, causes and possible available treatments of some of the chromosomal mutations. (Down's, Klinefelter's and Turner's syndrome).
- Describe the symptoms, causes and possible available treatments of some of the gene mutations (Sickle cell anaemia, Phenylketonuria).

Introduction

The bright stained bodies in figure 23.4 are human "instructions" called **chromosomes,** but they cannot be read in the usual way. Instead using a special code (on DNA) that can be "understood" by other special molecules, they direct all the chemical reactions that take place in your body. Instructions in the chromosomes determine such things as whether your hair is red or brown and whether you are male or female. The chromosomes are made up of DNA and protein. The Mendel's "factors" now called **genes,** are specific segments of DNA.

23.1 Chromosomal Theory of Inheritance

Charles Darwin's and Mendel's work laid the foundation for formulating a research based theory of heredity. Darwin was first, who in 1864 suggested that traits could be transferred from parents to offsprings in the form of **units**. He named these units a "**gemmules**" or factor. While in 1865, Mendel proposed that traits are governed by separate and distinct units, termed "**elementens**" or **factors**. Mendel's work remained unnoticed till 1900. However, Mendel's hereditary principles were rediscovered by three European scientists, **Hugo de Vries**, **Carl Correns** and **Erich Won Tschermak**. However, **Carl Correns was named rediscoverer of Mendel's work** because he republished the Mendel's work and proposed laws from his work *i.e.* law of dominance, law of segregation and law of independent assortment. He was first, who suggested that there is a central role of chromosomes in hereditary.

23.1.1 Origin of Chromosomal Theory of Inheritance

Definition:- This theory revealed that "**genes,** the units of inheritance, are located on the **chromosomes**, thus these act as carriers of heredity". Many scientists had contributed

in this respect, the contribution of these scientist are given below:

Fig. 23.1: Walter Fleming

i) Contribution of Walter Fleming and Waldeyer

Chromosomes were first observed by German embryologist Walter Fleming in 1882, when he was examining the rapidly dividing cells of salamander (an amphibian) larvae, Waldeyer, assigned the name "**Chromosome**" (chromas; color: soma; body). In eukaryotic cells chromosomes are composed of DNA and proteins while in prokaryotic cells it is made of only DNA. (Fig.23.1)

ii) Contribution of Karl Correns

Fig. 23.2: Karl Correns

German geneticist Karl Correns (1900) put forward this idea, in one of his published papers, in which he explained the relationship of heredity units with chromosomes. However, he had not given any supportive evidence for this idea. (Fig.23.2)

iii) Contribution of Theodor Boveri and Walter Sutton

Theodor Boveri, a German biologist was one of the leading cytologists of his time. Between 1896 and 1904, he carried out experiments on sea urchin (an echinoderm) eggs, studying the behavior of the cell nucleus and chromosomes during meiosis and after fertilization.

The independent studies by Walter Sutton (1902-04) and Boveri's (1902) contributed to **chromosomal theory of Inheritance.**

Walter Sutton, an American cytologist studied meiosis in cells of **plain lubber grasshopper** (*Brachystola magna*). He was a young, graduate student who produced remarkable and detailed drawings of his finding in cytology. As a result of his observations, he (1902-4) made the connection between the behavior of chromosomes during meiosis and Mendel's laws of heredity.

Boveri and Sutton's chromosomes theory linking chromosomes and heredity had faced serious objections. According to many investigators, Mendalian traits are determined by the factors located on chromosome. If these genes separate due to segregation of chromosomes. The independent assortment of genes is reflected by the independent assortment of chromosomes in meiosis then the number of genes are much greater than the number of chromosome pairs that the organism possesses.

The objections of investigators were cleared with advancement in scientific understanding, development in cytology and after the contribution of T. H. Morgan. (Fig.23.3)

Water Sutton Theodor Boveri Thomas Hunt Morgan

Fig. 23.3

23.1.2 Contribution of T. H. Morgan

Thomas Hunt Morgan (1910) a Cytologist began his famous work on fruit fly. His work showed without any doubt that:

- The gene for eye color in fruit flies is located on the "X" chromosome and hereditary factors can be exchanged between the "X" chromosomes of an individual.
- The result of Morgan's studies led to a greater understanding of how genes are arranged on chromosomes and how genetic material can be exchanged (during crossing over) in meiosis.
- He was awarded the Nobel prize for physiology (Medicine) in 1933.

Thus all above contributions confirmed that the chromosomal theory of inheritance was not proposed by a single scientist, but rather the collaborative result of many researchers work over multiple decades.

Walter S. Sutton described the parallel behavior between genes and chromosomes. (Table 23.1)

Table 23.1: Parallel behavior of Genes and Chromosomes During Meiosis

S.No.	Behavior of Genes	Behavior of Chromosomes
i)	The genes that control the particular characteristics mostly occur in pairs.	Diploid cell contain the pairs of homologous chromosomes.
ii)	Pairs of the genes separate during the gamete formation so that the gametes have only one of the paired genes.	Each gamete cell has only one out of a homologous pair of chromosome *i.e.* gametes are haploid (n).
iii)	When the gametes unite the gene pairs are formed again.	When the gametes unite during the fertilization chromosome pairs restore again in pair. The zygotes are diploid (2n).
iv)	Genes are transmitted from one generation to the next and remain as unchanged units.	Individual chromosomes are transmitted from generation to generation as unchanged structure.
v)	There is independent assortment of genes *i.e.* possible gene combination can be calculated.	There is independent assortment of chromosomes *i.e.* possible chromosomes combination can be calculated.

23.1.3 Structure of Chromosomes

Chromosomes (Chomo = colored; soma = body) are compact coils of thread like structure, clearly visible only during cell division, so named because chromosomes take up stains easily when being prepared for microscopy. After cell division *i.e.* during interphase, these become uncoiled and look like very fine network called chromatin network (DNA and proteins). Thus DNA of eukaryotic cell most often occurs in the form of chromosomes. They carry information necessary for cell to exist. Chromosomes allow the organisms, whether unicellular or multicellular to survive.

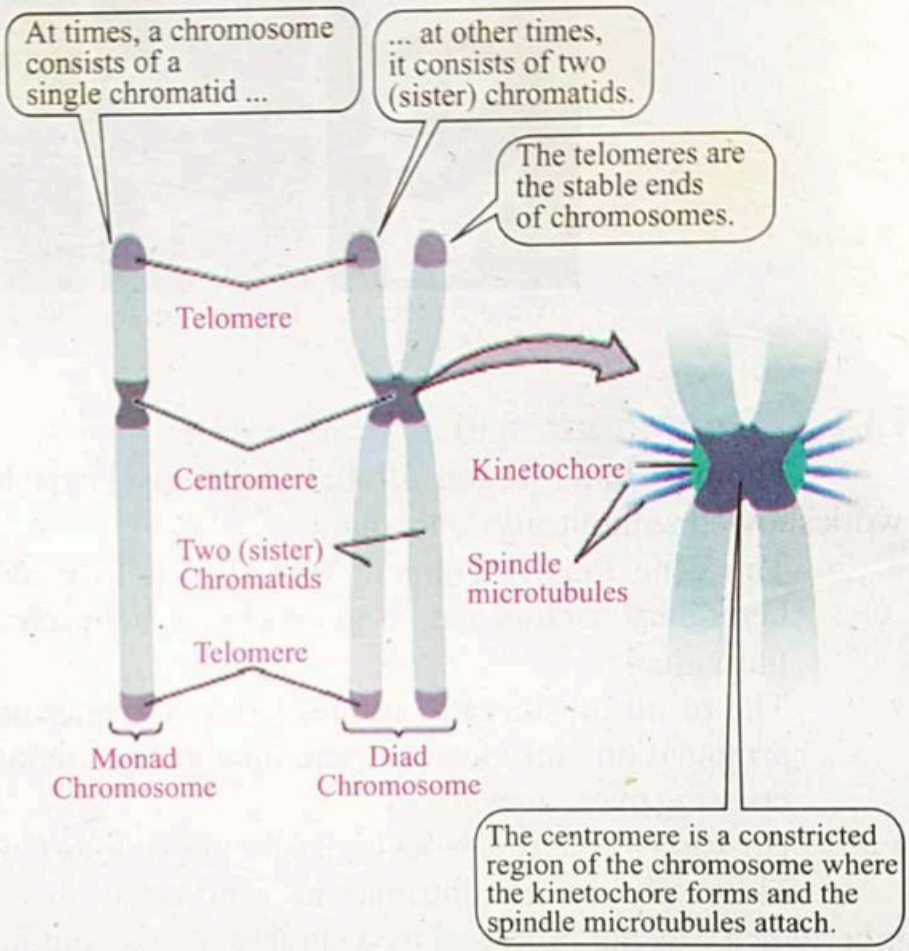

Fig. 23.4: Monad and Diad Chromosomes

They were first recorded by a German embryologist Walther Fleming in 1882, in rapidly dividing cells of **Salamander larvae**. Later chromosomes were observed in all eukaryotic cells and found linear while circular in prokaryotes.

The number of chromosomes vary from species to species and remains constant in each species generation after generation. ***Penicillium*** (a fungus) has only one pair, in fruit fly 4 pairs, mosquito 3 pairs, lettuce 9 pairs, corn 10 pairs, Honey bee 16 pairs, frog 13 pairs, mouse 20 pairs, human 23 pairs, monkey 24 pairs, camel 35 pairs, sugarcane 40 pairs and some ferns have more than 500 pairs.

Karyotype

It is a particular array of chromosomes that an individual possesses, which sometime may differ even among individuals of the same species, chromosome vary in size, shape, number, centromeric position, number and arrangement of genes.

Most species of animals and plants are **diploid** (having two sets of chromosomes), many plants are **polyploids** (more than two sets of chromosomes). There are many plants like, Bryophytes and many fungi are **monoploid** (Haploid).

The term "**haploid**" is referred to the number of chromosome exactly half than the somatic number of chromosomes *e.g.* gametes and mostly spores are haploid. (Fig.23.4)

Structure/Components of Chromosome

Typically, a chromosome is made of chromatids and a centromere (Primary constriction).

A typical **diad** (duplicated state) chromosome consists of two strands while **monad** (unduplicated state) chromosome has one strand called chromatid. Each **chromatid** is made up of a long DNA molecule which is tightly coiled along with **histone proteins**. The duplicated chromosome narrows down in one region along its length to form point of union called **primary constriction** or **centromere**. The both sides of primary constriction are covered by disc-shaped proteins known as **kinetochore**, the attachment site for microtubules that move the chromosome during nuclear division.

Some chromosomes may have another point of union along the length of each chromatid called **secondary constriction** or **nuclear organizer**. It gives rise to nucleoli during interphase. The portion of chromosome after secondary constriction becomes a knob like structure called **satellite**, contains useless sequence of DNA known as **junk DNA**. The terminal ends of each chromosome are called **telomeres** which prevent the two chromosomes to attach with each other from their ends.

Shape, Types of Chromosomes based on the location of the centromere

There are four types of chromosomes:

1. **Metacentric** are "V" shaped chromosome, the centromere is located in centre of chromatids.

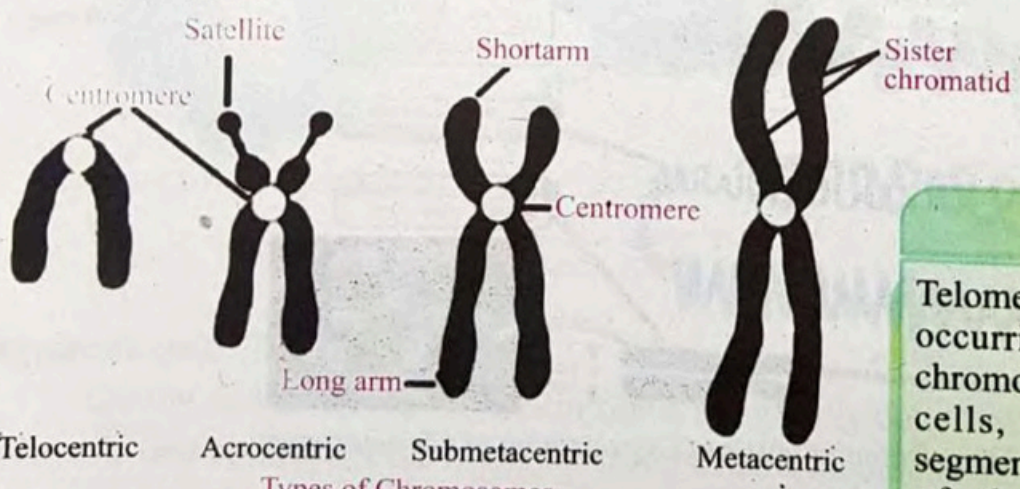

Fig. 23.5: Types of Chromosomes

Telomere

Telomere, segment of DNA occurring at the ends of chromosomes in eukaryotic cells, made of repeated segments of DNA that consist of the sequence 5' end TTAGGG-3' end.

2. **Submetacentric** are "L" shaped chromosomes, their centromere is either below or above the centre of the chromatids.
3. **Acrocentris** are "J" shaped chromosomes, the arms of one side of centromere are very short and other side very long.
4. **Telocentric** are "i" or rod shaped, the centromere is at the tip or at one end of chromosomes. (Fig.23.5)

23.1.4 Chemical Composition of Chromosomes

Chromosomes are **nucleoprotein** in nature. A typical chromosome contains about 60% proteins, 40% DNA and a significant amount of RNA (because DNA is the sites of RNA synthesis). Each duplicated chromosome has almost two identical DNA molecules.

An average size human chromosome has approximately 5cm long DNA that consists of about **140 million nucleotides**. In the cell the DNA is coiled allowing it to fit into a much smaller space. (Fig.23.6)

Interesting Information

It is estimated that the amount of information, a single chromosome contains would fill about 280 printed books each book with 1000 pages. Each nucleotide corresponds to a word and each page had about 500 words on it.

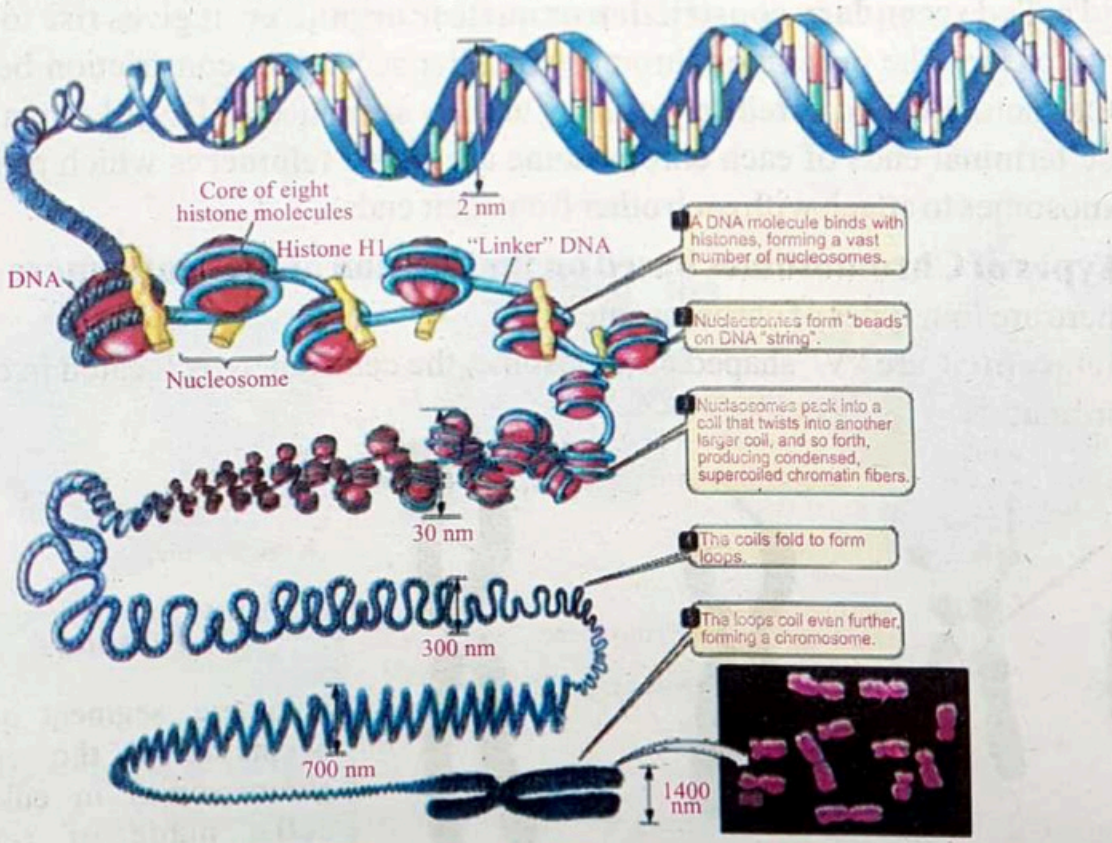

Fig. 23.6: Different levels of Organization of Chromosomes

Ultra Structure of Chromosome

The detailed structure of a molecule under electron microscope is called ultra

structure. The ultra-structure of chromosome revealed that each chromosome is made of repeated units called nucleosomes. About every 200 nucleotides of the DNA duplex is coiled around a core of eight histone protein (octamere) forming a bead like complex called **nucleosome** or **chromomere**. The **octamere** made up of four types of histone, two of each **H_2A, H_2B, H_3 and H_4**. The **histone** proteins possess positive charge, due to abundance of positive charged basic amino acids, **arginine** and **lysine**. Therefore, histones are strongly attracted to the negatively charged phosphate groups of the DNA. A small segment of DNA between two successive nucleosomes is called **linker or spacer DNA**. This is associated with another molecule of histone called **linker histone (H_1)**. Thus in this way the whole DNA which is 2 nm thick turns into chain of bead like appearance known as **nucleosome string** about 10nm thick. This immediately begins to coil again about its axis to form yet another thicker fibre called **chromatin solenoid** (about 30 nm).

During **interphase** *i.e.* in **G_1 and G_2 phases**, the chromosomes are in form of **chromatin fibres**. The chromatin is either in highly condensed form known as **heterochromatin**, which mostly do not express or less or non-condensed form called **euchromatin**, it becomes condensed during cell division and its genes can be expressed after cell division. (Fig.23.7)

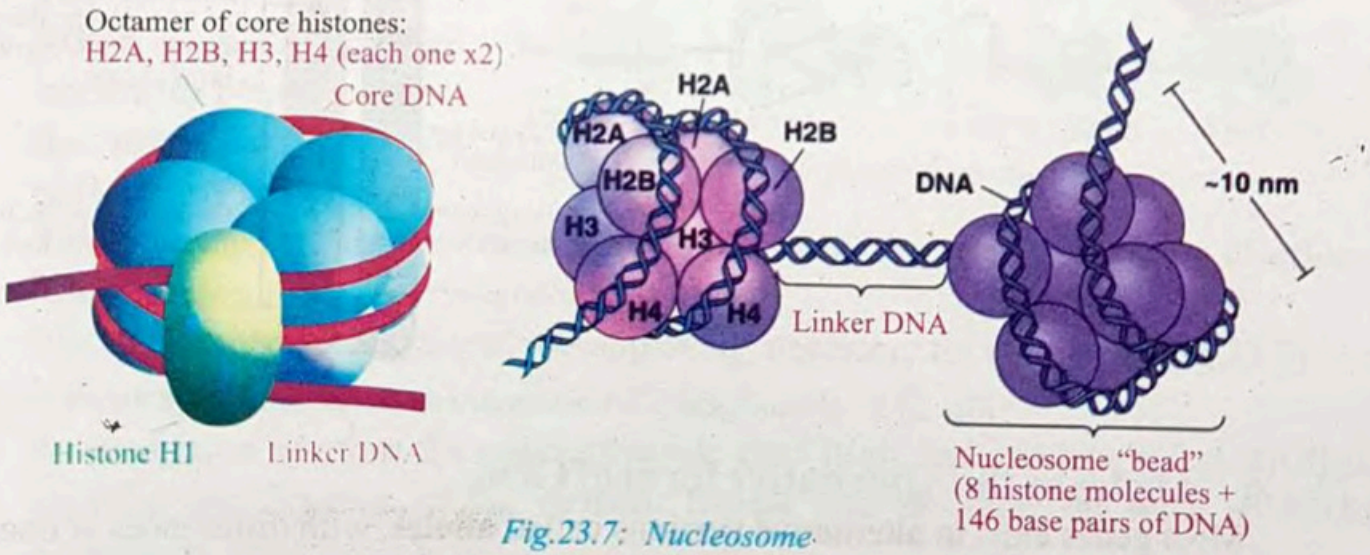

Fig.23.7: Nucleosome

Supercoil and Chromatids

During cell division, chromatin fibres are greatly coiled, which have diameter of 300nm further coiling occurs when the string of nucleosomes wraps up into higher order coils called super coils (about 700nm). The super coil is established into the chromatids and chromosome.

23.1.5 Molecular Concept of a Gene

The units of inheritance are called gene, which are composed of nucleotides sequence of a short specific segment of DNA, which transcribes an mRNA. The mRNA encodes the sequence of amino acid of a particular polypeptide.

Earlier, many names were used for genes by different scientists such as **gemmules** (by Darwin in 1868), **elementens** (by Mendel in 1865), **factors** (by Correns 1900), **pangens** (by De Vries in 1890). The present name **gene** was introduced by Wilhelm Johansson in 1909, while the term **genetics** was first used by William Bateson in 1906. The particular place or location where a gene resides is called **gene locus** (Plural = loci). (Fig.23.8)

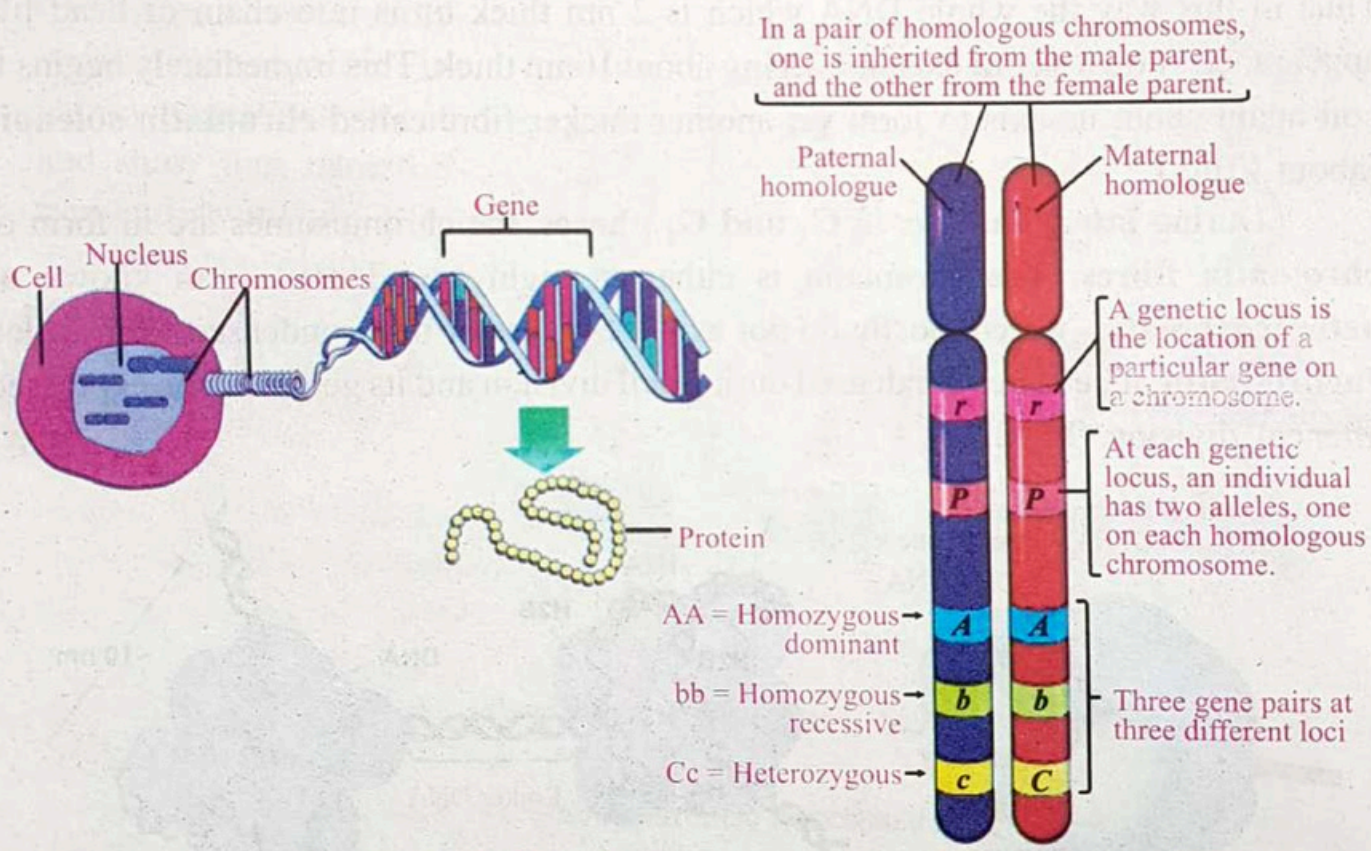

Fig. 23.8: Homologous Chromosomes and Gene

23.1.6 Alleles as the Alternative form of Gene

Most genes exist in alternative versions called **alleles**, with differences at one or more nucleotide positions in the DNA. The alleles related to the same trait occupy the same locus, such as gene of ABO blood group *i.e.* **"I" (isoagglutinogen)** exist in three different alleles **(I^A, I^B, i),** which are found on the same locus at chromosome No.9. The allele which fully expresses is called the **dominant** such as **"I"** allele, while the allele which either does not express or no noticeable effect on the organism's appearance is called **recessive**, such as **"i".**

23.2 DNA as the Hereditary Material

The chromosomal theory of inheritance had confirmed that heredity units are found in the chromosome. It was known that the chromosomes contain both DNA and protein, but it was not confirmed, which one acts as hereditary information. Many experiments were performed by different researchers to confirm this issue.

23.2.1 Experiment of Griffith

The first **evidence** of hereditary nature of DNA was provided by British microbiologist **Fredrick Griffith** in 1928. He made some unexpected observations while experimenting with pathogenic bacteria, ***Streptococcus pneumonae***.

This pathogen is found in two types:

1. One type has a poly-saccharide capsule, it's colony appears as smooth and shiny thus named S-type and is virulent.
2. The other type is devoid of polysaccharide capsule, it's colony is rough thus named R-type, which is non-virulent.
3. When Griffith injected mice with S-type bacteria, the mice died of blood poisoning (Pneumonia).

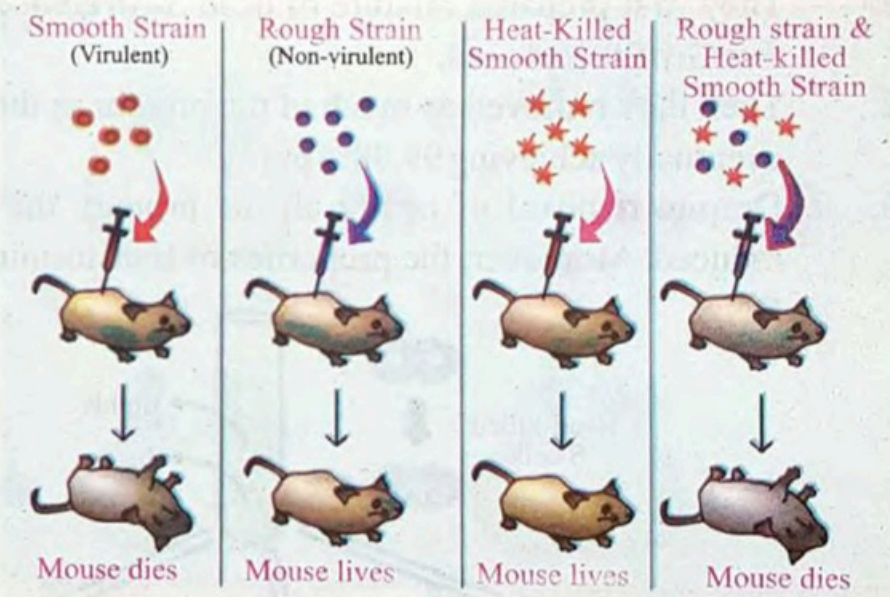

Fig. 23.9: Griffith's Experiments on Mouse

4. When he injected R-type bacteria to similar mice, the mice showed no ill effects (blood poisoning).
5. The Griffith observed that coat was apparently necessary for virulence. (Fig.23.9)

Decisive experiment

1. To determine whether the polysaccharide coat itself had virulent effect, Griffith injected dead bacteria of the **virulent S-type** into the mice; the mice remained perfectly healthy.
2. As a control, he injected mice with a mixture containing dead S-bacteria of the virulent strain and live R-type bacteria, each of which by itself did not harm the mice, when induced separately.

Result: Unexpectedly, the mice developed the disease symptoms and many of them died. The blood of the dead mice was found to contain high levels of live, **virulent**

Streptococcus (**S-type**) bacteria, which had surface protein. Somehow, the information specifying the polysaccharide coat had passed from the dead, virulent S-type bacteria to the live, coatless R-type bacteria in the mixture, thus permanently transforming the coatless R-type bacteria into the virulent S-type variety.

This transfer of genetic material from one cell to another which may alter the genetic makeup of the recipient cell, is called **transformation**.

23.2.2 Work of Avery, Macleod and McCarty

In 1944, in a classic series of experiments, Oswald Avery along with Colin Macleod and Maclyn McCarty repeated Griffith's experiments and characterized what they referred to as the transforming principle.

1. They first prepared mixture of dead ***S-Streptococcus*** and live ***R-Streptococcus*** that Griffith had used.
2. Then they removed as much of the protein as they could from their preparation, eventually achieving 99.98% purity.
3. Despite removal of nearly all the protein, the transforming activity was not reduced. Moreover, the properties of transforming principle resembled those of DNA.

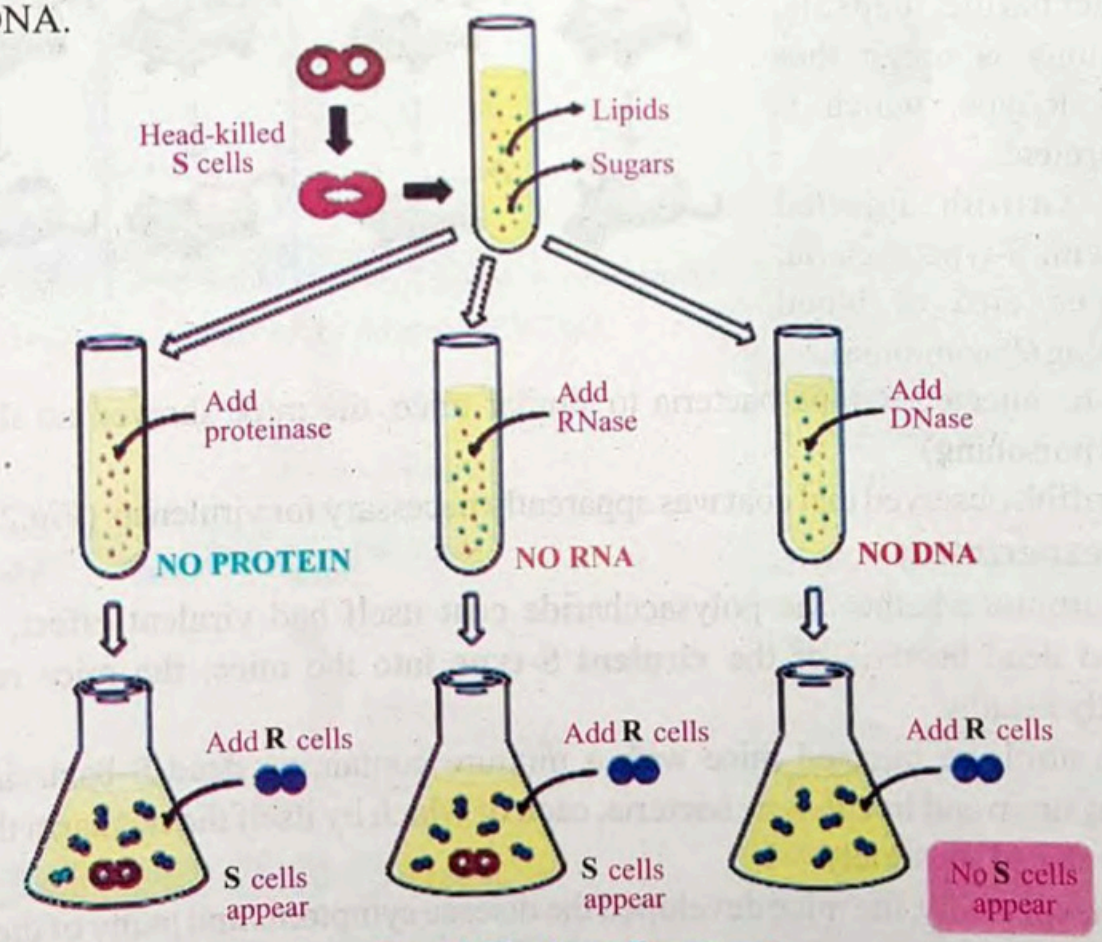

Fig. 23.10: Avery Experiment

4. The protein digesting enzymes or RNA digesting enzymes did not affect the transforming activity, but the DNA digesting enzyme DNAase destroyed all the transforming activity.

23.2.3 Hershey and Chase Experiment

Alfred Hershey and Martha Chase (1952) experimented with **bacteriophage T_2** and provided additional evidence supporting Avery's conclusion. Bacteriophages attack on bacteria, these viruses are made of DNA and protein, just like chromosome. In some experiments they labelled viruses with radioactive isotope ^{32}P, which was incorporated into the newly synthesized DNA of growing phage.

In other experiments, they labelled viruses with radioactive isotope ^{35}S, which is present in their protein coats. (Fig.23.11)

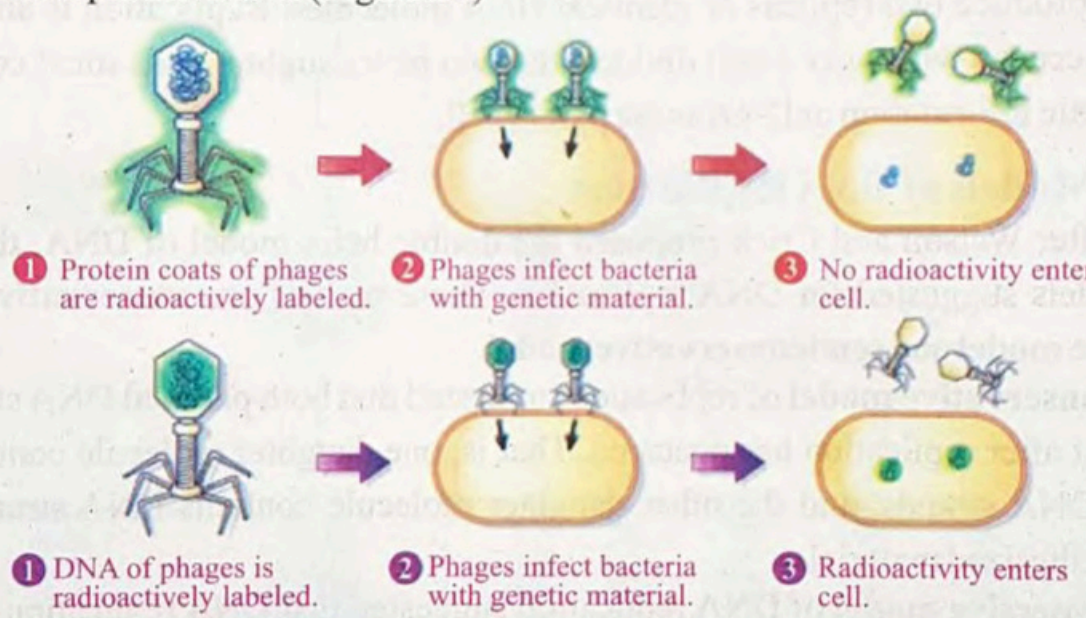

Fig. 23.11: Hershey and Chase Experiment

Exposure of Bacteria to labelled Viruses

Now one bacterial culture was exposed to radioactive ^{32}P labelled viruses and other culture was exposed to radioactive ^{35}S labelled viruses.

The bacterial cells were agitated violently in a blender to remove the protein coats of the infecting viruses from the surfaces of the bacteria.

When bacteria were tested for the presence of label, it was found that bacteria had lost nearly all of radioactive ^{35}S label. However, ^{32}P label was present in bacteria of the other group.

Bacteriophage T_2 is more properly called enterio-bacteriophage T_2. It is a virulent bacteriophage, which infects ***Escherichia coli*** bacteria, it contains linear double-stranded DNA. It is tailed phage.

It is because ^{35}S was only present in protein coat while ^{32}P was present in DNA that had transferred to the interior of the bacteria.

Confirmation

It was confirmed when viruses were released from the infected bacteria. The viruses released from ^{32}P culture were labelled while viruses released from ^{35}S culture were unlabelled.

Thus, it was proved by Hershey and Chase that the hereditary information injected into the bacteria that specified the new generation of viruses was DNA and not protein.

23.3 DNA Replication

DNA replication is the process by which a double stranded DNA molecule is copied to produce two replicas or identical DNA molecules. Replication is an essential process, because whenever a cell divides, the two new daughter cells must contain the same genetic information or DNA as the parent cell.

23.3.1 Models of DNA Replication

After Watson and Crick proposed the double helix model of DNA, there were three models suggested for DNA replication. These models are **conservative model**, **dispersive model** and **semiconservative model**.

1. **Conservative model** of replication suggested that both parental DNA strands are kept intact after replication has occurred. That is, one daughter molecule contains both parental DNA strands, and the other daughter molecule contains DNA strands of all newly synthesized material.
2. **Dispersive model** of DNA replication suggested that DNA replication results in two DNA molecules that are mixture of parental and daughter DNA. In this model, each individual strand is a patchwork of original and new DNA.
3. **Semiconservative model** of DNA replication revealed that the two strands of parental DNA isolate and each of these serves as template for synthesis of a new DNA strand. It produces two copies of the original DNA molecule, each of which contains one of original strand, and one newly synthesized strand.

23.3.2 Meselson and Stahl Experiments

The experiment was performed by Mathew Meselson and Franklin Stahl in 1958, which evaluated the three models of DNA and won Nobel Prize. In this experiment, it was concluded finally that the replication of DNA occurs according to semiconservative model. (Fig.23.12)

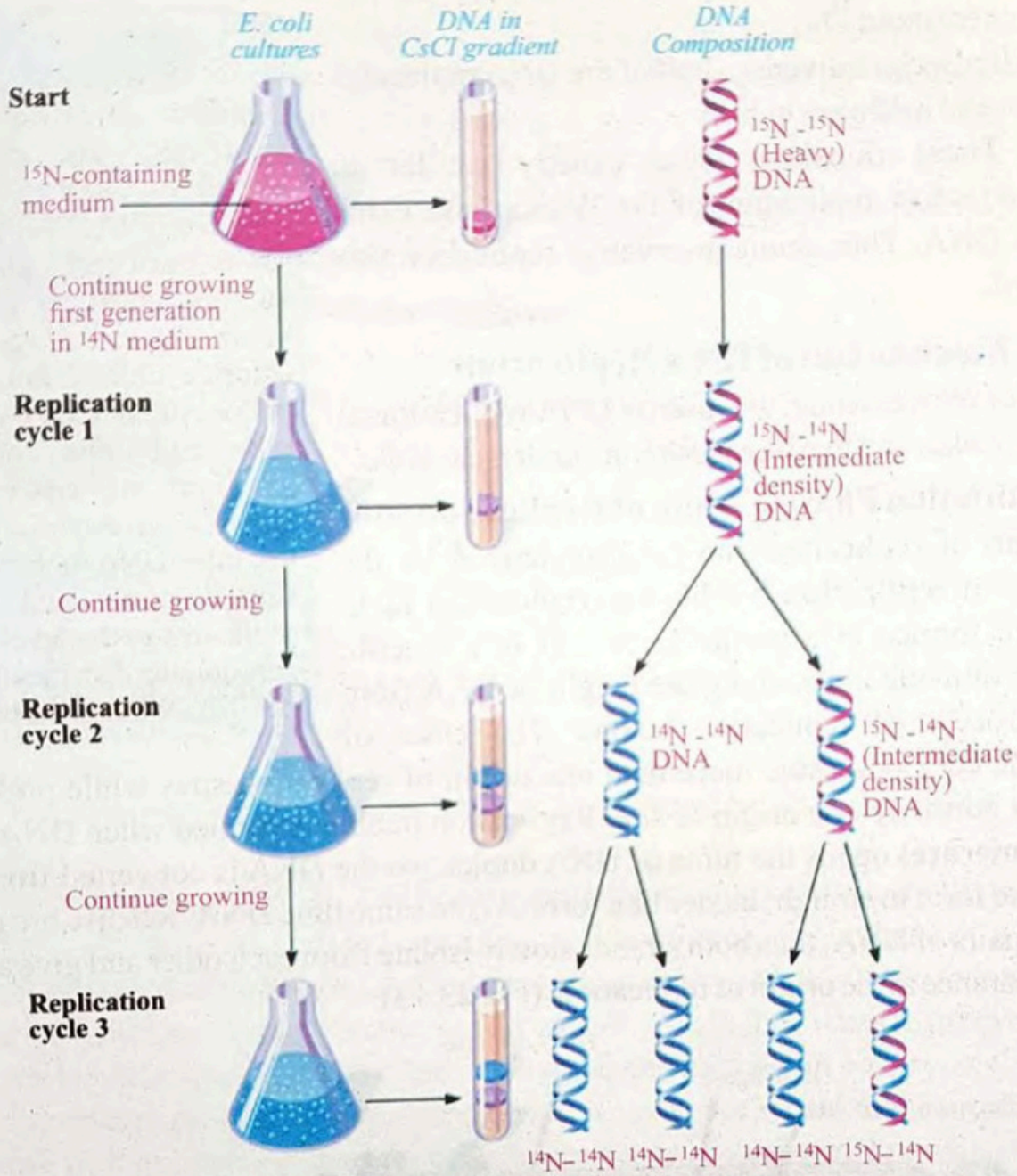

Fig. 23.12: Meselson-Stahl Experiment

The confirmation of semiconservative replication by Meselson and Stahl

The semiconservative replication of DNA was tested in 1958 by Mathew Meselson and Frank Stahl in California institute of technology.

The two scientists grew bacteria for several generations in a medium containing the heavy isotopes of ^{15}N (heavier).

So the DNA of the bacteria was eventually denser than normal (^{14}N lighter).

Now they transferred the growing bacteria to a new medium containing the lighter isotope ^{14}N. After one division only hybrid DNA molecules were in the cells (one strand

^{15}N and other strand ^{14}N).

After second division, half of the DNA molecules were light and half were hybrid.

Result: These divisions were exactly similar to semiconservative replication of the Watson and Crick model of DNA. Thus semiconservative replication was confirmed.

Extra Information

Cesium chloride (CsCl) solution were made by Meselson and Sthal, to dissolve DNA. They spun the solution at a very high speed in an ultracentrifuge for many hours. The ions of cesium and chloride pushed towards the bottom of solution containing tube and thus formed a gradient of cesium and chloride was established in the test tube. DNA molecule were settled down and formed sediments to the level of their appropriate densities ($^{15}N^{15}N$, $^{14}N^{14}N$, $^{15}N^{14}N$) in the test tube.

23.3.3 Mechanism of DNA Replication

For convenience, we discuss DNA replication in different phases and to make it easy and understandable.

1) Initiation Phase (Origin of Replication site)

The origin of replication site is characterized by the formation of **replication bubble** and **replication fork**, which are formed at a particular site. It is a specific sequence of nucleotides along the length of DNA from where process of replication begins. The DNA of eukaryotic cells possesses more than one origin of replication sites while prokaryotic DNA has normally one origin of site. Replication bubble is formed when **DNA gyrase (topoisomerase)** 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** break down the base pairs of DNA, thus both strands slowly isolate from each other and give a bubble like appearance at the origin of replication. (Fig.23.13)

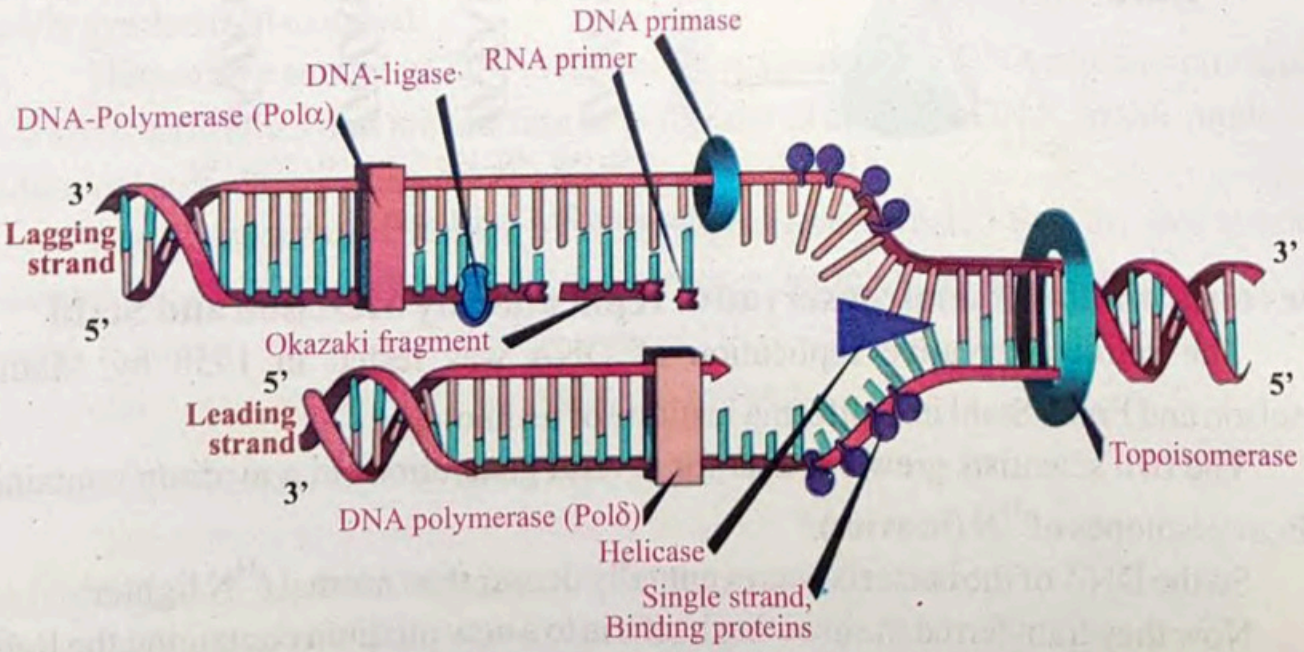

Fig.23.13: Process of DNA Replication

After breakdown of base pairs, the DNA strands are prevented to pair up again by specific proteins, known as **Single Stranded Binding (SSB)** proteins. Now, these isolated strands of DNA will act as **template strand** in next phase and direct the synthesis of daughter strands along themselves. Each side of replication bubble is now termed as replication fork which is a site on a DNA molecule at which uncoiling of the helices and synthesis of daughter molecules are both side occurring.

2) Elongation Phase (Polymerization)

This phase is referring to the formation of two types of daughter strands along the template strand *i.e.* **leading and lagging strands**. Both daughter strands are synthesized by **DNA polymerase** but this enzyme has a property that it cannot work on its own unless some nucleotides arranged on template. Therefore, **RNA primer** (a short oligonucleotide (10-20) strand of RNA) acts as initiation site for the activity of DNA polymerase. The enzyme **primase** helps in the synthesizing of primer.

Mechanism of DNA Polymerase III activity

DNA polymerase III is a dimer (made of two units) and each unit further consists of several subunits. It adds nucleotide at 3-OH group (*i.e.* carbon No.3 of deoxyribose), thus the direction of replication becomes 5′ to 3′ end (5′ carbons to 3′ carbon). One subunit of DNA polymerase III also helps in proof reading *i.e.* removes the mismatch nucleotide.

The two subunits of DNA polymerase III are interlinked by a small polypeptide chain, first subunit works on one template and continuously synthesizes a daughter strand towards **replication fork** (leading or continuous strand). While the second subunit allows to polymerize daughter strand up to a specific length then it has to jump back (100 to 200 nucleotides in prokaryotes and 1000-2000 nucleotides in eukaryotes) to a new primer to perform polymerization again. Thus the growing strand that runs away from replication fork by forming short fragments interrupted by primers known as **Okazaki fragments**. This discontinuous growing strand is called **lagging strand**.

Termination Phase

i) 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.

ii) The replacement of primers of DNA nucleotides is carried out by DNA **polymerase-I** that have dual function *i.e.* besides polymerase it also acts as exonuclease (removes primer).

iii) 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.

iv) 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.

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

Extra Information

DNA polymerase adds nucleotides in growing template strand at a rate of some 1000 nucleotide/second.

23.4 Central Dogma of Biology (Gene Expression)

All the organisms use the same basic mechanism of reading and expressing of genes, which is often referred to as **central dogma**. The genes reside in DNA. The genetic information (genes) flows down into mRNA (this process is called **transcription**), which is then converted **(translation)** to polypeptide chain (one or more polypeptide chains unite to form protein).

Thus the gene expression includes transcription and translation processes or we can say that proteins are a link between the genotype (DNA) and phenotype (synthesize of protei

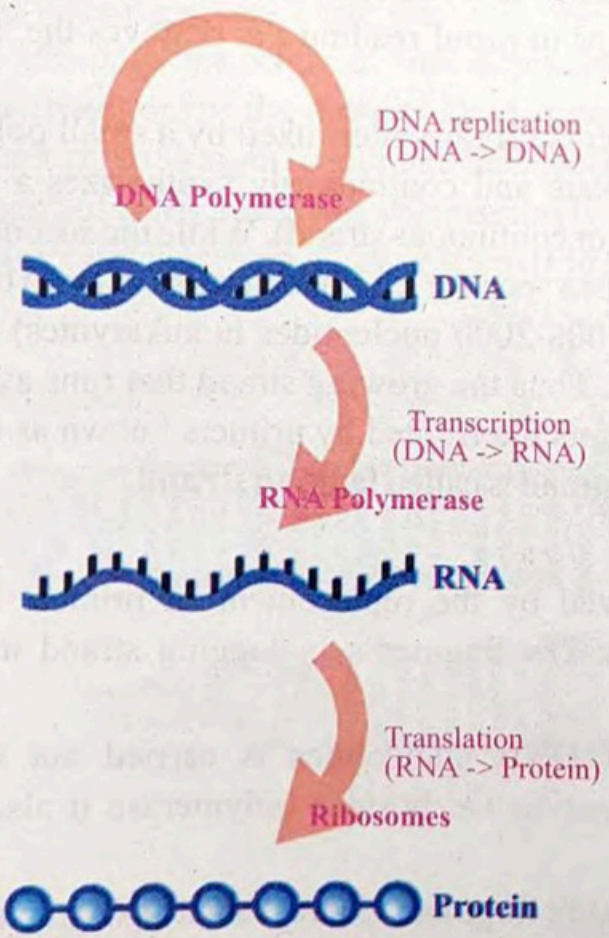

Fig. 23.14: Central Dogma of Biology

3 Types of DNA polymerase

I DNA Polymerase I: It is relatively small enzyme which catalysis the replacement of RNA primers by DNA nucleotides in termination phase of replication. Thus it provides a support to the DNA polymerase III in the main replication.

ii. DNA Polymerase II: It involves the repairing process of DNA damage during the life time of a cell.

iii. DNA Polymerase III: It is the main enzyme that synthesizes both daughter strands along the template process. It is 10 time larger and complex than other two polymerases.

23.4.1 Gene and Genetic Code

Gene is the specific sequence of nucleotides in DNA which determines the amino acid sequence of protein while **Genetic code** is the combination of three nucleotides, which specify a particular amino acid or the relationship between amino acids sequence and nucleotide sequences, known as genetic code.

The genetic codes are coded language which are placed on one of the two strands of DNA, which is called **sense or coding strand** *i.e.* 3′ to 5′ and while the other strand is called **antisense / non-coding / template strand** (*i.e.* 5′ to 3′ end). The codes are based on "alphabet" consisting of only four types of nucleotides adenine (A), guanine (G), Cytosine (C) and thymine (T). These bases are variously arranged in DNA to form code words known as codes. Each code word is a unique combination of 3′ letters (bases). During transcription these **codes** are passed (as written record) to mRNA called **codons**. The codon on mRNA eventually is

Extra Information

The three nucleotide sequence on DNA is called code while its complementary sequence on mRNA is called codon. The complementary sequence of codon on tRNA is called anticodon.

Interesting Information

Codes are universal but genetic code of mitochondrial DNA, however, showed that genetic code is not quite universal, for example, UGA instead of stop codon, it code for tryptophan amino acid, AUA instead of isoleucine code for methionine and AGA, AGG instead of arginine for stop codon.

Table 23.2: Genetic Codon

First Base of Codon	Second Base of Codon: U		Second Base of Codon: C		Second Base of Codon: A		Second Base of Codon: G		Third Base of Codon
U	UUU	Phenylalanine phe	UCU	Serine ser	UAU	Tyrosine tyr	UGU	Cysteine cys	U
	UUC		UCC		UAC		UGC		C
	UUA	Leucine leu	UCA		UAA	STOP codon	UGA	STOP codon	A
	UUG		UCG		UAG		UGG	Tryptonphan trp	G
C	CUU	Leucine leu	CCU	Proline pro	CAU	Histidine his	CGU	Arginine arg	U
	CUC		CCC		CAC		CGC		C
	CUA		CCA		CAA	Glutamine gin	CGA		A
	UUG		UCG		UAG		UGG		G
A	AUU	Isoleucine ile	ACU	Threonine thr	AAU	Asparagine asn	AGU	Serine ser	U
	AUC		ACC		AAC		AGC		C
	AUA		ACA		AAA	Lysine lys	AGA	Arginine arg	A
	AUG	Methionine met (start codon)	ACG		AAG		AGG		G
G	GUU	Valine val	GCU	Alianine ala	GAU	Aspartic acid asp	GGU	Glycine gly	U
	GUC		GCC		GAC		GGC		C
	GUA		GCA		GAA	Glutamic acid glu	GGA		A
	GUG		GCG		GAG		GGG		G

interpreted as a single amino acid in a polypeptide chain. There are total 64 codons possible from an "alphabet" of four letters. Out of 64 codons, 3′ are **non-sense codon** which act as termination or **stop codons** (UGA, UAG and UAA), while rest of 61 are sense codons that encode specific amino acids. One of this sense codon is called start codon (**AUG code for methionine amino acid**) that must be located at the beginning of all the sequences that code for amino acid chains (polypeptide). (Table:23.2)

23.4.2 Characteristics of Codons

The common characteristics of codons are:

Genetic Code is degenerative: Some amino acids are encoded by a single codon (AUG = Methionine and UGG = Tryptophan). Some other encoded by more than one codons, *e.g.* isoleucine (AUU, AUC and AUA), proline (CCU, ACC, ACA and ACG), Leucine (CUU, CUC, CUA, CUG, UUA, UUG), *etc.* This property of genetic code that some amino acids are coded by more than one codon, is called degeneracy.

Triplet codon: Three nucleotides code for one specific amino acid.

Genetic code is universal: It is same in most organisms *e.g.* AUU for isoleucine, UUU for phenylalanine.

No Punctuation: There is no punctuation between successive codon on mRNA or DNA.

Genetic Code is Non-overlapping: mRNA sequence AUGGUAGCG is not read as AUG/UGA/AGC, *etc.* it will be read as AUG/GUA/GCG. (Fig.23.15)

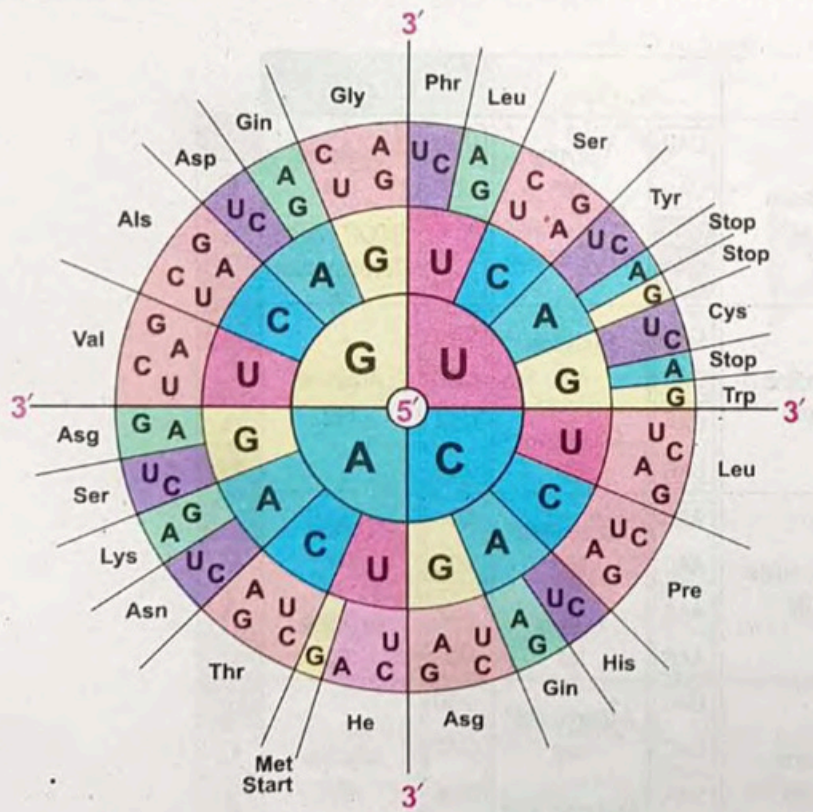

Fig. 23.15: Genetic Codon Wheel Diagram

Interesting Information

Codon is always in triplet form. Each codon consist of three nucleotides, usually cross ponding to a single amino acid.

23.4.3 Transcription

Transcription is the first step in gene expression. It involves copying a gene's DNA sequence to make an RNA molecule. RNA polymerase is the main transcription enzyme.

Extra Information

In human, 45 sense codons are recorded so far instead of 61 sense codons.

Mechanism of Transcription

The process of transcription can be divided into three phases: initiation, elongation and termination. (Fig.23.16)

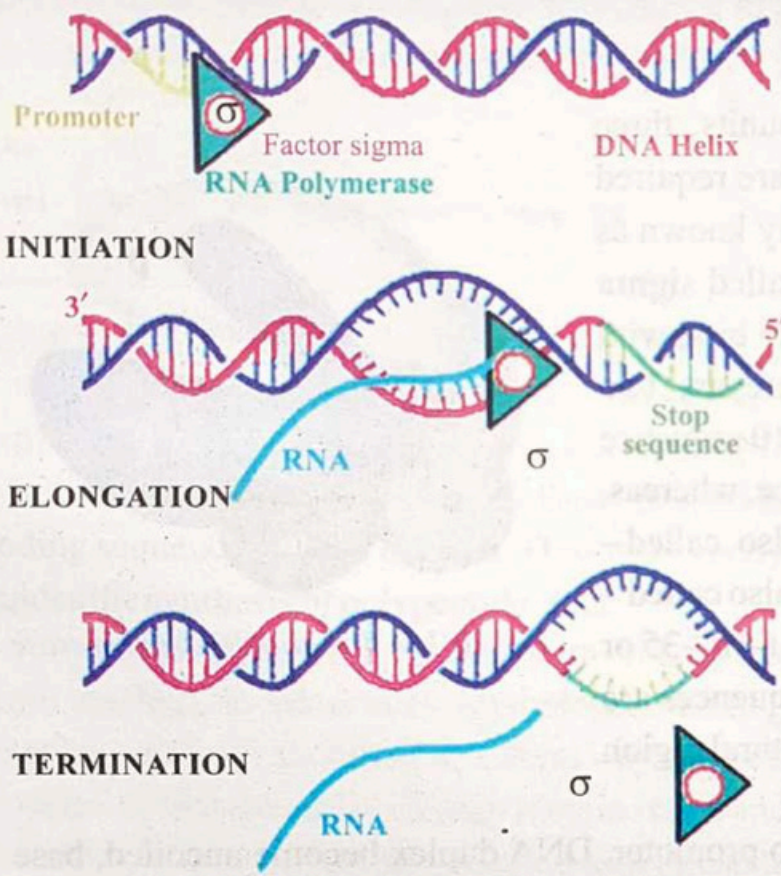

Fig. 23.16: Three steps of Transcription

Eukaryotic Cell

These cells contain membrane bound organelles including nucleus. Eukaryotic organisms may be single celled or multi celled such as human, plants, insects, birds, fungi, *etc.*

Prokaryotic Cells

These cells do not contain prominent nucleus and membrane bound organelles. These are always single celled *e.g.* bacteria and cyanobacteria.

Initiation phase

Transcription initiates with the binding of RNA polymerase at promoter region. It is regulator region of gene where binding site for RNA polymerase is located.

The RNA polymerase synthesizes RNA from **5′ to 3′ direction**. In **prokaryotes**, only one type of RNA polymerase that is responsible for the synthesis of all three major types of RNAs while in **eukaryotes**, three types of RNA polymerase, RNA polymerase-I for rRNA, RNA polymerase-II for messenger RNA (mRNA) and RNA polymerase-III for tRNA. (Fig.23.17)

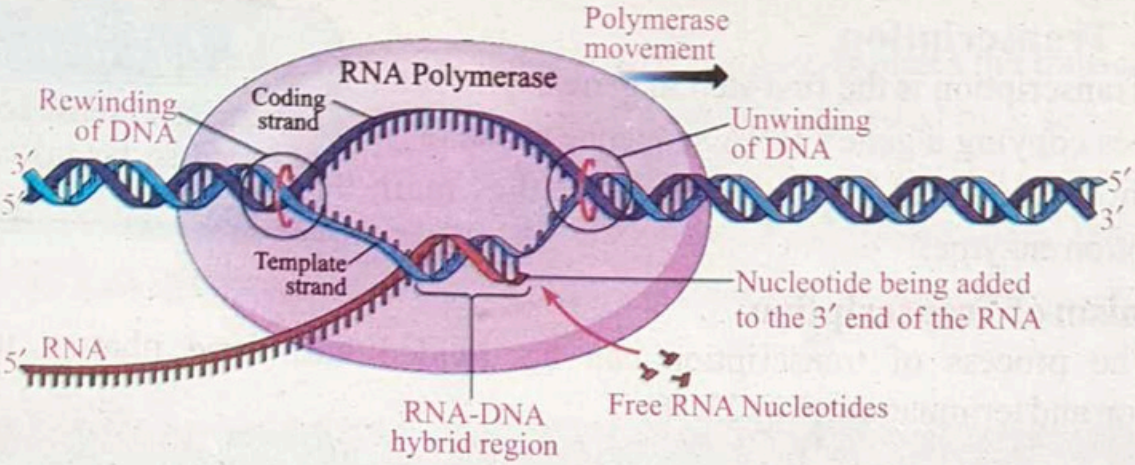

Fig. 23.17: Mechanism of Transcription

These enzymes have four subunits, three subunits *i.e.* **alpha, beta, beta prime** are required for polymerase activity and collectively known as **core enzyme**. The fourth subunit is called **sigma factor,** required for RNA polymerase to bind with promoter region. In prokaryotes, there are two binding sites *i.e.* TATAAT, also called 10 sequence and TTGACA, also called – 35 sequence, whereas, in eukaryote, **TATAAT (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.

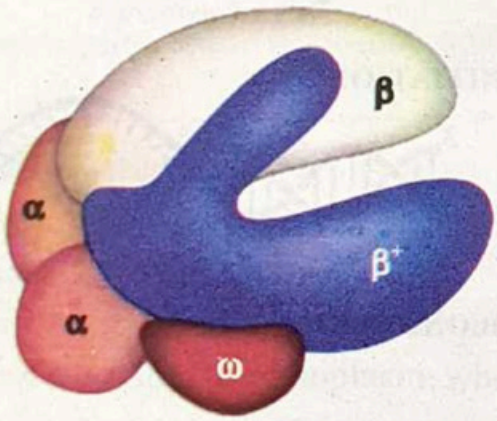

Fig. 23.18: Bacterial RNA Polymerase

When RNA polymerase binds to promoter, DNA duplex become uncoiled, base pairs are broken down and a bubble like structure called the transcription bubble, is appeared. (Fig.23.18)

Elongation Phase

This phase is also polymerization phase, as soon a sigma subunit of RNA polymerase binds to promoter, transcription begins and sigma factor is released. The rest of enzyme, which is now called core enzyme, extends the polymerization of ribonucleoside triphosphate (rNTP).

In elongation phase, RNA polymerase keeps on moving from 5′ to 3′ direction towards the terminator region. The RNA polymerase copies the DNA sequence accurately at a rate of 30 to 40 nucleotides / second.

Termination Phase

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

Table 23.3: Differences between mechanism of transcription between Prokaryotic and Eukaryotic Organisms

S.No.	Prokaryotes	Eukaryotes
i)	Three RNA polymerase enzymes are involved.	Only one polymerase enzyme is involved.
ii)	DNA is circular.	DNA is linear.
iii)	Transcription starts only from one point.	Transcription starts from may points.

24.4.4 Post Transcriptional Modification of mRNA (mRNA processing)

It is a process by which newly synthesized mRNA (primary mRNA or immature mRNA) is transformed into mature mRNA (functional mRNA).

In prokaryote, this process is not needed because it has no **intron** (non-protein coding sequence) and no nucleus. Thus it is directly released into the cytoplasm, where it guides the synthesis of polypeptide chain.

In eukaryotes, mRNA has to travel long distance from nucleus to ribosomes (cytoplasm). During this journey, mRNA is modified in several ways, cap and tail is added so that the molecule may remain stable and save the mRNA from variety of nucleases and phosphatases enzymes. The cap is the form of **GTP (7-methyl triphosphate guanosine)** which is linked with the first nucleotide of mRNA by 5 to 5 to Triphosphate Bridge. The tail is in the form of **poly A (poly-adenylic acid)** link to 3 end of the mRNA (about 30-500 nucleotides long).

Extra Information

The phosphatases and nucleases degrade nucleic acids by hydrolyzing the phosphodiester bond.

Difference between Primary mRNA and Secondary mRNA (mature RNA)

The primary mRNA in eukaryotic cells comprise many non-coding sequences called **introns** and protein coding sequences called **exons**. Thus these introns from a primary mRNA transcript are to be removed. (Fig.23.19)

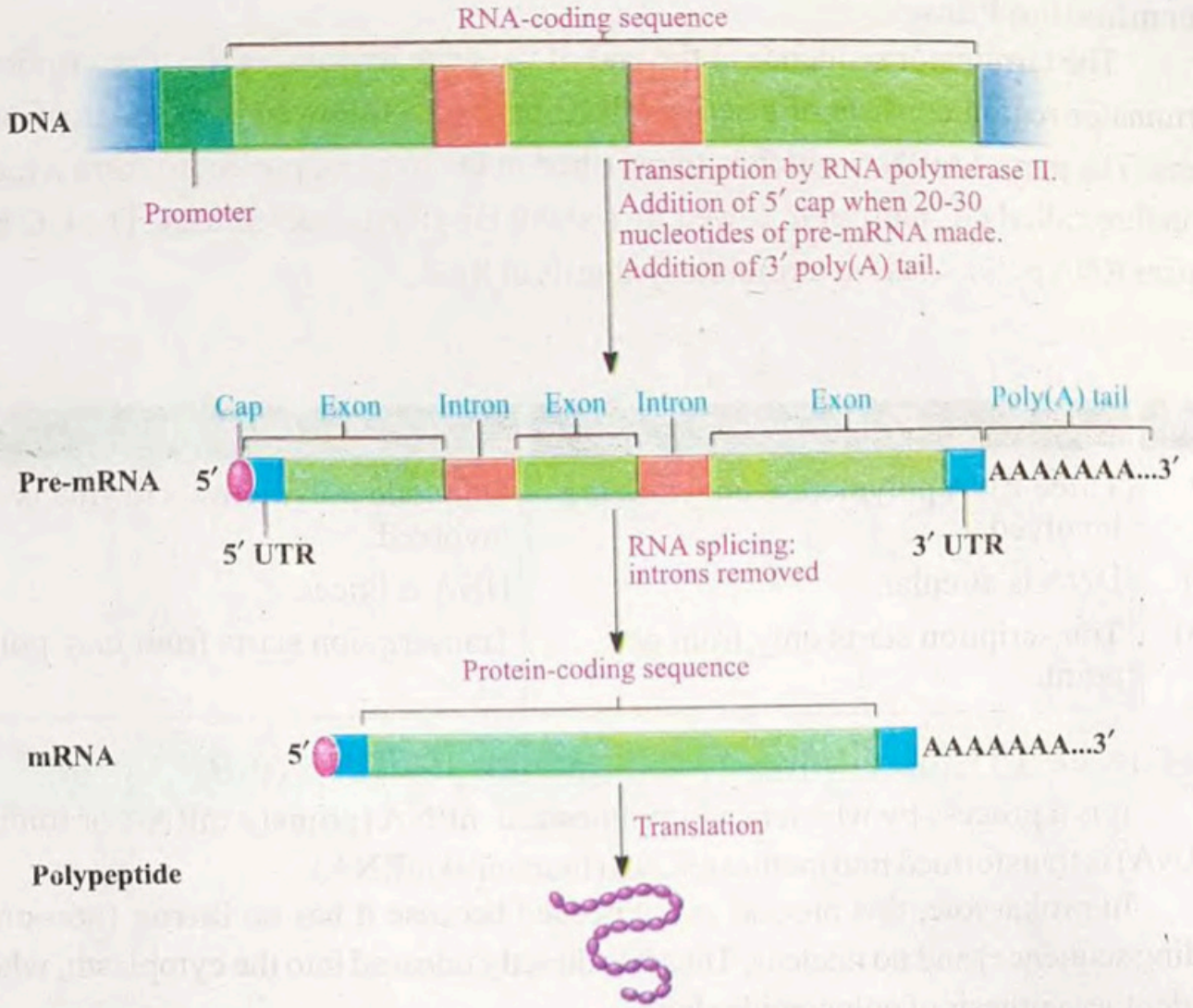

Fig. 23.19: mRNA Processing

The removal of introns and maturation of primary mRNA to **functional and secondary mRNA** is called RNA splicing. This process is completed by spliceosome. A **spliceosome** is a large and complex molecular machine found primarily, within the nucleus, which is assembled from **small nuclear RNAs (snRNA)** and approximately 80 proteins. It removes introns from a primary mRNA. Later on the spliced exon fragments are joined together with the help of **RNA ligase enzyme**.

23.4.5 Translation (Protein Synthesis)

Translation is the formation of protein with the help of RNA. It is second stage of gene expression or protein synthesis. In translation, mRNA is decoded by the ribosome to produce a specific amino acid chain (Polypeptide) that will later folds into active protein.

In **prokaryotic cells**, translation occurs freely in the cells cytoplasm while in **eukaryotic**, occurs across the membrane of the endoplasmic reticulum.

The process of translation can be divided into four phases: activation, initiation,

elongation and termination.

i) Activation

The store house of cytoplasm contains inactive amino acids. They should be activated before they react with tRNA. The amino acids are activated when they react with ATP in the presence of activating enzyme, **aminoacyl tRNA synthetase**.

Amino acid (AA) + ATP + Enzyme AA.AMP.Enzyme Complex

Now the same activating enzyme catalyzes the attachment of amino acid to specific tRNA. (Fig.23.20)

AA + AMP + Enzyme Complex + tRNA AA.tRNA.AMP.Enzyme complex

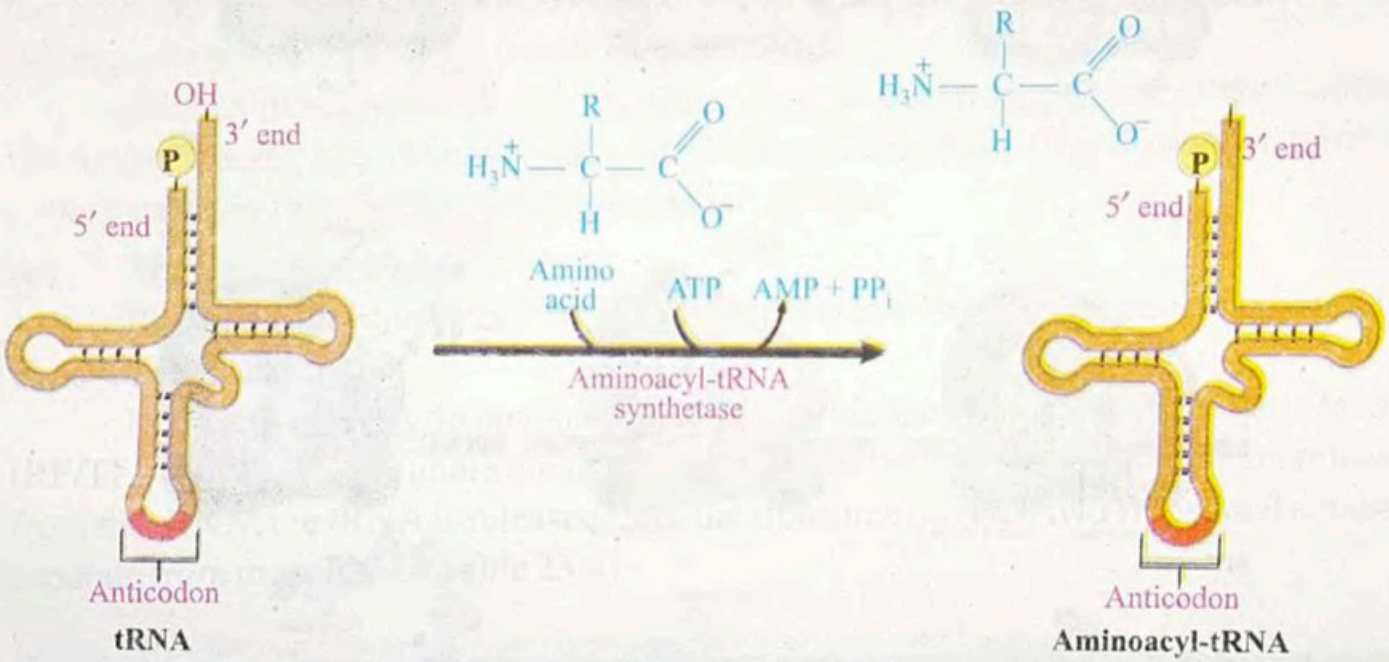

Fig. 23.20: tRNA with Activated Amino Acid

ii) Initiation (Formation of initiation complex)

First the separation of two subunits of ribosome occurs, then initial portion of an mRNA molecule binds to an rRNA molecule in a small ribosomal subunit in the presence of initiation factors (IF_3). Now a tRNA molecule carrying chemically modified initial amino acid, methionine (known as N-formyl methionine) binds to small ribosomal subunit at P-site (peptidyl site) where peptide bond will form. This binding is controlled by an enzyme called initiation factors (IF_1 and IF_2). There are two other sites which will form A-site (for aminoacyl site), where successive amino acids bearing tRNA will bind and the E-site (for exit-site) where empty tRNA will exit the ribosome.

After the initiation complex has formed, the large ribosome subunit binds to small subunit. This exposes the mRNA codon adjacent to initiating AUG codon and preparing

it for interaction with another amino acid bearing tRNA molecule at A-site. Now initiation factors (IF_1, IF_2 and IF_3) are released and reutilized. (Fig.23.21)

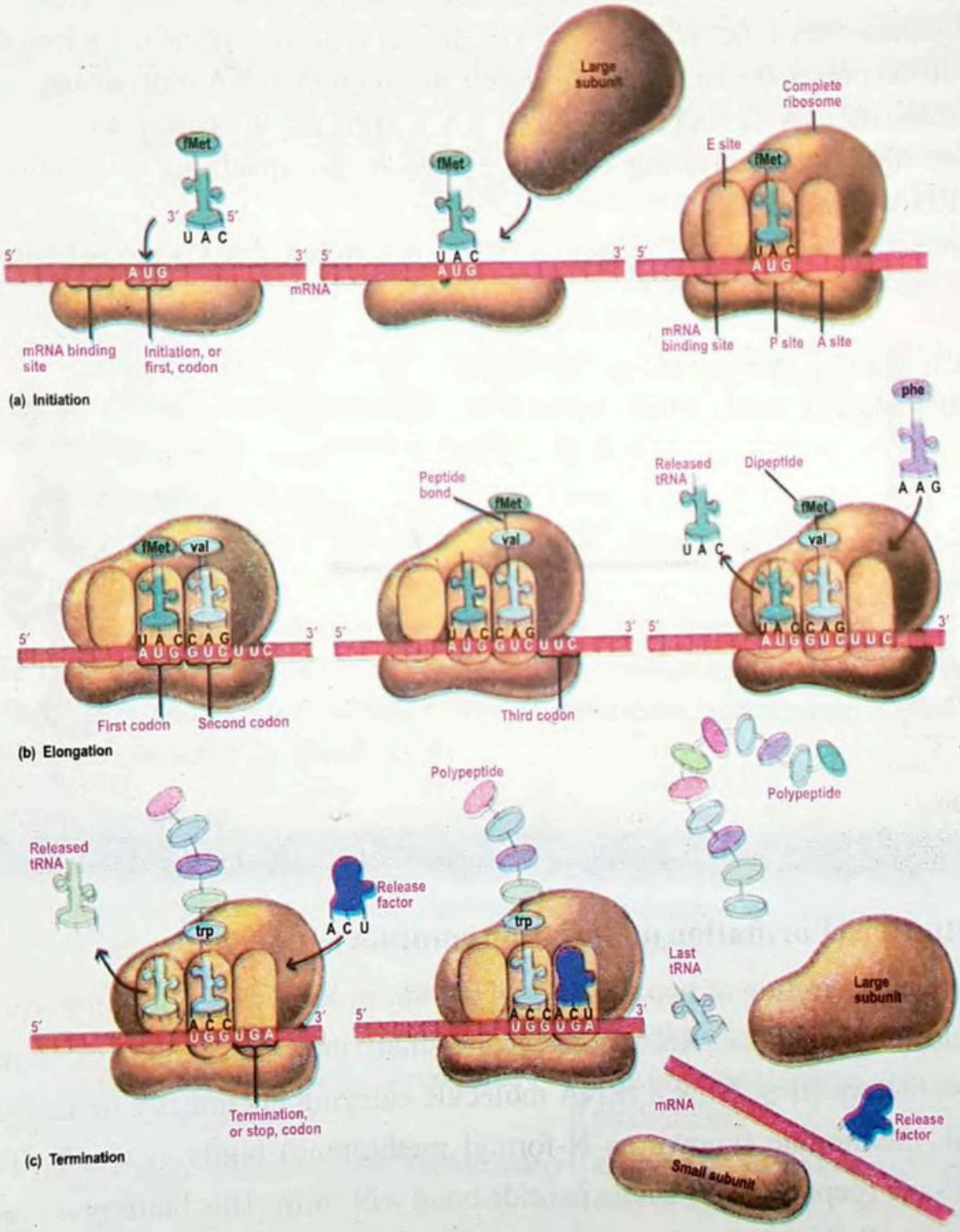

Fig. 23.21: Steps of Translation

iii) Elongation Phase

During this phase ribosomal units move along mRNA, amino acids are brought by tRNAs, which are linked together to form a polypeptide chain.

The Binding of Second Aminoacyl tRNA

When a tRNA molecule with the appropriate anticodon appears, enzyme called **elongation factors** assist in binding it to the exposed mRNA codon at the A site.

The two amino acids undergo a chemical reaction, catalyzed by the large ribosomal subunit which releases the initial methionine from its tRNA and attaches it by a **peptide bond** to the second amino acid in the presence of enzyme, **peptidyl synthetase.**

The ribosome now moves (translocate) three more nucleotides along the mRNA molecule in the $5' - 3'$ direction, guided by other elongation factors. This movement translocate the initial tRNA to the E-site and liberates it from the ribosome, repositions the growing polypeptide chain (at this point containing two amino acids) to the P-site, and exposes the next codon on the mRNA at the A-site.

When a tRNA molecule recognizing that codon appears, it binds to the codon at the A-site, placing its amino acid adjacent to the growing chain. The chain then transfers to the new amino acid and the entire process is repeated.

iv) Termination Phase

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 the release factors (RF/TF), the RF/TF 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. (Table 23.4)

Table 23.4 Difference between Protein Synthesis in Prokaryotes and Eukaryotes

S.No.	Prokaryotes	Eukaryotes
i)	Ribosomes are 70s (small subunit 30s and large 50s).	Ribosomes are 80s (small subunit 40s and large 60s).
ii)	It occurs in the cytosol of cytoplasm.	It occurs in both cytosol and endoplasmic reticulum *i.e.* in RER.
iii)	The initiating amino acid is modified N-formyl Methionine.	The initiating amino acid is modified, it is methionine.
iv)	mRNA is polycistronic (synthesis of many protein).	mRNA is monocistronic (synthesis of only one protein).
v)	Need single initiation factors.	Need more than one initiation factors.
vi)	Only one releasing factor.	Two releasing factors.

23.5 Regulation of Gene Expression

Regulation of **gene expression** means the control of amount and timing of

appearance of a gene. The genes of our body cells either turn on or turn off in response to signals that come from external or internal environment. The body of adult human being contains more than 37 trillion cells, the genome of all cells is same. However, all genes do not express in each and every body cell, only some genes are turned on. Our body is composed of about 200 types of cells, which differ on the basis of differential gene expression *i.e.* expression of different genes by cells with the same genome.

23.5.1 Importance of Regulation of Gene Expression

It is essential for both prokaryotes and eukaryotes as it increases the adaptability and versatility of an organism. The regulation of gene expression is extremely helpful to the cells for the fulfilment of their proteinaceous needs, derives the process of cellular differentiation, morphogenesis and physiology. It also helps to create different types of body cells. If regulation of gene expression is disturbed, some serious diseases may occur such as cancer.

Morphogenesis

It is shaping of an organism by embryological process of differentiation of cells, tissues and organs and the development of organ systems according to genetic "blueprint" of the organism and environmental conditions.

23.5.2 Methods of Gene Regulation

The regulation of gene expression is either positive or negative.

Regulatory protein: If the expression of gene is quantitatively increased due to the activator proteins which are specific regulatory proteins, then it is called **positive gene regulation.**

Repressor protein: If the expression of genes is seized, due to presence of some specific regulatory protein known as **repressor protein**, then it is called **negative gene regulation.**

23.5.3 Lac Operon (An Example of Negative and Positive Control of Gene Expression)

In bacteria and viruses, a cluster of genes having related functions that are regulated as a unit is called an **operon**. These genes are:

1. **Structural genes**, which direct the synthesis of enzymes having related functions.
2. A **promoter**, which marks the starting point for transcription of the genes.
3. An **operator**, which acts as an on or off switch. The operator region is either located within the promoter or overlaps it and is the region that serves as a binding site for RNA polymerase.

***Escherichia coli* (*E. coli*)** is one of the bacterium species, scientists study to learn about gene expression in prokaryotes. Interestingly, scientists discovered that if the sugar lactose is not present in the environment of a population of *E. coli*, the bacterium has very few enzymes present within their cells that can take lactose into the cell and break it down. *E. coli* is "fed" on lactose, such as when you drink a glass of milk, the bacterium quickly manufactures the enzyme that does this job. Scientists discovered that the metabolism of lactose in *E. coli* is programmed by a cluster of genes they named the **lac operon**. (Fig.23.22)

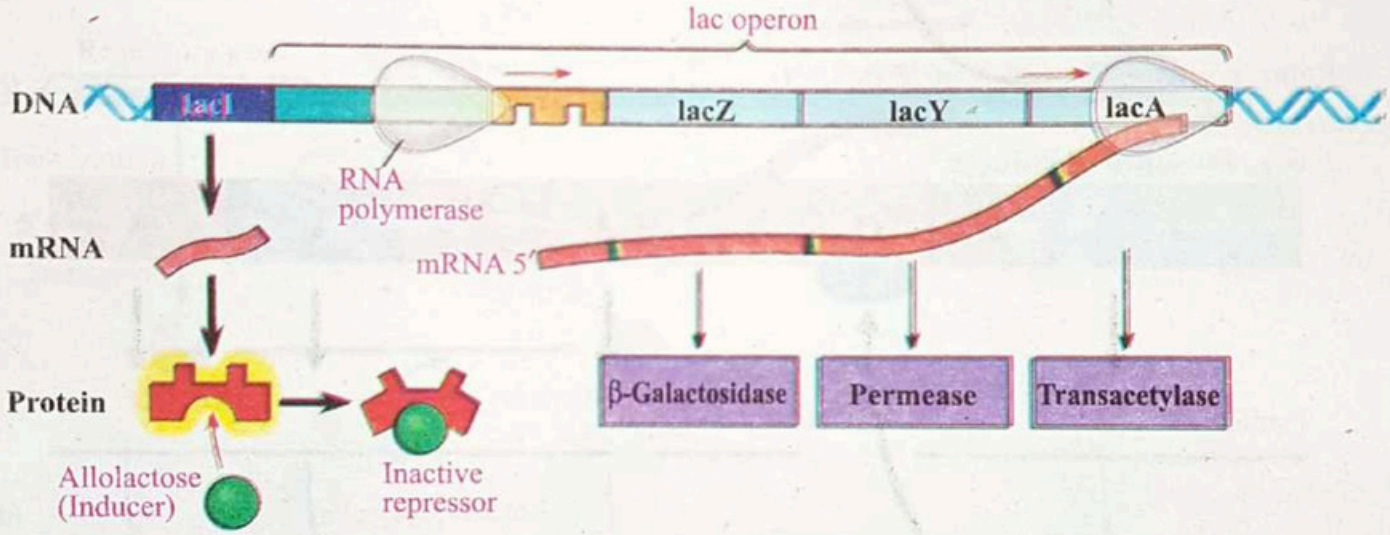

Fig.23.22: Lactose Present, Repressor Inactive, Operon on

The lac operon has three genes (**lac-Z, lac-Y and lac-A**) that direct the synthesis of enzymes that metabolize milk sugar (lactose). It has become one of the most widely studied operons in bacteria and is often used as an example of gene expression in prokaryotes.

Mechanism of Negative Control

The lac operon is on (meaning it is transcribed) until transcription is switched off (block). This type of system operates, by **negative control**. The off switch is a protein known as the **lac repressor**, which is produced by a regulatory site and fit into the operator region of the lac operon like key fits into a lock. Thus it blocks the attachment of RNA polymerase to the promoter and transcription cannot occur. When lactose is present in the cells environment, however, it binds to the repressor, changes its shape. The repressor is no longer able to bind to the operator, and the cell is able to produce the enzymes that direct the metabolism of lactose. (Fig.23.23)

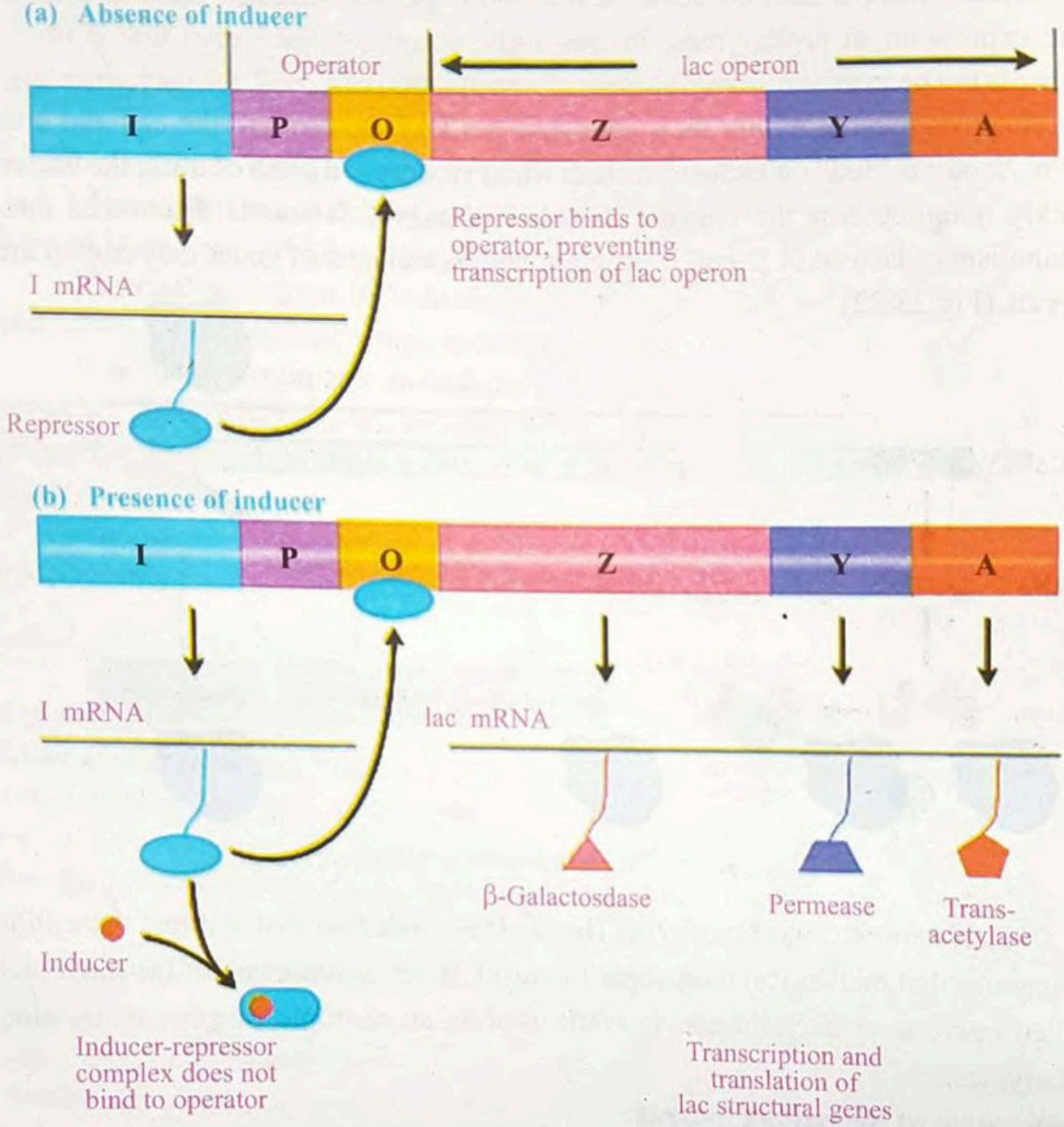

Fig.23.23: Mechanism of Negative control of Gene Expression

Mechanism of Positive Control

The lac operon is on unless it is switched off by a repressor; some operons must be switched on by proteins called activators. This type of control is called **positive control**. Activators bind to a specific nucleotide sequence at or within the promoter and stimulate transcription. Operons regulated by both activators and repressors have both positive and negative control. Regulatory sites code for activators proteins as well as for repressor proteins. (Fig.23.24)

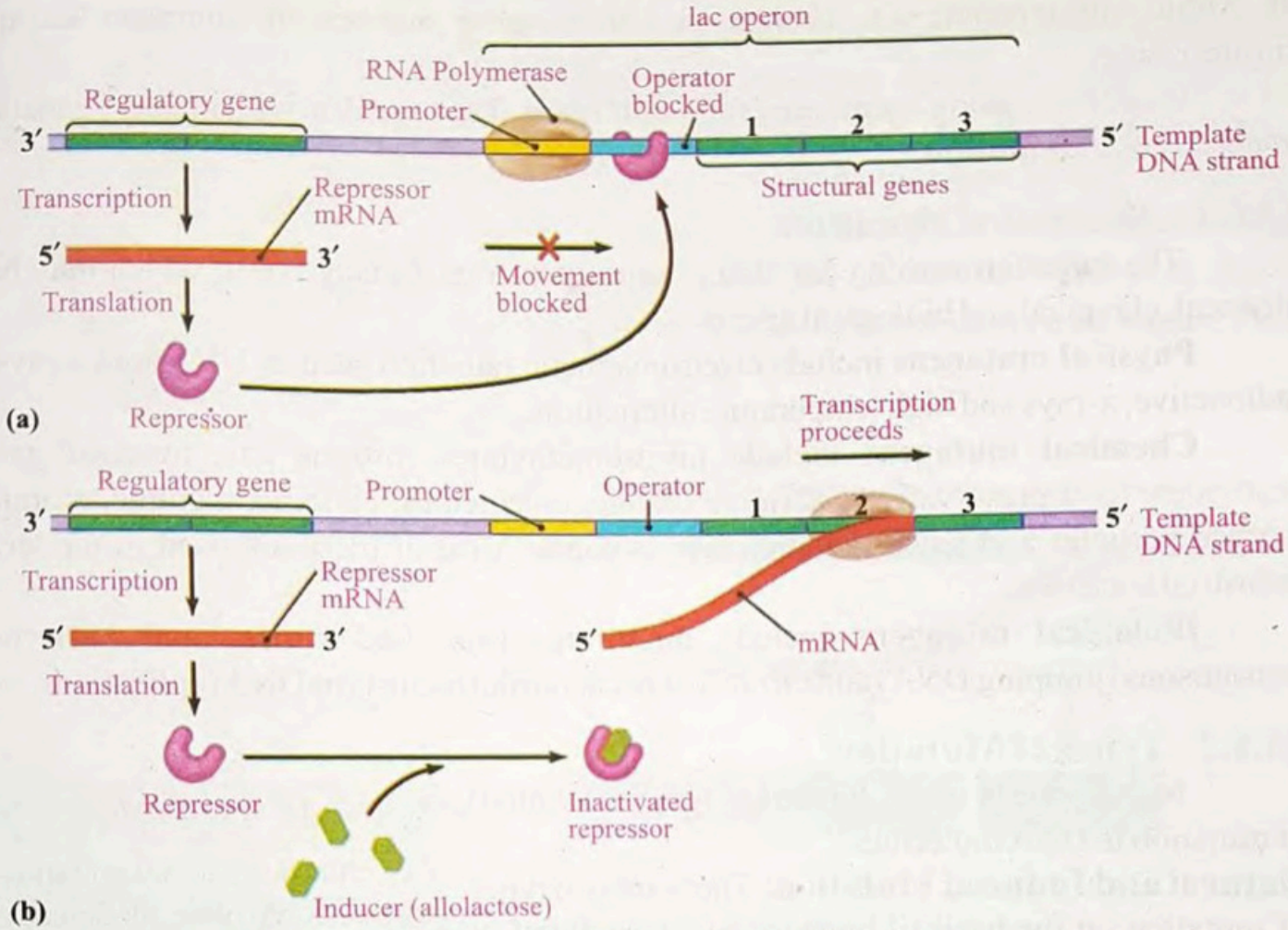

Fig.23.24: Mechanism of Positive Control of gene Expression

23.5.4 Relationship of Gene Expression with Introns and Exons (in Eukaryotes)

In eukaryotes primary mRNA is processed in the nucleus and then mature mRNA is exported to the cytoplasm provides many opportunities for regulating gene expression that are not available in prokaryotes. Such as the regulation at RNA processing level is alternative RNA splicing, in which different mRNA molecules are produced from the same primary transcript, depending on which RNA segments are treated as exons and which as introns. Regulatory proteins which are specific to a cell type control intron-exon choice by binding to regulatory sequences within the primary transcript.

23.6 Mutation

Mutation is an alteration in the genetic material (genome) of a cell of a living organism or of a virus that is more or less permanent and make up a new allele in the population. It can be transmitted to the cells or the virus descendants. Mutation range in size from change in a single DNA nucleotide (codon) to a large segment of chromosome

or whole chromosome *i.e.* change in chromosome number or complete set of chromosome.

Mutation causing agents are called **mutagens**. The organism with mutated genetic material is called **mutant**.

23.6.1 Sources of Mutation

The mutation causing agents *i.e.* **mutagens** are of many types, which may be physical, chemical and biological agents.

Physical mutagens include electromagnetic radiation such as UV, gamma rays, radioactive, x-rays and high temperature alternation.

Chemical mutagens include nitrosomethylurea, nitrous gas, mustard gas, pesticides, food preservatives, acridine orange, colchicines, caffeine, nicotine, atomic oxygen particles and reactive radioactive isotopes. Most of these are used in modern industrial societies.

Biological mutagens include micro-organisms like viruses and bacteria, transposons (jumping DNA) and errors that occur during meiosis or DNA replication.

23.6.2 Types of Mutation

Mutagenesis is the formation (origin/creation) of mutation in DNA molecules.

Natural and Induced Mutation: There are two types of mutation on the basis of mutagenesis, *i.e.* natural or spontaneous and induced. The **spontaneous mutation** takes place naturally and automatically due to internal or external factors. The **induced mutation** is occurred by external factors for the establishment of new verities of organisms.

Alkaptonuria

It occurs due to point mutation there is enzyme deficiency and homogenitsic acid does not further change into 4-maley acetic acid. Thus urine becomes black when expose to air.

Gene and Chromosomal Mutation: There are two other types of mutations on the basis of site of mutation and to what extent *i.e.* gene mutations and chromosomal mutations.

i) Gene Mutation may be point mutations and frame shift mutations.

Point mutation causes

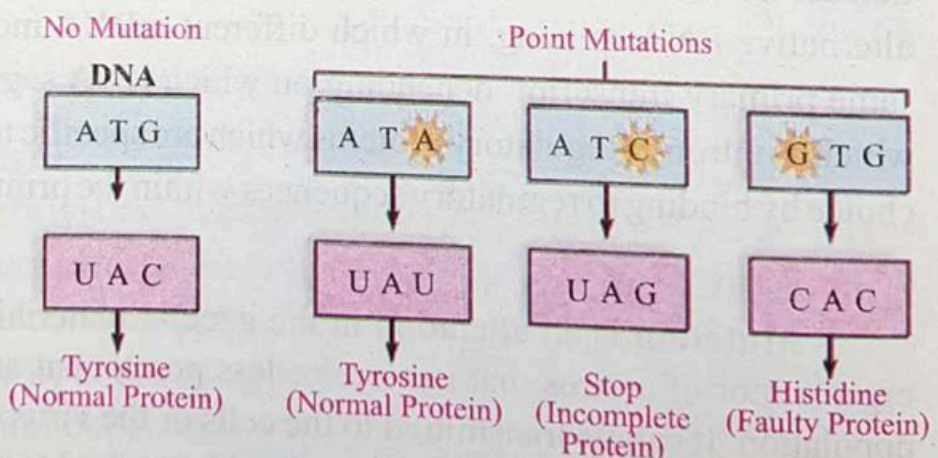

Fig.23.25: Point Mutation

change of one or few nucleotides in the DNA. Some point mutations occur due to spontaneous pairing errors (purine replaced by purine, pyrimidine replaced by pyrimidine, purine replaced by pyridine and vice versa) *e.g.* sickle cells anaemia, phenylketonuria. (Fig.23.25)

In **frame shift mutation** one or more nucleotides either deleted or inserted in the DNA of gene. This results in completely new sequence of codon and a non-functional protein is produce. Thus it is fatal. (Fig.23.26)

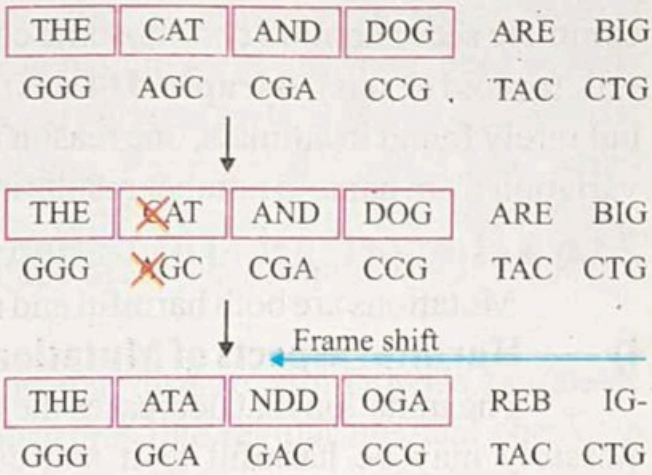

Fig. 23.26: Frame Shift Mutation

ii) Chromosomal Mutation or Chromosomal Aberration: This type of mutation causes change in the structure or number of chromosomes.

Change in Chromosomal structure occur during meiosis, when due to certain mutagen chromosome is broken down into many pieces but later on reunite, its new pattern become change from original one.

These may be:

Deletion or Deficiency

Deletion or deficiency, as the name shows is the loss of a segment of a chromosome or of a part of the genes.

Duplication

When a part of chromosomes is repeated or present more than once, it is called **duplication** *i.e.* segment of a chromosome is in excess.

Inversion

When a part of chromosome becomes inverted it is called **inversion**. It can be identified genetically by the alteration of the genetic map of the chromosome.

Translocation

Transfer of a segment of chromosome to a non-homologous chromosome is called **translocation**.

23.6.3 Change in Chromosome Numbers

This occurs due to non-disjunction during meiosis, change in chromosome number due to addition or loss of one or more chromosomes is called **aneuploidy.** Exampies are, **monosomy** (2n – 1) *e.g.* Turner's syndrome, **nullisomy** (2n – 2) loss of a pair of chromosomes, **Trisomy** (2n+1) *e.g.* Klinefilter's syndrome and Down's syndrome, Tetrasomy (2n+2) addition of a pair of homologous chromosomes.

There is another condition in which an organism shows a change in one or more

complete set of haploid chromosome called **euploidy.** Examples are, **monoploid** (single set), triploid (3 sets), **tetraploid** (4 sets), **pentaploidy** (5 sets), *etc.* It is favorable in plants but rarely found in animals, one reason is that the sex balance is important in animals and variation from haploid number results in sterility.

23.6.4 Importance of Mutations

Mutations are both harmful and useful for organisms.

i) Harmful aspects of Mutations

The mutation that decreases the fitness of organisms in their environments, which possibly may be harmful to it and causes serious effect *e.g.* cancer, developmental abnormalities like cleft palate, microcephaly, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, heredity disorders like sickle cell anaemia, haemophilia, *etc.*

ii) Useful aspects of Mutations

Sometime mutation increases the fitness of organisms to their environment. It is also helpful to originate new species *i.e.* evolution because less favorable mutations are removed from the gene pool by natural selection. The more favorable ones tend to accumulate which ultimately leads to origin of new species by natural selection.

23.6.5 Chromosomal Mutation or Chromosomal Aberrations

There are many types of chromosomal mutations. Here we will discuss causes, symptoms and possible treatment of some of these.

i) Down's Syndrome

It is also called **mongolism**. The affected person contains an extra autosomal chromosome number 21 (trisomy 2n+1). It was first described in 1866 by J. Langdon Down. For this reason, it is called Down's Syndrome. (Fig.23.27)

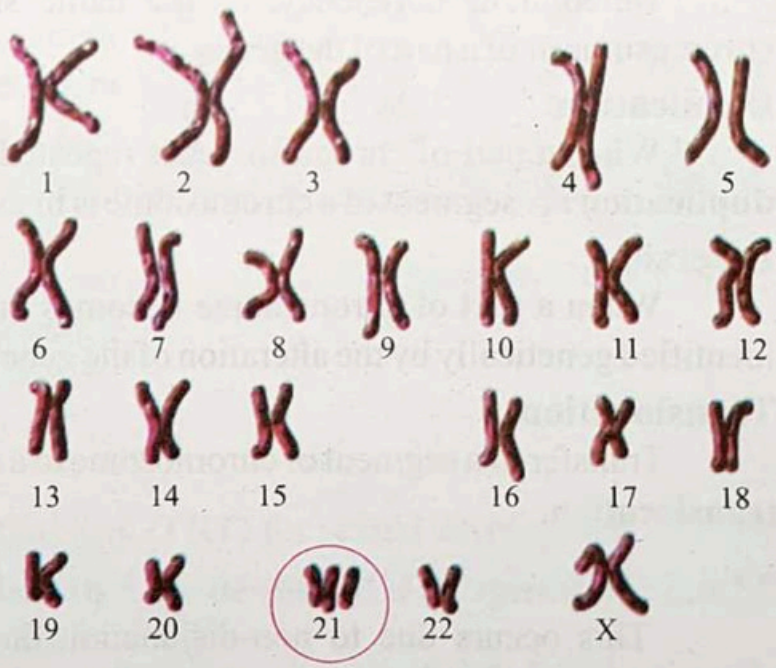

Fig. 23.27: Down's Syndrome

Cause:

During gamete formation, the non-disjunction occurs in autosome number 21st and the resulting gamete (either egg or sperm) with 24 chromosomes is produced. The fertilization of such gametes produces a child having 47 chromosomes (2n+1).

Symptoms of Abnormalities: In the individuals the maturation of skeletal system is delayed, so person having Down's syndrome are generally short and have poor muscle tone, in addition, they are mentally retarded, defected nervous system and blood vascular system. Some other symptoms are protruding tongue, flat nose, flat broad face, small ears, small mouth, short hands with short fingers, gap between, large toe (thumb) and second toe, rounded head, excessive skin at the nape of the neck, squint eyes. Their life expectancy is approximately 16 years.

Treatment: There is no treatment for chromosomal disease. But Down's syndrome can be managed to some extent by taking few measures like regular medical check-up and screening medications, surgery, counselling and support.

ii) Klinefelter's Syndrome

It is sex chromosome non-disjunction, occurs only in male. Dr. Henry Klinefelter described it in 1942.

Cause and Symptoms: If the XX gamete joins a Y gamete, the result is quite serious. The XXY zygote develops into a sterile male who has, in addition to male genitalia and male characteristics, also possesses some female characteristics, such as breast, high pitched voice, some have a lower than average intelligence (occur in about 1/600 male birth). They are sterile, because small testes (no sperm productions), poorly developed male secondary sexual characters, wide hips like female, tendency to tallness, long legs, short trunk and shoulder equal to hip size. (Fig.23.28)

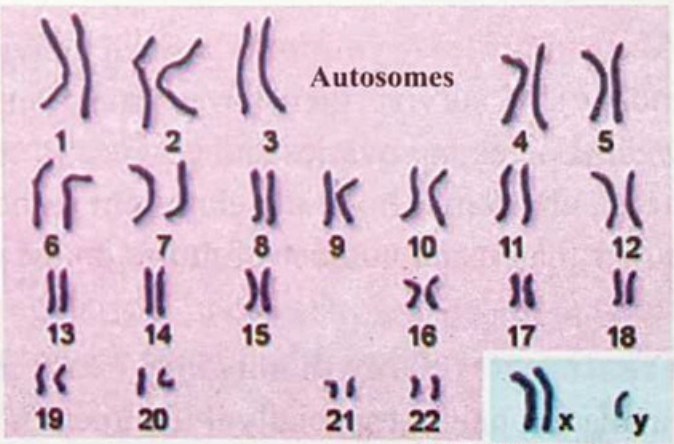

Fig. 23.28: Klinefilter's Syndrome

Treatments

- **Testosterone Replacement Therapy (TRT)** for sexual development like males around the age of puberty, it can help a boy have more normal body development. They can live normal, confident boy-like life.
- The **treatment usually continues throughout a man's life** but does not help infertility.

iii) Turner Syndrome

It is found in females with missed X-chromosome **2n-1(44+XO)**. The (44+XO) is female, (44+OY) is male who cannot survive.

Cause: It is caused by **non-disjunction of sex chromosomes pair** during paternal or maternal meiosis. The normal females have two X chromo-somes, but in Turner syndrome one of the X chromosomes is absent *i.e.* with only 45 chromosomes (44 autosomes + Y, or 44 autosomes + X). In 1938, Henry Turner first described it. (Fig.23.29)

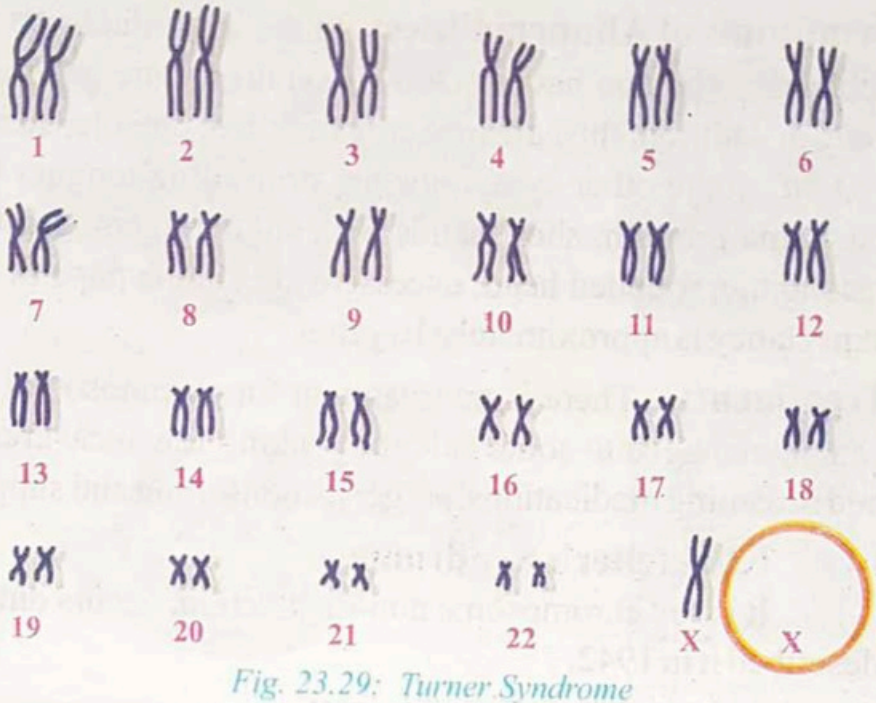

Fig. 23.29: Turner Syndrome

Abnormalities (Symptoms): Such individuals do not survive long pregnancy (aborted mostly), if survive then have female appearance. They have short stature (height), webbed neck, no ovaries and germ cells *i.e.* infertility, a low **hairline** at the back of the **neck, abnormal bone development** (especially the bones of the hands and elbows), a larger than usual number of **moles** on the skin, **oedema** or extra fluid in the hands and feet.

Treatments: **Growth hormone** treatments can improve growth and influence a girl's final adult height especially if treatment is started early enough in childhood. **Estrogen replacement treatment (ERT)** helps the girl develop the physical changes of puberty, including breast development and menstrual periods. This treatment is often started when a girl reaches about age 12 or 13.

23.6.6 Gene Mutation

Some examples of gene mutations are as under:

Sickle Cell Anaemia

The sickle cell anaemia is also known as **Hemoglobin SS disease (Hb SS).**

Cause: It is autosomal recessive trait, which is caused by, Point Mutation-Base substitution, a defect in hemoglobin. Acutely the 6^{th} amino acid *i.e.* **glutamic acid** in the **beta** chain of the normal hemoglobin is replaced by **valine.** The abnormal sickle cell hemoglobin is called Hb^S which have **lost the oxygen binding capacity**. Due to this hemoglobin the **shape of the red blood cells** is changed. The red blood cells become **crescents or sickles shaped.** These cells **deliver less oxygen to the body's tissues.**

Sickle cell anaemia is due to homozygous recessive gene which he or she may get from their both parents. (Fig.23.30)

Symptoms: The **painful Episodes** (called crises) which can last from hours to many days. These crises can cause pain in the bones of the back, the long bones, and the chest. When the anaemia becomes more severe, symptoms may include: fatigue, fever, paleness, Jaundice damage various organs. Rapid heart rate shortness of breath.

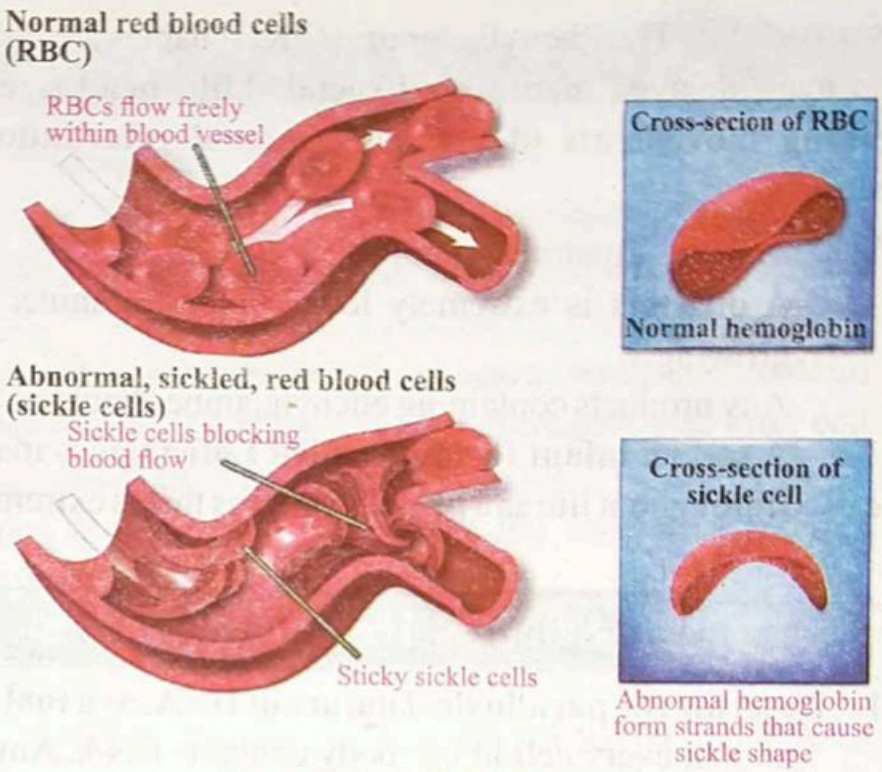

Fig. 23.30: Sickle Cell Anaemia

Treatment: The goal of treatment is to manage and control symptoms to limit the number of crises.

For A Sickle Cell Crises Includes

Blood transfusions (may also be given regularly to prevent stroke); **Medicines** to relieve crises and plenty of **Fluids**. **Bone marrow or Stem cell transplants** can cure sickle cell anaemia. **Folic acid** supplements should be taken.

Phenylketonuria (PKU)

A rare (Point mutation) condition in which a baby is born with the inability to properly break down an amino acid phenylalanine is called Phenylketonuria.

Cause: It is also due to **autosomal homologous recessive gene.** In a healthy baby phenylalanine is converted into **tyrosine** by the enzyme **phenylalanine hydroxylase**, while affected baby possess defective enzyme, which converts phenylalanine into toxic phenylketones, that accumulate and **damage central nervous system.** (Fig.23.31)

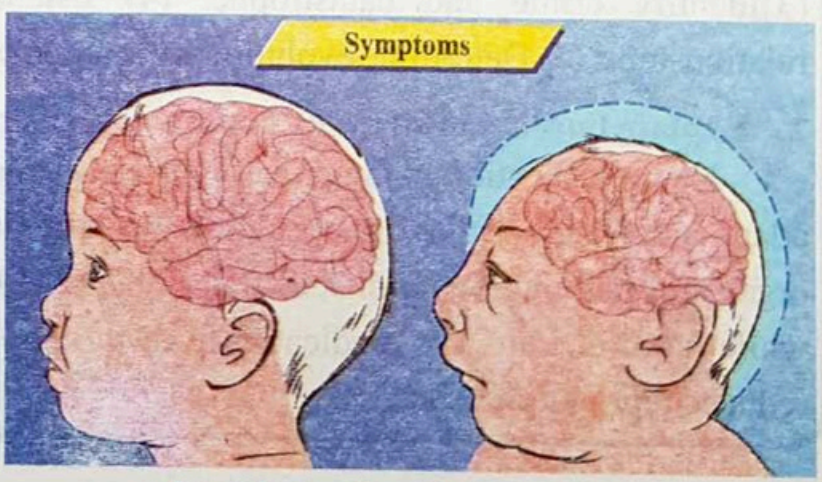

Fig. 23.31: Phenylketonuria

Symptoms: The Phenylketonuria (PKU) babies are characterized by lighter **skin, hair** and **eyes**, delayed **mental and social skills**, **head size** below normal, **hyperactivity, jerking movements of arm/legs**, **mental retardation**, **seizures**, **skin rashes** and **tremors**, *etc.*

Treatments: Treatment involves:

- A diet that is extremely low in phenylalanine, particularly when the child is growing.
- Any products containing phenylalanine should be avoided such as, milk, eggs.

A special **infant formula called Lofenalac** is made for infants with PKU. It can be used throughout life as a **protein sources** that is extremely low in phenylalanine.

Science, Technology and Society (STS)

1. Describe the paradoxical nature of DNA, as a tool of geneticists and forensics.

Almost every cell in our body contains DNA. Any two people share on average 99.9% of their DNA meaning that only 0.1% of your DNA is unique to you. Each human cell contains 3 billion DNA base pairs. Out of these 3 billion base pairs 3 million are different. That's more enough to provide a profile that accurately identifies a person. DNA is often left behind a crime scene in the form of hair, blood, saliva and semen. To identify individuals, forensic scientists have scanned 13 DNA regions or loci that vary from person to person and use the data to create a DNA profile of that individual (sometimes called a DNA fingerprint). Some examples of DNA uses for forensic identification: (1) Identify potential suspects whose DNA may match evidence left at crime scenes. (2) Exonerate persons wrongly accused of crimes. (3)Identify crime and catastrophe. (4) Establish paternity and other family relationships. (5) Determine evolutionary relationships, *etc.*

2. Explain how harmful mutations have been eradicated by nature.

Natural selection is the process through which populations of living organisms adapt and change. A harmful mutation is a mutation that decreases the fitness of the organisms. Through natural selection favourable traits are transmitted to generation while harmful traits are eradicated from the population due to premature death or reduced reproductive success.

SUMMARY

- The term "Chromosome" was proposed by Waldeyer.
- Each typical chromosome consists of two strands known as chromatids and both are attached with each other at a point known as centromere or primary constriction.
- Heterochromatin in highly condensed and unexpressed region while euchromatin is highly condensed during cell division while become non-condensed after cell division and the genes of this region are also expressed.
- Hershey and Chase claimed that the virus DNA, not the virus protein, was hereditary material.
- Replication bubble is formed when DNA helicase and topoisomerase enzyme work at origin of replication.
- The complete strand of DNA is known as antisense because mRNA is complementary to this strand.
- The genetic codes are almost same in all organisms thus known as universal.
- In translation mRNA is decoded by the ribosome to produce a specific polypeptide that will later fold into an active protein.
- The natural and automatic mutation occurs due to internal or external factors are called spontaneous mutations.
- Down syndrome is characterized by trisomy (2n+1) *i.e.* having an extra copy of 21st autosome.
- The strand of the DNA, which is transcribed is called coding or sense strand.
- The agents that cause mutations are called mutagens.
- Klinefelter's syndrome is characterized by 2n+1 (44+XXY), i.e., trisomy of sex chromosomes.
- Turner syndrome is characterized by 2n-1 (44+OX) or (44+OY).
- The gene mutation makes up a new allele in the population.
- Phenylketonuria and sickle cell anaemia are the examples of gene mutation.
- Organism or cell in which mutation is occurred is called mutant.

EXERCISE

SECTION-I: OBJECTIVE QUESTIONS

Multiple Choice Questions (MCQs)

A. Select the correct answer

1. Morphological characteristics of chromosomes are collectively called:
   (a) Holotype (b) Karyokinesis
   (c) Karyotype (d) Neotype
2. Mongolism is also known as:
   (a) Down's syndrome (b) Klinefelter's syndrome
   (c) Turner's syndrome (d) Jacob's syndrome
3. All are related to turner's syndrome, except:
   (a) Short stature (b) Webbed neck
   (c) Broad face (d) Without ovaries
4. The human chromosomes are composed of
   (a) DNA+RNA (b) DNA+Lipid
   (c) DNA+RNA+Protein (d) DNA only
5. Synthesis of a new DNA strand begins with
   (a) a DNA primer (b) an RNA primer
   (c) an Okazaki fragment (d) DNA polymerase I
6. The chromosomes were first discovered in 1882, by
   (a) Morgan (b) Walther Fleming
   (c) Carl Correns (d) Waldeyer
7. The number of chromosomes in Monkey is
   (a) 46 (b) 48
   (c) 50 (c) 44
8. The strand of DNA that elongate towards the replication fork
   (a) Lagging (b) Leading
   (c) Primer (d) Okazaki
9. The number of tRNA in human are
   (a) 45 (b) 60
   (c) 61 (d) 35
10. Anticodons are present on
    (a) mRNA (b) tRNA
    (c) DNA (d) rRNA

11. The initiation codon is
(a) UUA (b) ACC
(c) AUG (d) GCG

12. Down's syndrome is autosomal non-disjunction of chromosome number
(a) 21 (b) 22
(c) 13 (d) 18

13. Which condition appears due to point mutation
(a) Turner's syndrome (b) Klinefelter's syndrome
(c) Sickle cell anaemia (d) Down's syndrome

B. Fill in the blanks.

1. The name chromosome was assigned by .....
2. The number of chromosome in frog is .....
3. The copying of mRNA from DNA is called .....
4. The strand of DNA that runs from replication fork is called .....
5. The sequence of 3 nucleotides on mRNA is called .....
6. Both UUU and UVC are codon of ..... amino acid.
7. The syndrome having trisomy of chromosome No.21 is ..... syndrome.
8. Phenylketonuria is an example of ..... mutation.
9. If a person has 44 autosomes + XXY, he will suffer from .....
10. Change in DNA structure is called .....

SECTION-II: SHORT QUESTIONS

C. Give the short answers of the following questions.

1. Differentiate between heterochromatin and euchromatin.
2. Write any three parallel behaviors between genes and chromosome.
3. Explain types of chromosomes on the basis of centromeric position.
4. Differentiate between conservative model and dispersal model of DNA replication.
5. Define RNA primer, primase and ligase.
6. Write difference between leading strand and lagging strand.
7. Write any three characteristics of codons.
8. Describe importance of regulation of gene expression.
9. Write differences between physical and chemical mutagens.
10. Describe useful aspects of mutation.
11. Describe harmful aspects of mutation.

12. Write cause of sickle cell anaemia.
13. Write treatment of phenylketonuria is possible.
14. Write the symptoms of Down's Syndrome.
15. Write symptoms of Turner's syndrome.

SECTION-III: EXTENSIVE QUESTIONS

Give detailed answers of the following questions.

1. Explain structure of chromosome.
2. Describe in detail the composition of chromosome.
3. Illustrate the experiment performed by Hershey-Chase.
4. Describe elongation phase of DNA replication.
5. Describe molecular concept of a gene.
6. Describe the experiment of Fredric Griffith.
7. Explain gene and genetic code.
8. Describe post transcriptional modification of mRNA.
9. Explain how prokaryotic and eukaryotic protein synthesis differ from each other.
10. Write an essay on Down's syndrome.