BIO 1412 - MOLECULAR BIOLOGY AND GENETICS.

1 DNA REPLICATION.
- 1.1 Semi Conservative DNA replication. ✓
- 1.2 Experiments of Meselson and Stahl. ✓
- 1.3 Enzymes involved and their roles. ✓
- 1.4 Leading and lagging strand synthesis. ✓

2 DNA TRANSCRIPTION.
- 2.1 Prokaryotic transcription.
- 2.2 Eukaryotic Post-transcription modification.

3 DNA TRANSLATION.
- 3.1 Genetic code.
- 3.2 Amino acids activation, initiation, elongation and termination in Prokaryotes.

4 REGULATION OF GENE EXPRESSION.
- 4.1 Importance of gene regulation
- 4.2 The Lac Operon System.
- 4.3 End product inhibition.

5 MUTAGENS AND GENE MUTATION.
- 5.1 Types of gene mutation.
- 5.2 Mutagenic effects.

6 CHROMOSOMAL THEORY OF INHERITANCE.
- 6.1 Discovery of Chromosomes.
- 6.2 Chromosome structure and function.
- 6.3 Genes and alleles.

7 CELL CYCLE AND CELL DIVISION. (I)
- 7.1 Cell cycle

7.2 Mitosis
7.3 Cytokinesis.

8 CELL DIVISION (II)
8.1 Meiosis I
8.2 Meiosis II

9 GENETICS.

9 MENDELIAN GENETICS.
9.1 Key concepts in genetics.
9.2 ~~Mendelian~~ Mendel's first and second laws.
9.3 Monohybrid cross / Dihybrid cross and test cross.
9.4 Punnet square.

10 AUTOSOMAL LINKAGE AND CHI SQUARED TEST

11 LETHAL GENES.

12 POST-MENDELIAN GENETICS.
12.1. Multiple alleles (ABO blood groups).
12.2 Quantitative traits
12.3 Genetic interactions.

13 SEX DETERMINANTS AND SEX LINKAGE.
13.1 Inheritance of sex and sex-linkage traits.
13.2 Colour blindness and hemophilia (X-linked human diseases).
13.3 Hormonal effects on sex expression.

INTRODUCTION.

The term molecular biology was first used in 1945 about 72 yrs ago by William Astbury who was refering to the study of the chemical and physical structure of biological macromolecules. by that time biochemists has discovered the many fundamental intercellular chemical rxns However the development of molecular biology had to await the studying of simple systems such as bacteria and viruses which yield information about the basic biological processes more readily than that occur in animal cells. In fact this was an important factor in rapid growth of molecular biology. It was believed that fundamental biological processes that govern the activity of simple organisms such as bacteria and viruses must apply to more complex cell only the details should vary.

The roots of molecular biology were established in 1953 when James Watson and Francis Crick proposed the double helical model of DNA structure. Most geneticists agreed that DNA is the genetic material and plays an important role in heredity. They also agreed that genes are made of DNA.

What is molecular Biology?

The term " " has more than one definition. Some define it very broadly as "the attempt to understand the biological phenomena at molecular level" but this defn makes molecular biology difficult to distinguish from biochemistry.

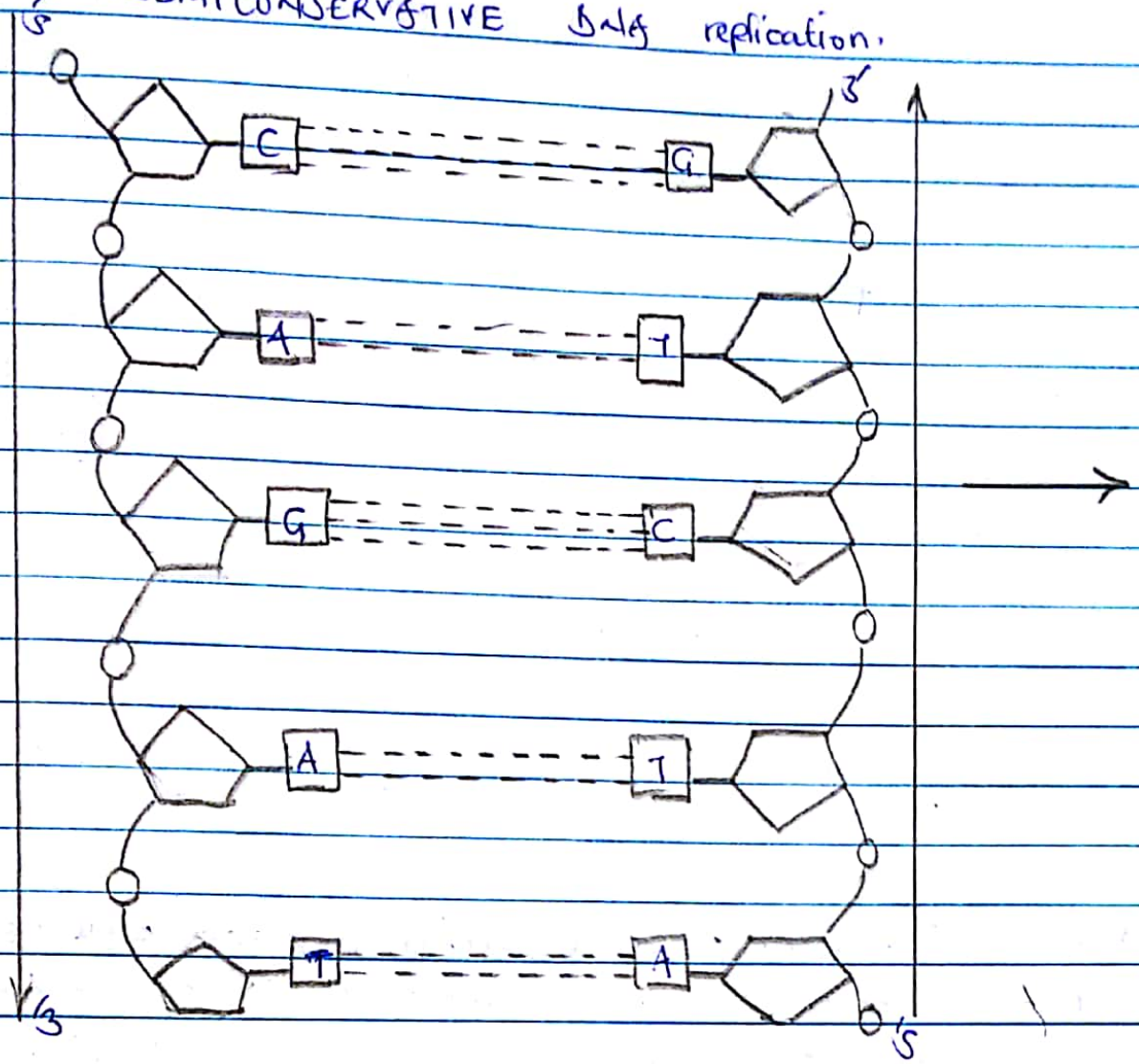
Another defn is more restrictive and therefore

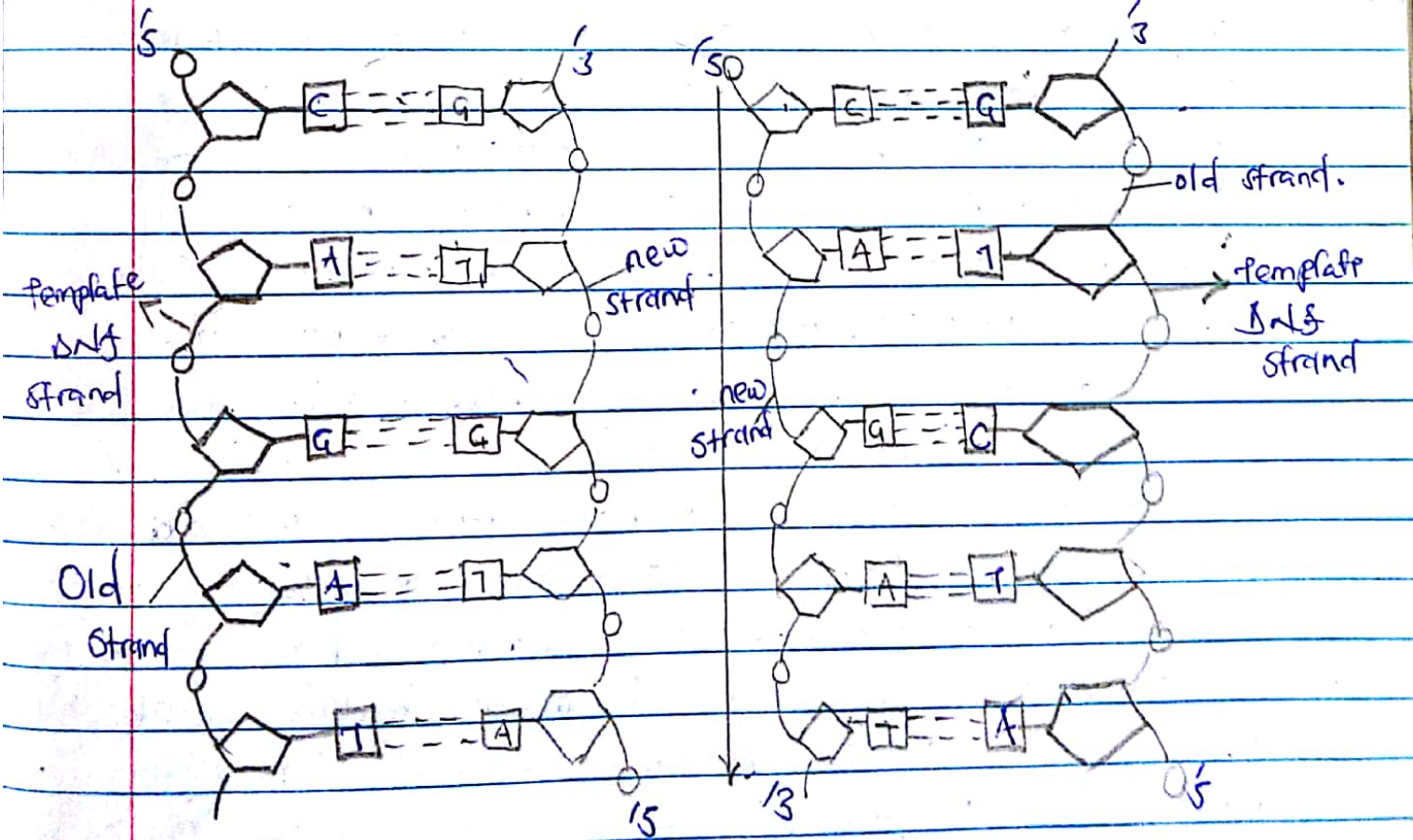
more useful " It is the study of genes structure and their functions at molecular level"
Molecular biology grew out of the disciplines of genetics and biochemistry.

Once the importance of DNA in genetic process was realised, work was intensified not only on the structural basis of this molecule but also on the relationship of its structure to its function, as a result many scientist asked a significant question which was; How does DNA serve as genetic basis for living processes?
The answer was believed to depend strongly on the chemical structure of DNA molecules. Their reserch concluded that for a molecule to serve the role of genetic material it must possess 4 major characteristics

1 Replication
2 Storage of information.
3 Expression of information.
4 Variation by mutation.

SEMI CONSERVATIVE DNA replication.





4 The Overall Replication Process.

In a second paper that followed Crick and Watson announcment of double helix, they stated their hypothesis for how DNA replicates. Their double helix modem suggested that DNA replates by semi conservative replication which includes the following steps.

1 Uncoiling the parent DNA molecule

2 Unzipping the hydrogen bond between the base pairs thus seperating the 2 strands and exposing the nucleotide sequence of each strand to serve as a template.

3 Synthesising 2 new strands by attachment of the correct complementary nucleotide to each single stranded template.

* B - Semiconservative DNA Replication suggested by Watson and Crick

DNA replication requeries a careful coordination of the actions of 30 different enzymes which separate the strands of existing DNA molecule, copying its template and 2 complete total molecules. Replication is an essential function of the genetic material and must be executed precisely if genetic continuity between cells is to be maintained following cell division. DNA replication is an enormous complex task / Consider for a moment that more than 3 billion base pair must within the 23 pairs of chromosomes of the human genome to duplicate faithfully the DNA of just one of the chromosome require a mechanism of extreme precision even an error rate of only 1 on a million will still creat 3000 errors during each replication cycle of a gene.

3 000 000 000 1/10^6

Watson and Crick recorded in the first paper that the double helix consist of 2 polynucleotides joined by hydrogen bonds between the bases that project from each of the strands. These hydrogen bond will only form if the correct bases are adjeet to each other. Adenine opposite T and G opposite C. If the correct bases are not present the H-bonds will not form and the double helix will be unstable.

Crick and Watson suggest in the second paper that the H-bonds between the bases could be broken and the 2 polynucleotides strands seperated. Each polynucleotide could then act as a template for the formation of a new polynucleotide. Deoxiribonucleotide would bind to the exposed base, the base in the deoxyribonucleotide forming H-bonds with the residue in the polynucleotide. The formation of the H-bonds or base pairing would ensure that the correct deoxyribonucleotide was placed in the correct position. A opposite T and G opposite C. Once the deoxyribonucleotide were in place they could be polymerised to form a new polynucleotide that was complementary to the original. In this way 2 double helices would be formed, each a perfect copy of the original. The mechanism that Watson and Crick suggested was called Semi conservative replication, since half the molecule is conserved. If this model is correct, each total molecule should contain one parental molecule chain and one newly synthesised nucleotide chain.

this prediction has been tested on both prokaryotes and eukaryotes.

Though other theoretical modes of replication are possible that also rely on the parental strands as a template.

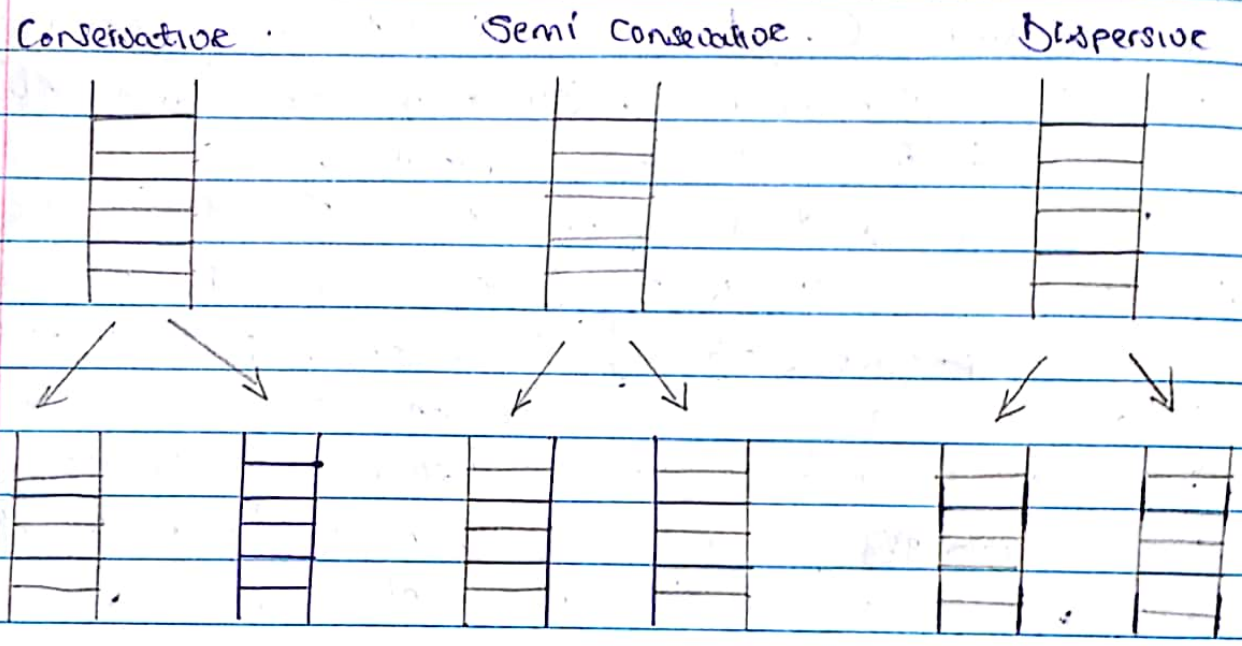
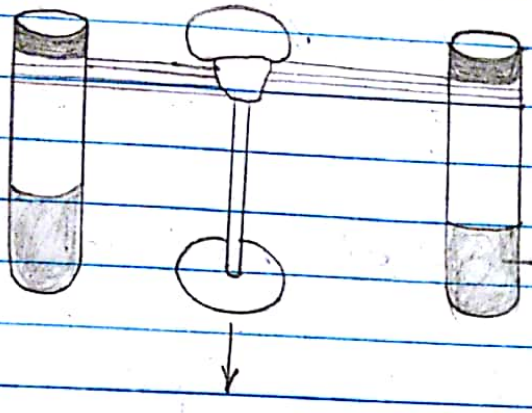


Fig 2: Results of one round of replication of DNA for each of the three (3) possible modes by which replication could be accomplished.

In conservative replication, complimentary polynucleotide chains are synthesised as described earlier following synthesis however the newly created strands then come together and the parental strand reassociate, the original helix as thus conserved. In the second alternative mode called dispersive replication parental ~~differential~~ strands are dispersed into new double helices following the replication. The dispersive replication results in total duplexes that consist of strands containing only segments of parental DNA and segments of newly synthesised DNA.

MESELSON AND STAHL OBTAINED EVIDENCE THAT SUPPORTS A SEMI-CONSERVATIVE MECHANISM.



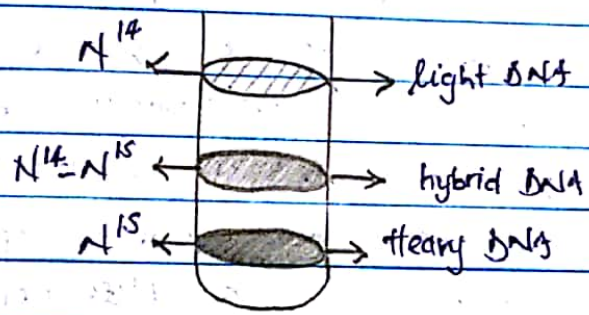
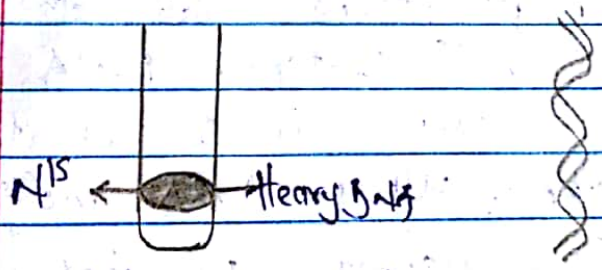
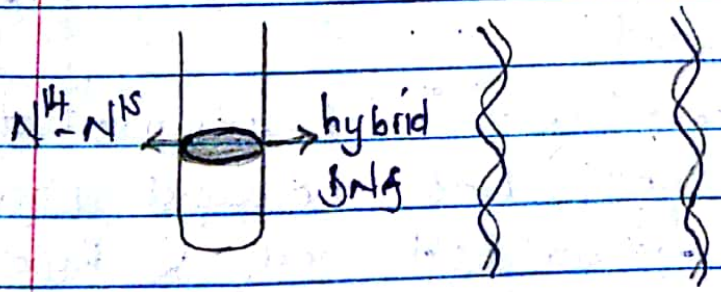


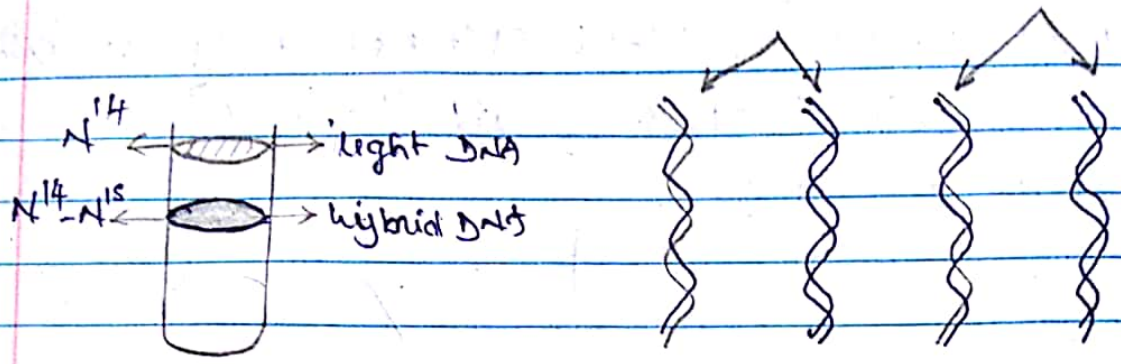
Fig 9a: Possible results when DNA is configured in CsCl.



(1) DNA when bacteria are grown in N^{15}.



(2) DNA after one division in N^{14}.



(3) DNA after 2 divisions in N^{14}.

Fig 3b: Results of Meselson and Stahl experiment.

It was 2 other scientist who thought up an ingenious series of experiments to show that E-Coli, a bacteria replicated its DNA using a semi conservative mechanism Meselson and Stahl published their results in 1958. Meselson and Stahl grew bacteria for several generations in a solution were the only source of Nitrogen was Ammonium Chloride. NH_4Cl. All the nitrogen in the NH_4Cl was N^{15} isotope rather than the common N^{14} isotope. After many generations, all the nitrogen in the bacteria was the N^{15} isotope. DNA isolated from such " had a greater mass that DNA containing the N^{14} isotope. When DNA molecules are centrifuge in CsCl density gradient, they seperate on the basis of density. Cells grown heavy N^{15} having dense strands after one division in light, Nitroge (N^{14})

DNA molecules are hybrid and have intermediate densities. After 2 divisions, DNA molecules seperate into 2 strands.. 1.- Light hybrid DNA and 2 hydrate DNA. These investigators knew that it would be posible to centrifuge DNA molecules in a gradient that seperate them on the basis of density

Meloson and Stahl first grew bacteria in a medium containing ^{15}N isotope so that only heavy DNA molecules were present in the cells. Then they switched the bacteria to a medium containing ^{14}N isotope. After I division only hybrid DNA were in the cells. After 2 divisions half the molecules were light and ½ were hybrid. This way exactly the results could be expected if DNA replication is semi conservative. The results of M and S experiment were consistant with semi-conservative mechanism for DNA replication. This was supporting evidence that DNA inside a living cell was in a form a double helix.

MECHANISM OF DNA REPLICATION IN PROKARYOTES.

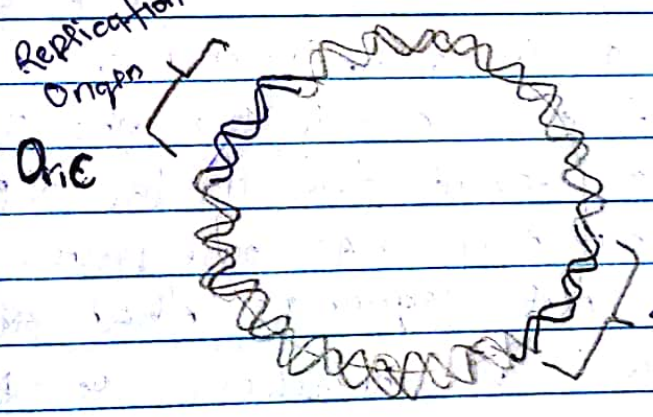
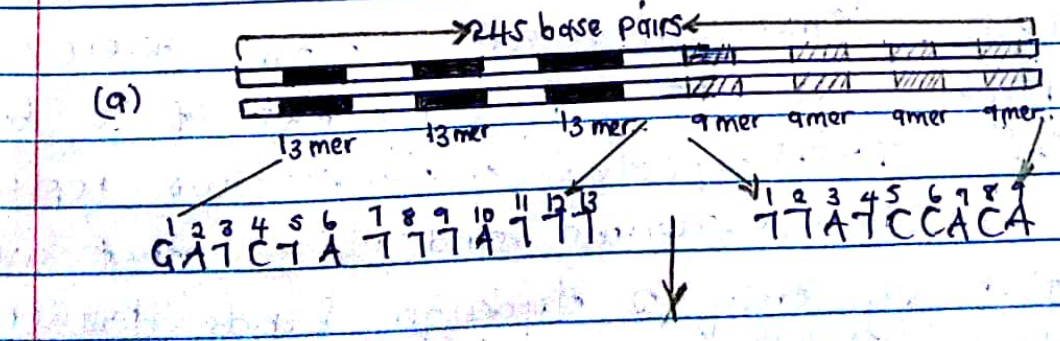


Fig 1: E coli Chromosome.



(b)

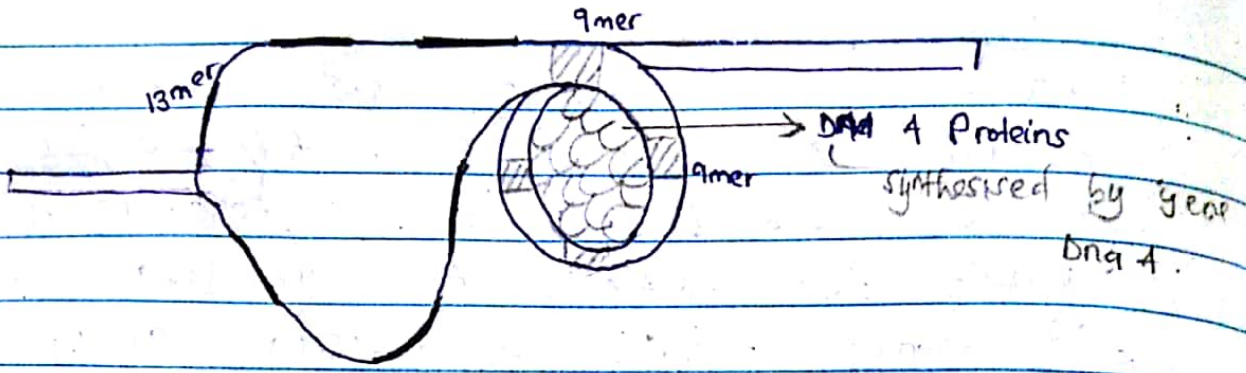


Fig 2: Origin of replication in bacteria (a) The origin of replication site (OriC) in E. coli is approximately 245 bp long. (b) the initiation of DNA replication requires the binding of DnaA proteins to the 9mers.

The machanism of Replication.

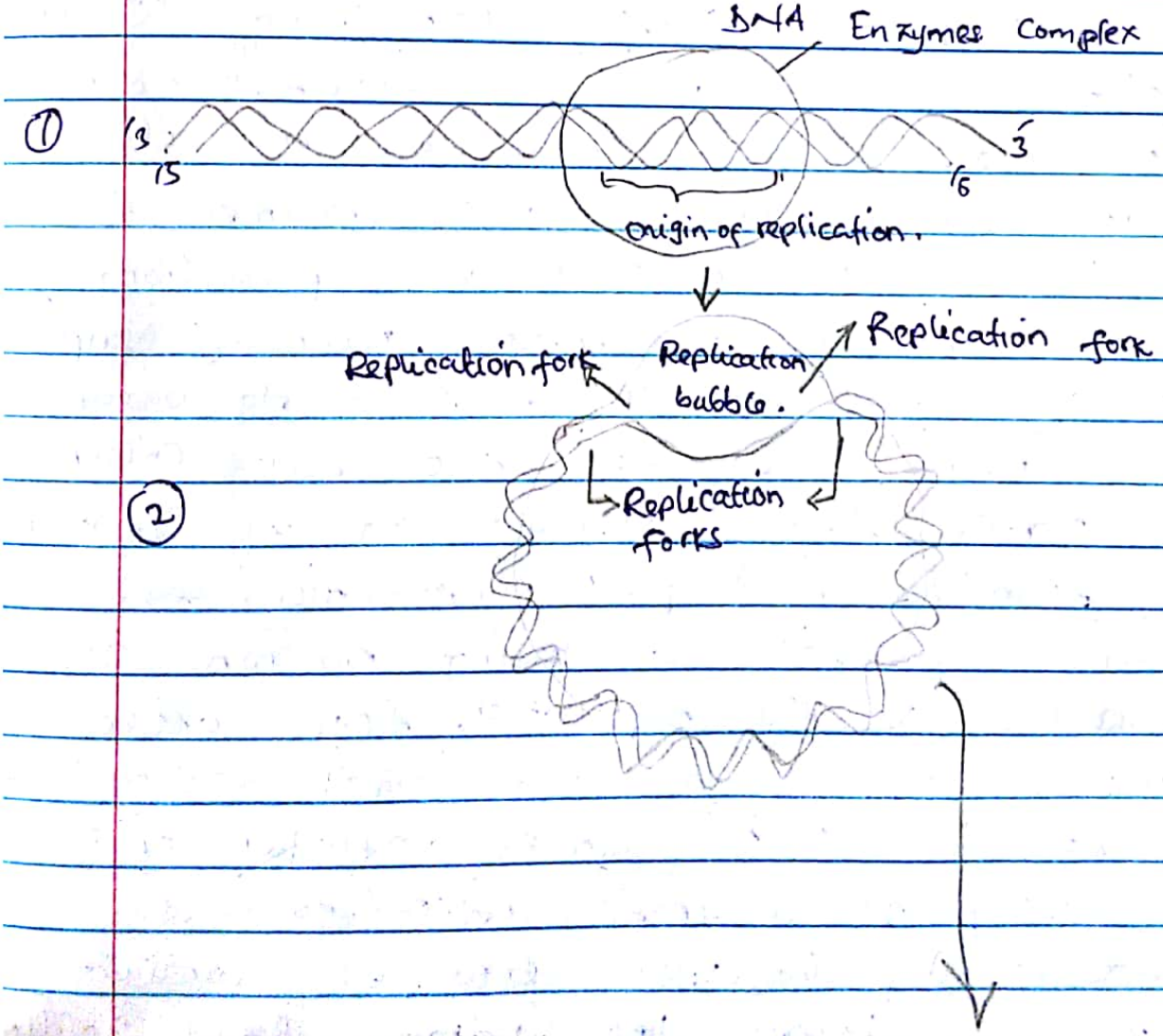
Can be divided into the following 3 main processes.

1 Initiation
2 Elongation
3 Termination

INITIATION OF DNA REPLICATION

DNA replication of the E. coli chromosome begins at a single site called the origin of replication (OriC) and proceeds ~~by~~ bidirectionally to a termination site (Ter) located approximately half way around the circular chromosome. The OriC site is approximately 245 base pairs long. They are composed of DNA sequences that attract the initiation proteins as well as stretches of DNA that are especially easy to copy. One part of the OriC site contains stretches of 13 base pairs called 13mers repeated 3 times where as second region consist of stretches of 9 base pairs called 9mers repeated 4 times. This replication origin is rich in ~~thymine~~ adenine and T. that are held together by only 2 hydrogen bonds rather than 3 hydrogen bonds between Guanine and Cytosine

Because the origin of replication is AT reach, less energy is required to separate the 2 strands than would be required if the origin were rich in CG. A bacteria genome which is contained in a circular DNA molecule of several million nucleotide pairs has a single origin of replication. The initiation of DNA replication requires the binding of DnaA proteins (specified Synthesised by gene DnaA) to the 9 mers. The formation of a DnaA complex causes the DNA to loop around the complex. This looping of the DNA stimulates the unwinding of the 2 strand in the portion of the OriC containing 13 mers.



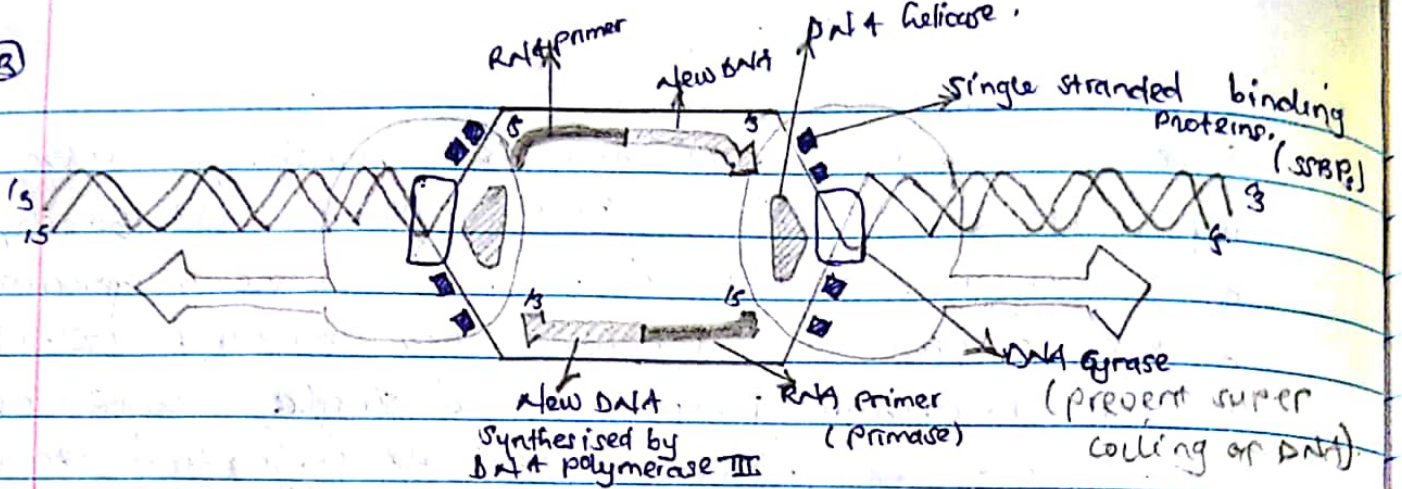


Fig 3: The initiation of DNA synthesis.

The initiation of DNA replication requires the binding of Dna A proteins (specified by dna gene) to the 9 mers. The formation of Dna A complex causes the DNA to loop around complex. This looping of the DNA stimulates the unwinding of the 2 strands in the portion of the Ori site containing 13 mers. It also attracts other proteins and enzymes to bind the DNA molecule. This step facilitates the subsequent binding of helicases enzymes to bind to the DNA and origin of replication. This enzyme require the energy normally supplied by the hydrolysis of ATP in order to break hydrogen bonds which hold the bases. Other proteins called single stranded binding proteins (SSBPs) stabilise this open conformation. As unwinding proceeds, a coiling tension is created ahead of the replication fork often producing super coiling. Such super coiling can be relaxed by DNA Gyrase, a member of a larger group of enzymes referred to as topoisomerases. The helicases enzyme unwind the helix and break the hydrogen bond holding the two strand together resulting in 2 separate

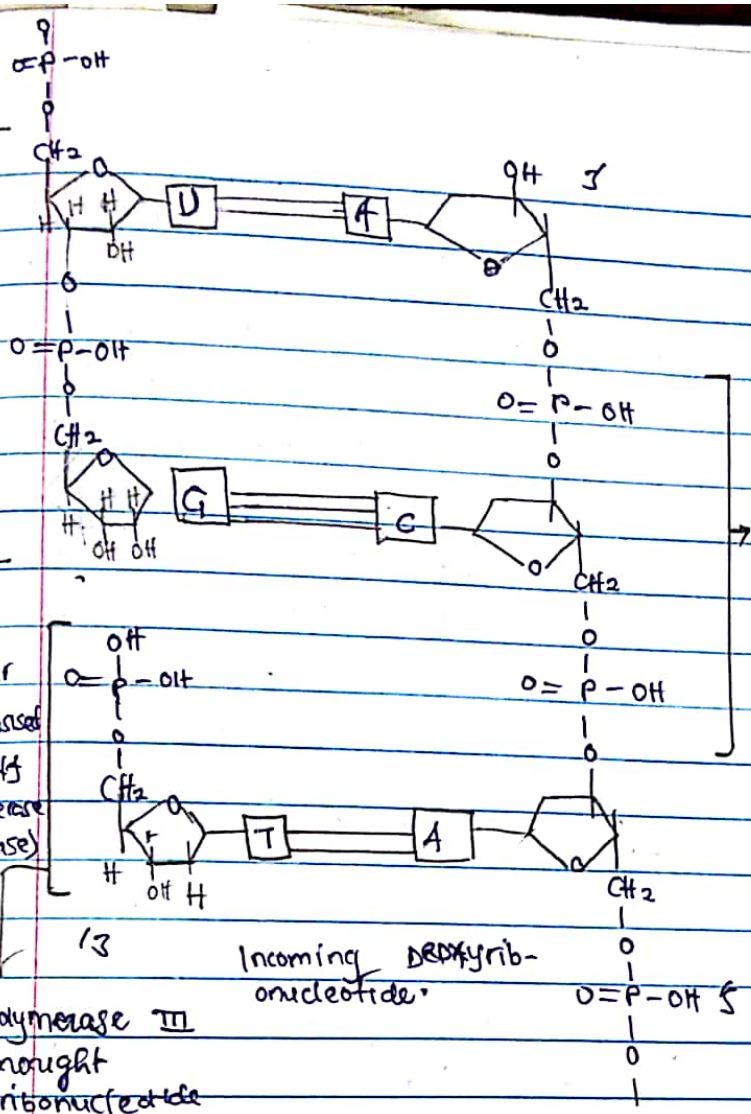
strands and opening up a replication bubble. At each end of a replication bubble there's a replication fork, a Y-shaped region. 2 replication forks are formed for the single replication origin. Once an initiation protein binds to DNA at the replication origin and helicases enzymes locally open up the double helix, it attracts a group of proteins that carry out DNA replication. This group cooperates as a protein machine with each member carrying out a specific function. As replication forks the replication machine is moving along with the DNA opening up the two strands of the double helix and using each strand as a template to make a new daughter strand. The 2 replication forks that are formed at replication origin move away from the origin in both direction, unzipping the DNA as they go. DNA replication in bacteria chromosomes is therefore termed as bidirection. The forks move very rapidly at about 1000 nucleotide pairs per second. Once a small portion of the helix is unwound, the process of synthesizing a daughter strand of DNA using the parental strand as template is carried out by the enzyme DNA polymerase III.

The intricate process of DNA replication does however depend on several enzymes and can be most easily understood by keeping in mind a few points concerning both the structure DNA molecules and the limitations of DNA polymerase III.

DNA polymerase III is unable to begin synthesizing

a chain of nucleotides but can only continue to add nucleotides to an already existing chain, Therefore DNA polymerase III requires a primer with a free 3' hydroxyl group under to elongate a polynucleotide chain. Since non is available in a circular chromosome, this prompted researchers to investigate how the first nucleotide could be added. They have emphasised that RNA and not DNA serves as the primer to initiates DNA synthesis A short segment of RNA (about 5-15 nucleotides long complementary to DNA is first synthesised on the DNA template. Synthesis of the RNA is directed by a form of RNA polymerase called primase which does not require a free 3' end to initiate synthesis. It is to this short segment of RNA that DNA polymerase III begins to add 5' deoxyribonucleotides, initiating DNA synthesis. At a later point, the RNA primers must be removed and replaced with DNA, this is thought to occur under the direction of DNA polymerase I.

2) Since the 2 strands of the double helix are anti-parallel to each other, that is one runs in the 5' to 3' direction while the other has opposite 3' to 5' direction. In the structure of DNA, the carbon atoms of the sugar component of each nucleotide are numbered. In order for the base pairs to form, the sugar components in one strand are upside down to the other. The end with the hydroxyl attached to the 3' called the '3' end' of the DNA strand, the end having the phosphate attached to 5' carbon is called the 5' end. There as the replication fork



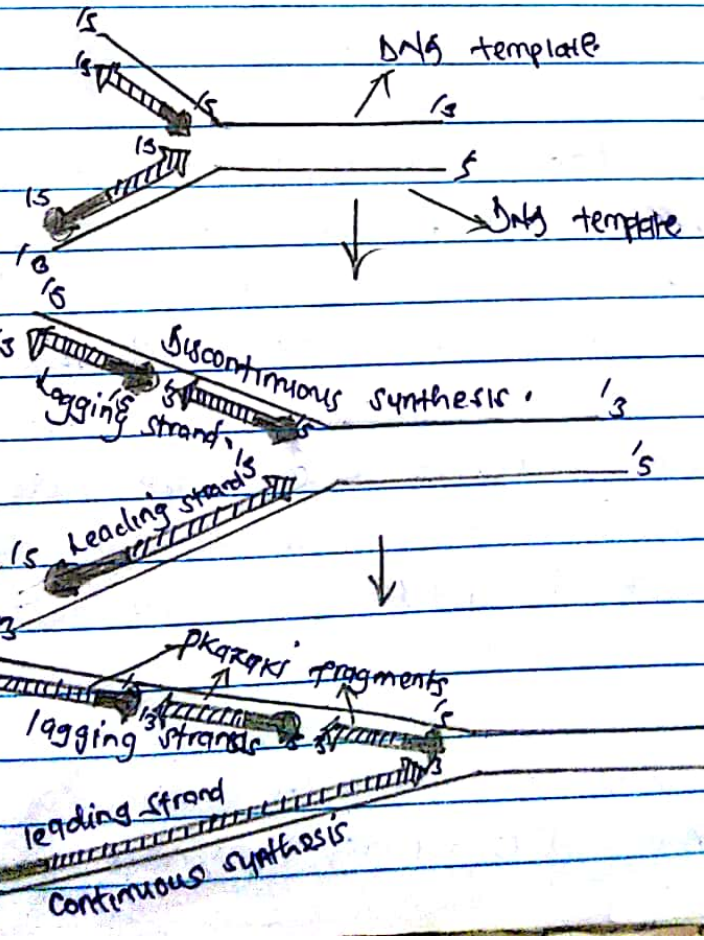


Fig 5: Opposite polarity of DNA synthesis along two strands.

moves along the parental DNA, the 2 new strands must grow in different directions. Because DNA polymerase III can catalyse the growth of the DNA only in the 5' to 3' direction, it can add new nucleotides only to the 3' end of the chain. As a result as the strands unwind and the replication fork progresses down the helix, only one strand can serve as a template for continuous DNA synthesis. This newly synthesised DNA is called the leading strand. As the fork progresses many points of initiation are necessary on the opposite DNA template resulting in discontinuous DNA synthesis of the lagging strand. In this way the 2 new strands can be synthesised simultaneously. This manner of synthesis produces short fragments of DNA (100-1000 bases long) called Okazaki fragments.

ELONGATION.

Elongation of new DNA at a replication fork is catalyzed by DNA polymerase III as nucleotides align with complementary base along the template strand of DNA. They are added by DNA polymerase III one by one to the growing end of the new DNA strand. The rate of elongation is about 1000 nucleotide pairs per second in bacteria, and 100 nucleotide pairs per second in human cells.

Discontinuous synthesis of DNA requires enzymes that both remove the RNA primer and unit

the okazaki fragment into the lagging strand. It is conformed that DNA polymerase I removes the primer and replaces the missing nucleotides. Joining the fragments appear to be the way of DNA ligase which is capable of catalysing the formation of the phosphodiester bond that seals the gap between the discontinuously synthesised strands. Evidence supporting the occurance of discontinuous DNA synthesis was first provided by Reiji and Tuniko Okazaki.

(v) PROCESS TERMINATION

Finally when replication is terminated, the protein is disassembled and the daughter DNAs seperate so that they segregate into their new cells.

PROOF READING (REPAIR) AND ERROR CORRECTION ARE AN INTEGRAL PART OF DNA REPLICATION. Although the action of DNA polymerase is very accurate, synthesis is not perfect and a non complementary nucleotide is occasionary inserted wrongly. It makes only about one error in every 10^6 nucleotide pairs replicated. Although A and T and G with C are by far the most stable base pairs other less stable base pairs e.g G with T and C with A can also be formed. Such incorrect base pair are formed much less frequently than correct ones but they occur often enough that would kill the cell through an accumulation of mistake if they were allowed to remain

To compensate for such ~~imperfections~~ inaccuracies the DNA polymerase all possess 3' to 5' exonuclease (exonuclease - an enzyme that breaks down nucleic acid molecules by breaking the phosphodiester bond at the 3' or 5' terminal nucleotide)

This property provides the potential for them to detect and remove a mismatched nucleotide. Once the mismatched nucleotide is removed 3' to 5' synthesis can again proceed. This process is called proof reading.

* DNA TRANSCRIPTION.

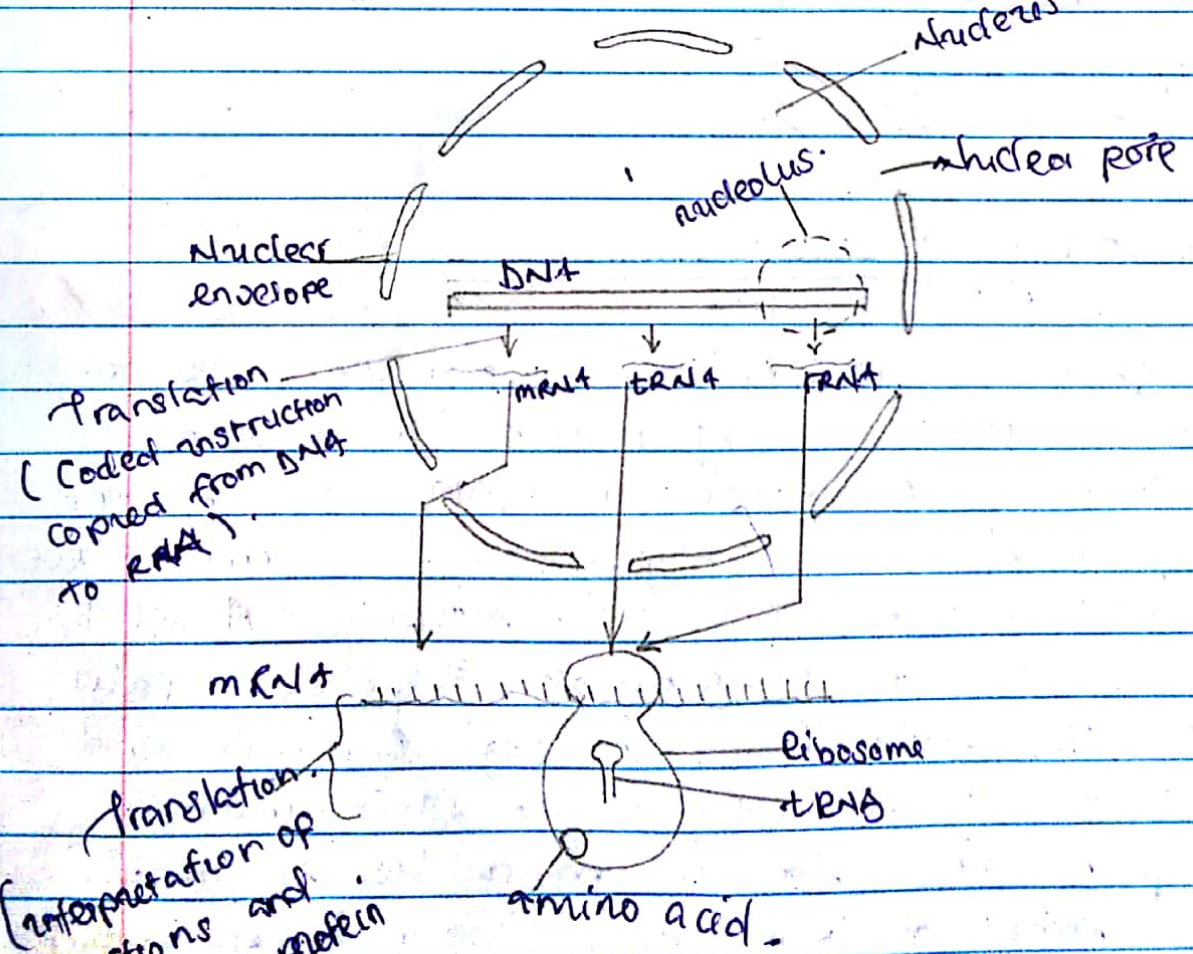


Fig 1: Summary of transcription and translation

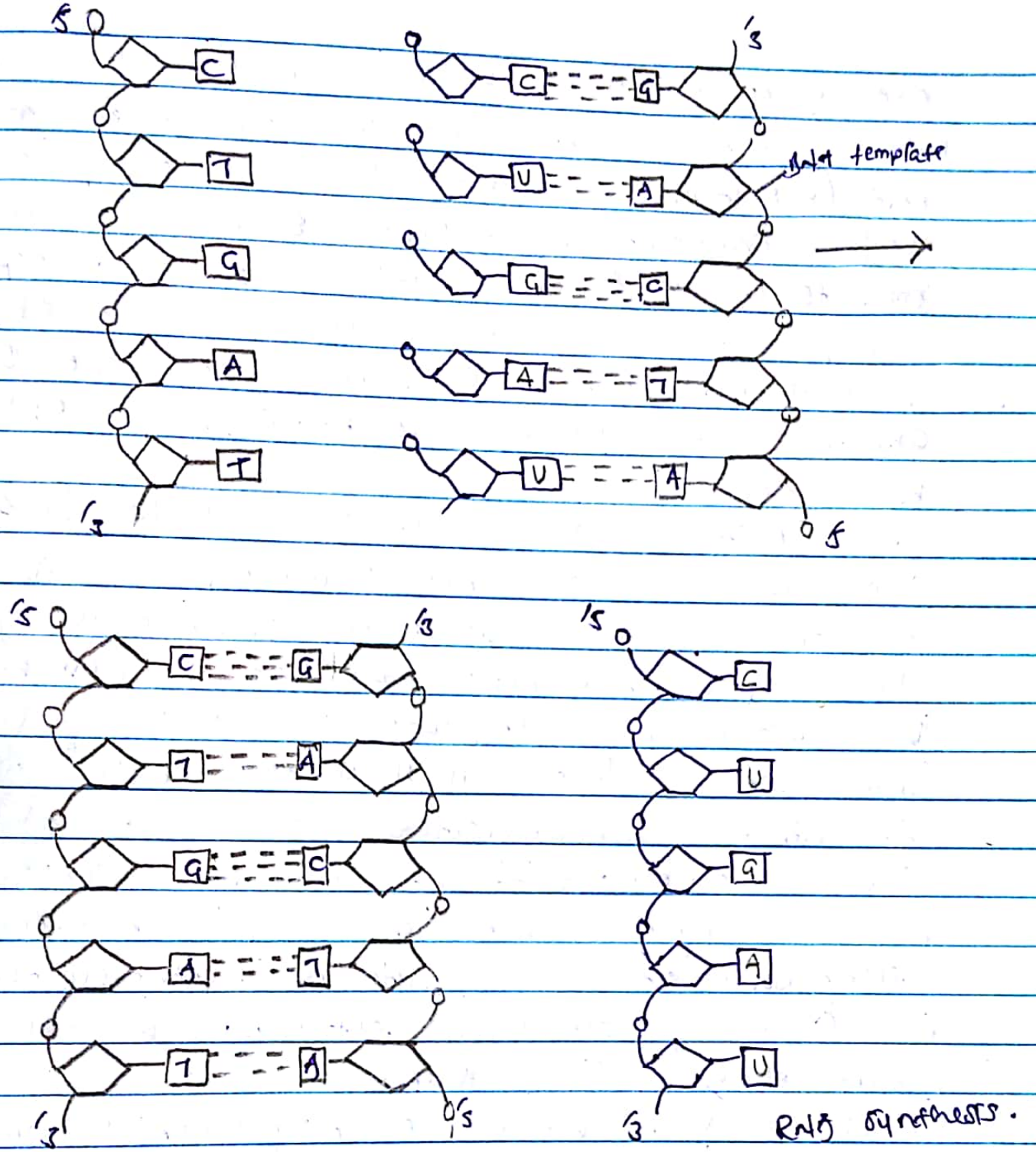


Fig 2: Transcription: RNA synthesis on DNA template.

When the information stored in the DNA is needed for use in the cell, a copy of the information must be made. Scientists say that the DNA is transcribed and the process is called transcription. Transcription uses DNA as a template for the synthesis of RNA molecule. The DNA determines the order of the ribonucleotide residues in RNA

RNA that carries the genetic information from the DNA out into the cell is called messenger RNA (mRNA). Ribonucleic acid is a polynucleotide of ribonucleotide residue. Each ribonucleotide consists of a ribose sugar group, a phosphate group and a base. There are four ribonucleotide one containing the base adinine (A), one the base Guanine, one the base Cytosine and and the base uracil.

The DNA double helix is separated into its two new strands by breaking H-bonds between the bases by DNA helicase enzyme. This exposes the bases and it is these bases that act as the template for the sequence of ribonucleotide that will make the mRNA molecule. An adinine ribonucleotide is exactly the right shape to H-bond with the thymine deoxyribonucleotide. As Guanine ribonucleotide with a cytosine deoxyribonucleotide, the Cytosine ribonucleotide with the Guanine deoxyribonucleotide and a uracil ribonucleotide with a Adenine

Once the ribonucleotide are in place, the are polymerised to make the RNA molecule. When this molecule is complete, it detaches from the DNA template and the DNA tips up to form the double helix again. The enzyme that catalyses the polymerisation of the RNA ribonucleotides is the RNA polymerase.

This way the information on the DNA that is stored in the order of nucleotide residues is transfered to the mRNA molecule.

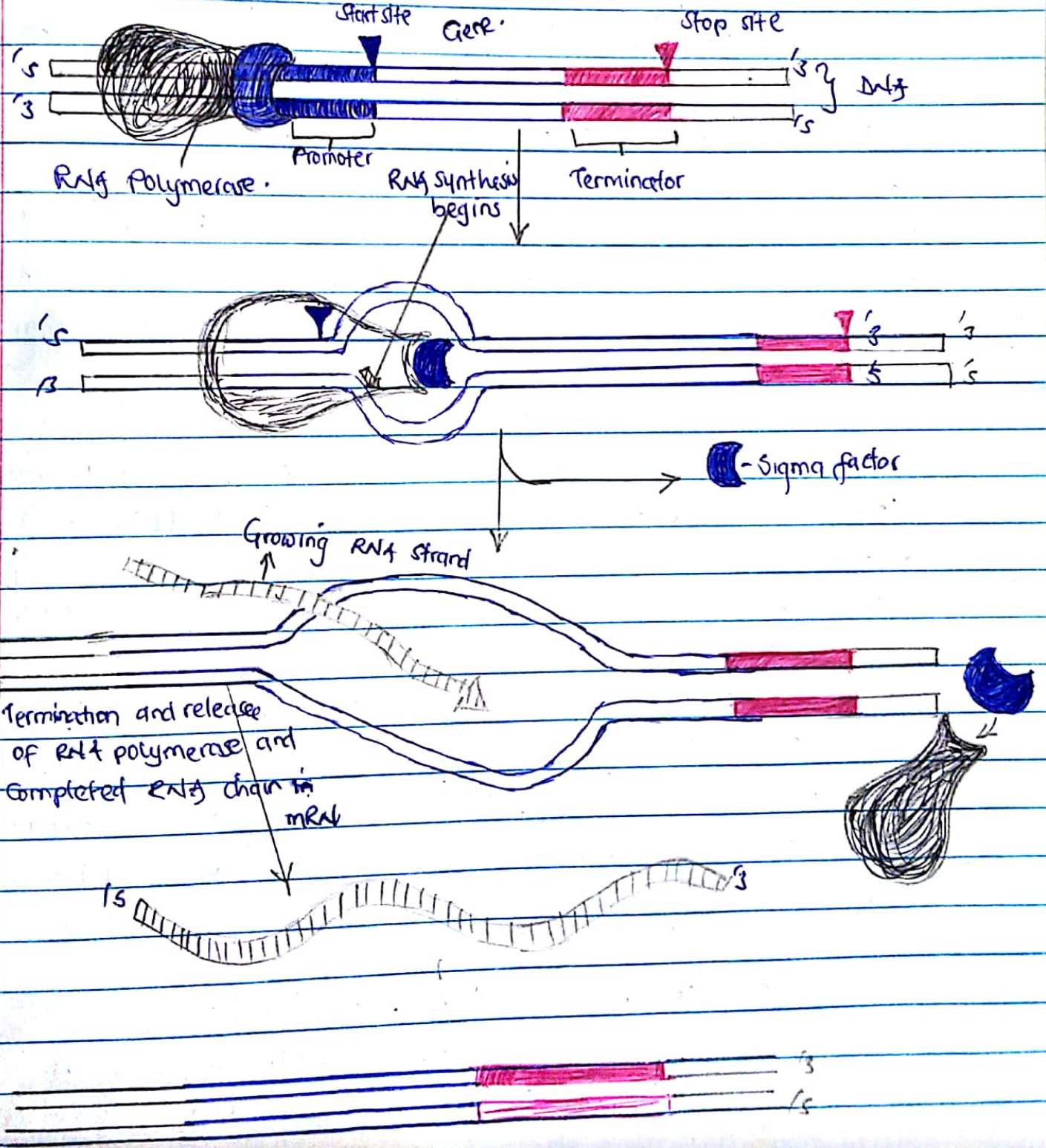
As the mRNA is made by base pairing deoxyribonucleotide to the bases in the DNA, the mRNA is not a copy of DNA but is complementary

DNA sequence of nucleotide residues in DNA was:

5' TTA GA CG TA G CCCCG A 3'

The sequence of nucleotide residues in mRNA will be

5' AAUCU GCAUCGGGCU 3'



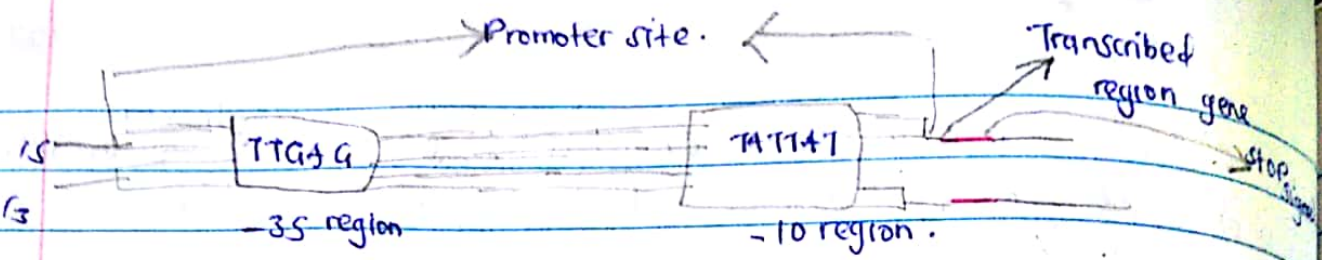


fig 1: Transcription of a bacterial gene by RNA polymerase

TTTTTTT

AAAAAAA

The initial step in transcription is referred to as template binding. In bacteria the site of this initial binding is established when the sigma(σ) subunit of RNA polymerase recognises specific DNA sequences called promoters. These regions are located upstream region from the point of initial transcription of the gene. It is believed that the enzyme explores a length of DNA until it recognises region and bind to about 45 nucleotides pairs of the helix. Divided into two short sequences, one is 5' TTGACA 3' is located 35 nucleotides upstream. The other sequence is 5' TATAAT 3' is located 10 nucleotides upstream from the site of initial transcription. Because it is rich in adenine and thymine residues it is called TATA box which is thought to ease the dissociation between the DNA strand so that RNA polymerase down to the promoter region.

Termination Signal in Bacteria.

Termination signal in E. coli also appear to have a distinct sequence of about 40 nucleotide pairs in length.

Initiation, Elongation and Termination for RNA Synthesis.

A subunit of bacteria RNA polymerase, called sigma factor (σ) primarily responsible for recognising the promoter sequence on DNA. Once it has recognised and bound to the promoter, RNA polymerase catalyses initiation, the insertion of the first five(5) ribonucleotide ~~catalyses~~ which is complementary to the first deoxyribonucleotide of the start site of the DNA template strand. As it is noted, no primer is required. Subsequent Ribonucleotide complements are inserted and linked together by phosphodiester bond as RNA polymerase proceed, this process continues in the 5' to 3' direction. After 10 ribonucleotides have been synthesised the sigma factor usually dissociates from the enzyme enabling the RNA polymerase to move forward and continue transcribing with it. As a result Chain elongation proceeds under the direction of the ~~E~~ core enzyme. In E.coli this proceeds at the rate of 50 nucleotides per second at 37°C. Eventually the enzyme traverses the entire gene until it encounters a specific nucleotide sequence that act as a termination signal, such termination sequences about 400 base pairs in length are extremely important in prokaryotes because of close proximity of the end of one gene and the upstream sequences of the adjacent gene.

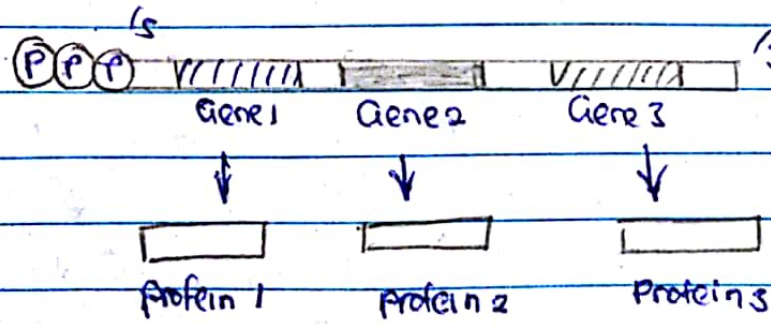
When the termination is achieved, the enzyme ceases to add ribonucleotides then it is released at a terminator and reassociates with a free sigma factor and searches for

a promoter where it can begin the process of transcription again. Also the transcribed RNA molecule is released from the DNA template. The end result of transcription is the synthesis of RNA molecule that is precisely complementary to the DNA sequence that represents the template strand of the gene.

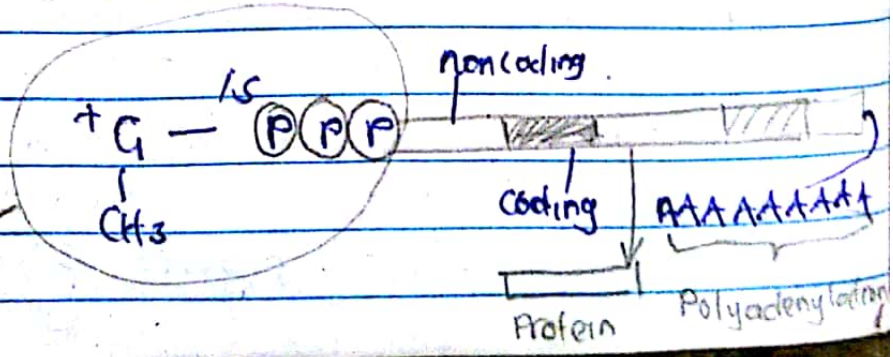
Transcription differs from DNA replication in several crucial features. Unlike a newly formed DNA strand, the RNA strand does not remain hydrogen bonded to DNA template strand. Instead just behind the region where the ribonucleotide are being added, the DNA reforms and displaces the RNA chain. Thus the RNA molecules produced by transcription are single stranded and they are copied from only a limited region of DNA, RNA molecules are very much shorter than DNA molecules.

→ Eukaryotic Post-transcription Modification.

a Prokaryotic mRNA



b Eukaryotic mRNA



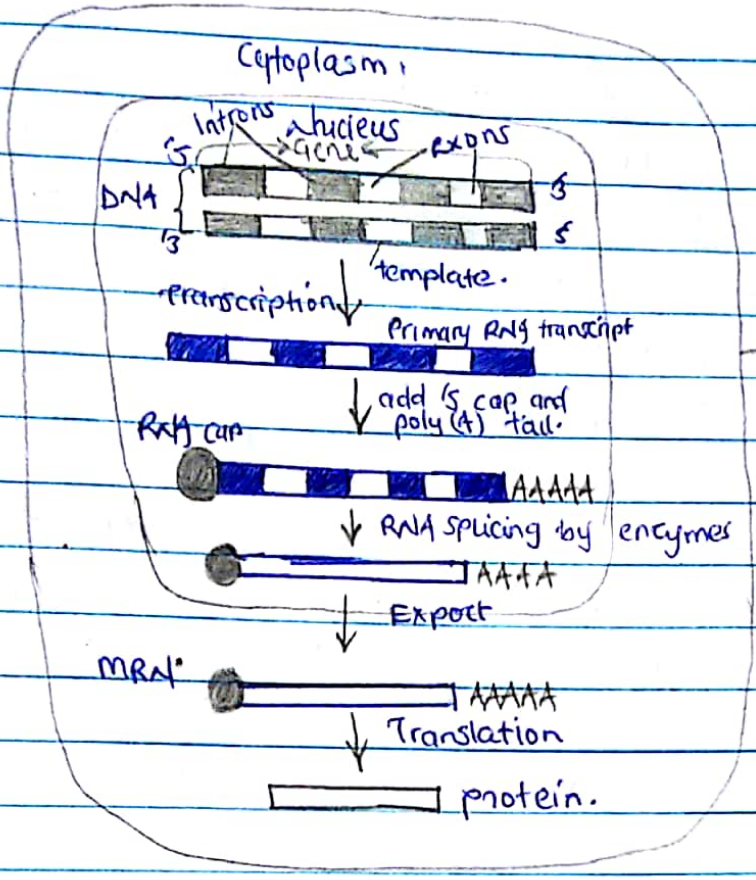


Fig A: Summary of the steps leading from gene to protein.

Eukaryotic RNAs undergo processing in the nucleus. Although the templating principle by which DNA is transcribed into RNA is the same in all organisms, the way in which the RNA transcripts are handled before they can be used by the cell appears a great deal between bacteria and eucaryotes. Bacteria DNA lies directly exposed to the cytoplasm which contains the ribosomes on which protein synthesis takes place. As mRNA molecules are transcribed, ribosomes immediately attach to the free 5 prime end of the RNA transcript and the protein synthesis starts. In eucaryotic cells by contrast, DNA is enclosed within the nucleus. Transcription takes place in the nucleus but protein synthesis on ribosomes in the cytoplasm so before the eucaryotic mRNA can be translated, it must transported out of the nucleus through small pores in the nuclear

envelope. Before the RNA exits the nucleus however it goes through several different RNA processing steps, in eukaryotes freely produced by transcription, but not yet processed is often called the primary transcript. Depending on which type of RNA is being produced, mRNA or some other type are processed in various ways before leaving the nucleus. Two processing steps that occur only on primary transcripts are (1) RNA capping and (2) Polyadenylation.

1. RNA Capping involves modification of the 5' end of the primary transcript. The 5' end is capped by the adding of a guanine nucleotide with a methyl group attached. Capping usually occurs just after the RNA polymerase has synthesized the 5' primary end of the primary transcript and but it has completed transcribing the whole gene.

2. Polyadenylation provides most newly transcribed mRNA's with a special structure at their 3' end or tail end. In contrast with bacteria where the 5' end of an mRNA is simply the end of the chain synthesized by the RNA polymerase, the 3' end of eucaryotic RNAs are first cleaved or split by an enzyme that cuts the RNA chain at a particular sequence of nucleotide, and is then finished off by a second enzyme that adds a series of repeated adenine (A) nucleotide, (a poly A tail) the poly A tail is generally a few hundred nucleotides long.

Table 1: The genetic Code

First position [5' end]	Second position				Third position [3' end]
	U	C	A	G	
U	Phe	Ser	Try	Cys	U
	Phe	Ser	Try	Cys	C
	Leu	Ser	STOP	STOP	A
	Leu	Ser	STOP	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Ala = alanine Arg = arginine Asn = asparagine Asp = aspartic acid
Cys = cysteine Gln = glutamine Glu = glutamic acid Gly = glycine
His = histidine Ile = isoleucine Leu = leucine Lys = lysine
Met = methionine Phe = phenylalanine Pro = proline Ser = serine
Thr = threonine Trp = tryptophan Try = tyrosine Val = valine

Amino acid.	Nom of codon		Total
2 = Phenylalanine	2	=	2
eu = Leucine	2+4	=	6
r = Serine	4+2	=	6
y = Tyrosine	2	=	2
s = Cystein	2	=	2
p = Tryptophan	1	=	1
o = proline	4	=	4
is = Histidine	2	=	2
n = Glutamine	2	=	2
rg = Arginine	4+2	=	6
le = Isoleucine	3	=	3
let = Methionine	1	=	1
r = Threonine	4	=	4
sn = Asparagine	2	=	2

These two modifications, caping and the polyadenylation are thought to increase the stability of the mRNA molecule and to facilitate its export from the nucleus to the cytoplasm.

EUKARYOTIC GENES ARE INTERRUPTED BY NON-CODING SEQUENCES.

Most eukaryotic RNA has to undergo a further processing step by they are transcribed. This step involves a far modification of the primary RNA transcript than capping or polyadenylation. In the 1970's, Cell biologists studing transcription in eukaryotic cells were surprised the behaviour of the RNA in the nucleus which seemed to be quite different from that of bacteria mRNAs, they found that nuclea RNAs by their guanine nucleotide caps and their poly A tails become shorter while in the nucleus although they retained both their caps and their tails. Then they asked themselves how could the middle part of an RNA shrink?. The answer to this came in 1977 with the unexpected discovery that the organisation of eukaryotic genes is fundamentally different from that of bacteria genes. In bacteria most proteins are encoded by uninterrupted stretch of DNA sequence. Most eukaryotic genes in contrast have their coding sequences interrupted by non-coding sequences called introns. The scattered pieces of codding sequences called exons are usually shorter than the introns

INTRONS ARE REMOVED BY RNA SPLICING.

To produce an mRNA in eukaryotic cells the entire length of the gene, including introns as well as exons is first transcribed into a long RNA molecule after capping and polyadenylation but before the RNA leaves the nucleus, all of the intron sequences are removed and the exons joined together. the result is a much shorter RNA molecule which now contains an uninterrupted coding sequence, when this step called RNA splicing has been completed, the RNA is a functional mRNA molecule that can now leave the nucleus and be translated into proteins. Introns are removed from RNA by enzymes that unlike most other enzymes are composed of complex of protein and RNA. these splicing enzymes are called small nuclear ribonucleoprotein particles (snRNPs). Snrnps are pronounced "snurps". At each introns a group of (snRPs) assembles on the RNA cuts out the intron and rejoins the RNA again releasing the removing the released entron.

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Sugar and phosphate repeat in the chain. they cannot carry genetic information, the bases do so.

4^3 of 3 letters are used. $4 \times 4 \times 4 = 64$ combination which over up 20 amino acid.

	Amino acid	No. of codon		Total
1	Phe - Phenylalanine	2	=	2
2	Leu - Leucine	2 + 4	=	6
3	Ser - Serine.	4 + 2	=	6
4	Tyr - Tyrosine	2	=	2
5	Cys - Cysteine	2	=	2.
6	Trp - Tryptophan	1	=	1
7	Pro - Proline	4	=	4
8	His - Histidine	2	=	2.

Nucleotide ⟶ Amino acid.

THE GENETIC CODE

One of the most remarkable facts of life is that each cell in an organism contains all the information required to determine all the characteristics of that whole organism. This information is stored in DNA and is known as the genetic code. The discovery that code has been one of the major scientific breakthroughs of the 20th century. It has given us an understanding of how genes function and it has opened the way for most of the recent developements in genetic engeering and biotechnology. The genetic code is used to convert the linear sequence of bases in DNA to the sequence of amino acids in protein. The words in the codes called codons are sequences of 3 bases on mRNA that specify one of the 20 common amino acids or the begining or end of the protein chain. For instance the codon UUC on mRNA specifies the amino acid phenylalanine. (The complementary sequence on DNA would be AAG) The 4 different bases in RNA (A, U, C and G) would form 64 different combination of 3 base sequences. The number of possible codons therefore exceeds the number of amino acids. So we find that several codons may code for the same amino acid. The codon AUG (Methionine) can either serve as a start signal to initiate translation or it can specify the amino acid methionine depending on where it occurs in the mRNA molecule. In addition, 3 Codons UAA, UAG and UGA are stop codons that specify the end of a protein.

The genetic code exhibits a number of characteristics.

1 The genetic code is written in linear form using the ribonucleotide bases that compose mRNA molecules as letters.

2 Each word within the mRNA contains 3 ribonucleotide letters, each group of 3 ribonucleotides called a codon specifies one amino acid.

3 The code is an ambiguous (each codon specifies only a single amino acid.

4 The code is degenerate or redundant (A given amino acid is specified by more than one codon) This is the case of 18 of the 20 amino acids.

The code degeneracy is basically of 2 types:

1 partial
2 Complete.

1 PARTIAL DEGENERACY.

- Occurs when first 2 nucleotides are identical but the 3rd nucleotides of the degenerate codon differs

e.g UUA
CCU
GGU

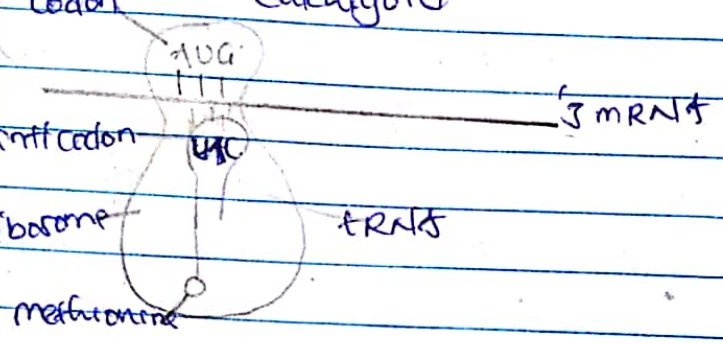
2 COMPLETE DEGENERACY

- Occurs when any of the 4 bases can take 3rd position and still be code for the same amino acid e.g UCU, UCC, UCA and UCG.

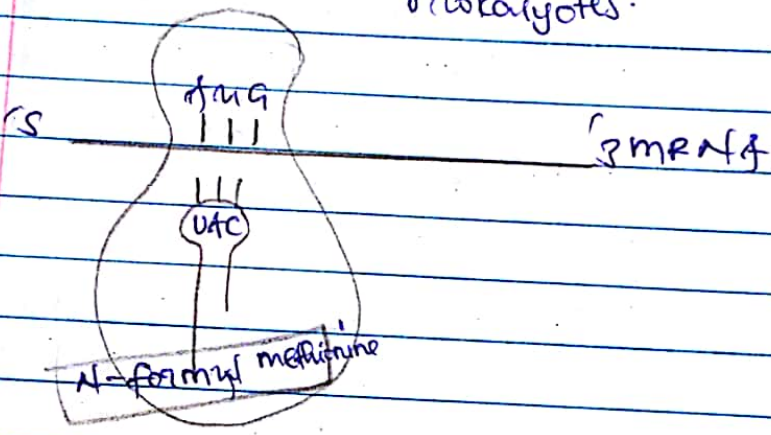
5 Some codes act as start codons in most organism AUG codon is the start for initiation codon. e.g the polypeptide starts either with methionine (Eucaryotes) or N-formyl methionine (prokaryotes)

4- Formal methionine - tRNA specifically binds to the initiation site of mRNA containing the AUG initiation codon.

Eucaryotes



Prokaryotes.



In rare cases GUG (valine) also serves as the initiation codon eg bacteria - protein synthesis normally GUG code for valine but normal AUG codon is lost by deletion only then GUG is used as initiation codon.

6 The code is non-overlapping in a translating mRNA molecules, the codons do not overlap but are read sequentially

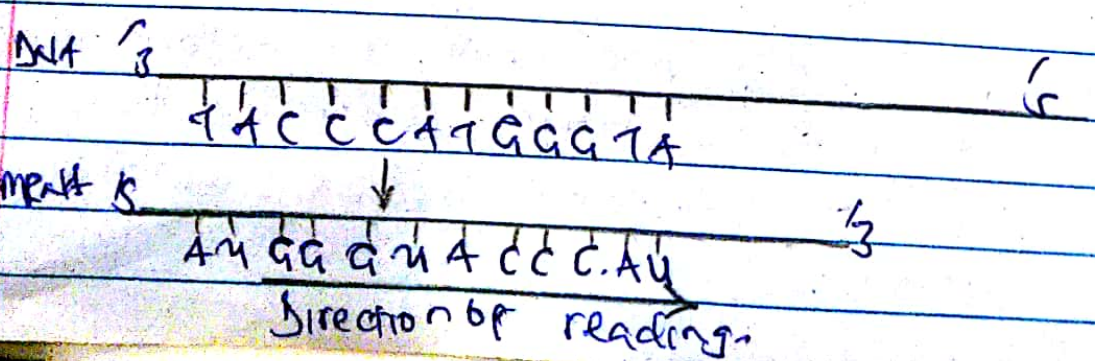
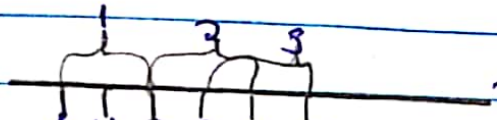


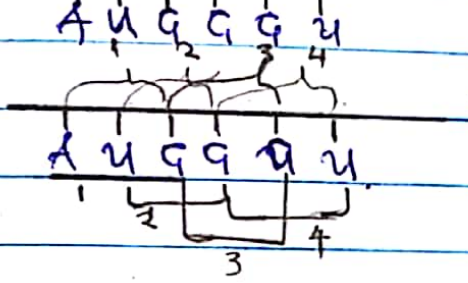
Fig 1

Bases in mRNA are read sequencially on the 5' to 3' direction in group of three bases thus a non-overlapping code means that a base in mRNA is not used for different codons

A) A U G G G U = 2 amino acids (non-overlapping).

wrong B) 

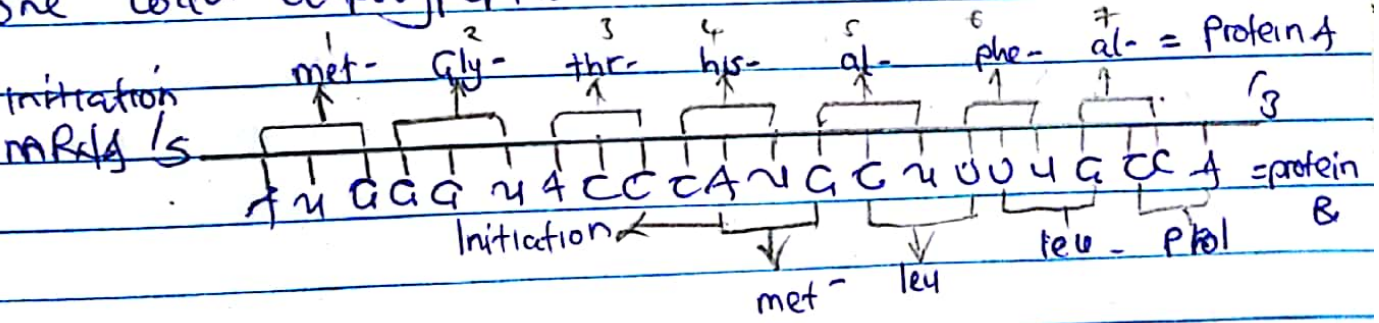
= 3 amino acids (overlapping)



= 4 amino acids (overlapping)

wrong C)

It has been shown that an overlapping code can mean coding four amino acids from six bases. However in actual practice, six bases code for more than 2 amino acids. Recently it has been shown that in some viruses there is a possibility of overlapping of genes and codons. In this case, a single mRNA may have multiple initiation points for translation. If so these point could create several different reading frames within the same mRNA. Thus specifying more than one codon a polypeptide.



In the above case due to overlapping genes, mRNA sequence initiated @ different AUG positions as a result, this will gave rise to 2 distinct proteins with 2 distinct amino acid sequences.

61 codons which specify 20 amino acids, cell should have 61 tRNA

31 exist

7 No internal punctuation ("comma") is used in the code. Thus the code is said to be commaless. Once translation of mRNA begins, the codons are read one after the other with no breaks between them.

8 Some codes act as stop codons. three codons - UAG, UAA and UGA are the chain stop or termination. They do not code for any of the amino acid. These codons are not read by any tRNA molecules but are read by some specific proteins called release factors (e.g RF_1, RF_2 and RF_3) in prokaryotes and RF in eukaryotes). These codons are called nonsense codons since they do not specify any amino acid.

9 Wobble hypothesis.

	Codon on mRNA	Amino acid.
1	GGU	Gly
2	GGC	Gly
3	GGA	Gly
4	GGG	Gly.

Since there are 61 codons specifying amino acids, the cell should contain 61 tRNA molecules each with different anticodon. However the number of tRNA molecule type discovered is much less than 61. This implies that the anti codons of tRNAs read more than one codon on mRNA. Some tRNA are constructed so they require accurate base pairing only at the first 2 positions of the codons and can tolerate a mismatch (or wobble) at the 3rd position. This wobble base pairing explains why so many of the alternated codons of the amino acid differ only in their 3rd nucleotide. Wobble base pairing

make it possible to get the 20 amino acid to their 61 codons with as few as 31 kinds of tRNA molecules. The exact nos of different kinds of tRNAs however differ from one species to the next.

10 Character of the Genetic Code.

The code is nearly universal. The code as used universally as all living organisms ranging from bacteria to man. Although a few slight differences in the code have been found, these are chiefly in the DNA of the mitochondria. Mitochondria have their own transcription and protein synthesis systems that operate quite independently from those of the rest of the cell and they are able to accommodate minor changes to the universal code.

Protein Synthesis.

Protein synthesis is the most complex biochemical transformation which cells perform and atleast 200 different proteins are required for the protein synthesis itself. Both in prokaryotes and eukaryotes, the mechanism of protein synthesis can be divided into the following 3 main steps:

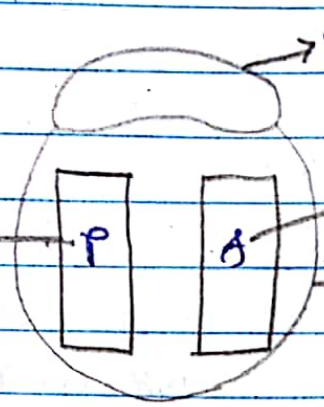
1 Initiation
2 Elongation
3 Termination.

The topic of protein synthesis is to explain how the information present in the sequence of bases (triplet codons) of the mRNA is translated in a sequence of amino acid in proteins

The minimum necessary materials for Protein Synthesis

1 Amino acids. (E.g 20 amino acids forming the pool of amino acids in the cytoplasm)

2 Ribosomes



Each of which comprises 2 subunit which exist as seperate subunits prior to the translation of mRNA and contain 2 tRNA binding sites. (The P site or peptydal site and A for amino acid site

3 mRNA

4 tRNA of several kinds.

5 Enzymes (a) Amino acid activation system (e.g Amino acyl - tRNA synthetase)

(b) Peptide polymerase system.

6 Ademosine Triphosphate (ATP) as energy source.

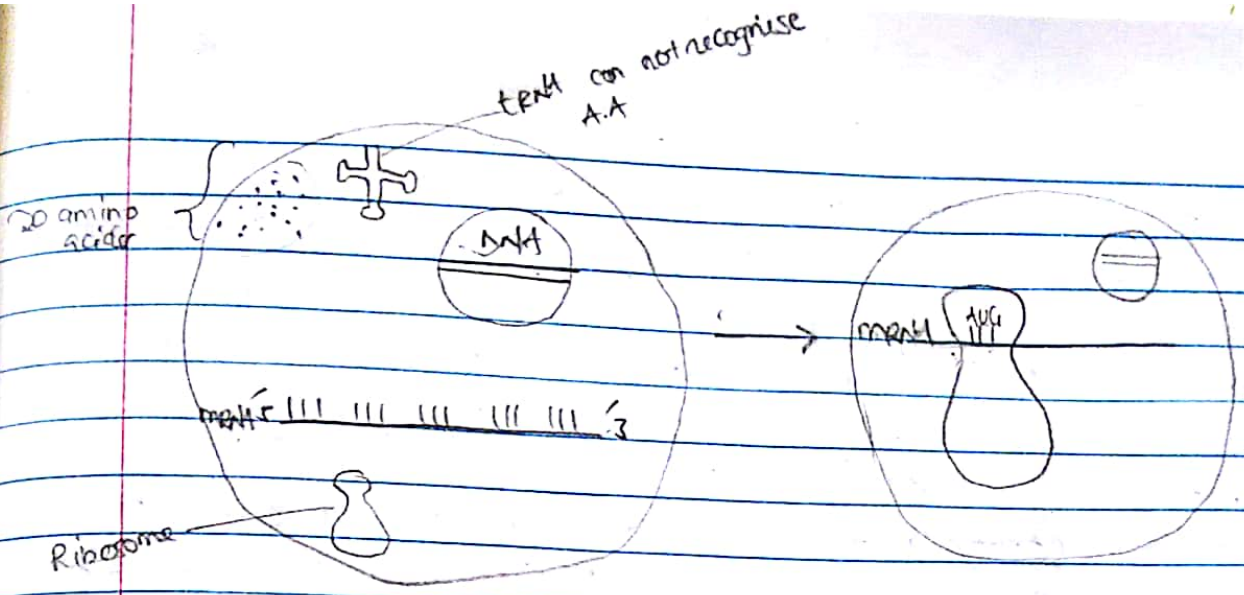
7 Guanosine Triphosphate (GTP) for synthesis of peptide bonds.

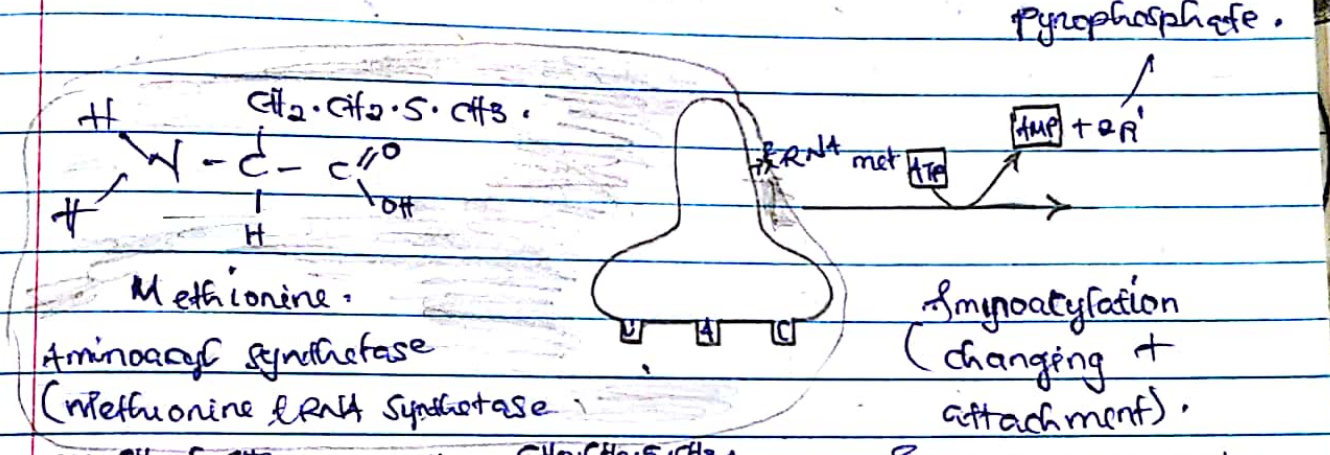
8 Soluble protein initiation and transfer factors.

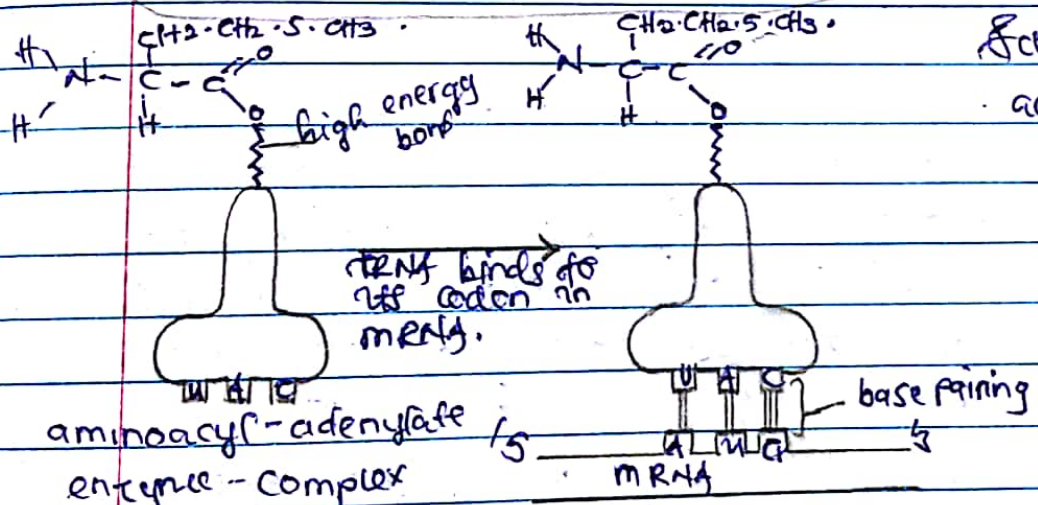
9 Various inorganic Cations (e.g K^+, NH4 and magnesium (Mg^{2+})

Various events of protein synthesis can be studied under the following headings:

1 Aminoacylation of tRNA (Formation of Aminoacyl-tRNA).







After result: Methionine is selected by its codon

Fig 1: Specific enzyme couple tRNA met to the correct amino acid methionine.

Aminoacylation

Amino acids alone do not come to the ribosome to be incorporated into protein instead they

are brought to the ribosome by the appropriate tRNA. The first step in incorporating an amino acid into a protein involves the amino acid attachment to its correct tRNA. This involves the following 2 steps.

1. Activation of amino acid

Each of the 20 amino acids occur in the cytoplasm in an inactive state. Each amino acid before its attachment with its specific tRNA is activated by a specific activating enzyme known as aminoacyl synthetase and ATP. The free amino acids react with ATP resulting in the production of amino acyl adenylate enzyme complex.

AA + ATP + Enzyme → AA-AMP-Enzyme
(amino acid) (aminoacyl synthetase). (Aminoacyl adenylate enzyme complex).

+ PP (pyrophosphate.

The rxn product aminoacyl adenylate and aminoacyl adenosine monophosphate) is bound to the enzyme in the form of a monocovalent complex. This aminoacyl adenylate enzyme complex esterifies to specific tRNA. The cell has atleast 20 aminoacyl synthetase enzyme for the 20 amino acid. Each enzyme is specific and it attaches with the specific amino acid without any error.

2. Attachment of Activated Aminoacid to tRNA.

The aminoacyl adenylate remains bound with enzyme until it collides with the specific tRNA molecule and the synthetase is recognised

by the ψ- loop of the specific tRNA. The aminoacyl residue of aminoacyl adenylate is transfered to the amino acid attachment site of tRNA where the carboxyl forms bond or linkage with the 3' off group of the ribose as a result AMP and the Enzyme are released and a final product aminoacyl tRNA is formed by the following step.

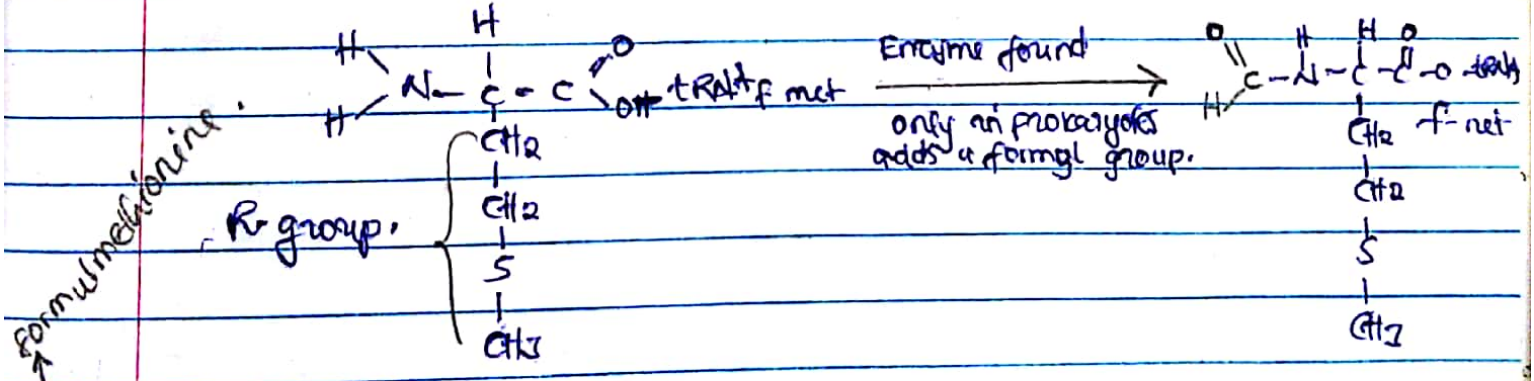
AA - AMP - Enzyme + tRNA → AA - tRNA + AMP + Enzyme.

The aminoacyl tRNA moves towards the site of protein synthesis eg the ribosomes with mRNA

5 Stages of Polypeptide Synthesis (Protein synthesis) ~~of (Amino~~ in prokaryotes.

Polypeptide synthesis in eukaryotes and prokaryotes follow the same overall mechanism though there are differences in detail. the most important being the mechanism of initiation.

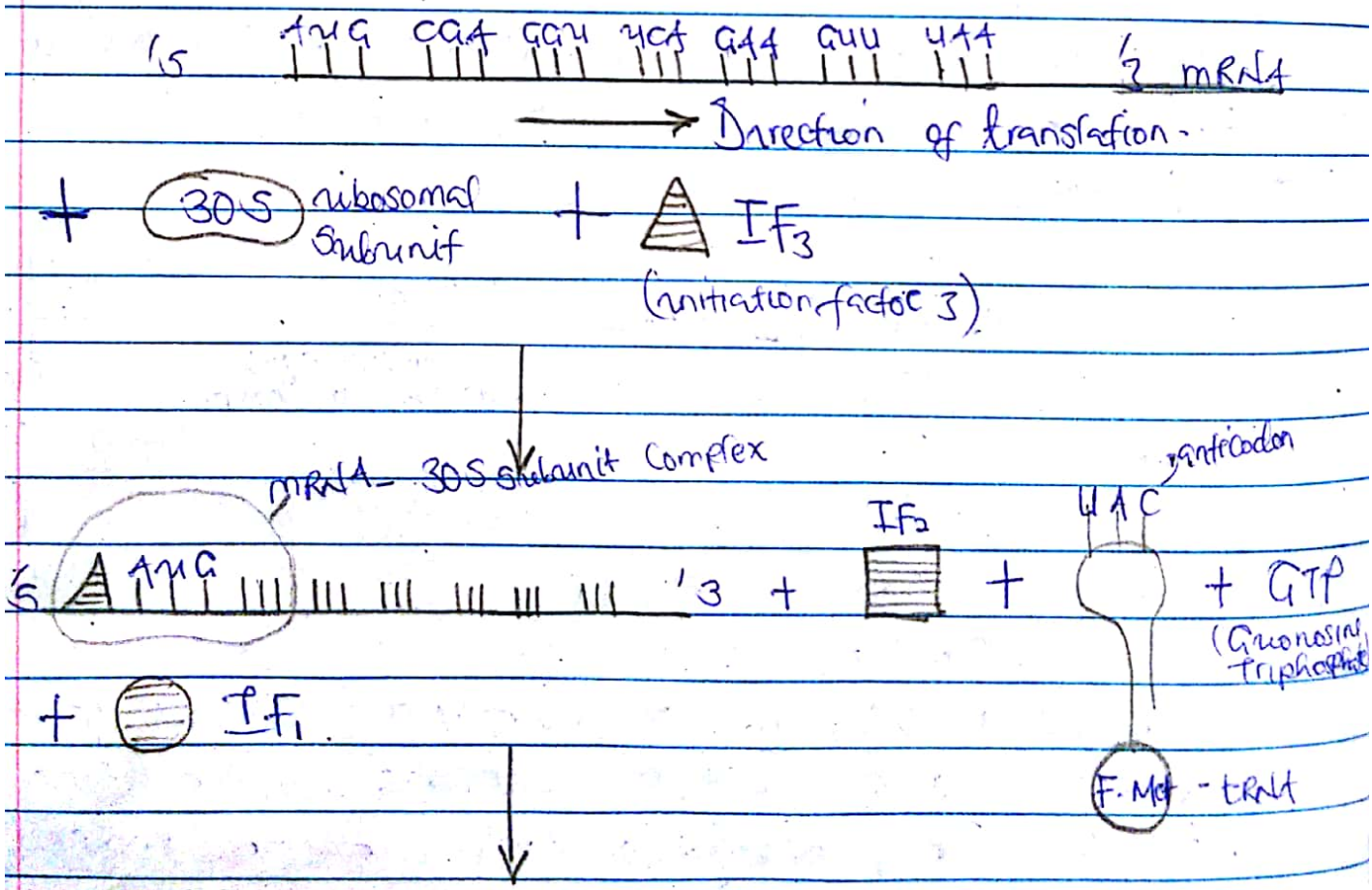
1. Initiation.

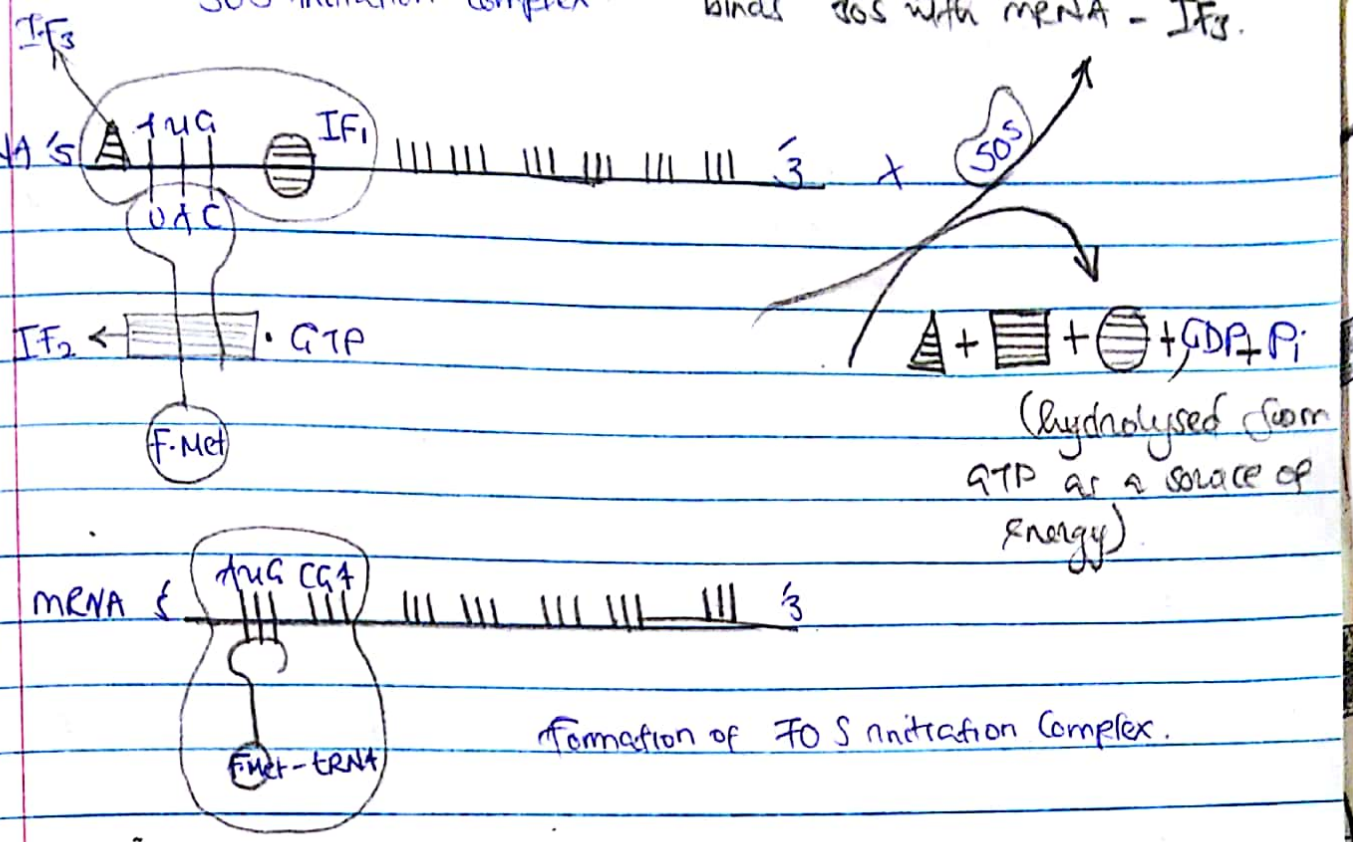


An important feature of initiation of polypeptide synthesis is the use of specific initiating tRNA molecule. In prokaryotes this tRNA molecule is charging (acylated) with the modified amino acid N-formyl methionine. The tRNA

is often designated $t_{RNA}^{f\text{-met}}$. Both $t_{RNA}^{f\text{-met}}$ for prokaryote and $t_{RNA}^{f\text{-met}}$ for eukaryotes recognise the codon AUG but only $t_{RNA}^{f\text{-met}}$ is used for initiation. The $t_{RNA}^{f\text{-met}}$ molecule is first acylated or charged with methionine and enzyme found only in prokaryote adding formyl to the amino group of methionine. In eukaryotes, the initiating tRNA molecule is charged with methionine but formylation does not occur.

Protein synthesis in bacteria begins by the association of 30S ribosomal subunit, an mRNA molecule and 3 proteins known as initiation factors (IF_s) such as IF_1, IF_2 and IF_3). and GTP. These molecules constitute the 30S complex.





Formation of 70S Initiation Complex.

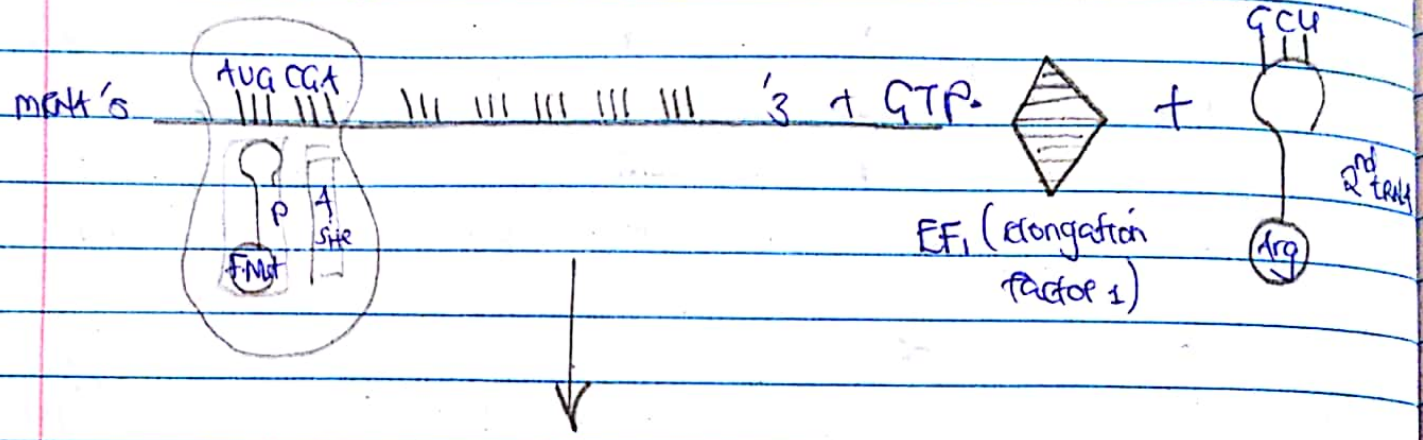
Formation of the 70S Initiation Complex places formyl-Methionine - tRNA in the P-Site.

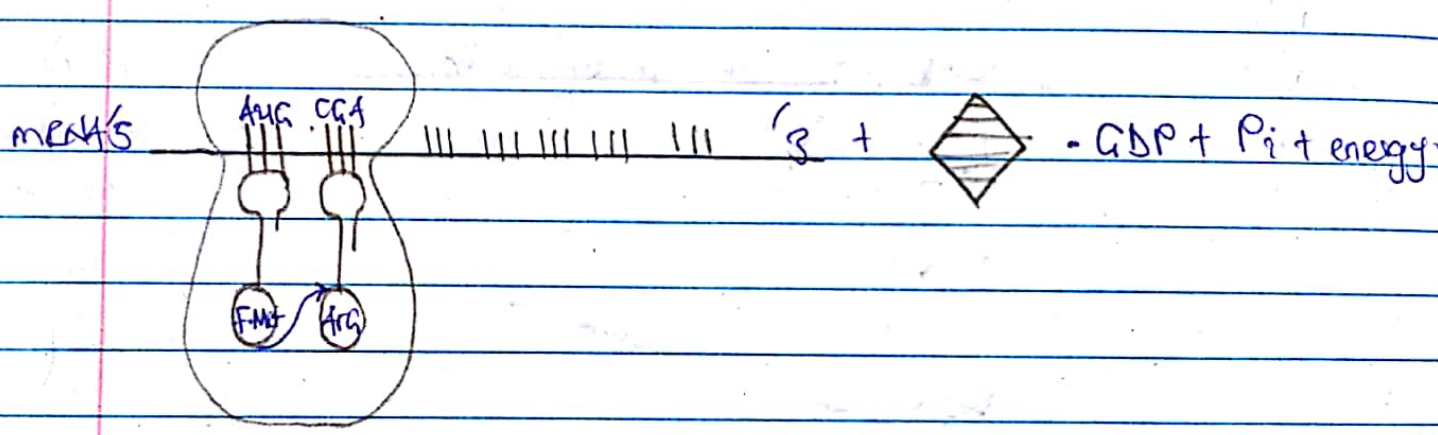
Protein synthesis starts with the association of 30S ribosomal subunit, mRNA and formyl-meth. tRNA to form a 30S Initiation complex. The formation of this complex requires GTP as a source of energy and 3 protein factors called IF_1, IF_2 and IF_3. One of those initiation factors IF_3 mediates the binding of mRNA to a 30S subunit complex. IF_3 also prevents the 50S and 30S subunit from coming together. IF_1 and IF_2 enhance the binding of initiation tRNA to the mRNA-30S subunit complex.

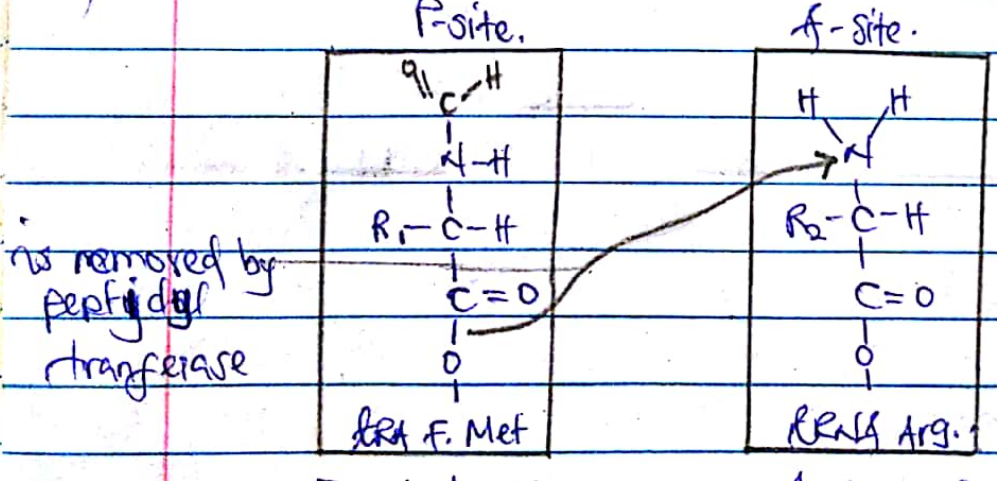
A 30S ribosomal subunit then joins a 30S initiation complex to form a 70S initiation complex. The bound GTP is hydrolysed in this step. The 70S initiation complex is ready for the elongation phase of the protein synthesis. The F.Met tRNA molecule occupies the P site on the ribosome. The other site for a tRNA molecule on the ribosome, the A-site is empty.

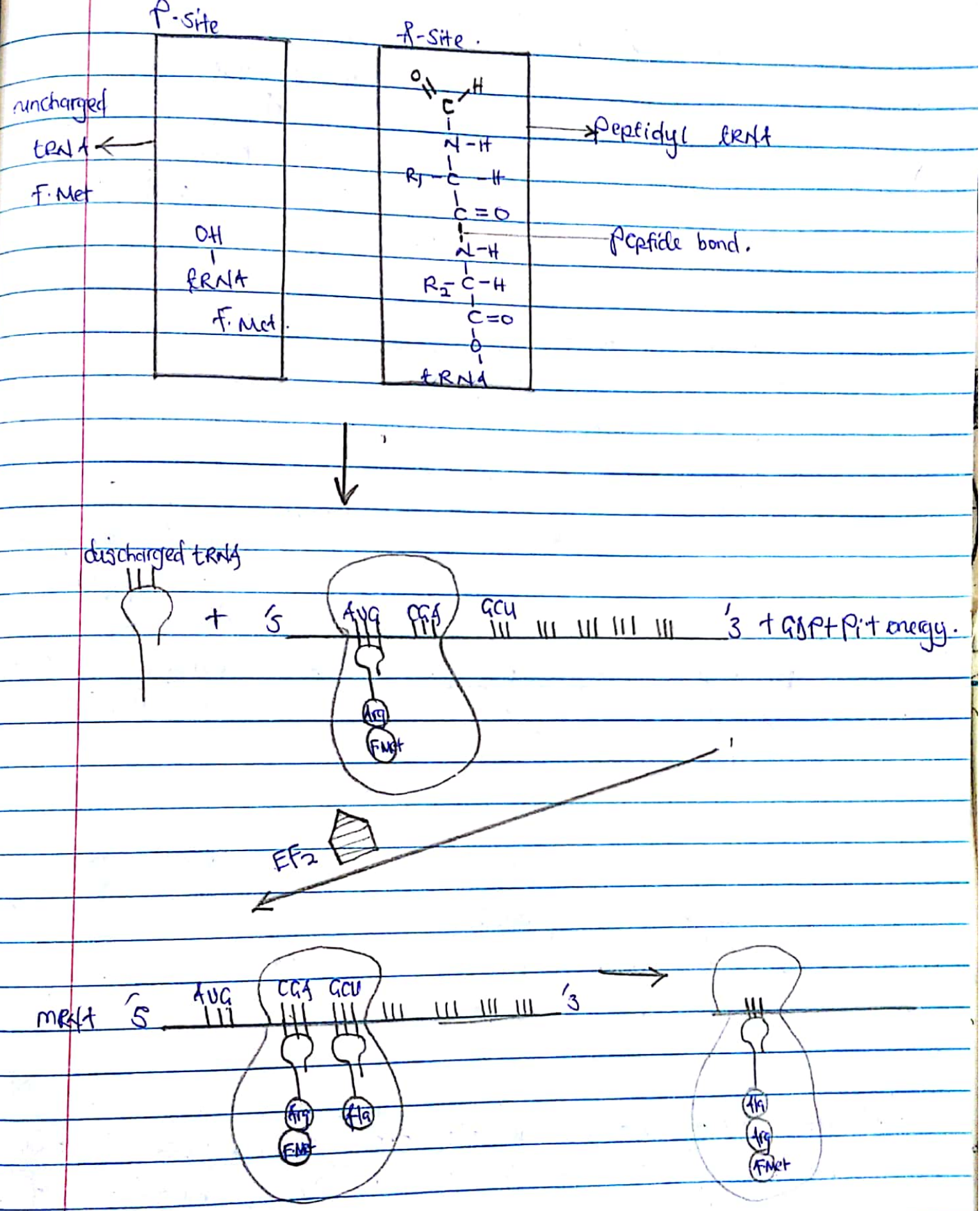
The important point now is that F. Met tRNA is positioned so that its anticodon pairs with initiating AUG codon on mRNA.

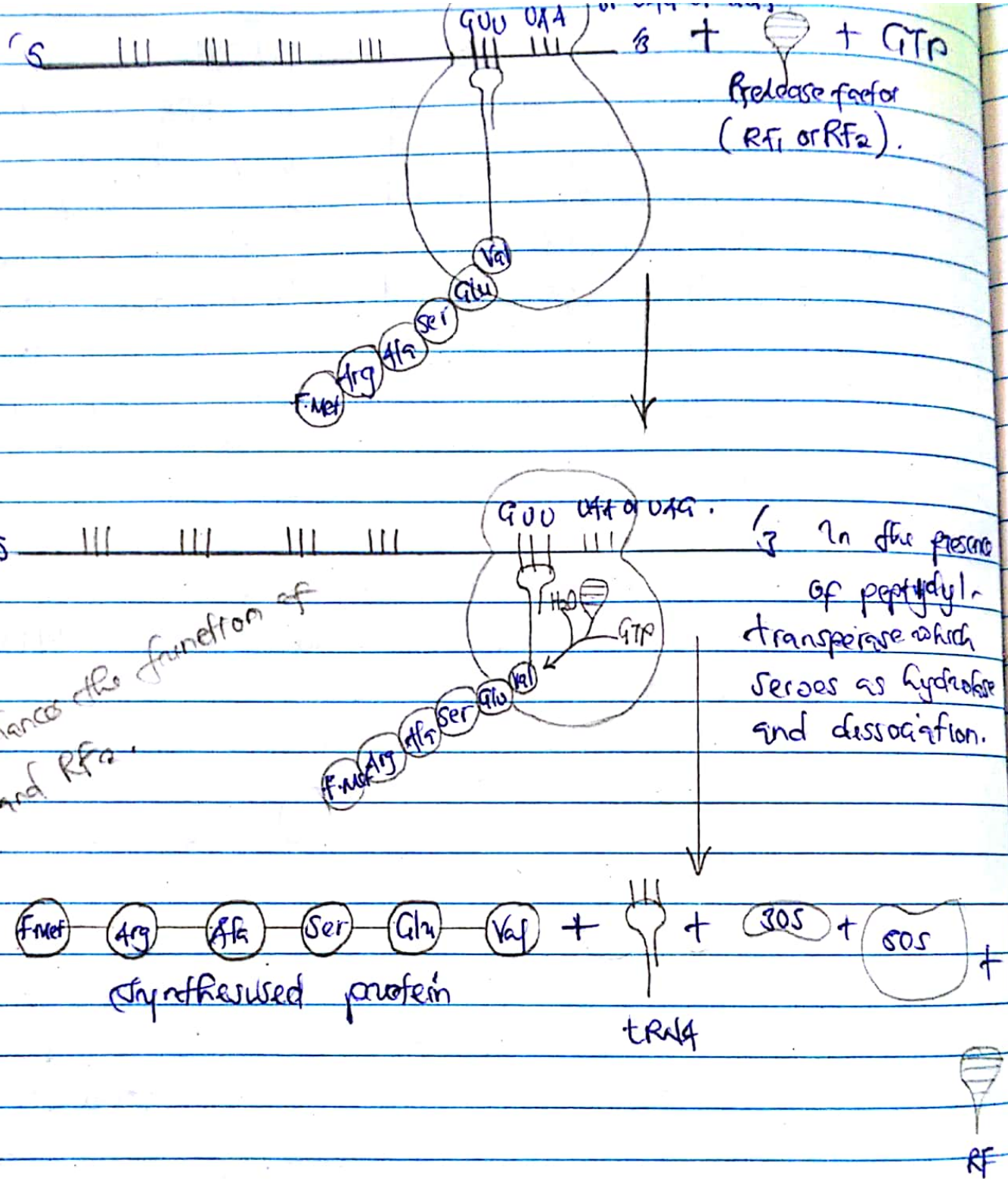
2 ELONGATION.








P-site
A-site.
uncharged
tRNA
F.Met
OH
tRNA
F.Met.
Peptidyl tRNA
Peptide bond.
discharged tRNA
+ 5'
AUG
CGA
GCU
3' + GTP + Pi + energy.
Arg
F.Met
EF2
mRNA 5'
AUG
CGA
GCU
3'
Arg
Ala
F.Met
Ala
Arg
F.Met

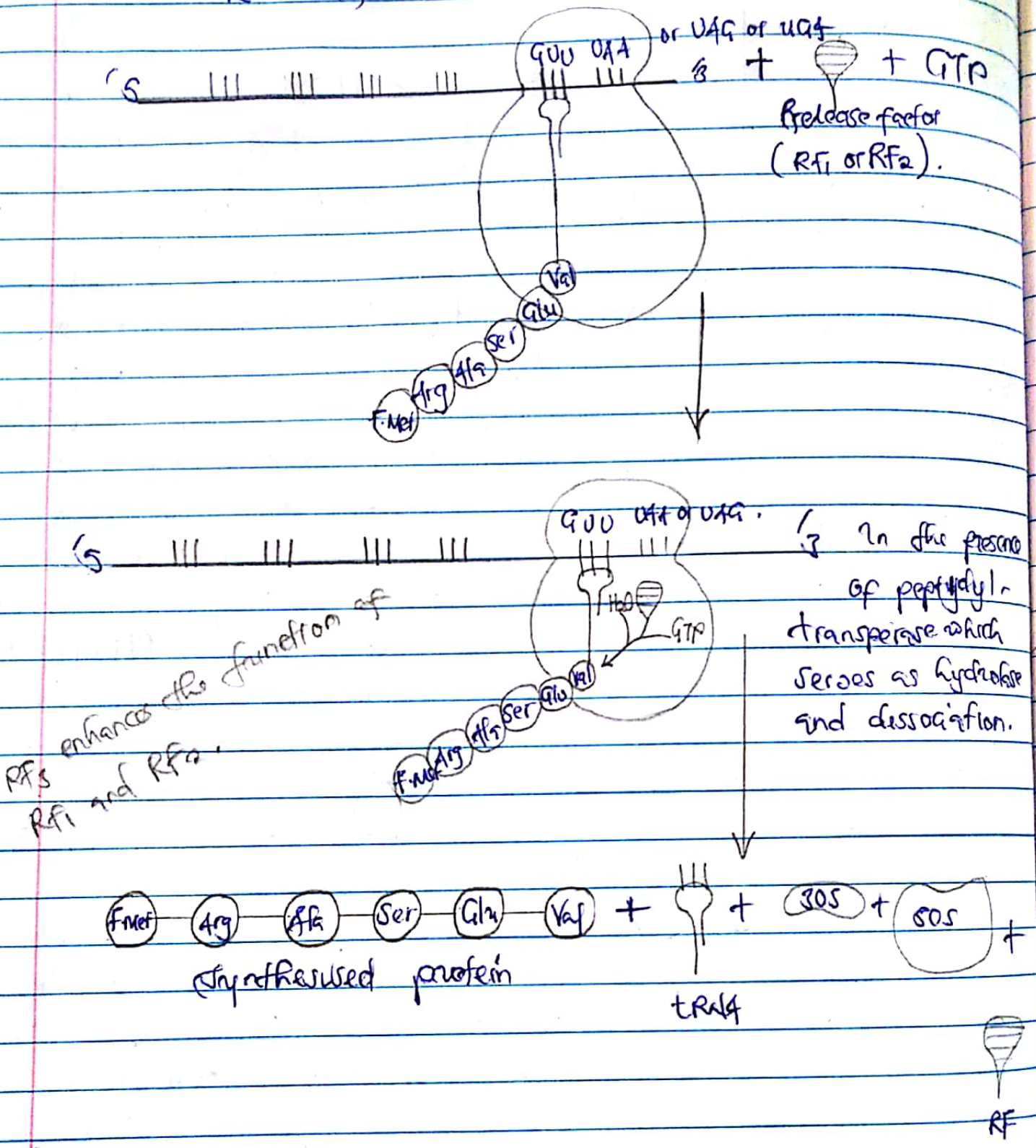


F-met tRNA Rmfres directly onto the P-site on the ribosome whereas all other aminoacyl tRNAs refsi the A-site and are subsequently translocated to the P-site.

2 ELONGATION

The elongation of polypeptide chain achieved by the

TERMINATION.



F-met tRNA directly into the P-site on the ribosome whereas all other aminoacyl tRNAs enter the A-site and are subsequently translocated to the P-site.

2 ELONGATION

The elongation of polypeptide chain achieved by the

following steps

a The second charged tRNA binds to the ribosome at the A-site with the help of the protein called elongation factors. EF1 carries a molecule of GTP correct hydrogen bonding with the mRNA template dictates a selection of a new tRNA and the activity of the EF1 ensures the proper positioning of the tRNA in the A-site. Such a placement activity needs energy that is provided by the hydrosis of GTP to GDP and a phosphate group. After performing its function, the EF1 protein dissociates from the ribosomes and in the cytoplasm is subsequently regenerated to its active form by another elongation factor EF2. At this point, both sites of the ribosome are occupied by tRNAs each of which carries an amino acid and each of which is hydrogen bonded to the template mRNA

b Formation of a peptide bond between the two amino acids.

To accomplish this job, the 1st amino acid of met is removed from its attachment to its tRNA and transferred to the free NH2 terminus of the second amino acid. The 1st amino acid is thus placed on top of the second, the resulting compound is a dipeptide. The rxn is catalysed by an enzyme associated with the 50s subunit and called peptidyl transferase. The energy for peptide bond formation is supplied by ATP.

c To get a dipeptide has been generated, continued synthesis requires that

the next codon should be made available and that the next tRNA be admitted to the A-site on the ribosome. This site being still occupied by dipeptide carrying tRNA, the problem is solved by a movement of the intact ribosome relative to the mRNA strand. This is called Translocation and consist of the following 3 steps:

i Ejection of discharged tRNA F.Met from the P-site.

ii Movement of tRNA dipeptide from the A Site to the P-site.

iii Movement of the ribosome in 5 to 3 direction by the length of one codon. This step requires the presence of an elongation factor EFG and GTP.

Hydrolysis of GTP enables EF3 to be released from the ribosome. After translocation, the A-site is empty ready to bind the next amino acyl-tRNA with an amino acid to start another round of elongation. As the process continues, the mRNA is progressively translated codon by codon from the 5' end to the 3 end.

3 TERMINATION.

Polypeptide chain elongation continues until the ribosome encounters a termination codon (either UAG or UAA). In the mRNA template, there are no tRNAs with anticodons complementary to the 3 termination codons. When the ribosome meets a " " , this codon is recognized by protein release factors (RFs) which bind

to the A (aminoacyl) site of the ribosome. The factor RF_1 identifies termination codons UAA and UAG while the factor RF_2 recognises the codon UGA, thus the release factors help the ribosome to reconise these triplade codons. The function of RF_3 seems to stimulate the activity. function of RF_1 and RF_2. The activity of these factors causes

i The termination of translation.

ii The release of the polypeptide chain from the tRNA. This is specifically done by the peptidyl transferase enzyme which now serves as a hydrolase enzyme

iii Dessociation of the 70S ribosome into its 30S and 50S subunit which leave the mRNA.

REGULATION OF GENE EXPRESSION IN PROKARYOTES.

Introduction.

The synthesis of particular gene products is controlled by mechanisms collectively called gene regulation Although cells contain the genetic capacity for a large number the synthesis of several of different products (proteins) not all of these products are present at any given time. Many being selectively activated only upon special occasion and in response to some environmental stimulus. E.g in Prokaryotes some enzymes are synthesised constitutively (continuously) indicating that transcription of mRNA is constantly occuring in them. However, other enzymes are synthesised only a need for their action arises.

And when this need has been achieved, enzyme synthesis stops. Transcription of mRNA in this case initiated only on demand and must therefore be subject to regulation. Exhaustively. Investigations have established that regulation of genes activity is in prokaryotes and eukaryotes may occur at 3 levels.

1 Transcription
2 Translation
3 Post-Translation.

The gene regulatory system in prokaryotes and eukaryotes are slightly differently from each other. Prokaryotes are generally free living unicellular organisms that grow & divide continually as long as environmental condition are suitable and the supply of nutrients are adequet. Thus their gene regulatory systems are adapted to provide the max. growth rate in a particular environment except when such growth would be detrimental. This procedure seems to apply to the 3 living unicellular eukaryotes such as yeast, algea and protozoa Clearly Really not all genes that are expressed produced that is activitated to produce a protein in all of the cells all of the time. This topic explains how gene expression is controlled in prokaryotes. Cells exert this control by determining which genes are to be switched on or off, those genes that are switched on will be transcribed and translated into a protein, those genes switched off will not. Gene regulation is best

understood in prokaryotes. Most studies of gene regulation have focused on Escherichia coli (E. coli) as a representated prokaryote.

Gene regulation is one of the most intensively studied areas of biological research today. Knowledge of what turns genes on and off will add greatly to the potential of such field as genetic engineering and medicine. Such information e.g may eventually help us how to cure cancer and prevent certain kinds of birth defects.

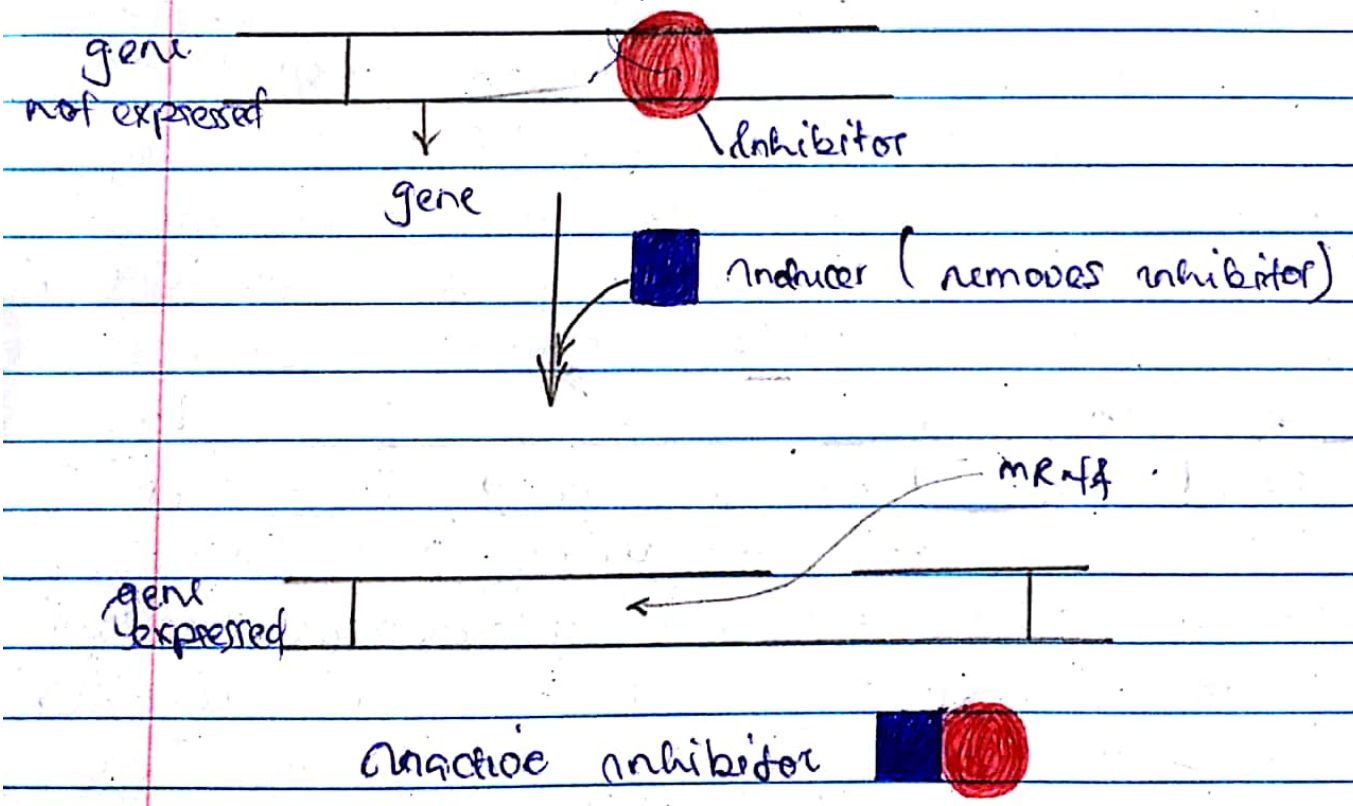
Constitutive genes are constanly transcribed.

Some genes produce proteins that are continously used by a cell e.g the enzyme involved in glycolysis are always needed to provide energy by cellular repiration. Such genes which are continually transcribed throughout the life of a cell called constitutive genes. Other genes however can be turned on and off, that is directed either to produce their protein product or to stop producing it. These regulated genes are the focus of this topic. Much of our understanding of gene regulation comes from studies of the intestinal bacterium E. Coli. Its availability & rapid growth when cultured in the laboratory have led to its extensive study. Our knowledge of the gene regulating mechanisms in E. Coli began with the contribution of the french investigators, Francis Jacob and Jacques Monod.

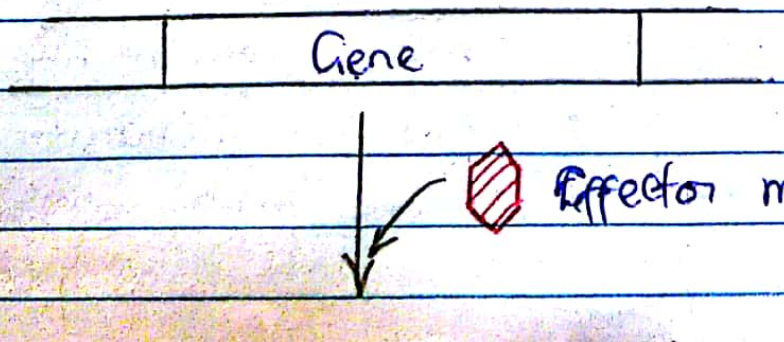
In the course of their research on E. coli Jacob and Monod studied the behavior of E.coli bacterium. When the bacteria was fed on a mixture of glucose and lactose, the bacteria first consumed all of the glucose and the temporally stopped growing until the genes of the lactose operon (Lac operon) become induced to provide the ability to metabolise lactose as a usable energy source.

Mechanisms of gene Regulation in Prokaryotes.

a) Negative Regulation.



b Positive regulation.



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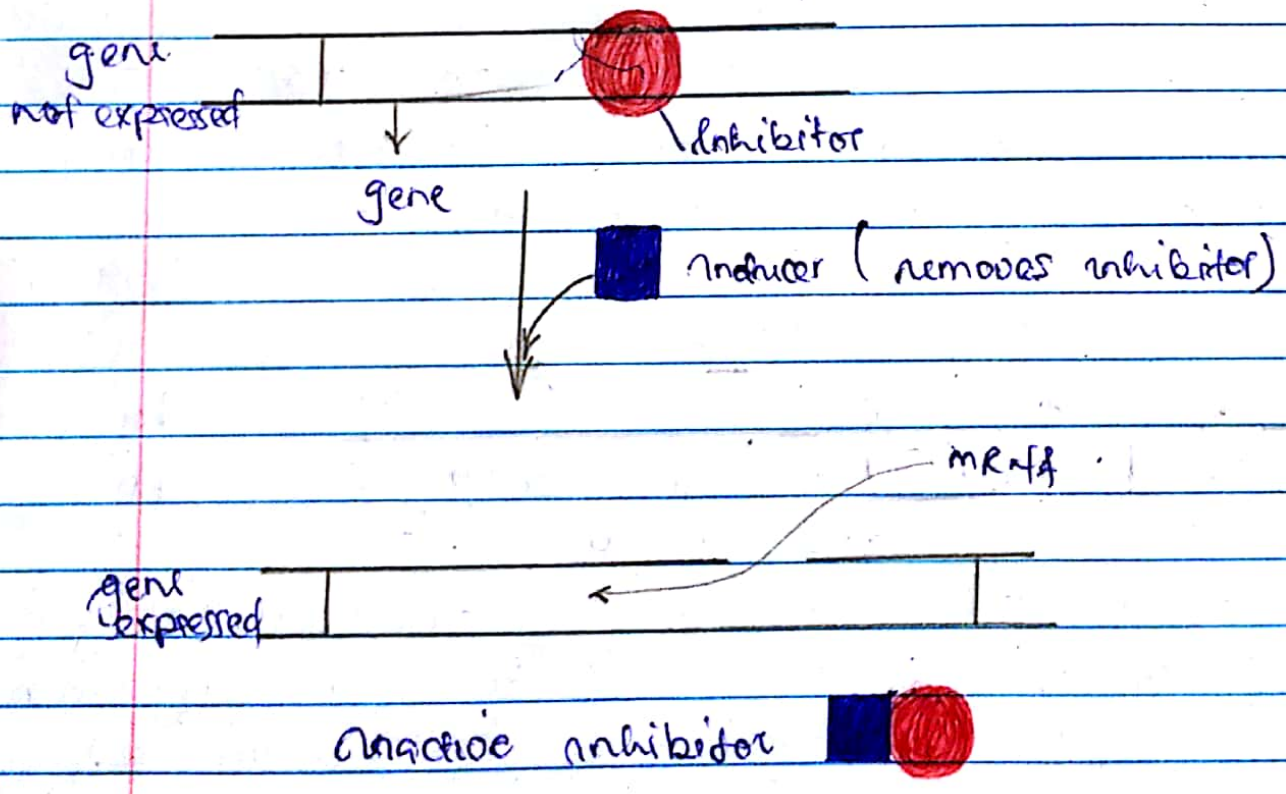


b Positive regulation.

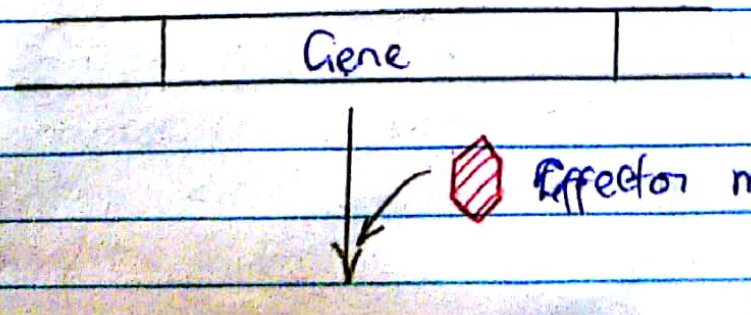


Fig 1: The distinction between negative and positive regulation. In negative regulation an inhibitor bound to the DNA must be removed before transcription can occur. In positive regulation an effector molecule must bind to the DNA.

In bacteria, there are 2 mechanisms on gene regulation at the level of transcription.

1 Negative regulation (2) Positive Regulation

In a negative regulated system an inhibitor is present in a cell and prevents transcription. A antagonist of the inhibitor called an inducer as needed to allow initiation of transcription. In a positively regulated system, an effector molecule (which may be protien) activated a promoter to inhibit the action of the inhibitor.

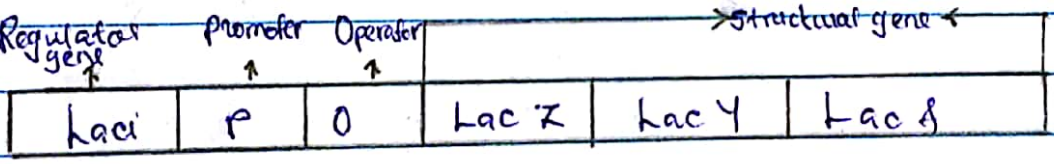


Fig 2: A gene map of the lactose Operon (Lac Operon).

Structural genes:

1 Gene Z contains 3063 base pair and codes for an enzyme β-galactosidase.

2 Gene Y contains 500 base pairs and codes for an enzyme Galactoside perimerase.

3 Gene A contains 800 base pairs and codes for an enzyme thiogalactoside transacetylase.

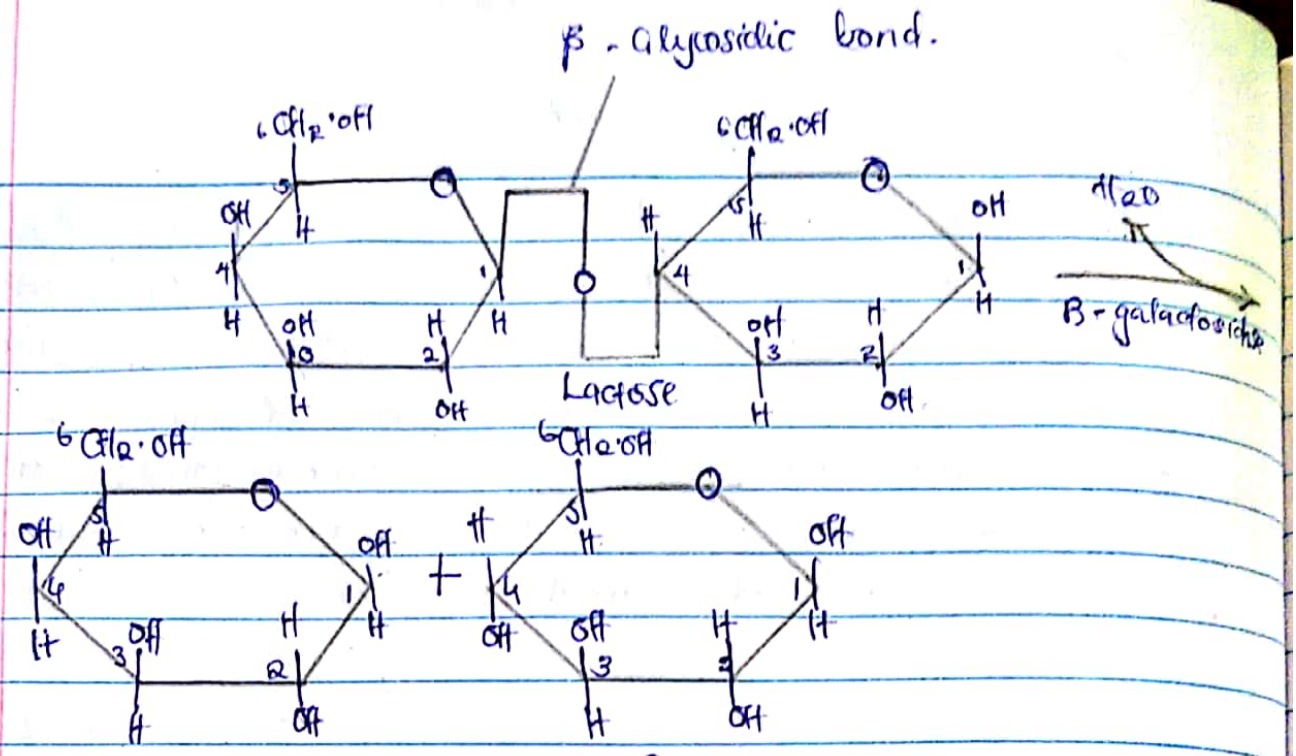


Fig 5: The hydrolysis of Lactose to Galactose and Glucose by the enzyme β-Galactosidase.

In 1961, Jacob and monod described how gene regulation in E. coli permitted it to produce the lactose digesting enzyme when it was given lactose as food. Since then similar mechanisms have been described not only in E.coli but in other bacteria as well. It appears that most if not all bacteria genes are organised into clusters called Operons. Operons are composed of 4 parts; (1) structural gene (2) promoter (3) Operator (4) regulator gene

Each operon includes several genes called structural genes that code for the synthesis of a group of enzymes that are involved in the same function e.g digestion of lactose Structural gene of Lac operon namely Z, Y and A whose products are involved in the breakdown of the sugar lactose, gene Z contains 3063 bp and codes for an enzyme

β-galactosidase which converts lactose into glucose and galactose while gene y contains 800 bp and codes for an enzyme galactoside permase which is a plasma membrane bound protein and facilitates the entrance of lactose into the cell. Gene a comprises 900 base pairs and specifies an enzyme thiogalactoside transacetylase which transfers an acetyl group from acetyl co-enzyme A (CoA) to β-galactoside, this enzyme is indirectly involved in lactose utilisation.

Transcription of messenger RNA begins when RNA polymerase recognises the promoter site on a strand of DNA. The promoter is that part of the operon where RNA polymerase binds to begin transcription of the structural genes. The structural genes of an operon all share a single promoter site. When RNA polymerase bind to this site, it transcribes all of the structural genes onto one mRNA strand which may go on to be translated into the individual proteins, However other features of the operon may prevent RNA polymerase from binding to the promoter site and thus may prevent transcription from occuring. Whether the structural genes of an operon will be transcribed is under the control of the operator. The operator is that part of the operon that acts as the control switch which can turn transcription of the structural genes on or off by allowing or preventing RNA polymerase to bind to the promoter. The operator in turn is regulated by a special part of the operon called

the regulator gene. This gene codes for the production of a protein that can bind to the operator. When this protein molecule called repressor or inhibitor binds to the operator it prevents RNA polymerase from binding to the promoter region of the operon. Thus the repressor protein represses the expression of the structural gene in the operon.

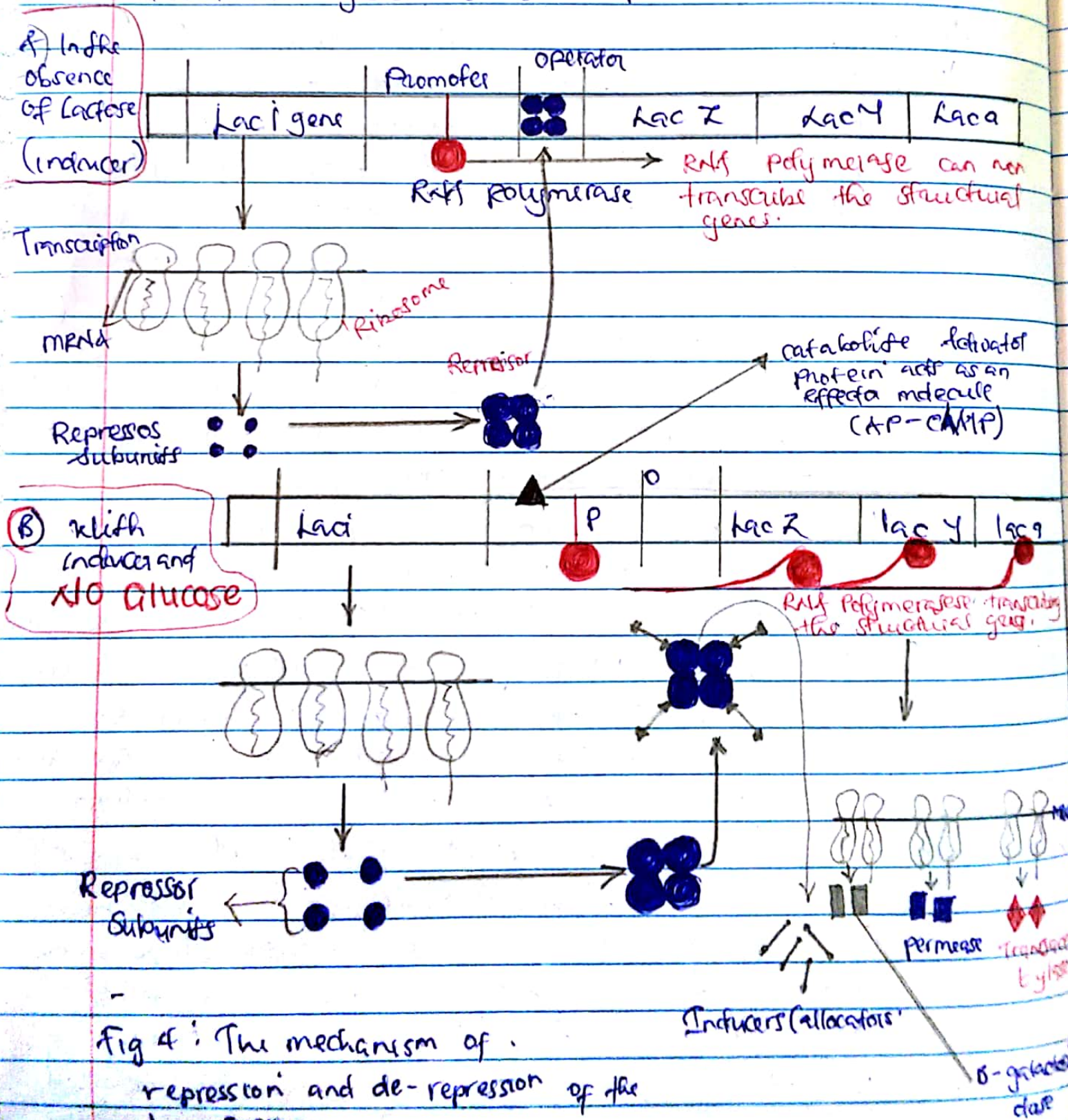


Fig 4: The mechanism of repression and de-repression of the Lac Operon.

The Lactose Operon is activated by the presence of Lactose.

The Lactose operon also designated the Lac operon controls the production of enzymes needed to digest Lactose in E. coli. It consists of 3 structural genes, regulator gene, an operator and promoter site. The structural genes code for 3 enzymes used in the digestion of Lactose.

1. An enzyme that breaks down Lactose into simpler sugars.
2. An enzyme that transports Lactose across a plasma membrane into a bacteria cell.
3. A 3rd enzyme that tranfers an acetyl group to acetyl CoA that facilitates the utilisation of Lactose sugar.

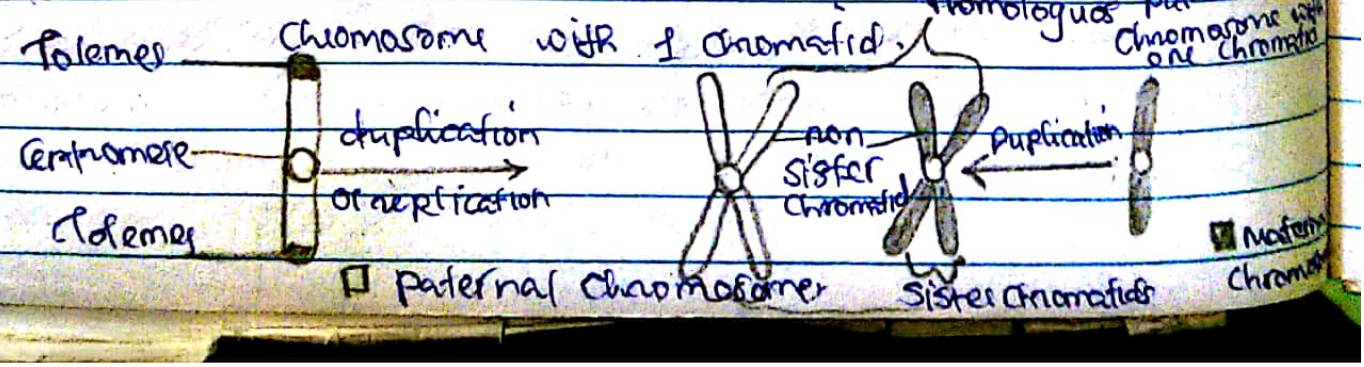
Unlike the structural genes which are regulated, the regulator gene that codes for repressor protein is constituted, that is, the regulator gene is always turned on and continually makes small amounts of the repressor protein. Under normal conditions in E. coli is that when Lactose is absent, this repressor protein binds to the operator site, blocking the promoter site in the process. As a result, RNA polymerase can not bind to the promoter site and ∴ cant began transcribing the structural genes. Thus where cant Lactose present, the " that code for the enzymes needed to digest Lactose are not been transcribed.

The Lactose operon is turned on when Lactose is present in E. Coli's environment. A few molecules of Lactose enter the cell and are converted to derivative of Lactose.

called allo lactose. This derivative attached to the repressor protein thereby modifying its shape so that the repressor protein can no longer bind to the operator site as a result the promoter site is unblocked and RNA polymerase binds to the promoter and begins transcribing the structural gene. The resulting mRNA molecule is translated forming the 3 enzymes that enable E. coli to digest lactose. When lactose once again becomes scarce in the environment no lactose derivative is available to bind to the repressor protein. The repressor attaches to the operator site preventing further transcription of the structural genes for the enzymes. This sort of control in which the presence of substrate induces the synthesis of an enzyme is known as inducible system. The expression of an inducible system is normally controlled by a repressor that keeps it turned off. The presence of the substrate (here lactose) inactivates the repressor allowing the structural genes to be expressed in protein synthesis. Inducible operons usually code for enzymes involved in the break down of nutrient molecule that provide the cell with energy.

DISCOVERY OF CHROMOSOMES.

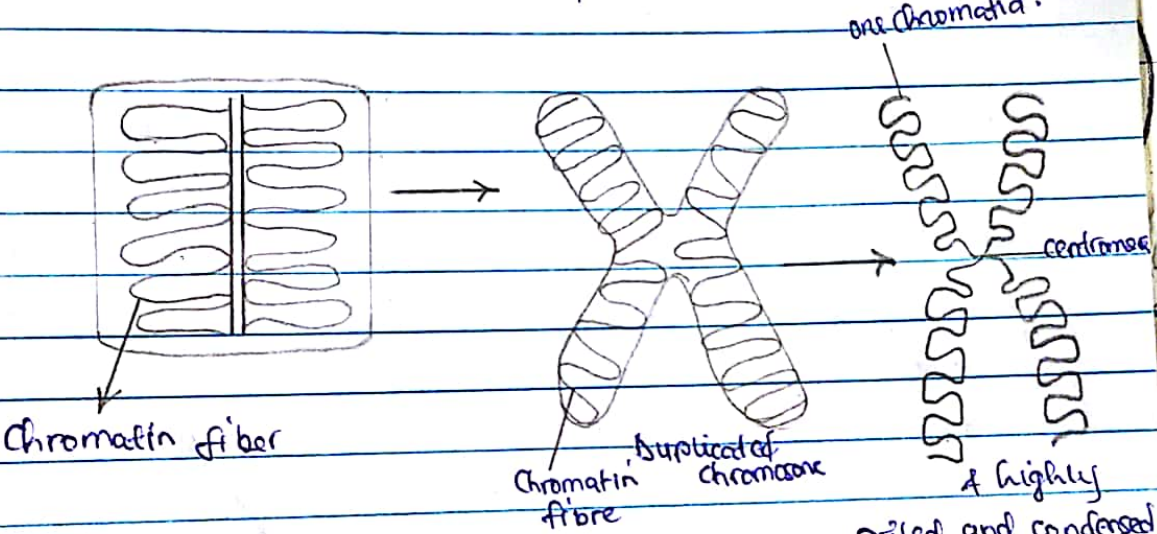
Chromosomes were first observed by

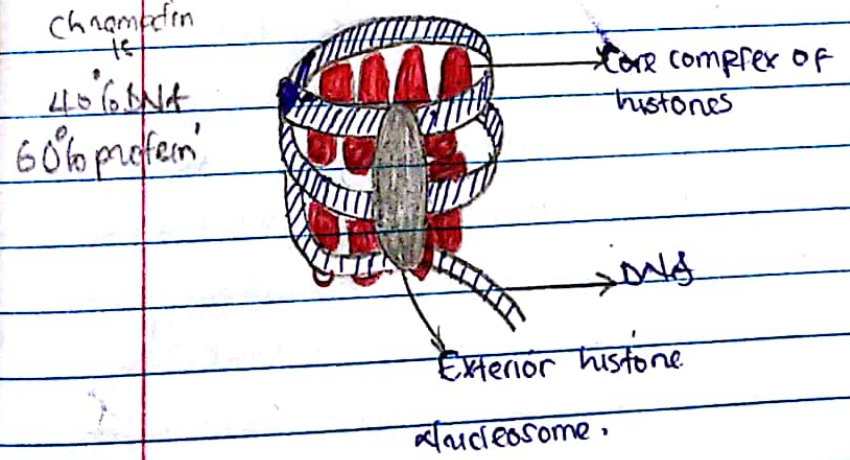


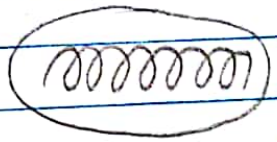
Chromosome with 1 chromatid.

by the biologists Walther Fleming in 1882 while he was examining the rapidly dividing cells of Salamander Larvae. when Fleming looked at the cells under a light microscope, he saw minute threads within the nuclei that appeared to be dividing lengthwise. Fleming called their division Mitosis based on the greek word Mitos meaning thread.

CHROMOSOME STRUCTURE.







Bacterial size is 0.003mm, The circumference of its DNA is 1.36mm.

Chromosomes are composed of Chromatids, a complex of DNA and protein. Most are about 40% DNA & 60% protein. The significant amount of RNA is also associated with chromosomes because Chromo are the sites of RNA synthesis.

A simple bacteria cell is a complex organism filled with specialised structures and able to respond to the range environmental factors. The genetic information for a bacteria requires a circle of DNA with a length of 1.36 mm that has to pack into a cell that is only 0.003 mm long. A human cell contains 46 DNA molecules whose total length is about 2.3 m all packed into a nucleus only 10 micron (um) = (0.001 mm) in diameter. The DNA in a cell must be well organised in order to pack that huge length into such a small space. There is a problem of understanding how a circle of DNA 1.36 mm long fits into bacteria cell and how 2.3 m of DNA fits into the nucleus. The DNA must be folded or coiled or looped but the packing must be done in such a way that the DNA does not break. The circular bacteria DNA is thought to be super coiled, the double helix is twisted and the circle sealed so that the twist can not fall out. The problem associated with packing eukaryotic DNA are much greater. In eukaryotes the DNA is arranged as chromosomes. Each chromosome contains 1 long DNA molecule in a human cell, each chromosome contains an average of 5cm (50000um) the chromosomes are only visible as seperate structures during cell division when the cell divides, the nuclear membrane breaks down and the chromosomes are distributed between the two daughter cells.

During cell division, each chromosomes is approx. 5 um long. Some how the 50 000 um of DNA is packed down so that it is 10000 times shorter. DNA is a nucleic acid, every phosphate group in DNA behaves as an acid at the pH of the cell around pH 7 all the phosphate groups have given up their H+ and are negatively charged. They are about 100000 000 phosphate groups in each of DNA molecules in the nucleus of the human cell, If each of these were negatively charged, there would be 46 rigid little rods each about 5cm long, inject the DNA in cells is neutralised. In bacteria cells, the DNA is neutralised by positive cation such Ca and Mg and 2 substances called Spermine and Spermidine. These all contain many basic groups that gain H+ at the pH of the cell and are ∴ positively charged. These positive charges neutralise the (-) charges on the DNA. Eukaryotic cells contain a family of proteins called histones. These histones contain many basic amino acid residues. Which again H+ at the cell pH and are ∴ positively charged, these positive charges neutralise the negative charges on DNA. Every 200 nucleotide the DNA is coiled around a core of 8 histone proteins forming a complex known as a nucleosome, Unlike most protein which have an overall (-) charge, histones are (+) charged due to an abundance of the bases amino acid Arginine & Lysine. They are thus strongly attracted the (-) charged

regulation of expression.

phosphate groups of the DNA. The histone cores thus act as magnetic forms that promote and guide the coiling of the DNA.

CHROMOSOME NUMBER.

Table 1: Chromosome number in selected eukaryotes

	Group	Total # of Chromosomes	Group	Total # of Chromosomes
1	Yeast	16	6. Garden Pea	14
2	Mosquito	06	7. Corn	20
3	Drosphila	08	8. Wheat	42
4	Honey bee	12	9. Sugar Cane	80
5	Silk worm	56	10. Frog	22
12	Human	46	11. Mouse	40
13	Chimpanzee	48	14. Horse	64
15	Chicken	78	16. Dog	76

Since their initial discovery, chromosomes have been found in the cells of all eukaryotes examined. Their # may vary from one species to another. Most eukaryotes have between 10 and 80 chromosomes in their body cells. Human cells each have 46 chromosomes consisting of 23 identical pairs. Each of these 46 chromosomes contains thousands of genes that play important roles in determining how a person's body develops and functions. For this reason, possession of all the chromosomes is essential to survival. Humans missing even 1 chromosome, a condition called Monosomy, do not survive in embryonic development.

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When the chromosomes are highly coiled and condensed at the time of cell division, it is possible to photograph and count them. Before nuclear division takes place, DNA replicates, thereafter each chromosome is duplicated and has two identical paits called sister chromatids. Sister chromatids are genetically identical that is they contain exactly the same genes. Sister chromatids are constricted and attached to each other at a region called the centromere. During the nuclear division, the centromeres divide and in this way each duplicated chromosome gives rise to two daughter chromosomes. Centromeres do not contain any genes, however, they do contain large segments of highly repetative DNA called alpha satellite DNA. This is thought to play a significant role in centromere function. The Centromere contains the kinetochore.

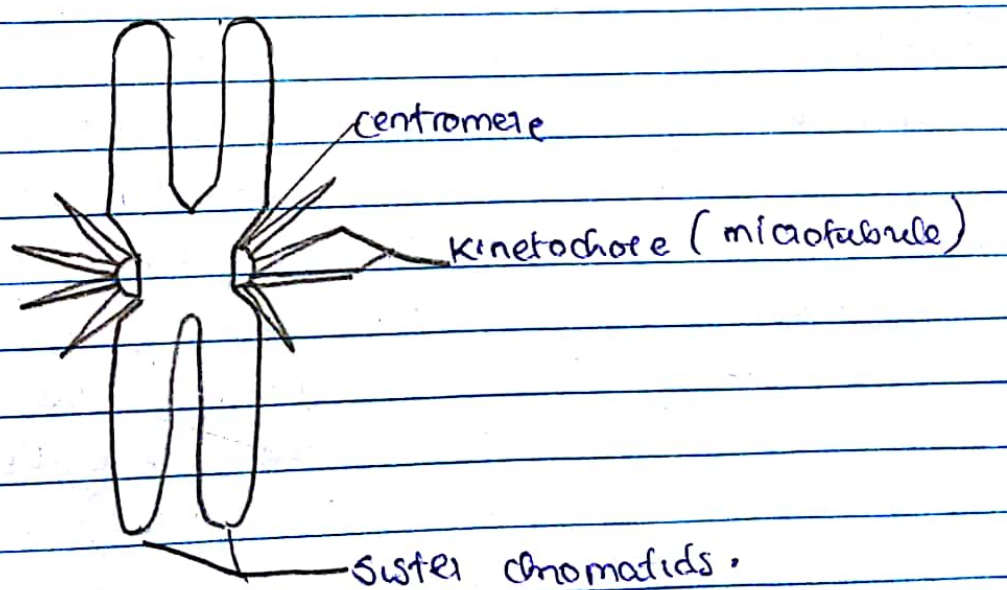
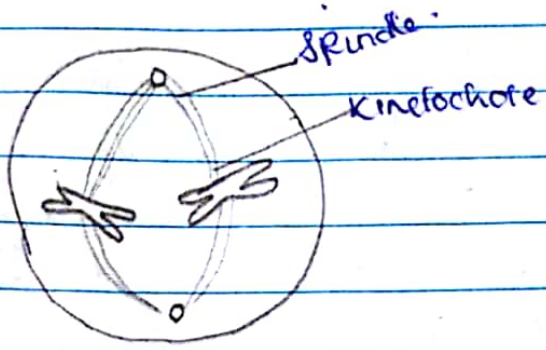


fig 1: A chromosome showing kinetochore.

Mark 16: 17-18
Acts 3:11
Luke 2:9-11



The centromere of each chromosome forms kinetochores, these structures lie on either side of the chromosome so that the kinetochore microtubules or fibres project in opposite directions. The fibres interact with the spindle often resulting in agitated chromosome movement
The centromeres and the telomeres are essential parts of chromosomes. The centromere is essential for chromosome segregation. The centromere is a specific region of the eucaryotic chromosome that becomes visible as a distinct morphological entity along the chromosome during condensation it serves as a central component of the kinetochore, a complex of DNA and proteins to which the spindle fibres attach and move the chromosomes in both mitosis and Meiosis. The kenetochore is also the site at which the spindle fibres shorten causing the chromosomes to move towards the poles. The centromere holds the two chromatids together until they seperate during cell division.

1) Somatic cell (body cell)
2) Sex cell

SEX CHROMOSOMES AND AUTOSOMES.

Human and animal chromosomes are categorised as either Sex Chromosomes or autosomes. Sex Chromosomes are 11 that determine the

Sex of an organism and they may also carry genes for other characteristics. In humans, sex chromosomes are either X or Y. Normal females have two X chromosomes and normal males have an X and a Y chromosomes. All of the other chromosomes in an organism are called autosomes. Two of the 46 human chromosomes are sex chromosomes. While the remaining 44 chromosomes are autosomes. Every cell of an organism produced by sexual reproduction has 2 copies each autosome, the organism receives 1 copy of each autosome from each parent, the 2 copies of each autosome are called Homologous chromosomes. Homologous chromosomes are the same size and shape and carry genes for the same traits. E.g if one chromosome in a pair of homologous chromosomes contains a gene for eye colour, the other chromosome have the same gene.

CHROMOSOMES EXIST IN PAIRS.

In somatic cells of complex organisms, the chromosomes are paired, thus the 46 chromosomes of each human cell are actually 23 pairs. One set of 23 was contributed by the female parent, the chromosomes of this set are refered to as Maternal chromosomes. The other set of 23 the paternal chomosomes, was contributed by the male parent. Each chromosome pair is different enough in size and shape that biologists can count and identify them.

A cell with chromosomes occuring in pairs is referred to as diploid or 2n. In humans, diploid # is 46 chromosomes (23 pairs) the reproductive cells or garmets can not be diploid. But it is hyploid or n.

Types of chromosomes.

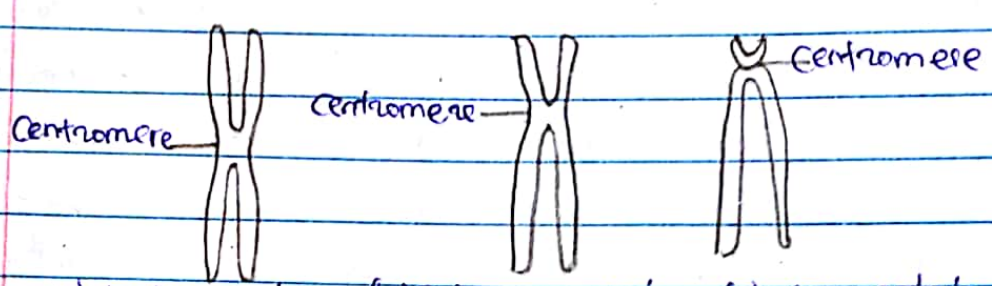


fig 2: Chromosome types.

Human chromosomes are classified by centromere position into 3 types; Metacentric with a more less central centromere and arms of approx. equal length.

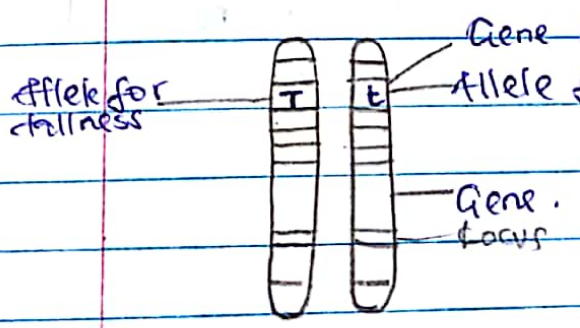
a) Submetacentric - with an off-centre centromere and arms of clearly different lengths.
b) Acrocentric - with the centromere near one end

TELOMERS.

Telomers are located at the end of chromosomes they consist of DNA and protein. The telomers appear to play a vital role in maintaining the stability of the chromosomes sealing the ends of linear DNA. They also seem to play an important role in regulating cell division. under normal situations, telomers boom shorter & shorter with cell division. When they have shorten to a certain extent

length, the cell stops dividing. If the telomers are removed, the chromosome disintegrates, it is thought that the ageing process may be linked to telomer damage. Telomers contain repeating sequences of bases which are synthesis with help of an RNA containing an enzyme called telomerase. Telomerase activity is supressed in normal human somatic cell, however, in cancerous cells, telomerase is active and maintains the telomere length, so that the cells continue to divide. It is thought that this abnormal retension of the telomers is involved in the development of some types of cancer.

GENES AND ALLELES



Homologous Chromosomes

In genetics a gene can be regarded as a specific length of DNA which occupies a position on a chromosome called Locus. The gene determines a particular characteristic of an organism in this case, the height of the plant. Mendel recognised that the two ways in which height could be expressed (tall and short) would be determined by factors, we call these factors Alleles. Alleles are different forms of the same gene which may differ

a way in which a particular characteristic such as the height of a plant is expressed more accurately an allele is a particular sequence of nucleotide base making up a gene. The phenotype (appearance) may be changed depending on which allele is expressed. An allele may or may not be expressed on the phenotype e.g a recessive will not be expressed if a dominant allele is also present. Thus in other peas, the genes for height is always found at the same locus on a particular pair of homologous chromosomes, but either the allele for tallness or shortness will be present at each locus. By convension, a gene is represented by a letter (s). The upper case letter represents the dominant allele and the lower case letter represents the recessive allele. T represents the allele for tallness t. represents the allele for shortness

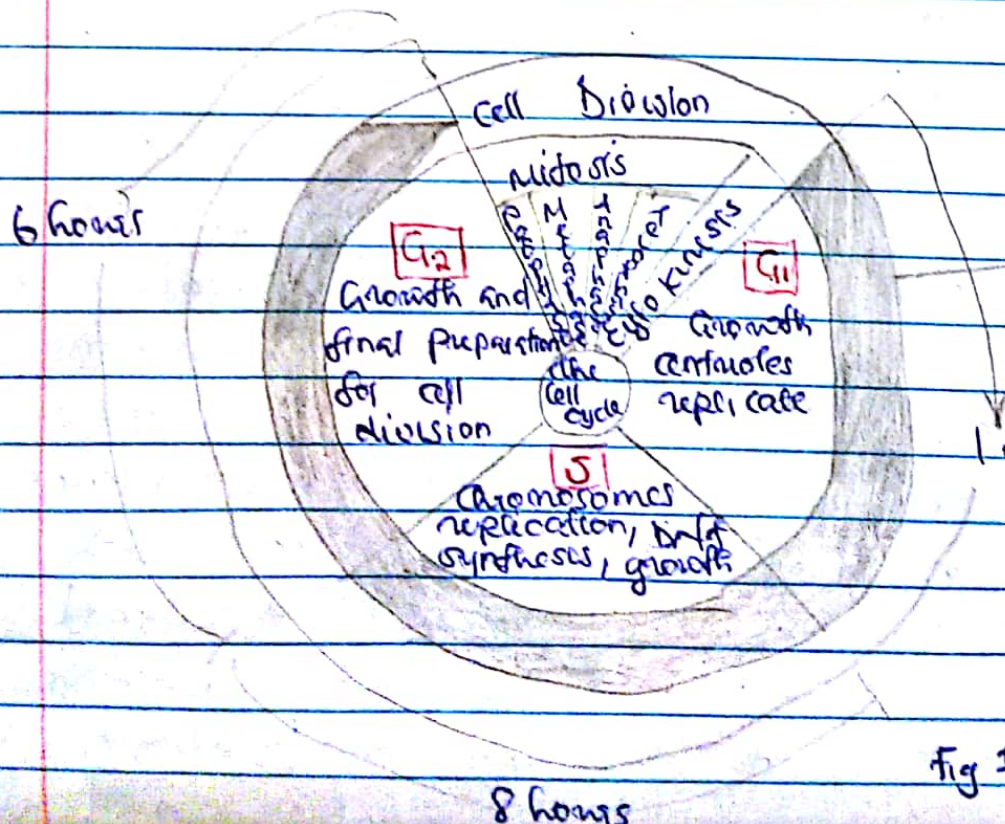


fig 1 The cell cycle.

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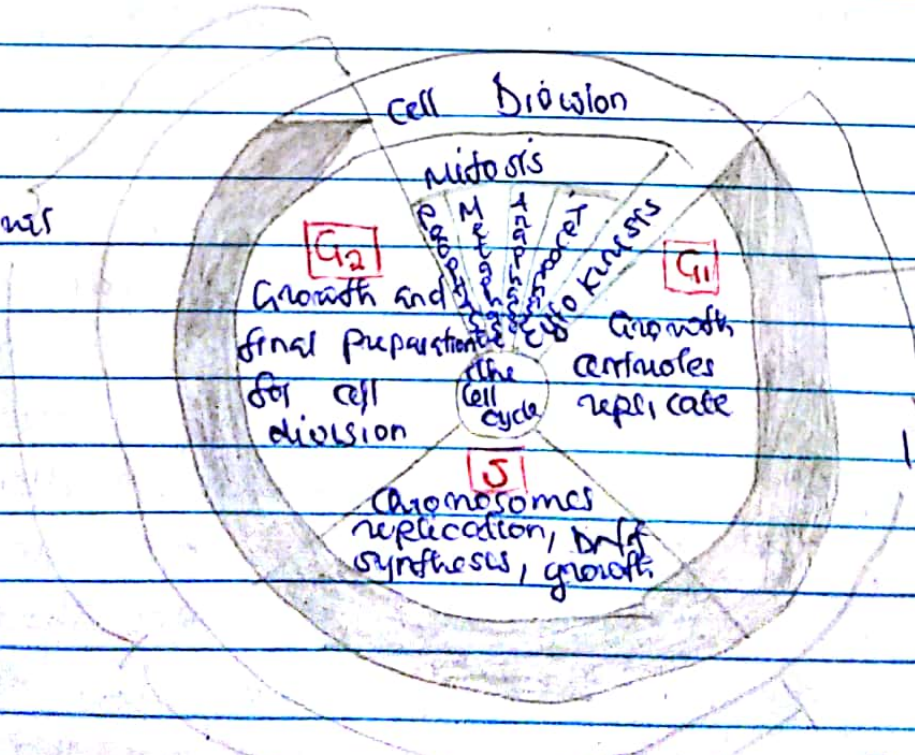

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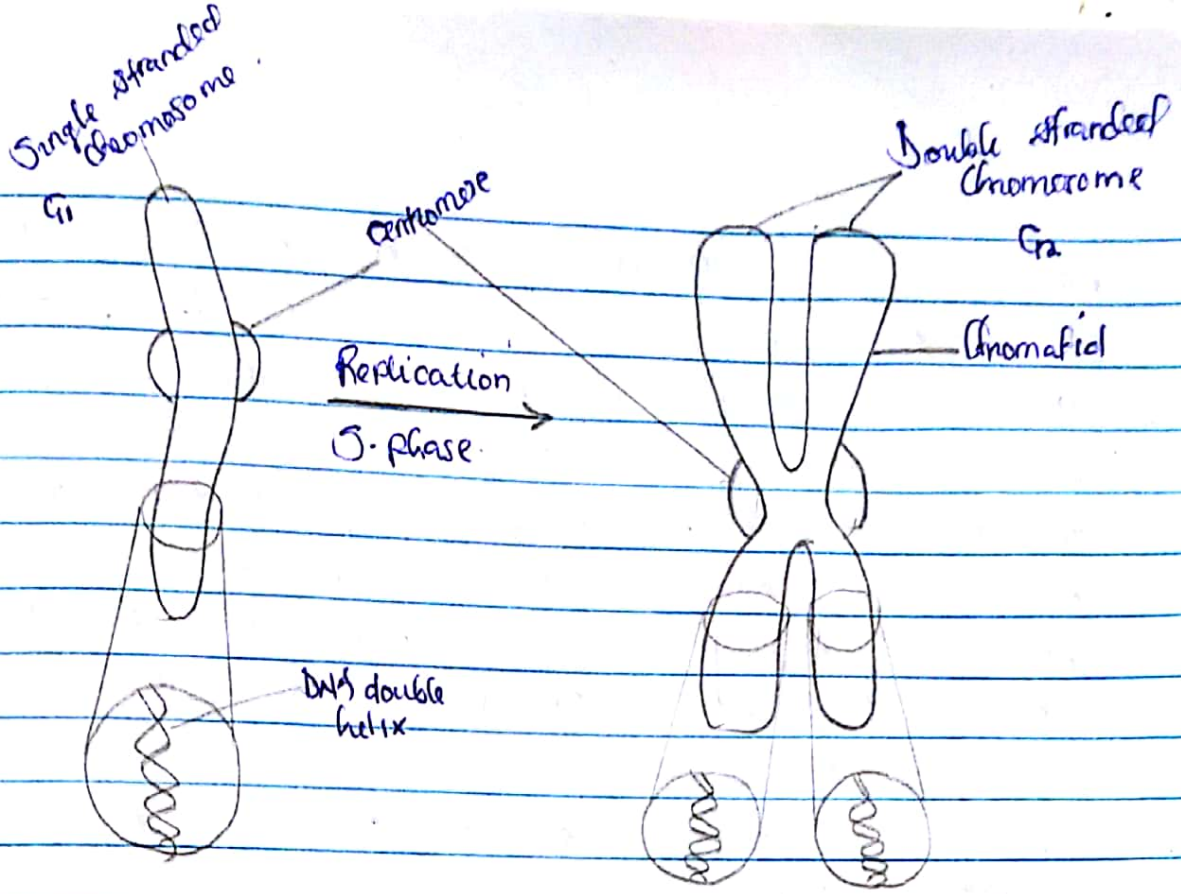


Fig 2: Changes in chromosomes structure are as a result of DNA replication during S phase.

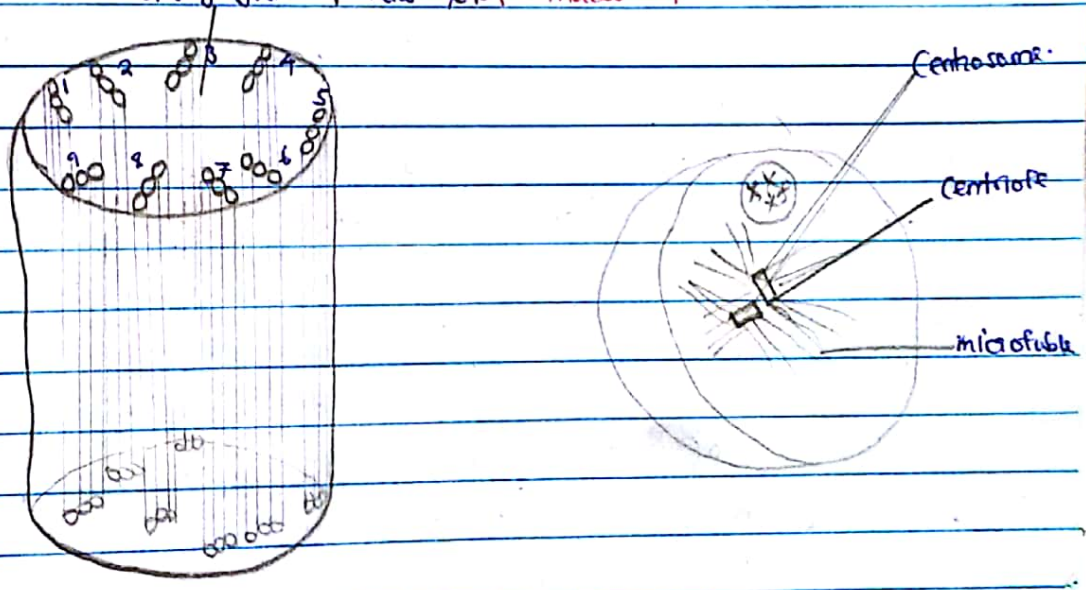


Fig 3: The centrosome and its component centrioles.

A human being life begins as a single cell called zygote formed by the union of an egg & sperm. By adult hood, our bodies consist of trillion of cells. What happened in the intervening years?

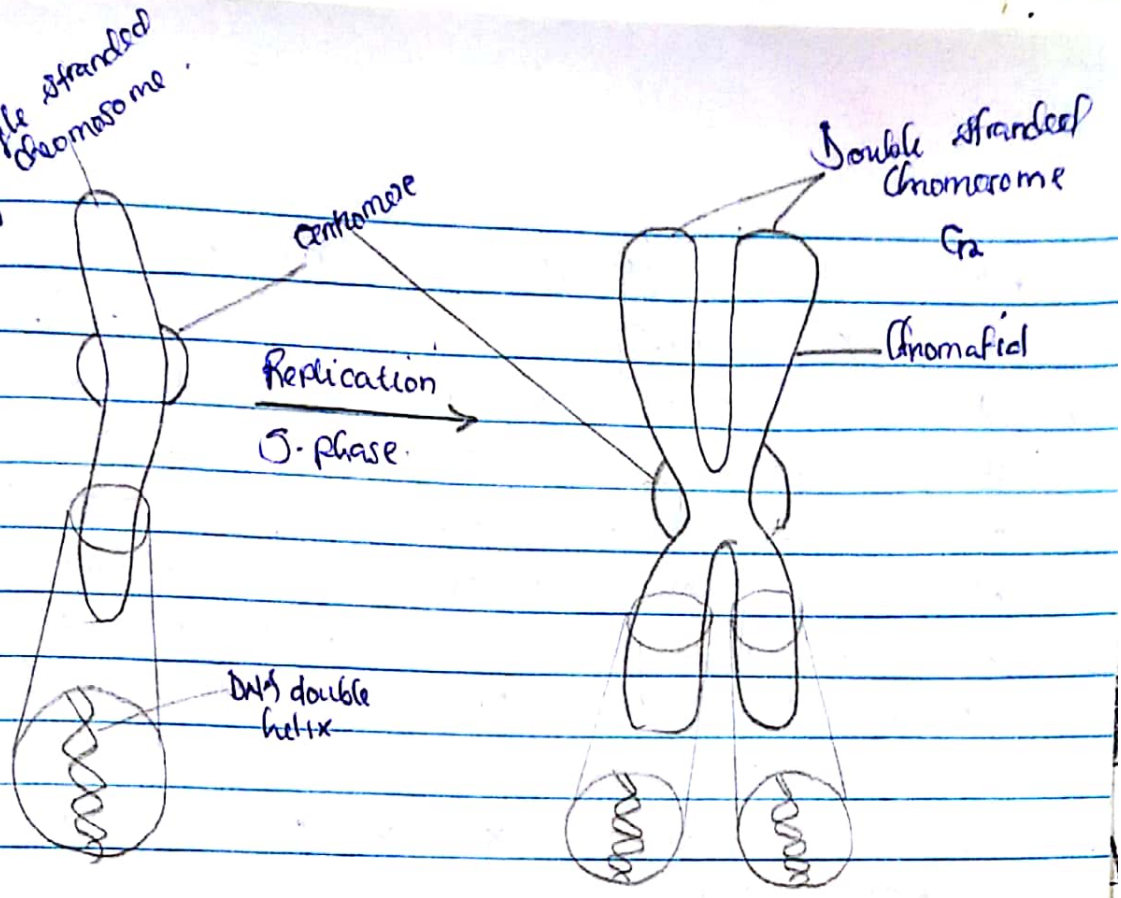


Fig 2: Changes in chromosomes structure as a result of DNA replication during S phase.

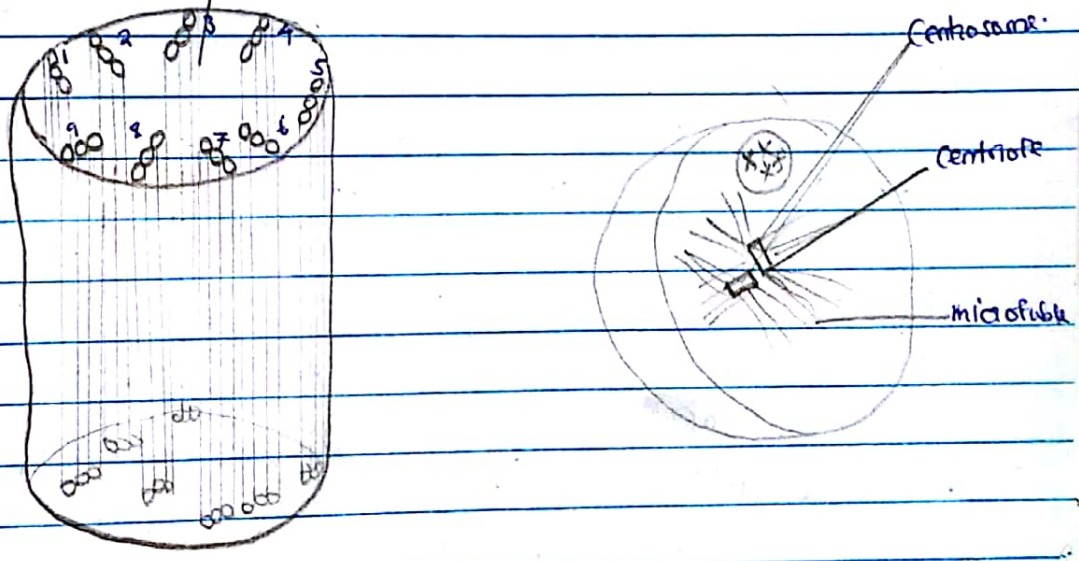


Fig 3: The centrosome and its component centrioles.

A human being life begins as a single cell called zygote formed by the union of an egg & sperm. By adult hood, our bodies consist of trillion of cells. what happened in the intervening years?

How did we go from a single to the multitudes of cells that make up tissues of a fully functional adult? Cell divisions happen over and over again. This cell division is diagramed as a cell cycle. The entire sequence of changes that a cell repeatedly goes through is called the Cell cycle. The cell cycle consists of 2 major phases. (1) interphase (2) cell division.

~~A human being~~ life begins

INTERPHASE.

Interphase is the period between cell divisions. It usually accounts for about 90% of the time that elapses during a cell cycle. but it is not a resting period as once thought, it is now known that interphase is a time of intense preparation of cell division, a time when the DNA, cytosol and organelles are duplicated. Such preparations ensure that when the cell divides, each of its daughter cells will recieve the essentials for survival. Interphase consists of 3 parts, G_1, S and G_2. S stands for synthesis (DNA synthesis) and G in G_1 and G_2 can stand for growth. All 3 parts of interphase are times of cell growth characterized by the production of organelles and the synthesis of protein and other macromolecules. There are countless events specific to certain parts of interphase. Eg during G_1, the centriole is duplicated and during the S phase, DNA is replicated.

DNA is the genetic material, Chromosomes are made of DNA and associated globular proteins called histones and are found in the cell nucleus. Depending on the phase of the cell cycle chromosomes may be either single or double strand with few exceptions (sperm, eggs and mature red blood cells in ~~some~~ adults are) Human cells have 46 chromosomes, these 46 carry an estimated 100 000 genes segments of DNA that influence cell structure and function by specifying proteins to be synthesised.

During G1, the chromosomes consist of single strand of DNA & proteins. When DNA is replicated during the S phase, the single stranded chromosomes change to double stranded structures. Each strand of a particular chromosome called chromatid has the same genetic information as the other strand. The 2 chromatids are held together at the region of the chromosome known as the centromere. Once all the preperation of interphase have been completed the cell is ready for the next ~~stage of~~ cell division.

Mitosis one type of cell division is process in which 2 identical cells called daughter cells are generated from a single cell. The original cell first replicates its genetic material and then distributes equally among its daughter cells.

MITOSIS : DIVISION OF THE NUCLEUS.

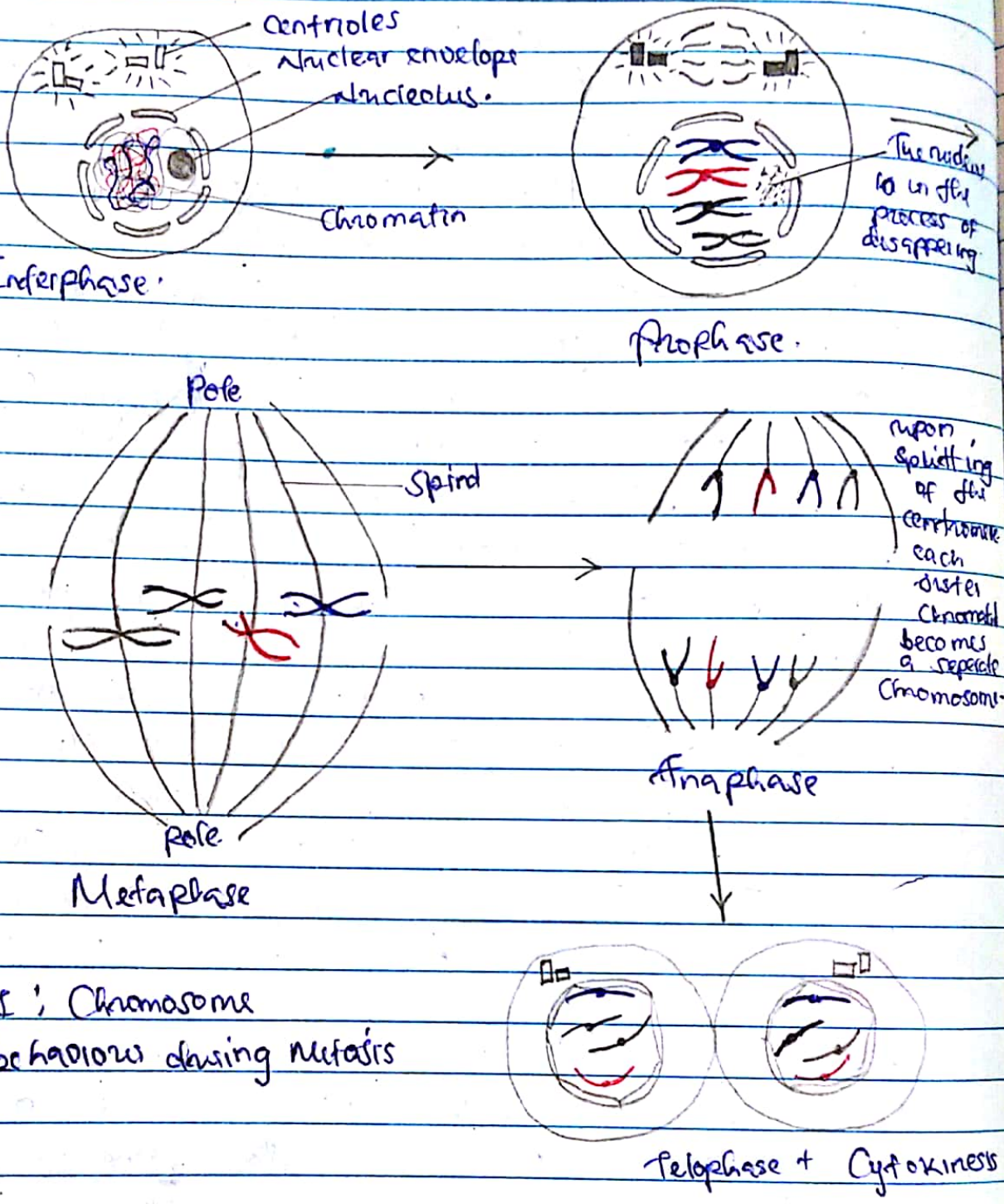


Fig 1 ; Chromosome behaviour during Mitosis

Along with a full compliment of each genetic material. Each daughter cell receives organells, macromolecules and cytosol from the original cell. Mitosis occurs in somatic cell which are all the cells of the body with the exception of eggs and sperms. Eggs and sperms are considered sex cells or gametes and they are formed through meosis a 2nd type of cell division in which

daughter cells end up with half the amount of genetic material in the original cells Somatic cell division occur continuously in the developing embryo and foetus and plays an important role in the growth and repair of body tissue in children. In other some cells such as nerve cells have been arrested in interphase for some time, having completely lost the ability to divide. Other cells such as liver cells stopped binding but they retained the ability to undergo cell division should the need for tissue repair and replacement arise. Still other cells actively divide through out life, Skin cell e.g continue to divide in others the on going cell division. Serving to replace the enormous numbers of cells death each day. somatic cell division consists of 2 processes that overlap in their timing. The first process division of the nucleus is called mitosis the 2nd of the cytoplasm is called cytokinesis and it occurs toward the end of mitosis.

MICROTUBULES

Microtubules are straight hollow rods made of the protein tubulin. often microtubules radiate out from the region near the nucleus called the centrosome within the centrosome is a pair of centrioles and each centrioles consist of

9 sets of triplete microtubules arranged in a ring. These microtubules near the nucleus are believed to provide support to the cell. They play a role in cell division, the process by which the nucleus and the cytoplasm of the cell split into 2 daughter cell. Cancer, a disease characterised by uncontrolled cell division is sometimes treated by administering drugs that halt cell division. These highly toxic drugs called chemotherapeutic agents work either the dismantling microtubules or preventing their assembly and thereby stopping cell division.

The diagram in fig 1 shows essential features for chromosome behaviour in mitosis. The process is divided into 4 stages, (1) Prophase (2) Metaphase 3) Anaphase (4) Telophase.
The stages have the following characteristics.

1 PROPHASE.
In interphase, the chromosomes have the form of extended filaments and can not be seen as discrete bodies with a light microscope, except for the presence of a dark body called nucleolus. The nucleolus has a diffuse granular appearance. The begining of prophase is marked by the condensation of chromosomes to form visibly distinct threads. Each chromosomes is already longitudinally double consisting of two closely associated sub units called Chromatids.

Each pair of chromatids is product of duplication of one chromosome in the S period of interphase. The chromatids in a pair are held together at specific region of the chromosome called the centromere. As prophase progressed, the chromosomes become shorter and thicker as a result of further coiling. At the end of prophase, the nucleolus disappears and the nuclear envelope disintegrates.

2 METAPHASE.

At the begining of metaphase, the mitotic spindle forms. The spindle is a bipolar structure. ~~Extending~~ between the centrosomes that consist of fibres of microtubules. The spindle fibres attach to each chromosome in the region of the centromere at a structure technically known as kinetochore. After the chromosomes are attached to spindle fibres, they move toward the centre of the cell until all the kinetochores lie on an imaginary plane which is called metaphase plate. Aligned on the metaphase plate, the chromosomes reach their max. contraction and are easy to be counted and examined for differences in morphology. ~~Anaphase~~

ANAPHASE

In anaphase, the centromere divide longitudinally and the 2 sister chromatids of each chromosomes move toward opposite poles of the spindle

Once the centromeres divide, each sister chromatid is regarded as a seperate chromosome in its own right. Chromosomes movement results in fast from progressive shortening of the spindle fibres attached to centromere which pulls the chromosomes in opposite direction towards the poles. At the completion of anaphase, the chromosomes lie in a group near opposite poles of the spindle. Each group contains the same ~~#~~ of chromosomes that was present in the original interphase nucleus.

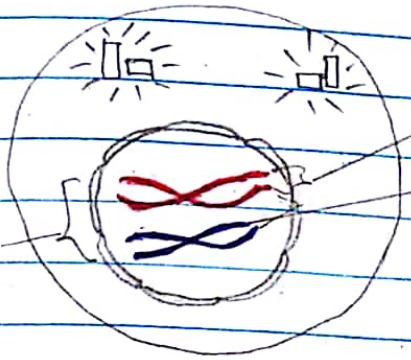
4 TELOPHASE.

In telophase, a nuclear envelope forms around each compact group of chromosomes. Nucleolus is formed and the spindle disappears. The chromosomes undergo a reversal of condensation until they are no longer visible as chromosomes, then the cytoplasm of the cell divides in 2, forming 2 identical daughter cells.

MEIOSIS: Diminution, Diminish, Dimidate = halves.

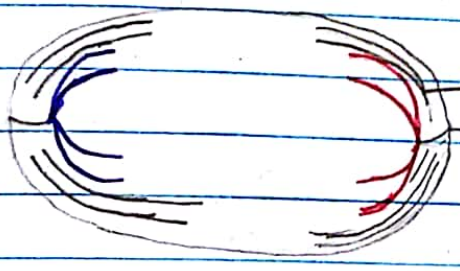
In meiosis, the chromatids become untwisted before the divide.

A.



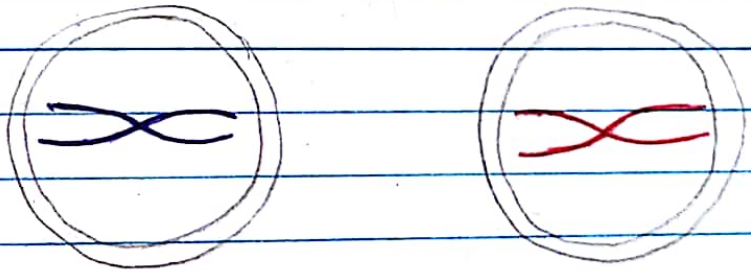
A. Homologous Chromosomes pair.

B.



B. Homologous Chromosomes Seperate.

C.



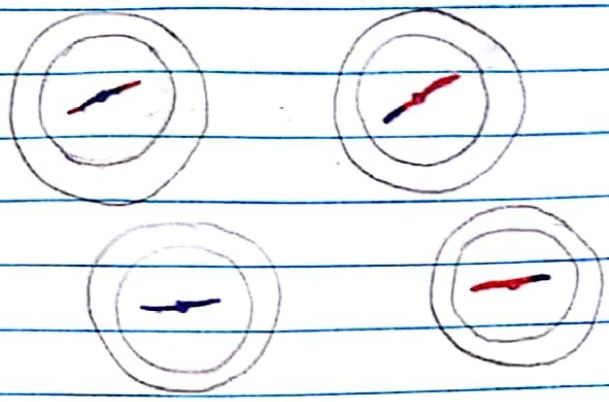
C. Daughter nuclei

The first meiotic division. (from Prophase I to Telophase I)

D.

D. Centromeres Split and Chromatids Seperate.

the colour difference is due to the crossing over.

E. 

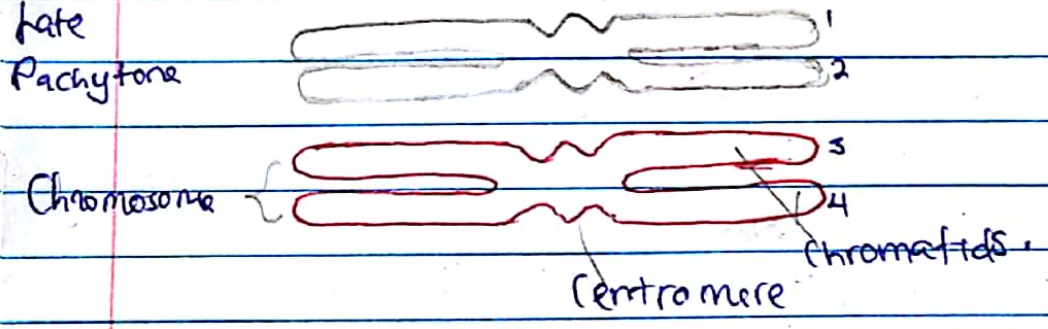
The second meiotic division which is resemble to Mitosis. from prophase II to telophase II

E: four daughter nuclei genetically different, the product of meiosis.

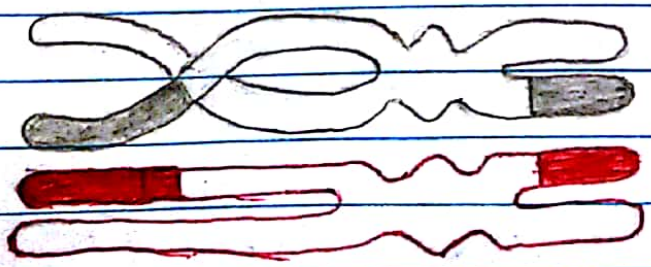
Fig 2; Overview of the behaviour of a single pair of homologous Chromosomes in meiosis.

PROPHASE I ; Synapsis and Crossing-over.

A. Synthesis : Homologous chromosomes pair together (Prophase I)

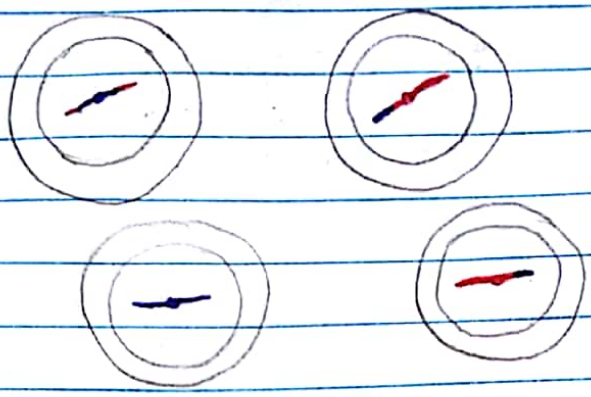


B. Chromatids break at corresponding points (Prophase I)



C. Chromatids rejoin to complete crossing over (phase I).

the colour difference is due to the crossing over.

E. 

The second meiotic division which is resemble to Mitosis. {from prophase II to telophase II}

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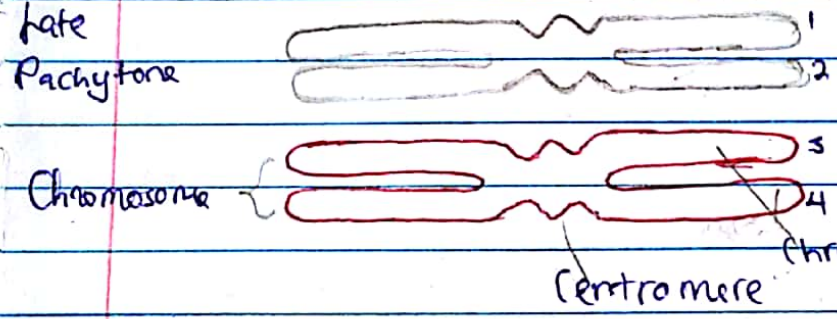

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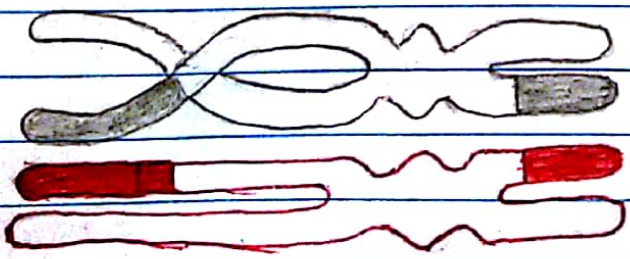

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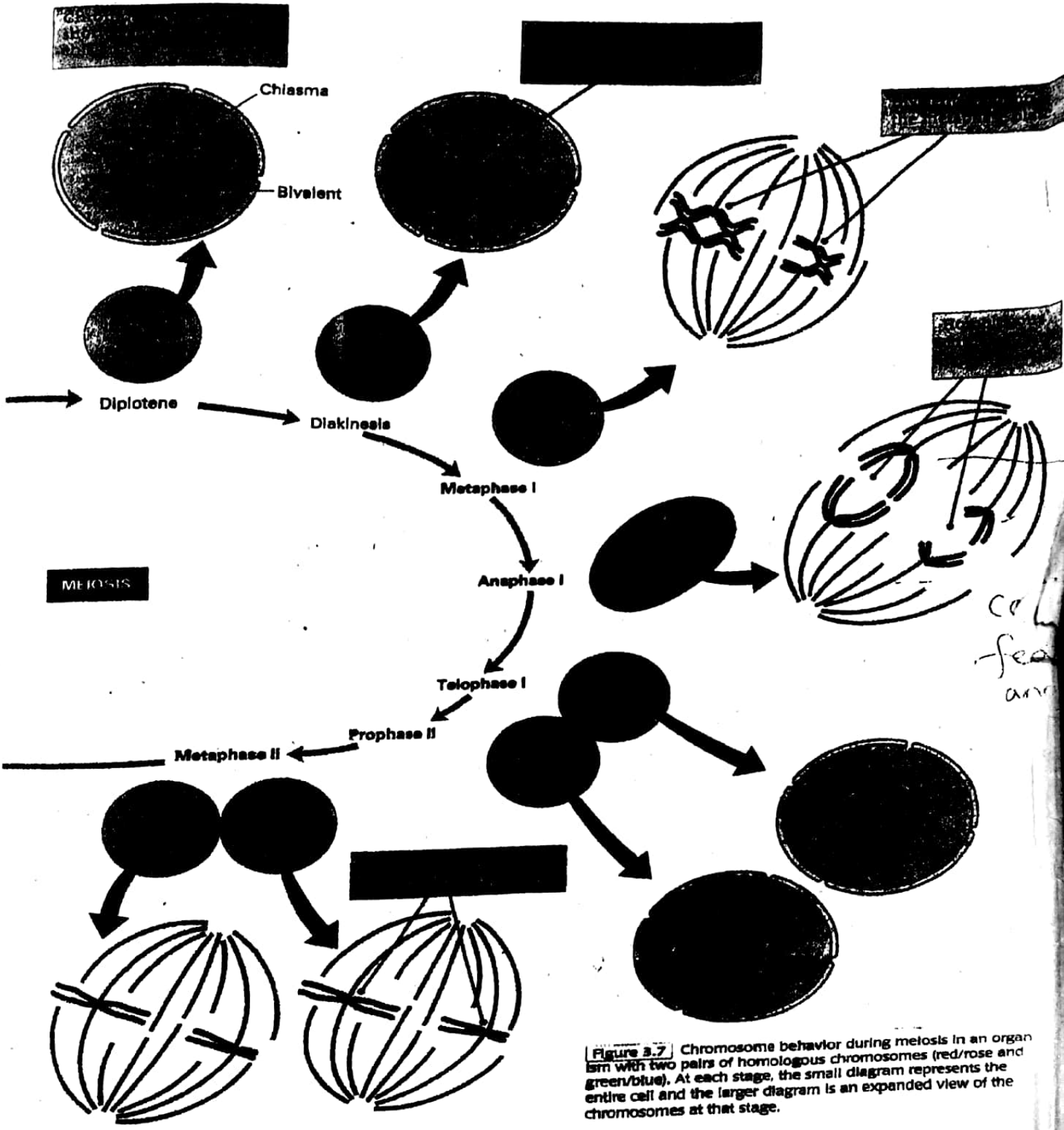
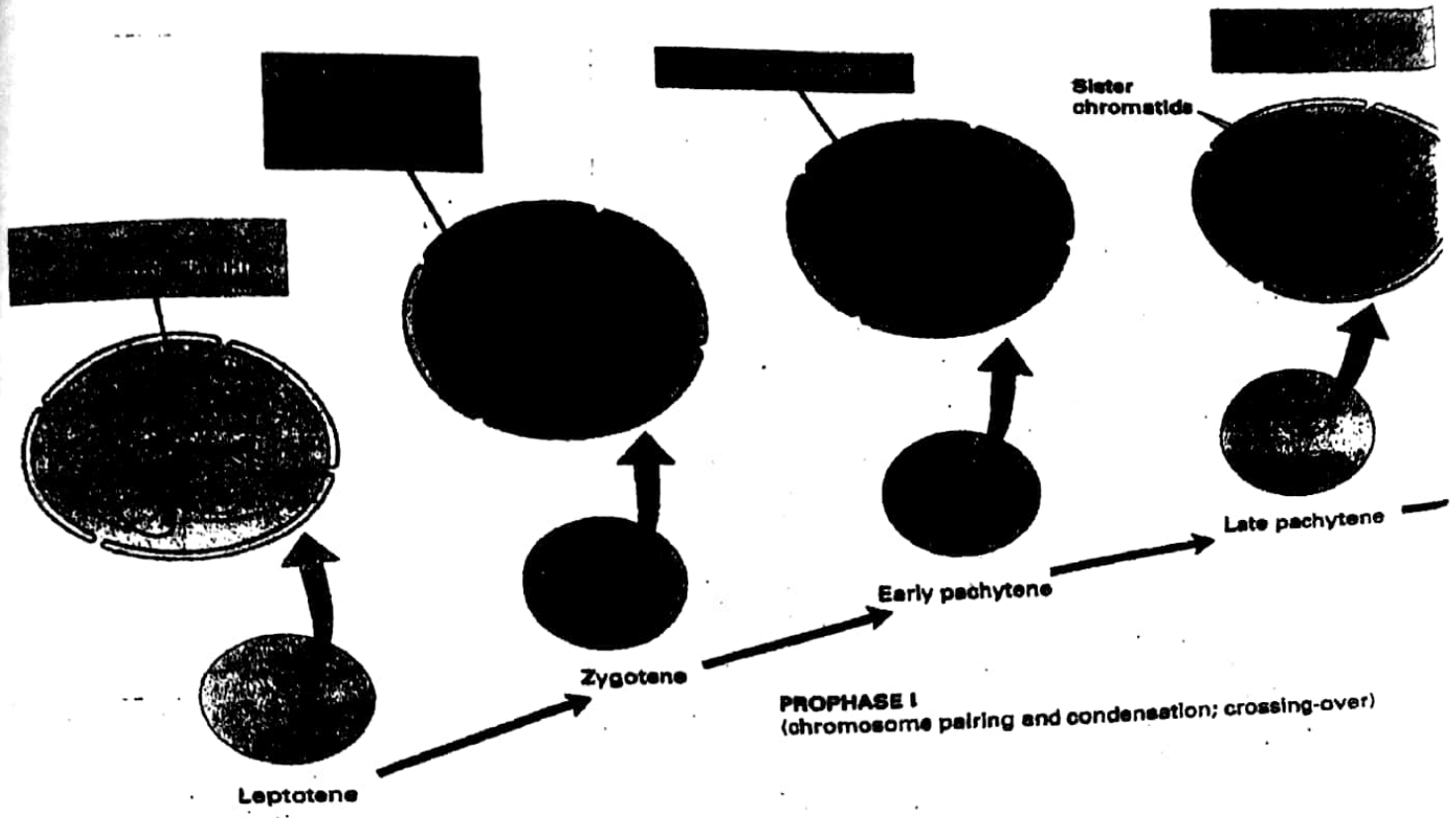
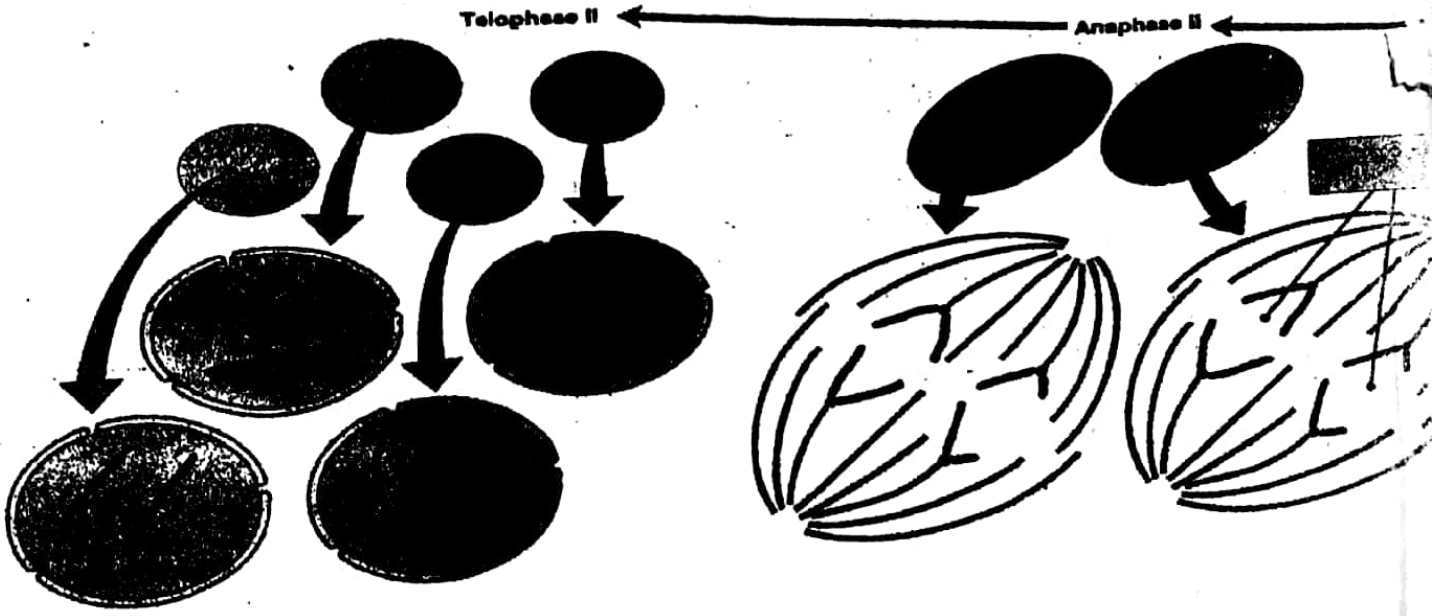


Figure 3.7 Chromosome behavior during meiosis in an organism with two pairs of homologous chromosomes (red/rose and green/blue). At each stage, the small diagram represents the entire cell and the larger diagram is an expanded view of the chromosomes at that stage.

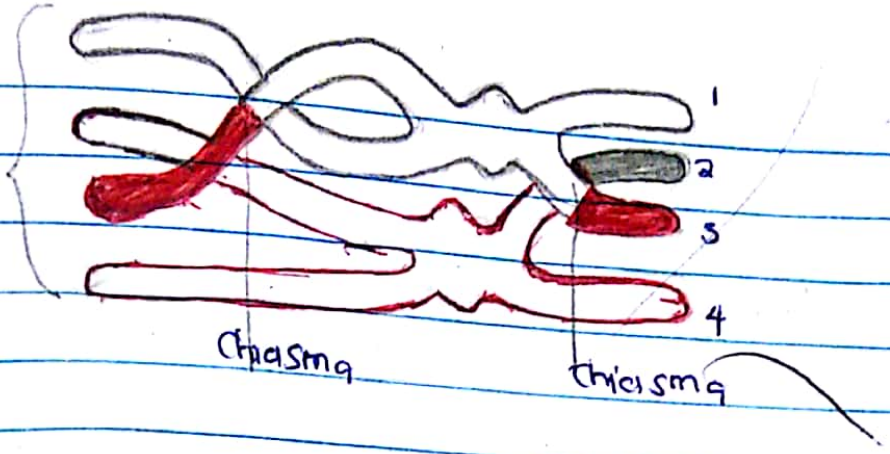


PROPHASE I
(chromosome pairing and condensation; crossing-over)

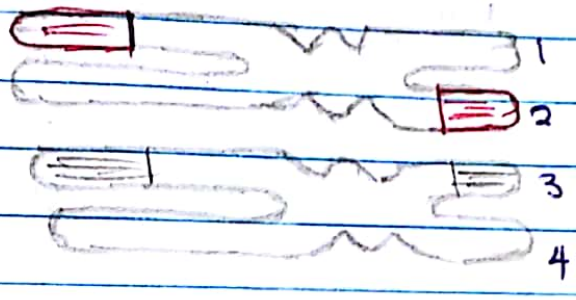


(1)

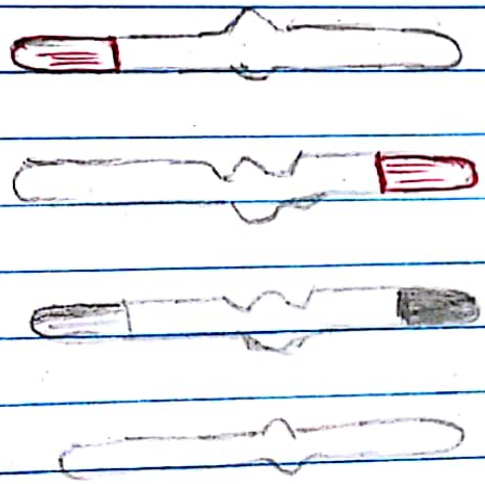
Diakinesis



D. Seperated Chromosomes following Meiosis I.



E. Seperated Chromatids following Meiosis II



Crossing Over can take plate with Chromatids

1 and 3
1 and 4
2 and 3
2 and 4

Fig 3; Crossing over

MEIOSIS RESULTS IN GAMETES THAT DIFFER GENETICALLY.

Meiosis the mode of cell division in which cells that are created contain only one member of pair of chromosomes present in the pre-meiotic cells known a diploid cell with 2 set chromosomes undergoes meiosis, the result is 4 daughter cells each genetically different and each containing only haploid set of chromosomes.

Meiosis consist of 2 successive nuclear divisions, the essentials of chromosome behaviour during meiosis are outline in fig 1. This outline affords an overview of meiosis as well as an introduction to the process as it takes place in a cellular context.

1 Prior to the 1st nuclear division, the members of each pair of chromosomes become closely associated along their length (part A) the chromosomes of pair with each other are said to be homologous chromosomes bcoz each member of the pair of homologous chromosomes is already replicated, it consist of duplex of 2 sister chromatids joined at the centromere. The pairing of the homologous chromosomes ∴ produces a 4 stranded structure.

2 In the 1st nuclear division the homologous chromosomes are seperated from each other, one member of each pair going to opposite poles of the spindle (part B). Two nuclei are formed each containing a haploid set of double chromosomes (part C).

3 The 2nd nuclear division is resembling mitotic division but there is no DNA replication. In metaphase, the chromosomes align on the metaphase plate and at anaphase the chromatids of each chromosome are seperated in opposite daughter nuclei (Part D). The net effect of the 2 divisions in meiosis is the creation of 4 daughter haploid nuclei, each contain the equivalent of a single sister chromatid from each pair of homologous chromosomes (Part E).

Note: Fig 2 does not show that at the time of chromosome pairing, the homologous chromosomes can exchange genes (Synapsis and crossing over)

Meiosis occurs in specialised diploid cells that give rights to haploid gametes. Meiosis (diminution) occurs in the cells of Ovaries (Oogonia) and testes (Spermatogonia) and reduces the nomber of chromosomes to (half) 1/2 the diploid (2n) number. The cells that results (eggs and sperms) are said to be haploid (n) or have the haploid number of chromosomes. Haploid cells have only one member of each pair of chromosomes found in diploid cells to maintain a constant and stable number of chromosomes in the next generations. Animals that reproduce sexually must produce gamete with 1/2 the chromosome # of their diploid cells. When the nuclei of the 2 gametes combine during fertilisation, the diploid # is

restored.

Meiosis begins after the G2 phase in the cell cycle. After DNA replication has occured a successive nuclear divisions take place designated Meiosis I and Meiosis II. Each division has a prophase, Metaphase, Anaphase and telophase. Two microtubule spindles function in meiosis just as they do in mitosis. The result of mitosis is 2 identical daughter cells each with same # of chromosomes as the parent cell where as the two nuclear divisions of meiosis result in four daughter cells each with 1/2 the # of chromosomes as the parent cell, more over these daughter cells are not genetically identical. Like mitosis, meiosis is a continuous process, and four Concurrence, biologists divide it into the following phases.

The first Meiotic division (from Prophase I to telophase II) reduces the chromosome number by half.

The first Meiotic division (meiosis I) is sometimes called the reductional division bcoz it divides the chromosome # in half. By analogy, with mitosis, the first meiotic division can split into the 4 Stages of prophase I metaphase I, anaphase I and telophase I. These stages are generally more complex than their counterparts in Mitosis. The stages and substages are summerized

follows:

1 Prophase I

This long stage lasts several days in most higher organisms and is commonly divided in 5 substages:

1 Leptotene
2 Zygotene
3 Pachytene
4 Diplotene
5 Diakinesis

These substages are descriptive terms that indicate the appearance of chromosomes at each substage.

1 In Leptotene.

Literally means "thin threads". Chromosomes first become visible as long thread structure. The pairs of sister chromatids can be distinguished by electron microscope

2 Zygotene. (paired threads).

It is a period marked by lateral pairing or synapses of homologous chromosomes begening at the chromosome tips.

Synapsis: this is pairing together of homologous chromosomes to form structure called bivalents or tetrads. When synapsis is complete, the chromosus are linked together through out their length.

3 Pachytene

During pachytene, condensation of the chromosomes continues. the term literally means (thin threads). and through out this period the chromosomes

continue to shorten and thicken. by late pachytene each bivalent consists of a tetrad of 4 chromatids Genetic diversity takes place during pachytene through a process called crossing over in which corresponding pieces of chromatids of maternal and paternal homologous (non-sister chromatids) are exchanged.

Crossing over:

Crossing over or chiasma formation takes place following synapsis. In this process, homologous chromatids break and rejoin at precisely corresponding points so that genetic material is exchanged between them. Crossing over is a random event causing two genetic recombination that is it generates new combinations of genes. The crossovers also called chiasmata (singular chiasma) can occur anywhere along the length of the chromosome, technically two or 3 chiasmata are formed on each pair of chromosomes in the production of human gametes. Gametes which contain new arrangement of genes are called recovenant types.

4 Diplotene:

means "double thread", the synapsed chromosomes become shorter and thicker and clearly double. The homologous chromosomes remain held together

5 Diakinesis

Means "moving apart". During diakinesis, the homologous chromosomes seem to repel each other and the segments not connected by

chiasma move apart. It is at this substage that the chromosomes attain their max condensation. Near the end of diakinesis, the formation of a spindle is initiated and the nuclear envelope breaks down.

METAPHASE I.

In metaphase I, the microtubules form a spindle apparatus just as mitosis were homologous chromosomes do not pair, each pair of homologous lines up in the centre of the cell with centromeres on each side of the equatorial plane.

ANAPHASE I.

In this stage homologous chromosome each composed of two chromatids joined at an undivided centromere seperate from one another and move to the opposite poles of the spindle. Chromosome seperation at anaphase I is the cytological basis of the segregation of alleles.

TELOPHASE I.

During telophase I, a nuclear envelope forms around each chromosome set, the spindle disappears and cytokinesis usually follows. The result is two cells each with a haploid set of chromosomes each containing 2 chromatids.

The second Meiotic division (from prophase II to telophase II)

PROPHASE II

Meiosis II is very similar to mitosis prior to start of meiosis prophase II, each centriol divides into two, during prophase II the sister chromatids chromatids condense while the nuclear envelope disappears and the spindle apparatus forms.

METAPHASE II

In metaphase II the sister chromatids attached to kinetochore microtubules align on the metaphase plate, much as chromosomes do in mitosis.

ANAPHASE II

During this, sister chromatids seperate at their centromeres. The seperated chromosomes now called daughter chromosomes are pulled to opposite poles.

TELOPHASE II

In telophase II, the nuclear envelope form around the chromosome sets at each pole, while the chromosomes become more extended, cytokinesis then occurs producing four daughter cells, each with a haploid set of chromosomes. because of crossing over, some chromosomes are seen to have recombined sigments of the original parental chromosomes. The end product of meiosis are 4 haploid cells, every cell

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has one copy of each chromosome sets but these copies are not identical to the original parental chromosomes due to crossing over in prophase I.

GENETICS.

- Historical perspective

Gregor Mendel found the science of genetics (1860) The foundation of our knowledge of genetics was made in the 19th Century by Grego Mendel (1822-1884). The general idea that prevailed in mendel's time was that inheritance was the result of the fusing of 2 parent traits. There was no clear understanding of a special role of the reproductive cells in inheritance, instead the entire body was thought to participate. People were linking inheritance to blood which of course plays no part in it. It was thought that 2 parents fused somehow their blood to produce an offspring that had a mixture of both bloods and therefore had traits intermediate between those of its parents. Medel changed all that with a series of experiments involving a garden pea. A number of distinct varieties differing in such characteristics, as height, flower, seed, what colour and seed shape exists in the garden peas. In each case, the characteristics exhibits 2 contrasting forms as for example tall and short. Mendel designed his experiment with garden pea plants carefully breeding his peas for many generations and carefully counting the number of plants with each trait in each generation, Mendel

Cultivated and tasted almost 28000 pea plants. His knowledge of mathematics enabled him to understand the F2 ratios and to see that they were a result of randomly, combining cells of the cellular factors. In each experiment, he focused on one or two pairs of contrasting characteristics. Medels conclusions lead to the foundation for understanding in organisms from peas to humans and revolutionalised ~~the~~ field of biology. Mendel's work indicated that inheritance of traits was not due to a blending but rather a transformation of specific units of inheritance now called genes. Mendel not only predicted the existance of genes but also that alleles, ~~that~~ the alternate forms of genes normally occur in pairs His results indicated that during the formation of gametes, haploid reproductive cells, the two alleles of a gene seperate from one another so that each gamete contains only one allele of each pair. During only one allele on each pair. During sexual reproduction, the allelic pairs are restored when an egg cell containing one allel combines with a sperm cell containing another allele. Thus Mendels research predicted meiosis and the existance of haploid and diploid cells Mendel published the results from his studies in 1866 in which he proposed two laws of inheritance in sexually reproducing organisms. He proposed the existance of a pair of factors controlling each character transmitted from parent to offspring, he therefore laid ground for the particulate theory of inheritance

However, no one paid attention to Mendel's results and most scientists rejected his results until early 1900.

What is Genetics?

The word genetics was coined by William Bateson in 1907. He used it to describe a new branch of of biology which began on the year 1900 after the re-discovery of Mendels work on hybridisation of garden peas. Genetics is the science of heredity. Heredity is the process that brings about similarity between parents and their offspring. By similarity we mean that when plants and animals reproduce they have progeny of their own species and not of some other kind. When human beings have offspring, they are human beings, ~~have offspring~~ they and not Chimpanzees or Rabbit or any other organism. The members of a family are all similar to one another and to their parents in their characters. But they also vary, in many minor ways (i) the details of their individual development and appearance. In the human population of more than 6 billion people, each one of us can be uniquely recognised and distinguished from all the others. The differences between the individuals of a family or of a species is referred to as Variation. When we study genetics therefore, we want to know how heredity can account for the differences between individuals; this is the reason that brothers and sisters who resemble each other are still unique individuals. The science of genetics attempts to explain

the mechanism and the basis for both similarities and differences between related individuals. It also describes the phenomenon of evolution. The heredity and variation play an important role in mechanism the formation of new species.

The biological science which deals with the mechanism of heredity and cause of ~~human~~ variations in living organisms (viruses, bacteria, fungi and plants and animals) is known as genetics.

HEREDITY AND ENVIRONMENT.

It is important at the begining to realise that variation has 2 causes. The differences that we observe between differences that we observe between individuals are only due to part to the internal factor of the cells that cause heredity. They are also partly accounted for by the external influence of the environment. In our own species (humans) it is quite easy to find example of inherited variation if we look at groups of people from widely seperated parts of the world. The individuals all have distint physical features that enable us to recognise the groups to which they belong. The variations include differences in the colour of the skin and hair, texture of hair, height, shape of the head, The differences are largely due to heredity because they are known to have been passed on in the same form for several centuries. Moreover, when people migrate and settle in different parts of the world, their offspring

retain their racial characteristics regardless of the environments of which they live. It is also obvious to us that not all differences between people are inherited; there are variations that arise due to the level of nutrition, others that are the result of exercise (for example large muscles) and some that may simply be due to accidents. There is no doubt that a person who lost a leg by accident will be able to have children with perfectly normal two legs. The development and appearance of human being is the out come of influences due to both heredity and environment.

1 GENOTYPE (Genome): It is the combination of genes an organism possesses

2 PHENOTYPE:
It is the characteristics or appearance shown by an organism.

3 HOMOZYGOTE (Homozygous) (Pure breeding).
This is an individual in which of the alleles of a gene pair are similar. (TT or tt)

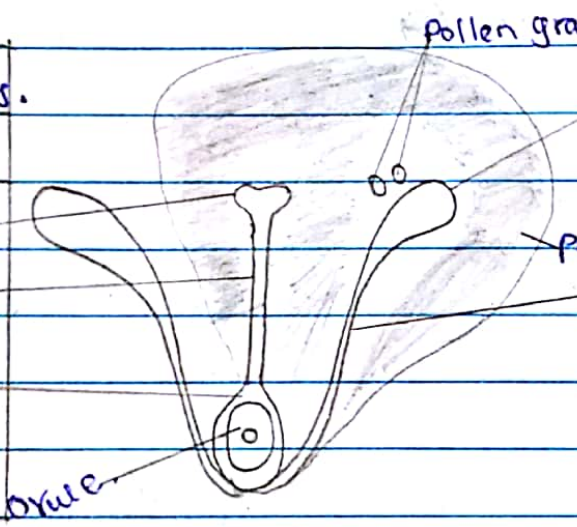
4 HETEROZYGOTE (hybrid)
Is an individual in which the alleles of a gene pair are dissimilar. (Tt or Bb)
An organism may be heterozygous for some characteristics and homozygous for others

5 DOMINANT AND RECESSIVE
An individual which is heterozygous for gene

normally displays the characteristics determined by one of the allelic pair. This is called the dominant allele. Its allelic partner is called the recessive allele. When an individual is homozygous for the recessive allele, the characteristics determined by the recessive gene is displayed.

MONOHYBRID CROSS OR THE FIRST LAW OF MENDEL OR MENDEL EXPERIMENTED WITH GARDEN PEAS.

Female parts.	Male Parts
Carpel	Stamen.
Stigma	Anther
Style	Filament
Ovary	Each pollen grain contains 2 sperms.
Each ovule contains an egg.	



Pisum Sativum (pea).

Mendel chose to study garden peas pisum sativum in 1856. He carried out many experiments crossing different varieties of pea plants. Pea plants are normally self fertilizing and can be maintained as pure-breeding lines meaning that the characteristics of the parent plant are translated unaltered to the off-spring generation after generation. Mendel cross fertilized between pure breeding lines showing contrasting characters, e.g he crossed together red and white flower varieties, tall and short plants, and

plants with smooth and wrinkled seeds to prevent self fertilization, I removed the stamen from the developing flowers of one variety, later he transfered pollen to the stigma of each flower from the right anther of the second variety. The seeds produced called hybrid seeds were collected and used to grow new plants in subsequent years.

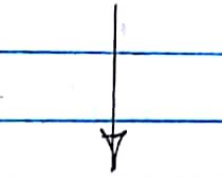
Phenotype.

Pure breeding parents

Red flower

×

White flower



First filial generation (F_1)

Self pollinate.

all red.

Second filial generation F_2.

705 red

224 white

Monohybrid ratio 3 : 1

Genotype.

Pure breeding Parents RR × rr

Homozygous red — Homozygous white.

Gametes. R r

Rr

Heterozygous red (hybrids.

Self pollination.

First filial generation gametes Rr × Rr

R r R r

RR Rr Rr rr

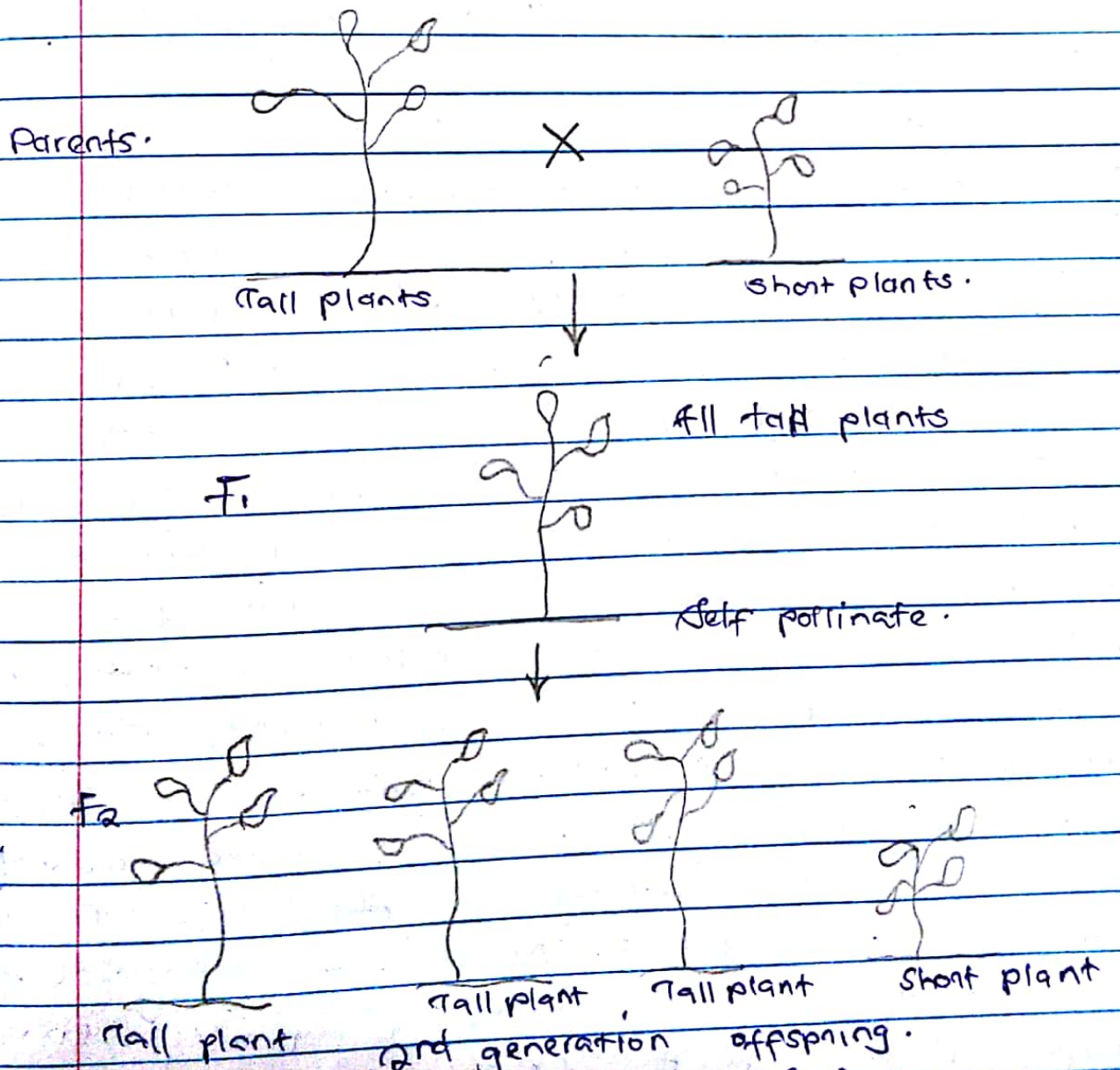
Red white

Punnett square.

♂	R	r
R	RR	Rr
r	Rr	rr

Mendels 1st experiments were designed to follow the inheritance of one well defined characteristic. This proceeded was to cross pollinate pure breeding variaties of the garden pea, collect the seeds and sow them the following year. The plants which grew were then allowed to self pollinate, and the seed were again collected. The characteristics of the plants which grew from these seed a year later, were carefully noted. One of the characteristics Mendel experimented with in

this way was flower colour. In one investigation, he crossed a pure breeding variety having red flowers with a pure breeding white flower variety. All the progeny (F_1) has red flowers but when self pollinated (selfed) the gave rise to 705 red flowered plants and 224 white flowered F_2 plants, a ratio of approximately 3 red to 1 white. This is known as a monohybrid ratio, about 1/3 of the red flowered F_2 plants were found to be pure breeding. The remained on selfing gave rise to red flowered and white flowered progeny.



just law

Genotype.

Parents TT x tt

Gametes (T) (t)

F1 Tt All tall plants self pollinate.

Tt x Tt

Gametes (T) (t) (T) (t)

TT Tt Tt tt

Tall plants Tall plants short plans.

Punnett Square.

♀ \ ♂	T	t
T	TT	Tt
t	Tt	tt

F2

TT - Homozygous tall } 3
Tt } Heterozygous tall }
Tt }
tt - Homozygous short. } 1

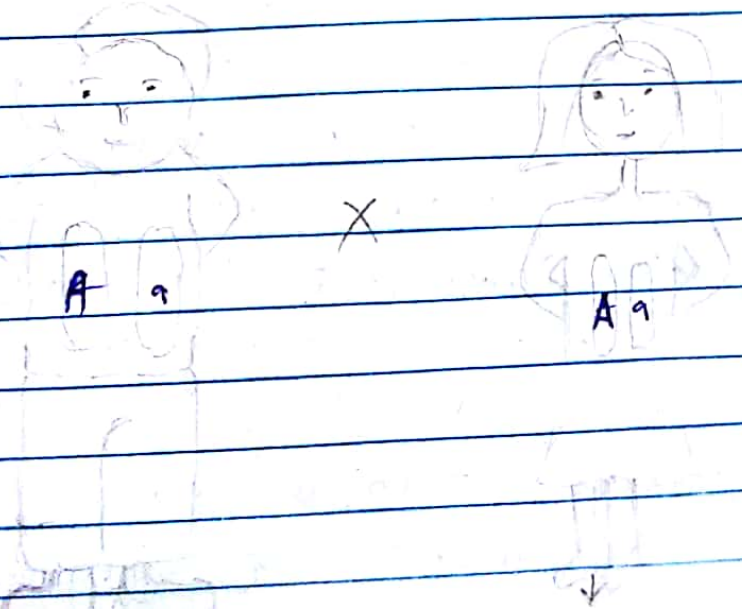
In a typical experiment, Mendel crossed a tall growing variety of pea with a short variety the offspring were not of some intermediate height but instead resembled their tall parent. If two of these offsprings were crossed a one offspring was allowed to fertilise itself then the short variety would occur and the ratio as 3 tall plants to one short plant.

No matter what trait Mendel studied in peas, he obtained the same results, the first generation always resembled one of the parents and the second generation possesed individuals with both traits but always in the 3:1 ratio. These results made Mendel to conclude that some traits can silently persist even though they aren't expressed. Therefore

An individual must contain two sets of instructions for a particular trait that is, the instructions must occur in pairs. The 3:1 ratio in 2nd generation indicated to Mendel that these pairs combine and recombine in accordance with the rules of probability.

These observations lead Mendel to formulate his first law of inheritance (law of segregation) which stated: "Of a pair of contrasting characters, only one can be represented in the gametes". The law can be more easily understood if symbols are used to represent the genes which determine the characteristics in question. Since all the F_1 plants had red flowers, it may be assumed that the allele for red colour (R) is dominant to the allele r for whiteness, the experiment may then be indicated as shown in punnett square.

THE OUTCOME OF MENDEL'S FIRST LAW OF INHERITANCE: SEGREGATION.



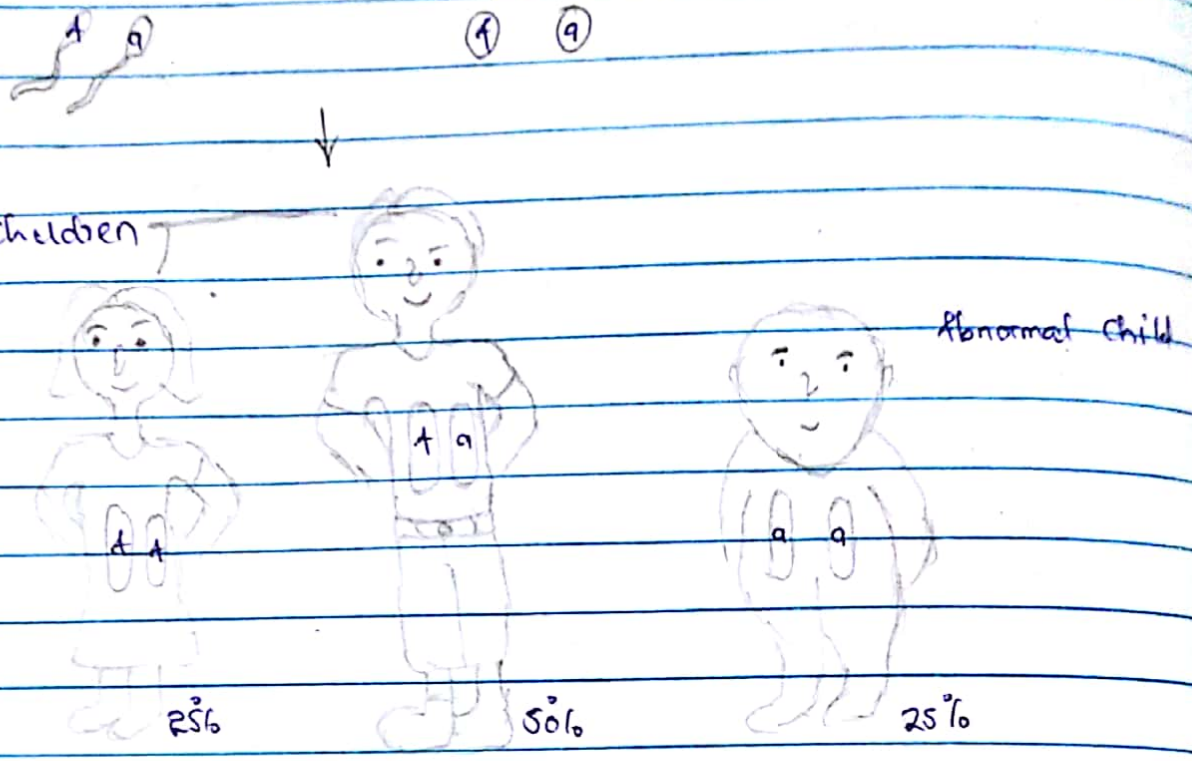


Fig 1 : Demonstration of of meiotic segregation of chromosomes explains Mendelian segregation of genes.

Mendel observed that the particles that determine genetic trait in peas are paired but are seperated (segregated in the gametes, so the gamete from each parent contributing a particle to the new zygote. Now that we understand meiosis, it is easy to explain Mendelian segregation. If we place the alleles of the gene of interest in this case A and a on a pair of homologous chromosomes in the parents, we see that segregation of the chromosome at Meiosis results in 1 of alleles to the gametes. When each parent provides each gamete bearing one of the ~~gametes~~ alleles to produce an offspring, the genotypes in ~~di~~ described in fig 1 are produced. If the aa genotype produces a disease, we see how it is produced from Aa parents who do not exhibit the disease as a result of segregation of

chromosomes at meiosis.

TEST CROSS.

~~Ascertaining that the~~ Producing

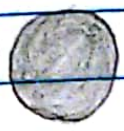
A test cross is carried out to determine the genotype of a particular individual when this is not known e.g in guinea pigs the allele for black colour B is dominant to the allele for brown b. The homozygous recessive type bb is brown but the homozygous dominant BB and the heterozygous Bb individuals are both black and quite indistinguishable in appearance. For a guinea pig breeder wishing to maintain a pure breeding black line or simple method of seperating these genotypes is possible. This is done by crossing the black individual with the homozygous recessive genotype bb. Note that all test crosses involve a cross with homozygous recessive. If a black individual is then all the offsprings of the cross must be black. However if the black individual is heterozygous half of the offsprings are expected to be brown.

DIHYBRID INHERITANCE.

Fig 1

Phenotype.

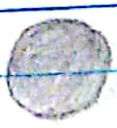
pure breeding parents.



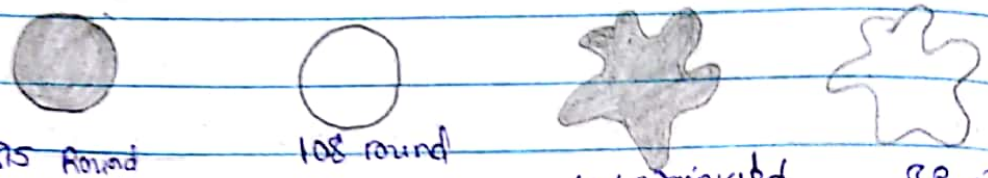
Round yellow seed.

Krinkled green seed.

F1 generation



All round yellow self pollination.



315 Round yellow. | 108 round green. | 101 wrinkled yellow | 32 wrinkled green.

Dihybrid ratio 9 : 3 : 3 : 1

Genotype.

Pure breeding parents RRYY × rryy

Homozygous round yellow. × Homozygous wrinkled green.

Gametes RY ry

F1 hybrid.

RrYy Round yellow.

Heterozygous

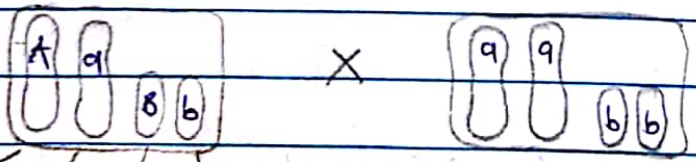
Self pollination.

F2 gamete.

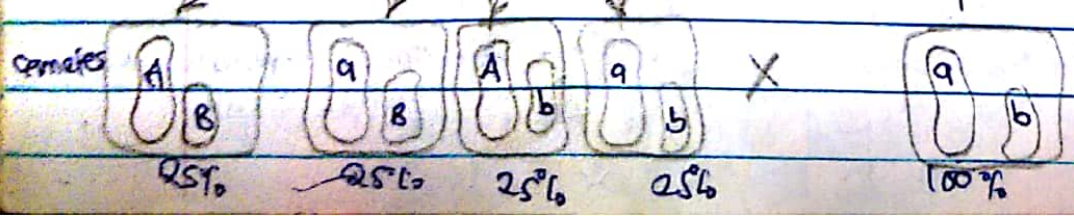
Fig 2. Punnett Square.

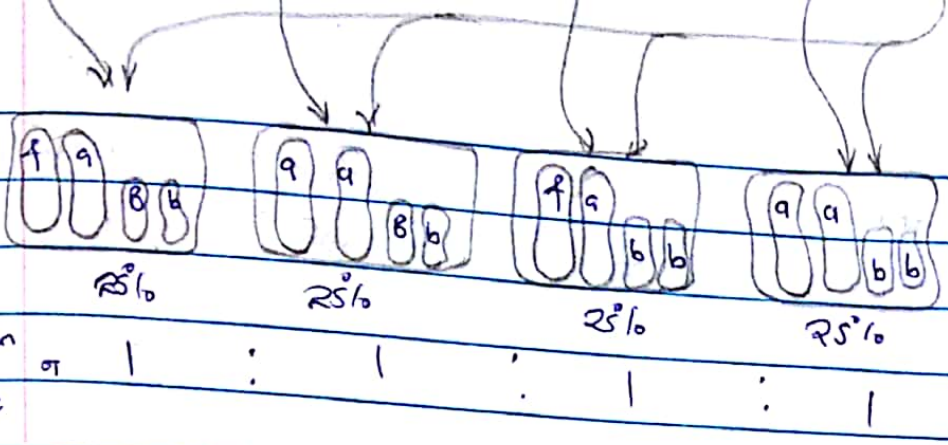
♀ / ♂	RY	Ry	rY	ry
RY	RRYY 1	RRYy 2	RrYY 3	RrYy 4
Ry	RRYy 5	RRyy *1	RrYy 6	Rryy *2
rY	RrYY 7	RrYy 8	rrYy +1	rrYy +2
ry	RrYy 9	Rryy *3	rrYy +3	rryy ▲1

Fig 3. parents



Meiosis Gametes





Mendel also studied 2 characteristics in the garden pea. In one of his experiments, he followed the inheritance of seed colour and texture (shape) he 1st crossed a pure breeding variety having round yellow seeds with another pure breeding variety having wrinkled green seeds. All the F_1 plant had round yellow seeds. The F_1 plant were then allowed to self pollinate and the colour and texture of the seed of the F_2 plants were noted. Mendel's results were as follows:

A total of 556 F_2 seeds were collected from these plants, comprising 315 round yellow, 108 round green, 101 wrinkled yellow and 32 wrinkled green. Round green and wrinkled yellow are new combinations of characters different from those shown by the original parent lines. They are therefore described as recombinant types. The expected F_2 genotypes is determined by the punnet square method. It shows F_2 phenotypes in the proportion 9 : 3 : 3 : 1 almost exactly as Mendel observed.

Mendel proposed a 2nd generalisation which is now know as Mendel's second law or the law of independent assortment. Mendel formulated the 2nd law of inheritance which stated "Each of a pair of contrasting characteristics segregates independently of any other pair."

CHROMOSOME BEHAVIOUR AND DIHYBRID INHERITANCE

The genes which determine the 2 contrasting features are located on different homologous chromosomes. Because the chromosomes of the homologous pair seperate independently of those of another pair the genes carried on the chromosomes seperate independently of each other. that explains the independent assortment.

THE DISCOVERY OF GENE LINKAGE.

Fig 4.

Phenotype.

Parents — Purple, Long. (flower colour, Pollen shape) × Red, round. (flower colour, Pollen shape.)

F_1 — Purple, Long.

↓ Self pollination.

F_2.

P/- means either pure because it could be anything.

Genotype.

Parents — P/P · L/L × p/p · l/l

Gametes — P. L and p. l

F_1 — P/p · L/l.

↓ Self pollination.

F_2.

Sweet Pea phenotypes observed in the F_2

	Phenotype and genotype	Number observed	Progeny expected from 9:3:3:1 ratio.
1	Purple, Long (P/- . L/-)	4831	3711
2	Purple, round (P/- . l/-)	390	1103
3	Red, long (p/p . L/-)	393	1303
4	Red, round p/p . l/l)	1338	435

MORGAN'S EXPERIMENT ON DROSOPHILA FLY.

Parents $Pr^+/Pr^+ . Vg^+/Vg^+ \times pr/pr . vg/vg$

Red eye . normal wing length — Purple eye . Vestigial wing.

↓

F_1 $Pr^+/pr . Vg^+/vg.$

Red eye — Normal wing.

He carried out a test cross

$Pr^+/pr . Vg^+/vg \times pr/pr . vg/vg.$

F_2 results.

1	$Pr^+ . Vg^+$	1339 →	Parental type
2	$pr . vg$	1195 →	Parental type
3	$Pr^+ . vg$	151 →	Non-Parental type
4	$pr . Vg^+$	154 →	Non-parental type
		2839.	

In the early 1900s William Bateson and R.C Punnett were studing inheritance in the sweet pea. They studies 2 genes, 1 effecting flower colour (P, purple and p, red) and the other effecting the shape of pollen grains (L, long and l, round) They crossed pure lines P/P . L/L (purple long) X p/p . l/l (red round) and derived F_1 - P/p . L/l (Heterozygous) to obtain F_2. Table 1 shows the proportions of each phenotype in the F_2 plants.

The F_2 phenotypes deviated from the expected 9 : 3 : 3 : 1 ratio. What is going on? This does not appear to be explainable as a modified Mendelian ratio. Note that 2 phenotypic classes are larger than expected. The purple long phenotype and the red round phenotype, As a possible

explaination for this, Bateson and Punnett proposed the F1 had actually produced more P.L and P.l gametes than would be produced by Mendelian independent assortment. The confirmation of Bateson and Punnett's hypothesis had to await the development of Drosophila as a genetic tool.

Thomas Morgan found the similar deviation from Mendel's 2nd law while studying 2 autosomal genes in drosophila. One of these genes affects eye colour (P_r, purple and P_r^+ red) and the other gene affecting wing length (Vg, Vestigial and Vg^+, normal) Morgan crossed $Pr/Pr \cdot Vg/Vg$ flies with $P_r^+/P_r^+ \cdot Vg^+/Vg^+$ and then test crossed the heterozygous F1 against the recessive one - ($Pr^+/Pr \cdot Vg^+/Vg$ X $pr/pr \cdot vg/vg$) Morgan's results were as shown in fig - . Obviously these F1 deviate drastically from the Mendelian prediction of the 1 : 1 : 1 : 1 ratio, the two largest classes are the combinations $Pr^+ \cdot Vg^+$ and pr/vg originally introduced by the homozygous parent flies. U can see that a test cross clarifies the situation. It reveals the allelic combinations in the gametes from one sex in the F1 thus clearly showing the linkage that could only be found from Punnett and Bateson's results. The test cross also reveals something new, there approximately a 1:1 ratio not only between the 2 parental types but also between the non parental types

P_1 V_g

F_1 V_g

Morgan suggested that the genes governing both phenotypes are located on the same pair of homologous chromosomes, this tendency of genes on the same chromosome to remain together is called linkage. Two genes of the same chromosome that are near to be linked.

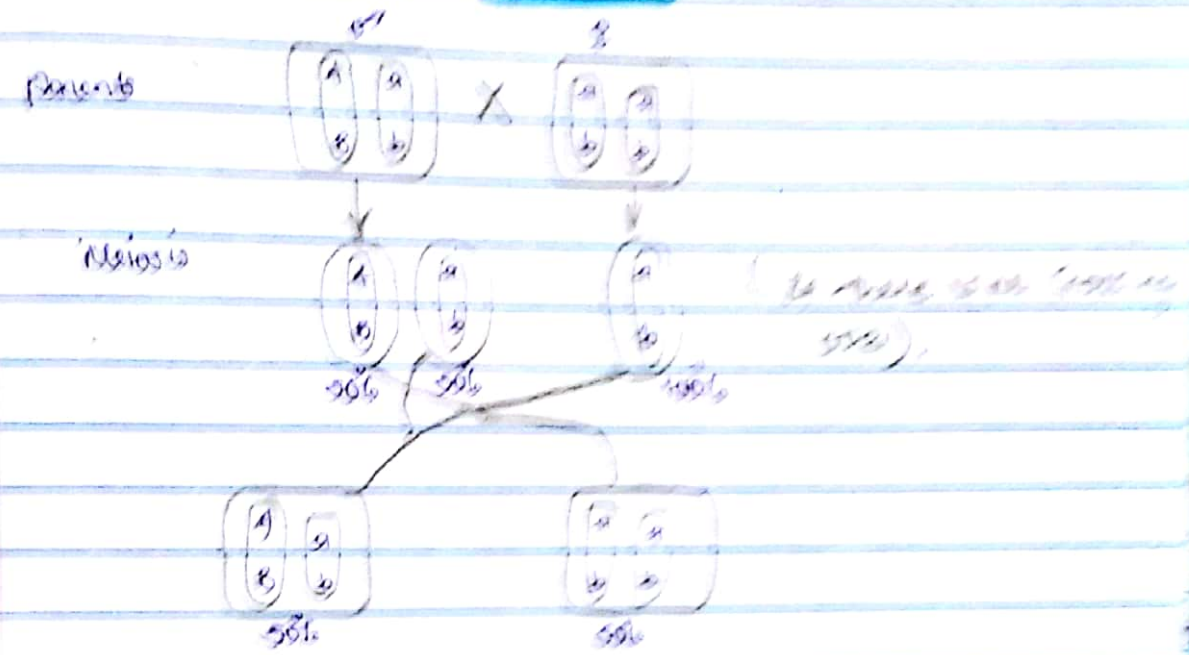
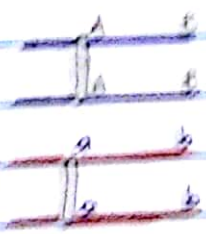
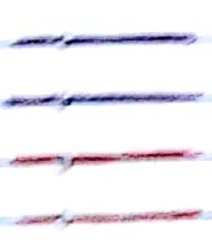
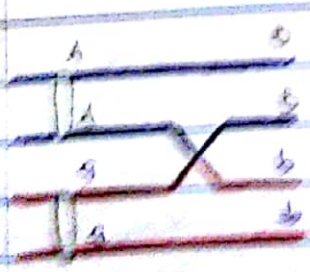


Fig 5 : Demonstration of how the independent assortment of closely linked loci.

RECOMBINATION

	Meiotic Chromosomes	Meiotic Products
Fig 1. Meiosis with no crossover between genes.		
Meiosis with a crossover between genes		

Pr^+ Vg^+

Pr Vg

Morgan suggested that the genes governing both phenotypes are located on the same pair of homologous chromosomes. The conclusion of genes on the same chromosome pair is termed linkage. Two genes on the same chromosome pair are said to be linked.

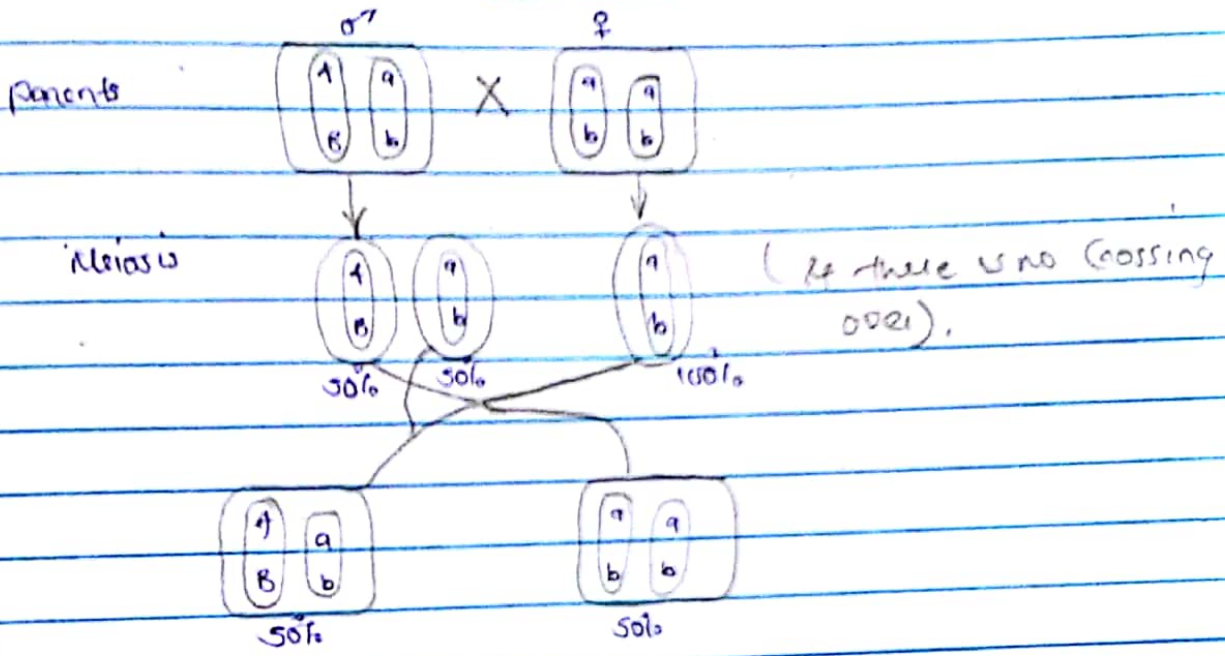
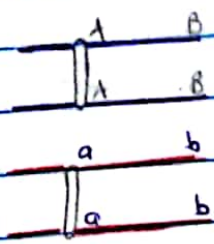
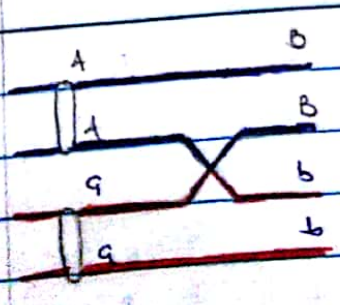


Fig 5 : Demonstration of absence of independent assortment of closely linked loci.

RECOMBINATION.

	Meiotic Chromosomes	Meiotic Products.
Fig 1 Meiosis with no crossover between genes.		 parental, parental, Parental, parental
Meiosis with a crossover between genes		 parental, recombinant, recombinant, parental.

Pr Vg

Morgan suggested that the genes governing both phenotypes are located on the same pair of homologous chromosomes. The conclusion of genes on the same chromosome pair is termed linkage. Two genes on the same chromosome pair are said to be linked.

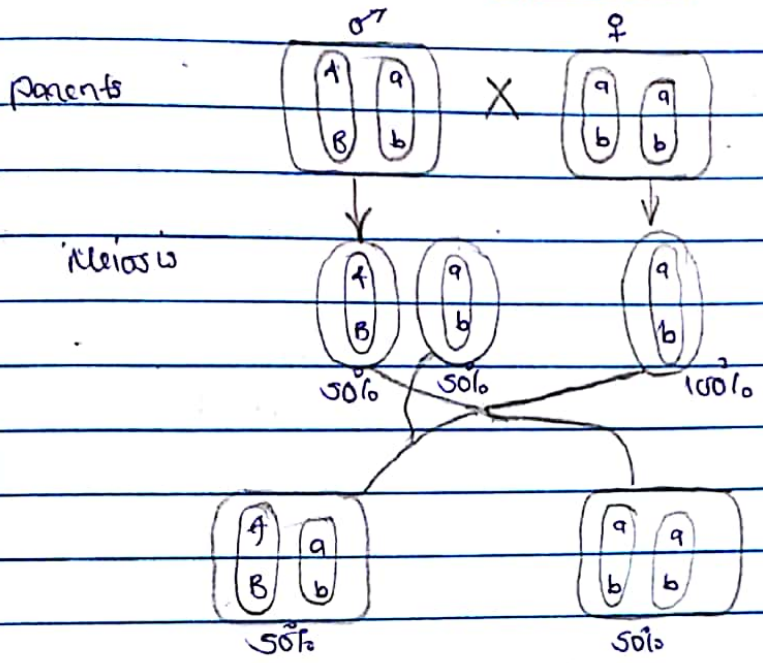


Fig 5 : Demonstration of absence of independent assortment of closely linked loci.

RECOMBINATION.

	Meiotic Chromosomes	Meiotic Products.
Fig 1 Meiosis with no crossover between genes.	A B / A B; a b / a b	parental, parental, parental, parental
Meiosis with a Crossover between genes	A B / A B; a b / a b	parental, recombinant, recombinant, parental.

non-sister

Fig 1: Recombinants arise from meiosis in which a Chromatids crossover between the genes under study.

Recombinant frequency (RF) or Cross Over value (COV) = total number of recombinant / total number of offspring x 100

Example of Morgan's results.

$Pr^+ . Vg^+$	1339	→ parental
$Pr . vg$	1159	→ parental
$pr^+ . vg$	151	→ Recombinant.
$Pr . Vg^+$	154	→ Recombinant
total	2839	

RF or COV = $\frac{154 + 151}{2839} \times 100 = 10.7\%$

less than 50% so it means chromosomes are linked

50% independent assortment

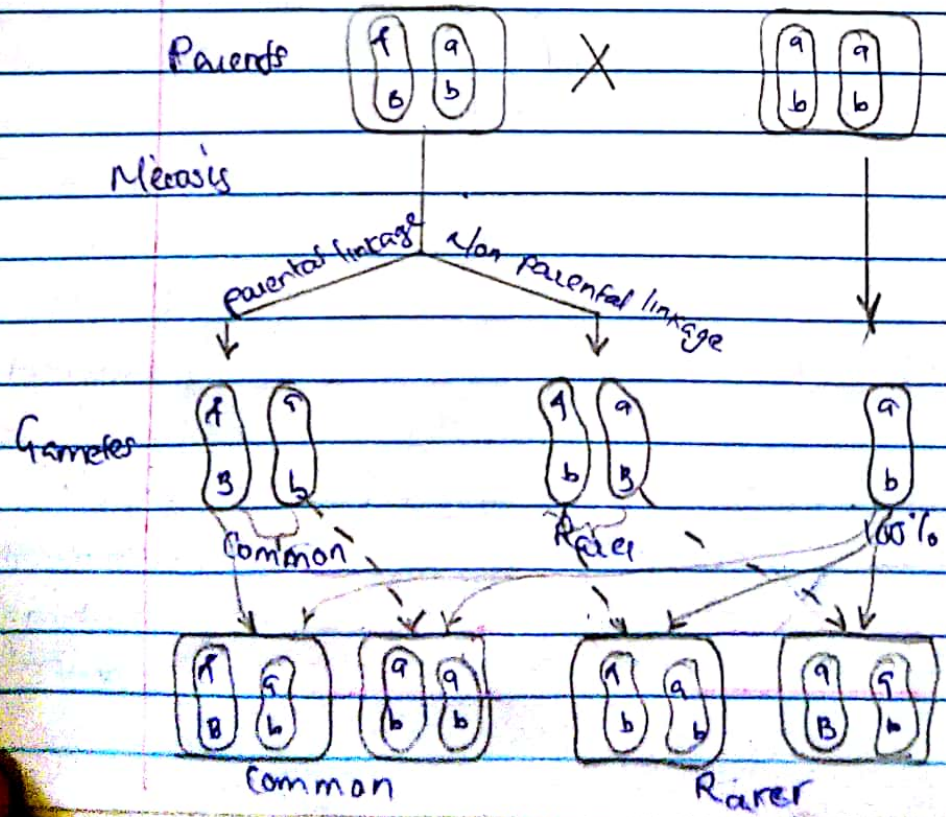


Fig 2: Demonstration of the effects of genetic recombination on the behaviour of non alleles at linked loci.

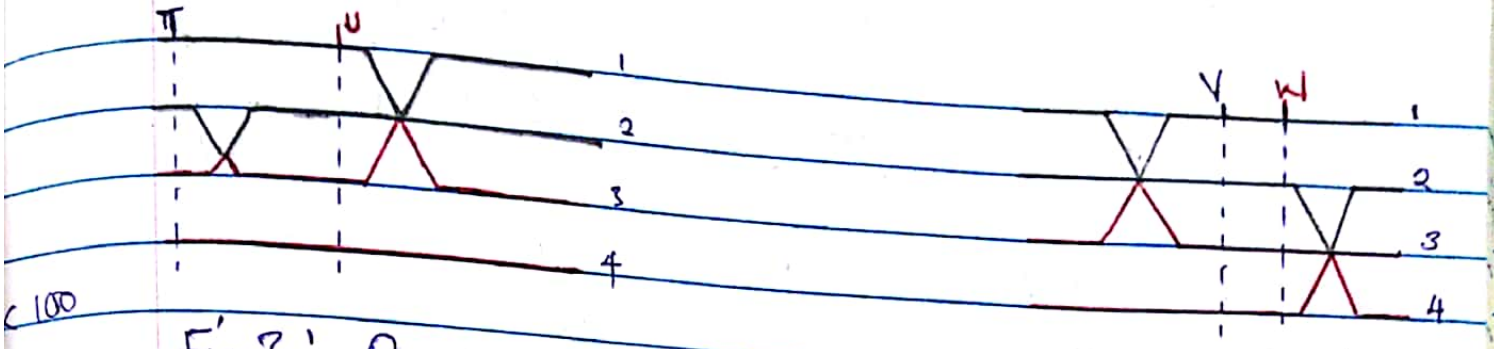


Fig 3: Proportionality between chromosome distance and recombinant frequency. In meiosis, Chromatids cross over at random along the chromosomes. The two genes T and U are further apart on a chromosome than V and W. Chromatids crossover between T and U in a larger proportion of meiosis than between V and W, so the RF for T and U is higher than V and W.

In modern genetic analysis, the main test for determining whether 2 genes are linked or non linked is based on the concept of recombination. Recombination is observed under independent assortment or crossing over during meiosis. Meiotic recombination is any meiotic process that generates a haploid product with a genotype that differs from both haploid genotypes that constitute the mother diploid cell. The product of meiosis so generated is called a recombinant.

1 RECOMBINATION BY INDEPENDENT ASSORTMENT.

Mendelian independent assortment is viewed with regard to recombination in fig 3: In a test cross, the two recombinant classes always make up 50% of the progeny, that is there is 25% of each recombinant type among the progeny. If we observe a recombinant frequency of 50% in a test cross, we can conclude that the 2 genes under study assort independently. The simplest interpretation of such a result

is that the 2 genes are on seperate chromosome pairs.

2 RECOMBINATION BY CROSSING OVER.

Crossing over also can produce recombinants, any two non sister chromatids can cross over. Meiosis with no crossing over between the 2 genes under study produces only parental genotypes of these genes. fig 1 for genes close together on the same chromosome pair, the physical linkage of parental allele combination makes independent assortment impossible and hence produces recombinant frequences significantly lower than 50%. We saw an example of this situation on Morgan's data were the recombinant frequency was (151 + 154) ÷ 2839 = 10.7%. This is obviously much less than 50% that we would expect with independent assortment. The recombinant ~~linkage~~ frequency arising from linked genes ranges from 0 - 50% depending on their closeness. The greater the distance between the linkage genes, the greater the change that non-sister chromatids would crossover in the region between the genes and hence the greater the proportion of recombinants that would be produced (fig 3).

LAWS OF PROBABILITY HELP TO EXPLAIN GENETIC EVENTS.

Mendel's 3:1 monohybrid and 9:3:3:1 dihybrid ratios are hypothetical predictions based of the following assumptions:

1 Each allele is either dominant or recessive.

2 Segregation occurs normally, no linkage

7 Independent assortment also occurs normally.
8 fertilisation is a random.

The last 3 assumptions are influenced by chanced events and therefore are subject to random fluctuation. This concept is called chance deviation. Eg in a monohybrid of height the result is 3/4 tall : 1/4 short these values predict the outcome of each fertilisation event, so the probability of each zygote having the genetic potential for becoming tall is 3/4 where as the potential for becoming short is 1/4 Probabilities range from zero where an event is certain not to occur to one where an event is certain to occur. In this section we consider the relation of probability to genetics. In genetics it is possible to evaluate observed deviations, when we assume that data obtained will fit a given ratio such as 3:1 or 9:3:3:1 then we establish what is called the Null hypothesis (H_0)

Null Hypothesis.

It is so named because the hypothesis assumes that there is no significant difference between the observed values and the expected values. The apparent difference can be attributed purely to chance. The null hypothesis is evaluated by using statistical analysis On this basis, the hypothesis may either be (i) accepted or (ii) rejected.

(i) It is accepted when the observed deviation from the expected is attributed to chance

alone. It will be rejected if the observed deviation from the expected is not attributed to chance alone. As a result the difference is significant. One of the simplest statistical test to access the null hypothesis is Chi-Square. (χ^2) analysis.

CHI-SQUARE (X^2) ANALYSIS EVALUATES THE INFLUENCE OF CHANCE ON GENETIC DATA.

i) Null hypothesis (H_0) establishes that the data obtained for monohybrid fit a given ratio of 3:1

ii) Calculation of X^2

The formula used in Chi-square analysis is

$$X^2 = \sum \frac{(\text{observed} - \text{expected})^2}{\text{expected}}.$$

In which Σ means the summation over all the classes of progeny.

$$X^2 = \frac{(O-e)^2}{e}$$

Where O - observed value for a given category.

e = expected value for that category.

Because (O-e) is the deviation (d) in each case then the equation can be reduced to;

$$X^2 = \frac{d^2}{e}$$

Example

A cross was carried out between plants of violet flowers with plants of white flowers. F1 was selfed and F2 results were as follows;

705 had violet flowers.
224 had white flowers. Calculate X^2 value and determine whether Ho is accepted or rejected.

Chi-square analysis

Total number of F_2 plants = 929.

Monohybrid cross

Expected ratio	Observed (o)	Expected (e)	Deviation (o-e) or d_1	$(o-e)^2$ or d_2	$X^2 = d^2/e$
3/4	705	696.75	8.25	68.0625	0.09768
1/4	224	232.25	8.25	68.0625	0.29306
Total	929	929			$\Sigma x^2 = 0.39$

Degree of freedom (df) = n - 1, where n = the number of different categories.

= 2 - 1 = 1 df.

Probability (P-value).

df	0.9	0.5	0.2	0.05
1	-	-	-	3.84
3	-	-	-	5.99
4	-	-	-	7.82
5	-	-		
6	-	-		
7	-	-		

P value = 3.84.

Since X^2 value is less than the p value, then the differences between observed and expected are not significant, so a result the deviation can be attributed to change and Ho is accepted

2 Dihybrid Cross.

Table 2; Chi-square analysis.

Expected ratio.	Observed (o)	Expected (e)	Deviation d = (o-e)	d^2	d^2/e
9/16	587	567	+ 20	400	0.705
3/16	197	189	+ 8	64	0.339
3/16	168	189	- 21	441	2.333
1/16	56	63	- 7	49	0.778
Total	1008	1008.			χ^2 = 4.155

P value = 7.81

Table 2 illustrates the results of F2. Calculate χ^2 and determine whether the H0 does fit the ratio of 9:3:3:1 or not.

Ans: Null hypothesis (Ho) established that the data obtained fit the ratio 9:3:3:1

Determine the df = n-1 = 4-1 = 3.

P-value.

df	0.05
1	3.84
2	5.99
3	7.81
4	9.48
5	11.07

P value > χ^2 value, ∴ Ho is accepted.

The χ^2 test tells us how often deviations from expectations will occur purely from the basis of chance! the proceedure is as follows:

1 State a simple hypothesis that gives a precise expectation. , In our ex. the best hypothesis is lack of linkage which yields an expected 9:3:3:1 ratio

2 Calculate x^2

x^2 is always calculated from actual numbers, never from percentages, fractions, or decimal fraction. The formula for calculating x^2 is as follows:

$$x^2 = \text{total of } \frac{(o-e)^2}{e}$$

Because $(o-e)$ is the deviation (d) in each case the equation can be reduced to $x^2 = d^2/e$.

3 Estimate p-value: Using x^2, we estimate the probability p of obtaining the observed results if the null hypothesis is correct. Before this can be done however, we must compute another item; the # of degrees of freedom (df) In the present context the # of df can be simply defined as df = number of classes - 1, in our example, df = 4 - 1 = 3. Once the # of df is determined, we can interpret the x^2 value in terms of a corresponding probability value (p) which is illustrated in the critical values of the x^2 distribution. Because this calculation is complex, we usually take the p-value from the standard table or graph.

4 Reject or accept the null hypothesis. Since x^2 value is less than the p value then the differences between the observed and expected aren't significant as a result the deviation can be attributed to chance and the Ho is accepted.

LETHAL ALLELS.

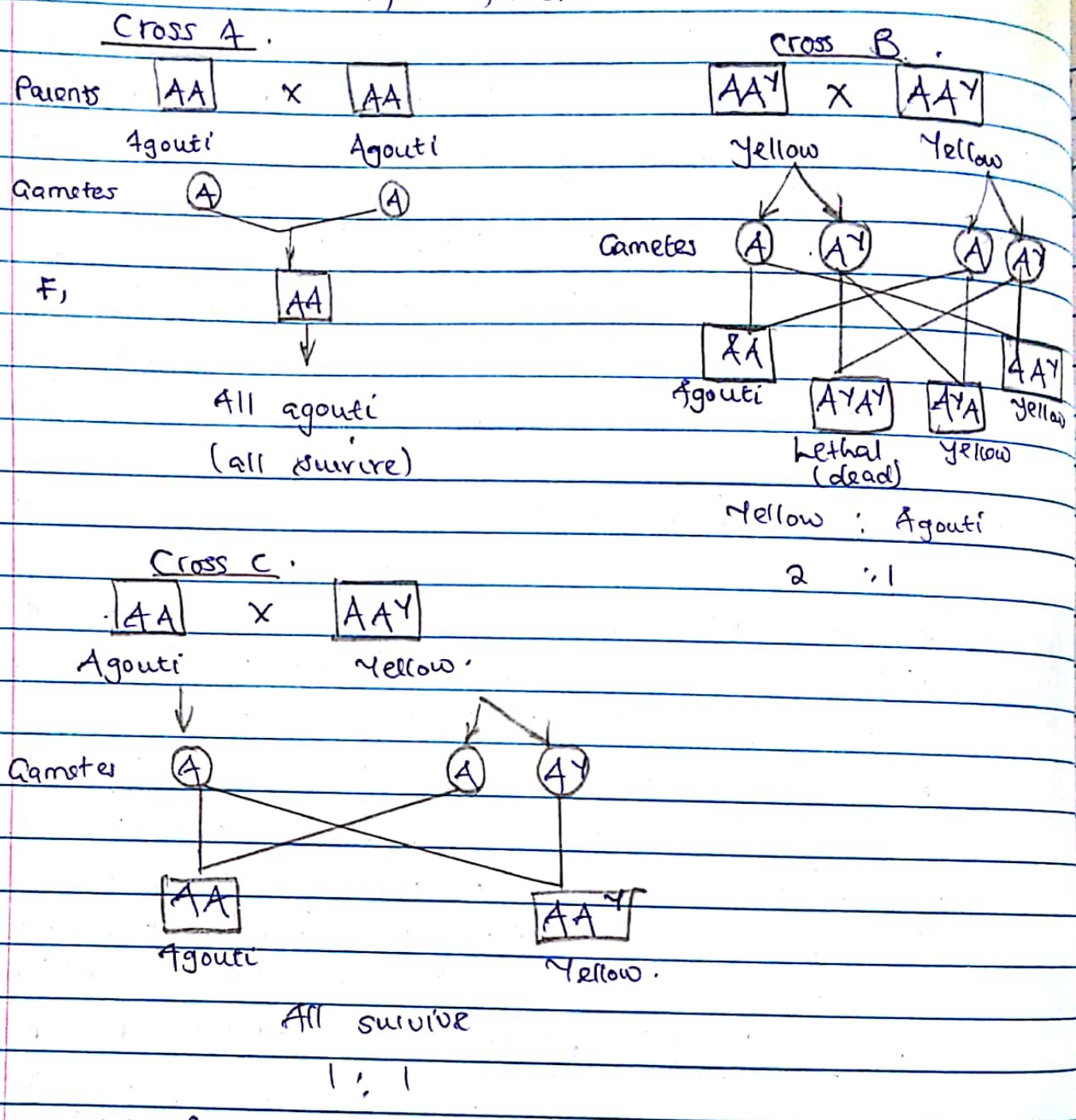


Fig 1: Inheritance patterns in 3 crosses involving the normal wild type Agouti allele (A) and the mutant Yellow allele (AY) in the mouse.

Such a mutation behaves as a recessive lethal allele and homozygous recessive individuals will not survive. The time of death will depend on when the product is essential. In mammals e.g the most occur during development, early childhood or even during after hood.

In some cases the allele responsible for a lethal effect when it is homozygous may also result in a distinctive mutant phenotype when it is present heterozygously. Such an allele is behaving as a recessive lethal but is dominant with respect to the phenotype e.g a mutation that causes yellow coat color in mice was discovered in the early part of the 20th century. The yellow coat varies from the normal agouti coat phenotype shown in fig 1. Crosses between the various combinations of the strains yeilds unusual results.

Crosses.

a Agouti × Agouti → All agouti
b Yellow × Yellow → 2/3 Yellow : 1/3 Agouti
c Agouti × Yellow → 1/2 yellow : 1/2 Agouti.

These results are explained on the basis of a single pair of allele. with regard to coat color the mutant yellow allele A^Y is dominant to the wild type agouti allele A. So heterozygous mice will have yellow coats However the yellow allele also behaves as a homozygous recessive lethal. Mice of the genotype A^YA^Y die before birth so no homozygous yellow mice are ever recovered.

Molecular analysis of the A gene in both normal agouti and mutant yellow mice has provided insight into how a mutation can be both dominant for one phenotypic effect (hair color) and recessive for another

embryonic development. The A^y allele is a classic example of a gain of function mutation. A allele have yellow pigment deposited as a band on the otherwise black hair shaft resulting in the agouti phenotype. The homozygous lethal effect has also been explained as a result of the molecular analysis of the mutant gene. It is the gene that is critical to embryonic development. In A^yA^y homozygote it causes lethality. note that the mutant allele behaves dominantly to the normal allele in controling coat color but it also behaves as a homozygous recessive lethal allele. the genotype A^yA^y doesn't survive.

MULTIPLE ALLELES (ABO blood groups)

Blood Composition

- Plasma protein.
  - Albumin
  - Immunoglobulin or antibodies
  - fibrinogen for blood clotting
- Cellular components.
  - Red blood cells
  - White blood cells

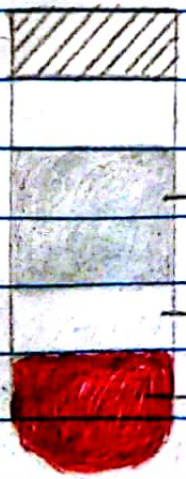


Fig 1: layering of blood components in anticoagulated and centrifugated blood samples.

Blood groups. Antigen-Antibody generator.

	Type A	Type B	Type AB	Type O
Red blood cell.	A-antigens. 	B-antigen. 	A and B antigens 	No A or B antigens. 
Plasma	 Anti-B antibodies	 Anti-A antibodies.	No anti-A or anti-B antibodies	 Anti A and Anti B antibodies both present.

Fig 2: ABO blood groups.

The entire human population can be divided into 4 groups of blood on the basis of the reaction between the blood of different individuals when mixed together. These groups are A, B, AB and O and they are known collectively as the ABO system. The capital letters stand for different types of glycoproteins present on the surface of the person's red blood cells. These glycoproteins are antigens similar to those found on the surface of bacteria. We all make antibodies against foreign antigens but not of course against those on our own red blood cells. The anti bodies are anti-A and anti-B. If an individual has a particular antigen on his or her red blood cells the corresponding antibody will not present in that person's own plasma. Thus a person belonging to blood group A has red cells with A-antigens on them, the plasma doesn't then contain Anti A antibodies but it does contain anti B antibodies

Platelets

A person belonging to group B has B antigens on the red blood cells and the plasma contain anti-A antibodies only. In a person with blood group AB, the red blood cells carry both antigens A and B and neither anti bodies are present in their plasma. Group O blood has neither antigens but both anti bodies. If blood of group A is given to a patient of blood group B the anti-A antibodies in the patients blood will cause agglutination forming clumps which may block the recepients blood vessels and later causing death as a result a knowledge of blood groups is important because transfusion of blood from one person to another may cause an immune respose in the recepient if the doners blood is of a different group AB response results in mass haemolysis Some of the donated red blood cells and oxygen carrage becomes affected. before haemolysis Some of the donors red cells agglutinate and the blockages occur in capillaries of vital organs usually with futile results. About 20 blood groups systems have been described in man, they are based on the antigen which form part of the red blood cell membrane The best known blood group System is ABO system. human red cells possess 1, both or neither of the 2 antigens called A and B. In the plasma are 2 iso antibodies called anti A and anti B.

Anti A is found in the blood group B individuals and anti B in group A individuals. Both anti A and anti B are in the blood of group O individuals and neither antibodies appears in the blood of group AB individuals. Table 2 shows the distribution of the antigens and the antibodies ABO system

Table 2 : The antigens and antibodies of the human ABO blood group system.

Blood group.	O	A	B	AB
Red cell antigen	-	A	B	A + B
Plasma antibody	Anti-A and anti B	anti-B	anti-A	-

Often genes have more than 2 alleles of a given locus though any one individual only two alleles can be present. An example of such multiple alleles is provided by the alleles controlling the ABO group system in humans. The ABO system is controlled by 3 alleles refered to as I^A, I^B and I^O. The I^A allele is responsible for the production of type A antigen, I^B is for type B antigen, I^O produces neither antigens. An individual may possess any of the following 6 genotypes: I^AI^A, I^AI^O, I^BI^B, I^BI^O, I^AI^B or I^OI^O We can list the various genotypes possibility and assign the appropriate phenotypes to each.

	Genotype	Antigene	Phenotype
1	$I^A I^A$	A, A →	A.
2	$I^A I^O$		
3	$I^B I^B$	B, B →	B
4	$I^B I^O$		
5	$I^A I^B$	A, B	AB.
6	$I^O I^O$	neither.	O.

The I^A and I^B alleles show equal dominance but each is dominant to I^O thus a person with genotype $I^A I^A$ or $I^A I^O$ belongs to the blood group A. A person with genotype $I^B I^B$ $I^B I^O$ belongs to blood group B. A person with genotype $I^A I^B$ belongs to blood group AB. A person with $I^O I^O$ belongs to group O

Note about Codominance.

Codominance means that the heterozygous genotype exhibit trait associated with both homozygous genotype. An example that illustrates codominance is found in AB blood group Both the A and the B express themselves equally.

It is evident that if a mother and her baby belong to group O, the father could belong to O, A or B but not to AB. How?

Father X Mother

$I^O I^O$ X $I^O I^O$

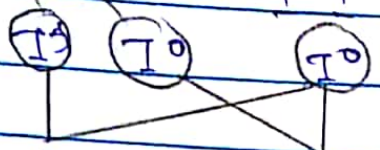
Gametes I^O I^O

Offspring $I^O I^O$

Father X Mother.

I^AI^O X I^OI^O

Gametes



Offsprings I^AI^O I^OI^O

$\frac{1}{2}$: $\frac{1}{2}$

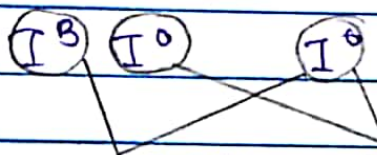
50% : 50%

1 : 1

Father X Mother

I^BI^O X I^OI^O

Gametes



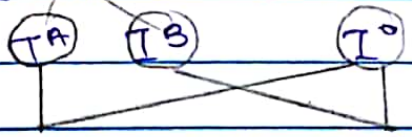
Offsprings I^BI^O I^OI^O

1 : 1

Father X Mother.

I^AI^B I^OI^O

Gametes



I^AI^O I^BI^O

1 : 1

Evidence of this kind is used in legal cases where the paternity of a child is in question. If a mother's blood group was B and her child is of group AB which group would the father belong to

GENETIC VARIATION.

Types of variation in a population.
Continuous variation against discontinuous variation.

If all members of two species have the same set of genes, how can there be genetic variation?

Ans: Genes come in different forms called alleles in a population for a given gene there can be from one to many different alleles, however because most organisms carry only one or two chromosome sets per cell any individual organisms can carry only one or two alleles per gene. The alleles of one gene will always be found on one chromosomal position. Allelic variation, as the basis for hereditary variation

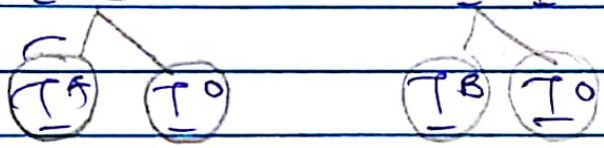
Types of variation in a population.

A useful classification is into continuous variation and discontinuous variation. discontinuous variations are often determined by alleles of a single gene. A good example of discontinuous organisms is albinism in humans. which concerns phenotypes of the character of skin pigmentation. In most people the cells of the skin can make a dark brown or black pigment called melanin. the substance that gives our skin its colour although always rare albinos are found in all races. They have a totally pigmentless skin and hair. The difference between pigmented and unpigmented is caused by 2 alleles of a gene taking part in melanin synthesis. Another exp. of discontinuous is distinguish between male or female human and also have

only one of A possible ABO blood groups A, B, AB or O. Most genes have more than 2 alleles, the inheritance of the human ABO blood groups provide an example of this situation known as multiple alleles, it also shows both dominance and codominance of the alleles concerned. A woman with blood group A and a man with B both of whom were heterozygous at the ABO locus could produce a child with any 1 of the ABO blood groups.

Parental phenotypes Female with b.g A x Male with B.

Parental genotype $I^A I^O$ $I^B I^O$



gametes

Offspring genotypes & phenotypes.

		Gametes from Woman. I^A	I^O
Gametes from man.	I^B	$I^A I^B$	$I^B I^O$
	I^O	$I^A I^O$	$I^O I^O$

Each time this couple have a child there is Unequal ($\frac{1}{4}$) probability that it will have any one of the blood groups, A, B, AB or O.

Continuous Variation.

Continuous variation of a character shows an unbroken range of phenotypes in the population. Measurable characters such as height, weight, are examples of such variations

Intermediate phenotypes are generally more common than extreme phenotypes and when phenotypic frequencies are plotted as a graph, a bell-shaped distribution is observed. In some such distributions, all the ~~enviro~~ variation is environmental has no genetic basis at all. In other cases, there is a genetic component caused by allelic variation of one or many genes. In most cases, there is both genetic and environmental variation. In continuous distributions, there is no one to one correspondence of genotype and phenotype. For this reason little is known about the types of genes under lying continuous variation and only recently have techniques become available for identifying and characterising them.

Parental phenotypes — 4x cm tall × 8x cm tall

Parental genotypes — aabb × AABB

Gametes — ab, AB

F1 genotypes — AaBb

F1 phenotypes — All 6x cm tall

Inter breeding the F1 generation Gametes from one parent.

AB	AB	Ab	aB	ab
Gametes from another Parent	AABB 8x cm	AABb₁ 7x cm	AaBB₂ 7x cm	AaBb 6x cm
Ab	AABb 7x cm	AAbb₂ 6x cm	AaBb₃ 6x cm	Aabb 5x cm
aB	AaBB 7x cm	AaBb 4 6x cm	aaBB₅ 6x cm	aaBb 5x cm

ab AaBb Aabb aaBb aabb

6xcm. 5xcm 5xcm 4xcm

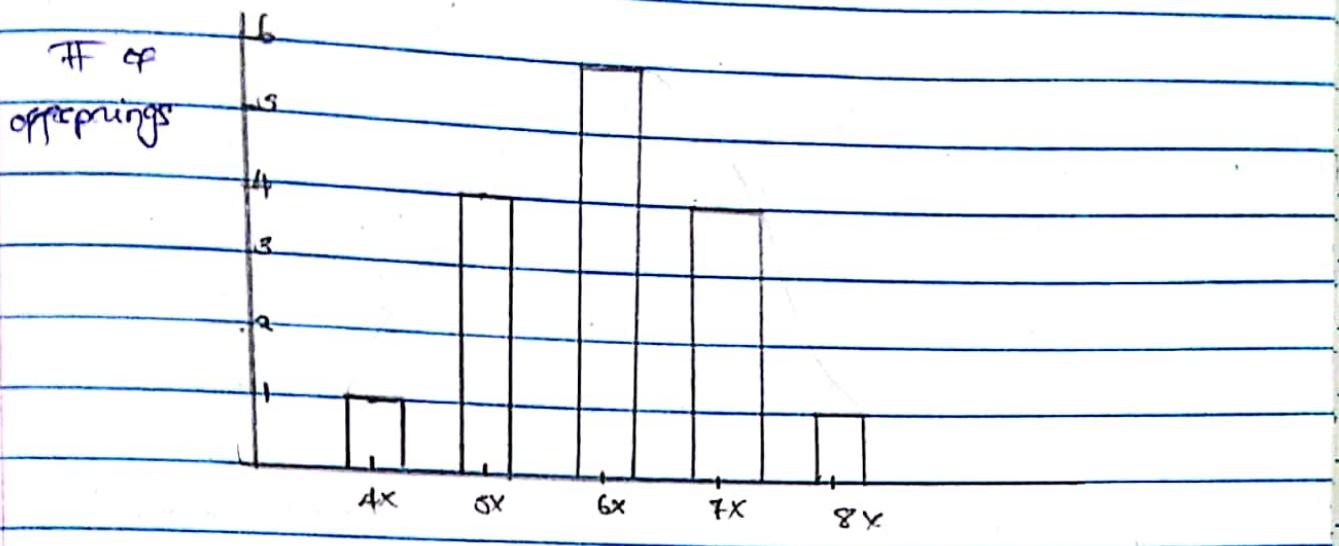


fig1 : The additive effect of alleles.

Potential height from genotype	4xcm	5xcm	6xcm	7xcm	8xcm
# of offsprings	1	4	6	4	1

Assuming that the effect of a a gene is additive and that (a and b) each contribute x cm to the height of the organism.
Whereas the dominant alleles (A and B) each increase the height by x cm.

Suppose that the height of an organism is controlled by 2 unliked gene loci that is on different chromosomes A/a B/b. The recessive alleles of both loci (ab) each contribute Xcm to the height of the organism whereas the dominant alleles (AB) each increase the height by 2x cm. If the effect of each gene is additive the homozygote recessive aa bb therefore is potentially 4X cm tall.

aabb AaBb Aabb aaBb aabb
6 6x cm. 5x cm 5x cm 4x cm

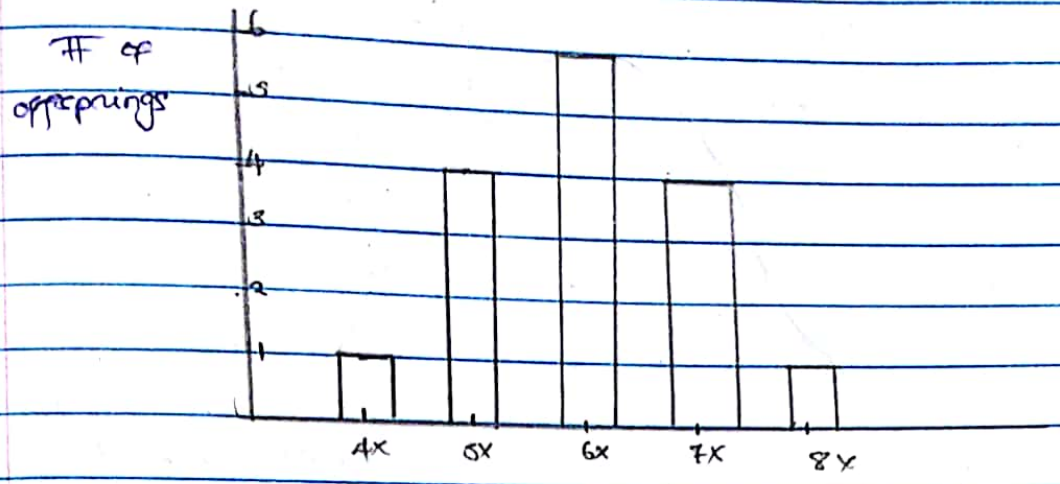


fig: The additive effect of alleles.

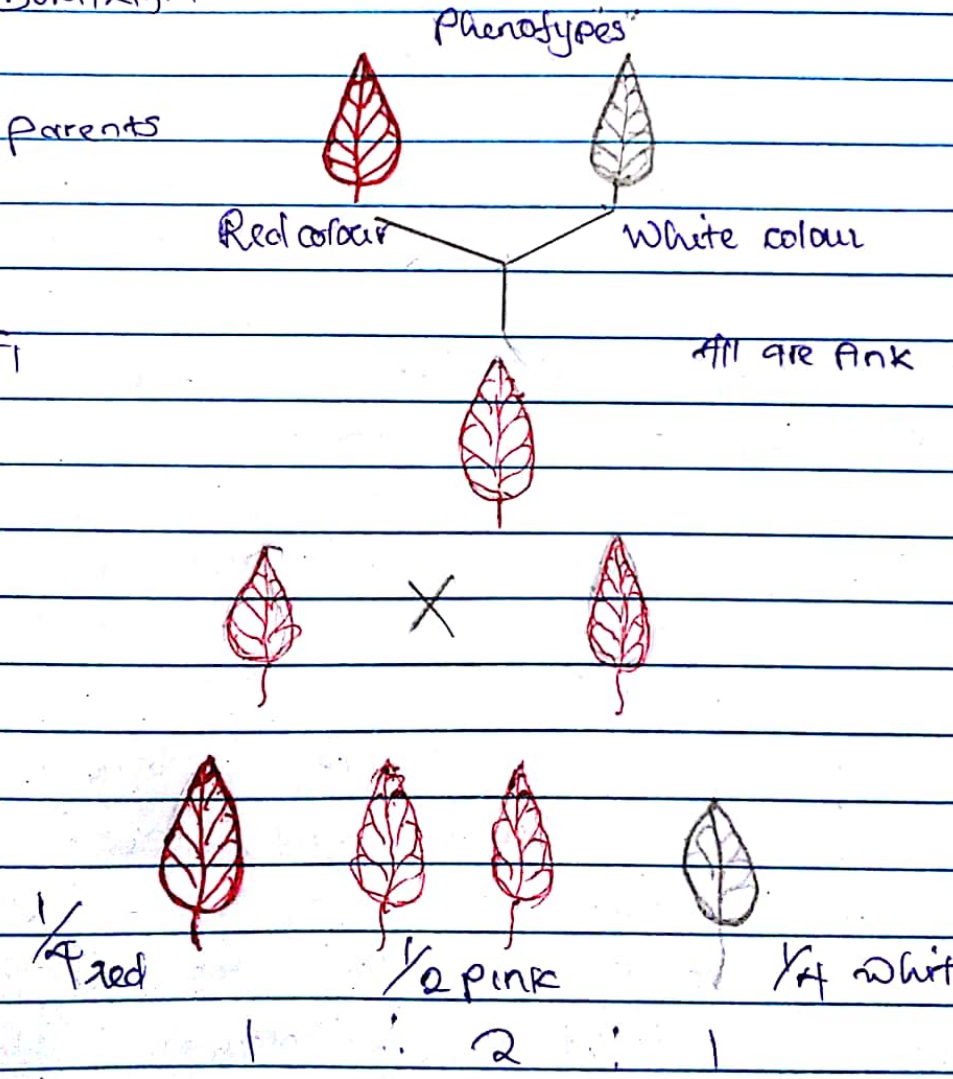
Potential height from genotype	4xcm	5xcm	6xcm	7xcm	8xcm
# of offsprings	1	4	6	4	1

Assuming that the effect of a gene is additive and that (a and b) each contribute x cm to the height of the organism.
Whereas the dominant alleles (A and B) each increase the height by 2x cm.

Suppose that the height of an organism is controlled by 2 unlinked gene loci that is on different chromosomes A/a B/b. The recessive alleles of both loci (ab) each contribute x cm to the height of the organism whereas the dominant alleles (AB) each increase the height by 2x cm. If the effect of each gene is additive the homozygote recessive aabb ~~bb~~ therefore is potentially 4x cm tall.

and the homozygote dominant AABB is potentially 8x cm tall, the other genotypes will fall between these extremes. Suppose that now the homozygote aabb and AABB are interbreeding, interbreeding the F1 generation gives all possible genotypes amongest the 16 possibilities. The results fall approx. on a normal distribution curve as shown in fig 1.

INCOMPLETE DOMINANCE, NEITHER ALLELE IS DOMINANT.



Genotypes

Parents R^1R^1 × R^2R^2

Red white

Gametes R^1 R^2

F_1 R^1R^2 all are pink.

R^1R^2 × R^1R^2.

Gametes R^1 R^2 R^1 R^2.

R^1R^1 R^2R^2 R^1R^2 R^1R^2

Red white Pink

1 : 1 : 2.

Fig 1: Incomplete dominance shown in the flower color of snapdragons.

Example: Inheritance of flower colour in Antirrhinum (snapdragon) flowers.

Contrary to the mendelian crosses, a cross between parents with contrasting traits may sometimes generate offspring with an intermediate phenotype. E.g. of plants such as Antirrhinum with red flowers are crossed with white flowered plants the offspring face pink flowers. Because some red pigment is produced in the F_1 intermediate red colour pink plants, neither red nor white color is dominant, such a situation is known as incomplete dominance. If the phenotypes is under the control of a single gene and two alleles where neither is dominant the result of F_1 Pink against pink flowers can be predicted. The resulting F_2 generation shown conforms the hypothesis that only one

pair of alleles determine these phenotypes. The genotype ratio is 1:2:1 of the F2 generation. Bcoz neither allele is dominant, the phenotype ratio is identical to the genotype ratio. Note that since neither of the alleles is recessive, we have chosen not to use lower and upper case letters as symbols instead we denote the red and white alleles as R^1 and R^2.

How are we to interprete lack of dominance whereby an intermediate phenotype characterises heterozygote the most accurate way to consider gene expression is quantitative way, In the case of flower color above, the mutation causing white flowers is most likely one way complete lose of function occurs. In this case it is likely that the gene product of the wild type allele (R^1) is an enzyme that participates a rxn leading to the synthesis of a red pigment. The mutant allele are to produces an enzyme that can not catalyse the rxn leading to pigment, the end result of that, the heterozygote produces only about half the pigment of the red flowered plant and the phenotype is pink.

The difference between incomplete dominance and codominance

Incomplete dominance means that the phenotype of the heterozygote is intermediate betwn case of homozygous plants: In Codominance means that the heterozygous exhibits the

Traits associated with both homozygous in both alleles are fully expressed equally.

GENE INTERACTION.

Ex: EPISTASIS.

Table 1: Inheritance of coat colour in mice

Agouti A } alleles.
Non-agouti a }

Black B } alleles
Brown b }

Coloured C } alleles.
Albino c }

Genotype	Phenotype
A* B* C*	Agouti (Grey).
aa B* C*	Black.
aa bb C*	Brown
A* bb C*	Cinnamon,
** ** cc	Albino

Note: * Either allele may be present.

Epistasis - interaction between genes such that one gene interferes with or prevents the expression of another gene. It occurs when an allele of one gene supresses the action of an allele of another gene. Coat color in mice is controlled by 3 different loci as outlined in Table 1. one locus carries a dominant allele A called agouti while the recessive allele a, non agouti.

An agouti individual has a band of yellow near the tip of each hair which modifies the overall appearance of the skin. The second locus is occupied by the alleles B or b responsible for black or brown pigmentation respectively. If C the dominant allele for coloured coat is present at the 3rd locus, then the phenotype of the mouse is determined by the alleles at the other 2 loci. However the homozygous recessive genotype cc at this locus produces a white or albino coat regardless of the alleles present. In other words the albino allele suppresses the action of the other genes.

INHERITANCE OF SEX AND SEX-LINKED TRAITS.

- Special chromosomes determine sex in many organisms.

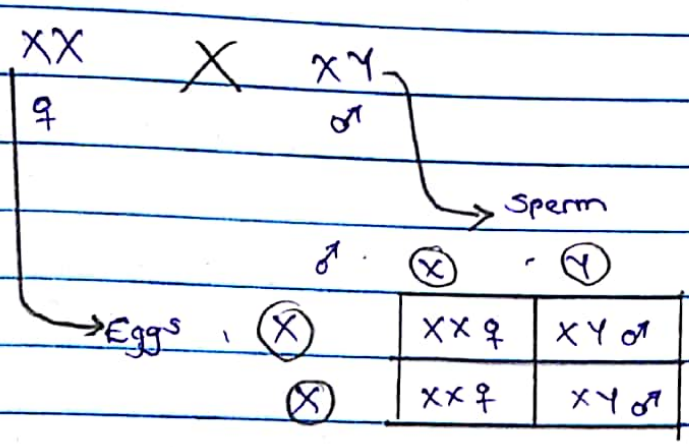


fig 1.

The female (♀) : Male (♂) ratio is 1 : 1

The sex chromosomes are an exception to the rule that all chromosomes of diploid organisms are present in pairs of morphologically similar homologous. As early as 1891, microscopic analysis have shown that one of the chromosomes in males of some insects such as grass hoppers doesn't have a homologue. This unpaired chromosome was called the X chromosome and it was present in all somatic cells of the males but in only half the sperm cells. The biological significance of this observation became clear when females of the same species were shown to have 2 X chromosomes. In other species in which the females have 2 X chromosomes, the male has 1 X chromosome along with a morphologically different chromosome refered to as the Y

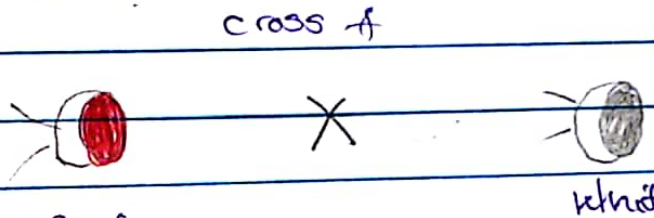
chromosome and it pairs with the X chromosome during meiosis in males because the X and Y share a small region of homology. The chromosomal constitution of males and females is a chromosomal mechanism for determining sex at the time of fertilisation. (Fig 1) Where as every egg cell contains an X chromosome half the sperm cells contain an X chromosome and the rest contain a Y chromosome. Fertilisation of an egg carrying X chromosome by the sperm carrying X chromosome results in an XX zygote which normally develops into a female. Fertilisation of an egg carrying X chromosome by a sperm carrying Y result in an XY zygote which normally develops into a male. A male receives his X chromosome from his mother and transmits it only to his daughter. The XX-XY type of chromosome and sex determination is found in mammals including humans, in many insects and in other animals as well as in some flowering plants. The X and Y chromosomes together constitute the sex chromosomes, this term distinguishes them from other pairs of chromosomes called autosomes. Although the sex is in control of the developmental switch that determines the earliest stages of female or male development, the developmental process itself requires many genes scattered throughout the chromosome complement including genes on the autosomes. The X chromosome also contains many genes with functions

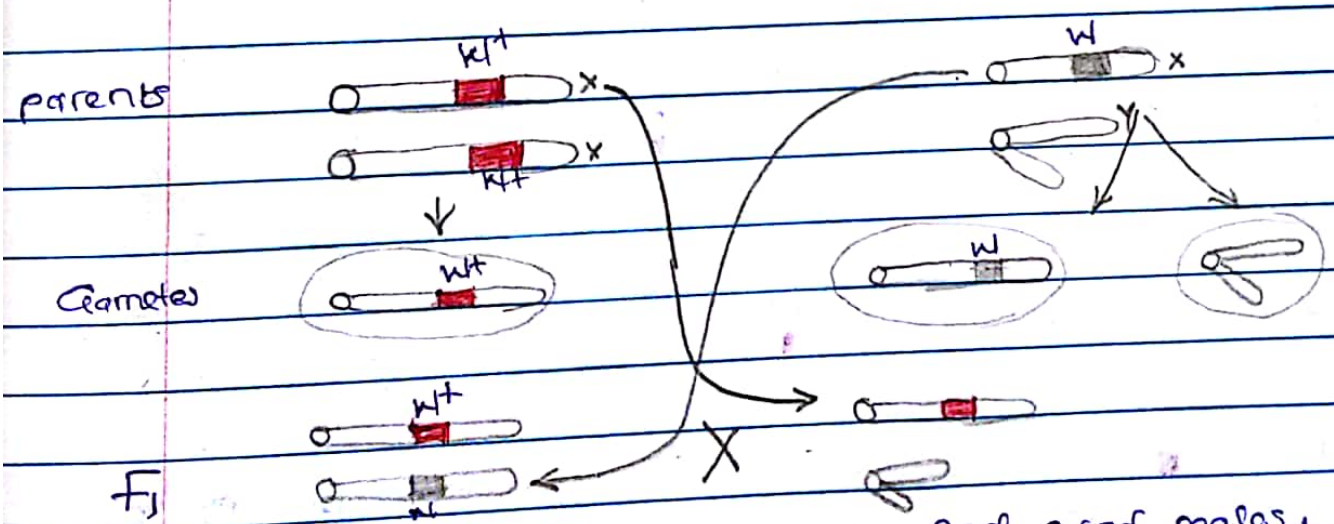
unrelated to sexual differenciation. In most organisms, the Y chromosome carries few genes other than those related to male determination. The Y chromosome contains unestimated 128 genes.

- X-linked genes are inherited according to sex.

The strong evidence that genes are in chromosom came from the study of a drosophila gene for white eyes.

Morgan's Study.

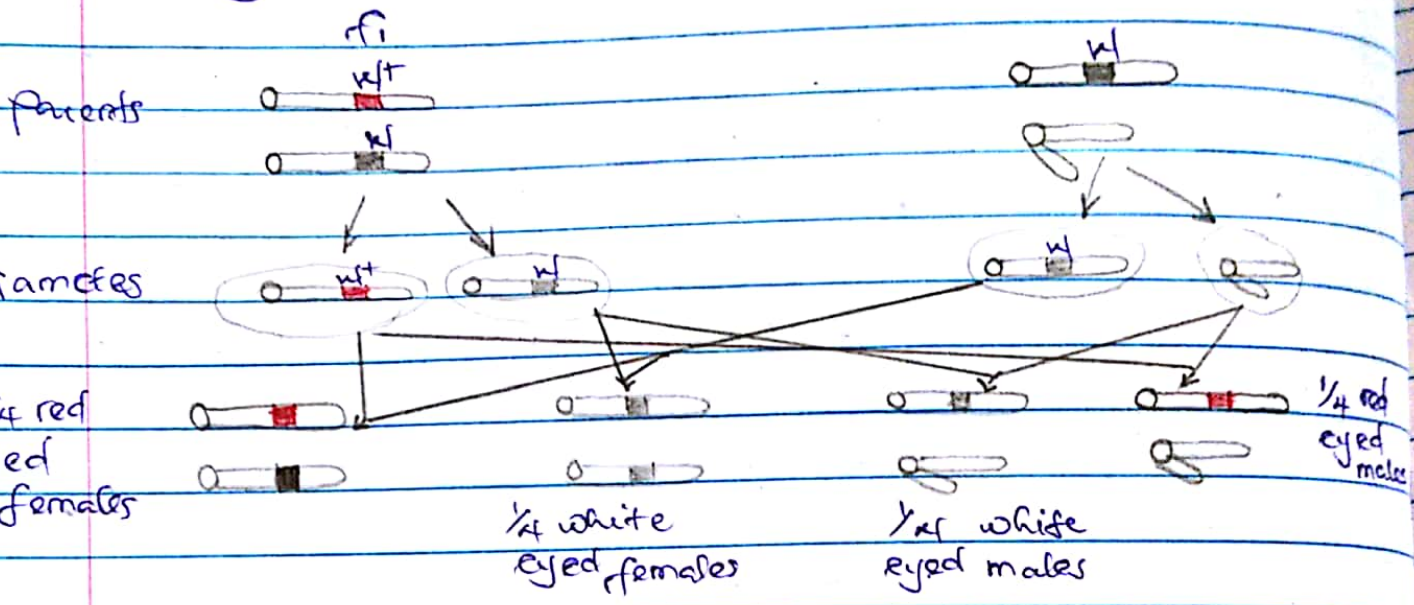




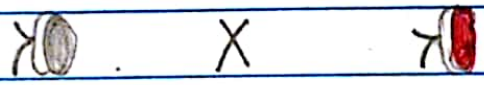
Morgan's Back Crossed

Red eyed female from F1

White eyed male homozygous

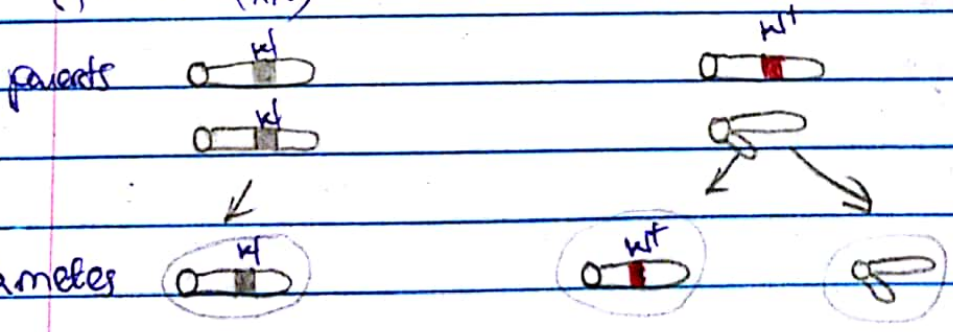


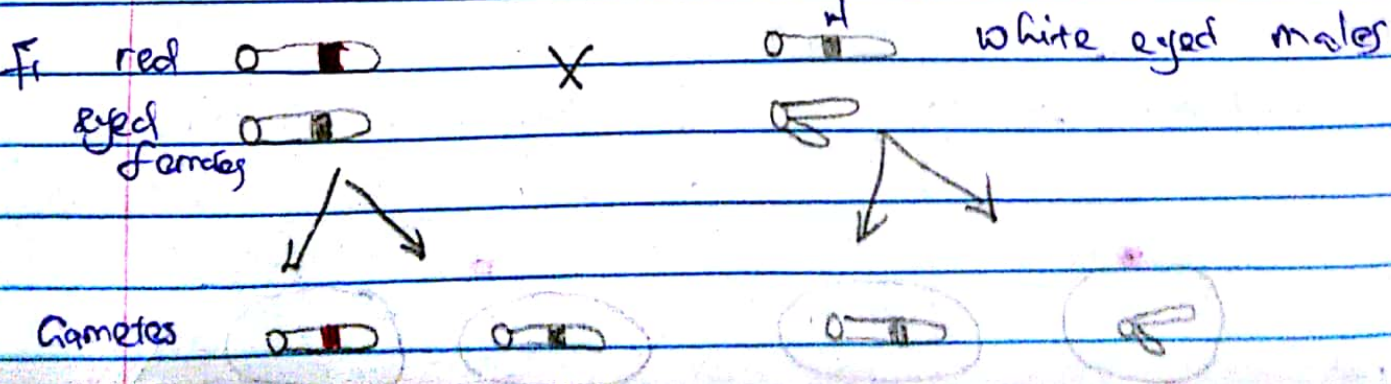
CROSS B.

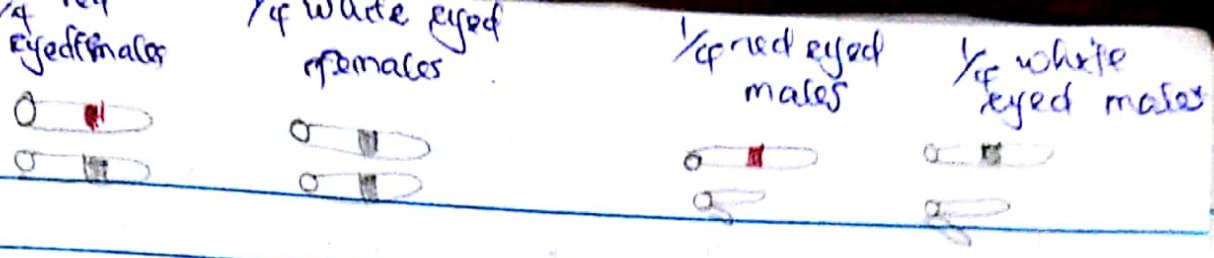


White eyed female (XX)

Red eyed male.

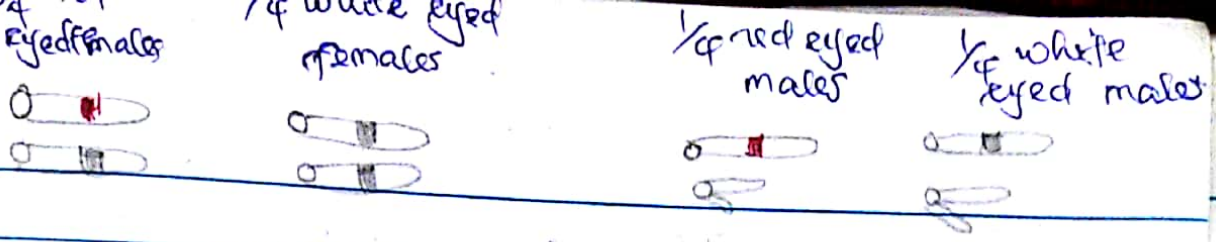






which prove to be present in the X chromosome Recall that in Mendel's process reciprocal crosses gave the same result, he did not matter which trait was present in male parent and which in female parent One of the earliest exceptions to this rule was found by Thomas Morgan in 1910 in an early study of a mutation in the fruit fly drosophila Melanogaster that had white eyes. The wild type eye colour is a red pigment although white eyes can result from certain combinations of autosomal genes that eliminate the ~~pigment~~ pigments individually, the white eye mutation that Morgan studied results in a metabolic block that knocks out red pigment.

Morgans study started with a single male with white eyes that appeared in a wild type lab population that had been maintained for many generation. In a mating of this male with ~~white~~ type female (cross A) all the f1 progeny of both sexes has red eyes showing that the allele for white eyes is recessive. If the f2 progeny from the mating of f1 males and females, Morgan observed 2459 red eyed females, 1011 red eyed males and 782 white eyed males The white eyed phenotype was somehow connected with sex bcoz all of the white eyed flies were males.



which prove to be present in the X chromosome Recall that in Mendel's process reciprocal crosses gave the same result, he did not matter which trait was present in male parent and which in female parent One of the earliest exceptions to this rule was found by Thomas Morgan in 1910 in an early study of a mutation in the fruit fly Drosophila Melanogaster that had white eyes. The wild type eye colour is a red pigment although white eyes can result from certain combinations of autosomal genes that eliminate the ~~pigment~~ pigments individually, the white eye mutation that Morgan studied results in a metabolic block that knocks out red pigment.

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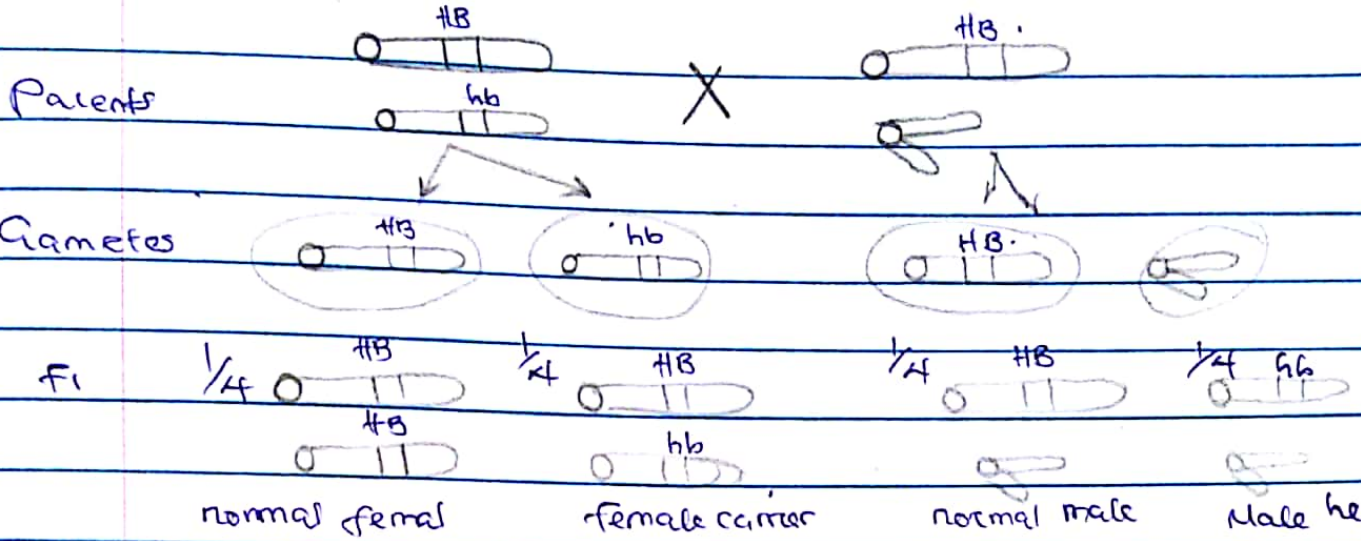
On the other hand, white eyes weren't restricted to males e.g when red eyed F1 females from the cross of wild type females against white males were back crossed with their white eyed fathers. The progeny consist of red eyed and white eyed females and red and white eyed males. In approximate equal numbers.

Key observation can from the mating of white eyed females with wild type male (cross B) all of the female progeny had red eyes but all of the male progeny had white eyes. This is the reciprocal of the cross A of wild type female (red) against white males which had yielded only wild type females and wild type males and so the reciprocal process gave different results. Morgan realised that reciprocal process would held different results if the allele for white eye were present in X chromosome. Thus as both the X-chromosome is transmitted in a different pattern by males and females and the Y chromosome doesn't contain a counterpart of the X gene, a gene located on the X-chromosome is said to be X-linked

HEMOPHILIA IS A CLASSIC EXAMPLE OF HUMAN X-LINKED INHERITANCE.

H^B is the normal allele for factor VIII
h^b is the abnormal allele for factor VIII



Hemophilia is a sex linked recessive trait with an interesting history. Hemophiliacs bleed excessively when injured because they are missing a certain protein required for blood clotting. The most seriously affected individuals may bleed to death after relatively minor cut. Hemophilia is sometimes refered to as a disease of royalty because of its incidence among male decendants of queen Victoria, but is also found in many non royal individuals. Sons born with hemophilia should have a family history of hemophilia were exempted from circumcision. Today treatment consist of blood transfussions and administration of factor VIII by injection. Unfortunately these treatments are very costly and have been associated with infection of the HIV I the virus that causes AIDS.