

INHERITANCE IN LIFE.

Heredity: Heredity is the transmission of particular characteristics from parent to offspring.

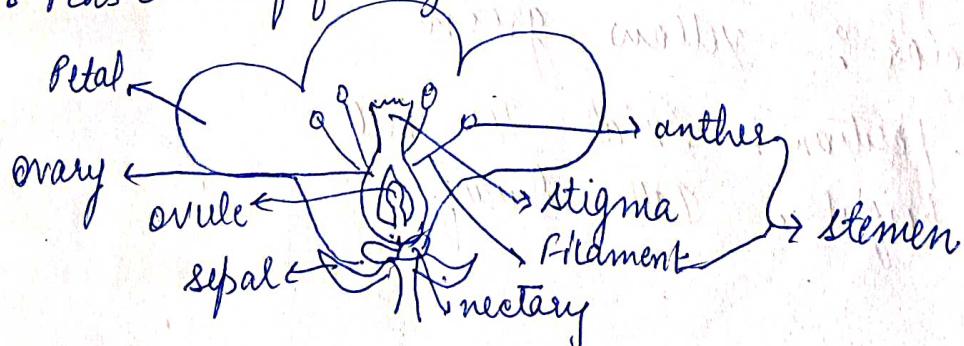
Mendel presented completely new theory of inheritance in the journal "Transactions of the Natural History Society of Brunn".

His work was rediscovered in 1900,

Mendel is often referred as the 'father of Genetics'. His experiments and principles collectively form "Mendelian genetics".

Mendelian Genetics (1822 - 1884)

- Studied garden peas
- 1st to use maths to examine outcomes of crosses
- Pea varieties with at least 7 easily distinguished traits
- Peas are small, easy to grow, short generation time
- Peas can self fertilize; bisexual



- Peas don't take up that much space in the monastery garden
- Fertilizing organs are enclosed in a kind of closed keel
- They self fertilize. And there is no risk that pollen from some other plant is going to get in there.
- You can open it up and pollinate.
- It's an ideal plant for doing genetics because we don't randomly

get much cross pollination.
more varieties are available.

- (1) selection of distinctive characters (^{tall} X dwarf, round X wrinkled green X yellow etc.)
- (2) Selection of true breeding varieties (that would show the same characters in the same way in the offspring in succeeding generations)
- (3) controlled fertilization

Seed shape: Round Wrinkled

Seed color: Yellow Green

Flower color: Purple White

Pod shape: Inflated Constricted

Pod color: yellow green

Flower position: Axial Terminal

stem height: Tall Dwarf

Monohybrid Cross (Pure breeds) \rightarrow selective experiment allowed him to

- ✓ In monohybrid cross Mendel selected one character for his experiment
- ✓ crosses were made between white flowered and purple flowered plants
- ✓ Pollens from the purple flowers were placed onto the stigma of white flowers.
- ✓ Allowed it to cross fertilization
- ✓ all the seeds in the pod resulted from this pollination were hybrids.

Purple \times white

1st Generation \rightarrow Purple color offsprings (white missing)

Purple (again with purple)

2nd Generation \rightarrow Purple and white offsprings

3:1

[Purple \rightarrow Dominant
white \rightarrow recessive]

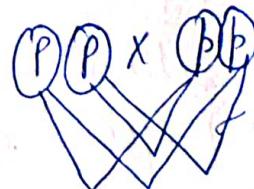
appeared in 2nd but less ratio of white

Dominant \rightarrow Big letter

Recessive \rightarrow small letter

Human has 46 chromosomes
(23)(23)
 \downarrow
M F

~~PP~~ \times ~~pp~~ \rightarrow ~~all~~
(homozygous condition)



Pp Pp Pp Pp
one dominant
one recessive

PP, pp \rightarrow true characters
bcz of Two set of char M & F

Punnet's Square

	P	P	
F ₁	p	Pp	Pp
	p	Pp	Pp

- one dominant alleles
- one recessive alleles

Since P is dominant, therefore no white colour.

	none	P	p
P	PP purple	Pp → Hetero purple	
p	pp purple	pp → Homozygous white	

→ 3:1 { By appearance }
color = { Phenotypic ratio }

→ with respect to Genotype
 2 Hetero and 1 Homo in purple
 → 1:2:1 and 1 homo in white

Observation and Interpretation of monohybrid Cross

- (1) The hybrid of offspring always resembled one of the parent, did not have an intermediate color.
- (2) The first filial generation plants had all purple flowers
- (3) Mendel referred to the trait expressed in the F₁ plants as dominant and to the alternative trait, which was not expressed in the F₁, as recessive.
- (4) The plants obtained from self pollination of F₁ generation exhibited the recessive trait (second filial F₂ generation)
- (5) Mendel counted the numbers of each type among the F₂ progeny amongst the 929 total F₂ individual. 705 had purple flower and 224 had white flowers.

- The genotype ratio $1:2:1$ is the really distinguished with true breeding dominant, not true breeding and one quarter true breeding.
- $\frac{3}{4}$ th of the F_2 individuals exhibited the dominant trait and $\frac{1}{4}$ th displayed the recessive trait. The ratio of dominant to recessive among the F_2 plants was always $3:1$.
- In the study of F_2 plants in later generations he found that one quarter that were recessive were always true breeding, where $\frac{1}{3}$ rd of the dominant F_2 were true breeding.
- For each pair of traits that Mendel examined, one alternative was not expressed in the F_1 hybrids although it reappeared in the F_2 .
- In the pairs of alternative traits one trait must have been latent in the F_1 generation.
- He concluded that the traits segregate among the progeny of a particular cross, and some plants express one trait, some exhibit others.

Law of Segregation

Whenever a pair of factors for character brought together in a hybrid, they segregate during the formation of gametes. Hence each gamete is pure with reference to this character.

— END OF MONOHYBRID CROSS —

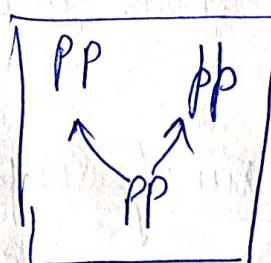
BACK CROSS - TEST CROSS (crossed F₁ with parents)

- A cross involving F₁ individuals with either of the two parents is called back cross.
- A back cross between the F₁ hybrid and dominant parental type will produce only dominant individuals.
- The cross between F₁ and recessive parents-type both the phenotypes appear in the progeny 50:50%. The cross between F₁ and recessive parents is called test cross (Pp × pp).

(First Gen with parent) Pp × PP

(Dominant parent)	P	P	P
	P	PP	Pp
(Recessive parent)	P	PP homo	Pp hetero
	p	p	p

Phenotypic → All purple
genotype → cannot be found



(Recessive parent) Pp × pp

	P	P	P
	p	Pp	Pp
	p	pp	pp
	p	p	p

→ 2 purple, 2 white
Phenotypic ratio → 1:1
genotypic → 1:1

2 Hetero, 2 homo.

To find genotype → Always cross with recessive breed.
1:1 + hetero
see dominant → pure breed.

Mendel proposed a simple model of heredity - (5 parts):

- (1) Parents transmit factors to offspring
- (2) Each individual receives 2 factors which code for the same trait.
- (3) Not all factors are identical. - alternative gene forms are called alleles
- (4) Alleles do not influence each other as alleles separate independently into gametes.
- (5) The presence of an ~~non~~ allele does not insure that the trait will be expressed.

Terminology:

Monohybrid: 1 character was carried along.

Dihybrid: 2 characters.

Genotype: Gene form (Dominant or recessive)

Phenotype: Physical appearance.

Alleles: Individual factors responsible for character

Dominant: which gets readily expressed in the new generation

Recessive: won't get really expressed, requires one more same type of allele

Homozygous: Both alleles are same.

Heterozygous: different type of alleles.

Haploid: 1 factor is given during gamete formation
(set)

Diploid: 2n → during gamete formation.

Genotype: total set of alleles of an individual.

PP = homozygous dominant

Pp = heterozygous \leftrightarrow

pp = homozygous recessive

Phenotype: outward appearance of an individual

In a homozygote (SS), the probability of producing a S gamete is 1
In a heterozygote (Ss); the probability of producing a S gamete is $\frac{1}{2}$ and s gamete is also $\frac{1}{2}$

Now consider the F₂ generation. The probable gametes here are S and s

Hence the probability of getting SS is $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4} = 25\%$ are homozygous dominant.

The probability of getting ss is $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$ i.e 25% are homozygous recessive.

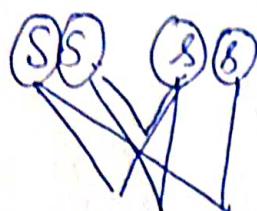
Adding probabilities: what is the probability of getting Ss and sS?

Probability of Ss (S from sperm and s from egg) = $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$

Probability of ss (s from sperm and S from egg) = $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$

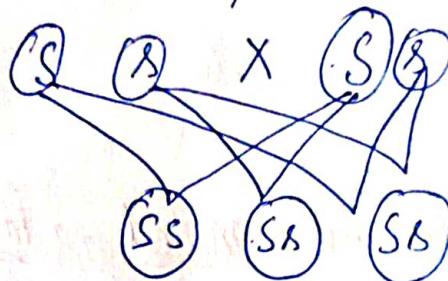
Both Ss and ss are heterozygotes and will have the same phenotype. Hence added probability is $\frac{1}{4} + \frac{1}{4} = \frac{1}{2}$ i.e 50% will be heterozygotes.

$$SS \times gg$$



$$Ss \quad Sg \quad Sg \quad Sg = F_1$$

$$Ss \times Ss$$



$$\frac{1}{2} \times \frac{1}{2} \quad \frac{1}{2} \times \frac{1}{2} \quad \frac{1}{2} \times \frac{1}{2} \quad \frac{1}{2} \times \frac{1}{2}$$

$$= \frac{1}{4} \quad \frac{1}{4} \quad \underbrace{\frac{1}{4}}_{\text{as same}} \quad \frac{1}{4}$$

$$\Rightarrow \frac{1}{4} \quad \frac{1}{2} \quad \downarrow \quad 25\% \rightarrow \text{Hetero}$$

Homo = 25% Hetero 50%

$$1 : 2 : 1$$

Dihybrid Cross

- mendel crossed a pea plant producing round yellow seeds with one producing green and wrinkled seeds of pure breed variety.

- In F₁ generation plant obtained producing only round yellow seeds

- If were allowed for self pollination to get F₂ generation

- In F₂ generation, 4 diff types of plants were produced that is

- Round yellow

- Round green

- Wrinkled yellow

- Wrinkled green.

- Phenotype ratio of 4 types of plants were 9:3:3:1

Dihybrid Cross: Examination of 2 separate traits in a single cross.

- F₀ gen - RRYY x rryy

The F₁ gen of a dihybrid cross (RrYy) shows only the dominant phenotypes for each trait

Round & Yellow x Green and Wrinkled → Parental
Dominant parent

F₁ → Round and Yellow



(Parental Generation)

RRYY x rryy
(RY) (RY) (ry) (ry)

F ₁	RY	RY
	RY	RY

F₁ × F₁ → RRYY x RRYY
homo. hetero.

[shape & colour]
both factors

⇒ (RY) (RY) (RY) (RY) x (RY) (RY) (RY) (RY)

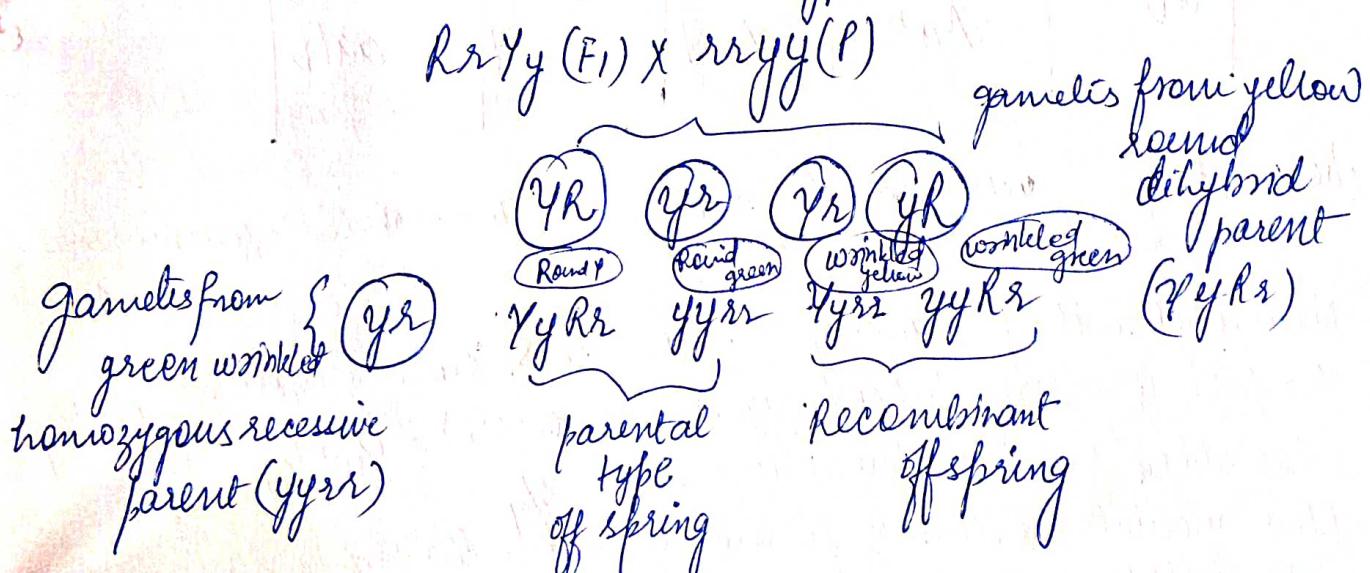
Principle of Independent Assortment (2^{nd} Law)

The factors for two or more pairs of contrasting characters are distributed independently of one another at the time of gamete formation.

In a dihybrid cross, the alleles of each gene assort independently.

Dihybrid Test Cross

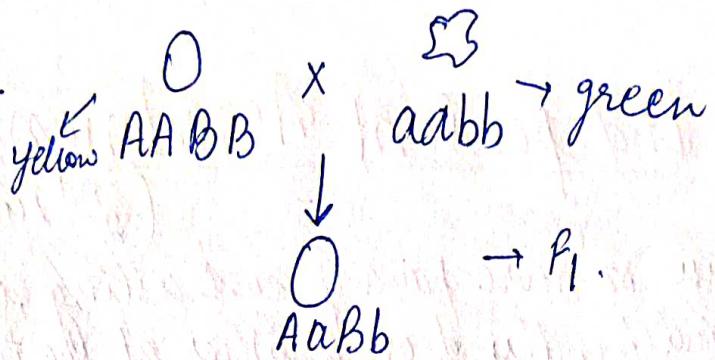
A dihybrid test cross involves crossing of the F₁ dihybrid with a double recessive parental type.



$$F_1 \rightarrow RrYy \times rryy$$



Bunnet Square



	AB	Ab	aB	ab	
AB	$AABB$	$AABb$	$AaBB$	$AaBb$	
Ab	$AA Bb$	\boxed{AAbb}	$AaBb$	\boxed{Aabb}	$\rightarrow P_2$
aB	$AaBB$	$AaBb$	\boxed{aaBB} green	\boxed{aaBb} green	
ab	$AaBb$	$Aabb$ \curvearrowleft	$aaBb$ green	$aabb$ \curvearrowleft green	

Phenotypic - yellow round green yellow wrinkled green wrinkled
 9 3 3 1

Now what is the probability of getting an ss monozygote? The prob of getting heterozygote (ie ss or ss) = $\frac{1}{4} + \frac{1}{4} = \frac{1}{2}$.
 The added prob ie (spherical seed) = $\frac{3}{4}$.
 Now calculate the prob of yellow seed using the above reasoning?
 It will be $\frac{3}{4}$.

Hence what is the added prob of getting a spherical seed and yellow seed = $\frac{3}{4} \times \frac{3}{4} = \frac{9}{16}$.

Since both events are independent i.e. independent assortment
 Probability of yellow seed = $\frac{3}{4}$

Probability of wrinkled seed = $\frac{1}{4}$

Hence the added probability = $\frac{3}{4} \times \frac{1}{4} = \frac{3}{16}$

Using same logic it is easy to calculate the prob of wrinkled yellow seed is $\frac{3}{16}$ and wrinkled green seed is $\frac{1}{16}$.

$RRYy \times rrYY$

Round is pure
double dominant

F_1 $\textcircled{R}Y\textcircled{hy}$ \textcircled{RY} \textcircled{hy} $\textcircled{hy}\textcircled{ry}$.

	RY	hy	\textcircled{RY}
ry	$RRyy$	$rrYY$	

RY hy
round yellow round green

- The chromosome theory of inheritance allows us to see the relationship between Mendel's law and Chromosome transmission.
- Mendel's law of segregation can be explained by the homologous pairing and segregation of chromosomes during meiosis.

Q Pure strain of mice. Brown colour fur \times grey colour fur

F_1 = Brown colour.

$F_1 \times F_1$ =

Dominant = ? (Brown)

Phenotypic ratio = ? 3:1

Genotypic ratio = ? 1:1

Same as monohybrid

Ans

Q mice having long hair with black \times white short hair

F_1 = Black short

F_2 = 9:3:3:1

↓ ↓ ↓ ↓
black short black long white short white long

black short dominant

Morgan's Experiment

In 1910 the American Geneticist Thomas Hunt Morgan, studying the fly Drosophila Melanogaster

Morgan selected a species of fruit fly Drosophila Melanogaster.
Fruit flies are prolific breeders.

Fruit flies ~~are~~ is having 4 pairs of chromosome

3 pairs are autosomes and 1 pair is sex chromosome

To get different varieties he carried out many breeding experiments

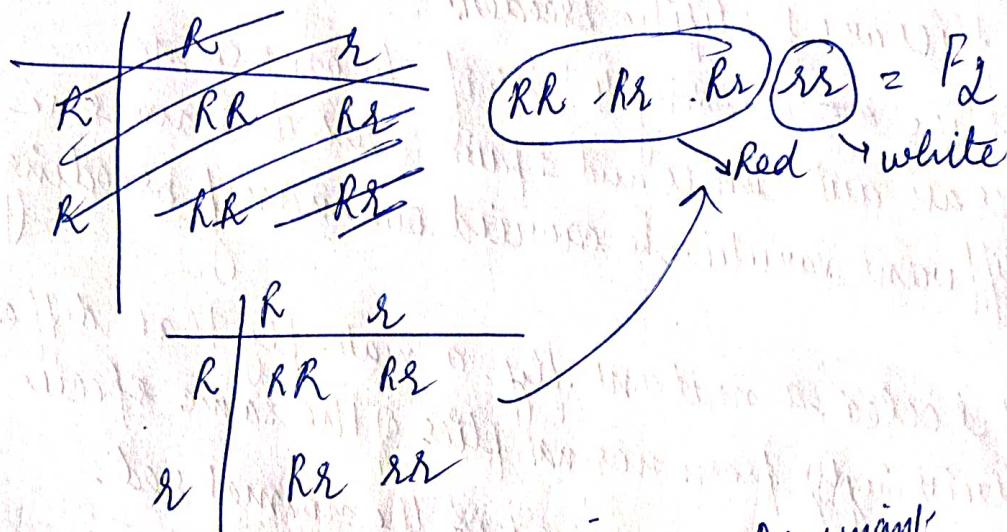
- He detected a mutant fly, a male fly that differed strikingly from normal flies of the same species.
- The eyes were white instead of the normal red.
- Morgan's discovery of a white eyed trait that correlated with the sex of flies was a key episode in the development of the chromosome theory of inheritance.
- He first crossed the mutant male to a normal female to see if either red or white eyes were dominant.
- All F_1 progeny had red eyes and Morgan \therefore concluded that red eye colour was dominant over white.
- Then he crossed flies from F_1 generation with each other.
- Eye color did indeed segregate among the F_2 progeny as predicted by Mendel's theory with an imperfect 3:1 ratio.
- Something was strange about Morgan's result, that was totally unpredicted by Mendel's experiments is all the white eyed F_2 flies were males.

Morgan's experimental evidence

red male white female ~~male~~ ♀

RR X rr

$F_1 = Rr Rr Rr Rr$

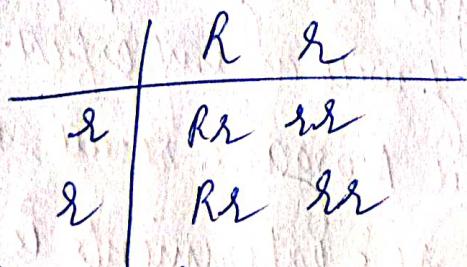


white male \times red female
↓
red male red female

↓ ↓
Red white Red Red
male male Female Female

F_1 with recessive parent \rightarrow Test Cross

Rr X rr



1:1 ratio

2 red and 2 white

But he observed \rightarrow Female white eye Drosophila

~~♂~~ XY XX → Homozygous
Female female respect to character

pair of alternative alleles, Homologous chromosome

$X^R Y$ $X^R X^R \rightarrow$ homozygous.

no alternative allele

Furner square

	X^R	Y
X^R	$X^R X^R$	$X^R Y$
X^R	$X^R X^R$	$X^R Y$

$\downarrow F_1$

$F_2 \Rightarrow X^R Y - X^R X^R$

	X^R	X^R
X^R	$X^R X^R$	$X^R X^R$
Y	$X^R Y$	$X^R Y$

Test cross

	$X^R Y$	$X^R X^R$
X^R	X^R	X^R
Y	$X^R Y$	$X^R Y$

Perhaps it was not possible to be a white eyed female fly? $\square \square \square$
Morgan test crossed one of his red eyed F_1 female progeny back to
the original white eyed male;

He obtained white eyed and red eyed males and females
So a female could have white eyes.

Why then were there no white eyed females among the progeny
of the original cross?

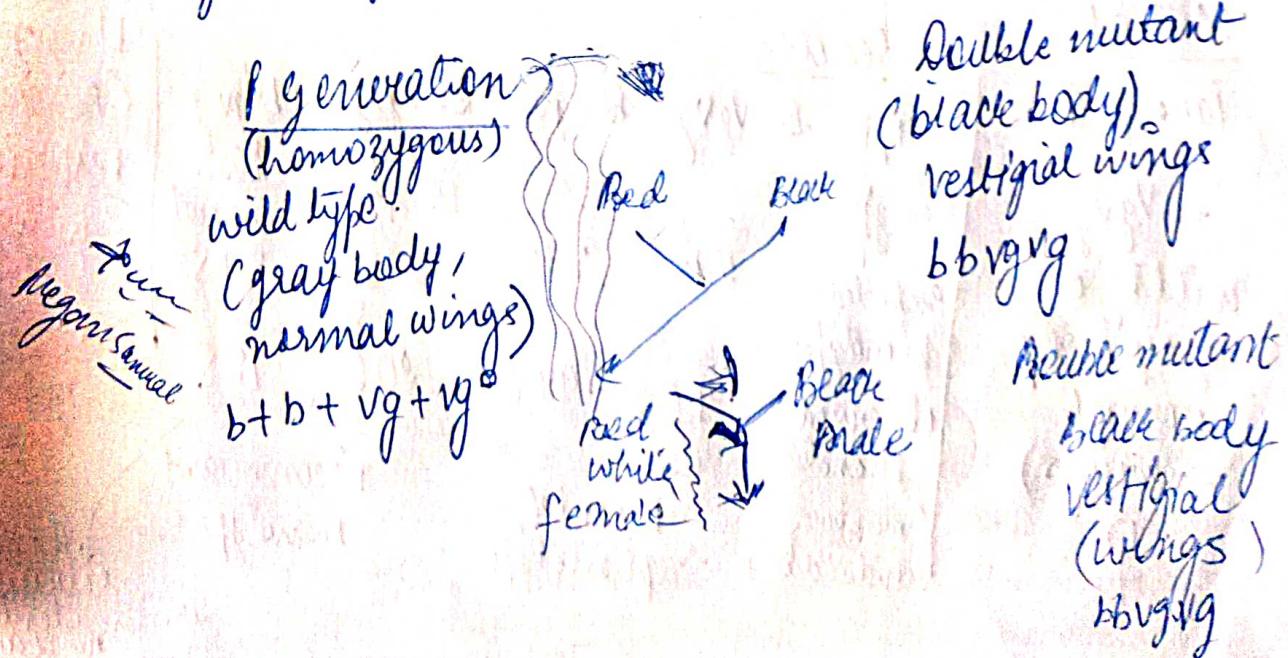
- The solution to Morgan's puzzle lies in the fact that in *Drosophila* white eye trait resides on the X chromosome and it is absent from the Y chromosome.
- Now we know that the Y chromosome carries almost very less functional genes. Y linked gene, there are very few Y linked genes. whereas X chromosome contain approximately > 1000 genes which are called X linked genes knowing that white-eye trait is recessive to the red eye trait, we can now see that Morgan's result was a natural consequence of the Mendelian Assortment of chromosomes.
- The trait that is determined by a factor on the X chromosome is said to be X linked.

X-linked genes in humans follow the same pattern of inheritance that fathers pass X linked alleles to all of their daughters but to none of their sons. In contrast mothers can pass X linked alleles to both sons and daughters.

If an X linked trait due to a recessive allele, a female will express the phenotype only if she is homozygous for that allele. Any male receiving the recessive allele from his mother will express the trait, for this reason more males than females have X linked recessive disorders.

- Morgan's experiment is one of the most important in the history of genetics.
 - The segregation of the white eye trait, evident in the eye color of the flies, evident with the segregation of the X chromosome
 - The gene that specifies eye color in *Drosophila* is carried through meiosis as part of an X chromosome.

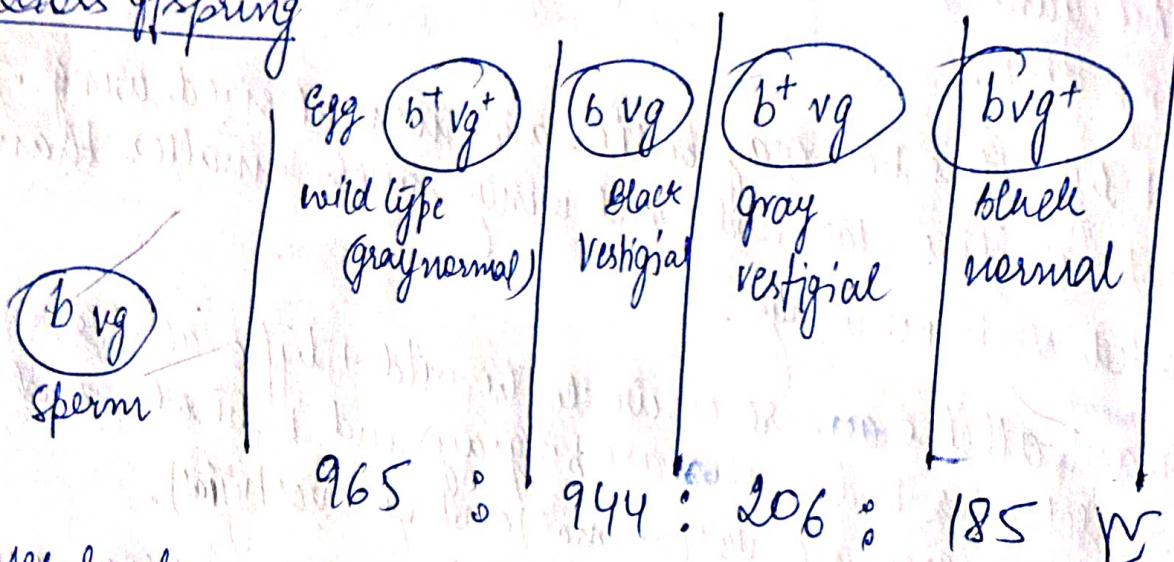
- In other words, Mendelian traits such as eye colour in *Drosophila* assort independently because chromosomes do
- Thus Morgan's results led to the general acceptance of Sutton's chromosomal theory of inheritance.
- The Morgan's *Drosophila* experiments for the body color and wing size.
- Wild type flies have gray bodies and normal sized wings. Double mutant flies black body and wings much smaller than normal called vestigial wings.
- mutant alleles are recessive to the wild type alleles.
- The alleles for body color are b^+ (gray) and b (black), and those for wing size are vg^+ (normal) and vg (vestigial).
- Morgan true breeding P (parental) generation, Flies wild type flies with black, vestigial winged flies - to produce heterozygous
- F₁ dihybrids (b^+b vg^+vg), all of which are wild type ~~fl~~
- in appearance.
- He then mated type-wild. F₁ dihybrid females with black, vestigial winged males. (test cross).



If genes are located on different chromosomes $1:1:1:1$

If genes are located on the same chromosome $\rightarrow 1:1:0:0$
and parental alleles are always inherited together

Testcross offspring



Some alleles do not assort independently.

Morgan's studies showed that the genes for body color and wing size in Drosophila are linked, so that their alleles do not assort independently.

Hypothesis: Alleles for diff characteristics always assort independently.

Method

Parent (P)
 $BbVvgv$
Wild Type -
gray body
normal
wings)

Results
 P_1
genotype
Expected phenotypes
Observed phenotype
(Number of individual)

	$BbVvgv$	$bbVvgv$	$Bbvgvg$	$bbVgvg$	$bbvgvg$	
	575	575	575	575	575	b^+V^+ (Black body, normal wings)
	965	944	206	185		♂ expected from Mendel's second law
						the actual results were inconsistent with the law.
						Recombinant phenotype

Conclusion

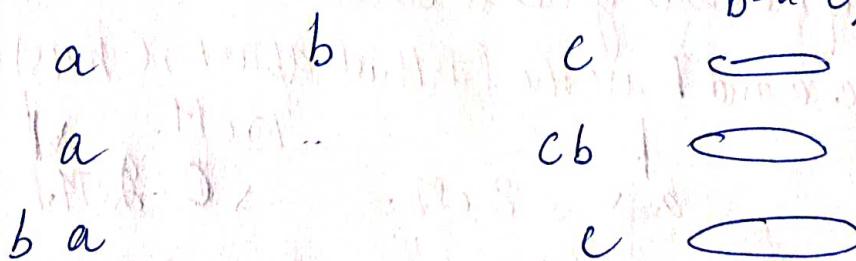
The hypothesis is rejected. These two genes do not assort independently but are linked (on the same chromosome)

Test cases offspring

965	944	206	185
wild type (gray-normal)	Black vestigial	gray Vestigial	Black normal
$b^+ vg^+$	$b vg$	$b^+ vg$	$b vg^+$
$b vg$	$b^+ vg$	$b vg$	$b^+ vg$
parental type offspring		Recombinant offspring	

$$\text{Recombination frequency} = \frac{391 \text{ recombinants}}{2300 \text{ total offspring}} \times 100 = 17\% \\ = 17 \text{ centiMorgan}$$

At the outset, we have no idea of the individual distances between the genes, and there are several possible sequences (a-b-c, a-c-b,



We make a cross $AAGB \times aabb$ and obtain an F_1 generation with a genotype $Aabb$. We test crosses these $AaBb$ individuals with $aabb$. Here are the genotypes of the first 1000 progeny:
 450 $AaBb$ 450 $aabb$ 50 $Aabb$ 50 $aaBb$
 (parental type) (Recombinant type)

Conclusion

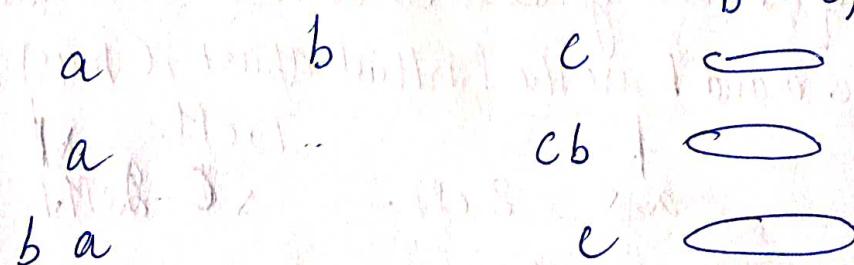
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$b vg$	$b vg$	$b vg$	$b vg$
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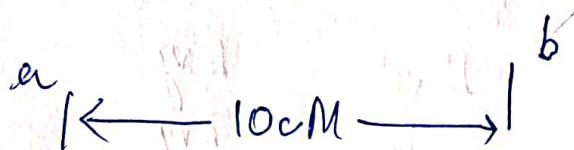
$AaBb$ (parental type)	$aabb$	$Aabb$	$aABb$ (recombinant type)
450	450	50	50

How far apart are the a and b genes?

What is the recombinant frequency? which are the recombinant types, and which are the parental types?

Recombinant frequency (a to b) = $(50+50)/1000 = 0.1$, so the map distance is

$$\text{Map distance} = 100 \times \text{recombinant frequency} = \\ 100 \times 0.1 = 10 \text{ cM.}$$



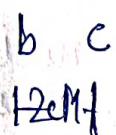
How far apart are the b and c genes?

We make a cross $BbCC \times bbcc$, obtain an F_1 generation, and test cross it, obtaining

490 $BbCc$, 490 $bbCc$, 10 $Bbcc$ and 10 $bbCc$.

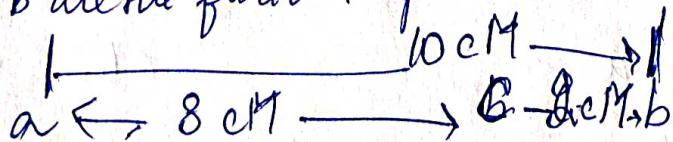
$$\text{Recombinant frequency (b to c)} = \frac{10+10}{1000} = 0.02$$

$$\text{Map distance} = 100 \times \text{recombinant frequency} = 100 \times 0.02 \\ = 2 \text{ cM.}$$



Which of the three genes is between the other two?

Because a and b are the furthest apart, C must be in between them.



These numbers add up perfectly, in most real cases, they will not add up perfectly because of multiple crossovers.

Genetic Disorder

- Physical and chemical disturbances, as well as errors during meiosis, can damage chromosomes in major ways or alter their number in a cell.
- The phenotype of an organism can also be affected by small scale changes involving individual genes.
Random mutations are the sources of all new alleles, which can be lead to new phenotypic trait.
- Alterations in chromosomal number
- Alterations in chromosomal structure

ALTERATION IN CHROMOSOMAL NUMBER

- members of a pair of homologous chromosome do not move apart properly during Meiosis I or sister chromatids fail to separate during Meiosis II
- If either of the aberrant gamete unites with a normal one at fertilization, the zygote will also have an abnormal number of a particular chromosome known as Aneuploidy.
- Fertilization involving a gamete that has no copy of a particular chromosome will lead to a missing chromosome in the zygote
 $(2n-1)$ is said to be monosomic ($2n-1$), trisomic ($2n+1$), polybolidy ($3n, 4n$).

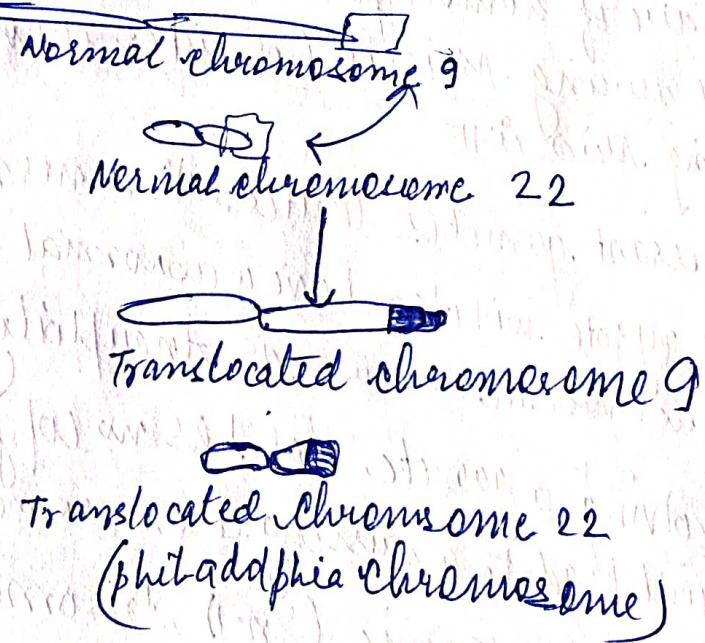
ALTERATIONS IN CHROMOSOMAL NUMBER

- Down Syndrome is often called Trisomy 21 → 3 chromosomes are present at 21st cell
- Symptoms → short stature, heart defects.
- Increased chance of developing leukemia and Alzheimer's disease
- Average life span shorter than normal and sexually sterile

Aneuploidy of sex chromosome

<u>Syndrome</u>	<u>Genotype</u>	<u>Frequency</u>
Klinefelter syndrome	XXY	1/500
Turner's syndrome	XO	1/2500
	XYY	1/1000
	XXX	1/1000

Chromosomal translocations



Autosomal Recessive inheritance

Autosomal Dominant inheritance

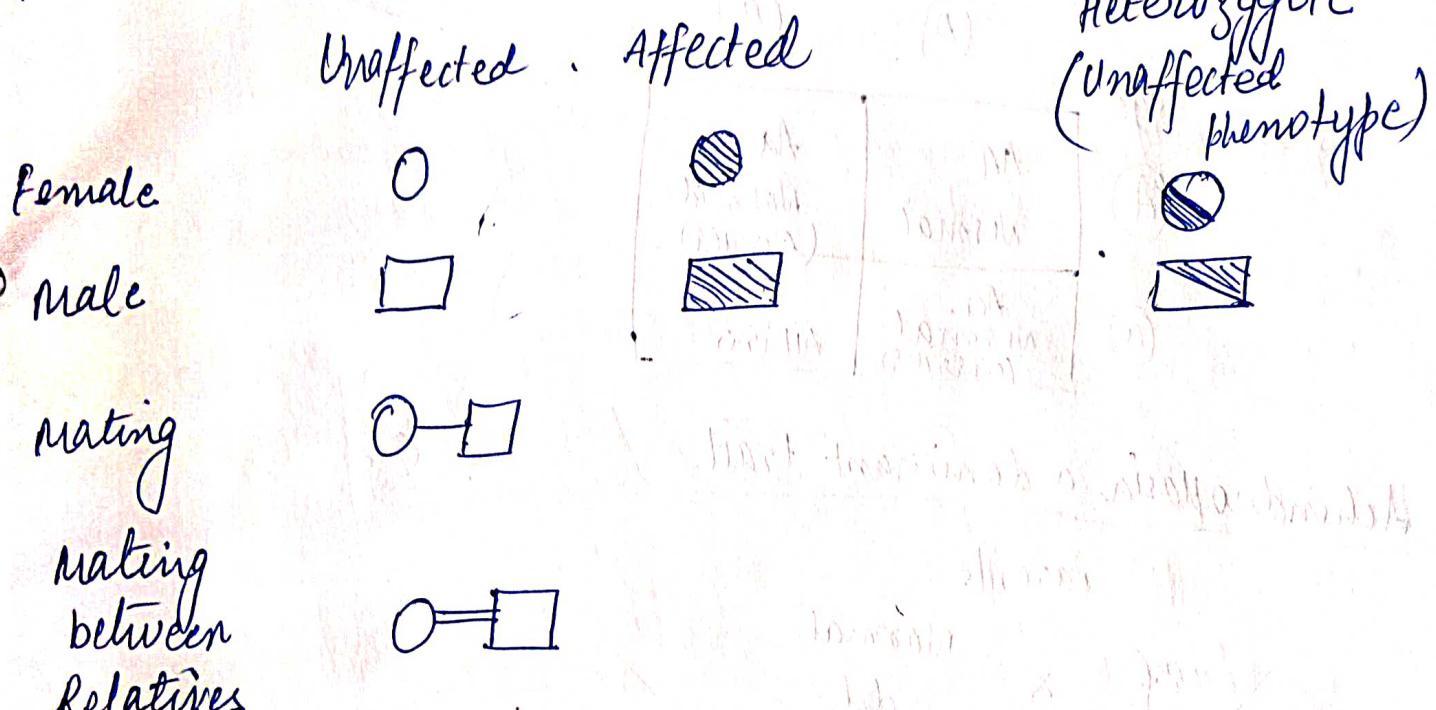
X-linked inheritance (dominant and recessive)

Y-linked inheritance

Pedigree Analysis

Collecting the information about a family's history for a particular trait and assembling this information into a family tree describing the traits of parents and children across the generations is the family pedigree.

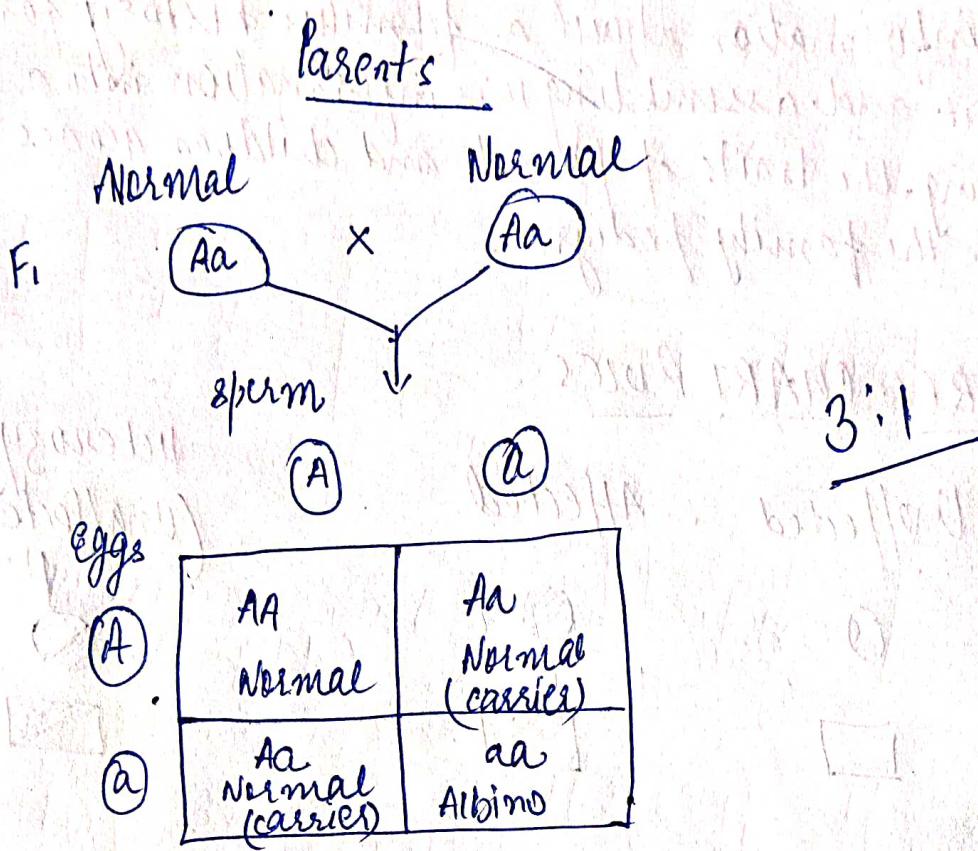
BASIC PEDIGREE CHART RULES



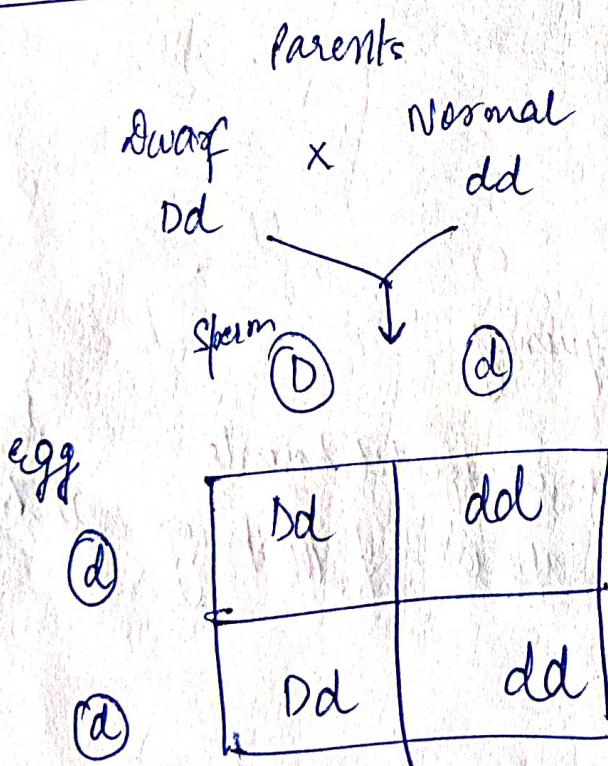
Autosomal recessive traits

- (1) Appears in both sexes with equal frequency.
- (2) Trait tends to skip generation.
- (3) Affected offsprings are usually born to unaffected parents.
- (4) When both parents are heterozygous, approx $\frac{1}{4}$ of offsprings will be affected.

Albinism a recessive trait



Achondroplasia a dominant trait



Analysis of Sex-linked traits in Humans.

- ① X-linked traits, like autosomal ones, can be analysed using pedigree.
- ② Human pedigree analysis, however is complicated by several factors.
 - (a) Data collection often relies on family recollections.
 - (b) If the trait is rare, and the family small, there may not be enough affected individuals, being classified as normal, to establish a mechanism of inheritance.
 - (c) Expression of the trait may vary, resulting in affected individuals being classified as normal.
 - (d) More than one mutation may result in the same phenotype and comparison of different pedigrees may show different inheritance for the 'same' trait.

X-linked Recessive Inheritance

- ① Human traits involving recessive alleles on the X chromosomes are X-linked recessive traits. A famous example is hemophilia among Queen Victoria's descendants.
- ② X-linked recessive traits occur much frequently among males who are hemizygous. A female would express a recessive X-linked trait only if she were homozygous recessive at that locus.
- ③ Some characteristic of X-linked recessive inheritance.
 - (a) Affected fathers transmit all the recessive allele to all daughters and to none of their sons.
 - (b) Father-to-son transmission of X-linked alleles generally does not occur.

- Other X-linked recessive traits are Duchenne muscular dystrophy and two forms of color blindness

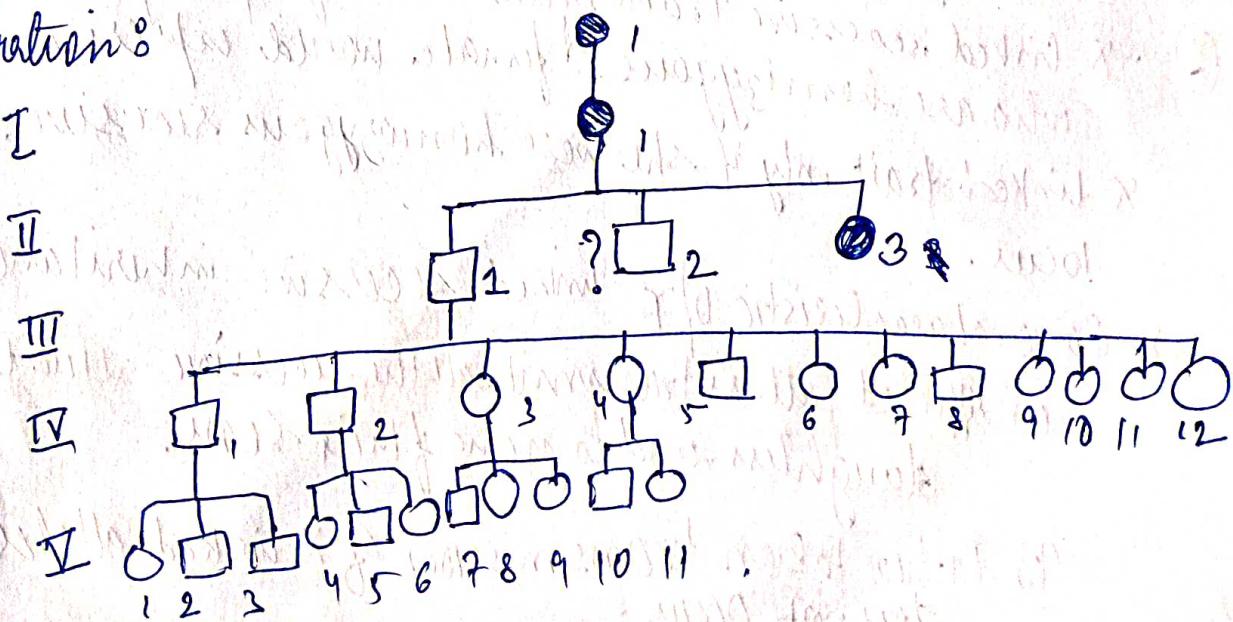
X-linked Dominant Inheritance

- ① Only a few X-linked dominant are known.
- ② Examples include:
 - (a) Heredity ~~intide~~: enamel hypoplasia (faulty and discolored tooth enamel)
 - (b) Webbing to the tips of toes
 - (c) Constitutional thrombopathy (severe bleeding due to lack of blood platelets)
- ③ Pattern of inheritance are the same as X-linked recessives, except that heterozygous females show the trait.
(although often in a milder form)

PEDIGREE SHOWING THE TRANSMISSION OF THE X-LINKED DOMINANT TRAIT OF FAULTY TOOTH ENAMEL

(b) Pedigree

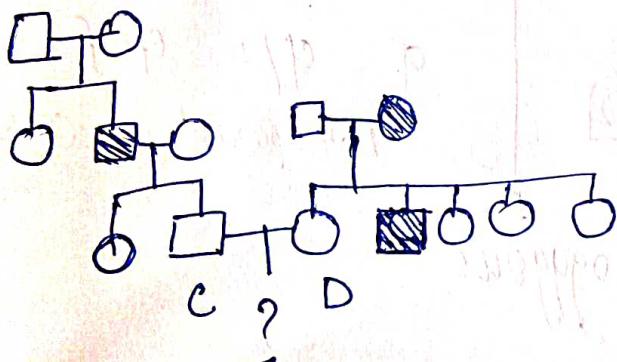
Generation:



Y linked Inheritance (Hollardie traits)

- there are fewer Y linked than X linked genetic disorder
- This is not surprising given that the Y chromosome is smaller and has many less genes than the X chromosome
- Y linked inheritance shows a pattern of transmission of the mutant phenotype from father to son and it is never observed in females.
- An example of a Y linked phenotypic trait is hairy ears.

Q2 Below is the pedigree for a family with a rare autosomal recessive disease



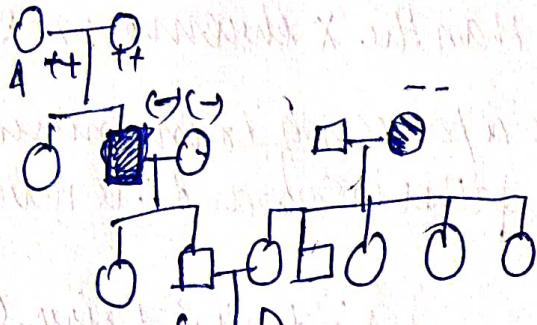
type of inheritance
Autosomal Recessive

[1, 1, 1]

- (i) what is the genotype of individual A ? Use "t" to indicate the wildtype allele and "—" to indicate the mutant allele (0.5 marks)
- (ii) what is the genotype of individual B and give the probability that she can be a carrier of the disease ? (1 mark)
- (iii) Individual C and D decide to have a child. what is the probability that the child will have disease show the cross (1 mark)
- (iv) what is the probability that the child of individual C and A will be a carrier of disease ? (0.5 mark)

Ans + means dominant

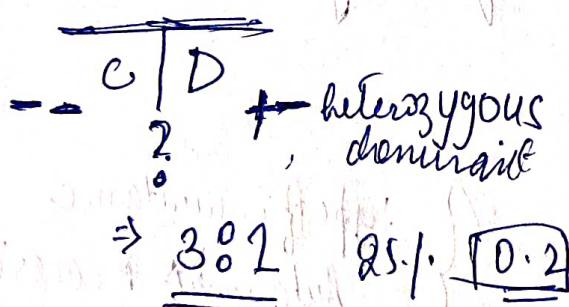
(i) - means recessive



(i) = + -

(ii) = maybe homo or heter dominant

(iii)



d/b

+ + cf
+ + + + +/cf

♀ ♀/+ cf/cf

Since both parents are carriers

(iv) 50% bz carrier means heterozygous

1:2:1

50%

Again, both parents are carriers, the probability of having a child who is a carrier is 1/2

UNIT - 3

①

~~Chromosomes~~
Lecture - 10 Bio.

- Archibald Garrod, an English physician in St. Bartholomew's Hospital in London observed rare disease 'Alkaptonuria' occurred more frequently among children of marriages between blood relatives
- He was able to explain the phenomenon in terms of Mendel's newly rediscovered laws
- Combining his biochemical and genetic analysis, Garrod concluded that Alkaptonuria is an 'inborn error in metabolism'.

1869, Friedrich Miescher, a Swiss biochemist working in Germany had isolated from pus soaked bandages supplied by a local hospital a substance he called nuclein.

Inheritance insures a continuity in from generation to generation - that lies even deeper than the chemical molecule. It lies in the structuring atomic groups.

Miescher then went on to study DNA from a Salmon Sperm.

Miescher initially believed that DNA is involved in the transmission of hereditary information. He soon rejected this idea, because his crude measuring techniques incorrectly suggested that egg cells contain much more DNA than sperm cells.

Edward Zacharias reported that extracting DNA from cells causes the staining of the chromosomes to disappear. Zacharias and others inferred that DNA is the genetic material.

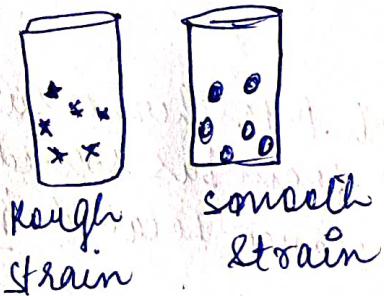
Incorrectly interpreted staining experiments led to the false conclusions that the amount of DNA changes dramatically within cells.

As a result from around 1910 to the 1940s most scientists believed that genes were made of protein rather than DNA

Griffith's Mouse Experiment

DNA as genetic material [Frederick Griffith]

Griffith was studying the pathogenicity (disease-causing capability) of his strains (Type II R and Type III S of *Pneumococcus* bacteria).



To begin, Griffith injected cultures of his rough strain into mice.

Rough strain

Two weeks after injection, Griffith found that the mice survived the introduction of the rough strain into their system.

Smooth strain

In the second experiment, Griffith wished to determine the pathogenicity (disease-causing capability) of his

smooth (type III) strain of *Pneumococcus* bacteria.

Two weeks after injection, Griffith found that the mice were killed as a result of the introduction of the smooth bacteria into their systems.

In his third experiment, Griffith determined whether the viability of the smooth strain was required for pathogenicity (disease causing capability). To do this he first needed to kill these bacteria by boiling them for a short period of time.

Now that the smooth bacteria were dead, Griffith could test whether or not they could cause disease in that state.

Two weeks after injection, Griffith found that the mice survived the introduction of the heat killed smooth strain into their systems.

Rough strain + Heat killed =
Smooth strain



The mixture was injected into mice, and the mice were incubated for two weeks.

After two weeks, Griffith found that the mice died.

That is correct! By heat killing the normally pathogenic smooth strain of bacteria, Griffith also ruptured these bacteria open, causing them to release components. One of these released components was then capable of transforming the normally non-pathogenic rough bacteria into a smooth form. ~~To view the end~~

The evidence for Griffith's hypothesis came from an investigation of the dead mice.

Living smooth bacteria recovered from the dead mouse.

When bacteria were recovered from the dead mice, Griffith cultured them and found living smooth bacteria. Griffith reasoned that the only way for this to have occurred was if living bacteria (rough, in this case) were instructed to become smooth bacteria. Griffith proposed the following explanation:

Griffith proposed that when the smooth bacterial culture was heat killed components present inside the smooth bacteria that caused the bacteria to be pathogenic might have been released into the media after death of the bacteria. Therefore when non-pathogenic, rough bacteria were introduced into the culture, once inside, the cellular components then transformed the living rough bacteria cells into living, smooth cells. Griffith therefore determined ~~the~~ cellular components transforming factors. At that time the exact molecule, that make up the transforming factor were not known.

Frederick Griffith's Transformation Experiment - 1928

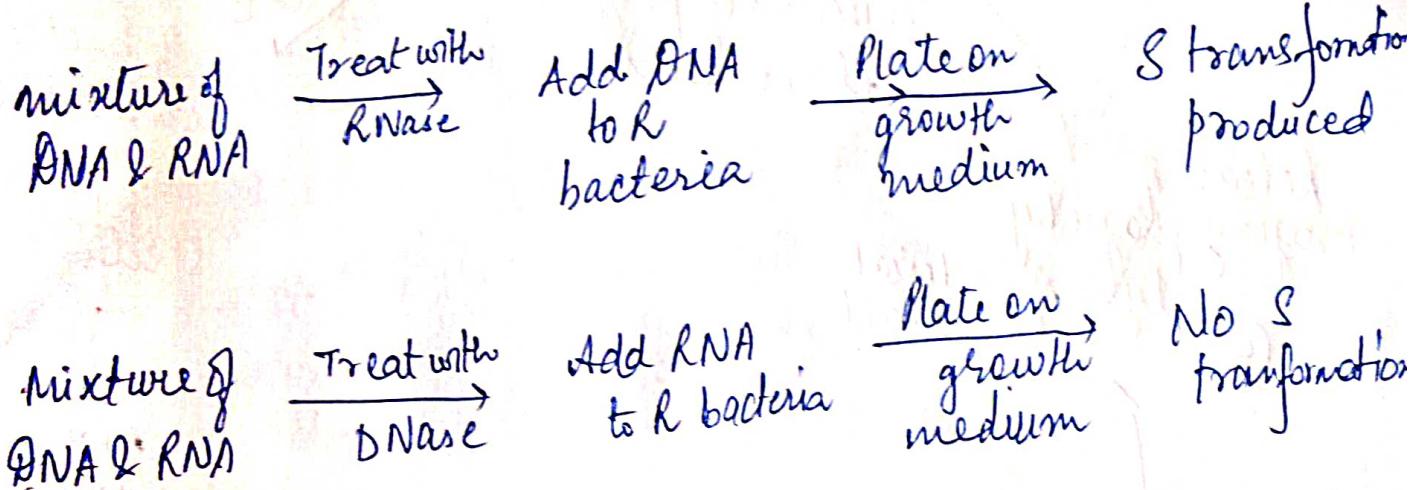
"Transforming principle" demonstrated with *streptococcus pneumoniae*.

Griffith hypothesized that the transforming agent was a "S" protein. But this way only a guess and Griffith turned out to be wrong.

(4)

Oswald T Avery's Transformation Experiment - 1944.

Determined that "S" DNA was the genetic material responsible for Griffith's results (not RNA)

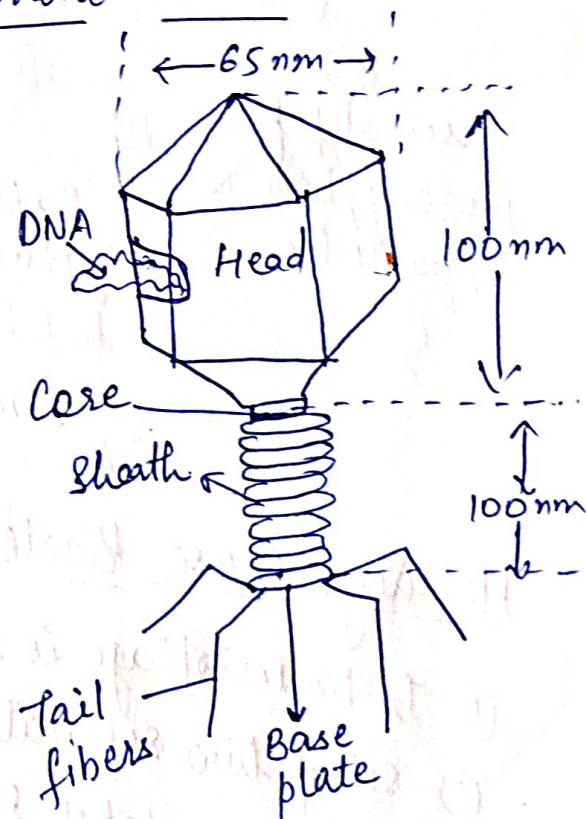


Hershey-Chase Bacteriophage Experiment - 1953

Bacteriophage = virus that attacks bacteria and replicates by invading a living cell and using the cell's molecular machinery

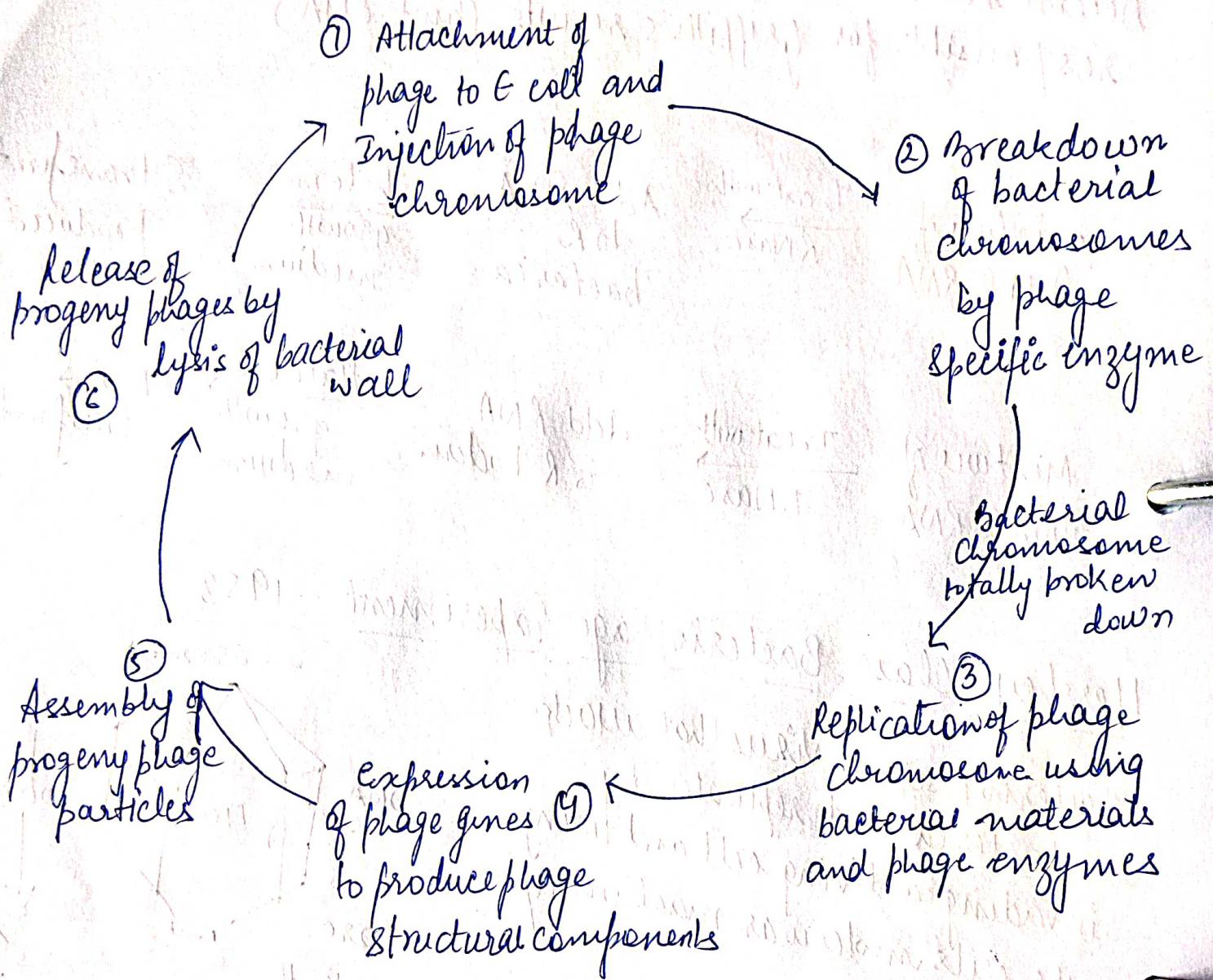
Structure of ϕ 2 phage

Bacteriophages are composed of DNA & protein



Life Cycle of virulent T₂ phage :

(6)



Hershey - Chase Bacteriophage Experiment - 1953

- ① T₂ bacteriophage is composed of DNA and proteins
- ② Set up two replicates:
 - Label DNA with ³²P
 - Label Protein with ³⁵S
- ③ Infected E. coli bacteria with two types of labeled T₂
- ④ ³²P is discovered within the bacteria and progeny phages whereas ³⁵S is not found within the bacteria but released with phage ghosts.

Conclusions about these early experiments.

Griffith 1928 & Avery 1944:

DNA (not RNA) is transforming agent

Hershey - Chase 1953

DNA (not protein) is the genetic material

Gierer & Schramm 1956 / Fraenkel-Cornat & Seiger 1957:
RNA (not protein) is genetic material of some viruses but no
known prokaryotes or eukaryotes use RNA as their genetic
material.

[Alfred Hershey won Nobel Prize in physiology or
Medicine 1969]

Nucleic Acid

James D Watson / Francis H. Crick 1953 proposed the Double Helix Model based on two sources of information.

① Base composition studies of Erwin Chargaff

- indicated double stranded DNA consists of ~ 50% purines (A, G) and ~ 50% pyrimidines (T, C)

amount of A = amount of T
" of G = " of C.

Erwin Chargaff, 1950 reported

- The base composition varies from species to another
- Within the species the number of A and T bases are equal and number of G and C bases are equal.

Peculiar regularity in the ratios of nucleotide bases

Adenine = Thymine

Guanine = Cytosine

C is 10% of A

Human A = 30.3%

T = 30.3%

G = 19.55%

C = 19.55%

Structure of DNA

James D Watson / Francis H. Crick in 1953 proposed the Double Helix Model based on two sources of information.

2) X-ray diffraction studies by Rosalind Franklin & Maurice Wilkins

(8)

Conclusion DNA is a helical structure with distinctive regularities, 0.34 nm & 3.4 nm.

- Linus Pauling at the California Institute of Technology
- Maurice Wilkins and Rosalind Franklin, King's College London

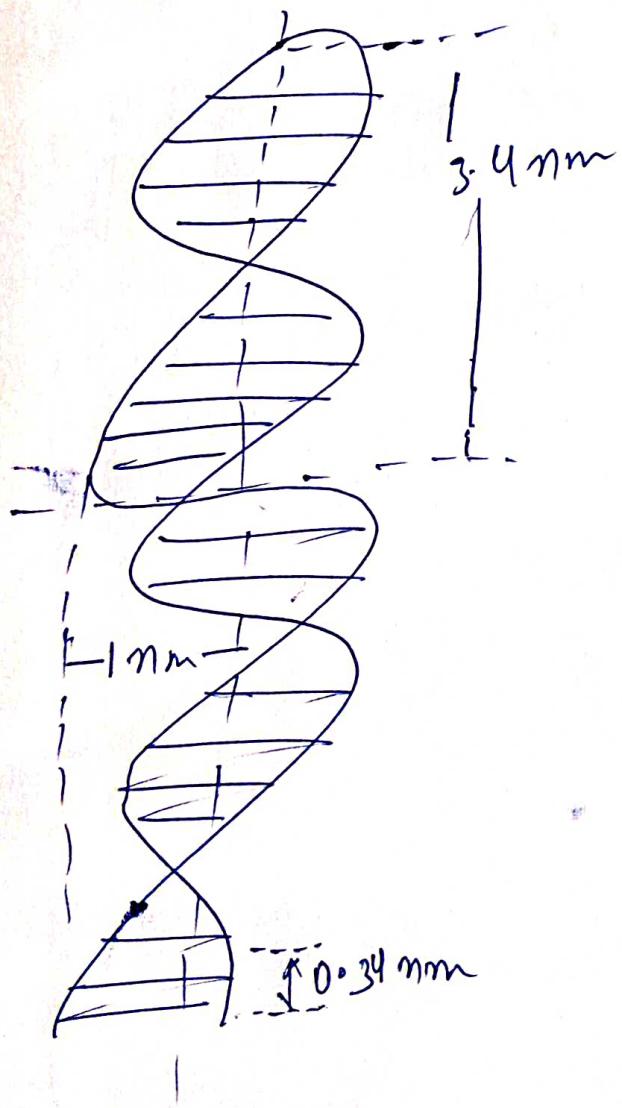
Rosalind Franklin proposed

- Hydrophobic nitrogenous bases in the molecule's interior
- Negatively charged phosphate group is wouldn't be forced to interior
- sugar phosphate backbones are anti parallel
- one full turn every 3.4 nm along its length with the bases stacked with .034 nm apart.
- Each full turn of the helix contains 10 base pairs.
- The nitrogenous bases of the double helix are paired in specific combination Adenine (A) with Thymine (T) and Guanine (G) with Cytosine (C)

G-C bond is stronger (3 hydrogen bonds)
A-T bond is weak (2 hydrogen bond)

In 1953 April James Watson and Francis Crick reported their molecular model for DNA: the double helix paper in the journal Nature. Watson and Crick along with Maurice Wilkins were awarded the Nobel prize in 1962.

(Sadly Rosalind Franklin died in 1958 at age of 38)



Nucleic Acids

- Nucleic acids are polymers of nucleotides that are 'storehouse of information' in a cell.
- Nucleic acids instructs the cell on;
 - how a cell should behave,
 - respond to the environment and
 - divide to make a new cell.
- Two main types;
 - DNA (deoxyribonucleic acid) &
 - RNA (ribonucleic acid)

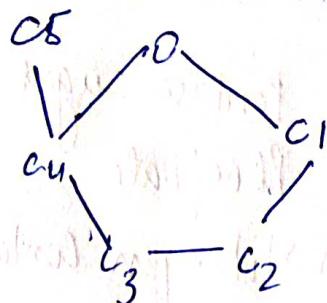
Nucleic Acids

①

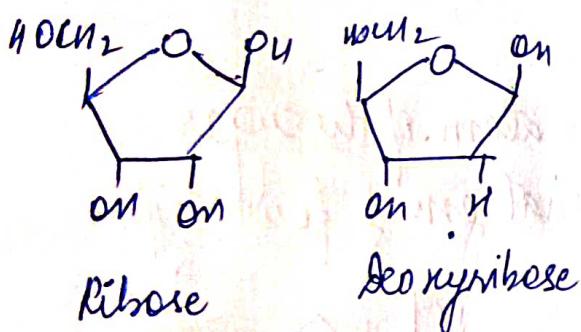
(1) Pentose Sugar

- In RNA, it is ribose, and
- In DNA, it is deoxyribose

(Deoxy → Minus oxygen)



Pentose Sugar



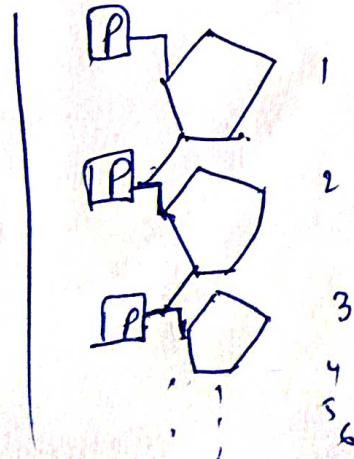
Structure of Nucleoside

(2) Phosphate

- The phosphate make the link that unite the sugar (called 'sugar phosphate backbone')
- Joins the 3rd carbon of one sugar to 5th carbon of the next one
- makes the pentose sugar to orient in the same direction

A, G → Purine (double ring structure)

U, T, C → Pyrimidine
(single ring structure)

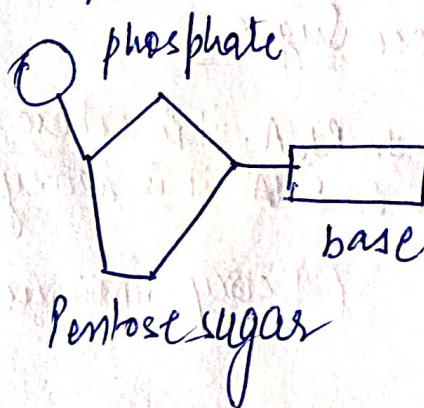


Structure of Nucleotide

②

- Nucleotides are basic units of Nucleic Acids.
- A nucleotide is composed of three types of molecules;

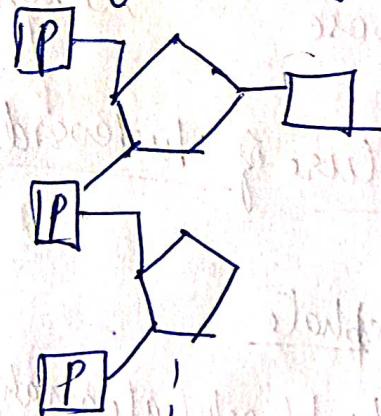
- (1) Pentose sugar
- (2) Phosphate
- (3) Nitrogen containing base



Structure of Nucleotide

(3) Nitrogen Containing base

- the bases are attached to the 1st carbon atom. of the sugar
- Both DNA and RNA contain combinations of four types of Nitrogen containing bases.



⑥

Structure of DNA

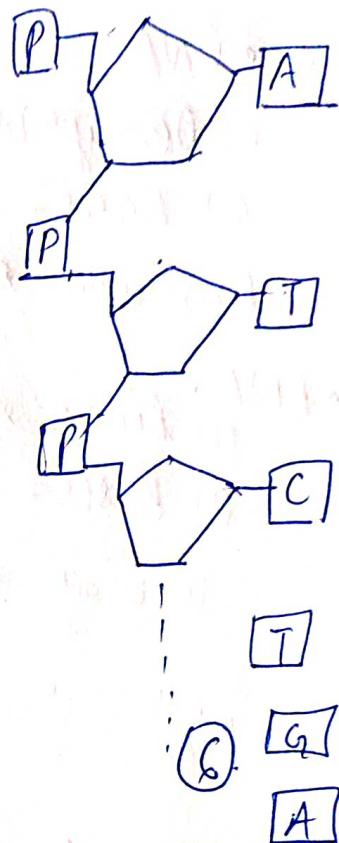
Composed of 3 parts

(1) Deoxyribose sugar (No 'O' in 2nd carbon)

(2) Phosphate group.

(3) One of 4 types of nitrogen bases:

- Adenine (A)
- Thymine (only in DNA) (T)
- Guanine (G)
- Cytosine (C)



Structure of RNA

RNA is single stranded molecule

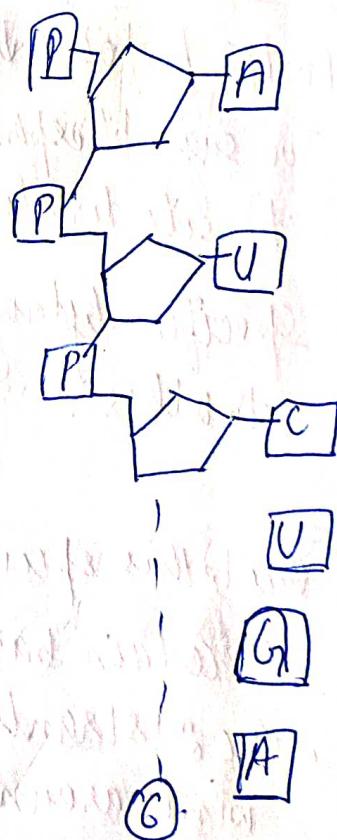
• Composed of 3 parts

(1) Ribose sugar (with O in 3rd carbon)

(2) Phosphate group

(3) One of 4 types of nitrogen bases:

- Adenine (A)
- Uracil (U) (only in RNA)
- Guanine
- Cytosine



DNA Vs RNA

- DNA

- (1) Deoxyribose sugar
- (2) Bases: Adenine, Thymine, Guanine, Cytosine
- (3) Double-stranded helix arrangement.

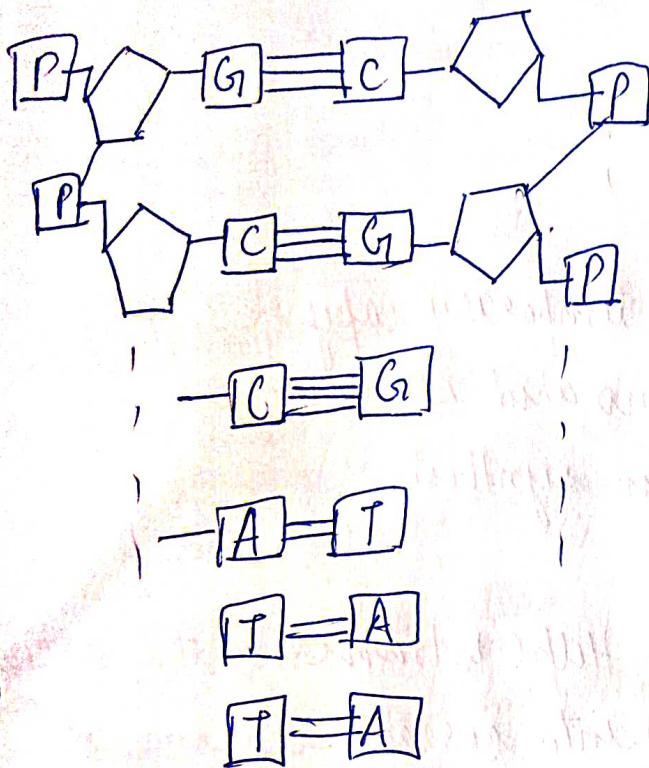
- RNA

- (1) Ribose sugar
- (2) Bases: Adenine, Uracil, Guanine, Cytosine
- (3) Single-stranded, no helix arrangement

DNA : The double helical structure

- Model proposed by Watson & Crick, 1953
- Two sugar phosphate strand next to each other, but running in opposite directions
- Specific Hydrogen bonds occur among bases from one chain to other.
 $A \equiv T$, $C \equiv G$
- Due to this specificity, a certain base on one strand indicates a certain base in the other.
- The strands intertwine, forming a double-helix that winds around a central axis.

(5)



- The sister strands of the DNA molecule run in opposite directions [antiparallel]

- Each base is paired with a specific partner:

A with T
G with C

- This the sister strands are complementary but not identical
- The bases are joined by hydrogen bonds.

- DNA stores information about:
 - how to copy, or replicate itself and cell.
 - codes for protein synthesis (specifies the order in which amino acids are to be joined to make a protein.)
 - Source of genetic information in a cell.
 - gives information to chromosome which is then passed from parent to offspring.

Functions of Nucleic Acids

- RNA has multiple functions ;
- Messenger RNA (mRNA) : temporary copy of a gene that specifies what the amino acid sequence will be during the process of protein synthesis.
- Transfer RNA (tRNA) : Help to translate the sequence of nucleic acids (codons) into correct sequence of amino acids during protein synthesis.
- Ribosomal RNA (rRNA) : Works as an enzyme to form the peptide bonds between amino acid in ribosome.

Experimental proof for DNA replication mechanism

- 3 possible models

(1) Semiconservative Replication
• Watson and Crick Model

(2) Conservative replication

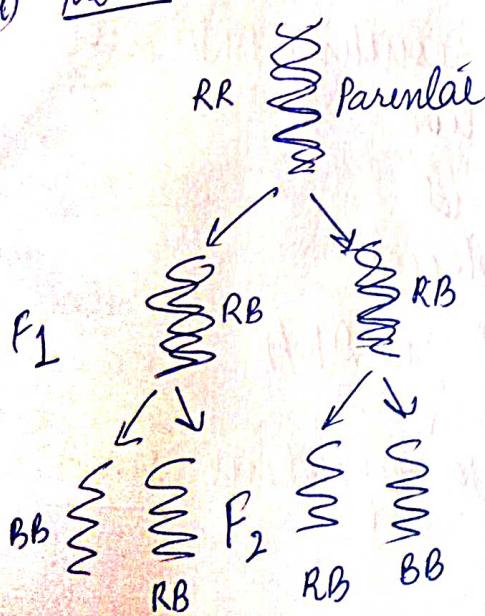
- The parental double helix remains intact
- Both strands of the daughter double helix are newly synthesized

(3) Dispersed replication

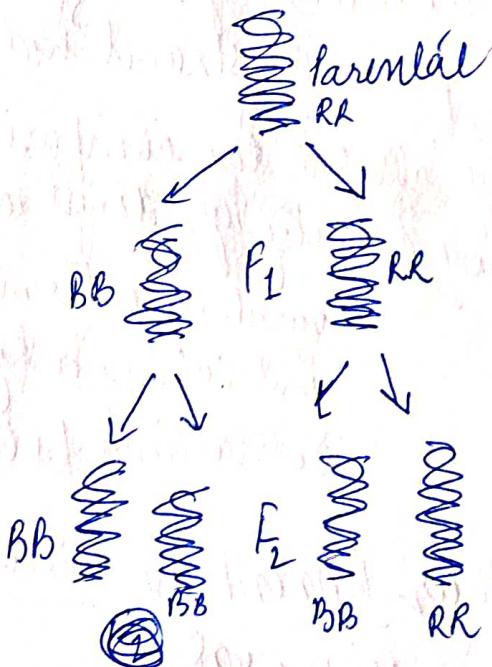
- At completion both strands of both double helices contain both original and newly synthesized material

Alternative model of DNA Replication

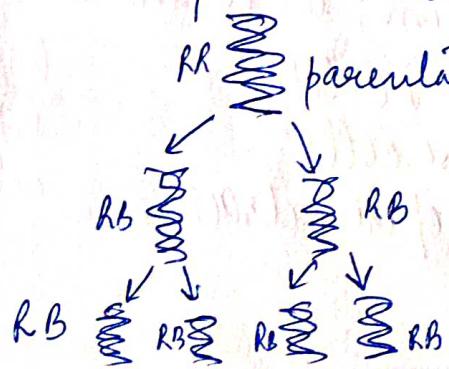
(a) The semiconservative model



(b) The conservative model



(c) The dispersive model



- (7)
- Matthew Meselson & Frank Stahl's Experiment 1958
- (Matthew)
- equilibrium density gradient centrifugation
- experiment allowed differentiation of parental and newly formed DNA.
 - Bacteria were grown in media containing either normal isotope of nitrogen (^{14}N) or the heavy isotope (^{15}N)
 - DNA banded after equilibrium density gradient centrifugation at a position which matched the density of the DNA.
 - heavy DNA was at a higher density than normal DNA
 - when bacteria grown in ^{15}N were transferred to Normal ^{14}N containing medium,
 - the newly synthesized DNA strand had the ^{14}N while the parental strand had ^{15}N .
 - They checked the composition of the resulting DNA molecules by density gradient centrifugation.
 - found an intermediate band
 - indicating a hybrid molecule
 - containing both ^{14}N and ^{15}N DNA

Arthur Kornberg discovered DNA dependent DNA polymerase

used 'in vitro' system; the classic biochemical approach.

- (1) Grow *E. coli*
- (2) Lysis cells
- (3) Prepare extract

- (4) Fractionate extract
- (5) Search for DNA polymerase activity using an ASSAY.

Requirements for DNA polymerase activity

- Template - (Basis of Heredity)
- dNTPs (not ATP, not NDPs, not NMPs) (building blocks)
- Primer - complementary bases at 3' end, removed
- Mg²⁺ - (Promotes reaction)
- By fractionation and added back) (DNA pol can't start)

DNA polymerase activities.

Primer has a free 3'-OH

incorporating dNTP has a 5' triphosphate

Pyrophosphate (PP) is lost when dNTP adds to the chain

Mechanism

Each dNTP provides the nucleophile (3'-OH) for the next round PP_i hydrolyzed to 2 PO₄²⁻

In Prokaryotes, ~~there~~ there are three main types of DNA polymerase.

Eukaryotic enzymes

Five common DNA polymerase from mammals:

- (1) Polymerase α (alpha): Nuclear, DNA replication, no proofreading.
- (2) Polymerase β (beta): Nuclear, DNA repair, no proofreading
- (3) Polymerase γ (gamma): mitochondria, DNA replication proofreading.
- (4) Polymerase δ (delta): Nuclear, DNA replication, proofreading.

(3)
(5) Polymerase E (epsilon) : nuclear, DNA repair (?)
proof reading.

- Different polymerases for the nucleus and mtDNA.
- Some polymerases proof read, others do not.
- Some polymerases used for replication; others for repair
- polymerases vary by species.

DNA Replication

- copying genetic information for transmission to the next generation.
- occurs in S phase of cell cycle
- process of DNA duplicating itself
- begins with the unwinding of double helix to expose the bases in each strand of DNA.
- each unpaired nucleotide will attract a complementary nucleotide from the medium
→ will form base pairing via hydrogen bonding
- enzymes link the aligned nucleotides by phosphodiester bonds to form a continuous strand.

Mechanism of Replication

- tightly controlled process
 - occurs at specific times during the cell cycle
- Requires - a set of proteins and enzymes.
→ requires energy in form of ATP.

- two basic steps :
 - initiation
 - elongation

Two basic components

- template
- primer

②

Three main functions of DNA synthesis reaction

- ① DNA polymerase I catalyzes formation of phosphodiester bond between 3'-OH of the deoxyribose (on the last nucleotide) and 5'-phosphate of the dNTP.
- ② Energy for this reaction is derived from the release of two of the three phosphates of the dNTP.
- ③ DNA polymerase 'finds' the correct complementary dNTP at each step in the lengthening process.
 - rate ≤ 800 dNPs/second
 - low error rate
- ④ Direction of synthesis is 5' to 3'

~~DNA polymerase~~
~~lives~~

DNA polymerase

- the enzyme that extends the primer;

Pel III -

- produces new strands of complementary DNA

Pel I - fill in gaps between newly synthesized Okazaki segments

- Additional enzymes / proteins

→ (1) DNA helicase -

unwinds double helix

(2) single stranded binding proteins -

• keep helix open

(3) Primase -

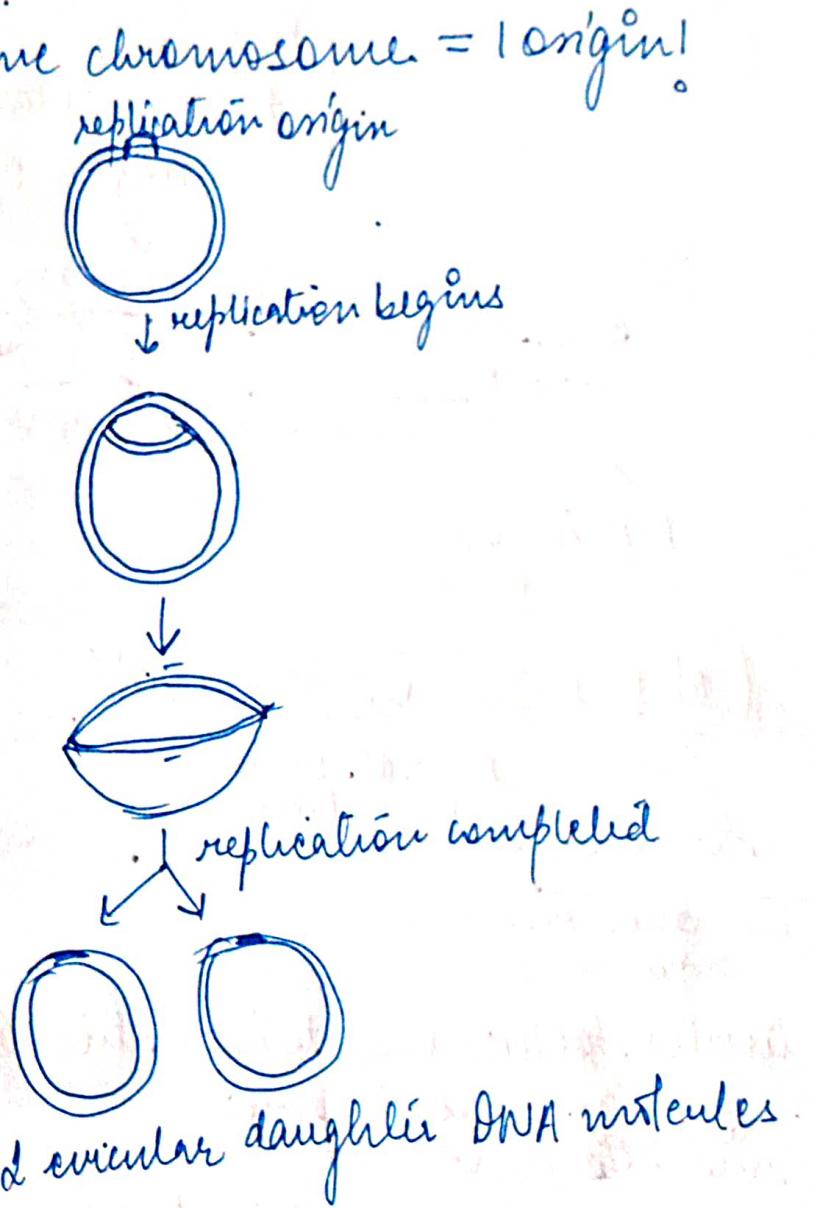
creates RNA primers to initiate synthesis

(4) Ligase - welds together Okazaki fragments

Prokaryotic origin of replication

(3)

- Bacteria have 1 origin of replication per one chromosome.
- They only have one chromosome = 1 origin!



Origin of replication

- ✓ Begins with double helix denaturing into single-strands thus exposing the bases.
- ✓ Exposes a replication bubble from which replication proceeds in both directions.
- ✓ DNA synthesis occurs from 5 prime to 3 prime

Replication proceeds in both directions (bidirectionally) from a single origin of replication on the prokaryotic circular chromosome ③

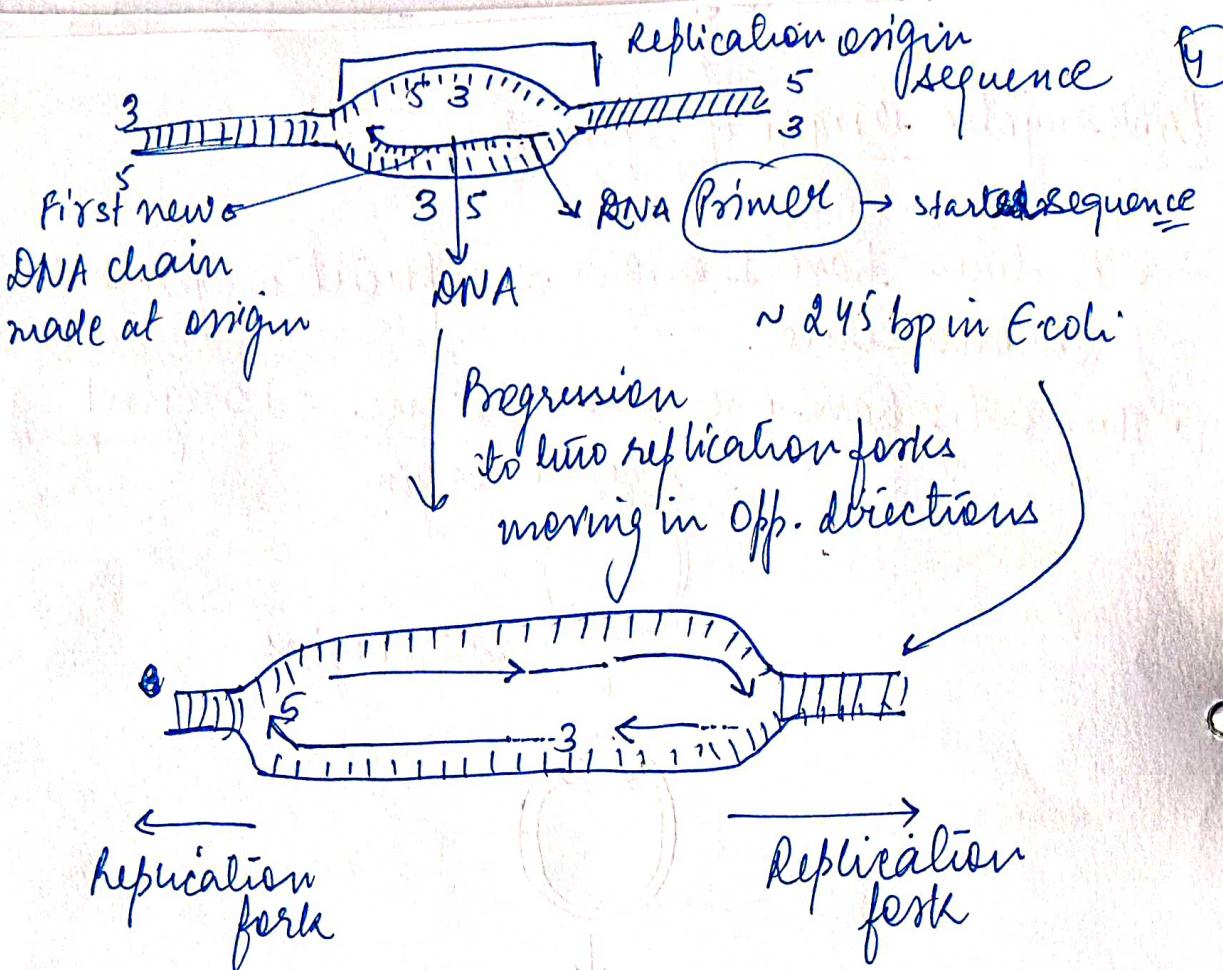
Replication proceeds in both directions (bidirectionally) from hundreds or thousands of origins of replication on each of the linear eukaryotic chromosomes.

Cont of model of replication in E. coli

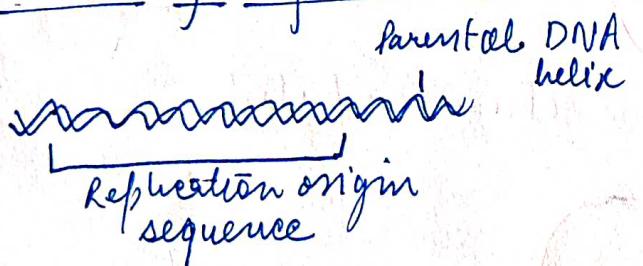
⑤ Primase synthesizes RNA primer, which is extended as DNA chain by DNA polymerase.

Initiation of replication, major elements:

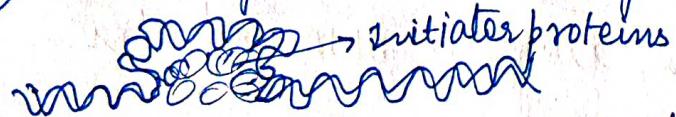
- ✓ segments of single stranded DNA are called template strands.
- ✓ Gymnase (a type of topoisomerase) relaxes the super coiled DNA.
- ✓ Initiator proteins and DNA helicase binds to the DNA at the replication fork and untwist and DNA using energy derived from ATP (Adenosine Triphosphate)
(Hydrolysis of ATP causes a shape change in DNA helicase)
- ✓ DNA primase next binds to helicase producing a complex called a primosome (primase is required for synthesis)
- ✓ Primase synthesizes a short RNA primer of 10-12 nucleotides, to which DNA polymerase III adds nucleotides.
- ✓ Polymerase III adds nucleotides 5' to 3' on both strands beginning at the RNA primer.



Model of Replication in E. coli



(1) Initiator proteins bind to replication origin



(2) DNA helicase binds to initiator proteins



Helicase loads onto DNA.



Helicase denatures helix and binds with DNA primase to form primosome.

(5)

Initiation of replication, mat

- RNA primer is removed and replaced with DNA by polymerase I, and the gap is sealed with DNA ligase
- single stranded DNA-binding (SSB) proteins (> 200) stabilize the single-stranded template DNA during the process.

DNA replication is continuous on the leading strand and semi-discontinuous on the lagging strand..

Unwinding of any single DNA replication fork proceeds in one direction

The two DNA strands are of opposite polarity, and DNA polymerase only synthesize DNA 5' to 3'

Solution: DNA is made in opposite direction on each template

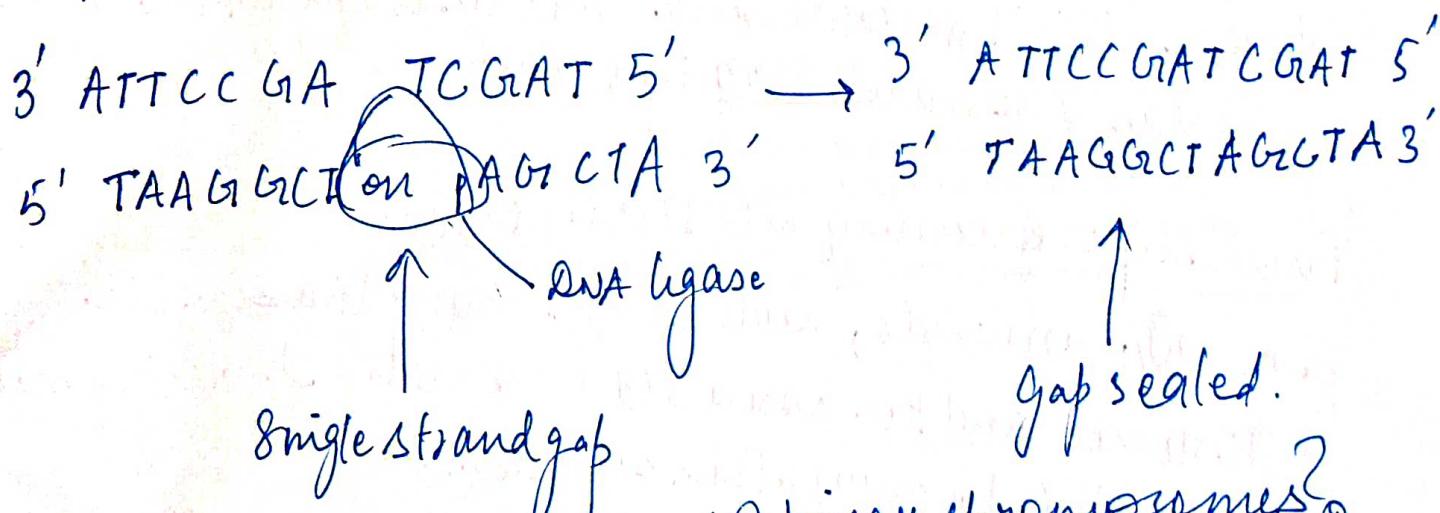
• leading strand: synthesized 5' to 3' in the direction of the replication fork movement.
continuous

requires a single RNA primer

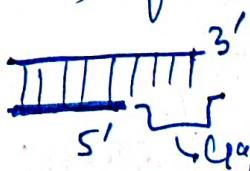
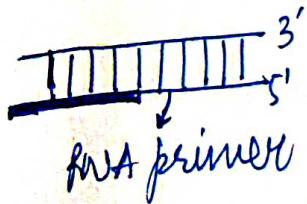
• lagging strand: synthesized 5' to 3' in the opposite direction
semi-discontinuous (i.e not continuous)

requires many RNA primers, DNA is synthesized in short fragments.

DNA ligase seals the gaps between Okazaki fragments with a phosphodiester bond.



What about the ends (or telomeres) of linear chromosomes?



DNA polymerase / ligase cannot fill gap at end of chromosome after RNA primer is removed. If this gap is not filled, chromosome would become shorter each round of replication!

- Sol:
- ① Eukaryotes have tandemly repeated sequences at the ends of their chromosomes.
 - ② Telomerase (composed of protein and RNA complementary to telomere repeat) binds to the terminal

- telomere repeat and catalyzes the addition of new repeats
- 3. Compensates by lengthening the chromosomes.
 - 4. Absence or mutation of telomerase activity results in chromosome shortening and limited cell division

what is Telomerase???

Telomerase also called Telomere terminal transferase is an enzyme made of protein and RNA subunits that elongates chromosomes.

The results of aging cells in an aging body. If telomerase is activated in a cell, the cell will continue to grow and divide. This "immortal cell" theory is important in two areas of research: aging & cancer

Final step - Assembly into Nucleosomes.

- As DNA unwinds, nucleosomes must disassemble
- Histones and the associated chromatin proteins must be duplicated by new protein synthesis.
- Newly replicated DNA is assembled into nucleosomes almost immediately.
- Histone chaperone proteins control the assembly.