- Archibald Garrod, an English physician in St. Bartholomew's Hospital in London observed rare disease 'Alkaptonurea'
- 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, Friedreich 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

Eduard 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 [Fredrick Griffith]

Griffith was studying the pathogenicity (disease-causing capability) of his strains (Type IIR and Type IIIS of Pneumococcus bacteria.

To begin, Greffith 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 IIIS) 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 occured was if living bacteria (rough, in this case) were instructed to become smooth 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 ~~that~~ 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.

Oswald T Avery's Transformation Experiment - 1944.

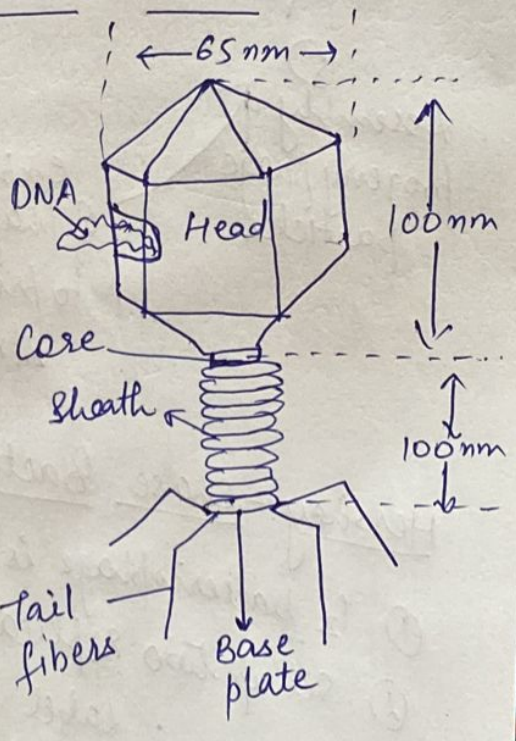
Determined that "IIIS" DNA was the genetic material responsible for Griffith's results (not RNA)

mixture of DNA & RNA → Treat with RNase → Add DNA to R bacteria → Plate on growth medium → S transformation produced

Mixture of DNA & RNA → Treat with DNase → Add RNA to R bacteria → Plate on growth medium → No S tranformation

Hershey-Chase Bacteriophage Experiment - 1953

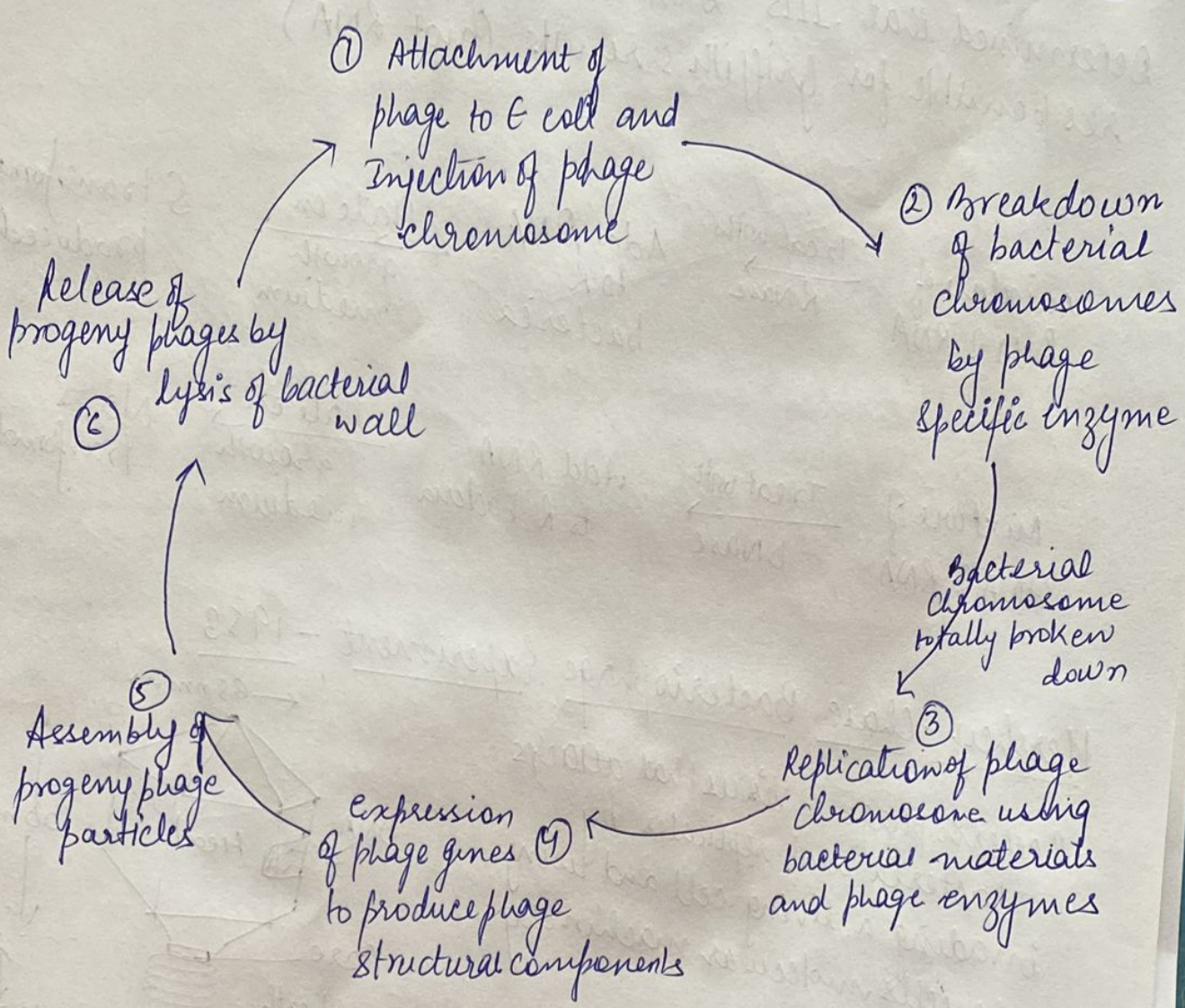
Bacteriophage = Virus that attacks bacteria and replicates by invading a living cell and using the cell's molecular machinery



Structure of T_2 phage

Bacteriophages are composed of DNA & protein

Life Cycle of virulent T_2 phage:



Hershey-Chase Bacteriophage Experiment – 1953

① T_2 bacteriophage is composed of DNA and proteins

② set up two replicates:
- Label DNA with ^{32}P
- Label Protein with ^{35}S

③ Infected E. Coli bacteria with two types of labeled T_2

④ ^{32}P is discovered within the bacteria and progeny phages whereas ^{35}S 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 & ~~Schr~~ Schramm 1956 / Fraenkel-Conrat & Singer 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

(a) The base composition varies from species to another
(b) 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 = Thymines
Guanines = 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

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 molecules 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 .0.34 nm apart.
- Each full turn of the helix contains 10 base pairs.

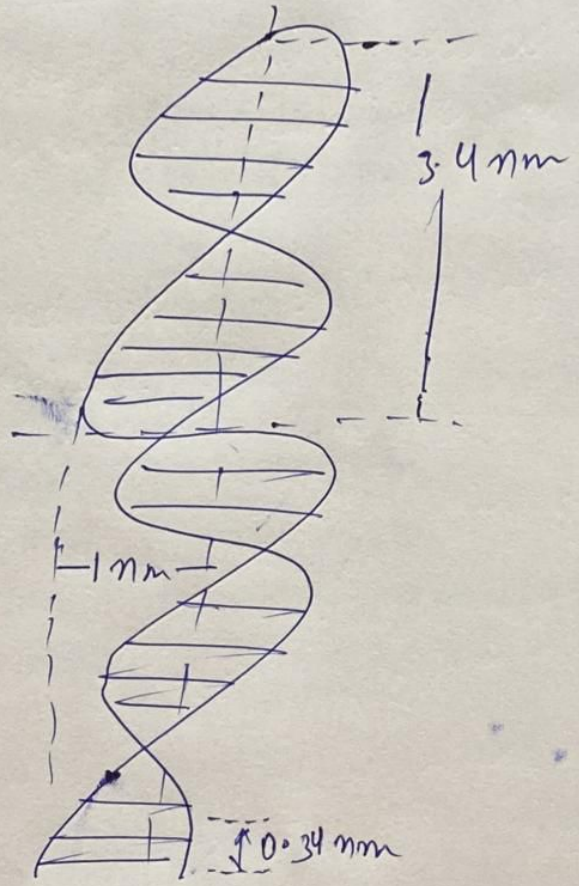
- The nitrogenous bases of the double helix are paired in specific combination Adenine (A) with Thymine (T) and Guanine (G) with Cytosine (C)

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)