How did scientists discover that genes are made of DNA?

- By the late 1800s, scientists knew that genetic information existed as distinct units called \textit{genes}.
- By the early 1900s, studies suggested genes were part of \textit{chromosomes}, protein and DNA complexes.

In 1928, a British medical officer, Frederick Griffith, worked to create a vaccine against \textit{Streptococcus pneumoniae}.

- The bacteria that causes pneumonia in mammals.

Two strains of the same bacteria.

- Nonpathogenic strain (harmless)
- Pathogenic strain (disease causing)

Griffith’s Experiment

Pathogenic Strain
- Heat Killed
- Mixed with Non-Pathogenic Strain

Some Harmless Cells Became Pathogenic
Bacterial Transformations

- Conclusions from Griffith’s Experiment
  - DNA was not destroyed in the heat-killed bacteria.
  - The bacteria’s information still made mice sick.

- **Bacterial transformations** are the incorporation of foreign genetic information into the cell’s chromosome.
Bacterial Transformations

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It wasn’t until 1943 that researchers discovered the transformed material was DNA.

What is DNA?

- Deoxyribose Nucleic Acid
- Chain of nucleic acids that contain the genetic blueprint (molecular make-up) of all organisms.
- A set of DNA molecules make up a gene.
- A set of genes make up a chromosome.

What is DNA?

- Deoxyribose Nucleic Acid
- There are 4 different nucleotides, nucleic acid bases.

  Adenine (A)
  Guanine (G)
  Thymine (T)
  Cytosine (C)
What is DNA?

- Deoxyribose Nucleic Acid
- In the 1940s, Erwin Chargaff observed the amounts of the nucleotides.

**Chargaff’s Rule:**
- Equal amounts of adenine and thymine.
- Equal amounts of guanine and cytosine.

DNA is a Double Helix

- Maurice Wilkins & Rosalind Franklin
  - Used a technique called X-ray diffraction to study molecular structure.
- Rosalind Franklin
  - Produced the first picture of the DNA molecule using this technique.

X-ray Diffraction bombards X-rays at a sample and analyzes the pattern of scattering.

From the X-ray diffraction pattern, they concluded that DNA:
- Has a uniform diameter of 2nm.
- Is helical.
- Consists of repeating subunits.

DNA is a Double Helix

- James Watson and Francis Crick analyzed Wilkins and Franklin’s data and determined:
  - The DNA molecule consists of two separate DNA polymer strands.
    - Within each strand, the phosphate of one nucleotide binds to the sugar of the next one, producing a sugar-phosphate backbone.
    - All nucleotides face the same direction in the DNA strand.
Nobel Prize for Medicine, 1962

- Awarded to Watson, Crick, and Wilkins for their discovery of the structure of DNA.
- Should have been awarded to Franklin as well.
  - Can be awarded no more than 3 individuals.
  - Cannot be awarded to someone after their death.
  - Rosalind Franklin died in 1958.

DNA is a Double Helix

Covalent bonding creates a Sugar-Phosphate backbone.

DNA consists of two separate strands facing the same direction, antiparallel.

The two strands are held together by hydrogen bonds.
Numbering Nucleotides

- All carbons in the nucleotide are numbered.
- The 3’ carbon always bonds with the phosphate group of the next base.
- DNA strands are always read 5’ to 3’.
  - A free phosphate group marks the 5’ end of a DNA sequence.
  - A free sugar marks the 3’ end.
DNA is a Double Helix

Three Possible DNA Helices

- Three possible helices can be constructed from the four nucleotides.
- B-DNA is the form found in all cells.
- A- and Z-DNA have alternate spacing of the helices and are found in certain circumstances.
  - A-DNA is found in RNA-RNA and RNA-DNA helices.
  - Z-DNA is only found in certain sequences.

DNA Replication

- When cells divide, the DNA must be copied so each daughter cell receives an exact copy.
- A cell must:
  - Replicate its DNA exactly one time before division
  - Divide after DNA replication
  - Have energy to do both

How does DNA Replication occur?
How does DNA Replication occur?

1. H-bonds separate between N-bases, forming two single helices.
2. Each helix makes a complementary strand using the parental strand as a template.
3. Two double helices are produced.

- **Semi-conservative replication**: each new strand contains one conserved parent strand and one newly synthesized strand.
Enzymes of Replication

- **DNA Topoisomerase**
  - Unwinds DNA supercoiled structures.
    - The DNA helix is coiled upon itself for compact storage, called *supercoiling*.

Enzymes of Replication

- **DNA Helicase**
  - Separates the DNA double helix by removing H-bonds holding nucleotide bases together.

Enzymes of Replication

- **DNA Polymerase**
  - Moves along each separate parental DNA strand and matches bases with complementary free nucleotides.
  - Synthesizes the new daughter strand from the 3’ to 5’ end.

Enzymes of Replication

- **DNA ligase**
  - Ties daughter pieces together.
  - Connects segments of discontinuous DNA synthesis.
DNA Replication, in detail

• After the topoisomerase unwinds the DNA, the DNA helicase creates replication bubbles throughout the strand to be copied.

DNA Replication, in detail

• DNA polymerase binds at the replication fork and begins copying.

DNA Replication, in detail

• DNA polymerase copies by either continuous or discontinuous synthesis.

DNA Replication, in detail

• Continuous synthesis:
  – Complete synthesis of the leading daughter strand moving toward the helicase.

• Discontinuous synthesis:
  – Synthesis of the lagging daughter strand in segments as the helicase closes the replication bubble.
  – Requires the DNA ligase to join segments.
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Leading Strand

Lagging Strand

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DNA Replication, in detail

- DNA ligase stitches daughter strands together, produced by discontinuous synthesis of the complimentary strand.
- Synthesis continues until the entire parental template strand is synthesized.

![DNA Replication Diagram](image)

Mistakes and Mutations in DNA Replication

- Mutations are changes in the DNA sequence that lead to defective genes.
- DNA polymerase mismatches every 1/10,000 bases.
  - Due to the speed of replication: 50 nt/sec in humans, 1000 nt/sec in some bacteria.
- DNA polymerase is capable of proofreading, increasing accuracy to 1 mistake per 1 billion base pairs.

Mistakes and Mutations in DNA Replication

- Most mistakes are **deleterious**, or harmful.
  - Changes to a protein’s sequence almost always renders the protein useless and unable to fold properly.
- Sometimes mutations are **neutral**, or have no effect.
- Very rarely, mutations can have a **beneficial** effect.
  - These are favored by natural selection and are the basis for the evolution of life.

Homework

- What types of mutations can occur during DNA replication that result in a newly-synthesized DNA strand of the same length as the template strand?

- Assume that in the process of creating a replication bubble during DNA replication, the helicase causes a substitution in the complimentary strand only. The mutation was not caught by proof-checking machinery and replication continued.
  - After two rounds of DNA replication (this first replication bubble starts the first round), how many strands of DNA carry the mutation (each half of the DNA double helix counts as one strand)?