Discovery of DNA
Discovery of DNA

- Friedrich Miescher, 1869, first isolates a substance from the nucleus of cells that he calls “nuclein.” His student, Richard Altmann, calls the substance “nucleic acid.”

- Used leucocytes as his source material to study biochemistry of nucleus
  - Bandages with pus

- Yet during these tests, Miescher noticed that a substance precipitated from the solution when acid was added and dissolved again when alkali was added

- Studied salmon sperm
  - Large amount

- Miescher also noticed that nuclein was not well diffusible and concluded that it must be a molecule with a high molecular weight.
Chromosome Theory

- 1902
- Inheritance from each parent
  - Two copies
    - One copy from each parent
    - Body cells 2 copies
    - Gamete one copy
- The chromosome theory of inheritance arose out of Sutton and Boveri’s careful observations of meiosis. It states that chromosomes are composed of Mendel’s hereditary determinants, or what we now call genes.

<table>
<thead>
<tr>
<th>PROCESS</th>
<th>DNA synthesis</th>
<th>Synopsis of homologous chromosomes</th>
<th>Crossover</th>
<th>Homologous chromosomes line up at metaphase plate</th>
<th>Sister chromatids line up at metaphase plate</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEIOSIS</strong></td>
<td>Occurs in S phase of interphase</td>
<td>During prophase I</td>
<td>During prophase I</td>
<td>During metaphase I</td>
<td>During metaphase II</td>
<td>Four haploid cells at the end of meiosis II</td>
</tr>
<tr>
<td><strong>MITOSIS</strong></td>
<td>Occurs in S phase of interphase</td>
<td>Does not occur in mitosis</td>
<td>Does not occur in mitosis</td>
<td>Does not occur in mitosis</td>
<td>During metaphase</td>
<td>Two diploid cells at the end of mitosis</td>
</tr>
</tbody>
</table>
In 1928 Frederick Griffith published a paper on his attempts to develop a vaccine for bacterial pneumonia. Pneumonia was leading cause of death in the 1918-1919 flu pandemic. Griffith worked with two strains of a bacterium, one pathogenic and one harmless. When he mixed heat-killed remains of the pathogenic strain with living cells of the harmless strain, some living cells became pathogenic. He called this phenomenon transformation, now defined as a change in genotype and phenotype due to assimilation of foreign DNA. Transforming material is genetic material.
**EXPERIMENT**

- Living S cells (control)
- Living R cells (control)
- Heat-killed S cells (control)
- Mixture of heat-killed S cells and living R cells

**RESULTS**

- Mouse dies
- Mouse healthy
- Mouse healthy
- Mouse dies

Living S cells
Oswald Avery: Transforming Material is DNA

- Griffith wanted to develop a vaccine and did not pursue transforming material
- Oswald Avery realized that the transforming material must be the genetic material and could experimentally determine what molecule coded for genes
  - Protein vs. DNA
- In February 1944, Journal of Experimental Medicine, entitled “Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Deoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III”.

Used two approaches
- Isolate pure molecules and test
  - DNA
  - Protein
  - RNA
  - Lipids
- Remove molecules by digestive enzymes
STUDIES ON THE CHEMICAL NATURE OF THE SUBSTANCE INDUCING TRANSFORMATION OF PNEUMOCOCCAL TYPES INDUCTION OF TRANSFORMATION BY A DESOXYRIBONUCLEIC ACID FRACTION ISOLATED FROM PNEUMOCOCCUS TYPE III BY OSWALD T. AVERY, M.D., COLIN M. MACLEOD, M.D., AND MACLYN McCARTY, M.D. (From the Hospital of The Rockefeller Institute for Medical Research) PLATE 1 (Received for publication, November 1, 1943)

### Table IV

<table>
<thead>
<tr>
<th>Transforming principle</th>
<th>Preparation 46</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilution</td>
<td>Amount added</td>
<td>Diff. growth</td>
<td>Colour/ form</td>
<td>Diff. growth</td>
<td>Colour/ form</td>
</tr>
<tr>
<td>10⁻⁵ mg.</td>
<td>1.0</td>
<td>+</td>
<td>SIII</td>
<td>+</td>
<td>SIII</td>
</tr>
<tr>
<td>10⁻⁴ mg.</td>
<td>0.3</td>
<td>+</td>
<td>SIII</td>
<td>+</td>
<td>SIII</td>
</tr>
<tr>
<td>10⁻³ mg.</td>
<td>0.1</td>
<td>+</td>
<td>SIII</td>
<td>+</td>
<td>SIII</td>
</tr>
<tr>
<td>10⁻² mg.</td>
<td>0.03</td>
<td>+</td>
<td>SIII</td>
<td>+</td>
<td>SIII</td>
</tr>
<tr>
<td>10⁻¹ mg.</td>
<td>0.01</td>
<td>+</td>
<td>SIII</td>
<td>+</td>
<td>SIII</td>
</tr>
<tr>
<td>10⁻⁰ mg.</td>
<td>0.001</td>
<td>−</td>
<td>R only</td>
<td>−</td>
<td>R only</td>
</tr>
<tr>
<td>Control None</td>
<td>−</td>
<td>−</td>
<td>R only</td>
<td>−</td>
<td>R only</td>
</tr>
</tbody>
</table>

* Solution from which dilutions were made contained 0.5 mg. per cc. of purified material. 0.2 cc. of each of these dilutions was added to quadruplicate tubes containing 2.0 cc. of standard serum broth. 0.05 cc. of a 10⁻⁴ dilution of a blood broth culture of RMA is added to each tube.

A solution containing 0.5 mg. per cc. was serially diluted as shown in the protocol. 0.2 cc. of each of these dilutions was added to quadruplicate tubes containing 2.0 cc. of standard serum broth. All tubes were then incubated with 0.05 cc. of a 10⁻⁴ dilution of a 5 to 8 hour blood broth culture of RMA. Transforming activity was determined by the procedure described under Method of titration.

The data presented in Table IV show that on the basis of dry weight 0.003 μg. of the active material brought about transformation. Since the reaction system containing the 0.003 μg. has a volume of 2.25 cc., this represents a final concentration of the purified substance of 1 part in 600,000,000.

### Diagram

Avery, McCarty, and MacLeod Experiment

Mice were given deadly bacteria with enzymes that destroyed...

- Carbohydrates
- Lipids
- Proteins
- RNA
- DNA

What were their conclusion?
IDENTIFICATION OF DNA AS THE GENETIC MATERIAL

- To fulfill its role, the genetic material must meet several criteria
  - 1. Information: It must contain the information necessary to make an entire organism
  - 2. Transmission: It must be passed from parent to offspring
  - 3. Replication: It must be copied
    - In order to be passed from parent to offspring
  - 4. Variation: It must be capable of changes
    - To account for the known phenotypic variation in each species