1936 - 1945

The History of Phage Research

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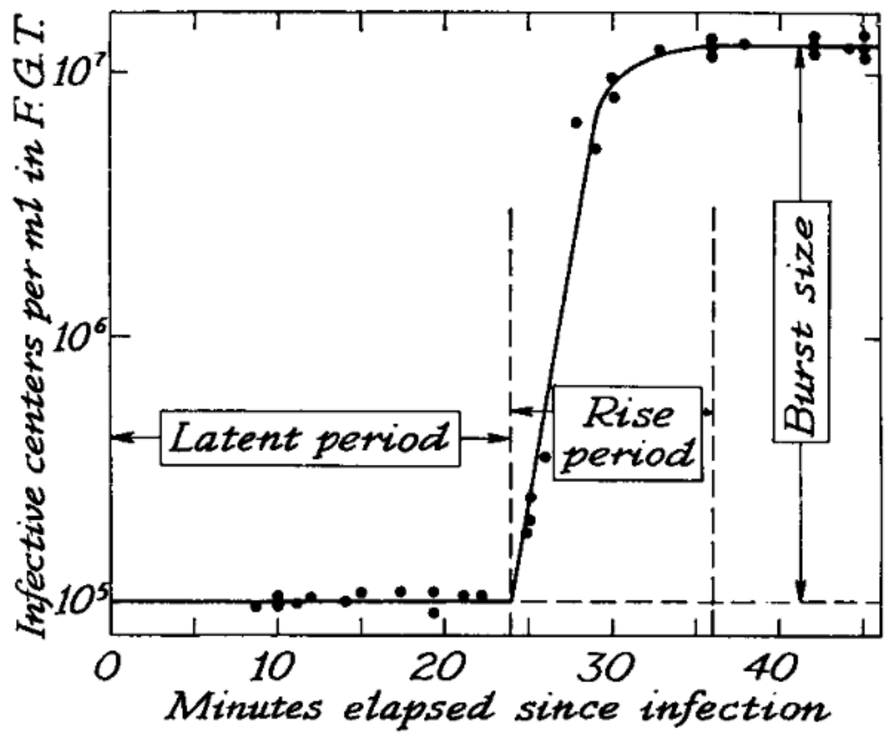
One-step Growth Experiment

1937-1939 – E.L. Ellis & Max Delbrück

- Three phage growth steps: (i) adsorption, (ii) growth upon or within the bacterium (latent), and (iii) release of phage (lysis/burst)
- Both latent period and the burst size could be determined with one-step growth experiment
- Plaque counting method to determine phage concentration was introduced
- Multiplicity of infection (MOI) was described



Doermann *et al.* 1952

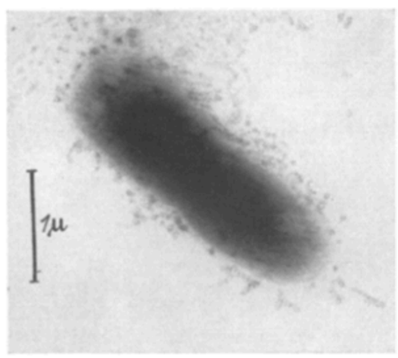


Fig. 1. III 133/39. Coli-Phagen an vorwiegend scharf begrenzter Bakterienoberfläche. Elektronenoptisch: 15000:1.

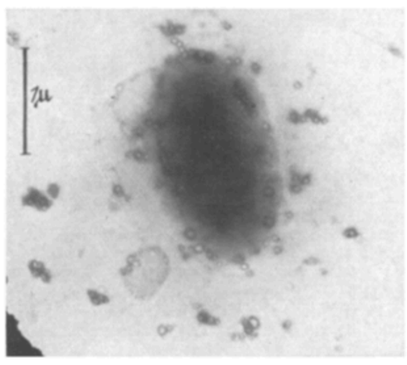


Fig. 3. II 702/39. Coli-Phagen an resistentem Keim mit erhaltener Membran. Elektronenoptisch: 14000:1.

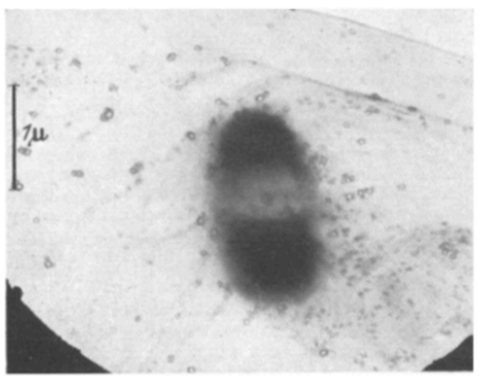


Fig. 2. III 137/39. Coli-Phagen an aufgelockerter, unscharf begrenzter Bakterienoberfläche. Elektronenoptisch: 14000:1.

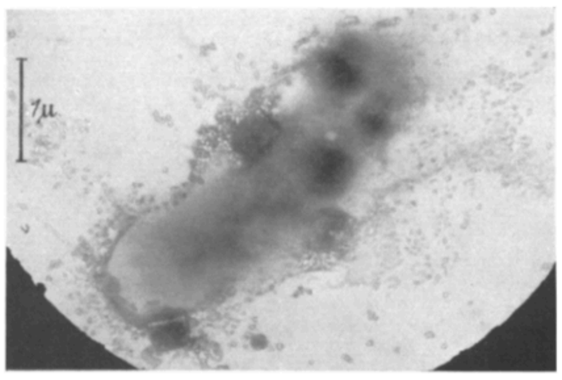


Fig. 4. III 139/39. Keim mit eingeschlossenen und anliegenden (ausgetretenen?) kristalloiden Bildungen und Phagen. Elektronenoptisch: 14000:1.

The first Electron Microscopy Image of Phage

1940 – Helmut Ruska

- First visualization of phage and bacterial lysis under an electron microscope
- Crystalized phage retain their lytic activity
- Increased abundance of round bodies indicate phage particles after bacterial lysis
- According to the EM resolution phage size was predicted to be 40 – 80 µm

Founding of the Phage Group

1940 – Delbrück, Luria, and Hershey

- Informal network of geneticists which later became influential in the new discipline of molecular biology in the 1950s
- Max Delbrück established "T-Series" (T1-T7) as model organisms
- In 1945 the group established the Summer Phage Course at Cold Spring Harbor laboratory which continues to this day

Delbrück & Luria

Alfred Hershey

Lysis from Within; Lysis from Without

1940 – Delbrück

1. $P/B = 1$ → **Phage to Bacteria Ratio**

(a) *Hanging Drop*

No changes in the shape of the bacteria were observed, only a gradual diminution in the number of bacteria.

2. $P/B = 200$ or greater

(a) *Hanging Drop*

The bacteria kept their normal size and rod shape up to about 20 minutes. Then suddenly within 1 or 2 minutes the large majority was transformed into spherical bodies of about the same volume and small refractive power. These spherical bodies were visible for a long time and only gradually decreased in number, some could be seen much distended and of oval shape.

Besides these spherical bodies there appeared a few very minute rods that were extremely motile.

- Lysis from within: Multiplication occurs after infection of a bacterium by a single phage particle. The cell contents are released without deformation of the cell wall.
- Lysis from without: Adsorption of phage particles on bacteria above a threshold causes destruction of the cell wall and distension of the cells. No new phage is formed.

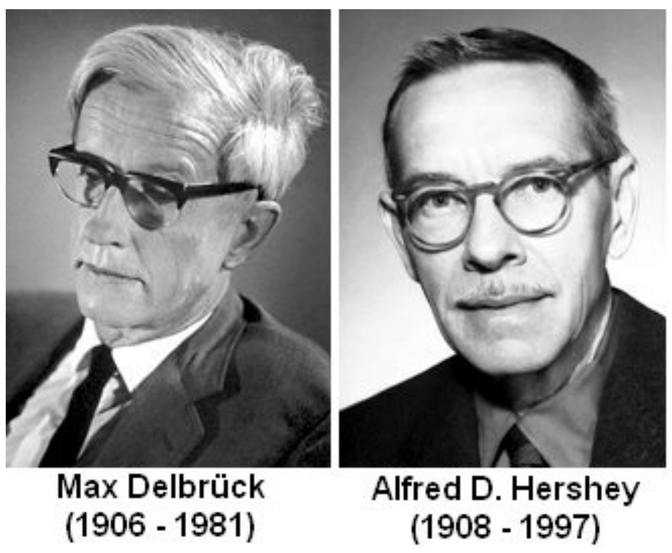
Ty Roach &
Emma George

1946 - 1955

The History of Phage Research

PHAGE RECOMBINATION

1946– HERSHEY & DELBRÜCK


Max Delbrück (1906 - 1981)
Alfred D. Hershey (1908 - 1997)

- Hershey and Delbrück independently discovered that different strains of phages can exchange or combine genetic material while in the same host cell.
- The mechanism of recombination remained unclear, but they speculated that recombination via "mating" took place after the multiplication of phage within the cell.

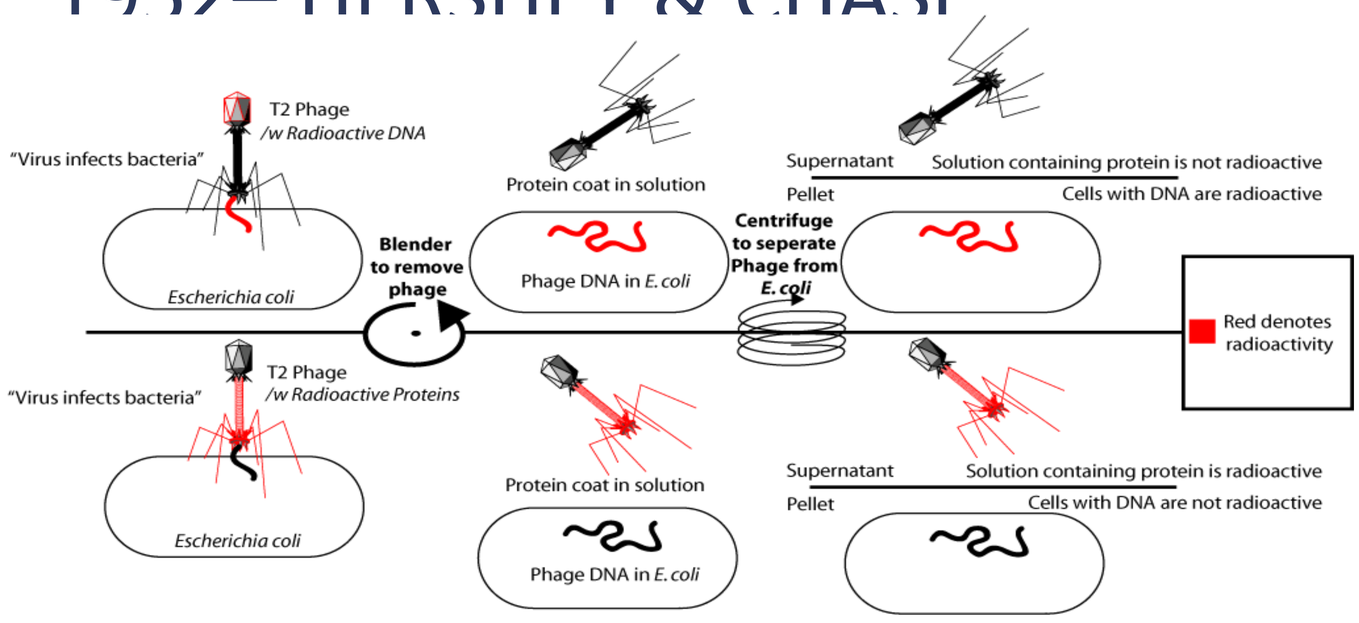
LYSOGENY

1950 – LWOFF & GUTMAN

- Lwoff and Gutman found that lysogenic phage are passed through generations of bacteria. No free phage were present inside lysogenic daughter cells, but sensitive bacterial strains were lysed when daughter cells were grown with the sensitive strains, showing that bacteria carry a non-infective phage structure.

DNA AS THE GENETIC MATERIAL

1952– HERSHEY & CHASE

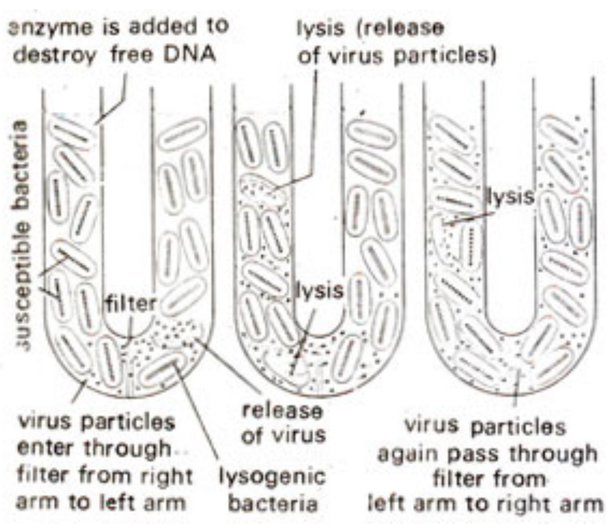


- Radiolabeled DNA and protein were used to demonstrate that viral nucleic acids and proteins have independent functions in phage.
- Hershey won the 1969 Nobel Prize along with Luria and Delbrück for their work on phage

TRANSDUCTION

1952 – ZINDER & LEDERBERG

- Transduction was discovered using a U-tube experiment where lysogenic bacteria containing a phage and bacteria susceptible to the phage were separated by a filter. Genetic material was transferred from the susceptible strain to the lysogenic strain, demonstrating that phage are vehicles for bacterial gene transfer.



Other Important Papers:

- Freeman 1951 – Phage contribute to bacterial virulence
- Luria 1952 – Bacterial hosts can influence the ability of a phage to infect other bacteria
- Franklin 1955 – Tobacco Mosaic Virus (TMV) rods are all the same length
  - -First to speculate that phage are hollow and that TMV was a single strand RNA virus