

1896 - 1925

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The History of Phage Research

The First Documentation of Lytic Activity

1896 – Ernest Hankin

- English bacteriologist working in India studying Cholera and other diseases.
- Published paper describing a marked antiseptic action against *Vibrio cholera* in the waters of rivers in India.
- Arguably the first documentation of lytic phage activity.



The First Documentation of Phages

1915 – Frederick Twort

- English bacteriologist who discovered bacteriolytic agents, but did not identify these agents as phages, and instead thought they were enzymatic.
“May it be a cultivable enzyme?” – Frederick Twort
- Published his discovery in *The Lancet* then joined the Army Medical Corps.
- Abandoned his pursuit of phages, and his work was largely ignored or forgotten.

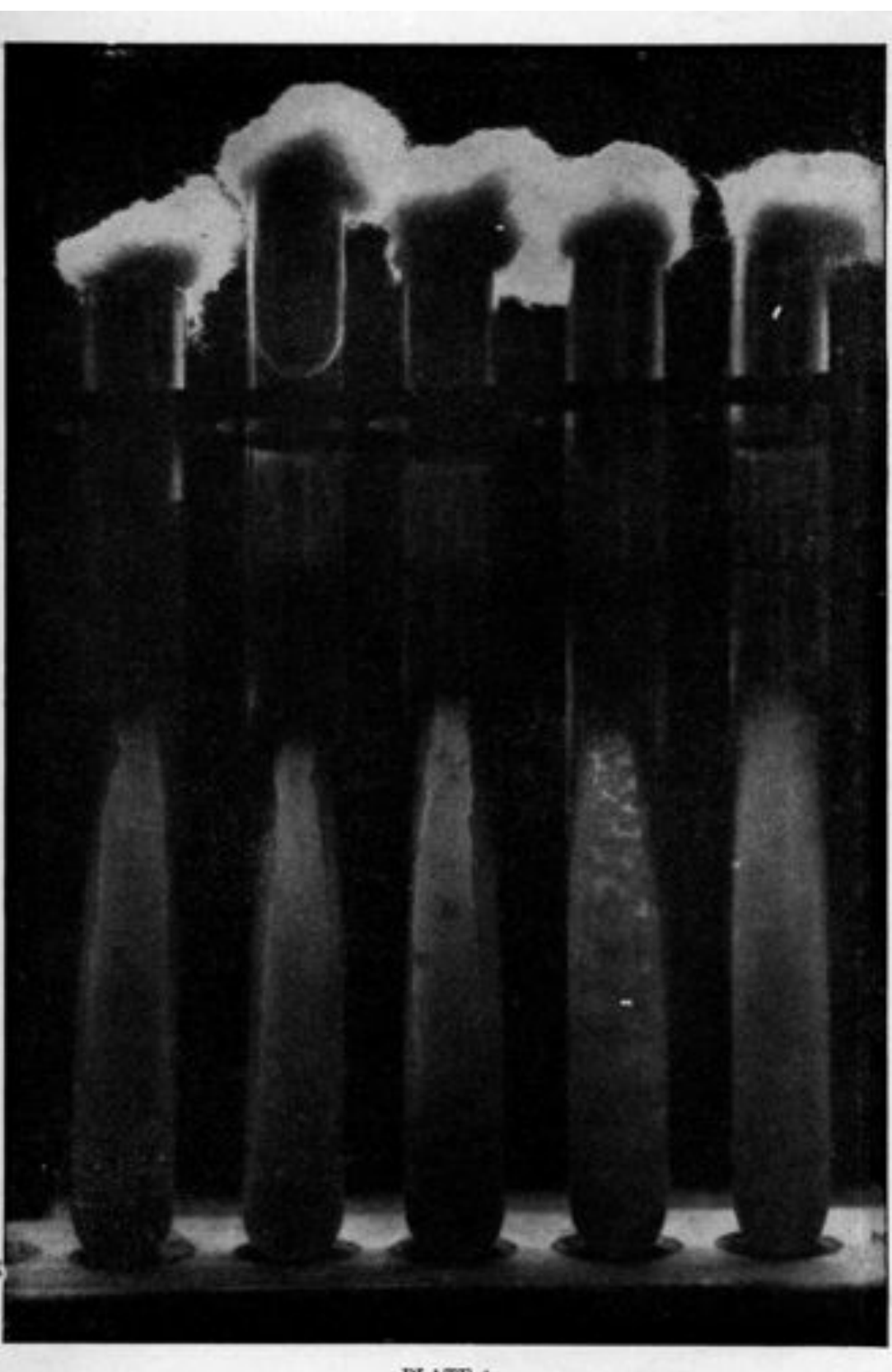
The First Discoverer (or Co-?) of Phage

1917 – Felix d’Herelle

- French-Canadian citizen – Independent of Twort, he discovered “an invisible antagonistic microbe of the dysentery bacillus”.
- On Sept. 3rd 1917 published his landmark paper “The Bacteriophage”.

“Bacteria are susceptible to infection and are hosts to ultramicroscopic, filter-passing agents, named Bacteriophages – eaters of bacteria”.

– Felix d’Herelle



The Fundamental Experiment

- A fecal sample was taken daily from an adult patient suffering dysentery.
- Feces were inoculated into broth, cultivated, and filtered through a Chamberland filter.
- Successive passages of the filtrate were inoculated to a culture of *Shiga bacilli*
- Instead of losing potency, it increased in lytic capacity.

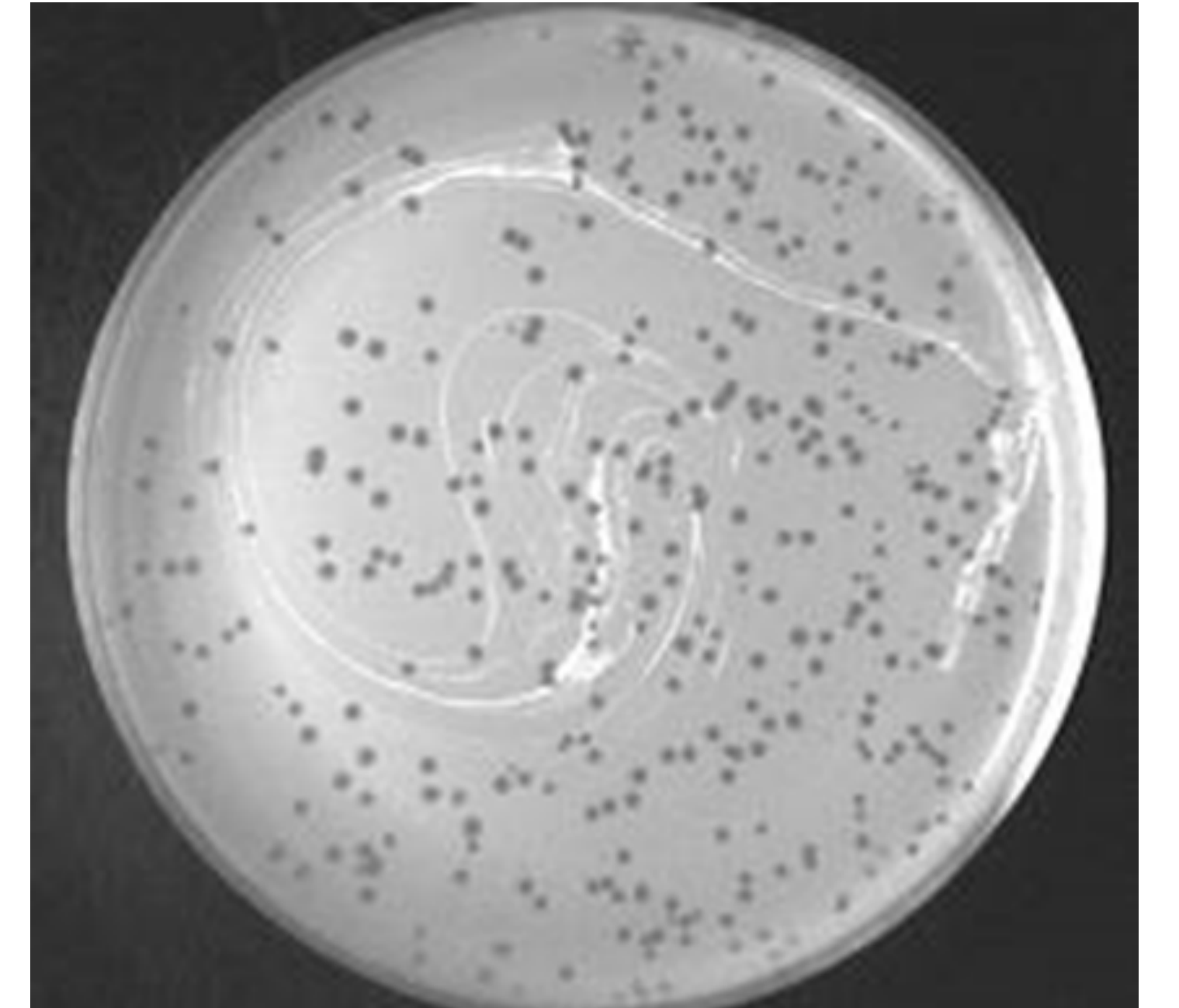
The Birth of Phage Therapy

1919 – Felix d’Herelle

- Isolated plaques from chicken feces, then successfully treated a plaque of chicken typhus
- After this successful experiment, tested the first ever application of phages on a human patient in 1919. The patient was healed of dysentery using phage plaques and Phage Therapy was born.

Plaque Assays

d'Herelle 1917, improved during 1920s and 1930s
Gratia-publishes top agar method 1936



- Accurate, reproducible method for phage quantification
- Allows quantification across range of concentrations
- Phenotypic character for study of heritable variation in phages.



1928 d'herelle and Ashenov's group poured bacteriophage into 15 village wells in India.

Cholera treatment Assam, India, 1928-1929

Treatment	n	Died	Survived
phage	62	7	55
no phage	81	63	18

Phage therapy: Progress and pitfalls

used extensively during 1920s
examined critically during 1930s

Bacteriophage therapy was successful in many patients against:

dysentery	<i>strep.</i>
typhoid	<i>V. cholera</i>
kidney infection	<i>B. pestis</i> (bubonic plague)
pyelitis	
<i>staph.</i>	

What happened?

lack of quality control. d'Herelle ensured quality phage; not all were so diligent. Straub and Applebaum, 1933 *JAMA*, test commercial products and find many inactive or ineffective.

Confounding results. Eaton and Jones, 1934 *JAMA* reviewed phage therapy results and found that Human and animal trials lacked controls, showed little effect of therapy, or conclusions were confounded by components of phage lysates.

Limitations. Phage therapy is not effective as a prophylaxis, only as a cure.

infrastructure to provide therapy requires facilities to isolate phages and cultural access to patients, a challenge in India during the 1930s and amid Gandhi's *satyagraha*.

Lysogeny

Phages are heritable
from bacterial spores

Spores heated above phage-lethal temperatures give rise to free phages after germination. Burnet and McKie (1929) conclude : "Permanence of lysogenic character...is part of the hereditary constitution of the strain."

Gratia (1923): Rough bacteria are resistant to large plaque phage, smooth bacteria resistant to small plaque phage.

Burnet (1929): Acquisition of O antigen results in loss of susceptibility to the "rough specific" salmonella phage.

Phage typing
antigens predict
phage susceptibility