

Closing the Circle: AD Hershey and Lambda I

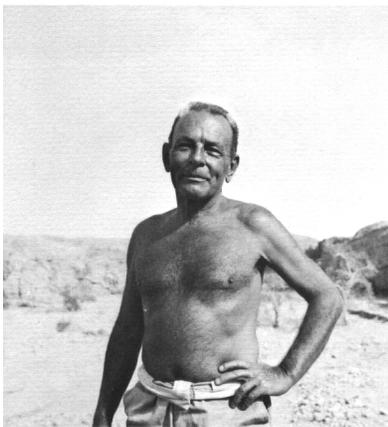
My studies of biology began with phage lambda in its heady days from 1962 to the mid '70s. Two of my senior colleagues introduced me to AD Hershey by reputation, but these were two **very different** reputations. Today I shall complete the circle by sharing with you my own experience with Al Hershey that culminated in 1971 with the publication of the Cold Spring Harbor monograph now called Lambda I.

One impression of Hershey was given to me by François Jacob, seen here with Hershey in 1963.

"I have one distinct memory of Al Hershey at a Cold Spring Harbor meeting. He gave one of his particular talks spending half the time looking at the board without talking. After that there were questions. One of the guys in the audience talked for a very long time at full speed, finally asking his question.

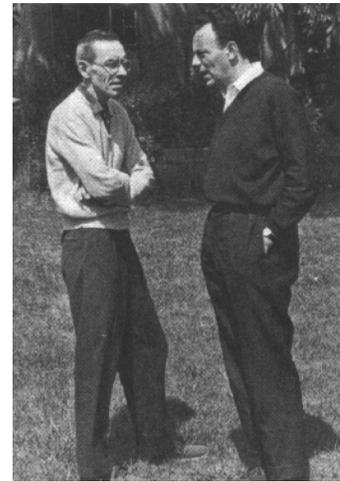
"After that Al looked deeply at the floor thinking very hard for about 3 or 4 minutes ... and finally said: NO!"

The other impression of Hershey was shared by Jean Weigle, that denizen of the Delbrück laboratory and the California desert who by his enjoyment of science brought



Jean Jacques Weigle.

so many of us into touch with lambda in preference to the more virulent phages. As Weigle and I worked together on the change in state of the DNA of lambda after infection, he read to me from a letter of Hershey's describing the development of methods of ultracentrifugation by which he could characterize the large unbroken DNA molecules of phage. These methods led to the discovery of lambda's cohesive ends by which it circularizes after infection. Said Hershey,



J. Mol. Biol. (1965) **12**, 620-629

**Intracellular State of the Chromosome
of Bacteriophage Lambda**

I. The Eclipse of Infectivity of the Bacteriophage DNA

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AND

J. J. WEIGLE

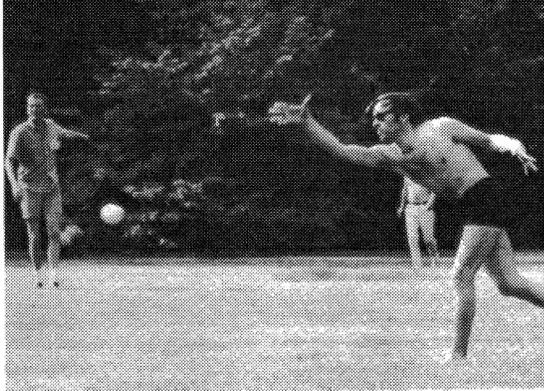
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"There is nothing more satisfying to me than developing a method. Ideas come and go, but a method lasts!"

Over the mid 1960s, I discussed with Hershey the issues surrounding lambda's DNA eclipse. I soon learned the deep reason for Jacob and Weigle's respect: Al Hershey had a passion for the truth, and even the famous success of the Hershey-Chase experiment did not close his open mind. No answer went unquestioned by Hershey. Indeed, when he had described the S^{35}/P^{32} experiment in lab meeting, he emphasized: note that about 1% of the S^{35} counts **did** enter the cell, and perhaps it contributes to the phage heredity (Waclaw Szybalski, personal communication). Hershey related to my study of the lambda DNA eclipse and maturation cycle as one way to determine whether more than polynucleotide synthesis was needed for infectious DNA. Indeed, his final scientific publication [Genes and Hereditary Characteristics, *Nature* 226:697-700 (1970)] focused on phenomena such as cortical inheritance that only now have moved to Stage Center with prion agents.



Ironically, it was Hershey's discovery of the cohesive ends of lambda DNA by ultracentrifugation analyses that afforded an explanation for the DNA eclipse/maturation cycle that Weigle and I had found.



M. Ptashne (pitching) and F. Stahl (outfielding), CSHSQB 1968. Photo by Roger Hendrix.

... nothing. Fine! Third page ... still nothing. **How is it possible?** At the last paragraph of page 4, an arrow was found, with a message: "**start here**" (Mark Ptashne, personal communication). [Postscript: Since this talk I have learned of at least one other early lambda investigator with the same story – Michael Yarmolinsky.]

All of you at Cold Spring Harbor know Jim Watson's talent for selecting the right person for the task. So you are not surprised that Al Hershey was asked by Watson to organize and edit the monograph on Bacteriophage Lambda consequent to a conference in September 1970. I was in Cold Spring Harbor that summer teaching the 25th (and final) Phage Course, together with René Thomas

I was not the only young lambda investigator who found Hershey's critical attitude and operationalism to be an invaluable guide. When Mark Ptashne purified lambda repressor, he wanted Hershey's critique of his manuscript. The first draft or two was returned with **everything** crossed out; an occasional phrase was marked Good! Finally, a draft came back that looked promising. First page ... nothing. Encouraging! Second page

The Bacteriophage Lambda

edited by

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Alfred Hershey
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COLD SPRING HARBOR LABORATORY, 1971

and Ariane Toussaint from Brussels. Al asked me to work with him on this project. What Al Hershey accomplished in this final major scientific effort involved a special blend of the critical taciturnity that Jacob and Ptashne had known, the fundamental trust in sound experimental methods that Weigle had noted, and the frank but warm collegiality that I came to enjoy. He wrote notes to individuals and to groups of authors, aiming for clarity and rigor. He made sure that each research paper was critically refereed. He starts with his own writing, giving us an inner view of why he was so taciturn. "Give it Hell!" he said to me, and to himself.

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Dear Bill

Here is another try at
Chapter 1.

EE

Give it Hell.

Here is one of his notes to everyone:

"I am sending this letter to all chapter authors because it cost me days of thought and it deals with the general problem of **saying what you mean**.

"I am Mr. Average Reader of your chapters. I am trying to put together a hearsay account of regulation that I have picked up from you and other authorities. In particular, I am trying to fill in things that I didn't see in your chapters, and to grasp the language and interpretations in the best way I can.

"Everybody including me seems to feel a need to revise terminology at this point. ... [But] let's try **not** to introduce any more words whose meaning cannot be found in the dictionary. The end result of this sort of naming is ... to use **three** words every time you mention one thing because at most you can hope that the reader will know **one** of them. I imagine some of the people who do this (philosophers, lawyers, and a few scientists) invoke the principle that redundant messages are resistant to noise. To oppose this view I offer the proposition that three synonyms, none of which can be found in the dictionary, make pure noise."

In November of 1970 Hershey culminated his campaign for clarity with a 2-page document called WORDS. Here are a few of his comments:

"map (verb). **Genes don't, geneticists do.**

lysogenic. **Means 'generating lysis', practically the same as 'lytic.'** **A temperate phage is not lysogenic, it is lysogengenic. 'Lysogenic' has become quite virulent.**

dilysoygenic?

lysogenic excision?

dilysoygenic excision??

These words have a fine ring until you ask yourself what they mean.

"CHOICES OF WORDS:

Clear but nasty: replication inhibition, lambdoid, transcription initiation, and too many others to list.

Nasty but interesting: 'heteroduplex mapping.' Here heteroduplex could be an adjectival noun, which is merely bad. It could also be an adjective and drive you crazy.

Unclear, nasty, and dull: 'immediate early.'

"I once observed to Chargaff that scientists don't have time to read each other's papers anymore. Speaking as an editor he said, **'They don't have time to read their own papers.'**

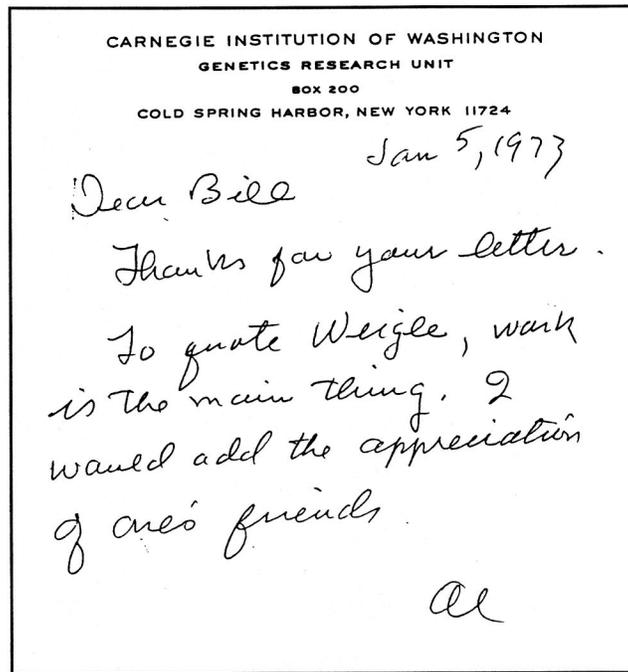
"I have lots of time.

Hershey

To all authors of general chapters
November 20, 1970"

After Lambda I, Al Hershey "moved on to other interests". He was in his early 60s, 25 years ago. (In the milieu of 1997, investigators of that age are "just reaching their prime"!)

My contact with Al and Jill Hershey came to involve opportunistic lunch or dinner meetings when I came to a Cold Spring Harbor meeting.



Al Hershey treasured his work and he treasured his friends. We can be grateful for the intensity with which he honored these treasures.

William F. Dove
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Cold Spring Harbor
July 10, 1997