My first phage experiments were performed in 1951, in a course given by Salvador Luria at the University of Illinois. Phage research has been my principal activity during the subsequent 60 years. This essay starts with how I came to be a graduate student at Illinois, then it recounts what happened later, to me and to the field of bacteriophage research.

How I entered the field
I graduated from the University of California, Berkeley with a major in Chemistry in 1950. My preferred career would have been novelistic, but I dismissed that as impractical. My parents, who had majored in English and Journalism, respectively, advised me to major in Science, because they thought that most of what they had learned at the university I would be able to learn on my own.

I had no ambition to do research. As an undergraduate, I expected to obtain my Bachelor in Science degree and go to work in the chemical industry. However, my interest in Physical sciences was morephilosophical than practical. From high school onward, the scientist I most admired was Albert Einstein.

Some of my most influential teachers at Berkeley were Joel Henry Hildebrand (Chemistry), Luis W. Alvarez (Physics), William Giauque (Thermodynamics) and Michael Doudoroff and Roger Stanier (Bacteriology). All these men provided the intellectual stimulation I craved. My tastes in teachers were not shared by all students; years later I encountered a young chemist from Berkeley who remarked, “I understand Giauque never prepared his lectures.” I guess he did not. The man was immersed in science, and his spontaneous thoughts were invaluable. I would have felt cheated had he given us yet another pre-organized show.

My application to graduate school was motivated mainly by a desire to postpone getting a real job. I applied for the program in Bacteriology because of the metabolically-based course taught by Doudoroff and Stanier. Roger Stanier’s advice was enormously helpful. Besides recommending me to Sol Spiegelman at University of Illinois, he helped arrange my enrollment in the summer Microbiology course at the Hopkins Marine Station taught by C. B. van Niel.

As a new graduate student at Illinois, I was immediately assigned a research project. My advisor, Sol Spiegelman, had a very special influence on me. My undergraduate professors in Chemistry had left me believing that the really important questions in biochemistry (e.g., the amino acid sequence of a protein) were almost impossible to attack. Undeterred by such obstacles, Sol bravely pursued questions on the control of enzyme synthesis by measuring overall parameters such as the rate of sugar utilization and analyzing them mathematically. His efforts from that period ended up having virtually no impact. Neither did my thesis research. With another advisor, my research might have been more mainstream, but my thinking would have been more earthbound. I owe Sol for liberating me from the mundane.

Luria moved to Illinois at the same time I arrived, which is how I found myself in his phage course the next year. The class had a high teacher/student ratio—two teaching assistants (George Streisinger and Bob DeMars) for eight students. We first went through the classical phage experiments and then undertook short individual research projects. Giuseppe “Joe” Bertani supervised my research project in Luria’s course and was a source of inspiration and critical advice during the next decade. Four of us (Joe, Seymour Lederberg, Bob DeMars and I) lived together in a rented house in Urbana my last year there.

Early career
I finished my thesis on “Long Term Adaptation in Yeast” in 1953 and joined the faculty of the University of Michigan, continuing research on yeast. In 1956, Joe Bertani invited me to spend the summer at Caltech. In Pasadena, I extended some experiments that Jean Weigle had started on the transduction of gal (discovered by Melvin Laurance Morse, Esther Lederberg and Joshua Lederberg1). Upon returning to Ann Arbor, I continued to work with λ and put the yeast research on hold.

I left Michigan in 1957. After another summer with Joe Bertani, then at the University of Southern California, and successive years at Cold Spring Harbor and the Institut Pasteur (with François Jacob), I spent nine years at the University of Rochester (only interrupted by a sabbatical year spent half in Naples with Enrico Calef and half in Stockholm with Joe Bertani at the Karolinska Institutet). That period of my career saw two principal accomplishments: the discovery of conditionally lethal mutants of λ and their use in determining the mode of attachment of prophage to the bacterial chromosome. I have described those years elsewhere.

Later career
In 1968, I moved from Rochester to Stanford, where I have studied phages continuously (though not exclusively) ever since. The phage work in my lab has focused on two themes: the regulation of integrase synthesis and the evolution of λ and its relatives. In both cases, our research has depended heavily on results from other laboratories.

My views on phage evolution were derived from limited observations on points of genetic exchange within a group collectively dubbed lamboids. This group (expanded from a set isolated by Jacob and Wollman3) has a functional map similar to λ but each lambdoid phage has large segments too dissimilar to λ to show sequence homology. Some of the junction points have microhomologies (too short to be recognized by general recombination enzymes such as RecA). My tentative conclusion was that the group is held together by intragroup recombination, which is more common than recombination with other groups. I regard the lambdoid phages as one species, i.e., a group of individuals whose similarity is perpetuated by intraspecific recombination.4 Certainly this is not the whole story, as revealed by wider surveys.
This species definition is broader than that of many population biologists, who restrict their concept of speciation to events that prejudice the recovery of hybrids originated in meiosis.

Investigations on *integrase* (*int*) regulation (executed in my lab by Mike Benedik, Desmond Mascarenhas, Don Court and Kaz Shimada) focused on the *int* promoter *pl* and its control by *cII* protein. During infection, *cII* protein stimulates transcription from *p* leading to the activation of integrase expression. In contrast, excision of prophage from the chromosome requires transcription from the major leftward promoter, *pL*, and another gene product, *excisionase*, in addition to *int*.

Our current work on *int* and its regulation developed from studies on lambdoid phage 21. My graduate student Stephanie Schneider investigated the attachment site of phage 21 for her thesis. Initially, nothing special was known about the site; the impetus was mainly to clear up some uncertainty as to whether its exact location differed from the sites of other lambdoid phages. It turned out to be more interesting. Phage 21 uses the same bacterial site (within the structural gene for *isocitrate dehydrogenase*) used by another DNA element (e14), which Chuck Hill at Penn State had found. Despite using the same site, phage 21 and e14 have different specificities, both for integration and excision. We identified specific determinants on the phage DNA and have a still unfinished task of finding all the determinants in the proteins.

But our main current activity concerns regulation of *int*. Whereas λ has a *cII*-specific *pl* promoter, no *cII* recognition sequence is positioned upstream of the *int* gene in phage 21. But there are several such sequences in a DNA segment downstream of *int*, whose RNA forms a stem and loop like that of the lambda *sib* sequence used in retroregulation. My long-term collaborator Alice del Campillo-Campbell and I are trying to define the mechanism whereby the downstream sequence may effect *cII* control.

In graduate school, I was convinced that five years was about the right time for an investigator to stay in a field. Whatever fresh approaches one introduced could be followed through by others and one has passed the steepest part of the learning curve. Thus, my lifelong study of λ was not planned. I extended my "five year limit" because developments from other areas, such as Benzer's work on T4, radically changed the methodology I was using with λ. After 1970, I devoted substantial time to other areas, but continued to study λ as well.

And why do I continue to do so now? Our current work fits into a larger picture of the control of lysogenization and how it evolved. I think this work should be done and I doubt that anyone else will have an incentive to do it. I hope that is sufficient justification for a Professor Emeritus who wants to spend his days in the lab.

**Directions of phage research**

Any field changes markedly during 60 years, and further shifts can frequently be foreseen. I have suggested what the future may bring based on projections of trends and my own cloudy crystal ball. As to the changes I myself have witnessed, most are common to many areas of biology and are probably familiar to most readers. Some turning points may be less obvious. For me, the first of these was the switch in emphasis away from the T phages to other material, especially λ, in the 1960s. Up to that time, the classical experiments of Hershey, Benzer and their followers had led to such an accumulation of information on T4 that a new investigator with a general question would almost automatically have chosen to work on it. I had grown up imagining that T4 would always have this advantage.

There is a story, perhaps apocryphal, that Max Delbrück was once approached by a young scientist with this question, "I just discovered several new phages. What is the first thing I should do with them?" To which Max replied, "Throw them away." Delbrück's plan that the phage community should concentrate its efforts on a few well-characterized phages served its purpose for about 30 years before becoming history.

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