



COMING OF PHAGE

*Celebrating the Fiftieth Anniversary
of the First Phage Course*



Gunther Stent, at the 1953 Symposium

l-r: Norton Zinder, Maurice Fox and George Streisinger in 1953



W. Hayes, E. M. Witkin and N. Zinder in 1953



R. Sinsheimer and J. Watson in 1953

Allan Campbell in 1984

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Cover: Electron micrograph of a T-series phage, taken by T.F. Anderson, circa early 1950s.

Back Cover: (top l-r) A.H. Doermann, D. Krieg, G. Bertani, C. Levinthal, F. Stahl, J. Dixon, N. Zinder, M. Chase, C. Chadwick, D. Fraser. Sitting: A. Hershey, M. Adams, R. Epstein and A. Garen at the phage meeting in 1953.

Many photographs used from the CSHL Archives were the original candid photos of Norton Zinder, Karl Maramorosch, Margaret Peggy Lieb and others.

INTRODUCTION

It is difficult to overemphasize the importance of the Cold Spring Harbor Bacteriophage Course on present-day biology, which has undergone tremendous change during the past 50 years. The Course also had a major impact on all of us who participated in it. It taught us to think in quantitative terms, to propose only such hypotheses as could be experimentally tested, and to rely on the power of genetics, especially microbial genetics. Our creativity was also stimulated by many bull sessions, Max's unrelenting criticism, and the many questions asked by Leo Szilard.

Just to initiate this endeavor, let me say a few words about how the Phage Course was woven into our lives and how it affected our scientific outlook. The life of my generation was a very complex one, because it was interrupted by the Second World War, often with catastrophic consequences. Many of the early Phage Course participants and invited lecturers have spent some years as soldiers or partisans, such as Leshek Kohn, François Jacob, Niccolo Visconti, and myself, or participated in the atomic bomb project, like Leo Szilard (who had a patent on the atomic pile), Aaron Novick, and R.B. Roberts, because phage research at that time was attracting the physicists, starting with Max Delbrück. Some of us were political refugees because of the Hitler and Stalin years of terror.

One of the examples was the life of Alexander (Leshek) Kohn, who participated in the 1951 Phage Course and whose cartoons of that time grace the walls of Blackford Hall. Recently, while preparing his obituary, I realized that his life prior to the Phage Course was a crazy quilt of science and war. My own life was also greatly affected by these difficult years when studies and science were intertwined with war, underground activities,



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Dr. Waclaw Szybalski, the only person to attend every Phage Meeting at Cold Spring Harbor since 1951.

concentration camps, the first wave of biotechnology of antibiotics in the late Forties and Fifties, microbial genetics, and the Phage Course. The lives of many other students of the early Phage Courses, like Gunther Stent, also have been strongly affected by these hectic war and early peace years, but though we might have already forgotten some of these less-than-pleasant events in our lives, we will never forget the Phage Course!

Waclaw Szybalski

A BRIEF HISTORY OF PHAGE AND BACTERIAL GENETICS AT COLD SPRING HARBOR

Cold Spring Harbor does not figure in the very beginnings of phage research, but it comes close. Though phage were discovered by Twort in 1915 and independently isolated and named by d'Herelle in 1917, they made little impact at the time. It was the work of Emory Ellis at Caltech and his collaboration with a German Rockefeller Fellow named Max Delbrück in the 1930s, that brought about the phage renaissance. Delbrück's first paper on phage was the famous "one-step growth curve" paper with Ellis, in 1938. Modern phage biology is often and probably rightly dated from this point.

The first bacteriophage deliberately introduced into a laboratory at Cold Spring Harbor arrived in the summer of 1941, with Max Delbrück and Salvador Luria.

Delbrück and Luria had met the previous December at the meeting of the American Physical Society. Delbrück, by then at Vanderbilt University, was enthused about phage but had run into technical difficulties. Luria had learned how to plate out phage from Eugene Wollman, father of Elie Wollman, at the Radium Laboratory in Paris, and was now applying these techniques in his laboratory at New York's College of Physicians

and Surgeons. After the meeting, they retired to Luria's lab for a "48-hour bout of experimentation." This was enough to persuade them to work together further. But where? Max had been invited to Cold Spring Harbor in the summer for the annual Symposium. Milislav Demerec, a maize geneticist-turned-Drosophilist, had recently assumed the directorship of Cold Spring Harbor, and reorganized the Laboratory around the question of the gene. The Symposium, which had mainly focused on biophysics and physiology, was this year to be on "Genes and Chromosomes." Demerec, like Delbrück, was convinced that the most important and interesting question in biology was the nature of the gene.



Max (sitting) and Salvador Luria at Cold Spring Harbor in the 1940s.

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Delbrück had been to Cold Spring Harbor in 1937, during a tour of several U.S. genetics labs sponsored by a Rockefeller Fellowship. He had disliked it at the time — it seemed sleepy and boring and no one seemed to talk to each other. Perhaps, though, working on phage with Luria would help Max overcome his "antipathy to the place." It was love at second sight; Max overcame his antipathy to the extent that in 1941 he spent his honeymoon at Cold Spring Harbor.

He and Luria continued to meet at Cold Spring Harbor in the summers during the war. While Demerec and most of the rest of the scientific staff at Cold Spring Harbor dedicated themselves to wartime research, Delbrück and Luria — a German and an Italian — were left alone to pursue their own experiments. In 1943 they teamed with Alfred Hershey, who was working at Washington University in St. Louis under J.J. Bronfenbrenner, one of the first Americans to take up phage research. The three men formed the nucleus of what we now think of as the phage group.

WHILE the world was at war, the phage group laid much of the foundation of molecular genetics. Following up on Delbrück and Emory Ellis' one-step growth curve, Delbrück and Luria demonstrated mutual exclusion, a term borrowed from physics to describe the observation that when two strains of virulent phage infected a bacterium, only one type of phage was produced when the cell burst. They also used the new RCA electron microscope at Woods Hole to take their first pictures of phage and at Cold Spring Harbor studied the effects of sulfa drugs on phage reproduction. In 1943, Luria's experimental design and Delbrück's mathematical model produced the fluctuation test, the first demonstration that bacteria could undergo genetic mutations. Many authors believe this paper marks the beginning of modern molecular genetics. The "Delbrück-Luria fluctuation test" is still used by molecular biologists to test for the occurrence of genetic changes in a variety of biological systems.

Delbrück consciously guided the phage revival, shaping the research culture as much as the data. Concerned that a lack of focus would result in data that couldn't be compared between labs, in 1944 Delbrück drafted the "phage treaty." This stipulated that all phage workers should study only



Norton Zinder, 1953

the seven "T" series phages and *E. coli* strain B. By standardizing the model system, Delbrück ensured a common language among phage biologists.

Language and communication generally were crucial to Delbrück's singularly social style of science. He was at his best when surrounded by challenging peers and bright young acolytes. Although Cold Spring Harbor presented him with a beautiful and solitary place to do experiments, the war caused the number of students and fellow scientists visiting the Laboratory to plummet. The summer courses, which had been held at the Cold Spring Harbor Bio Lab since its opening in 1890, had stopped. The annual Symposium was canceled in 1943, which further reduced the number of visitors. Cold Spring Harbor became a lonely place for a phage researcher.

Delbrück soon changed that. In his Vanderbilt University lab during the winter of 1944-45, he rehearsed a new course to be taught at Cold Spring Harbor that summer. The course was designed to attract new researchers of the right sort into

phage biology. It was loosely based on his own research career in America. Beginning with the one-step growth curve, it moved on to mutual exclusion, the fluctuation test, and other experiments. It required considerable mathematical skills, including calculus. Delbrück was adamant that phage biologists should come from the quantitative side of science, not the “stamp collecting” side. To ensure this, he gave an entrance examination for the summer course. The exam tested students’ abilities in “multiplication and division of large numbers” and calculus.



A.H. Doermann and Salvador Luria in 1953

From the start, the students were at least graduate students and many were post-doctorates. Many had a background in physics. Prior to the phage course, summer courses at Cold Spring Harbor had been geared toward college students. Six brave souls passed the exam and came to Cold Spring Harbor during the summer of 1945. Among them were Rollin Hotchkiss, who had just joined Oswald Avery’s Rockefeller Institute lab; Hermann Kalckar, a research associate at the NYC Public Health Research Institute; Thorbjorn Sigurgeirsson,

an Icelandic researcher on a Rockefeller fellowship; Martha Barnes Baylor, a research associate in chemistry at the University of Illinois, Urbana; Phyllis Margaretten, a graduate student in the same department; and Stuart Mudd, from the University of Pennsylvania Medical School. Delbrück taught the course, assisted by A.H. Doermann and J.H. Reynolds.

Despite its novel, highly professional flavor, the course was appropriate for Cold Spring Harbor. Since the turn of the century, Cold Spring Harbor had prided itself on “quantitative biology.” At the turn of the century, under Charles Davenport, this meant a sort of quantitative ecology. Later, often disastrously, Davenport applied quantitative measures to human behavioral traits. Under Davenport’s son-in-law, Reginald Harris, in the 1920s and 1930s, quantitative biology was represented by physiology and biophysics. When Demerec became director in 1940, he recognized that the question of the nature of the gene was at that time the most important in biology. This change in emphasis was so dramatic that the Rockefeller Foundation, which had supported the Bio Lab since 1931, remarked that the Bio Lab had undergone a “reorganization” under Demerec. Administratively, little had changed; intellectually, however, it was a major shift.

Delbrück brought to Cold Spring Harbor his own concept of quantitative biology. Borrowing intellectual tools from physics, Delbrück’s statistical approach was not out of line with the biometry and biophysics of previous generations. A student in the first phage course, Hermann Kalckar, said,

“Delbrück introduced me to quantitative biology and genetics through his first phage course....At that time, few biochemists thought along the lines of Poisson distributions....It is impossible,

however, to grasp the fundamental aspects of natural selection and population dynamics — so beautifully illustrated by the Luria-Delbrück fluctuation test — without paying attention to Poisson distributions, exponential equations, etc. And so Delbrück, who is uncompromising when something crucial is at stake, set an entrance examination on such matters for all who applied to take his course.”

Despite its small size, the course was considered a success. Demerec, who seems to have tried to hire nearly every prominent geneticist of the time, tried to attract Delbrück to the Carnegie Department of Genetics that fall. Delbrück was known to be less than content at Vanderbilt, so Demerec inquired as to whether he would consider coming to Cold Spring Harbor. Delbrück responded with his view of the future of phage research. “At present,” he wrote, “phage research is branching out in two directions.” The first, the study of “model viruses,” involved basic research on viruses and viral growth for their own sake. The second, “which uses phages merely as an experimental tool in the isolation and characterization of bacterial mutants,” was more applied and led to bacterial genetics and studies such as antibiotic resistance. The first group consisted of those interested in the gene; the second of those with broader concerns in genetics and medicine. The two were distinct, Delbrück said, but inseparable. Scientists interested in phage growth could hardly ignore mutant strains, and those concerned with mutations had to consider the growth cycle.

These two areas, Delbrück said, opened up so many possibilities that many new scientists were needed. This would require, among other things, a strong graduate program to attract young scientists into phage biology. “I consider it of equal importance



(l-r) Raymond Appleyard, George Bowen and Martha Chase in 1953

to bring new men into phage research as to do the research ourselves,” Delbrück said. Unfortunately, Cold Spring Harbor lacked a graduate program. Delbrück said he would consider moving to Cold Spring Harbor if an arrangement could be negotiated whereby graduate students from Columbia could do their thesis research at Cold Spring Harbor. Demerec’s reaction is not recorded, but the plan died and Delbrück later moved to Caltech.

THE Symposium returned in 1946, and it was a landmark for the new molecular biology. The title was “Heredity and Variation in Microorganisms.” Many of the growing phage group were there. Al Hershey announced his isolation of host-range phage mutants, which let him demonstrate genetic recombination in phage, as did the experiment of Delbrück and Bailey. Joshua Lederberg presented his dissertation data, collected in Ed Tatum’s lab at Yale, on recombination in *E. coli* strain K-12 using, among other selective agents, the phage T1 to select for the very rare recombinant (prototroph) cells. This work was to culmi-



Phage meeting attendees, 1954. In the front row, from the right, participants included Francis Crick, Sydney Brenner, Milislav Demerec, Al Hershey. Jim Watson is the third face from the top, down the lefthand edge.

nate 10 years later in the 1956 genetic maps of Hayes, Wollman, and Jacob that reflected uni-directional transfer of genes from the Hfr cells into F-cells. The 1946 Symposium was the first of a series ('51, '53, '56, '61, '63 and '66) of important Cold Spring Harbor Symposia where new phage results were disseminated to the molecular genetic community and new scientists were brought into the fold.

Delbrück taught the phage course for the first three summers. He was assisted in 1945 by A.H. Doermann and J.H. Reynolds, and in 1946 by W.T. Bailey, Jr. In 1947 Delbrück was joined by Mark Adams, a student from the previous year, as co-instructor. Scientists taking the course under Delbrück included Vernon Bryson, Harriet Taylor, and Samuel Cohen [1946], Philip Morrison, Leo Szilard, Aaron Novick, and Wolf Vishniac [1947]. In 1948 Mark Adams, of NYU College of Medicine, took over the instructorship of the phage course. Delbrück lectured often in the course, but was not listed as an instructor. With the exception of the summer of 1952, Adams continued to teach the course until 1954, assisted by various stu-

dents of his from NYU, including Nancy Collins, Maryda Swanstrom, and Evelyn Wade. The course continued to grow under Adams' direction, stabilizing at about 14 students per summer. A series of lectures were added, given mainly by previous students of the course and colleagues of students and instructors. Students during these years included Seymour Benzer, Bernard Davis, Peggy Lieb, Gunther Stent, and Seymour Wollman [1948], G. Bertani, Sol Goodgal, and Norton Zinder [1949], Philip Hartman and Marguerite Vogt [1950], Waclaw Szybalski [1951], Frank Stahl [1952], Julius Marmur [1953], and Bob Edgar [1954]. Throughout the remainder of the 1950s, the course was team-taught by different combinations of A.H. Doermann, Salvador Luria, George Streisinger, of the Carnegie Department of Genetics at Cold Spring Harbor, and Frank Stahl. Bob Edgar taught the course for many of the summers of the 1960s, assisted by Charles Steinberg of Oak Ridge and others. Herschel Roman took the course in 1956, Anna-Marie Skalka in 1962, Dan Nathans in 1964, Tom Caskey in 1967. In the second half of the 1960s, the course lacked the consistent leadership

of one or a few instructors, but high-quality scientists led the group nonetheless. Instructors included Millard Susman, Stahl and Steinberg back again for another summer, Allan Campbell, Carston Bresch, Hatch Echols, Michael Yarmolinsky, Bob Weisberg, Max Gottesman, and in its final year of 1970, Bill Dove and Rene Thomas.

Delbrück's influence thus extended well beyond his actual leadership of the course. Nearly all of the instructors throughout the history of the phage course were either former students in the course or had other connections to Delbrück. The phage course graduates formed the trustworthy core of those whose results Delbrück could trust. If an outsider tried to contribute to the phage canon, Delbrück was known to dismiss him with the comment, "But he hasn't taken the phage course!"

Simply doing all of the experiments and listening to the lectures was not enough to enter the ranks of the initiated. One also had to survive "graduation." At the end of the course, Delbrück, whose sense of humor was as legendary as his curt style of intellectual discourse, staged a graduation ceremony. This evening of merriment involved skits, silly costumes, and considerable amounts of ethanol-fortified drinks. The introduction to the second edition of the festschrift for Delbrück's 60th birthday shows Delbrück on the steps of Jones lab playing Ariel in a phage group production of Shakespeare's *A Midsummer Night's Dream*. Not all their entertainment was quite so cultured, however; like young people at summer camp, they also did their share of mischievous pranks, including letting the air

out of each others' tires and food fights in Blackford dining hall. Food fights, in fact, became an annual tradition at Cold Spring Harbor, until the installation of carpeting forced the Lab to put the kibosh on such antics.

The phage group of the 1940s was an extended family, with Delbrück as *pater familias*. Their ranks were relatively small but growing rapidly. New recruits came into the group every year, most by taking the phage course. Cold Spring Harbor was the site for the "family" retreat each summer. The instructors and lecturers, most of whom were graduates of the course and the rest were Delbrück intimates, returned each summer and mingled with the new



The 1951 phage course. Instructor Mark Adams is front row, center.

members of the group. Scientists brought their families and everyone stayed on the bucolic campus. Spouses and kids enjoyed the tennis courts and beach while the scientists mixed agar, plated out new crosses, and counted plaques. Much science was done on the tennis courts and beach as well. The phage group scientists worked, played, and ate together, and ideas for new experiments sprouted like grass through cracks in conversations about children, sports, or clothes.



Phage course graduations. Above (l-r), Rollin Hotchkiss, Charlie Steinberg, Salvador Luria, Frank Stahl, Al Hershey. At left, a well-potted Vernon Bryson.



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Accommodations were less than elegant. A lucky few instructors and summer researchers retained small apartments in the Firehouse, Williams, and Hooper. Students initially stayed in tents, Hooper, or in Blackford, the general feeling being that of a "summer camp of science." The shorts-and-sandals atmosphere promoted an easy familiarity within the group. All pretensions and formalities were dropped. Scientists called one another by their first names, regardless of their prestige. The camaraderie made it easier to maintain the style of ruthless critique for which they became known. The phage group scientists knew that when Delbrück listened to your new

pet theory and said bluntly, "I don't believe a word of it," it was nothing personal — in fact it was a friendly challenge. Outside the lab, he or anyone else who had seemed just as harsh, might invite you for a swim or buy you a beer. Among the phage group, ideas were separated from personalities. A person gave birth to an idea, but then cast it out like a balloon into the surrounding atmosphere. At that point it ceased to belong to any one person; the other members poked and pushed at it, tried to see if it would pop. It wasn't you they criticized, it was the idea.

By 1950, Delbrück began to withdraw from the group he had started. As it became increasingly clear that biochemistry and molecular techniques were needed to answer many of the emerging questions about phage, Delbrück began to turn to *Phycomyces* to examine the genetics of sensory physiology. He continued to summer at Cold Spring Harbor, of course, but his guest lecture was now on *Phycomyces*. Phage

research at Cold Spring Harbor, however, continued to flourish. In 1950, the annual phage meeting moved to Cold Spring Harbor. The first had been held in March, 1947 in Nashville, Tennessee with eight participants: M. H. Adams, T. F. Anderson, S. Cohen, M. Delbrück, A. H. Doermann, A. D. Hershey, M. Zelle, and S. E. Luria. This first meeting at Cold Spring Harbor was scheduled immediately following the end of the course, so that new recruits could be inducted straightaway into the phage community. Also that summer, a spin-off course on bacterial genetics, was offered by Evelyn Witkin — who, as a graduate student at Columbia had done her dissertation work at Cold Spring Harbor and was now a staff member — and Milislav Demerec.

The bacterial genetics course reflected the second aspect of Delbrück's 1945 predictions about phage biology; interest in viruses was definitely spreading to bacterial genetics in general. With this course, the intellectual balance at Cold Spring Harbor shifted decidedly in favor of microorganisms. In 1951, Demerec noted that "in 1941 about thirty per cent of the Symposium papers reported research carried on with *Drosophila*, and only six per cent dealt with microorganisms; whereas this year only nine per cent of the papers relate to *Drosophila*, and about seventy per cent to microorganisms." This, Demerec emphasized, did not reflect a decrease in *Drosophila* research, but rather a dramatic increase in the



Max Delbrück, Aaron Novick, Leo Szilard and Jim Watson in 1953

number of researchers studying microorganisms. In 1950 also, Demerec succeeded in bringing Al Hershey to the Carnegie. After attempts to hire Delbrück and Luria, at last Demerec had succeeded in attracting one of the original phage troika to Cold Spring Harbor. He would not be disappointed.

What for many was the climax of this phase of phage research came in 1952 and 1953. In 1952, Al Hershey and his assistant Martha Chase performed their famous "blender experiment," which demonstrated that T phage injected DNA and not protein into their bacterial host, and that that information was sufficient for the virus to reproduce and lyse the bacterial cell. Of course, Avery's group at Rockefeller had shown in 1945 that DNA was the "transforming principle" in the conversion of *Pneumococcus* bacteria from the benign "rough" form to the virulent "smooth" form. The phage scientists certainly knew of Avery's work, yet at the time there was little conceptual framework within which to place Avery's results. The Hershey-Chase results, however, could be fitted with



The top of Al Hershey's blender, in which famous phage were puréed.



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Above, Sydney Brenner, François Jacob, and Seymour Benzer in 1985. Right, Benzer in 1953.

Avery's, and the *Pneumococcus* work clearly facilitated the acceptance of the Hershey-Chase result. The blender experiment, though a cruder demonstration than Avery's, was in the common language of the phage group, and therefore fit more easily into what they then thought. It was the penultimate piece of the puzzle of Demerec and Delbrück's great question, "What is the gene?"

The final piece fell into place the next year. The Watson-Crick structure of DNA, devised at Cambridge, was announced at the Cold Spring Harbor Symposium of 1953. The Laboratory had just completed a new auditorium for the meeting. Delbrück was an organizer of the Symposium, which was on "Viruses." In a now-famous story, at the last minute he added Watson's name to the list of invited speakers. Watson and Crick's first *Nature* paper had just come out in April. Delbrück further ensured that the paper would be a centerpiece of the meeting by passing out copies to all the atten-



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dees. When Delbrück thought something was important, he made sure everyone knew about it.

The phage scientists on the staff at Cold Spring Harbor had the same sense of fun as the summer visitors. Wacław Szybalski, who joined the staff in 1953, recalls a "mountaineering expedition" up the side of the Animal House (today McClintock Laboratory), led by Alan Garen and Niccolo Visconti, from Hershey's group. The exposed bricks at the corners of the building made a thin ladder up the two-story building to the overhanging roof. The top was the hardest part, Szybalski says,

"because you had to hang out there and pull yourself up onto the roof... You have to be slightly drunk, because it's risky."

With the solution of the problem of the nature of the gene, phage scientists began to break down the strictures laid down by Delbrück that had so effectively focused the early phage work. Delbrück's two prongs of phage research diverged, with bacterial genetics gaining in prominence and taking on a life of its own, distinct from phage research. Common to both camps, however, was an increasing interest in the biochemistry of their systems. No longer could Delbrück's black box approach to the gene

Those interested in problems of phage growth and basic biology began to move to other systems. The phage treaty was broken and scientists began to explore the lysogenic phages. One of the most important was phage λ . Esther Lederberg found in 1951 that the familiar *E. coli* strain K-12 is lysogenic for λ and the data were presented in Lederberg et al.'s paper at the 1951 Cold Spring Harbor Symposium. The λ /K-12 system became the focus of the work in the 1950s and 1960s on repression, the operon, and the genetic code. As a lysogenic phage, λ became central in efforts during the 1950s and 1960s to tease out the flow of genetic information through the cell. As



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Hershey's group in 1952. (l-r) Niccolo Visconti, Martha Chase, Hershey, Constance Chadwick, Neville Symonds, June Dixon, Alan Garen.

suffice. Seymour Cohen, phage course class of 1947, was a leader in this new emphasis on biochemistry. Many workers headed off into bacterial genetics. Phage group scientists interacted with the bacterial geneticists, lecturing in the summer course, sitting in on lab exercises. By then the new stars of this field were youngsters like Evelyn Witkin, Alan Garen, Franklin Stahl, Julius Marmur, Philip Hartman, and Norton Zinder.

Hershey wrote in the compendium he edited on λ , the λ system provided one of the first links between genetics and DNA structure. Such connections are, of course, a hallmark of modern molecular biology.

In 1958, Lwoff, Jacob, and Monod and their colleagues at the Pasteur Institute began their spectacular series of experiments that led to the operon model of the gene as well as to the prediction and subsequent



David Botstein and Alfred Hershey in 1968

demonstration of messenger RNA. At Caltech that same year, Matt Meselson and Frank Stahl developed their Cesium gradient sedimentation technique and demonstrated the semi-conservative replication of DNA predicted by Watson and Crick's double helix model. In 1960, Jacob and Monod published their operon model of the gene. That year also, two groups — Meselson, Sydney Brenner, and François Jacob at Caltech and Jim Watson, François Gros, and Walter Gilbert at Harvard — independently obtained the first experimental evidence for

messenger RNA. Though carried out elsewhere many of these results were presented in the 1961 Symposium at Cold Spring Harbor, where scientists knew they would receive an attentive, critical hearing.

Hershey's group continued working on phage, however. Throughout the 1950s, he and his group continued working on T-series phages, meticulously establishing the detailed mechanism of genetic recombination and phage chromosome structure. They described the process and products of genetic recombination, including the mating event, mechanism of recombination, and relationship between DNA replication and recombination. With Elizabeth Burgi, Hershey studied the composition of the phage chromosome, including demonstrating that noninfective phage DNA is active and functionally equivalent to normal DNA and analyzing the base composition in different segments of the phage chromosome. Anna-Marie Skalka was working in Hershey's group by 1963, studying genetic transcription in K-12/ λ . She did beautiful work using competition experiments characterizing the transcription process and messenger RNA from the various segments of the λ chromosome. Rudolf Werner, another staff member working on phage in the 1960s, examined Jacob's hypothesis that phage replication occurred at one or a very few locations.

In 1966 Demerec made one of his last contributions to science. The informal numerical system of naming bacterial strains that was used in the early days became unwieldy as the field grew. Years earlier, Demerec

devised a system of nomenclature that assigned a unique name to each strain and conveyed some sense about the nature and location of its mutation. E.A. Adelberg and A.J. Clark independently developed a similar system, but when they learned their system was essentially merely a refinement of Demerec's earlier system, they published together, with Demerec as senior author. This effort was typical of some of Demerec's most important contributions; like the *Drosophila* Information Service he developed with Calvin Bridges and the *Drosophila* Stock Center he established at Cold Spring Harbor in the 1920s, the nomenclatural system for bacterial genetics helped unify a growing field and provide common ground for communication. Demerec died later that year.

By the late 1960s, phage research at Cold Spring Harbor was giving way to new work on animal viruses. Delbrück, of course, had a hand in launching this new virus field, when in 1953 he nudged Renato Dulbecco toward animal viruses. Cold Spring Harbor offered its first course on animal viruses in 1958, taught by Herman Oser, with among its students, Purnell Choppin. Two years later, Richard Franklin and Ed Simon took over as instructors before giving way in 1964 to Phil Marcus and Gordon Sato. In 1968, when Jim Watson became director of the Laboratory, he made tumor viruses the main focus of science at Cold Spring Harbor.

IN 1970 the phage course was taught for the last time at Cold Spring Harbor. But phage research itself did not stop and, in



Ahmad Bukhari and Martha Howe in 1975

fact, this was the year that Ahmad Bukhari initiated research on phage Mu here, as a postdoc in David Zipser's lab, having earlier worked with Mu in Denver with Larry Taylor. In 1972 Ahmad Bukhari organized a three-week Mu workshop. According to Ariane Toussaint, the main aim of the workshop was to bring together all the people who had been turning up mutants and prophage deletions, let them get to know one another, and produce a detailed genetic map. It was successful on all counts. Mu research continued at Cold Spring Harbor throughout the 1970s in the labs of Bukhari, David Zipser, Hajo Delius, and Ernesto Bade. Bukhari, Bade and Regine Kahmann began as postdocs with Zipser and later got their own labs; another of Zipser's postdocs, Martha Howe, also made substantial contributions to Mu genetics. Rashika Harshey, who came as a postdoc of Bukhari in 1979, became a staff member in 1981.

Much of the material in later phage courses was incorporated into the bacterial genetics courses of the 1970s. By 1974, bacterial genetics had changed so dramatically that many pioneering techniques were now considered quite basic. To keep the flavor of the vanguard that it had always had, the



Frank Stahl lounging on the lawn with the next generation of bacterial geneticists, 1980.



Harrison (Hatch) Echols

course was renamed "Advanced Bacterial Genetics," taught first by Jeffrey Miller whose highly successful 1972 lab manual *Experiments in Molecular Genetics* (13,100 copies through 1994) presented many of the experiments that had been at the heart of past bacterial genetics courses. After three years, Jeffrey bowed out with David Botstein, Ron Davis, and John Roth presiding in the late 1970s. By this time cloning, recombinant DNA, and the use of transposons as laboratory tools were effecting a major change in molecular biology. The advanced bacterial genetics course offered graduate students, postdocs, and principal investigators an opportunity to learn these techniques and in doing so it spread their use to many new laboratories. Most importantly, the instructors collected their wisdom into a sizable lab manual, *Advanced Bacterial Genetics*, published by the Cold Spring Harbor Laboratory Press in 1980, which brought the new techniques of

recombinant DNA to an even wider audience through the sale of 9,800 copies.

In 1981, Tom Silhavy, Lynn Enquist, and Mike Berman took over the course and introduced the use of gene fusions to analyze gene expression *in vivo*. This period resulted in another influential lab manual, *Experiments with Gene Fusions* (6,312 copies sold). After five years, George Weinstock, Russ Maurer, and Peter Berget took over as instructors. Among their innovations was the introduction of pulsed field gel electrophoresis. In 1991, Stan Maloy, Valley Stewart, and Ron Taylor began leading ABG. In addition to continuing to incorporate the latest techniques, Maloy says they have consciously re-integrated older techniques of classical genetic analysis that still have considerable power. They also maintain a Delbrückian style of exchange, more polite than Delbrück, but with the same intolerance of muddled thinking and shoddy data. Thus, the past traditions of phage and bacterial genetics continue to invigorate this active area of research.

The phage meeting continued uninterrupted through the summer of 1993 but with changed names — "Phage and Bacterial Regulatory Mechanisms" being modified in 1983 to "Molecular Genetics of Bacteria and Phages." For the most part it has remained devoted to basic themes common to all bacteria and so remained a place where basic as opposed to applied science was emphasized.

Clearly, phage and bacterial research and Cold Spring Harbor have a long and mutually reinforcing tradition. This 50th anniversary meeting reflects the blend of history and current science that infuses and invigorates modern phage and bacterial genetics research.

l-r: N. Harter, E. Bade, A. Toussaint, N. Symonds, R. Kahmann in 1978

Gisela Mosig
in 1988Bob Weisberg
in 1978

l-r: J. Newton, A. Hershey, E.R. Signer, J. Davies and R. Davis in 1966