COLD SPRING HARBOR LABORATORY OF QUANTITATIVE BIOLOGY

ANNUAL REPORT 1966

The phototropic response of Phycomyces, shown by a succession of pictures at 5 minute intervals; magnification 20x. (Photograph by Lois Edgar)

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COLD SPRING HARBOR, LONG ISLAND, NEW YORK

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MILISLAV DEMEREC 1895-1966

The evolution of the Laboratories at Cold Spring Harbor was unusual because it could be attributed almost entirely to the vision and enterprise of two men: first, Charles B. Davenport, who was Director of the Carnegie Institution's Department of Genetics until 1941; and second, Milislav Demerec, who succeeded him and was, in addition, the Director of the Long Island Biological Association's Biological Laboratory. The death of Dr. Demerec, in April this year, marks therefore the end of an era—an era that began with the science of genetics in its infancy, when Demerec came to Cold Spring Harbor as a young Ph.D. in 1923, and has ended with molecular biology and the deciphering of the genetic code.

Early in the twenty years of his directorship, Demerec transferred his own interests from classical genetics to microbial genetics and, at the same time, made the Cold Spring Harbor Laboratories into a center for research and post-doctoral training in this new field. This accomplishment, which today can be summarily dismissed in a single sentence, was all the greater because of the unpromising material with which it was wrought. For, at the time he became Director, the Biological Laboratory had suffered some ten years of reduced circumstance and must have seemed an improbable instrument for such a far-seeing and enlightened policy.

With this vision, he combined a remarkable degree of energy, optimism and ingenuity. Numerous legends tell of his flair for achieving great objectives with the simplest of means. Less well known are the difficulties he must have had to overcome in order to accomplish what he wanted.

The Laboratory itself, as it is known today to thousands throughout the world, remains the proper monument to his unfailing endeavor.

DIRECTOR'S REPORT

The introduction to last year's Annual Report reviewed the progress made by the Laboratory in restoring its finances and rehabilitating its physical plant. The Laboratory of Quantitative Biology had, at that time, been in existence for two years, and we were able to report that, thanks primarily to an increase in symposium book sales, the cash position of the Laboratory had been raised to a reasonably healthy level and that we had embarked on a general restoration of the physical plant.

During the past year, the restoration of the physical plant has continued, with the aid of grants from the National Science Foundation and the New York Science and Technology Foundation. We have adhered to our policy of repairing the most valuable and least dilapidated buildings first. As a result, we are at the stage where slightly more than half the total capital value of the buildings, in terms of replacement value, represents buildings that are now fully repaired. This has been accomplished at the cost of about $100,000. At the same time, we have increased the level of spending on general maintenance by about $25,000 per annum, in order to preserve what has been accomplished. The remaining buildings, being in worse shape, will require a further expenditure of about $500,000 if they are to be similarly restored (or, where appropriate, replaced).

During the year, the Long Island Biological Association acquired for the Laboratory from Mrs. de Tomasi five acres of land that lie within the general boundaries of the Laboratory. The importance of this acquisition to the long-term prospects of the Laboratory cannot be over-emphasized.

The third and most important task was to seek some form of endowment which would ensure that the Laboratory can recruit scientific staff. The problem of the lack of endowment has arisen repeatedly in the history of the Laboratory. As long as the Carnegie Institution of Washington carried on its full-scale operation at Cold Spring Harbor, the presence of a year-round scientific staff was assured. However, once it became known that the Carnegie Institution intended to withdraw, the task of creating some form of endowment acquired an urgency which it had not had before. After all, it is only by being able to draw upon some independent funds for some part of each staff member's salary that the Laboratory can consider itself, in any proper sense, the employer of scientists. Without endowment, the staff will inevitably dwindle. And without staff, the Laboratory will cease to exist. It would be fitting, therefore, to be able to say that some start had been made in this quest for endowment. There is, however, no such news to report.

At the end of this year, Dr. Margolin will be leaving the Laboratory to take up a staff appointment at the Public Health Research Institute of the City of New York. This is a severe loss to the Laboratory, for his researches on gene function in bacteria have been exceptionally productive in recent years and he has exerted, each year, a strong influence on the conduct of the summer courses in Microbial Genetics.

Scientifically, the most conspicuous feature of the year was the June symposium on the "Genetic Code." During the past three years and as a result of work in many laboratories throughout the world, the code has been shown to be essentially the same for all forms of life on this planet and has been completely deciphered. The Symposium was the first international meeting expressly devoted to the code itself and the book that results will constitute the most authoritative account of the code. It was not surprising, therefore, that the meeting was the largest ever to be held at Cold Spring Harbor, both in terms of the number of papers presented and the size of the audience.

This year the Laboratory has extended its publishing activity beyond the usual symposium volume and has produced a book of essays by some of Prof. Max Delbrück's collaborators and friends that commemorates his 60th birthday. Although the book could have been produced by any of several publishing houses, it seemed appropriate that it should be published by the Cold Spring Harbor Laboratory. For, Delbrück was responsible for starting, in 1945, the Cold Spring Harbor postdoctoral courses in Microbial Genetics and is at present responsible for the newly-created course in Phycomyces.

The following pages contain reports of the various scientific activities of the Laboratory. Since detailed reports of the Carnegie Institution's Department of Genetics appear in the Yearbook of the Carnegie Institution, only the briefest report is given here.

John Cairns,
Director

BACTERIAL GENETICS

Laboratory of
P. Margolin,
R. Bauerle,
J. Kemper,
S. Friedman

The past year has been devoted to a study of the mechanisms which initiate and regulate gene expression and of the nature of stable aberrations of the chromosome of *Salmonella typhimurium*.

Dr. Jost Kemper has been analyzing the nature of a mutational event which simultaneously affected the leucine gene cluster and the neighboring arabinose gene cluster. The investigations, at this point, have indicated that the initial event probably involved a stable translocation and inversion which led to alterations in cotransducing capacity for that region of the chromosome. Furthermore, crosses with strains bearing other chromosomal aberrations result in recombinant progeny which appear to harbor stable duplications of small segments of the chromosome.

Dr. S. Friedman's studies of a strain harboring an altered operator of the leucine operon have confirmed the previous observations which suggested that the leucine genes were responding to a catabolite repressor. Current evidence suggests that a specific catabolite repressor gene is located between the *cysB* and *trp* gene clusters on the *S. typhimurium* chromosome and that the changed specificity of the altered leucine operator causes it to respond to the catabolite repressor gene product.

Investigations of the functioning of the tryptophan gene cluster by Dr. Ronald Bauerle has revealed that the first enzyme specific to the tryptophan biosynthetic pathway (anthranilate synthetase) consists of a complex of the protein products of the first and second genes of the cluster. The second enzyme of the pathway (phosphoribosyl transferase) is the protein product of the second gene alone, which can carry out the second enzymatic step either while naturally complexed to the first gene product or when artificially isolated from it.

The organization of the tryptophan operon was found to differ from operons studied by other workers. It consists, sequentially, of an operator, a promoter-like element which initiates gene expression, the first two structual genes, a second promoter-like initiating element and the last three structural genes. The presence of the operator is essential for tryptophan regulation of gene expression. However, the presence of the initiating elements alone permits expression of the genes at a low basal constitutive level. The nature of the function of the two initiating elements results in identical rates of synthesis of all the enzyme products of the five tryptophan genes, under conditions of derepression. Under conditions of repression, the products of the last three genes are synthesized at about twice the rate of the products of the first two genes. This latter phenomenon results in an apparent discoordinate regulation of the genes of a single operon.

Studies with chemical mutagens indicate that it is possible to create initiating elements by mutation. The effectiveness of 2-aminopurine suggests that many nucleotide sequences exist which are potential initiating elements for gene expression and which require only a single DNA base-pair transitional mutation to acquire the initiating function.

THE CHROMOSOME OF ESCHERICHIA COLI

Laboratory of J. Cairns, C. I. Davern

Isolation of the bacterial chromosome in one piece. C. I. Davern and P. DeLucia: There are some 2.8 x 10^9 daltons of DNA in the unreplicated chromosome of *Escherichia coli*. The contour length of the unreplicated chromosome, measured by autoradiography (approximately 1mm), corresponds to the length expected if the DNA in the chromosome is contained within a single molecule. Previous attempts at isolating a molecule of DNA of this size from *E. coli* have not been successful. Instead, molecules from ⅛th to 1/16th the chromosome DNA equivalent have been isolated by Berns and Thomas, and by Massie and Zimm. Although great care was taken in both instances to minimize shear, their methods involved sample transfer from the isolation system to the measuring system, and hence some shear must have been unavoidable. Nevertheless, Massie and Zimm felt that the size of the molecules they isolated was a consequence of dissolution of protein linkers joining DNA subunits into a single chromosome structure. In the hope of resolving the problem of the arrangement of DNA in the *E. coli* chromosome, a method was devised for extracting and measuring the size of the isolated DNA in the same system so that the shear associated with transfer was avoided.

The technique used involved the lysis of spheroplasts by means of the dual action of a detergent, Sarkosyl, and the proteolytic enzyme, pronase. The spheroplasts were lysed directly in buffer floating on top of CsC1 solution in which the DNA was to be banded by density gradient equilibrium centrifugation. The measurement of the size of the DNA so isolated was indirect, in that it was based on the assumption that a chromosome, whose DNA was labeled for a portion of its replication cycle with the density marker 5-bromouracil, would only yield DNA banding in the CsC1 gradient at an intermediate position between that of normal and hybrid BU DNA, if it was isolated in one piece.

The DNA extracted from cells, whose chromosomes had been labeled for one-third of a replication cycle, banded with a unimodal distribution at an intermediate density in the gradient, indicating that the chromosome had been isolated in one piece.

It is possible, despite the presence of pronase during this extraction, that conditions may not have been favorable for the dissolution of protein linkers in this experiment, and that Massie and Zimm's model for the chromosome may be correct. The complete solution to this problem must await the isolation of the chromosome in one piece, followed by pronase treatment in the absence of shear, to check for the existence of protein linkers.

The formation of P1 transducing particles in relation to the replication state of the DNA in the E. coli chromosome. C. I. Davern and P. De Lucia: P1 bacteriophage can act as an agent for generalized tranduction. Ikeda and Tomizawa have shown that transducing particles of P1 contain a piece of the host DNA molecule in the place of the P1 DNA molecule. In addition, the transducing particle appears to contain a piece of protein, approximately half a million in molecular weight, and bound covalently to the DNA molecule. This observation, together with the fact that the frequency of transducing particles in a P1 lysate is equivalent to approximately one per burst, suggested the possibility that only a particular region of the chromosome may be suitable for maturation into a transducing particle. Since the phage is a generalized transducer, such a particular region can only be constant in relation to the growing point. This hypothesis was tested by uniformly density-labeling a population of C600 thy-cells with 5-bromouracil for a number of generations, then infecting such a population with P1 at various times after transfer to thymine medium. The change in density gradient profile for a particular transducing particle (that carrying the methionine locus) was measured as a function of transfer time at infection. The change in the profile was continuous with transfer time, and compatible with availability of any region of the chromosome for maturation into a transducing particle.

The organization of DNA in human chromosomes. J. Cairns: Autoradiographs of DNA extracted from cultured human cells, that had been labeled with H^3-thymidine for various periods, were prepared some years ago. But, what with one thing and another, they were not looked at until this year. The results show unexpectedly that the DNA in each chromosome is apportioned into one hundred or more separate sections or replicons, which are joined end-to-end and are duplicated independently. The rate of duplication of these individual sections (in terms of microns of DNA duplicated per minute) is much lower than the duplication rate of bacterial and virus DNA. It remains to be determined whether these findings (which have recently been confirmed by others) have any bearing on the mechanisms of control and differentiation that are used by higher organisms.

MUTAGENIC POLYMERASES

J. Speyer, J. Karam, A. Lenny

Further studies on the mutagenicity of mutants in gene 43 (specifying DNA polymerase) of T4 bacteriophage have been made in an attempt to characterize the kinds of mutations that can be induced by such mutator genes.

In a survey of 40 temperature sensitive mutants in gene 43 we have found 5 with sufficient mutagenicity to cause a striking heterogeneity of plaque morphology in the mutator-carrying stocks. In the appropriate suppressor host some nonsense mutants of gene 43 were found to be mutagenic. For a given nonsense mutant the degree of mutagenicity is suppressor-dependent, as would be expected on the basis of the difference in amino acid substitution effected by these suppressors.

So far only two of these mutagenic mutants, L-56 and L-88, have been studied in connection with their mutagenic specificity. Neither of them can revert frame shift mutations or induce deletions. They differ in their ability to revert various point mutants, thus indicating the possibility of complexity in the catalytic function of the polymerase.

These mutators can at least promote the AT-GC transition in that they stimulate the ochre to amber conversion. Almost all the mutations induced by the mutagenic polymerase are revertible by the same polymerase. This revertibility indicates that base changes are promoted in both directions. As yet it is not known if transversions can be induced by them.

Since different ochre mutations in the same gene are converted by a given mutagenic polymerase with quite different frequencies to amber, its mutagenicity may be affected by the neighboring bases in the DNA.

STRUCTURE AND FUNCTION OF PHAGE DNA's

Laboratory of A. D. Hershey, E. Burgi, R. M. Ehring, L. J. Ingraham, A. M. Skalka, M. G. Smith, R. Werner

Internal Structure of Lambda DNA. Hershey and Burgi: Lambda DNA is unusual among known DNA's in that different parts of the molecule differ considerably in base composition. We found that the left third of the molecule contains 56 per cent guanine-plus-cytosine and that most of the remainder contains only about 47 per cent, but we were unable to pursue the analysis owing to lack of suitable methods.

More recently, Nandi, Wang, and Davidson showed that mercury ions combine preferentially with adenine-thymine base pairs in DNA, and that for a mixture of DNA's the buoyant density of the several mercury complexes in cesium sulfate solution depends strongly on base composition. We and Davern found that separation of DNA's by density-gradient centrifugation could be much improved when tubes were spun in an angle rotor instead of in the usual swinging buckets. By combining these two methods, we have succeeded in learning somewhat more about the internal structure of lambda DNA.

Native lambda DNA forms a single narrow band, confirming other evidence that all the molecules are similar in composition. When the molecules are broken in two and then analyzed in the same way, the fragments separate into three bands. This result, first seen by Laura Ingraham and Anna Marie Skalka, puzzled us for some time. Properly understood, it reveals practically all we know about the structure of lambda DNA. We give first the explanation, then its proof.

What we call half-length fragments of lambda DNA are products of single breaks per molecule. The fragments actually vary in length between one-third and two-thirds of the original molecular length. The molecule itself is made up of at least three dissimilar segments. At the left end is a stretch, measuring about 0.42 of the total length, that is uniform in composition and contains 56 per cent GC (guanine plus cytosine). Next comes a section of length 0.1 to 0.2, containing only 41 per cent GC. The remainder of the right half contains about 46 per cent GC.

According to this model, all fragments including the left molecular end and not exceeding 0.42 in length have the same density and form the left band. Fragments including the left end and exceeding 0.42 in length vary in density depending on length and are increasingly numerous as their length approaches 0.5; they form the middle band. The composition of right ends does not depend strongly on length and all lengths appear in the right band. The observed density distribution can be reconstructed theoretically on the basis of the stated model.

Inman (University of Adelaide) examined in the electron microscope lambda DNA that had been partially denatured by heating. He found a major site of incipient denaturation at the center of molecular length, and two minor acentric sites, presumably in the right half of the molecule. Our finding of a large segment of low GC content at the molecular center is consistent with his results. We haven't yet looked specifically for AT-rich segments near the right end of the molecule, but it is clear that there are no large ones near the left end.

Our results confirm earlier evidence that the right and left ends of the lambda DNA molecule differ by about 10 percentage units in guanine-plus-cytosine content. What does this mean about the composition of individual genes within each segment? In principle this question can be answered by analyzing sufficiently small DNA fragments, as in the following experiment.

P^{32}-labeled DNA recovered from central fractions c · the left and right bands (left molecular ends and right molecular halves, respectively) was fragmented to a molecular weight of 7.5×10^5 (about 1000 nucleotide pairs), and the two preparations were separately analyzed by recentrifugation in Hg-Ca_2SO_4. The results show that left molecular ends contain practically no stretches of 1000 nucleotide pairs with a GC content as low as 46 per cent, and that right molecular halves contain practically no such stretches with a GC content as high as 56 per cent. Thus all or most of the individual genes in each part of the molecule reflect the composition of that part as a whole. This conclusion supports the idea that different genes in a given part of the molecule have unknown functional attributes in common.

For two reasons, this method of analysis underestimates the homogeneity in composition of the small fragments. First, owing to the small size of the fragments, their distributions in the salt-concentration gradient are broadened by diffusion. Second, small fragments exhibit a higher average density in the presence of mercury than does the same DNA in the form of larger pieces. This effect may be the result of the exposure of single-stranded ends at breakage points, the ends combining preferentially with mercury. Whatever its explanation, the effect is not likely to be equal in all fragments, and so may broaden the density distribution for a second reason unrelated to base composition.

We intend to pursue the analysis further, partly to see how far the methods will permit us to go, partly in the hope of relating the peculiar structure of lambda DNA to some of its many functions.

Base-Sequence Homologies. Ingraham, Ehring, Hershey:

Intramolecular homology. In principle, one might expect base-sequence homologies in DNA to reflect both species-specific and gene-specific characters. Species-specific homology could be recognized if different parts of the DNA of a single species interacted more strongly than DNA's of different, unrelated species.

Ehring has found that right and left end quarters of lambda DNA interact as measured by the homology test of Bolton and McCarthy. The interaction is weak but probably sufficient to exclude purely accidental resemblances. Perhaps it is remarkable that any resemblance at all is found in this case, since the two ends of the lambda DNA molecule are quite dissimilar in composition. The example was chosen for technical reasons: left and right ends can be isolated in adequately pure form (ends, by virture of their ability to join to each other; left and right by virtue of their very different buoyant densities in a mixture containing mercury).

The interaction in this instance could, of course, be a special case, perhaps related to the very efficient interaction between the ends of the native molecules. Comparable tests with other parts of the DNA molecule will be more difficult technically but now seem worth a try.

Coli-lambda homology. Cowie and McCarthy of the Dept. of Terrestrial Magnetism of Carnegie Inst. of Washington first demonstrated base-sequence homology between the DNA's of lambda and *E. coli.* Their finding furnished a physical clue to the close relationship between virus and host that is visible at both functional and genetic levels. Cowie and Hershey examined left and right ends of lambda DNA and a segment (b_2^+) defined by a genetic deletion. They found that all three parts of the lambda DNA molecule interacted with *E. coli* DNA. Owing to limitations in the preparative methods then available, they did not stress quantitative aspects of the data, but in fact all their fractionated materials interacted less strongly with bacterial DNA than unfractionated lambda DNA does.

Comparable tests with better materials demonstrate again that all parts of the lambda DNA molecule tested can react with coli DNA. They also show that the strongest reaction occurs with fragments containing 46 per cent GC, derived from the right half of the molecule. This result, together with the weak reaction of short right ends observed by Cowie and Hershey, suggests that there may be a long homologous segment just to the right of the molecular center. We have not yet tried to verify the inference.

The results show clearly that we are able to detect locally specific structural relationships among DNA's. When adequately defined, such relationships ought to be intelligible in terms of biological function.

Lengths of homologous sequences. Results already presented indicate that regions of homology with the bacterial chromosome are dispersed among all large sections of the lambda DNA molecule. How long are these regions?

In experiments of the sort already described, one breaks lambda DNA into fragments about one-eightieth the length of the molecule and asks how many of them can attach to coli DNA and how many cannot. The classification is not black and white, because the answer depends somewhat on the conditions of test, but it is clear that at least 30 per cent can attach specifically.

The results are clear. The fragments bind to lambda DNA with 100 per cent efficiency throughout the molecular-weight range from 160,000 to about 12,000. The efficiency of binding then falls steeply to 15 per cent at 5000 daltons. The loss of ability to bind may be a direct effect of the small size, or may signify unknown side effects of the enzyme.

The same fragments bind to coli DNA with 100 per cent efficiency over the molecular-weight range from 160,000 to nearly 20,000, and still bind with 65 per cent efficiency at 12,000. Thus if fragmentation releases nonhomologous pieces, their average size does not exceed about 10,000 daltons or 30 nucleotides. For purposes of discourse we describe this situation by saying that when a long fragment binds to coli DNA it does so because of base-sequence homology that is imperfect but usually extends the full length of the fragment. The results of other, less careful experiments indicate that this description applies to fragments ranging in size up to at least 4 per cent of the total molecular length. Therefore the 30 per cent homology originally reported by Cowie and McCarthy is distributed over the lambda DNA molecule in not more than eight sections that together span one-third of the molecular length.

Transcription of Lambda DNA in Phage-Infected Bacteria. Skalka: Analysis of messenger RNA formed at different times after infection of bacteria with phase lambda reveals two distinct phases of transcription. During the early phase, transcription is slow, and mainly confined to the AT-rich half of the DNA molecule. During the late phase, transcription is faster, and both halves participate about equally. Skalka reached these conclusions partly by hybridization tests with separated molecular halves of the DNA, partly by analysis of the nucleotide composition of the messenger.

By means of competition experiments, one can determine whether the same or different genes in a given part of the molecule are transcribed at different times. Skalka tested, for example, the ability of unlabeled RNA extracted from cells during the late phase of transcription to compete in the binding of labeled, early-phage messenger to the individual molecular halves of lambda DNA. This type of analysis revealed three categories of messenger produced by transcription from the right half of the molecule: one formed only at early times, one formed only at late times, one formed at both times. RNA produced by transcription from the left half of the molecule could not be clearly subdivided and may represent a single class formed slowly at early times and rapidly at late times.

These results indicate that lambda DNA contains at least four sets of genes whose transcription is subject to independent or semi-independent control. Among these, the one most readily amenable to analysis is the set comprising the GC-rich left end of the molecule, probably genes responsible for directing the synthesis of the structural proteins of the phage particle. It is almost necessary to suppose that these late genes function in response to some signal generated by the functioning of one or more early genes. If so, one has to identify the signal, the signal-generator, and the mechanism of response.

Chloramphenicol is a drug that interferes rather specifically with protein synthesis, not directly with genetic transcription. Skalka finds that addition of the drug to bacterial cultures before or at the time of infection with phage permits messenger synthesis that continues without acceleration for 35 minutes or more. At both early and late times, the messenger synthesized in the presence of the drug resembles early messenger in that it hybridizes preferentially with right halves of lambda DNA. These results suggest that a particular phage-specific protein gives the signal for the late phase of transcription.

Replicating DNA. Smith and Skalka: In bacteria infected with phage lambda, but not, so far, in those infected with T4 or T5, a ring form of DNA can be seen (Young and Sinsheimer; Bode and Kaiser). It apparently consists of two continuous, circular strands forming a supercoiled helix, since it resembles in many respects the structure of that description found in polyoma virus and analyzed by Vinograd. Its formation in lambda-infected bacteria permits a test of the hypothesis that DNA molecules replicate in circular form.

Smith and Skalka find that the ring form of lambda DNA is not a major precursor of the DNA eventually incorporated into phage particles. On the contrary, H^3-thymidine fed to cultures while DNA synthesis is in progress scarcely enters rings at all. Instead it promptly appears in structures that resemble in several respects very long threadlike molecules of DNA. The rings, on the other hand, seem to be formed chiefly from the DNA of the infecting phage particles, and to persist during the course of the infection. This finding is consistent with the results of Bode and Kaiser, who found that DNA from infecting lambda phage particles is converted into rings in "immune" bacteria in which DNA synthesis does not occur.

Evidently the ring form of lambda DNA does not replicate as such. It could play a direct role in initiation of DNA synthesis, or could, as suggested by Bode and Kaiser, be a form of DNA to which replication is expressly forbidden.

Replicating Points in T4 DNA. Werner: A bacterium is supposed to contain a single DNA molecule that replicates at one or a very few growing points to generate Y-shaped structures containing the parental duplex ahead of the fork and two daughter duplexes (one strand parental, one strand newly synthesized) behind the fork. According to ideas of Jacob, Brenner, and Cuzin, this seemingly inefficient way to duplicate a very long DNA molecule is the efficient way to ensure the proper segregation of daughter molecules to daughter cells.

A bacterium infected with phage T4 contains about 17 molecular equivalents of DNA that could be replicating. (The figure cited was measured by Koch and Hershey in 1959 for the related phage T2.) In the past most people assumed that all 17 molecules were replicating, probably independently of one another. The results of Smith and Skalka just presented change the issues somewhat. If several molecular equivalents of DNA are replicating as a single tandem structure there is a segregation problem of sorts, though it places no obvious constraint on the mechanics of replication. However, one can imagine at least three alternatives concerning the number of growing points: one per molecular equivalent of DNA, one per larger hypothetical unit of replication, or one per bacterium. John Cairns pointed out a year or two ago that there was no very compelling reason for ignoring the third alternative and so he is partly responsible for Werner's current activities. Werner also benefits from the advice of Cedric Davern, who was a pioneer in the development of the applicable experimental techniques.

The specific experiment is basically that designed by Bonhoeffer and Gierer some years ago to count the number of growing points in the DNA of a single bacterial cell. They fed C^{14}-labeled 5-bromouracil to growing bacterial cultures for a fraction of a generation time. Under the conditions of their experiment, 5-bromouracil enters DNA in place of thymine. Thus short sections in each branch of the Y immediately behind a growing point should be "hybrid" in structure: one strand containing radioactive 5-bromuracil, the other thymine. All parts of the DNA ahead of or distant from a growing point should contain thymine only. According to these expectations, DNA extracted from the cells and fragmented to sufficiently small size should contain all its radioactivity in hybrid structures. Hybrid structures can be recognized because their buoyant density in cesium chloride is increased in a decided and characteristic manner by the substitution of bromine for methyl groups.

Two measurements are possible. The size of fragments to which the DNA must be reduced in order to liberate radioactive pieces of hybrid density measures the lengths of individual hybrid sections. The total amount of radioactivity incorporated into DNA measures the sum of the lengths of all hybrid sections. This sum, expressed per bacterium and divided by the individual length, gives the number of growing points per bacterium.

Needless to say, there are numerous difficulties in this type of experiment, and still more when it is applied to phage-infected bacteria. Werner believes that he has encountered and circumvented most of them. His experiments so far completed show that there are more than six growing points per bacterium infected with phage T4, and about one per molecular equivalent of phage-precursor DNA in the cells. Apparently the unit of replication is the T4 chromosome as defined by the DNA content of a finished phage particle, and the infected cell contains a number of such units that replicate continuously.

This Symposium was the 31st in the series initiated by the Long Island Biological Association. As usual, many people had a hand in designing the program and adding to its usefulness in many ways. In particular we are indebted to Drs. Crick, Holley, Nirenberg, Speyer, and Watson. There were 88 speakers and the meeting was attended by about 350 people.

OPENING ADDRESS: F. H. C. CRICK, M.R.C. Laboratory of Molecular Biology, Cambridge, England: "The Genetic Code: Yesterday, Today, and Tomorrow."

CODONS IN VITRO

M. NIRENBERG, T. CASKEY, R. MARSHALL, R. BRIMACOMBE, D. KELLOGG, B. DOCTOR, D. HATFIELD, J. LEVIN, F. ROTTMAN, S. PESTKA, M. WILCOX and F. ANDERSON, National Institutes of Health, Bethesda, Maryland: "The RNA code and protein synthesis."

J. H. MATTHAEI, H. P. VOIGT, G. HELLER, R. NETH, G. SCHOCH, H. KUBLER, F. AMELUNXEN, G. SANDER and A. PARMEGGIANI, Max-Planck-Institut, Göttingen, Germany: "Specific interactions of ribosomes in decoding."

H. G. KHORANA, H. BUCHI, H. GHOSH, N. GUPTA, T. M. JACOB, H. KOSSEL, R. MORGAN, S. A. NARANG, E. OHTSUKA and R. D. WELLS, University of Wisconsin, Madison: "Polynucleotide synthesis and the genetic code."

D. SOLL, J. CHERAYIL, D. S. JONES, R. D. FAULKNER, H. HAMPEL, R. M. BOCK and H. G. KHORANA, University of Wisconsin, Madison: "sRNA specificity for codon recognition as studied by the ribosomal binding technique."

H. HAYASHI and K. MIURA, Nagoya University, Nagoya, Japan: "Anticodon sequence as a possible site for the activity of transfer RNA."

C. LETENDRE, A. M. MICHELSON and M. GRUNBERG-MANAGO, Institut de Biologie Physico-Chimique, Paris, France: "Oligonucleotide inhibition of amino acid attachment."

DIRECTIONS OF READING

G. STREISINGER, Y. OKADA, J. EMRICH, J. NEWTON, A. TSUGITA, E. TERZAGHI and M. INOUYE, University of Oregon, Eugene: "Frameshift mutations and the genetic code."

R. THACH, T. A. SUNDARARAJAN, K. F. DEWEY, J. C. BROWN and P. DOTY, Harvard University, Cambridge, Massachusetts: "Translation of synthetic messenger RNA."

W. M. STANLEY, Jr., M. A. SMITH, M. B. HILLE and J. A. LAST, New York University College of Medicine, New York: "Studies on the translation of the genetic message: I. Preparation of oligonucleotide messengers of specified base sequence."

A. J. WAHBA, M. SALAS and W. M. STANLEY, Jr., New York University College of Medicine, New York: "Studies on the translation of the genetic message: II. Translation of oligonucleotide messengers of specified base sequence."

U. MAITRA, S. N. COHEN and J. HURWITZ, Albert Einstein College of Medicine, New York: "Specificity of initiation and synthesis of RNA from DNA templates."

W. SZYBALSKI, H. KUBINSKI and P. SHELDRICK, University of Wisconsin, Madison: "Pyrimidine clusters on the transcribing strand of DNA and their possible role in the initiation of RNA synthesis."

D. S. HOGNESS, W. DOERFLER, J. B. EGAN and L. W. BLACK, Stanford University Medical School, Palo Alto, California: "The position and orientation of genes in λ and λdg DNA."

IN VIVO CODE AND POLARITY

M. E. REICHMANN, A. Y. CHANG, L. FAINMAN and J. M. CLARK, Jr., University of Illinois, Urbana: "The satellite tobacco necrosis virus in studies of genetic coding."

M. G. WEIGERT, E. GALLUCCI, E. LANKA and A. GAREN, Yale University, New Haven, Connecticut: "Characteristics of the genetic code in vivo."

C. YANOFSKY, J. ITO and V. HORN, Stanford University, Stanford, California: "Amino acid replacements and the genetic code."

H. G. WITTMANN and B. WITTMANN-LIEBOLD, Max-Planck-Institut, Tübingen, Germany: "Protein chemical studies of two RNA viruses and their mutants."

A. O. W. STRETTON, S. KAPLAN and S. BRENNER, M. R. C. Laboratory of Molecular Biology, Cambridge, England: "Nonsense codons."

POLARITY

A. NEWTON, Institut Pasteur, Paris, France: "Translation of the *lactose* operon of *Escherichia coli.*"

M. H. MALAMY, Princeton University, New Jersey: "Frameshift mutations in the lactose operon of *E. coli.*"

R. H. BAUERLE and P. MARGOLIN, Cold Spring Harbor Laboratory of Quantitative Biology, New York: "A multifunctional enzyme complex in the tryptophan pathway of *Salmonella typhimurium:* Comparison of polarity and pseudopolarity mutations."

R. G. MARTIN, H. J. WHITFIELD, Jr., D. B. BERKOWITZ and M. J. VOLL, National Institutes of Health, Bethesda, Maryland: "A molecular model of the phenomenon of polarity."

B. N. AMES and H. J. WHITFIELD, Jr., National Institutes of Health, Bethesda, Maryland: "Frameshift mutagenesis in Salmonella."

U. HENNING, G. DENNERT, R. HERTEL and W. S. SHIPP, University of Cologne, Germany: "Translation of the structural genes of the *E. coli* pyruvate dehydrogenase complex."

F. IMAMOTO, J. ITO and C. YANOFSKY, Stanford University, California: "Polarity in the tryptophan operon of *E. coli*."

PUNCTUATION

N. D. ZINDER, D. L. ENGELHARDT and R. E. WEBSTER, Rockefeller University, New York: "Punctuation in the genetic code."

G. N. GUSSIN, M. R. CAPECCHI, J. M. ADAMS, J. E. ARGETSINGER, J. TOOZE, K. WEBER and J. D. WATSON, Harvard University, Cambridge, Massachusetts: "Protein synthesis directed by RNA phage messengers."

M. C. GANOZA, Rockefeller Univerity, New York: "Polypeptide chain termination in cell-free extracts of *E. coli*."

K. A. MARCKER, B. F. C. CLARK, J. S. ANDERSON, MRC Laboratory of Molecular Biology, Cambridge, England: "N-formyl-methionyl-sRNA and its relation to protein biosynthesis."

H. DICKERMAN, E. STEERS, B. G. REDFIELD and HERBERT WEISSBACH, National Heart Institute, Bethesda, Maryland: "Formylation of *Escherichia coli* methionyl-sRNA."

M. S. BRETSCHER, MRC Laboratory of Molecular Biology, Cambridge, England: "Polypeptide chain initiation and the characterization of ribosomal binding sites in *E. coli*."

P. LEDER and H. BURSZTYN, Weizmann Institute of Science, Rehovoth, Israel: "Initiation of protein synthesis. The role of formyl-accepting methionyl-tRNA."

A. RICH, E. EIKENBERRY and L. MALKIN, Massachusetts Institute of Technology, Cambridge, Massachusetts: "Experiments on hemoglobin polypeptide-chain initiation and on the shielding action of the ribosome."

CONTROL OF GENE EXPRESSION

P. MARGOLIN and R. H. BAUERLE, Cold Spring Harbor Laboratory of Quantitative Biology, Cold Spring Harbor, N. Y.: "Determinants for regulation and initiation of expression of tryptophan genes."

A. L. CLINE and R. M. BOCK, University of Wisconsin, Madison: "Translational control of gene expression."

P. I. MARCUS and J. M. SALB, Albert Einstein College of Medicine, New York: "Control of viral RNA translation as the mechanism of interferon action."

D. SHEPPARD and E. ENGLESBERG, University of California, Santa Barbara: "Positive control in the l-arabinose gene-enzyme complex."

G. M. TOMKINS, E. B. THOMPSON, S. HAYASHI, T. GELEHRTER, D. GRANNER and B. PETERKOFSKY, National Institutes of Health, Bethesda, Maryland: "Tyrosine transaminase induction in mammalian cells in tissue culture."

P. A. MARKS and F. CONCONI, Columbia University College of Physicians and Surgeons, New York: "Polyribosomes and control of hemoglobin synthesis."

S. NAONO and F. GROS, Institut de Biologie Physico-Chimique, Paris, France: "Control and selectivity of λ DNA transcription in lysogenic bacteria."

A. SKALKA, Genetics Research Unit, Carnegie Institution of Washington, Cold Spring Harbor, New York: "Multiple units of transcription in phage lambda."

O. SIDDIQI, B. N. APTE and M. P. PITALE, Tata Institute of Fundamental Research, Bombay, India: "Genetic regulation of aryl sulphatases in *Aspergillus nidulans*."

J. R. ROTH, D. F. SILBERT, G. R. FINK, M. J. VOLL, D. ANTON, P. E. HARTMAN and B. N. AMES, National Institutes of Health, Bethesda, Maryland and Johns Hopkins University, Baltimore, Maryland. "Transfer RNA and control of the histidine operon."

J. R. BECKWITH, E. R. SIGNER and W. EPSTEIN, Institut Pasteur, Paris, France and Harvard Medical School, Boston, Massachusetts: "Transposition of the *lac* region of E. coli.

J. SCAIFE and J. R. BECKWITH, Harvard Medical School, Boston, Massachusetts: "Mutational alteration of the maximal level of *lac* operon expression."

TRANSFER RNA: CHEMISTRY

J. T. MADISON, G. A. EVERETT and H. K. KUNG, U. S. Department of Agriculture, Ithaca, New York: "Yeast tyrosine tRNA."

H. G. ZACHAU, D. DUTTING, H. FELDMAN, F. MELCHERS and W. KARAU, University of Cologne, Germany: "Serine-specific transfer ribonucleic acids. XIV. Comparison of nucleotide sequences and secondary structure models."

U. L. RAJBHANDARY, A. STUART, R. D. FAULKNER, S. H. CHANG and H. G. KHORANA, University of Wisconsin, Madison: "Nucleotide sequence studies on yeast phenylalanine sRNA."

P. L. BERGQUIST, University of Auckland, New Zealand: "Degenerate transfer RNAs from Brewers yeast."

M. N. LIPSETT, National Institutes of Health, Bethesda, Maryland: "Disulphide bonds in soluble RNA."

R. H. DOI and B. GOEHLER, University of California, Davis: "Conformation and binding efficiency of lysyl-tRNA."

R. S. HAYWARD, G. L. ELICIERI and S. B. WEISS, Argonne Cancer Research Hospital and University of Chicago, Illinois: "Ribonucleic acid sulfurtransferase activity."

J. OFENGAND, University of California Medical Center, San Francisco: "A new nucleotide in the tRNA of *E. coli*."

B. WEISS and C. C. RICHARDSON, Harvard Medical School, Boston, Massachusetts: "End-group labeling of nucleic acids by enzymatic phosphorylation."

TRANSFER RNA: FUNCTION

J. D. SMITH, J. N. ABELSON, B. F. C. CLARK, H. M. GOODMAN and S. BRENNER, MRC Laboratory of Molecular Biology, Cambridge, England: "Studies on *amber* suppressor tRNA."

J. CARBON, P. BERG and C. YANOFSKY, Stanford University School of Medicine, Palo Alto, California: "Missense suppression due to a genetically altered tRNA."

N. K. GUPTA and H. S. KHORANA, University of Wisconsin, Madison: "Missense suppression on tryptophan synthetase."

U. Z. LITTAUER, M. REVEL and R. STERN, Weizmann Institute of Science, Rehovoth, Israel: "Coding properties of methyl-deficient phenylalanine transfer RNA."

A. PETERKOFSKY, C. JESENSKY and J. D. CAPRA, National Institutes of Health, Bethesda, Maryland: "The role of methylated bases in the biological activity of *E. coli* leucine tRNA."

E. WAINFAN, P. R. SRINIVASAN and E. BOREK, Columbia University, New York: "Can the methylation of tRNA serve a regulatory function?"

J. R. FRESCO, A. ADAMS, R. ASCIONE, J. GREER, D. HENLEY and T. LINDAHL. Princeton University, New Jersey: "Divalent Cations and the Molecular Structure of Functional Transfer RNAs."

K. H. MUENCH, University of Miami School of Medicine, Miami, Florida: "Chloroquine-mediated conversion of transfer ribonucleic acid of *Escherichia coli* from an inactive to an active state."

TRANSFER RNA: INTERACTIONS

B. P. DOCTOR, J. E. LOEBEL and D. A. KELLOGG, Walter Reed Army Institute of Research, Washington, D.C.; "Studies on the species specificity of yeast and *E. coli* tyrosine tRNAs."

W. E. BARNETT and J. L. EPLER, Oak Ridge National Laboratory, Oak Ridge, Tennessee: "Multiple aminoacyl-RNA synthetase systems and the genetic code in Neurospora."

F. C. NEIDHARDT and C. F. EARHART, Purdue University, Lafayette, Indiana: "Phage-induced appearance of a valyl sRNA synthetase activity in *Escherichia coli*."

C.-T. YU, Rockefeller University, New York: "Multiple forms of leucyl sRNA synthetase of *E. coli*."

N. SUEOKA, T. KANO-SUEOKA and W. J. GARTLAND, Princeton University, New Jersey: "Modification of sRNA and regulation of protein synthesis."

R. H. DOI and I. KANEKO, University of California, Davis: "Transfer RNA patterns of *Bacillus subtilis* during sporulation and growth."

H. SUBAK-SHARPE, W. M. SHEPHERD and J. HAY, University of Glasgow, Scotland: "Studies on sRNA coded by Herpes virus."

TRANSFER RNA AND RIBOSOMES

F. O. WETTSTEIN, University of California, Berkeley: "Differential in vivo aminoacylation and utilization of homologous species of *E. coli* transfer RNA."

C. S. McLAUGHLIN, J. DONDON, M. GRUNBERG--MANAGO, A. M. MICHELSON and G. SAUNDERS, Institut de Biologie Physico-Chimique, Paris, France: "Stability of the messenger RNA-sRNA-ribosome complex."

M. TAKANAMI, University of California, Berkeley: "The 5'-termini of *E. coli* ribosomal RNA and f2 bacteriphage RNA."

D. HATFIELD, National Institutes of Health, Bethesda, Maryland: "Oligonucleotide-ribosome-AA-sRNA interactions."

J. G. FLAKS, P. S. LEBOY, E. A. BIRGE and C. G. KURLAND, University of Pennsylvania and University of Wisconsin: "Mutations and genetics concerned with the ribosome."

R. HEINTZ, H. McALLISTER and R. SCHWEET, University of Kentucky, Lexington: "The active ribosome complex."

S. PESTKA and M. NIRENBERG, National Institutes of Health, Bethesda, Maryland: "Codeword recognition on 30 S ribosomes."

INFIDELITY OF INFORMATION TRANSFER

L. GORINI, G. A. JACOBY and L. BRECKENRIDGE, Harvard Medical School, Boston, Massachusetts: "Ribosomal ambiguity."

J. DAVIES, Harvard Medical School, Boston, Massachusetts: "Streptomycin and the genetic code."

I. B. WEINSTEIN, S. M. FRIEDMAN and M. OCHOA, Jr., Frances Delafield Hospital, New York: "Fidelity during translation of the genetic code."

B. J. McCARTHY, J. J. HOLLAND and C. A. BUCK, University of Washington, Seattle and University of California, Irvine: "Single-stranded DNA as a template for in vitro protein synthesis."

J. F. SPEYER, J. D. KARAM and A. B. LENNY, Cold Spring Harbor Laboratory, New York: "On the role of DNA polymerase in base selection."

G. E. MAGNI and P. P. PUGLISI, University of Parma, Italy: "Mutagenesis of super-suppressors in yeast."

G. VON EHRENSTEIN, Johns Hopkins University School of Medicine, Baltimore, Maryland: "Translational variations in the amino acid sequence of the α-chain of rabbit hemoglobin."

D. B. RIFKIN, D. I. HIRSH, M. R. RIFKIN and W. KONIGSBERG, Rockefeller University, New York and Yale University Medical School, New Haven, Connecticut: "A possible ambiguity in the coding of mouse hemoglobin."

K. B. JACOBSON, Oak Ridge National Laboratory, Oak Ridge, Tennessee: "A test of tRNA as amino acid adaptor in hemoglobin synthesis."

ORIGINS OF THE CODE

C. R. WOESE, D. H. DUGRE, S. A. DUGRE, M. KONDO and W. C. SAXINGER, University of Illinois, Urbana: "On the fundamental nature and evolution of the genetic code."

H. SUBAK-SHARPE, R. R. BURK and L. V. CRAWFORD, University of Glasgow, Scotland: "An approach to evolutionary relationships of mammalian DNA viruses through analysis of the pattern of nearest neighbor base sequences."

POST GRADUATE TRAINING COURSES

Summer 1966

Many new fields have been developing in biology during the last ten years that do not fall into any particular subject but equally involve biochemistry, biophysics and genetics. As a result, most research workers have had to enlarge the extent of their professional competence: the biochemist has at last been forced to familiarize himself with genetics, and the geneticist has had to learn some biochemistry. This process of re-education, which could only be carried out with difficulty in most universities, tied as these are to a rigid curriculum, is being accomplished through a series of courses for qualified scientists held each summer at Cold Spring Harbor. The courses are given by a staff drawn from institutions all over the world and have already been attended by many hundreds of scientists drawn from disciplines as far apart as medicine and nuclear physics. In conjunction with these courses, the Laboratory invites about 50 prominent investigators as seminar speakers. This program of seminar speakers provides an extensive review of current research in these fields.

During the summer of 1966, four courses were given, designed to acquaint the student with some of the techniques used in bacterial virus research, in bacterial genetics research, in the microbiology of animal viruses, and cultured animal cells, and in the physiology of Phycomyces. Each course consisted of intensive laboratory and discussion periods, as well as formal seminars.

1) BACTERIAL GENETICS: June 15th to July 6th.

Dilution and plating techniques; mode of origin of bacterial variants; induction of mutation; isolation and characterization of auxotrophs; mutagen specificity and reversions; sexual recombination and genetic mapping in *Escherichia coli;* transduction and determination of the linear order of mutational sites in *Salmonella typhimurium;* abortive transductions; characterization of suppressors and reversions by transduction; isolation and characterization of transforming DNA; transformation in *B. subtilis* and *H. influenzae.*

INSTRUCTORS:

S. H. Goodgal, University of Pennsylvania
J. Gross, Microbial Genetics Research Unit, London
P. Hartman, Johns Hopkins University
Assistant: E. Ehlinger

SEMINARS:

Ernst Freese, National Institutes of Health: "The regulation of alanine and alanine dehydrogenase in Bacillus subtilis."
Ethan Signer, Institut Pasteur: "Transposition of the Lac Operon of *E. coli.*"
Chandler Fulton, Brandeis University: "Round and round the *E. coli* chromosome goes."
Paul Margolin, Cold Spring Harbor Lab.: "Lox mutation's eye view of a bagel."
H. Ozeki, National Institutes of Health, Tokyo, Japan: "Transduction of λ Phage in P1 by *E. coli.*"
Alan Garen, Yale University: "In Vivo characteristics of the Genetic Code."
Mario Capecchi, Harvard University: "Studies on in vitro protein synthesis."
Sanford Lacks, Brookhaven National Laboratory: "Identification of single-site and multi-site mutations in Pneumococcus."
Julius Marmur, Albert Einstein Med. School: "Studies on the B. subtilis chromosome."
Richard Novick, New York Public Health Research Institute of New York: "Genetic control of plasmid replication and maintenance in S. aureus."
Robert Martin, National Institutes of Health: "Translation of the histidine operon — nonsense."

STUDENTS:

Israel D. Algranati, Ph.D., New York University Medical Center, New York
Andrew J. Becker, Ph.D., Albert Einstein College of Medicine, New York
Robert J. Bishop, M.S., Princeton University, New Jersey
Giovanni R. Cassani, Dr. Pharm. Chem., University of Kentucky, Lexington, Ky.
John H. Caster, B.S., St. Louis University, Missouri
Stanley N. Cohen, M.D., Albert Einstein College of Medicine, New York
Francesco, DeLorenzo, M.D., NIAMD, National Institutes of Health, Bethesda, Maryland
Martin Dworkin, Ph.D., University of Minnesota, Minneapolis
Audree V. Fowler, Ph.D., University of California, Los Angeles
Tadeusz Klopotowsky, Dr. Med. Sc., Polish Academy of Sciences, Warsaw, Poland
Samuel W. Luborsky, Ph.D., National Institutes of Health, Bethesda, Maryland
William H. McClain, B.S., Purdue University, Lafayette, Indiana
Wim J. Möller, Ph.D., Johns Hopkins University, Baltimore, Md.
George W. Rayfield, Ph.D., University of Pennsylvania, Phila.
Margarita Salas, Ph.D., New York University School of Medicine, New York, N. Y.

Masao Takeda, Ph.D., The Rockefeller University, New York
Joel S. Trupin, Ph.D., National Heart Institute, National Institutes of Health, Bethesda, Md.
Eladio Vinuela, Ph.D., New York University School of Medicine, New York
H. Hollis Wickman, Ph.D., Bell Telephone Laboratories, Murray Hill, New Jersey
Robert Yuan, B.S., Albert Einstein College of Medicine, Bronx, New York

2) BACTERIAL VIRUSES: July 10th to July 31st.

Preparation and assay of virus; isolation of virus-resistant bacterial mutants; resistance patterns of bacterial mutants; serological classification of viruses; kinetics of neutralization of virus by antiserum; one-step growth; estimation of intracellular virus; bursts from single cells; isolation of virus mutants; chemical induction of virus mutants; genetic recombination in phage T4 and phage T1; fine structure mapping and complementation tests with rII mutants; ultraviolet inactivation and photoreactivation; multiplicity reactivation; inactivation of genetic markers and gene function; lysogenic bacteria and temperate viruses; lysogenization and transduction.

INSTRUCTORS:

Millard Susman, University of Wisconsin
Frances Womack, Vanderbilt University
Assistant: Mrs. Wojtowicz

SEMINARS:

C. A. Thomas, Johns Hopkins University: "Phages, circles and terminal redundancies."
Fred Frankel, University of Pennsylvania: "On observing vegetative DNA."
D. J. McCorquodale, Mass. Inst. of Tech.: "The little piece in T5 injection and function."
Robert Haselkorn, University of Chicago: "Synthesis and function of messenger RNA in T4-infected *E. coli*."
Ann Skalka, Carnegie Inst. of Washington: "Structure and function of λ DNA."
Charles Radding, University of Michigan: "Physiological genetics of phage λ."
Edward Kellenberger, University of Geneva and Kansas State University: "Electron microscope studies on morphopoiesis of T4."
Edward Goldberg, Tufts University: "Correlation of physical and genetic length in T4."
J. Karam, Cold Spring Harbor Lab.: "Mutagenesis by the DNA Polymerase in T4."
Gisela Mosig, Vanderbilt University: "Distances separating genetic markers in T4 DNA."
R. S. Edgar, California Inst. of Technology: "The head bone connected to the tail bone."

STUDENTS:

Andrew J. Becker, Ph.D., Albert Einstein College of Medicine, Bronx, N. Y.
Florence Cahn, B.A., Massachusetts Institute of Technology, Cambridge, Mass.
John H. Caster, B.S., St. Louis University School of Medicine, St. Louis, Mo.
Ananda M. Chakrabarty, Ph.D., Biochemistry Division, University of Illinois, Urbana, Illinois
Stanley N. Cohen, M.D., Developmental Biology, Albert Einstein College of Medicine, Bronx, New York
David B. Fankhauser, B.A., Johns Hopkins University, Baltimore, Maryland
Maria C. Ganoza, Ph.D., National Institutes of Health, Bethesda, Maryland and the Rockefeller University, New York, N.Y.
Max E. Gottesman, Ph.D., The Rockefeller University, New York, N.Y.
Theodore Gurney, Jr., Ph.D., Massachusetts Institute of Technology, Cambridge, Mass.
Jost Kemper, Ph.D., Cold Spring Harbor Laboratory of Quantitative Biology, Cold Spring Harbor, New York
Stanley P. Leibo, Ph.D., Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee
Daniel H. Levin, Ph.D., Lab. of Biophysics, Division of Laboratories, Beth Israel Medical Center, New York, N.Y.
Leon J. Lewandowski, B.S., Wistar Institute, Philadelphia, Pennsylvania
Carl R. Merril, M.D., National Institutes of Health, Bethesda, Maryland
Wim J. Möller, Ph.D., Dept. of Biophysics, Johns Hopkins University School of Medicine, Baltimore, Maryland.
Harold C. Neu, M.D., Dept. of Medicine, Columbia University College of Physicians and Surgeons, New York, N.Y.
John W. Quigley, M.S., Rutgers University, New Brunswick, N.J.
Woollcott K. Smith, M.S., Statistics Dept., Johns Hopkins University, Baltimore, Maryland
Hiroko Watanabe, M.D., Royal Victoria Hospital, Montreal, Canada.
Robert Yuan, B.S., Dept. Molecular Biology, Albert Einstein College of Medicine, Bronx, New York.

3) MICROBIOLOGY OF VERTEBRATE CELLS AND QUANTITATIVE ANIMAL VIROLOGY: August 4th to August 25th.

INSTRUCTORS:

P. I. Marcus, Albert Einstein College of Medicine
G. Sato, Brandeis University
Assistants: H. Lipshitz, Mrs. Gurney

SEMINARS:

H. Eagle, Albert Einstein College of Med.: "Biochemistry of Cultured Mammalian Cells."
R. Robbins, Albert Einstein College of Med.: "Cell ultrastructure, function, and life cycle."
S. Dales, Rockefeller University: "Electron microscopy of Animal Viruses."
E. Pfefferkorn, Harvard Medical School: "Use of conditional-lethal mutants to study the genetics and biochemistry of an arbovirus."
J. Darnell, Albert Einstein College of Med.: "RNA Synthesis in Normal and Poliovirus-infected cells."
D. Summers, Albert Einstein College of Med.: "The Function and Products of the Polycistronic Poliovirus mRNA."
G. Sato, Brandeis Universitv: "*In vitro* Studies on Differentiated Cells."
H. Hanafusa, Public Health Research Institute of the City of New York: "Rous Sarcoma Virus Defectiveness."
J. Littlefield, Harvard University: "Hybridization of Cells in Culture."
Kenneth Paigen, Roswell Park Memorial Inst.: "Genetic Regulation Mechanisms in Higher Organisms."
H. Temin, University of Wisconsin: "Carcinogenesis by Rous Sarcoma Virus."
L. Sachs, Weizmann Inst. of Science: "An *in vitro* analysis of the mechanism of carcinogenesis."
P. I. Marcus, Albert Einstein College of Med.: "Translation as a Control Mechanism in normal, cancer, and interferon-treated Cells."
W. Joklik, Albert Einstein College of Med.: "Nucleic acid Synthesis in HeLa Cells infected with Vaccinia virus."
I. Tamm, Rockefeller University: "Replication of Drug-sensitive, Resistant or Dependent Picorna Viruses."
R. Franklin, University of Colorado Med. School: "The Structure of Replicating Viral RNA."
R. Simpson: "The Genetics of Animal Viruses."

STUDENTS:

Stanley Cohen, Ph.D., Dept. of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee
Clarence Colby, Jr., B.S., University of Kentucky, Lexington, Kentucky
Harry V. Gelboin, Ph.D., Chemistry Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland
Gisela Mosig, Dr. rer. nat., Dept. of Molecular Biology, Vanderbilt University, Nashville, Tennessee
Yozo Nakata, M.D., Ph.D., Division of Biology, Albert Einstein College of Medicine, Bronx, New York
Richard Roblin, M.S., Biological Laboratories, Harvard University, Cambridge, Massachusetts
David Schechter, M.D., Dept. of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts
Arthur B. Schneider, B.S., School of Medicine, University of Chicago, Chicago, Illinois
Wendell M. Stanley, Jr., Ph.D., Dept. of Biochemistry, New York University Medical School, New York.
Richard A. Steeves, M.D., Dept. of Medical Biophysics, University of Toronto, Ontario, Canada
Norman Talal, M.D., NIAMD, National Institutes of Health, Bethesda, Md.
Mamoru Watanabe, Ph.D., Dept. of Molecular Biology, Albert Einstein College of Medicine, Bronx, New York
Charles Weissmann, Ph.D., Dept. of Biochemistry, NYU School of Medicine, New York, N.Y.
Robert G. Wilson, Ph.D., Chemistry Branch, Carcinogenesis Studies, National Cancer Institute, NIH, Bethesda, Maryland

4) PHYCOMYCES COURSE: August 4th to August 25th.

Life cycle (sexual and asexual); production and germination of zygotes; growth of excised sporangiophores and uptake of labeled compounds, chromatography of single sporangiophores; iron lung experiments; photoplasmic streaming, microscopic observation of growing zone; observation of photogrowth response; experiments on dark adaptation; sunrise experiments; phototropic responses with blue light in air, oil and water; stationary responses on turntable; Shropshire's proof of lens effect; phototropic inversion of Reichardt, Varju and Castle.

During the course a number of new experiments and techniques were attempted. The most startling of these concerns dark adaptation which occurs at a rate that apparently is independent of temperature.

INSTRUCTORS:

M. Delbrück, California Institute of Technology
D. S. Dennison, Dartmouth College
W. Shropshire, Smithsonian Institution
Assistant: Lois Edgar

SEMINARS:

Thurm, (1) "Comparative ultrastructure of ciliary sensory receptors"
(2) "Comparison of the acoustico-laterals sensory system with mechano-sensitivity of motile cilia"
(3) "Properties of microtubules and ciliary rootlet filaments"

Shropshire, "Phytochrome"

STUDENTS:

Kostia Bergman, B.A., Biology Division, California Institute of Technology, Pasadena, Calif.
Donald S. Berns, Ph.D., Division of Laboratories & Research, New York State Dept. of Health, Albany, New York
Mark S. Guyer, B.A., Amherst College, Amherst, Massachusetts
Martin A. Heisenberg, Doktor-Examen, University Tubingen, Germany
David Kotelchuck, Ph.D., Physics Department, Vanderbilt University, Nashville, Tenn.
Gerhard Meissner, Dr. rer. nat., Technical University, Berlin, Germany
William D. Phillips, Ph.D., Central Research Department, E. I. duPont de Nemours Company, Experimental Station, Wilmington, Delaware
Burton M. Pogell, Ph.D., Dept. of Biochemistry, Albany Medical College of Union University, Albany, New York
Ronald H. Ruby, Ph.D., University of California, Santa Cruz, Calif.
Ulrich Thurm, Max-Planck-Institut-für Biologie, Tübingen, Germany
Rudolf K. Werner, Dr. rer. nat., Carnegie Institution of Washington, Genetics Research Unit, Cold Spring Harbor, N.Y.

SUMMER GUEST INVESTIGATORS

Originally conceived as an informal, summer haven where scientists may meet their colleagues, the laboratories at Cold Spring Harbor continue to play host to a group of active workers who spend the summer here. They come to teach the courses, pursue independent projects, write, and collaborate with others in related fields.

In the informal summer atmosphere at Cold Spring Harbor, the scientific activities are enhanced intellectually by the presence of this group.

SUMMER GUEST INVESTIGATORS

R. Haselkorn; University of Chicago
T. August, L. Shapiro, P. Klein, G. Meadors, M. A. Murphy, H. Watanabe, M. Watanabe; Albert Einstein College of Medicine
S. Colowick, M. Colowick, P. Cassidy; Vanderbilt University
S. Goodgal, J. Michalka, J. Gunther; University of Pennsylvania
M. Fox, D. Brown, G. Cooper, T. Gurney, E. Kataja, R. White; Massachusetts Institute of Technology
R. Novick, L. Fooner; Public Health Research Institute of the City of New York
I. C. Gunsalus, C. F. Gunsalus, A. Chakrabarty, S. Frean, K. Kreiss, S. W. Queener; University of Illinois
K. Paigen; Roswell Park Memorial Institute of Health Research

REPORTS OF SUMMER GUEST INVESTIGATORS

SUPPRESSION OF PHAGE MUTANTS BY OCHRE SUPPRESSORS

R. Haselkorn

1. *RNA phage.* In order to study induction of the ochre (UAA) to amber (UAG) transition by fluorouracil in vivo, thereby obtaining evidence for or against participation of the complementary strand in RNA phage replication, it was necessary to isolate an ochre mutant of an RNA phage. The phages Qβ, MS-2, and f_{Can} were tested on the following strains: CA 165 (*su* B), H12R7a (*su* 4) and U11R1d (*su* 5). All phages gave unsuitable plaques on *su* B. The efficiency of plating of Davern's set of MS-2 ambers was found to be 0.1 to 0.2 for most ambers on *su* 4 and *su* 5, relative to CR63. However, several hundred plaques of a nitrous acid treated stock were picked on *su* 4 and *su* 5, without finding a single ochre. Individual plaques of the MS-2 ambers plated on *su* 4 were then tested by replating and found to contain 10-50% revertant phage. It seems likely

that the poor suppression by ochre suppressors coupled with the large burst size for RNA phage makes it impossible to isolate ochre mutants.

2. *T4.* One result of interest from the preceding work is that *su* 4 and *su* 5 do transmit RNA phage ambers. On the other hand they fail to transmit amber or ochre mutants of T4 in the rII cistrons. In order to determine whether this lack of transmission was general for T4 ambers, a set of mutants in gene 43 (DNA polymerase) was tested. Of 20 mutants, 13 plate on *su* 4 and 10 plate on *su* 5. Another set of ambers in genes involved with late functions was tested, and all failed to plate on either strain, with the exception of amber H26 (lysozyme) which plates on *su* 4. Thus, *su* 4 and *su* 5 behave similarly to the Cambridge ochre suppressor strains, in that they transmit only those T4 ambers whose lesion is in a protein required in small amounts.

The pattern of suppression of the 20 mutants in gene 43 is very characteristic for a given suppressor, offering the potential for classification of suppressor strains. To this end they were tested on Yanofsky's suppressors, called amber 1, 2, and 3, and ochre A, B, and C. From the patterns, it appears that Yanofsky's am 2 and am 3 are identical and similar to Garen-Brenner am 2. Yan ochre A is similar to *su* 5, Yan ochre B is similar to Brenner *su* B, and Yan ochre C is similar to *su* 4, which in turn is probably identical with Brenner *su* C. However, the Yanofsky strains, which are derivatives of W3110, are more efficient than their Garen counterparts, which are derived from HfrC. For example, the spot tests on *su* 4 and Yan *su* C are consistent for 18 of the 20; 2 which are minus on *su* 4 are positive on *su* C. The agreement between *su* 5 and *su* A is for 16 of the 20; 4 which are minus on *su* 5 are positive on *su* A. Finally, Yan ochre B suppresses several ambers in structural genes (am A355, A452, E18) which are not suppressed by any other known ochre suppressor strain.

3. *Lambda.* The preceding results suggest that the efficiency of ochre suppression can depend upon the background within which the suppressor must operate. To determine to what extent these results are unique to T4 infection, the Garen strains were cured of lambda by displacement with λ_{i434}, and then tested for their ability to suppress λ_{sus} mutants. In general, all λ_{sus} mutants in cistrons A-E (concerned with head formation) plate on *su* 4 and *su* 5. The plating efficiencies range from 0.01 to 1, relative to C600. λ_{sus} mutants in cistrons G-L also plate on both strains. The efficient suppression of the mutants in cistrons A-E suggests that T4 puts a greater strain upon the capacity for ochre suppression than does lambda.

The results with T4 ambers suggest that the ratio of suppressor to anti-suppressor (chain terminating sRNA?) for a given suppressor can be host dependent. The comparison with lambda further suggests that this ratio is altered by T4 infection. In the case of a particular missense suppressor, Carbon, Berg, and Yanofsky found the strain-dependent level of suppression to be due to different levels of an amino acid activating enzyme, although the su+ gene product is an sRNA. While such a model accounts for the strain-dependent nonsense suppression we observed, it is also possible that the constitutive level of chain-terminating sRNA (for example) varies from strain to strain.

RNA BACTERIOPHAGE

T. August,
L. Shapiro,
P. Klein,
G. Meadors,
M. A. Murphy,
H. Watanabe,
M. Watanabe

The activities at Cold Spring Harbor this summer were primarily concerned with studies of RNA bacteriophage.

Following on work carried out during previous summers, some 56 RNA phage isolates were tested by Miss M. A. Murphy and Dr. M. Watanabe for their immunologic relatedness to phage R-23. R-23 is immunologically similar to a large group of RNA phage, f2, MS2, R-17 and others, with the exception of Qβ. Three phage isolates, all from Glen Cove sewage, and probably containing a single phage type, were found to be completely resistant to antisera to R23. Other biologic, biochemical, and physical properties of this phage are now being pursued.

Genetic studies were initiated with the isolation of amber mutants of R-23 and Qβ by Mr. G. Meadors and Dr. H. Watanabe. By use of the nitrous acid technique of mutagenesis, some 25 mutants were isolated. These mutant phage are to be used in studies of certain biochemical properties of RNA phage replications.

Dr. T. August continued a research program currently centered on the purification and characterization of the RNA-dependent RNA polymerase of Qβ infected *E. coli.* Significant progress was attained during the summer in arriving at a large scale, 200-fold purification. Dr. L. Shapiro studied some of the immunologic properties of this Qβ RNA

polymerase to determine whether the enzyme is synthesized *de novo* or is related to the host RNA polymerase. Further biochemical studies were carried out by Mr. P. Klein in the isolation of DNA polymerase.

THE rII GENE

S. Colowick,
M. Colowick,
P. Cassidy

We continued our studies to determine whether the physiological defect in rII mutants of bacteriophage T4 may be due to a failure in ATP synthesis in the infected cells. Using an improved method for measuring ATP content, we confirmed that K12(λ) cells infected with rII mutant phage show a sharp fall in ATP content at around 8 to 10 minutes after infection, while cells infected with wild type phage show a sustained rise in ATP content. This observation was extended to a variety of hosts containing the rII-blocking prophage λ. Prior to this abrupt fall, the time course of the ATP changes is quite similar in the cells infected with wild type or mutant phage, showing a sharp initial drop in ATP content at 1 to 1.5 minutes after infection, followed by a rise to above the initial level. Phage ghosts prepared by osmotic shock of either the wild type or mutant phage caused a very rapid decrease in ATP corresponding to almost complete loss of ATP within 2 minutes from those cells which were killed by the ghost treatment. There was no secondary rise in ATP after the fall in ghost-killed cells. The results suggest that the initial fall in ATP on infection with phage is related to the attachment process, but that the secondary rise in ATP is a consequence of infection. Since this rise is seen in rII as well as wild type infection, the cell wall repair process after attachment appears to occur normally in the rII-infected cell.

TRANSFORMATION OF H. INFLUENZAE

S. Goodgal,
J. Michalka,
J. Gunther

This past summer Jay Gunther, Jack Michalka, and Sol Goodgal identified and initiated the purification of DNases activated on DEAE. It has been known for many years that crude extracts of *H. influenzae* prepared in various ways contain little or no detectable activity against transforming DNA. These extracts can be kept for several months at 4°C without appreciable loss. However, when such extracts were absorbed to a DEAE column and then eluted, a number of peaks that inactivate transforming DNA were found. Our objective is to correlate these activities with activities directed against DNA during the process of transformation, in particular the enzymes which inactivate the transforming DNA after uptake, and the enzymes which break part of the donor DNA down to small fragments or nucleotides. (This latter activity probably acts on single-stranded material.)

A number of the nucleases found after DEAE treatment are unstable on storage. However, a major peak which has a pH optimum at approximately 5 is quite stable and has been purified somewhat by protamine sulfate precipitation and gel filtration. At least one of the enzymes, inhibited in crude extracts, can be released by RNAse treatment. The nature of the nuclease inhibition, and further purification and identification of the nucleases present in *H. influenzae*, are being pursued at our laboratory in Philadelphia.

M. Fox,
D. Brown,
G. Cooper,
T. Gurney,
E. Kataja,
R. White

Ray White, a graduate student at M.I.T., was successful in improving the spheroplast system for detection of infective T4 DNA and made progress in studying the specific effects that particular markers may have on genetic recombination.

Geoffrey Cooper, an undergraduate at M.I.T., investigated the action of methylated xanthines as inhibitors of "dark repair" of UV-induced lesions and as mutagenic agents.

Daniel Brown and Ted Gurney attempted to confirm the former's experiments on the transformation of *E. coli*.

PLASMIDS IN S. AUREUS

R. Novick,
L. Fooner

Novick: Centrifugation in sucrose gradients was employed in an attempt to demonstrate a DNA fraction corresponding to an extrachromosomal element (the penicillinase plasmid) in *Staphylococcus aureus*. The cells were allowed to lyse on top of the gradient and were then centrifuged for various times at either neutral or alkaline pH. The results showed that the DNA does not fragment, but produces a major peak with S-230, a minor peak with S-115, and a second minor peak with S-35. The second minor peak is about the right size, and the right proportion of the whole, to be the extrachromosomal element. Its identity, however, remains to be established.

Equilibrium centrifugation in CsCl gradients was used for an examination of phage particles carrying a high frequency transducing element, p11de, derived from a plasmid. These particles were found to be slightly less dense than the plaque-forming particles. Labeling with 5-BUDR showed that the p11 de element multiplies extensively during growth of the helper phage, whereas only a very small number of p11 de elements are present in uninfected cells in which the replication of the p11de element is apparently under the control of its plasmid-related genes.

Fooner: Attempts were made to isolate and characterize operator-constitutive (O^c) and super-repressor (i^s) mutants of the control system for penicillinase production. The parental strain for these isolations was a plasmid merodiploid, carrying a pair of wild-type inducible (i+p+) plasmids. Constitutive mutants arising in this diploid should be O^c, whereas negative mutants should be i^s, if penicillinase control is analogous to β-galactosidase control. Both constitutive and negative mutants were isolated from the merodiploid, and their analysis is in progress.

METABOLIC PATHWAYS IN PSEUDOMONAS

I. C. Gunsalus,
C. F. Gunsalus,
A. Chakrabarty,
S. Frean,
K. Kreiss,
S. W. Queener

Regulation: The reaction pathways of polycyclic terpene oxidation and of aromatic biogenesis were chosen for a study of cell and species expression of enzyme formation and action. The terpenes accommodate the structural diversity required to elucidate the mechanisms of regulation of catabolic specificity, while the aromatic systems furnish a branched pathway leading to free cell monomers for study of gene transfer and regulation.

1. Frean and Queener have prepared mutants of the camphor-oxidizing prototroph, *Pseudomonas putida* strain C1, clone types B and S, that are blocked in aromatic biosynthesis and regulation; strains with lesions in camphor oxidation had been isolated the previous summer by A. von Arendonck. The strains prepared are resistant to tryptophan analogues (b-methyl and β-methyl) and to 3-methyl-anthranilate, and will grow on shikimate or full aromatic pool.

2. Chakrabarty, using *Ps. putida* strain C1 and phages α and pf, has shown both phenotypic and genotypic conversion of clone type B to S. Phage α carries a locus for α-lysin which converts B to S with shift in adsorption from α to pf; α-resistant cells, selected from a confluent B lawn, are genotypically S and plate pf but not α. Phage α mutants of altered host range (h_1, h_2), plaque morphology (m, minute) and α-lysin production (1^-) were selected from spontaneous and UV-treated preparations and found to map in the sequence h_1, m, l, h_2.

C. F. Gunsalus has selected cell variants that cross the lines of clone type and host range of phages α, pf, t, a_1 and a_2. These should permit the use of the phages with cam$^-$, try$^-$, and ara$^-$ mutants in efforts to clarify a system of genetic recombination in saprophytic pseudomonads with a broad nutritive range for carbon-energy sources.

K. Kreiss has learned to grow phages on *Serratia marcescens*. Using the Hershey P^{32} method, she has estimated the minimal DNA of stationary cultures of *Ps. putida, E. coli* and an unusual contaminant coliform.

PHAGE CONFERENCE

August 28—August 31, 1966

Following the completion of the summer program, the auditorium and housing facilities were used for the annual phage conference, a four-day meeting attended by most of the active phage workers in the country. It was attended by more than 200 people.

Sunday, August 28, 2:30 P.M.

Chairman—M. Fox (Dept. Biol., M.I.T.).

H. O. Smith, M. Levine (Dept. of Human Genetics, Univ. of Michigan): "P22 mutants affecting the integration and normal attachment of prophage."

N. Yamamoto (Fels Res. Inst.): "Function of P22 in strains lysogenic for P221^{b}."

R. Hodgetts (Yale Univ.): "A study of newly-established λ-lysogenic cells superinfected with P1."

J. Zissler (Dept. Biol., M.I.T.): "Lambda lysogenization in hosts diploid for lysogenization site."

R. A. Cross, M. Lieb (Dept. Microbiology, Univ. S. Cal.): "Effect of genes N and O on heat induction of λ-Ct."

M. Lieb (Dept. Microbiology, Univ. S. Cal.): "λ induction: conversion of the host after induction of a defective λ prophage: synergism between heat and UV induction: mutations in gene N affecting heat induction."

H. Herschman, D. R. Helinski, (U. Calif., San Diego): "Induction of colicinogenic bacteria."

R. Rolfe (Dept. Microbiol., St. Louis Univ.): "Thymineless death and prophage induction in recombination deficient *E. coli*."

Sunday, August 28, 7:30 P.M.

Chairman—C. Bresch (Grad. Res. Ctr. S.W., Dallas)

R. Shleser (Dept. Biol. Sci., Purdue U.): "Gene function in the phage S13."

I. Tessman, E. S. Tessman (Dept. Biol. Sci., Purdue U.): "Mapping the genes of phage S13."

E. S. Tessman (Dept. Biol. Sci., Purdue U.): "Gene function in phage S13."

R. A. Baker, I. Tessman (Dept. Biol. Sci., Purdue U.): "Genetic recombination of phage S13 in recombination-deficient hosts."

G. Mosig (Vanderbilt Univ.): "Distances between genetic markers on the DNA molecule of T4."

H. L. Kellman, W. V. Howes (Dept. Biol. Chem., Univ. of Illinois): "Episomal genetic integrity in *E. coli* during inhibition by λvir."

Monday, August 29, 9:15 A.M.

Chairman—G. Stent (Virus Lab., Univ. Cal., Berkeley)

I. Kvelland (Dept. Genetics, Univ. of Wash.): "Genetic studies of 5BU-substituted T4D."

P. Vigier (Dept. of Genetics, Univ. of Wash.): "Comparison of T4 het frequencies under normal conditions and with inhibition of DNA synthesis."

I. Kvelland (Dept. of Genetics, Univ. of Wash.): "Influence of homozygous deletions on the average length of heterozygous regions in T4D."

John W. Drake (Dept. of Microbiol., Univ. of Ill.): "Size of the T4 Mating Region."

Rudolf Werner (Genetics Res. Unit, Carnegie Inst.): "The number of replication sites in T4-infected *E. coli*."

W. Rüger, E.K.F. Bautz (Rutgers Univ.): "Non-repeating nucleotide sequences in Phage T4."

N. A. Barricelli (Dept. Genetics, Univ. of Wash.): "Recent measurements of HNO_2-mutant clone-size distributions in phage T4 and the duplication of the injected DNA strands."

A. W. Kozinski, R. Miller (Dept. Med. Genetics, Univ. of Penn.): "Replication of T4 DNA and its Tertiary Structure."

E. W. Six, C. Connelly (Dept. Microbiology, Univ. of Iowa): "Helper-dependent multiplication of phage P4."

Monday, August 29, 2:30 P.M.

Chairman—C. I. Davern (Cold Spring Harb. Lab.)

R. H. Krieg (Dept. Bact., Univ. of Cal., Los Angeles): "Genetic factors of *E. coli* determining suppression of the amber mutant phenotype of T4."

W. Szybalski, H. Kubinski, K. Taylor, P. Sheldrick (McArdle Lab., Univ. of Wisc.): "Role of pyrimidine-rich clusters on transcribing DNA strands."

W. Szybalski, Z. Hradecna, K. Taylor (McArdle Lab., Univ. of Wisc.): "Separation of λ DNA strands: Switch in the orientation of the transcription process."

C. Hill (Dept. Biochem., Univ. of Wisc.): "Control of Host m-RNA after T4 Infection."

A. Joyner, B. Butler, L. Pilarski, H. Echols (Dept. Biochem., Univ. of Wisc.): "Macromolecular synthesis during λ development."

John F. Pulitzer (Dept. Biophysics, Univ. of Chicago): "RNA synthesis in development of T4 and SPO."

I. Baldi, J. Doskocil, R. Haselkorn (Dept. Biophysics, Univ. of Chicago): "Synthesis and function of mRNA in T4 infected *E. coli*."

T. Kasai, E. K. F. Bautz (Rutgers Univ.): "Regulation of Phage T4 RNA Synthesis."

D. Shub (Dept. of Biol., M.I.T.): "Role of RNA in regulation of protein synthesis in phage-infected *B. subtilis*."

A. M. Chakrabarty (Biochem. Div., Univ. of Illinois): "Genetic regulation of a lytic enzyme production by a *Pseudomonas* phage."

Monday, August 29, 7:30 P.M.

Chairman—K. Paigen (Roswell Park Mem. Inst.)

R. J. Grasso (Roswell Park Mem. Inst.): "Physiological factors influencing restriction and modification of λ phage in *E. coli*."

H. Drexler (Dept. Microbiol., Bowman Gray School Med., Wake Forest College): "Host-controlled modification: the fate of the restricted genome in a non-permissive host."

M. Gefter (Albert Einstein Coll. Med.): "Methylation of DNA in bacteriophage."

N. E. Melechen (Dept. Microbiol., St. Louis Univ. School Med.): "Methylation and P1 induction."

E. Yarosh (Dept. Biol., M.I.T.): "T4 interference with the replication of MS2."

T. Sueoka (Dept. Biol., Princeton): "Modification of sRNA after phage infection."

Tuesday, August 30, 9:15 A.M.

Chairman—R. Sinsheimer (Div. Biol., Caltech)

M. P. Oeschger (Dept. Microbiol., Johns Hopkins Univ.): "Differential synthesis of phage-specific proteins in MS2-infected *E. coli* treated with Actinomycin D."

I. Algranati, E. Vinuela, G. Feix and C. Weissman (Dept. Biochem., N.Y.U.): "Phage-specific proteins in *E. coli* infected with MS2 or with the amber mutant MU-9."

R. L. Erikson (Dept. Pathology, Univ. Colorado Med. School): "The biological activity of phage R17 replicative intermediate RNA."

M. Watanabe (Albert Einstein Coll. Med.): "RNA phage replication."

W. Erdahl, R. Unger, D. Pratt (Dept. Bacteriology, Univ. Wisc.): "DNA synthesis by M13 amber mutants."

W. Salivar (Dept. Bact., Univ. Wisc.): "Properties of double-length particles of coliphage M13."

D. L. Engelhardt, R. E. Webster, N. D. Zinder (Rockefeller Univ.): "Polarity of translation *in vitro* of f2 RNA."

H. Robertson (Rockefeller Univ.): "Polarity of translation of f2 RNA."

T. August (Dept. Molecular Biol., Albert Einstein Coll. Med.): "RNA Phage."

Tuesday, August 30, 2:30 P.M.

Chairman—W. Szybalski (McArdle Lab., Univ. Wisc.)

D. R. Krieg (Dept. Bact., Univ. of Calif., Los Angeles): "Mutagenesis."

Gamow & Gamow (Dept. Microbiol., Univ. Col. Med. Ctr.): "Nature of B/1 mutants caused by nitrosoguanidine."

D. Parma (Dept. Gen., Univ. Wash.): "Genetic experiments with the partial phages of the T4 mutant amE290g."

M. Susman (Dept. Genetics, Univ. Wisc.): "The effects of 9-aminocridine on phage assembly."

S. Altman (Dept. Mol. Biol., Vanderbilt Univ.): "The synthesis of Phage T4 DNA in the presence of acridine."

L. D. Simon (Inst. Cancer Res.): "Infection of *E. coli* by T2 and T4 as seen in the Electron Microscope."

J. V. Israel (Dept. Human Gen., Univ. Mich. Med. School): "In vitro mechanism of assembly of phage P22 heads and base plate parts."

D. H. Walker (Institute for Cancer Res.): "More on P1 morphological variants."

M. Baylor (Marine Biol. Lab., Woods Hole)

Tuesday, August 30, 7:30 P.M.

Chairman—H. Echols (Dept. Biochem., Univ. of Wisconsin)

Z. Hradecna (McArdle Lab. for Cancer Res., Univ. Wisc.): "Comparison of UV and X-ray sensitivities of several *B. subtilis* phages in repair-impaired hosts."

R. Haselkorn, R. Luftig (Dept. Biophysics, Univ. of Chicago): "Properties of cyanophage (blue-green algae virus)."

N. Yamamoto (Fels Res. Inst.): "Further studies on the genetics homology between serologically unrelated phages."

I. Takahashi (Res. Unit in Biochem., McMaster Univ.): "Transducing fragments in phage PBS-1 of *B. subtilis*

R. Novick (Pub. Health Res. Inst. of N. Y.): "A cryptic high-frequency transducing phage in *Staph. aureus*."

M. Gough (Dept. Human Genetics, Univ. of Mich.): "Circularity in the phage P22 linkage map."

Wednesday, August 31, 9:15 A.M.

Chairman—H. T. Epstein (Dept. Biol., Brandeis)

H. V. Aposhian (Dept. Microbiol., Tufts Univ.): "Deoxythymidylate-5'-nucleotidase: An enzyme found in *B. subtilis* infected with phage SP5C."

M. Nishihara (Dept. Microbiol, Tufts Univ.): "A novel dCMP deaminase – the enzyme found after SP8 infection."

D. H. Hall, I. Tessman (Dept. Biol. Sci., Purdue Univ.): "The genes controlling thymidylate synthesis."

N. Couse (Dept. Gen., Univ. of Wisc.): "The timing of lysis of T4-infected bacteria."

D. MacDonald Green (Dept. Biology, Univ. of Pittsburgh): "The determination of the uniqueness of the DNA molecule of phage SP82."

I. Rubenstein (Dept. Mol. Biophysics, Yale): "Heterogeneity in the sedimentation rate of whole molecules of T5 DNA."

H. Lozeron, W. Szybalski (McArdle Lab for Cancer Res., Univ. Wisc.): "Banding of RNA in mixed CsC1-Cs_2SO_4 gradients."

L. W. Wendt (Dept. Biochem., Univ. of Cal., Berkeley): "Effects of phenethyl alcohol on surface properties of *E. coli*."

NATURE STUDY COURSES

Children of Ages 6 to 16

During the summer of 1966, twenty four courses in Nature Study were conducted in two monthly sessions. The enrollment this year was 263 students. The course offerings included:

General Nature Study (ages 6, 7)
General Ecology (8, 9)
Bird Ecology (8, 9)
Seashore Life (10, 11)
Fresh Water Life (9, 10)
Fresh Water Biology (10, 11)
Plant Insect Relationships (8, 9)
Entomology (10, 11)
Vertebrate Zoology (10, 11)
Geology (10, 11)
Advanced Bird Study (10, 11)
Plant Ecology (12-14)
Ichthyology-Herpetology (15, 16)
Conservation (12-14)

INSTRUCTORS

Mr. Otto A. Heck, M.S., Assistant Professor of Biology at Trenton State College, Trenton, N. J., was in charge. The additional staff members were:

Mrs. Barbara Church, M.S., Science Teacher, Jerusalem Avenue High School, Bellmore. L. I.

Mr. Herbert Atkinson, M.S., Science Coordinator, Hicksville Junior High School, L. I.

Miss Virginia Jones, B.S., Graduate Student in Conservation and Natural History, Michigan State University.

Mr. Alexander Pepe, M.A., Science Teacher, East Side School, Cold Spring Harbor, L.I.

In addition to the instructors, each class had an assistant to help on the field trips and in laboratory work.

Several evening film showings were included in the courses, to which parents were invited.

The Laboratory gratefully acknowledges the seventh year contribution of the Huntington Federal Savings and Loan Association. This provided nature study scholarships for 15 students of the Huntington elementary schools.

NATURE STUDY WORKSHOP FOR TEACHERS

The eleventh annual Workshop in Nature Study was offered from June 27th to July 15th, 1966. This program was designed to familiarize elementary and secondary school teachers with the natural environment of the Long Island area, including the animals and plants living there; and those aspects of the environment which affect these organisms. There were field trips to ponds, streams, seashore, woodlands, fields, and other natural habitats, for purposes of collecting and first-hand study, with indoor laboratory work-time divided between lectures and practical work. The experiences of the course are designed to help teachers in their classroom science activities.

Ten teachers attended the workshop. Upon satisfactory completion of the requirements of the course, teachers were entitled to two in-service credits awarded by the New York State Department of Education. Instructors were Mr. Otto Heck and Mrs. Aline Dove.

FINANCIAL REPORT

For the period May 1, 1965—April 30, 1966

As of April 30, 1966, our assets were as follows:		
Cash	$110,758.89	
Accounts receivable	56,300.41	
Inventory of books	12,678.00	
Prepaid expenses	4,459.45	
Certificate of time deposit	25,985.41	
Investments—U. S. Government obligations (market value $29,736.15)	29,380.85	
Land, buildings and equipment	521,805.60	
Total		$761,368.61
Our liabilities were as follows:		
Accounts payable	$ 26,608.55	
Unexpended grants and contracts	80,739.40	
Deferred income	4,933.33	
Net worth	649,087.33	
Total		$761,368.61
For the year 1965-1966, our receipts were as follows:		
Grants and contracts		$304,750.69
Contributions:		
Sponsors and Friends	$ 44,591.79	
Carnegie Institution of Washington	25,732.67	
Long Island Biological Association	1,303.26	
Wawepex Society	3,200.00	$ 74,827.72
Book Sales (Cold Spring Harbor Symposia on Quantitative Biology)	67,657.37	
Dining hall and dormitories	66,522.94	
Tuition fees	27,942.50	
Summer laboratory fees	3,300.00	
Symposium registration fees	2,560.00	
Interest on time deposit and U. S. Government obligations	1,869.91	
Miscellaneous	937.82	
Total		$550,368.95
Our expenditures were as follows:		
Research and educational programs	$276,091.42	
Administration and general	79,076.40	
Plant operations and maintenance	99,324.16	
Publications	43,899.72	
Dining hall and dormitories (inc. provision for depreciation)	67,281.65	
Total		$565,673.35
Excess of Expenditures over Income 1965-1966		($15,304.40)

GRANTS AND CONTRACTS

May 1, 1965 to April 30, 1966

Grantor	Investigator	Total Award	Grant Number
	RESEARCH GRANTS		
National Science Foundation	Dr. Cairns	$50,900.00	GB-4055*
National Science Foundation	Dr. Davern	76,200.00	GB-4001*
National Institutes of Health	Dr. Margolin	20,312.00	5-K3-GM-6887-03
National Institutes of Health	Dr. Margolin	55,213.00	GM-07178-06
National Institutes of Health	Dr. Speyer	38,337.00	GM-12371-02
The Rockefeller Foundation	Dr. Cairns	85,000.00	RF-63042
	TRAINING GRANTS		
National Institutes of Health	Summer Courses	47,865.00	GM-890-10
National Science Foundation	Phycomyces Workshop	20,000.00	GB-3149*
	SYMPOSIUM GRANTS		
Atomic Energy Commission		7,000.00	AT(49-12)-2781
Air Force Office of Scientific Research		5,000.00	AF-AFOSR-426-65
National Institutes of Health		12,050.00	CA-02809-10
National Science Foundation		8,500.00	GB-3575
	SPECIAL GRANTS		
National Science Foundation	Interim Support and Development	73,900.00	GB-3727*
New York State Science and Technology Foundation	Support of Graduate Teaching & Research Programs	31,130.00	SSF(5)-14

*These grants cover a two-year period

LABORATORY STAFF 1966

COLD SPRING HARBOR LABORATORY

John Absmeier
Ronald Bauerle
John Cairns
Donald Caldarelli
Anne Carhart
James Connolly
Cedric Davern
Paula De Lucia
Ruth Divan
David Dunn
Madeleine Dunn
Donald Eckels
Stephen Friedman
Leonora Frisch
Gloria Gillies
Maryalice Gladding
Harriet Hershey
Jim Karam
Jost Kemper
Albert Lenny
Rosanne Levitt
Barbara Lutjen
Paul Margolin
Joseph McDonald
William McDonald
Agnes Meyer
Bernadine Miller
Blanche Mrazek
Dorothy Nilsson
John B. Philips
William Reddy
Lorraine Reinhold
Deanna Robbins
Doris Schoonmaker
Guinevere Smith
Willette Smith
Joseph Speyer
Albert Taylor
William Van Houten
Hildegard Walter
Harry White
Arthur Zerfass

GENETICS RESEARCH UNIT, CARNEGIE INSTITUTION OF WASHINGTON

Phyllis Bear
Elizabeth Bocskay
Jennie Buchanan
Elizabeth Burgi
Ruth M. Ehring
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