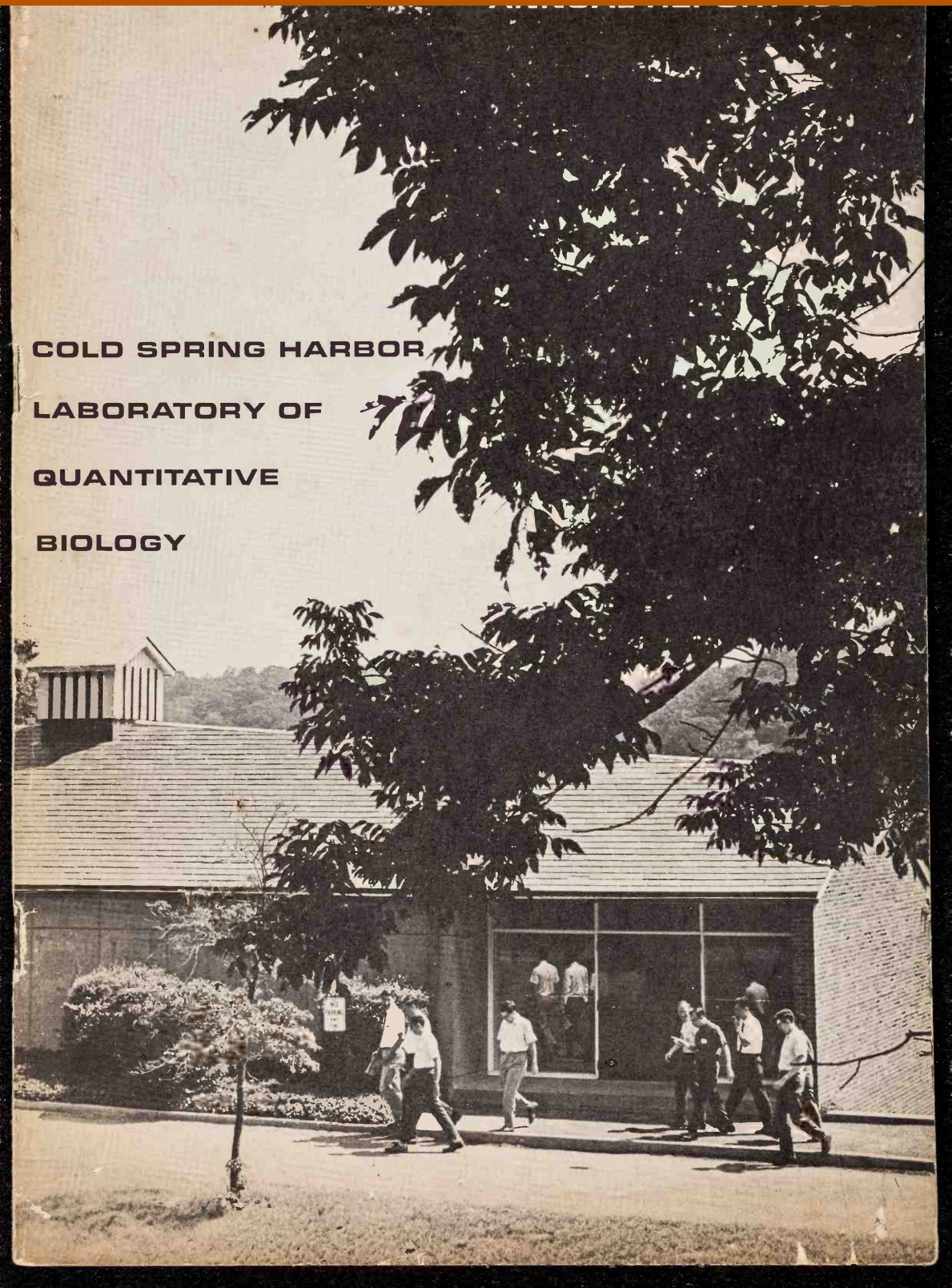
COLD SPRING HARBOR LABORATORY OF QUANTITATIVE BIOLOGY



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ANNUAL REPORT 1965

COLD SPRING HARBOR, LONG ISLAND, NEW YORK

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DIRECTOR'S REPORT

The introduction to last year's Annual Report described the formation of the Laboratory of Quantitative Biology out of the Department of Genetics of the Carnegie Institution and the Biological Laboratory of the Long Island Biological Association. The task of the new organization was 1) to find sufficient funds to rescue the Laboratory from the immediate perils of its financial position and so provide a "breathing space" in which the more basic problems of the Laboratory could be solved; 2) to seek financial support for a long-overdue rehabilitation of the physical plant; and 3) to seek some form of endowment in order to ensure that the Laboratory could recruit staff and, in the future, be spared the repeated financial crises that had plagued its past. As more than two years have elapsed since the creation of the Laboratory of Quantitative Biology, it is probably not being unduly precipitate to review the progress made by the new organization in these various endeavors.

The first of these tasks—that of rescuing the Laboratory from its immediate financial plight—has been accomplished, and the exact details are given in the Financial Report on page 25.

The second exercise—that of rehabilitating the physical plant—is proceeding more slowly. In 1964, a small grant from the National Science Foundation allowed the Laboratory to carry out an engineer's survey of all its buildings. This survey showed that almost one million dollars would be needed to make up for the neglect of maintenance that had had to be practiced in previous years. For, most of the Laboratory holdings were in urgent need of repair, and several had passed beyond the point of repair. In the second year, the National Science Foundation followed up their grant for that survey with one to pay the architectural fees for a general site development plan and to pay for certain repairs on those few buildings that are undeniably worth saving. As a result, rough floor plans of all buildings on the grounds have been prepared, an accurate map of the property has been drawn, and substantial improvements have been made in the Dining Hall kitchen. In addition, repairs are under way to the Dining Hall, the Lecture Hall, Jones Laboratory, and the Carnegie Laboratory. However, most of the work and the entire Development Plan, *per se,* lie ahead.

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 nor, apparently, even the prospect of it.

Scientifically, the year has been notable for the addition of a new course to the summer program. At the instigation of Professor Max Delbrück, who started the course on bacterial viruses in 1945, a course was held this summer on the light-sensitive fungus, Phycomyces. It will be held again in the summer of 1966 and then may be modified or, perhaps, enlarged to cover other facets of receptor physiology.

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,
L. Corwin,
S. Friedman

The bacterial genetics group has continued to explore questions involving base analogue mutation, the mechanism of transcription of genetic information into messenger RNA, genetic fine structural organization and the regulation of gene expression in *Salmonella typhimurium*.

Extension of the studies of 2-aminopurine mutagenesis to 135 leucine auxotrophs has led to the following ideas. Mutation by 2-aminopurine results from incorporation of this analogue in place of one of the normal purines and subsequent "mis-pairing" with the alternate pyrimidine. Pairing of 2-aminopurine with thymine is about 10 times as frequent as with cytosine. Reversion by 2-aminopurine of the two classes of mutant sites (adenine-thymine and guanine-cytosine) can be characterized and distinguished in terms of the frequency of induced reversions and the dependence upon DNA replication for expression of all potential induced revertants. There is a high level of correlation between high frequency reversion and independence from the requirement for DNA replication for expression. This is in conflict with the concept of mRNA transcription by means of templating from one of the two DNA strands. A model for transcription has been developed involving indirect templating, utilizing an allosteric RNA polymerase which responds to information contained in both DNA strands.

Dr. Ronald Bauerle has continued the studies of the organization and the regulation of expression of the tryptophan gene cluster. Recent results indicate that this cluster of five genes is divided into two semi-independent units of 2 and 3 genes respectively. The capacity for expression is determined independently for the two units while the capacity for regulation of the degree of expression by tryptophan appears to be determined by a single operator-like element which controls all five genes.

Studies of the regulating elements of the leucine operon have been continued by Dr. S. Friedman. These have shown that the mutant leucine operator of the operator negative mutant *leu 500* can undergo a second mutation which leads to a catabolite repressible phenotype of this biosynthetic pathway. Further studies suggest that this second change has merely altered the degree of response to the foreign repressor which had created the leucine auxotrophy of the original *leu 500* mutant.

The *car* locus of Salmonella had been originally characterized as being involved in carbohydrate utilization, since its deletion led to a citrate requirement for growth. Dr. Lawrence Corwin of the Walter Reed Army Research Institute spent 5 weeks in this laboratory studying *car* mutants. These studies have indicated that the *car* locus is associated with the regulation of uptake of specific trace elements. The *car* mutants have greatly increased sensitivity to cobalt and chromium and were protected by the chelating activity of citrate.

THE CHROMOSOME OF ESCHERICHIA COLI

Laboratory of
J. Cairns,
C. I. Davern
P. De Lucia

This research project had its origin in the finding that the chromosome of *Escherichia coli* is apparently a single molecule of DNA which is circular during the time it is being duplicated. Now, the structure of two-stranded DNA is such that the strands can separate only if one end of the parent molecule rotates relative to the other end. This unwinding process, in the case of bacteria growing at maximum speed, must occur at a rate of about 20,000 r.p.m.

Since closed circles of two-stranded DNA could not be unwound, it follows that there must be some form of swivel at the point of closure of the circle (where the two daughter molecules are joined to the far end of the parent molecule). This combination of the need for postulating a swivel and the need for some energy-consuming mechanism for driving the very rapid rotation of the whole molecule, suggested that the swivel itself may be the site of the rotating mechanism (or "spinner").

An effort was made, therefore, to prove (or disprove) the existence of such a mechanism, which drives DNA replication even though acting at a distance.

The most direct prediction of this hypothesis is that a break in the circle, on either side of the replicating region, will prevent the continued act of unwinding and should, therefore, stop replication instantaneously.

The decay of P^{32}, which has been incorporated into DNA, is known occasionally to produce two-strand breaks and, equally important, is known to produce little or no effect at a distance. (Unlike other radioactive isotopes, P^{32} produces such a low density of ionizations near the origin that the indirect effects of the decay upon neighboring structures can be neglected.)

Various experiments were performed, therefore, to determine whether the decay of P^{32} in the bacterial chromosome would stop replication even when occurring at a distance from the point of replication. The results may be summarized as follows:-

(a) Most strains of *E. coli* can apparently repair most P^{32}-induced breaks, at least to the point where such breaks do not constitute a barrier to the extension of replication. However, there is a delay in the onset of DNA replication after such decay, suggesting that replication stops completely until the integrity of the chromosome is restored.

(b) Certain strains that are unusually sensitive to P^{32}-decay and X rays apparently cannot effect such repairs. For these strains, DNA synthesis is stopped by P^{32}-decay anywhere in the chromosome (but not by such decay occurring in other parts of the cell).

The results go some way toward confirming the hypothesis. However, the confirmation is by no means complete. Firstly, these experiments are not measuring transmitted torque, *per se*, and so only bear obliquely upon the hypothesis; though the experiments suggest that some "signal" is indeed being transmitted along the chromosome to the region of replication, they do not show what form this signal has. Secondly, it is conceivable that the region of replication is sensitive to DNA breakdown products and that the whole effect we observe is due to trivial causes. The experiments are, therefore, incomplete, and some other approach is needed in order to show directly the form of the signal that acts at a distance.

PROTEIN SYNTHESIS I

Laboratory of
J. Speyer,
J. Karam,
A. Lenny

We have been working on in vitro protein synthesis, studying some of the variables which cause this system to misread messenger RNA.

One criterion of misreading is the extent to which amino acids other than phenylalanine are incorporated by ribosomes programmed for phenylalanine incorporation by polyuridylic acid. Dimethyl sulphoxide (DMS) was found to cause in vitro misreading. These effects may have biologic validity if they cause phenotypic repair in vivo. Using a bacteriophage: bacterium system (T_4 and *E. coli*) we found that r_{11} point mutations could be suppressed by DMS as well as by alcohol and Streptomycin (Sm), agents which had been shown by others to cause misreading of the messenger RNA in vitro.

Several mutants were studied and it was observed that some mutants were suppressed by alcohol and DMS, some by Sm, and some by both. If in all cases this suppression is at the protein synthesis level – an effect via RNA synthesis is not ruled out – the results indicate that the above specificity is due to suppression of different codons

by Sm than those affected by DMS and alcohol. Although both alcohol and DMS cause extensive misreading in vitro and in vivo, neither was lethal to *E. coli*, in the concentrations used. DMS was found to be a mutagen for phage, as is Sm. This mutagenesis may be attributed to the defective proteins synthesized when messenger RNA is misread. A likely protein whose defective state may cause such errors in DNA replication (mutations) is the enzyme DNA polymerase. Dr. R. S. Edgar, who was here this summer, generously gave us bacteriophage mutants containing various errors in the gene for DNA polymerase. This error is manifest at elevated temperature by an inability to replicate the phage DNA. Some of these mutants were found to be highly mutagenic for certain bases.

This is being studied further because these observations bear on nucleic acid replication and the mechanism of mutagenesis.

Dr. Jim Karam has joined in this work. He is an N.I.H. postdoctoral fellow, and comes from the University of North Carolina. Dr. Peter Lengyel, a coworker at New York University, has spent six months in our laboratory. His work is described separately; we are collaborating in some other work aimed at elucidating a ribosomal function.

PROTEIN SYNTHESIS II

Laboratory of
P. Lengyel,
A. Skoultchi,
J. Gallardo

Nonsense mutations completely inhibit the expression of the gene in which they are located and also partially or completely inhibit the expression of genes more distal to the operator than the mutated gene itself (polar mutations).

The lac operon in *E. coli* consists of an operator sequence and sequences containing the genetic information for β-galactosidase, β-galactoside permease and β-galactoside transacetylase (acetylase) in this order.

We have found that the amount of acetylase formed in *E. coli* strains containing different kinds of nonsense mutations in the β-galactosidase gene depends on the temperature of growth of the culture. In some of the mutants there is no detectable acetylase if grown at 42°, while it reaches 15% of the wild type level if grown at 25°.

Since the acetylase gene is exactly the same in these mutants as in the wild type, it must be the translation itself that is temperature dependent—not the polymerization of the enzyme monomer, and not the enzyme itself. Ambiguity in cell free protein synthesizing systems, (e.g., the promotion of leucine incorporation by poly U) shows a similar temperature dependence. It is not known at this time whether this similarity is accidental or if it reflects a common error mechanism.

STRUCTURE OF BACTERIOPHAGE

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

Lambda DNA. Burgi and Hershey: Burgi is continuing her analysis of the structure of the ends of lambda DNA molecules, and has arrived at a specific but still hypothetical model, which should be testable in due course.

One of the requirements in this and other work is a practical method for the separation of right and left halves of lambda DNA molecules. In collaboration with C. I. Davern, we found that equilibrium density-gradient centrifugation in an angle rotor is a serviceable method. It is based on the principle that bands formed at an oblique angle to the tube axis in the spinning rotor spread apart when the rotor is stopped and the tube is brought to a vertical position. Although there is not theoretical gain in resolution under these circumstances, there is the practical one that the expanded bands are less subject to mechanical mixing when the fractions are collected.

Weak Spots in T5 DNA. Ingraham and Hershey: When a solution of T5 DNA is stirred to generate the minimum rate of shear that will break the molecules, fragments 0.4 and 0.6 of the original molecular length are produced. These can be separated by chromatographic or centrifugal fractionation. When the fragments of 0.6 unit length are broken in turn, fragments 0.4 and 0.2 unit long appear. This behavior must be contrasted with that of some other phage DNA's, which do not show preferred breakage points but pull apart near their centers for purely mechanical reasons.

The breakage pattern of T5 DNA can be explained by several models, at least three of which are potentially distinguishable.

1. Two weak spots may lie at positions 0.4 and 0.6 of the molecular length from either end. According to this model, the 0.4 unit fragments resulting from the first and second breaks would be identical mixtures of pieces from both ends of the molecule.

2. Two weak spots may lie at positions 0.4 and 0.8 of the molecular length from a specified end. In this model, the 0.4 unit fragments resulting from the first and second breaks would represent different and nonoverlapping segments of the molecule.

3. The molecule may contain four weak spots dividing it into five segments of equal length. In this model, the 0.4 unit fragments resulting from the first break would be an equal mixture of the two ends, and those resulting from the second break would consist partly of ends and partly of subterminal sections. Thus the second breakage product would contain parts absent from the first, but not vice versa.

We explored these possibilities by application of the DNA homology test of Bolton and McCarthy. The experiments showed that the 0.4 unit fragments resulting from the first and second breaks each contain sequences absent from or less frequent in the other, but they also contain many common sequences. These results exclude models 1 and 2 but not 3, and suggest additional possibilities.

Besides model 3, two principal alternatives remain. The structures may resemble that of model 1 if the two weak spots are of unequal strength or are situated at slightly unequal distances from the molecular center. Or model 2 may be correct if different parts of the molecule contain both unique and common base sequences. The interesting possibility that different molecular parts contain similar sequences has already arisen in our work with lambda DNA and will have to be pursued with that DNA whose parts can be isolated without ambiguity.

The structure of the weak spots is unknown. One obvious possibility is that they are points at which one of the two polynucleotide chains of the molecule is already broken. The hypothesis is plausible inasmuch as several people have found evidence of single-strand breaks in T5 DNA but not in some other phage DNA's. Such breaks are detected by measuring molecular weights in terms of sedimentation rates of the DNA in single-stranded form. In our experience the results do not support the hypothesis stated, because the sedimentation rates do not indicate sufficient uniformity of size of the polynucleotide chains to explain the rather precise locations of the weak spots. Both the method and its application to T5 DNA require further study.

T4 Phage Particles with Incomplete Genomes. Mosig: Exceptional particles of phage T4 can be isolated that prove to contain a single DNA fragment two-thirds of the standard length. The particles are individually noninfective, but have the interesting property that two or more of them can cooperate, in a single bacterium, to regenerate complete chromosomes. Apparently the particles have incomplete genomes, and the missing parts are different in different particles, so that one particle can supply what is absent in another. That idea underlies the following experiments.

When a single bacterium is simultaneously infected with a normal phage particle and with a defective particle that is genetically marked, the marker from the defective particle may appear in the phage progeny. In this type of experiment, different markers are "rescued" from the defective particles with identical frequencies, independently of their map position. The actual frequency of rescue of a single marker is about two-thirds, as expected from the length of DNA in the particles. These results show that the rescue is highly efficient, that the DNA molecule and the genome are colinear, and that the two-thirds length is cut at random from an effectively circular genome. The results are consistent with other evidence that the genetic map of phage T4 is circular, and that the DNA molecules are "circularly permuted."

Genetic Recombination with Exceptional Particles of Phage T4. Ehring: Mosig's present work began with her observation that genetic recombination frequencies in phage T4 were correlated with the buoyant densities of the phage particles entering into the crosses. In particular, particles of low density showed high recombination frequencies. The particles of low density were subsequently resolved into two classes: viable particles with slightly curtailed DNA molecules (class 3) and inviable particles with DNA molecules only two-thirds the normal length (class 5). Particles of class 5 yield many recombinants for understandable reasons: the phage progeny are necessarily multiparental in origin. Ehring has now made crosses with purified particles of class 3. Yields of recombinants do not differ from those in comparable crosses with particles of average DNA content. Therefore, recombination frequencies in crosses with phage particles of the majority class do not depend on the lengths of chromosomal redundancies, or at any rate this test failed to reveal such dependence.

Genetic Linkage in T4 DNA Molecules. Goldberg: Modified bacteria (spheroplasts) can be infected with modified T4 phage particles (particles treated with urea to alter the specificity of attachment). If T4 DNA is present at the time of infection, a few per million of the phage progeny will show genetic markers derived from the DNA. The complicated system (first developed by van de Pol, Veldhuisen, and Cohen) is probably needed to get DNA into the cells, or to get it in without excessive enzymic degradation. The efficiency is inconveniently low with present techniques, but that does not seriously interfere with the experiments. The unusual feature of the system is that fragmented and denatured DNA can still contribute genetic markers. Since DNA fragments are not infective by themselves, even in principle, the genetic contribution by the DNA may be thought of as a rescue of markers by incorporation of specific nucleotide sequences into multiplying chromosomes.

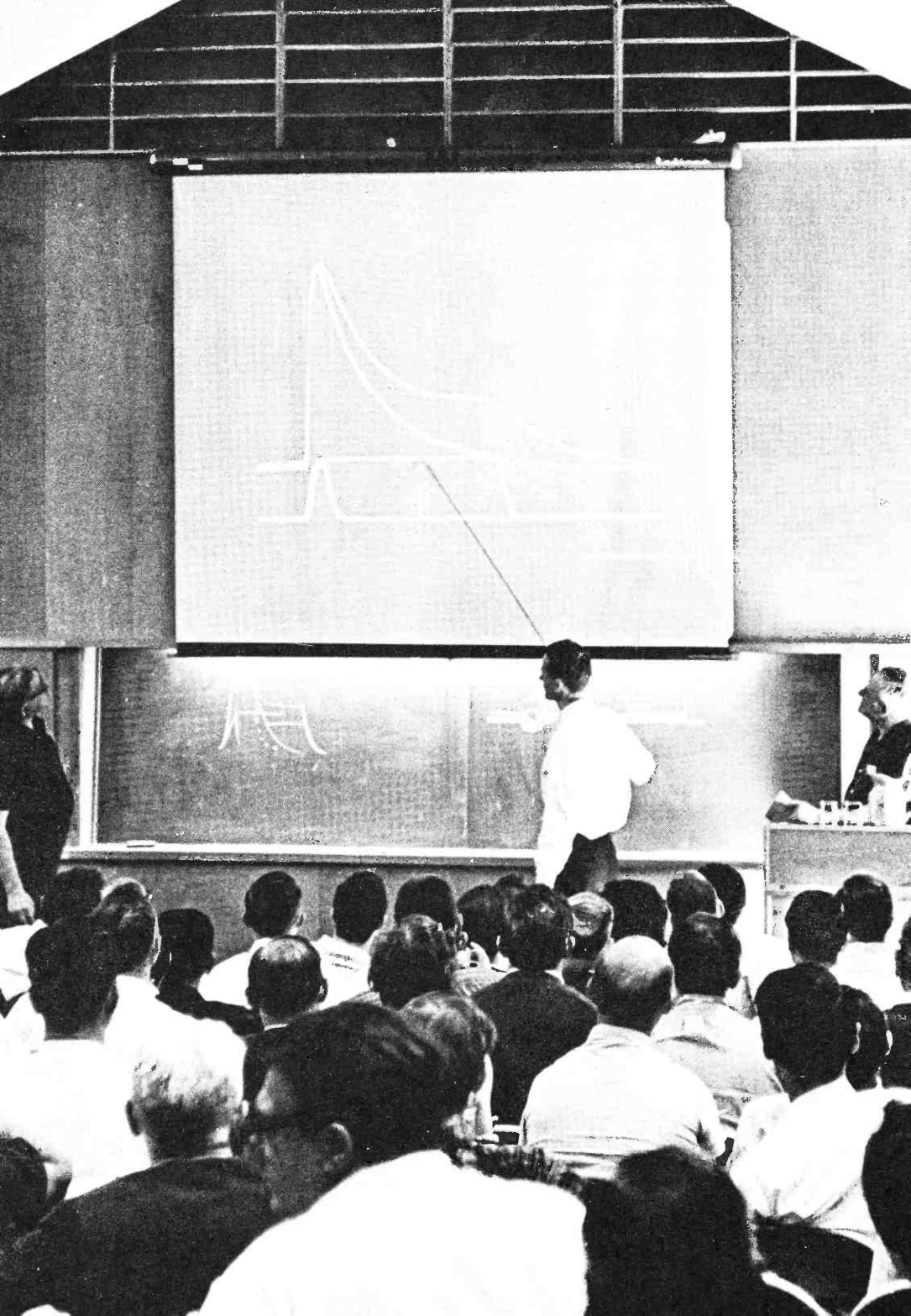
If the DNA is doubly marked, the frequency of joint rescue of both markers provides a measure of genetic linkage. The actual measurement takes the form of a ratio between the number of phage particles showing both markers and the total number showing a specified one of them. This measure is influenced both by the initial rescue and by subsequent genetic recombinations, and is therefore inferior in principle to Mosig's test, which apparently depends only on the presence or absence of markers in the DNA fragments. The advantage of the system introduced by the Dutch workers is that the DNA fragments can be experimentally modified.

Replicating DNA. Smith: Smith has studied the properties of the phage-precursor DNA. Its density is the same as that of DNA extracted from phage T5, which shows that it has the expected base composition and is not attached to appreciable amounts of non-DNA material. It sediments as a single, very broad band, most of which moves faster than DNA extracted from phage particles. The fast-sedimenting DNA is sufficiently fragile under shear to suggest a long, threadlike structure. An examination in the electron microscope by MacHattie at the Johns Hopkins University showed, in fact, long threadlike structures without noticeable branching. Fragmentation of the DNA has not yet revealed any preferred subunit length. On denaturation in alkali, the DNA sediments more or less like denatured DNA from phage particles, at a rate suggesting that both are composed of relatively short polynucleotide chains.

Genetic Transcription in Bacteria Infected with Phage Lambda. Skalka: Transcription of specific genes can be studied only in a few favorable instances. In phage lambda, gross differences in base composition of the two halves of the DNA molecule permit analysis along somewhat different lines. One can ask, for instance: Where in the molecule does transcription start? An appropriate experiment is performed as follows. Bacteria are infected with phage lambda. At any desired time thereafter, radiophosphate is fed to the culture for a period of two minutes, the culture is promptly chilled to stop synthetic activities, and RNA is extracted from the cells. The variable in different experiments is the time after infection at which the examination is made. The labeled RNA extracted from the cells consists of several types, among which only that matching lambda DNA in base sequence is of interest in the present context. It is isolated, and its amount judged, by annealing to lambda DNA according to the technique of Bolton and McCarthy.

Lambda messenger RNA comprises only about 5% of the total RNA labeled at early times after infection, but amounts to 30% of that labeled at 30 minutes. The same trend has been reported by Sly and Adler. The guanine-plus-cytosine content of the RNA, not previously measured, is low at early times and high at late times. This trend is reproducible, as are the individual analyses, but the absolute values vary somewhat in different experiments. Finally, the purine content of the labeled RNA is high at all times (in double-stranded DNA it is necessarily 50%), probably because only the pyrimidine-rich strand of the DNA is read, as has been found also for phages SP8 and alpha.

That transcription does start mainly in the right half of the DNA molecule is confirmed by annealing tests. Messenger RNA synthesized at early times anneals almost exclusively to right halves of lambda DNA, whereas messenger synthesized between 30 and 32 minutes after infection anneals with equal efficiency to both halves.



XXX. "SENSORY RECEPTORS"

This symposium was the 30th in the series initiated by the Long Island Biological Association in 1933. 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. Delbrück, Bullock, Brown, Davis, Hartline, Lettvin, and MacNichol. There were 52 speakers of whom 24 came from outside the United States. More than 170 people attended the meetings.

The program naturally divided itself into several sections: The General Physiology of Receptors—Mechanoreceptors—Hearing—Olfactory Receptors—Electrical and Chemical Receptors—Photoreceptors—and, finally, a section on Data Processing. The full list of papers is given below.

OPENING ADDRESS: M. DELBRUCK, Calif. Inst. Technology, Pasadena.

GENERAL PHYSIOLOGY

H. GRUNDFEST, Columbia University, N.Y. "Electrophysiology and Pharmacology of Different Components of Bioelectric Transducers."

D. M. EASTON, Florida State Univ., Tallahassee. "Impulses at the Artifactual Nerve End."

W. R. LOWENSTEIN, Columbia Univ., N.Y. "Facets of a Transducer Process."

P. GRAZIADEI, University College, London, England. "Sensory Receptor Cells and Related Neurons in Cephalopods."

MECHANORECEPTORS

D. E. GOLDMAN, U. S. Naval Medical Research Inst., Bethesda, Md. "The Transducer Action of Mechanoreceptor Membranes."

P. GORNER, Freien Univ., Berlin, Germany. "A Proposed Transducing Mechanism for a Multiply-Innervated Mechanoreceptor (Trichobothrium) in Spiders."

U. THURM, Max-Planck Inst., Tubingen, Germany. "An Insect Mechanoreceptor. I: Fine Structure and Adequate Stimulus. II: Receptor Potentials."

G. M. SHEPHERD and D. OTTOSON, Karolinska Institutet, Stockholm, Sweden. "Response of the Isolated Muscle Spindle to Different Rates of Stretching."

D. OTTOSON and G. M. SHEPHERD, Karolinska Institutet, Stockholm, Sweden. "Receptor Potentials and Impulse Generation in the Isolated Spindle During Controlled Extension."

HEARING

J. WERSALL, A. FLOCK, and P.-G. LUNDQUIST, Karolinska Institutet, Stockholm, Sweden. "Structural Basis for Directional Sensitivity in Cochlear and Vestibular Sensory Receptors."

A. FLOCK, Karolinska Institutet, Stockholm, Sweden. "Transducing Mechanisms in Lateral Line Canal Organ Receptors."

J. E. HAWKINS, Univ. of Michigan, Ann Arbor. "Cytoarchitectural Basis of the Cochlear Transducer."

M. LAWRENCE, Univ. of Michigan, Ann Arbor. "Dynamic Range of the Cochlear Transducer."

L. NAFTALIN, St. Georges' Hospital, Lincoln, England. "Some New Proposals Regarding Acoustic Transmission and Transduction."

H. DAVIS, Central Inst. for the Deaf, St. Louis, Mo. "A Model for Transducer Action in the Cochlea."

OLFACTORY RECEPTORS

L. M. BEIDLER, Florida State Univ., Tallahassee. "Comparison of Gustatory Receptors, Olfactory Receptors, and Free Nerve Endings."

D. G. MOULTON, Florida State Univ., Tallahassee. "Differential Sensitivity to Odors."

D. TUCKER and T. SHIBUYA, Florida State Univ., Tallahassee. "A Physiologic and Pharmacologic Study of Olfactory Receptors."

J. Y. LETTVIN and R. C. GESTELAND, Massachusetts Institute of Technology, Cambridge. "Speculations on Smell."

ELECTRICAL AND CHEMICAL RECEPTORS

C. EYZAQUIRRE and H. KOYANO. "Origin of Sensory Discharges in Carotid Body Chemoreceptors."

R. W. MURRAY, Univ. of Birmingham, England. "Receptor Mechanisms in the Ampullae of Lorenzini of Elasmobranch Fishes."

M. V. L. BENNETT, Columbia Univ., New York. "Electroreceptors in Mormyrids."

J. BOECKH, K. E. KAISSLING, and D. SCHNEIDER, Max-Planck Inst., Tubingen, Germany. "Insect Olfactory Receptors."

M. L. WOLBARSHT, Naval Medical Research Inst., Bethesda, Md. "Receptor Sites in Insect Chemoreceptors."

JULIUS ADLER, Univ. of Wisconsin, Madison. "Chemotaxis in *Escherichia coli*."

L. VINNIKOV, Academy of Sciences of U.S.S.R., Leningrad. "Principles of Structural, Chemical, and Functional Organization of Sensory Receptors."

PHOTORECEPTORS

R. HUBBARD, D. BOWNDS, T. YOSHIZAWA, Harvard Univ., Cambridge. "The Chemistry of Visual Photoreception."

C. D. B. BRIDGES, Univ. of London, England. "Absorption Properties, Interconversions, and Environmental Adaptation of Pigments from Fish Photoreceptors."

R. A. WEALE, Univ. of London, England. "Highlight Intensities and Photo-Chemical Reactions of Human Visual Pigments in situ."

G. WALD and P. BROWN, Harvard Univ., Cambridge, Mass. "The Mechanism of Human Color Vision and Color Blindness."

R. M. EAKIN, Univ. of Calif., Berkeley. "Evolution of Photoreceptors."

O. TRUJILLO-CENOZ, Inst. de Invest. de Ciencias Biol., Montevideo, Uruguay. "Structural Organization of the Arthropod Eye."

E. YAMADA and T. ISHIKAWA, Kyushu Univ., Fukuoka, Japan. "Fine Structure of the Horizontal Cells in some Vertebrate Retinae."

J. E. DOWLING and B. B. BOYCOTT, Johns Hopkins Univ., Baltimore, Md. and Univ. College, London, England. "Organization of the Primate Retina: Fine Structure of the Inner Plexiform Layer."

W. A. HAGINS, N.I.H., Bethesda, Md. "Electrical Signs of Information Flow in Photoreceptors."

J. W. KUIPER, J. T. LEUTSCHER-HAYELHOFF, Natuur Kundig Lab. der Rijks Univ., Groningen, Netherlands. "Linear and Non-linear Responses from Compound Eye of Calliphora erythrocephala."

A. BORSELLINO, M. G. F. FUORTES, and T. G. SMITH, Univ. of Genoa, Italy and N.I.H., Bethesda, Md. "Visual Responses in Limulus."

R. M. BENOLKEN, Univ. of Minnesota, Minneapolis. "Regenerative Transducing Properties of a Graded Visual Response."

H. STIEVE, Zool. Inst., Aachen, Germany. "Interpretation of the Generator Potential in Terms of Ionic Processes."

K. T. BROWN, K. WATANABE, M. MURAKAMI, Univ. of Calif. Medical Center, San Francisco. "Early and Late Receptor Potentials of Monkey Cones and Rods."

R. A. CONE, Harvard Univ., Cambridge, Mass. "Early Receptor Potential of the Vertebrate Eye."

W. L. PAK, Univ. of Chicago, Illinois. "Some Properties of the Early Electrical Response in the Vertebrate Retina."

J. Y. LETTVIN, J. R. PLATT, G. WALD, K. T. BROWN, General Discussion: "Early Receptor Potential."

W. E. REICHARDT, Max-Planck Inst., Tubingen, Germany. "Quantum Sensitivity of Light Receptors in the Compound Eye of the Fly Musca."

J. SCHOLES, The Univ. of St. Andrews, Scotland. "Discontinuity of the Excitation Process in Locust Visual Cells."

R. L. PURPLE and F. A. DODGE, Univ. of Minnesota, Minneapolis and Rockefeller Inst., New York. "Interaction of Excitation and Inhibition in the Eccentric Cell in the Eye of Limulus."

H. B. BARLOW, Univ. of Calif. Berkeley. "Optic Nerve Impulses and Weber's Law."

A. L. BYZOV, Acad. of Sciences, U.S.S.R., Moscow. "Functional Properties of Different Cells in Cold-Blooded Retina."

T. TOMITA, Keio Univ., Tokyo, Japan. "Electrophysiological Study of the Mechanisms Subserving Color Coding in the Fish Retina."

R. L. deVALOIS, Indiana Univ., Bloomington. "Analysis and Coding of Color Vision of the Primate Visual System."

DATA PROCESSING

A. BORSELLINO, C. A. TERZUOLO, R. POPPELE, Univ. of Genoa, Italy and Univ. of Minn., Minneapolis. "Transfer Functions of the Slowly Adapting Stretch Receptor Organ of Crustacea."

M. J. COHEN, Univ. of Oregon, Eugene. "The Dual Role of Sensory Systems: Detection and Setting of Central Excitability."

D. BURKHARDT, Zool. Inst. der Univ., München, Germany. "Mechanoreception in Orthropoda."

E. GETTRUP, Univ. of Copenhagen, Denmark. "Sensory Mechanisms in Locomotion: The Campaniform Sensilla of the Insect Wing and their Function during Flight."

J. E. AMOORE, U.S. Dept. of Agriculture, Albany, Calif. "Psychophysics of Odor."

POST GRADUATE TRAINING COURSES

Summer 1965

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 1965, 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. (This last course was initiated this year, and is therefore in the same stage of development that the course on bacterial viruses was twenty years ago.) 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
Joseph S. Gots, University of Pennsylvania
Assistants: E. H. Postel, M. G. Prato

SEMINARS:

Paul Howard-Flanders, Dept. of Microbiology, Yale University School of Medicine: "Synapsis and Integration in Genetic Recombination."

Gordon Lark, Dept. of Physics, Kansas State University: "Regulation of Chromosome Replication in *E. coli.*"

Kenneth Sanderson, Dept. of Biology, Brookhaven National Laboratory: "Conjugation Analysis in *Salmonella typhimurium.*"

Elias Balbinder, Dept. of Bacteriology & Botany, Syracuse University: "The Fine Structure of the Tryptophan Operon in *Salmonella typhimurium.*"

Michio Oishi, Dept. of Biology, Princeton University: "Replication of Spore DNA of *B. subtilis*"

Louis Baron, Walter Reed Army Research Institute: "Transfer of Episomes Between Bacterial Genera."

Alan Garen, Inst. of Molecular Biology, Yale University: "Mutations That Alter the Genetic Code of Bacteria."

V. N. Iyer, Microbiology Research Inst., Canada Dept. of Agriculture: "Integration and Recombination in DNA-mediated Transformation"

Richard Novick, The Rockefeller Institute: "Extra Chromosomal Heredity in Bacteria"

Maurice Fox, Dept. of Biology, Mass. Inst. of Technology: "The Mechanism of Integration of Transforming DNA"

Don Helsinki, Dept. of Biology, Princeton University: "Structural Characterization of Colicins and Their Genetic Determinants"

Matthew Meselson, The Biological Laboratories, Harvard University: "Some Aspects of Genetic Recombinations"

H. O. Halvorson, University of Wisconsin: "The Timing of Enzyme Synthesis in Synchronous Cultures of Yeast"

STUDENTS:

J. D. Baldeschwieler, Ph.D., Dept. of Chemistry, Harvard University
G. Bemski, Ph.D., Albert Einstein College of Medicine
R. Ehring, Ph.D., Carnegie Institution of Washington, Genetics Research Unit
C. F. Fox, Ph.D., Dept. of Biological Chemistry, Harvard Medical School
M. Goulian, M.D., Massachusetts General Hospital
D. D. Henley, Ph.D., Princeton University
R. R. Hewitt, Ph.D., M.D. Anderson Hospital & Tumor Institute, University of Texas
L. M. Joshi, M.Sc., Brookhaven National Laboratory
S. Koenig, Ph.D., IBM Watson Laboratories
J. D. Karam, B.S., Biochemistry Dept., University of North Carolina
N. M. Kredich, M.D., NIAMD, National Institutes of Health
B. P. Llanes, B.S., Dept. of Microbiology, New York University
A. Maeda, Ph.D., Dept. of Genetics, University of Wisconsin
U. Maitra, Ph.D., Dept. of Molecular Biology, Albert Einstein College of Medicine
M. Matsuhashi, Ph.D., University of Wisconsin Medical School, Dept. of Pharmacology
A. Novogrodsky, M.D., Dept. of Molecular Biology, Albert Einstein College of Medicine
A. M. Skalka, Ph.D., Carnegie Institution of Washington, Genetics Research Unit
A. M. Van Arendonk, B.A., University of Illinois
C. Wagner, M.S., Dept. of Biochemistry, Vanderbilt University
Yun-Chi Yeh, Dept. of Biological Chemistry, University of Michigan Medical School

2) BACTERIAL VIRUSES: July 8th to August 3d.

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:

R. S. Edgar, California Institute of Technology
C. Steinberg, Oak Ridge National Laboratory
Assistants: R. Russell, J. King

SEMINARS:

J. D. Watson, Harvard University, Cambridge, Mass.: "In Vitro Suppression"
M. Smith, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.: "Phage Chromosomes"
T. F. Anderson, Institute for Cancer Research, Philadelphia, Pa.: "Structure of Bacteriophages"
J. Wiberg, University of Rochester, New York: "Biochemical Genetics of T4"
N. Zinder, Rockefeller Institute, New York: "Little Phages"
K. Paigen, Roswell Park Memorial Institute, New York: "Host Induced Modification"
W. Dove, University of Wisconsin, Madison: "Life Cycle of the Lambda Chromosome"
A. Campbell, University of Rochester, New York: "Steric Effects in Lysogenization"
Cyrus Levinthal, Massachusetts Institute of Technology, Cambridge, Mass.: "Phage Proteins and Messenger Stability"
G. Streisinger, University of Oregon, Eugene, Oregon: "Phenotypes and Genotypes"
F. Womack, Vanderbilt University, Nashville, Tennessee

STUDENTS:

G. Bemski, Ph.D., Albert Einstein College of Medicine
A. J. E. Colvill, Ph.D., University of Chicago
E. J. Fleissner, Ph.D., Rockefeller Institute
M. Gabor, Dr. Nat. Sci., Rockefeller Institute and Hungarian Academy of Sciences, Budapest
S. A. Galton, Ph.D., Polytechnic Institute of Brooklyn
I. C. Gunsalus, Ph.D., University of Illinois
A. F. Holloway, Ph.D., University of Manitoba
S. P. Karplus, B.A., Columbia University
T. R. Lindahl, M.D., Princeton University
S. W. Luborsky, Ph.D., National Institutes of Health
J. M. Lucas-Lenard, Ph.D., Rockefeller Institute
U. Maitra, Ph.D., Albert Einstein College of Medicine
B. L. Marrs, B.A., Western Reserve University
M. Matsuda, Ph.D., New York University Medical Center

A. D. McLachlan, Ph.D., California Institute of Technology and Trinity College, Cambridge, England

K. Moldave, Ph.D., Tufts University School of Medicine

A. Muhammed, Ph.D., Oak Ridge National Laboratory

A. Novogrodsky, M.D., Albert Einstein College of Medicine and Weizmann Institute of Science, Rehovoth, Israel

R. M. R. Rao, Ph.D., University of Illinois and National Chemical Laboratory, Poona, India

W. S. Shipp, B.S., University of Chicago

3) MICROBIOLOGY OF VERTEBRATE CELLS AND QUANTITATIVE ANIMAL VIROLOGY: August 5th to August 26th.

Preparation of primary and secondary chick and mouse embryo cell cultures; preparation of chick embryo cultures of heart fibroblast, lung, kidney, and iris epithelium; HeLa cells and L cells–growth in mass culture and in clones: isolation of clonal sublines of cells; tests for PPLO in cell cultures and elimination of PPLO. Karyotype analysis of cloned populations of cells. DNA and RNA synthesis in the division cycle of mammalian cells–an introduction to quantitative autoradiography. Plaque assay of Newcastle Disease Virus (NDV) on chick embryo cells. Assay and properties of rabbit pox virus. Hemagglutination assay of NDV and influenza. Quantitative neutralization with specific antiserum (anti-NDV). Animal virus growth in monolayer cell culture, effect of antimetabolites on viral growth. Histochemistry of viral infection, phenotypic mixing of NDV, genetic recombination of poxviruses, morphological transformation of cells by Rous sarcoma virus.

INSTRUCTORS:

P. I. Marcus, Albert Einstein College of Medicine
G. Sato, Brandeis University

SEMINARS:

H. Eagle, Dept. of Cell Biology, Albert Einstein College of Medicine, Bronx, N.Y.: "Biochemistry of Cultured Mammalian Cells"

C. Morgan, Dept. of Microbiology, College of Physicians and Surgeons, Columbia University, N.Y., N.Y.: "Electron Microscopy of Animal Virus Development"

E. R. Pfefferkorn, Dept. of Bact. & Immunology, Harvard Medical School, Boston, Mass.: "Conditional Lethal Mutants of Sindbis Virus"

R. Perry, Institute for Cancer Research, Philadelphia, Penn.: "On the Site of Cellular RNA Synthesis"

E. Robbins, Depts. of Microbiol. & Immunol., and of Cell Biology, Albert Einstein College of Medicine, Bronx, New York: "Cell Ultrastructure and Function"

S. Penman, Dept. of Biochemistry, Albert Einstein College of Medicine, Bronx, N.Y.: "Cellular Organization and Poliovirus Growth"

W. Joklik, Dept. of Cell Biology, Albert Einstein College of Medicine, Bronx, N.Y.: "Nucleic Acid Synthesis in HeLa Cells Infected with Vaccinia"

G. Sato, Dept. of Graduate Biochemistry, Brandeis University, Waltham, Mass.: "In Vitro Studies on the Mechanism of ACTH Action"

A. Granoff, St. Jude Hospital, Memphis, Tenn.: "Virus-Antibody-Cell Interaction"

R. Simpson, The Public Health Research Institute of The City of New York, N.Y., N.Y.: "The Genetics of Animal Viruses"

L. Crawford, The Biological Laboratories, Harvard University, Cambridge, Mass.: "Human Wart Virus DNA"

B. Roizman, Dept. of Microbiology, University of Chicago, Chicago, Illinois: "Nonpermissiveness in Infected Mammalian Cells"

R. Wagner, Dept. of Microbiology, The Johns Hopkins University, Baltimore, Maryland: "Interferon"

P. I. Marcus, Dept. of Microbiology & Immunology, Albert Einstein College of Medicine, Bronx, N.Y.: "Rubella Virus and Intrinsic Interference"

H. Nitowsky, Mount Sinai Hospital, Baltimore, Maryland: "Regulation of Enzyme Activity in Cell Culture"

H. Green, Dept. of Pathology, New York University School of Medicine, New York, N.Y.: "Differentiated Function in Cultured Fibroblasts"

J. Darnell, Depts. of Biochemistry and Cell Biology, Albert Einstein College of Medicine, Bronx, N.Y.: "Following Newly Formed RNA in HeLa Cells"

T. T. Puck, Dept. of Biophysics, University of Colorado School of Medicine, Denver, Colo.: "Cell Life Cycle Analysis"

STUDENTS:

R. J. Ash, M.S., University of Cincinnati Medical School
H. C. Birnboim, M.D., Albert Einstein College of Medicine
K. D. Brown, M.S., New York University Medical Center
Kiven-Sheng Chiang, B.S., Princeton University
M. Gabor, Dr. Nat. Sci., Rockefeller Institute
J. Kowal, M.D., Albert Einstein College of Medicine
A. Landy, B.A., University of Illinois
Z. J. Lucas, M.D., Stanford Medical School
A. I. Meisler, M.D., United States Naval Hospital
K. H. Muench, M.D., University of Miami
V. E. Shashoua, Ph.D., Massachusetts Institute of Technology
B. J. Smith, Ph.D., Albert Einstein College of Medicine
M. G. Smith, Ph.D., Cold Spring Harbor Laboratory of Quantitative Biology
M. Takeda, Ph.D., Rockefeller Institute

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; protoplasmic 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 concern stimulus storage during arrested growth, avoidance response, and the demonstration by Thurm of the feasibility of perfusing and injecting sporangiophores.

INSTRUCTORS:

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

SEMINARS:

W. Shropshire, "ATP response of Phycomyces to light stimuli."
M. Dennison, "Responses of Phycomyces to mechanical stretching."
M. Delbrück, "Survey of sensory transducers."
U. Thurm, "Comparative ultrastructure on sensory transducers."
U. Thurm, "The hair-plate sensilla of insects."
W. Pak, "Early receptor potentials of the vertebrate retinal rod."
D. Luck, "The mitochondria of Neurospora."
S. Luria, "All-or-none responses of bacterial cell membranes to bactericins."

STUDENTS:

G. H. Adam, Ph.D., Brown University
R. K. Clayton, Ph.D., Kettering Research Laboratory
T. G. Ebrey, M.S., University of Chicago
E. Goodell, B.S., California Institute of Technology
W. L. Pak, Ph.D., University of Chicago
E. Silverstein, Ph.D., Downstate Medical Center
U. Thurm, Ph.D., Max-Planck Institut für Biologie
A. Winfree, Princeton University
K. L. Zankel, Ph.D., California Institute of Technology

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

J. T. August, L. Shapiro, B. Schwartz, B. Ginsberg, M. Watanabe; Albert Einstein College of Medicine
A. Bernheimer, D. Luria, L. Schwartz; NYU School of Medicine
S. Colowick, M. Colowick, P. Cassidy; Vanderbilt University
R. S. Edgar, R. Russel, J. King; California Institute of Technology
I. C. Gunsalus, R. Rao; University of Illinois
S. E. Luria; Massachusetts Institute of Technology
R. Novick; Rockefeller Institute
K. Paigen; Roswell Park Memorial Institute of Health Research, Inc.
U. Thurm; Max-Planck Institut fur Biologie
F. Womack; Vanderbilt University

REPORTS OF SUMMER GUEST INVESTIGATORS

T. August,
M. Watanabe,
B. Schwartz,
B. Ginsberg,
L. Shapiro

The projects we worked on this past summer at Cold Spring Harbor are the following:

Dr. M. Watanabe, a postdoctoral fellow, and Mr. B. Schwartz, a student in the M.D.-Ph.D. program here at Albert Einstein College of Medicine, studied techniques for the isolation of RNA bacteriophage. Their work primarily involved methods for the selective inhibition of DNA but not RNA bacteriophage with certain drugs, i.e., mitomycin, streptonigrin, 5-fluorodeoxyuracil, rubidomycin and nalidixic acid. Using these techniques, they isolated and began the characterization of phage from several different sewage areas. They also found that another drug, phleomycin, inhibited RNA phage multiplication in *E. coli* and began a study of the mechanism of this inhibition. This study benefited considerably from the advice and suggestions of members of the laboratory staff and summer visitors.

Mr. B. Ginsberg, another student in the M.D.-Ph.D. program, and I worked on the purification of RNA virus RNA polymerase enzymes. Our principal effort was in developing the use of the polyacrylamide gel electrophoresis technique for purification of this and other enzymes. The uninterrupted working schedule at Cold Spring Harbor was mandatory in these experiments.

Mrs. L. Shapiro, a predoctoral student, continued her studies on base analogue incorporation in vitro with an RNA virus RNA polymerase.

EXTRACHROMOSOMAL INHERITANCE IN BACTERIA

R. Novick,
L. Fooner

Genetic analysis of the penicillinase plasmids of *Straphylococcus aureus* was continued along two lines:

A. (L. Fooner). Previous work had shown that the ability of phage preparations to transfer by transduction the capacity to produce penicillinase is inactivated exponentially by UV and has a UV-sensitive target about the same size as that of the viable phage particle. This was interpreted as suggesting that the penicillinase determinant has no genetic homolog in the plasmid negative recipient cell with which the UV-inactivated plasmid can recombine and be rescued. Our study was designed to find out whether in similar experiments using a plasmid-positive recipient, rescue of UV-inactivated plasmid-transducing elements could take place. The results obtained were that UV irradiation of the transducing phage preparation stimulates recombination between the donor and recipient plasmids by 3-4 fold over the unirradiated control. Significant rescue of donor plasmid markers could not, however, be demonstrated. These findings were interpreted as suggesting that at least two types of UV damage occur. One type inactivates the entire plasmid, no part of which can then be rescued by subsequent recombination within the recipient cell. The other type does not inactivate the element but markedly enhances the probability of its undergoing recombination with a homologous element in the recipient cell. It remains to be seen whether these different UV effects result from two chemically different types of damage or from a single type of chemical damage that produces different genetic effects according to its location in the plasmid.

B. (R. Novick). A high-frequency transducing element for one of the plasmids had previously been discovered. This element was isolated in a transductant in a cross in which phage produced by UV induction of the donor strain 8325 (γ_w) was used to infect the recipient strain 8325. The donor plasmid, γ, bears, in addition to the penicillinase marker, determinants of resistance to mercuric iron and to erythromycin. Selection was for erythromycin resistance. The transductant clone under consideration was found to have received, of the known plasmid markers, only the erythromycin resistance determinant, and to produce erythromycin-transducing elements in the proportion of 10-50% of the plaque-forming units produced. The results obtained during the summer, in studying this system, were: Strain 8325 harbors two non-coimmune prophages, P1 and P2. P1 is a generalized transducing phage while P2 is ordinarily incapable of mediating transduction either of chromosomal or of extrachromosomal genes. When the transduction of erythromycin resistance was carried out using low multiplicities of infection and an apparently nonlysogenic recipient, 1030, the majority of the transductants were nonlysogenic, sensitive to P1 and P2 and unable to produce either plaque-forming particles or erythromycin-transducing particles. But when such transductants were lysogenized, either with P1 or with P2, they became capable of producing erythromycin-transducing particles at high frequency as well as the expected plaque-forming units of the appropriate phage. Further, when the nonimmune, nonlysogenic transductants were lysogenized with either of two additional, apparently unrelated phages, 80α or PQ4, they again became capable of producing Hft lysates. Phage 80α is ordinarily a generalized transducing phage while PQ4 is ordinarily incapable of mediating transduction. Further study of the nature and genetic makeup of this high-frequency transducing element is in progress.

MODE OF ACTION OF BACTERIAL TOXINS

Alan W. Bernheimer

Purified preparations of two bacterial toxins, (a) streptolysin S, which is formed by pathogenic streptococci, and (b) alpha toxin, which is produced by pathogenic staphylococci, were studied. Both toxins are lethal for laboratory animals and are potent cytolytic agents, in vitro. They destroy cells by altering the cell membrane but the biochemical nature of the lesions produced in the cell membranes is not understood. The cytotoxicity of streptolysin S can be inhibited by minute amounts of certain phospholipids including some of those known to be essential constituents of membranes. It follows that the action of the toxins might involve enzymic alteration of the membrane phospholipids, and the experiments carried out were designed to test the hypothesis that purified phospholipids might be hydrolyzed by one or both toxins.

Mixtures of toxins and phospholipids buffered with phosphate at pH 7.4 were incubated at 37° for 3 to 5 hours. The reaction mixtures were evaporated to dryness under reduced pressure, the residues extracted with ethanol, benzene, or petroleum ether, and the extracts analyzed by thin layer chromatography. The lipids employed were phosphatidyl choline, phosphatidyl serine, phosphatidyl ethanolamine and diphosphatidyl glycerol. In no instance was splitting of phospholipid demonstrable. Splitting of diphosphatidyl glycerol was not excluded because it could not be recovered from the reaction mixture with the solvents employed. The negative results suggest that the toxic proteins do not function as enzymes, but perhaps as substances having a strong affinity for a particular membrane constituent in analogy with an antibody for antigen.

THE rII GENE

S. P. Colowick,
M. S. Colowick,
P. Cassidy

Studies were continued on the ATP content of bacteriophage-infected *E. coli* cells, with the aim of determining whether the rII region of the phage genome has to do with the control of ATP synthesis. In this connection, some rII mutants of phage T_2 were selected, in order to study the effect on ATP content of sequential infection with complementary mutants. However it was found, contrary to expectation, that complementation was largely abolished, with T_2rII as well as T_4rII phages, when the time between infection and superinfection was 5 min or longer. Other studies indicated that primary infection with a T_2rII or T r+ phage did not prevent subsequent propagation of a superinfecting T_2h phage. The results suggest that expression of a functional rII cistron may be extremely short-lived when a complementary functional cistron is not present simultaneously.

PHAGE CONFERENCE

August 29—September 1, 1965

Following the completion of the summer program, the auditorium and housing facilities here were utilized for the annual phage conference, a four-day meeting attended by most of the active phage workers in the country. Fifty-eight papers were presented in the program listed below; the conference was attended by 190 people.

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

Chairman—C. A. Thomas (Dept. Biophys., Johns Hopkins)

Katherine Brooks (Dept. Mol. Biol., Berkeley): "Induction of λ in a recombination deficient strain of *E. coli*."
Lia Fischer-Fantuzzi (Dept. Biol., M.I.T.): "Cryptic and cryptogenic λ prophages."
L. Siminovitch (Ontario Cancer Inst., Toronto): "Defective lysogeny in K12 (λ)."
J. Zissler (U. Rochester): "Steric facilitation in lysogenization by phage λ."
G. M. Kayajanian (U. Rochester): "The relation between the number of genetic markers carried by selected gal− transducing phage and the densities of these λdg."
Rosemary Eskridge (Roswell Park, Buffalo): "Genetic specificity of host-controlled variation."
R. Hausmann (S. W. Center, Dallas): "Mutual exclusion in phages related to T3."
B. A. Molholt (Indiana U.): "Mechanism of non-glucosylated T-even phage restriction."
S. E. Luria (Dept. Biol., M.I.T.): "Revel-Luria. Genetics of restriction of non-glucosylated T-even phages."
Kay Fields (Dept. Biol., M.I.T.): "Mechanism of P2 prophage interference against T-even phages."
E. Yarosh (Dept. Biol., M.I.T.): "Interference between T4 and MS2."

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

Chairman—S. E. Luria (Dept. Biol., M.I.T.)

R. Doherty (Dept. Bioch., Stanford): "λ DNA strand selective transcription by *E. Coli* polymerase in vitro."
Anne Joyner, L. Isaacs, W. Sly, H. Echols (Dept. Bioch., U. Wisc.): "Genetic control of λm-RNA and λ DNA replication after induction or infection."
Ann Skalka (Dept. Genetics, Carnegie Inst.): "Genetic transcription in phage λ."
M. Terzi (Dept. Biol., M.I.T.): "RNA and protein synthesis in λ-infected cells."
M. H. Green (Dept. Biol., LaJolla): "The repressor of phage λ."
D. Shub (Dept. Biol., M.I.T.): "Functional stability of various m-RNA molecules produced by SP-01."
R. Haselkorn (Dept. Biophys., U. Chicago): "The synthesis and functioning of late and early m-RNA in *E. coli* B infected with T4."
J. Hosoda (Dept. Biol., M.I.T.): "Acrylamide gel analysis of T4 proteins and their control."
M. Levine, L. W. Cohen (Med. Sch., U. Michigan): "The electrophoretic analysis of proteins synthesized after infection with phage P22."

Monday, August 30, 9:30 A.M.

Chairman—Cyrus Levinthal (Dept. Biol, M.I.T.)

D. Hall, I. Tessman (Dept. Biol. Sci., Purdue): "A study of T4-induced dCMP deaminase."
J. S. Wiberg (U. Rochester Sch. Med.): "Biochemical studies identifying genes in *am* and *ts* mutants of T4 that control dCTPase and thymidylate kinase."
M. L. Dirksen (Dept. Biophys., Johns Hopkins): "dCMP-hydroxymethylases isolated from the permissive host CR63."
S. P. Champe (Dept. Biol. Sci., Purdue): "Biochemical studies on T4 amber mutants."
J. W. Little, A. D. Kaiser, I. R. Lehman (Dept. Bioch., Stanford): "Purification and characterization of λ exonuclease."
I. Takahashi, F. Tomita (McMaster U., Ontario): "Degradation of *B. subtilis* DNA during the multiplication of a transducing phage."
Tamiko Kano-Sueoka (Dept. Biol., Princeton): "Modification of leucyl-sRNA after phage infection."
R. Rolfe (Dept. Biol., M.I.T.): "Polyribosomes in phage T4 infection."
Joyce Emrich (Inst. Mol. Biol., U. Oregon): "The effect of frame-shift mutations on the lysozyme of phage T4."
H. Eddleman (Dept. Biol. Sci., Purdue): "Polypeptides in T4."
D. Engelhardt, R. Webster, N. D. Zinder (Rockefeller Inst.): "In vitro synthesis of a suppressible coat mutant of f2."

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

Chairman—A. H. Doermann (Dept. Genetics, U. Washington)

J. Abelson (Dept. Biophys., Johns Hopkins): "The structure of the T5 DNA molecule."
D. Freifelder, A. K. Kleinschmidt (Div. Med. Phys., Berkeley): "Evidence for strand breaks in T7 from electron micrographic measurements."
P. D. Ross, R. L. Scruggs (N.I.H.): "Viscosity studies of the DNA of T4 mutants."
F. M. Kahan (Dept. Chem., Harvard): "The basis for the unusual physical properties of DNA from *Subtilis* phages PBS-2 and SP8."
H. Lozeron, W. Szybalski (McArdle Lab., U. Wisc.): "Incorporation of 5-fluorodeoxyuridine into the DNA of *B. subtilis* phage PBS-2."
H. Kubinski, Z. Opara-Kubinska, W. Szybalski (McArdle Lab., U. Wisc.): "Patterns of interaction between denatured DNA of T phages and poly-IG or poly-U."
A. W. Kozinski, P. B. Kozinski (Wistar Inst., Phila.): "Initiation of T4 DNA replication."
T. H. Lin, A. W. Kozinski (Wistar Inst., Phila.): "Thymine economy in T5-infected *E. coli* B."

Tuesday, August 31, 9:30 A.M.

Chairman—R. S. Edgar (Div. Biol. Caltech)

Sylvia M. Zottu (Dept. Bioch., U. Wisc.): "Biological and chemical studies on bacteriophage Chi."
D. H. Walker (Inst. Cancer Res., Phila.): "Morphological variants of P1."
G. N. Gussin (Biol. Labs., Harvard): "Complementation between amber mutants of phage R17."
June Rothman (Rockefeller Inst.): "Heterozygosis in phage f1."
D. Pratt (Dept. Bact. U. Wisc.): "Conditional lethal mutants of coliphage M-13."
R. Erikson (Sch. Med., U. Colorado): "Some observations on the structure of phage specific double-stranded RNA."
C. Weissmann, M. Billeter, E. Vinuela, M. Libonati (N.Y.U. Sch. Med.): "The role of double-stranded RNA in the replication of phage MS-2."
H. F. Lodish (Rockefeller Inst.): "Gene action and control in the replication of the RNA phage, f2."
D. Denhardt (Biol. Labs., Harvard): "The mechanism of ϕx-174 replication."
T. Naito, N. Yamamoto (Fels Res. Inst., Phila.): "Phage sensitivity and mutation of *S. typhimurium*."
N. Yamamoto (Fels Res. Inst., Phila.): "Formation of P221 phage."
M. Takahashi, N. Yamamoto (Fels Res. Inst., Phila.): "Genetic cross between serologically unrelated bacteriophages P22 and P221b."

Tuesday, August 31, 7:30 P.M.

Chairman—T. F. Anderson (Inst. Cancer Res., Phila.)

L. A. MacHattie, C. C. Richardson, D. A. Ritchie, C. A. Thomas (Dept. Biophys., Johns Hopkins): "Physical evidence for a terminal redundancy in T*2 DNA molecules."
G. Mosig (Dept. Genetics, Carnegie Inst.): "Circular permutation of incomplete T4 genomes."
E. Shahn, A. W. Kozinski (Wistar Inst., Phila.): "Are progeny phages containing parental DNA of a different-than-average density?"
E. Goldberg (Dept. Genetics, Carnegie Inst.): "Length between genetic markers on T4 DNA."
M. Rhoades (Dept. Biophys., Johns Hopkins): "The structure of intracellular P22 DNA."
D. J. Cummings (Dept. Microbiol., U. Colorado Med. Center): "Internal organization of λphage DNA."
V. C. Bode (Dept. Biol. Chem., U. Maryland): "Intracellular forms of λ DNA."
W. F. Dove (McArdle Lab., U. Wisc.): "The development of the λ chromosome."
D. Hoffman, I. Rubenstein (Dept. Mole. Biophys., Yale): "Physical studies of λ lysogeny."
B. Egan (Dept. Bioch., Stanford): "Genetic activity of λDNA fragments."
C. A. Thomas (Dept. Biophys., Johns Hopkins): "The mechanism of genetic recombination."
D. Ritchie (Dept. Biophys., Johns Hopkins): "Terminal heterozygosis in T2."

Wednesday, September 1, 9:30 A.M.

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

L. M. Kozloff (Dept. Microbiol., U. Colorado): "Pteridine conjugates as phage structural components."
J. J. Protass, D. Korn (N.I.H.): "Selective inhibition of phage T4 maturation by Actinomycin D."
M. Piechowski (Dept. Genetics, U. Wisc.): "T4 maturation in the presence of puromycin."
M. Susman (Dept. Genetics, U. Wisc.): "The effects of acridines on phage T4 development."
S. D. Silver (Virus Lab., Berkeley): "The basis of acridine resistance in mutants of bacteriophages T2 and T4."
T. Furukawa, N. Yamamoto (Fels Res. Inst., Phila.): "Inactivation of P22 by ferrous ion."
D. B. Fisher (Biol. Sci., Princeton): "Some biochemical evidence for the Luria-Latarjet effect."
W. Harm (W. W. Center, Dallas): "Repair effects in phage irradiated by natural sunlight."
E. Shahn, A. W. Kozinski (Wistar Inst., Phila.): "On a mechanism of DNA rescue from UV-inactivated T4 phage."
R. Levisohn (Dept. Biol. Sci., Purdue): "Phenotypic reversion of T4*r*II phage mutants by hydroxylamine."
A. H. Doermann (Dept. Genetics, U. Wash, Seattle): "Genetic analysis of phages made in the presence of FUDR."
W. V. Howes (Dept. Biol., Ill. Inst. Techn.): "A phase-mediated interruption of translation in *E. coli*."

NATURE STUDY COURSES

Children of Ages 6 to 16

During the summer of 1965, thirteen courses in Nature Study were conducted in two monthly sessions. The enrollment this year was 299 students. The course offerings included:

General Nature Study (ages 6, 7)
General Ecology (8, 9)
Bird Ecology (8, 9)
Earth Science (10, 11)
Botany-Entomology (9, 10)
Fresh Water Biology (10, 11)
Entomology (10, 11)
Vertebrate Zoology (10, 11)
Seashore Life (10, 11)
Advanced Ecology (12-14)
Plant Ecology (12-14)
Ichthyology-Herpetology (15, 16)
Invertebrate Zoology (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.

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 sixth year contribution of the Huntington Federal Savings and Loan Association. This provided nature study scholarships for 17 students of the Huntington elementary schools.

NATURE STUDY WORKSHOP FOR TEACHERS

The tenth annual Workshop in Nature Study was offered from June 28th to July 9th, 1965. 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.

Twenty-two 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.

LABORATORY SUPPORT

As in previous years, most of the support for the Laboratory has come from Federal grants. A list of all grants and contracts is given on page 26.

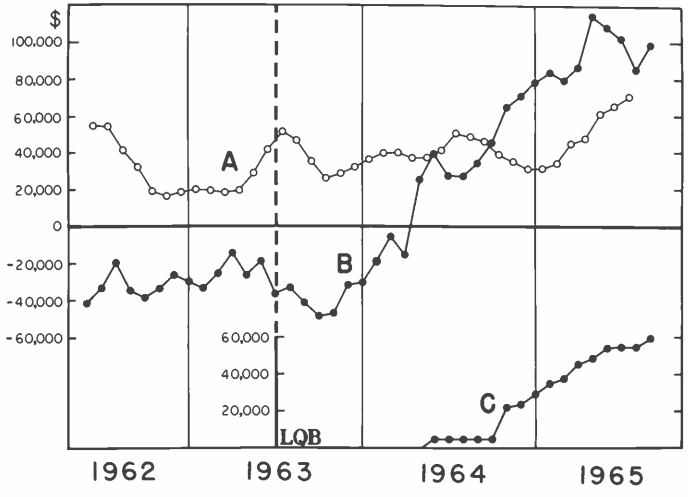
General support for the operation of the Laboratory has come from the Long Island Biological Association ($9,362 in the fiscal year ending April 30, 1965); from the Carnegie Institution of Washington ($25,421); from the Hoyt Foundation ($5,000); and from the Foundation for Microbiology through Dr. Selman A. Waksman ($5,000). In addition, a contribution of $2,500 has been received from each of several industrial organizations, and contributions of $50 or more have been received from many scientists and others throughout the country; these are listed later in this report as "Sponsors" and "Friends," respectively.

During the past year, the immediate financial position has continued to improve. This trend is shown graphically (below), where the monthly disbursements, the cash reserve, and the progress of the fund drive by the new Laboratory are all shown on the same scale. From this comparison certain significant facts emerge:

I). The curve of total monthly disbursements (curve A) shows that the Laboratory of Quantitative Biology has largely succeeded in keeping its expenses pared down to the absolute minimum level that its predecessor, the Biological Laboratory, had been forced to maintain; in other words, the general neglect of maintenance was allowed to continue. (The slight increase in year-round, as opposed to summer disbursements, is attributable to the inclusion of certain expenses previously met by the Carnegie Institution.)

II). The sharp rise in the cash reserve (curve B), seen to begin at the end of 1963, was due mainly to a great increase in the sales of Symposium volumes. Recently, however, this increase in cash reserve has been maintained as a result of the fund-raising activities of the Laboratory (curve C).

III). The present cash reserve is equal to about two months' average disbursements. It is therefore not so large that we could embark with impunity upon a large scale act of rehabilitation, the cost of which has been estimated at about $750,000. Still less could we plan to sequester any of this reserve as an endowment.



A. Total monthly disbursements by the Biological Laboratory and, from July 1963, its successor, the Laboratory of Quantitative Biology.

B. The unobligated cash reserve of the Laboratory.

C. That part of the cash reserve which has accumulated as a result of the Laboratory's fund drive.

FINANCIAL REPORT

For the period May 1, 1964—April 30, 1965

As of April 30, 1965 our assets were as follows:

Cash	$111,894.40	
Accounts receivable	31,493.60	
Inventory of books	9,980.14	
Prepaid expenses	1,593.98	
Certificate of time deposit	25,000.00	
Investments—U. S. Government obligations (market value $24,987.47)	24,853.29	
Land, buildings and equipment	514,978.20	
Total		$719,793.61

Our liabilities were as follows:

Accounts payable	28,296.92	
Unexpended grants and contracts	47,091.96	
Deferred income	4,441.00	
Dr. William J. Matheson bequest	20,000.00	
Net worth	619,963.73	
Total		$719,793.61

For the year 1964-1965, our receipts were as follows:

Grants and contracts		$277,832.00
Contributions:		
Sponsors	37,500.00	
Friends	7,512.07	
Carnegie Institution of Washington	25,421.50	
Long Island Biological Association	9,362.18	
Wawepex Society	3,200.00	$ 82,995.75
Book Sales (Cold Spring Harbor Symposia on Quantitative Biology)	84,192.48	
Dining hall and dormitories	59,556.86	
Tuition fees	25,230.85	
Summer laboratory fees	3,000.00	
Symposium registr ion fees	2,780.00	
Interest on time deposit and U. S. Government obligations	453.35	
Miscellaneous	185.69	
Total		$536,226.98

Our expenditures were as follows:

Research and educational programs	$254,949.45	
Administration and general	53,546.66	
Plant operations and maintenance	74,456.39	
Publications	35,541.40	
Dining hall and dormitories (inc. provision for depreciation)	64,542.33	
Total		$483,036.23

Excess of Income over Expenditures 1964-1965 $ 53,190.75

GRANTS AND CONTRACTS

May 1, 1964 to April 30, 1965

Grantor	Investigator	Total Award	Grant Number
	RESEARCH GRANTS		
National Science Foundation	Dr. Cairns	$116,400.00	GB-1690*
National Institutes of Health	Dr. Margolin	19,579.00	5-K3-GM-6887-02
National Institutes of Health	Dr. Margolin	47,637.00	GM-07178-05
National Institutes of Health	Dr. Speyer	64,755.00	GM-12371-01
National Institutes of Health	Dr. Umbarger	19,662.00	GM-07675-04
National Institutes of Health	Dr. Umbarger	8,164.00	AI-03501-05
The Rockefeller Institute	Dr. Cairns	85,000.00	RF-63042**
Ass'n. for The Aid of Crippled Children	Dr. Umbarger	6,500.00	
Nat'l. Ass'n. for Retarded Children	Dr. Umbarger	6,500.00	
	TRAINING GRANTS		
National Institutes of Health	Summer Courses	47,866.00	GM-890-09
National Science Foundation	Undergraduate Research Participation	14,000.00	GE-4192
National Science Foundation	Pseudomonas Mtg.	2,700.00	GB-2608
National Science Foundation	Phycomyces Course	20,000.00	GB-3149
	SYMPOSIUM GRANTS		
Atomic Energy Commission		7,000.00	AT(49-9)-2544
Air Force Office of Scientific Research		5,000.00	AF-AFOSR-426-64
National Institutes of Health		12,050.00	CA-02809-10
National Science Foundation		3,500.00	GB-2255
	SPECIAL GRANTS		
National Science Foundation	Site Survey and Repair of Sewage Disposal System	45,600.00	GB-2266

*This grant covers a two-year period
**This grant covers a five-year period

LABORATORY STAFF

1964 - 1965

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*Guest Investigator

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Geigy Chemical Corporation
The Hoyt Foundation
International Business Machines Corp.
The Lilly Research Laboratories
Eli Lilly and Company
The Merck Company Foundation
Monsanto Fund
Union Carbide Corporation
The Upjohn Company

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