

LONG ISLAND BIOLOGICAL ASSOCIATION

ANNUAL REPORT

OF

THE BIOLOGICAL LABORATORY

COLD SPRING HARBOR
LONG ISLAND, NEW YORK

~~1952~~ 1953



LONG ISLAND BIOLOGICAL ASSOCIATION

INCORPORATED 1924

ANNUAL REPORT

OF

THE BIOLOGICAL LABORATORY

FOUNDED 1890

SIXTY-THIRD YEAR

1952 - 1953

The Biological Laboratory was organized in 1890 as a department of the Brooklyn Institute of Arts and Sciences . It was financed and directed by a Board of Managers, consisting mainly of local residents. In 1924 this group incorporated as the Long Island Biological Association and took over the administration of the Laboratory.

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John K. Roosevelt Oyster Bay, N. Y.

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E. C. MacDowell Cold Spring Harbor, N. Y.
William B. Nichols Syosset, N. Y.
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Caryl P. Haskins Haskins Laboratory, New York
B. P. Kaufmann Carnegie Institution
Grinnell Morris Oyster Bay, N. Y.
Arthur W. Page Huntington, N. Y.
Franz Schneider Oyster Bay, N. Y.
Howland B. Stoddard Cold Spring Harbor, N. Y.

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Robert Chambers Marine Biological Laboratory
George W. Corner Carnegie Institution of Washington
Th. Dobzhansky Columbia University
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Ernst Mayr American Museum of Natural History
Mrs. Walter H. Page Cold Spring Harbor, N. Y.

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Blackford, Eugene 1890-1904	James, Walter B. 1926-27
Matheson, Wm. J. 1905-23	Page, Arthur W. 1927-40
Blum, Edward C. 1923	Murphy, Robert Cushman 1940-1952
Williams, T. S. 1924-26	

Laboratory Directors

Dean, Bashford 1880	Davenport, C. B. 1898-1924
Conn, Herbert W. 1891-98	Harris, Reginald 1924-36

Ponder, Eric 1936-40

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Abbott, Lyman 1896-1901	Flinsch, Rudolph 1909-17
Atkins, C. D. 1915-23	Francis, Mrs. L. W. 1923
Ayer, J. C. 1930-33	Frick, Childs 1924-29
Ayres, H. M. 1892-1900	Gager, C. S. 1915-17
Backus, T. J. 1890-1901	Hall, C. H. 1890-95
Blackford, Eugene 1890-1904	Harris, R. G. 1930-36
Blackford, Mrs. Eugene 1906-17	Harrison, R. G. 1926-51
Bleecker, C. M. 1926-45	Healy, A. A. 1896-1921
Bleecker, T. B. 1946-51	Heckscher, August 1902-17
Blum, E. C. 1923	Hendrix, Joseph 1890-97
Boody, D. A. 1890-1917	Hoagland, C. N. 1890-98
Brackett, G. C. 1904-08	Hooper, F. W. 1890-1914
Brower, G. V. 1899-1917	Hoyt, Colgate 1902-17
Brown, Addison 1890-1913	Hulst, G. D. 1894-1900
Brown, J. S. 1908-17	Huntington, L. D. 1894-1900
Bumpus, H. C. 1903-12; 1927-30	James, O. B. 1926-41
Butler, N. M. 1903-17	James, W. B. 1902-17; 1924-27
Cochran, D. H. 1890-1902	Jennings, H. S. 1924-27
Cole, K. S. 1940-43	Jennings, Walter 1906-17; 1924-33
Cole, W. H. 1934-52	Levermore, C. H. 1896
Coombs, W. J. 1890-1910	Johnson, D. S. 1924
Crittenden, W. H. 1922-23	Jones, F. S. 1899-1909
Crozier, W. J. 1928-44	Jones, J. D. 1890-95
Davenport, C. B. 1903-44	Jones, O. L. 1890-1913
Davenport, W. B. 1916-17	Jones, Mrs. O. L. 1907
de Forest, H. W. 1912-17; 1924-25	Jones, W. E. 1903-06
de Forest, R. W. 1902-17	Kahn, Mrs. O. H. 1924
Denbigh, J. H. 1923	Leffingwell, R. C. 1924-32
Detwiler, S. R. 1928-42	Lloyd-Smith, Wilton 1928-40
Doubleday, F. N. 1908-11	Low, Seth 1890-1902
Draper, George 1924-32	Lucas, F. A. 1905-17
Field, Marshall 1924-47	Lusk, Graham 1909-17
Fisher, G. C. 1924	MacCracken, H. M. 1890-1905
Fisk, H. D. 1924	Mather, Frederic 1890-1900

Matheson, W. J. 1901-22	Seamans, C. W. 1906-15
Mayer, A. G. 1903-17	Shapley, Harlow 1943-51
Merle-Smith, Mrs. Van S. 1931-50	Stimson, H. L. 1925-36
Mickleborough, John 1890-1917	Smith, H. C. 1913-17
Mills, D. H. 1946-52	Stewart, J. H. J. 1893-1917; 1924-26
Montant, A. P. 1902-09	Stockard, C. R. 1924-39
Morgan, T. H. 1924-28	Stratford, William 1890-1917
Newberry, J. S. 1890-93	Straubenmuller, Gustav 1911-17
Nichols, Acosta 1927-45	Strauss, Albert 1914-17
Nichols, J. W. T. 1910-17	Stutzer, Herman 1911-23
Noyes, H. F. 1902-21	Taylor, H. C. 1926-42
Osterhout, W. J. V. 1927-41	Thompson, Edward 1903-17
Overton, Frank 1924	Tiffany, L. C. 1892-1917
Palmer, L. M. 1899-1913	Urey, H. C. 1934-49
Parshley, H. M. 1924-33	Vanderbilt, W. K. 1924-43
Peabody, Julian 1911-17	Walter, H. E. 1924-43
Perkins, A. C. 1890-92	Webb, Alexander 1890-1902
Ponder, Eric 1937-41	Weld, F. M. 1914-17
Pratt, H. I. 1929-30	Wetmore, C. W. 1902-07
Prime, Cornelia 1909-17	White, S. V. 1890-1905
Raymond, J. H. 1890-1900	Williams, T. S. 1910-30
Rumsey, Mary H. 1924	Wilson, E. B. 1903-17
Swingle, W. W. 1924-44	Wood, Willis, D. 1926-52
Schiff, J. M. 1931-50	Woodbridge, C. L. 1894-1901
Schiff, M. L. 1924-31	Woodward, J. B. 1890-96
Scott, Donald 1911-17	Woodward, R. B. 1890-1914

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Stimson, Henry L. 1944-50

Walter, H. E. 1943-45

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Mrs. Winthrop Neilson
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William B. Nichols
Mrs. John W. Nields
Juliet Nourse
Charles P. Noyes
Mrs. Charles P. Noyes
Mrs. D. Chester Noyes
Mrs. D. Grinnell Noyes
Laurence G. Noyes
John Osborn
Mrs. John Osborn
Arthur W. Page
Mrs. Arthur W. Page
A. W. Page, Jr.
Mrs. Walter H. Page
Mr. Paul G. Pennoyer
Mrs. Paul G. Pennoyer
Isabel Peters
William C. Pierce
Mrs. E. Kaplan Pivnick
Collier Platt
Francis T. P. Plimpton
Keith R. Porter
Richard L. Porter
Mrs. Edward Everett Post
Frederic R. Pratt
Mrs. Frederick R. Pratt
H. Irving Pratt
Mrs. H. Irving Pratt

Richardson Pratt
Theodore H. Price
Paul Pryibil
Mrs. Paul Pryibil
Hale Pulsifer
Mrs. Hale Pulsifer
E. Racker
Roland L. Redmond
Mrs. Roland L. Redmond
Mrs. Lansing P. Reed
Mrs. Gordon Rentschler
Oscar W. Richards
Bernard J. Ridder
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Harry C. Robb
Charles S. Robertson
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Archibald B. Roosevelt
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George Emlen Roosevelt
John K. Roosevelt
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Walter N. Rothschild, Jr.
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Theodore F. Savage
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John M. Schiff
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REPORT OF THE DIRECTOR

The most important event of the past year was the completion of the building program of the Cold Spring Harbor Laboratories, resulting in a Lecture Hall to be used jointly by the Biological Laboratory and the Department of Genetics, and two new laboratory buildings for the Department of Genetics. This project, planned since 1946 and under construction since August, 1951, was finally completed in the spring of 1953. Formal opening ceremonies were held on May 29. Members of the Long Island Biological Association who live in the vicinity, a few of their friends, the staffs of the laboratories, and representatives of the trustees and officers of the Carnegie Institution of Washington and the Carnegie Corporation of New York gathered that evening in the Lecture Hall for a simple inaugural function.

The group was welcomed by Mr. Amyas Ames, President of the Association, who pointed out the unusual architectural features of the Lecture Hall—no parallel surfaces, no vertical walls, wave-shaped ceiling, and baffled rear wall—all designed for good acoustical effect. He recognized Mr. William Haible, the architect in charge of the building, who received enthusiastic applause. Mr. Ames stressed that the Lecture Hall "is dedicated to a purpose, and that purpose is the understanding of one man with another—understanding between scientists who will be brought together here to exchange ideas." The President introduced the Director of the laboratories, M. Demerec, who spoke briefly concerning the history of the two organizations.

The principal speaker of the evening was Dr. Vannevar Bush. He pointed out that here at Cold Spring Harbor we have "collaboration between two of the oldest scientific organizations in this country, Carnegie Institution of Washington and the Long Island Biological Association—a harmonious, effective, mutually beneficial collaboration." This joint effort is now going on under the shadow of war, but we must continue "to build those edifices of the mind without which not even the defense of the country is worth while." He emphasized the fact that the Carnegie Institution believes it should maintain its independence, and carefully refrain from that type of government subsidy which may carry control with it. Consequently the Institution may have to forego elaborate and expensive equipment; but "the day is not yet past when men with brains and very simple equipment and very simple methods can accomplish great things."

Dr. Bush said further that the Carnegie Institution carries on research in many fields: in astronomy and the earth sciences, in archeology, and in three branches of biology—embryology, plant physiology and photosynthesis, and, here in Cold Spring Harbor, heredity or genetics. In all the fields of science, particularly astronomy and physics, revolutionary progress is being made because of the rapid development of new methods. "But there is no science that is more fascinating, more intriguing, than the science of biology as it today flourishes. . . . Even the evolution of the stars is a simple matter, compared to the things that we approach when we investigate the great problem of life . . . And genetics shares this general tendency of the biological sciences."

Dr. Bush concluded as follows:

"For those who can delve into biological science as it begins to unfold today, there is an enormous challenge. If I were a young man I am sure that that would be the field I would plunge into. Every day it becomes far more attractive; and it touches the lives of all of us in countless ways. Moreover, those who here—on Long Island, in these laboratories—can delve into biological science are privileged indeed; for they can do so with no thought whatever as to the utility of their results. They can do so with no interference whatever on the part of any government, or any dictator, or any board of trustees, or anyone else—guided only by their own instincts as to what is important and what is worth while, judged only by their peers, with the entire world before them and with no interest except to enlarge the understanding of mankind, of his environment, and of himself. And they can do it in an atmosphere of scholarship, surrounded by men who are honored everywhere for their accomplishments, in a Mecca to which come the greatest men of the world in their field, in pleasant surroundings, and under the spur of keen competition—keen competition among equals on a pleasant and cordial plane. It is the purpose of the Carnegie Institution of Washington to extend this sort of privilege to a company of scholars. It is a privilege of you neighbors on Long Island to extend this opportunity to men of genuine intellect, who can qualify, and who can thus bear the torch for all the rest of us, in delving into some of the mysteries of life.

"And in these days when we fear that all of these efforts may be terminated in a struggle of desperate nations, in these days when our national problems bear heavily upon us, in these days when we all have to think tough thoughts, it is very much worth while to have among us a company that is bearing forward the understanding of many, for no reason whatever except that it is the privilege of man to try to understand.

"To this purpose these laboratories and this auditorium are dedicated. These buildings are a symbol of that confidence which we all have in the intellectual effort of those who will utilize it."

After the ceremonies in the Lecture Hall, staff members of the two laboratories held demonstrations of some of their current research in the new laboratory buildings, which were open for inspection.

Another very significant event of the past year was the purchase of property from the Estate of Mary E. Jones, which borders on the north the property on which the laboratory buildings are located, and extends along Bungtown Road towards the parcel adjoining the Sand Spit beach, acquired about ten years ago through gift and purchase from Mrs. Henry W. de Forest. The area of the new property is about 20 acres. One half of it was purchased by the Long Island Biological Association, and the other half by the Carnegie Institution of Washington. With the exception of two pieces of land, consisting of about 10 acres, the two laboratories now control all property along the Bungtown Road on the western shore of the inner harbor. The new property includes a swampy area transected by numerous streams originating from local springs, and a sandy area, as well as a well-wooded section. It is well adapted for experimental studies of a

wide variety of plants and animals in their natural habitat, and it will be used for this purpose by scientists working at the laboratories. In addition, the acquisition of this property insures the privacy that is essential for efficient operation of the laboratories.

Research

Wallace has been studying the effect of radiations on the genetic structure of populations of the common fruit fly (*Drosophila melanogaster*). Since the preliminary results of these studies did not confirm expectations based on previous data from radiation genetics, analyses of the gene contents of these populations have been made. During the past year it has been found that populations—even unirradiated ones—are extremely heterogeneous. Calculations have indicated that the vast majority, perhaps 90% or more, of gene loci in an average individual are occupied by different alleles. A partial explanation of this extreme heterozygosity has been found in the fact that individuals carrying different alleles of various genes are less influenced by environmental variations than are "homozygous" individuals, that is, individuals carrying identical alleles at each gene locus. Since developmental stability in the presence of a changing environment would be a trait with high selective value in populations, it is now possible to understand the evidence of genetic heterogeneity in natural populations and the consolidation of this diversity into coadapted gene pools characteristic of semi-isolated populations. Since speciation stems from differences between gene pools of isolated populations, the results of Wallace's experiments contribute toward a better understanding of speciation and evolutionary processes.

King, also working with *Drosophila*, is studying the manner in which resistance to insecticides is inherited. His first aim is to develop strains of flies resistant to DDT, which will later be used in crosses. Experiments have been started with two strains of flies, one collected in Syosset and the other an old laboratory strain. Results show that resistance to DDT is being built up slowly, and also that its progress is considerably faster in the Syosset strain.

Bryson, Rosenblum, and their collaborators have been engaged in a study of the reasons some strains of bacteria will replace others in mixed populations, a problem of theoretical importance as well as important to medicine and to the chemical industry. A detailed study has been made of the chemical products that accumulate in the environment of mixed cultures, and the effects of adding these substances artificially. Ways of controlling the direction of selection, by introducing mutant genes or modifying the environment, have been discovered. A particular strain may be made to replace another, or to disappear, as a result of experimental variations in genetic constitution, oxygen tension, or acidity.

This group of experimenters has accumulated further evidence, by means of manganous-induced mutations, that profound qualitative differences exist between induced and spontaneous mutants resistant to bacteriophage. The large number of different metabolic disturbances found

among the phage-resistant induced mutants suggests several alternatives, and provides problems for further study.

Szybalski's studies of the patterns of development of bacterial resistance to various antibacterial agents have shown that the development of one-step already known to be associated with streptomycin, also applies to isoniazid and para-aminosalicylic acid. He has analyzed cross-resistance patterns in *Bacillus megaterium*, using 41 antibiotics, and found that the general picture is similar to that obtained previously with three other bacteria, confirming the general rule, that the resistance pattern depends on the drug rather than on the organism.

Szybalski has also been able to obtain the first experimental proof that bacterial resistance to a mixture of two drugs develops with a much lower frequency than resistance to either of the drugs used alone.

During the summer, A. H. Bernheimer, of the New York University College of Medicine, investigated saline extracts of the fruiting bodies of 70 species of fungi for the presence of agglutinins for human erythrocytes of blood groups A, B, and O. Agglutinins were found in 15 species, but they were nonspecific. Bernheimer also studied the origin of hemagglutinins present in the hemolymph of certain insect larvae, and found that they are not associated with the presence of parasites, as had been suggested by some scientists. A. S. Fox, of the Ohio State University, carried on an immunogenetic analysis of several isogenic stocks of *Drosophila*. His results indicated that the antigenic differences among them are quantitative rather than qualitative. R. D. Hotchkiss, J. Marmur, and A. Evans, of the Rockefeller Institute, worked on methods for the study of biochemical characters in *Pneumococcus*, and developed and tested several synthetic media. W. Szybalski, of this Laboratory, and T. C. Nelson, of Vanderbilt University, found that 30 strains of *Escherichia coli* resistant to radiation were also highly resistant to furadroxyl, and that 37 strains resistant to furadroxyl were also resistant to radiation, indicating that both agents select the same class mutants. H. A. Abramson, of New York, A. R. Goldfarb, of the University of Chicago, and E. Ames, of Cold Spring Harbor, continued with experiments to isolate from ragweed pollen the compound that causes asthma, and also continued other studies of the cause and alleviation of allergies.

As in previous summers, several guests were occupied with writing. B. Glass, from Johns Hopkins University, wrote a summary of the symposium on phosphorus metabolism and a paper on the dynamics of interracial mixtures. S. Granisk, of the Rockefeller Institute, completed a review paper for the International Congress of Biochemistry in Paris. K. Maramorosh, also of the Rockefeller Institute, prepared two papers; and A. Sandow, of New York University, wrote a review of a book.

Symposium

A hundred and twenty-five scientists interested in the functions and interactions of nerves met from June 6 to 13, 1952, to take part in discussions on the subject of "neurons," the cells that make up the brain,

spinal cord, and nerves. Three lectures daily by prominent neurophysiologists were interspersed with group discussions on many phases of nerve action.

Messages carried by nerve cells, some of which extend from the toes to the base of the brain, are studied by scientists in the form of small physical and chemical changes, traveling from one end of a nerve cell to the other. Electrical changes that accompany nerve activity can be seen by means of cathode ray tubes like those used in television. Many chemical changes can be followed by the use of radioactive isotopes, and new techniques make it possible to measure the tiny amounts of oxygen used by nerve cells when at rest and when active.

Sixteen years ago a similar topic was discussed at the fourth Cold Spring Harbor Symposium. Since 1936 many important advances have been made, two outstanding developments being the electron microscope, which reveals details of structures never seen before, and ultrafine electrodes, which can be placed within the tiny neurons to investigate their electrical activity.

The 23 speakers represented a number of medical and research centers, including the Rockefeller Institute, Johns Hopkins University, Yale and Harvard Medical Schools, the California Institute of Technology, Massachusetts Institute of Technology, the Central Institute for the Deaf in St. Louis, Karolinska Institutet in Stockholm, University College in London, and the Sorbonne in Paris. Nerve research abroad was represented by twelve participants who came from Australia, England, France, Japan, and Sweden.

On Sunday, June 8, the group was entertained at a beach picnic by Dr. and Mrs. Donald Scott, Jr., at their home in Lloyds Neck. The following Wednesday the visiting scientists joined with members of the laboratories in an evening of square dancing led by Dr. E. C. MacDowell.

Teaching

The Nature Study Course was again given by Dr. Pauline James, of the Department of Biology, Texas College of Arts and Industries, Kingsville, Texas. She was assisted by Mrs. Ruth Moore, of Memphis, Tennessee. This course is designed to stimulate interest in nature among the young people of the community, by quickening their observation of the many plants and animals around them, by teaching them how to find the answers to questions raised by their observations, and by helping them realize that careful and accurate study of the smaller incidents we can all observe contributes greatly toward expanding our knowledge of natural phenomena. The course was divided into four sections according to the ages of the pupils, and was attended by 47 young people. On the afternoon of the closing day an exhibition was held to demonstrate the activities of the various classes to parents and friends.

For the eighth consecutive year a three-week course was offered in techniques and problems of research with bacterial viruses. It was taught by Dr. A. H. Doermann, of Oak Ridge National Laboratory, and had a

capacity enrollment of eighteen students. A series of five special seminars was arranged in connection with the course.

The course in bacterial genetics was given for the third year, and was conducted by V. Bryson and M. Demerec in collaboration with Jessie Hanson, E. L. Labrum, and I. Galinsky. This course emphasizes the newer methods used in the study of heredity in bacteria, and some of the recent studies in this field. There was an enrollment of 16 students and 2 auditors.

A course on cytology of microorganisms was given for the first time during the summer of 1952, by Dr. E. D. DeLamater, assisted by Drs. Mary E. Hunter and Sydney Yaverbaum of the University of Pennsylvania. Fourteen students were enrolled in this course.

Scholarships

The John D. Jones Scholarship was divided among the following people: Elizabeth M. E. Burgi, Cornell University; Dr. Bentley Glass, Johns Hopkins University; Aviva Jabotinsky, Weizmann Institute; Don T. Parker, University of Wisconsin; Robert A. Roosa, University of Connecticut; and Franklin W. Stahl, University of Rochester.

Lectures

Lectures were held throughout the summer of 1952 in cooperation with the Department of Genetics of the Carnegie Institution. The speakers were members of the laboratories and special visitors; Dr. J. C. King was in charge of arrangements. The speakers and titles were as follows:

- June 26: Stuart Mudd, University of Pennsylvania. Light and electron microscope studies of *E. coli* - coliphage interactions.
- July 10: J. J. Wolken, Rockefeller Institute. The fine structure of chloroplasts and some speculation on mechanisms of operation.
- July 24: Alan S. Fox, Ohio State University. Genetic control of enzymatic and antigenic specificity in *Drosophila* and *Neurospora*.
- August 14: Bentley Glass, Johns Hopkins University. The dynamics of racial intermixture—an analysis based on the American Negro.
- August 28: Kenneth Paigen, Department of Genetics. Biochemical heterogeneity in mitochondria.

Special Events

On Sunday, September 21, more than two hundred members and friends of the Association attended a demonstration and tea in Blackford Hall. This open-house demonstration, which has become an annual fall event, is held so that members may learn informally about current research at the Laboratory, and become more closely acquainted with the work they help to support. The scientific exhibits included projects of the regular staff of the Laboratory, summer guests, and staff members of the Department of Genetics of the Carnegie Institution. Dr. James C. King gave a brief talk on "Weapons and Tactics in the war against Insects," in which he discussed the broad principles underlying his research program dealing

with the resistance of insects to insecticides. The serving of tea and refreshments by members of the Women's Committee was efficiently organized by Mrs. Philip Wadsworth, chairman of the Entertainment Committee, with the cooperation of Mrs. Edward S. Blagden, Mrs. Duncan B. Cox, Mrs. Herbert Glasier, Mrs. Cecil F. Gordon, and Mrs. Anderson Hewitt.

Dining Room

The Blackford Hall dining room was in operation from May 29 to September 2, 1952, under the management of Mrs. Alice Varro. Resident members of the Department of Genetics, as well as guests of the Laboratory, were accommodated there during the summer. Meals were served to approximately 200 people.

Buildings and Grounds

Efforts to modernize our buildings and keep them in repair have been continued during the past year. Hooper House was repainted on the outside, and its windows were gone over. Partitions between rooms on the upper floor, which had been damaged by insects, were repaired. Williams House received a coat of paint on the outside. Much-needed toilet facilities were installed in the John D. Jones Laboratory. Extensive repairs were made to the sea wall adjacent to the Laboratory buildings. A piece of ground to the north of the Nichols building was leveled off and adapted for use as a parking place for cars.

Finances

The expenses of full-time research are being met by grants received from the National Tuberculosis Association, the Army Chemical Corps, the Atomic Energy Commission, the Office of the Surgeon General of the Army, and the Office of Naval Research. Symposium expenses are partially covered by the grant of the Carnegie Corporation for that purpose. During the past year three new grants were received for research, namely: a second grant from the Army Chemical Corps, for research on factors inducing resistance to transmissible mouse leukemia, with Dr. E. C. MacDowell in charge; a grant from the Office of the Surgeon General of the Army, for research on the genetic nature of resistance to insecticides developed by populations of *Drosophila melanogaster*, carried on by Dr. James C. King; and a grant from the Office of Naval Research, for studies dealing with microbial resistance to chemical and physical agents, conducted by Dr. W. Szybalski.

In common with many other educational and research institutions, however, we are having some difficulty in connection with funds for the upkeep of grounds and buildings, and for other general expenses of caring for a plant that includes about 60 acres of land and 20 buildings and cottages. During the last few years these expenses have considerably increased, because of the depreciation of the dollar and the consequent rise in wages and cost of supplies.

Acknowledgments

It gives me great pleasure to acknowledge the support given the Laboratory by the members of the Association. Their contributions play an important part in providing for the upkeep and overhead of the Laboratory, and are most essential for its continued existence.

The Women's Committee, under the chairmanship of Mrs. George S. Franklin, made an important contribution toward the support of the scientific work of the Laboratory; and its Entertainment Committee, with Mrs. Philip Wadsworth as chairman, provided refreshments for the Open House Tea and Exhibit in September.

The Laboratory is grateful to Mrs. Van S. Merle-Smith for her gift of three used refrigerators.

Grateful acknowledgment is made of the contribution of the Wawepex Society toward the upkeep of buildings and grounds and of the John D. Jones Scholarship maintained by that Society.

The Laboratory recognizes with gratitude the research grants made by the National Tuberculosis Association, the Army Chemical Corps, the Atomic Energy Commission, the Office of the Surgeon General of the Army, and the Office of Naval Research, and the grant of the Carnegie Corporation of New York for expenses of the Symposium.

REPORTS OF LABORATORY STAFF

Genetic and Biochemical Studies of Bacteria

V. Bryson, E. D. Rosenblum, H. Hershey, H. Deiches, and I. Dittman

Experiments on Selection with Mixed Populations of E. Coli.— In recent years geneticists have become increasingly interested in problems of selection. The suitability of microorganisms for the study of such problems has long been evident through the existence in the older literature of elaborate descriptive tracts on "life cycles" or on the fluctuation of discontinuous varieties in bacterial and protozoan cultures. By the introduction of suitable genetic markers, individual strains of a single bacterial species may be followed in mixed cultures containing two or more marked strains. Selective viability may then be observed using chromatographic techniques or other analytical methods to determine the chemical cause of selective pressures accumulating in the culture fluid. Witkin has already shown that in aging mixed cultures of *Escherichia coli* the radiation-resistant strain B/r is rapidly replaced by the radiation-sensitive strain B. On periodic subculture no replacement is observed.

More recently we observed that numerous supplementary amino acids are able to influence selection in mixtures of B and B/r, but no component of sterile filtrates or amino acid found in these filtrates by paper chromatography is definitely established as the selective agent responsible for the relatively greater viability of strain B. It was soon found that selection may be profoundly modified by mutations other than resistance to radiation. In performing the experiments, all possible combinations of radiation-sensitive strain B incorporating either the lactose-negative marker or its wild-type allele were made with lactose-positive and lactose-negative strains of radiation-resistant B/r. Also, lactose-positive and lactose-negative strains similar in respect to radiation resistance were set up in mixed culture. Fermentation properties were determined by plating on MacConkey medium, and radiation resistance was ascertained by exposing streaks of bacteria to 30 ergs/mm²/sec of ultraviolet radiation and observing them under the microscope after incubation for three hours at 37° C. The specific conclusion to be drawn from these experiments is that the selective advantage of strain B over B/r in nutrient broth is reversed if both strains are lactose negative. It was also noted that in aerated nutrient broth with high pH the lactose-negative strains were favored over lactose-positive, regardless of the distribution of factors for radiation resistance. The experiments emphasize the failure of mutations to act in a neutral manner, even under conditions not assumed to involve their primary phenotypic properties.

Further tests were performed by making mixtures of strains resistant to specific bacteriophages. It is known that phage-resistant cells have a relatively poor selective value when in competition with the parent strain. When strains resistant to phage T6 and others resistant to T1 were grown together, it was found that the higher selective advantage of B/6 strains was to some extent dependent on the particular B/6 mutant employed.

Competitive growth experiments provide a further method of differentiating among strains that might seem identical on preliminary isolation.

Experiments with the Turbidostat.—Continued refinements in the design of the turbidostat have been made since the preliminary plans were drawn up in 1949. Strains of *E. coli* resistant to terramycin and a quaternary ammonium compound have been produced by use of the selector "attachment." Preliminary experiments suggest that resistance to high concentrations of penicillin may not be produced so easily. One possibility is that organisms are able to grow in concentrations of penicillin that are bacteriostatic on a long-term basis, even to first-step mutants. Present attention has been shifted from resistance studies to more fundamental problems raised in other laboratories by use of the chemostat in the direct investigation of mutation.

Differences in Nucleic Acid Content of Specific Bacterial Strains — The ribose nucleic acid content of several radiation-sensitive and radiation-resistant *E. coli* strains was determined by the orcinol test and compared with the desoxyribonucleic acid levels derived by the diphenylamine procedure. DNA/RNA ratios ranged between .20 and .39 in duplicate experiments on four strains. Since the range of values obtained in duplicate experiments was as great as differences between unlike strains, no corroboration was obtained in these limited tests of the observation of higher DNA values in strain B/r noted by Morse and Carter.

Metabolic Effects of the Mutagenic Agent Manganous Chloride.—Demerec and Hanson have presented extensive evidence that manganous ion may be used to induce reversions from streptomycin dependence to nondependence in strain B/r/Sd-4 of *E. coli*. Manganous ion may be adsorbed by nucleoprotein, and the possibility exists that its mutagenic effects come about through some intermediary interference with normal metabolism. The process of mutation is so little understood by biologists that the intracellular chemical changes that may be found associated with genetic change cannot easily be fitted into a cause-and-effect scheme. The problem is made more difficult by the fact that most chemical changes produced by mutagenic agents are found in all the treated cells, yet only a very small proportion will become genetically modified. Therefore the action of manganous ion on metabolism is not necessarily related to its mutagenic effect.

To study the metabolic consequence of treatment with manganous ion, the bacteria were exposed by the procedure of Demerec and Hanson, including the use of 0.3 M NaCl preceding the .04% MnCl₂. As controls, cells were suspended in 0.7% NaCl. In an additional experiment, .04% MgCl₂ was used. Cell suspensions were incubated for four hours at 37° C, recentrifuged, suspended in phosphate buffer at pH 6.8, and put in Warburg vessels. Oxygen uptake was then measured, using 0.01 mM of carbon source per ml. Substrates employed were glucose, glycine, arabinose, pyruvate, succinate, and acetate. As a result of these experiments, it may be stated that Mn ion, as here used, reduces the respiratory metabolism of the cells on exogenous substrates, without depressing

endogenous respiration. Preliminary treatment of the bacteria with distilled water, or by other techniques known to reduce the rate of mutation following Mn treatment, were equally effective in preventing the Mn depression of metabolism. The most that may be concluded is that induced mutation from exposure to Mn ion may be associated with (but not necessarily caused by) interference with normal respiratory metabolism. Mg ion, which is not a mutagen, does not have similar effects.

Another clue that mutation may be associated with general changes in cellular metabolism has been obtained in studies of multiple mutation. Last year we reported that ultraviolet-induced mutations to phage resistance frequently proved to be auxotrophic strains with nutritional requirements not known to occur in populations of spontaneous mutants. These studies have been extended to include a total of 239 independently derived mutants induced by ultraviolet irradiation or treatment with manganous chloride. The mutants were isolated by exposing populations of bacteria to phage T1, after treating with the mutagen. Several auxotrophs have complex nutritional requirements that have not yet been identified. Mutants with known requirements include strains unable to grow on minimal medium (M9 agar) without addition of adenine, serine, tryptophane, the aromatic amino acids, methionine, methionine or cystine, arginine plus methionine, threonine, valine plus isoleucine, histidine or adenine, histidine, proline or glutamic acid, thiamine, threonine, cystine, pantothenate, pyridoxine, or nicotinamide.

This varied collection of auxotrophic strains establishes on an even firmer basis the conclusion that ultraviolet- or manganous-induced mutants, in this experiment, differ from spontaneous not only in quantitative frequency but also in qualitative properties. Among 239 spontaneous mutants, no requirement for any nutrient other than tryptophane was ever found.

Three interpretations are possible. According to the first, the induced class includes a group of auxotrophs with nutritional requirements derived from the manifold effects of a single mutation—though the mutation may be unique for many of the different strains. By this hypothesis, either a system of multiple alleles or a large number of loci is involved in producing phage resistance. A related explanation is that many or all phage-resistant as auxotrophic strains. It is assumed that the metabolic insufficiency (auxotrophy) results in an intracellular environment in which the virus cannot multiply, resulting in resistance.

A second explanation is provided by assuming that there are catenary pathways of biosynthesis leading to the necessary precursors for phage synthesis. The various mutants then represent blocks in different positions along the chain of intermediate syntheses leading to sensitivity. The varied nature of the mutants found, together with the fact that addition of the required nutrient does not convert phage-resistant auxotrophs to sensitivity, tends to rule out this explanation.

Another interpretation is related to the recent evidence that induced mutation may be preceded by a genetically labile state. Demerec and

Witkin provide data (Carnegie Year Book No. 48) supporting the concept of a labile phase after treatment with mutagenic agents. The existence of apparently unrelated phenotypic changes that appear to have arisen simultaneously—for example, phage resistance and methionine requirement—may represent the consequence of simultaneous mutation at two loci resulting from a higher probability of multiple mutation among cells than expected on the basis of the product of individual mutation rates. Recombination tests with suitable strains are required to locate the factor (or factors) responsible for multiple phenotypic changes observed in mutants selected on phage T1. Extensive studies of prototrophs obtained by further mutation of phage-resistant auxotrophs show that the nutritional deficiency may be lost without change in the pattern of phage resistance. The ratio of phage hyper sensitive to phage-resistant mutants among prototrophs of independent origin-derived from phage-resistant auxotrophs is characteristic of the particular auxotroph being studied.

In another study, it was found possible to inhibit the action of streptomycin by interfering with cellular metabolism, accomplished either by reducing the available nutrition of the bacteria or by direct application of bacteriostatic agents. Cells were washed and placed in different liquid substrates containing 50 mcg of streptomycin per ml. Assays to determine the number of viable cells were made hourly for a four-hour period. As has been noted for penicillin by other investigators, streptomycin is most effective as a sterilizing agent under conditions that would permit cell multiplication in the absence of the drug. Thus, washed cells suspended in saline show little loss of viability at four hours. If a carbon source is present the viability is reduced to about 1% and if a nitrogen source is also added even fewer cells are able to survive the test period. The most rapid killing occurs in broth, or in broth supplemented with glucose. None of sixteen amino acids present in 0.2% concentrations was able to provide for an efficiency of streptomycin action equivalent to that of broth.

As a further test of the relation of substrate to streptomycin action, *E. coli* was exposed to the antibiotic either with or without growth in a so-called adaptive substrate. Without implications as to the enzyme level of the cell, adaptive substrates are here defined as those in which cells require a relatively long lag before the substrate becomes efficiently metabolized. As would be predicted, cells grown in lactose or arabinose (adaptive substrates) before exposure to antibiotic are sterilized more rapidly by added streptomycin in the presence of these carbon sources than if the cells are grown in glucose and are therefore unadapted. Lactose- and arabinose-grown cells are quickly inactivated by streptomycin in a glucose substrate wherein no adaptation is required for rapid oxidative activity. *E. coli* may be made to remain relatively viable in a salt-glucose medium containing streptomycin, if metabolism is inhibited by .002 M iodoacetate. Again, emphasis is directed to the rate of killing or bacteriostasis as a function of metabolic rate. Several lines of evidence suggest that streptomycin action may be more intimately related to the assimilation of nitrogen than to respiratory activity.

Bacterial Resistance to Antimicrobial Agents

Waclaw Szybalski

The work reported here was aided by a research grant from the National Tuberculosis Association.

Resistance to Isoniazid.—Immediately following the announcement of the discovery of isoniazid (isonicotinyl hydrazid), a new potent antimycobacterial agent, studies were started on the patterns of development of bacterial resistance to this drug. We found that the inhibitory concentration of isoniazid is approximately 5 mcg/ml for three saprophytic mycobacteria (*M. ranae*, *M. smegmatis*, and one unclassified *Mycobacterium* sp.). Resistant cells are present in the sensitive population and are able to form colonies at any concentration of isoniazid up to 3000-5000 mcg/ml. Thus, the thousandfold resistance develops in a single step (streptomycin pattern). Isoniazid-resistant mutants are originally present in the sensitive population, which could be easily demonstrated by the Lederbergs' replicate plating or by the Luria and Delbruck variance test. Mutation rate determined by the P(O) method amounts to 1.3×10^{-6} per bacterium per generation. Thus, for *M. ranae* the mutation rate to isoniazid resistance is approximately a thousand times higher than that to complete streptomycin resistance.

Interaction Between Isoniazid and Other Antimycobacterial Agents.—The one-step resistance pattern and high mutation rate to isoniazid resistance limit the usefulness of this drug. The most obvious solution lies in the use of isoniazid in combination with some other unrelated antimycobacterial drugs. Streptomycin and PAS (*p*-aminosalicylic acid and its salts) seem to be best suited for this purpose. If two unrelated drugs are simultaneously present, the chances are much smaller that a particular cell will be resistant to both agents. This principle explains the great effectiveness of multiple chemotherapy and may be one of several mechanisms responsible for so-called synergism. For example, *M. ranae* mutates to high-degree streptomycin or isoniazid resistance at the rate of 10^{-9} or 10^{-6} , respectively. Therefore, the expected rate of mutation to double resistance ought to be the product of the individual rates, that is, 10^{-15} per bacterium per generation. However, technical limitations bar the experimental confirmation of this extremely low value. Natural resistance to high concentrations of PAS, in this case, made the use of saprophytic mycobacteria impractical.

Fortunately, we have observed that *Bacillus megaterium* is moderately sensitive to isoniazid and PAS. It mutates to practically complete isoniazid or PAS resistance in one clear-cut step, and does not produce mutants of intermediate resistance. The high mutation rates (6×10^{-5} for isoniazid and 1×10^{-6} for PAS) make the determination of mutation rate to double resistance technically feasible. The theoretical figure should be $6 \times 10^{-5} \times 10^{-6} = 6 \times 10^{-11}$ per bacterium per generation. Our experimental value (8×10^{-10}) is somewhat higher, indicating that a cell which has undergone a single mutation may mutate the second time at a

higher rate. The experimentally determined mutation rates to PAS resistance are identical for both the isoniazid-resistant and the parental strains. However, for PAS-resistant *B. megaterium* the mutation rate to isoniazid resistance equals approximately 1.3×10^{-4} per bacterium per generation.

The other phenomena upsetting the value of multiple chemotherapy are cross-resistance and antagonism. Complete cross-resistance nullifies the usefulness of the combination of isoniazid and iproniazid (1-isonicotinyl 2-isopropyl hydrazine), which, chemically, are very closely related. Fortunately, no cross-resistance between isoniazid, streptomycin, and PAS has been noticed.

Antagonism between two drugs is another phenomenon encountered during simultaneous drug application. We observed it with mycobacteria exposed to the inhibitory concentrations of isoniazid supplemented with subinhibitory concentrations of streptomycin. When a suspension of *M. ranae* is plated in the presence of isoniazid (10- to 100-fold inhibitory concentration), only 10^{-4} to $10^{-2}\%$ of the cells develop colonies. If streptomycin is added to these isoniazid plates at concentrations between 1/10 and 9/10 of the inhibitory level, almost 100% of the cells develop colonies. These, however, grow more slowly than colonies on control plates containing only streptomycin at the same subinhibitory concentrations. If both drugs are present at concentrations well over the inhibitory threshold, the principle of multiple chemotherapy applies and no colonies appear.

This antagonistic effect of streptomycin on isoniazid action holds true for three different saprophytic mycobacteria, including streptomycin-sensitive and partially or completely resistant strains. In all cases, however, this is only for streptomycin concentrations neighboring the inhibitory threshold. Consequently, for three strains resistant to 0.5, 5, and 25000 mcg/ml streptomycin, the ranges of its antagonistic concentrations are 0.05 - 0.45, 0.5 - 4.5, and 400 - 20,000 mcg/ml, respectively. The colonies isolated from isoniazid-containing plates, with or without antagonistic concentrations of streptomycin, were composed predominately of isoniazid-resistant cells; their streptomycin sensitivity was unchanged. It might be thought either that isoniazid-inhibited bacteria become dependent on subinhibitory concentrations of streptomycin or that this antibiotic causes all cells to mutate to isoniazid resistance. Additional experiments, however, show that subinhibitory concentrations of streptomycin (and also of aureomycin and terramycin, but not of PAS, viomycin, neomycin, or nicotinaldehyde thiosemicarbazone) slow down the metabolism or reproductive activity of the cells to the level where the cell may multiply very slowly, and consequently withstand the isoniazid action. During this slow initial growth, isoniazid-resistant mutants ultimately appear within every colony and, under these conditions multiplying more rapidly, outgrow the sensitive cells.

This mechanism seems to be responsible for many other reported cases of antagonism between antibiotics, as for instance, the antagonistic effect

of low concentrations of aureomycin or terramycin on the action of penicillin, etc.

"Natural" and "Artificial" Penicillin Resistance in Staphylococci.—Penicillin-resistant staphylococci are generally divided into two groups: "natural," which are produced in vivo and "artificial" or "induced," produced in vitro. These two groups differ chiefly in that "naturally" resistant staphylococci, isolated from patients, owe their resistance to the production of the penicillin-destroying enzyme, penicillinase, while "artificially" resistant staphylococci do not produce penicillinase and generally possess a diminished virulence and a reduced rate of growth, which is often associated with metabolic deficiencies. Upon repeated subculturing, "natural" penicillin resistance seems to be a more stable property than "artificial" resistance.

Our experiments have shown that a pure culture of *Micrococcus pyogenes* var. *aureus* contains both types of penicillin-resistant mutants. The "artificial," non-penicillinase-producing mutants are far more numerous and, since they are truly resistant, are able to form colonies from single cells in a rather wide range of penicillin concentrations (0.015-0.1 units/ml). Thus, these are easily isolated in vitro, and were exhaustively studied genetically by Demerec.

The "naturally" resistant cells are at least 10,000 times less numerous, and a single cell can form a colony at penicillin concentrations only barely higher than the inhibitory ones. Thus, we were able to isolate a few penicillinase producers only after inspecting numerous gradient plates (Szybalski, *Science* 116, 46, 1952) prepared from independent inocula. These cells form colonies which are situated only very close to the boundary of confluent growth and are surrounded by a faint halo formed by satellite growth in the zone of penicillinase action. These penicillinase producers are easily overlooked during in vitro screening, but due to their virulence and other unchanged growth characteristics, they may be selected in vivo, especially in those regions of the tissue where penicillin levels are close to the inhibitory ones.

Cross-resistance Studies.—The studies described in the Annual Report of 1951 were extended to several other toxic agents and two additional organisms: gram-positive *Micrococcus pyogenes* var. *aureus* and acid-fast *Mycobacterium ranae*. The following agents were used: aldinamide (Lederle), amicitin, aureomycin, (chlortetracycline), aureothrycin, bacitracin, carbomycin, (magnamycin), chloramphenicol, cinnamycin, circulin, catenulin, erythro-mycin, furacin, (and several derivatives), gramicidin, grisein, illudins M and S, isoniazid, iproiazid, licheniformin, marasmic acid, 5-methoxy-p-teluquinone, micrococcin, mycomycin, (Abbott), neomycins, netropsin, nicotinaldehyde thiosemicarbazone, nisin, sodium-p-aminosalicylate (PAS), patulin, penicillin, pleocidin, pleuromutilin, polymyxins, prodigiosin, rhodocidin, streptomycins, streptothricin, subtilin, terramycin (oxytetracycline), thiolutin, tyrocidine, vinactin, viomycin, xanthomycin, xanthothricin, and several other antibiotics identified by their code names like PA-89 (Pfizer), X-206, X-464, and X-537-A (Hoffman-LaRoche).

The general conclusions will be essentially the same as derived from previous studies with *Escherichia coli* (Annual Report, 1951) but they show differences in many details, and comprise a larger number of antimicrobial agents.

Aureomycin- and terramycin-resistant strains of *M. ranae* and *M. pyogenes* show a high degree of cross-resistance, which is in agreement with the recently reported great similarity in chemical structure of these antibiotics. They do not show an appreciable degree of cross-resistance with other antibiotics, and in this respect *M. ranae* and *M. pyogenes* differ from *E. coli*, which has demonstrated complete cross-resistance between aureomycin, terramycin, chloramphenicol, and a unidirectional relationship with penicillin and netropsin. Recent studies with *Bacillus megaterium* resistant to erythromycin and carbomycin show unidirectional cross-resistance, and relate these antibiotics to the aureomycin-terramycin group.

A second group of antibiotics related by cross-resistance is a large class of polypeptides and streptomycin-like antibiotics. Resistant strains of *M. pyogenes* show a high degree of cross-resistance between polymyxin B, circulin, licheniformin, catenulin, neomycin, pleocidin, streptothricin, viomycin, and vinactin. Strains resistant to these agents are also partially resistant to streptomycin, and a few of them also have an increased resistance to subtilin and netropsin. Other bacterial polypeptides like bacitracin, nisin, and tyrocidine do not seem to be related to each other or to the rest of the previously described group.

M. ranae seems to show a higher selectivity within this second group. A high degree of cross-resistance is exhibited by strains resistant to viomycin and vinactin; all our studies indicate that these two substances are microbiologically identical. Neomycin- and catenulin-resistant strains also show a high degree of cross-resistance. But there are quantitative differences between their entire bacterial spectra when these are studied with other resistant strains. There is a pronounced relationship between licheniformin, polymyxin B, and circulin. However licheniformin is more highly active on the microgram basis and the strains which are permanently resistant to it are much more easily isolated. Otherwise there is only a small degree of cross-resistance within this second group. There are a few exceptions; for example, polymyxin B- and catenulin-resistant *M. ranae* are highly resistant to streptomycin and viomycin, and the vinactin-resistant strain is 60-1000 times less susceptible to neomycin and catenulin. Using *M. pyogenes*, it was possible to demonstrate pronounced cross-resistance between antibiotics X-206 and X-464 and some unidirectional relationship between these two and micrococci, subtilin, tyrocidin, and mycomycetin. Antibiotic X-537-A does not show any relationship to this group when studied with *M. pyogenes*, but subsequent studies with *B. megaterium* reveal a high degree of cross-resistance between all three X-antibiotics, with a small degree of cross-resistance towards mycomycetin, tyrocidine, and subtilin but none towards micrococci.

The above-described group of antibiotics was not studied with *M. ranae*, with the exception of mycomycin, which in this case shows a cross-resistance relationship with bacitracin, chloramphenicol, and PA-89. (There was none shown with *M. pyogenes*, and it was unidirectional with *B. megaterium*.) Complete cross-resistance was noted for illudin M and illudin S. Illudin M is 5 times more active than illudin S against *M. ranae* and 100 times less active against *B. megaterium*.

Exposure of *M. ranae* to isoniazid or iproniazid results in a selection of highly isoniazid-resistant strains, but the low activity of iproniazid is not pronouncedly changed. There is no cross-resistance between isoniazid-resistant strains and other potent antimycobacterial agents like PAS and thiosemicarbazones; high natural resistance of *M. ranae* to these two agents diminishes the significance of this observation.

We have observed that several strains of *M. ranae* (e. g., resistant to licheniformin, circulin, polymyxin, netropsin, and penicillin) display an increased degree of resistance or an enhanced mutation rate to isoniazid. However, isoniazid sensitivity of independently isolated chloramphenicol-resistant strains varies from a threefold increase to a fiftyfold decrease.

Using direct exposure we were not able to select strains resistant to any of the following drugs: nisin, patulin, and thiosemicarbazone (*M. ranae*), or xanthomycin, marasmic acid, X-537A, and thiosemicarbazone (*M. pyogenes*). In several other cases, the increase of resistance was very low (less than twofold for iproniazid-resistant *M. ranae* and for nisin-, patulin-, PAS-, and 5-methoxy-p-toluquinone-resistant *M. pyogenes*). However, when the direct exposure of *B. megaterium* to nisin or subtilin failed to select resistant strains, the bacitracin- or tyrocidine-resistant mutants proved to be four or six times more resistant.

We did not notice any examples of high-degree collateral sensitivity with the single exception of penicillin-resistant, non-penicillinase-producing *M. pyogenes*, which was fifty times more sensitive to nisin than its parental strain.

The remaining antibiotics listed in the beginning of this section (i.e., those not discussed above) either do not show relationship with the tested toxic agents, or it was not possible to select strains resistant to these drugs. These studies may prove to be helpful in the attempts to clarify the classification of antibiotics of unknown chemical structure, on the basis of their microbiological behavior.

Bacterial Dependence on Toxic Agents.—It is a known fact that a large proportion of streptomycin-resistant mutants become dependent on this antibiotic. Reports also exist in the literature on chloramphenicol-dependent *Klebsiella* and sulfonamide-dependent *Neurospora*.

We have observed two cases of partial dependence, using *M. pyogenes* var. aureus resistant to chloramphenicol or to penicillin. One out of twenty independently isolated chloramphenicol-resistant strains grew very poorly in the absence of this drug. In the range of 1/4 to 5 times the inhibitory concentration, the growth of this mutant was strongly stimulated, which showed especially clearly on the gradient plate. It was possi-

ble to obtain a similar stimulation substituting for chloramphenicol 1/2 to 5 times the inhibitory concentrations of pleuromutilin.

During the isolation of penicillin-resistant *M. pyogenes*, we observed a certain percentage of very poorly growing colonies. These are sometimes described as "small colony variants" (G-forms). Two out of 30 of these colonies failed to grow upon transfer to a penicillin-free nutrient agar. They do grow, however, on gradient plates in the area of 1 to 20 times the inhibitory concentration of penicillin. The growth and viability of this strain was very poor.

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Radiations and Populations

Bruce Wallace, Carol V. Madden, Gloria Cosillo

Edward McGunnigle, and Barbara Stuard

The work reported below was done under contract No. AT-(30-1)—557, United States Atomic Energy Commission. We wish to acknowledge the help of Clara Garth, Jane Haworth, Lillian Riecke and Henry Gardner.

In three previous annual reports we have presented data pertaining to the fitness or adaptive values of populations of *Drosophila melanogaster* exposed to X- and gamma-rays. It was found that populations exposed to continuous, low-intensity gamma radiation have lower adaptive values than the control population but that a population exposed to a single large dose of X-rays has a higher adaptive value than the same control. We have also presented data indicating that, although lethal chromosomes tend to lower the viability of heterozygous individuals, the average viability of individuals heterozygous for random pairs of chromosomes is relatively independent of the viability effects of these same chromosomes when homozygous.

During the past year less emphasis has been placed upon analysis of the regular sampling of chromosomes taken from the populations and more effort has been expended on experiments designed to reveal the nature of coadapted gene pools—the complexes of genes retained in populations as those producing the highest average adaptive values.

One experimental approach to the problem of analyzing genetic systems is through a study of variation arising by recombination. Five nonlethal second chromosomes were taken from each of two experimental populations (Nos. 1 and 3) and females were made that were homozygous for these ten chromosomes or heterozygous for the 45 possible pairs of these chromosomes. Crossover chromosomes were isolated from these females, and these latter chromosomes were rendered homozygous. Approximately 100 crossovers from each of the 55 combinations were analyzed for lethals; 60 of the nonlethals from each combination were analyzed for viability effects as well. Further studies were made of the bristle numbers characteristic for the crossover chromosomes and of an inherited female sterility factor included unwittingly in the original material.

In brief, two types of analyses were made on the data—a qualitative analysis, in which arrays of crossover chromosomes recovered from one combination were compared visually with the arrays recovered from other combinations; and a quantitative study that consisted of an analysis of variance. The qualitative analysis revealed that two chromosomes giving highly similar crossovers when in combination can give very dissimilar crossovers when each is in heterozygous combination with a third chromosome. The analysis of variance indicated that many of the effects of crossover chromosomes on viability were effects derived specifically from a given combination; these effects could not have been predicted from a knowledge of the crossover products of the same chromosomes in other combinations. The conclusion drawn from this study is that within a population

gene loci are not occupied by single "wild-type" alleles; rather, it seems as if series of multiple alleles occupy most gene loci and that different combinations of these alleles can differ drastically from one another. Such a situation would help explain the independence of the viabilities of individuals homozygous for a series of chromosomes and of individuals heterozygous for a series of randomly chosen pairs of these same chromosomes.

One of the problems confronting a student of *Drosophila* populations is an adequate description of the types of chromosomes as determined by their effects on viability. Lethals and semilethals offer no problem because their effects contrast sharply with "normal" chromosomes. However, among the "normal" chromosomes there are many with demonstrably deleterious effects on viability—subvitals—and, at the other end of the viability scale, chromosomes resulting in exceptionally high viabilities—supervitals. Estimations of the frequencies of these two classes in populations have been unsatisfactory. A new method was developed during the past year that made it possible to give more accurate estimations of the frequencies of sub- and supervitals. The mean viability of "quasi-normal" homozygotes and heterozygotes can be determined experimentally. The "real" spreads of viabilities on either side of these means can be estimated by deducting variances resulting from sampling and experimental error from the observed variances. When the means and standard deviations of the viabilities of homozygous individuals and of the heterozygous, control individuals are known, the calculation of frequencies of sub- and supervitals is extremely simple; one merely decides on the basis of the control series what levels shall be taken as characteristic of subvitality and supervitality and then calculates the proportion of the real homozygous distribution below or above these levels. In our young, experimental populations about 40% of all chromosomes are subvital. Supervitals are found only in the irradiated populations and then only with low frequencies—4% or less.

While calculating experimental variances for the above analysis, it became apparent that this type of variance is characteristic of homozygous cultures but not of heterozygous ones. If replicate cultures of homozygous and heterozygous crosses are made either by transferring the parents periodically to new culture bottles or by using sibs of the original parents for other, parallel cultures, one expects each of the replicated cultures to yield the same percentage of wild flies. This expectation is fulfilled in the case of replicated cultures yielding individuals heterozygous for pairs of second chromosomes. In the case of bottles yielding homozygous individuals, on the other hand, the frequency of wild flies in different replicate cultures may vary much more than one would expect from chance. We can conclude that heterozygous individuals are better buffered against varying environmental conditions. The constancy of the viability of these individuals reflects greater homeostatic abilities.

By altering the sequence of events recorded in this report of our year's activity we can outline the following hypothesis concerning the genetic structure of a population. First, heterozygous individuals are more

homeostatic than homozygous individuals. Second, selection for genotypes resulting in high viabilities under a variety of environmental conditions (including genetic environment) is also selection for increased heterozygosity. Third, an increase in heterozygosity requires the establishment of multiple allelic series (isoalleles) at many loci. Fourth, only those alleles that are mutually compatible with the alleles at the same and other loci will be retained in a population. Fifth, since alleles retained within one population need not be mutually compatible with alleles retained in another, we say that the gene pool of a population is coadapted. Much of our current work is concerned with testing and expanding this hypothesis.

The Genetics of Resistance To Insecticides

James C. King

The work reported here was done under contract DA-49-007-MD-327 with the Medical Research and Development Board of the United States Army. I wish to acknowledge the conscientious assistance of Robert G. Binder.

During the past decade one of the most perplexing problems of insect control has been the speed and extent to which natural populations of insect pests have developed resistance to the newly discovered insecticides. The resistance shown by natural populations appears rather definitely to be hereditary but very little is known about the genetic mechanisms which produce it. Workers in the field of insect control realize that fundamental research on this problem is necessary to obtain knowledge on which practical control programs can be based. The present contract is one of several let by the Army Research and Development Board with the view to filling gaps in our theoretical knowledge of the nature of resistance.

The program of research envisages building up resistant strains, analyzing the resistance genetically, investigating the manner in which resistance is acquired and the way in which it can be lost or weakened, and testing the cross-resistance of resistant strains to different insecticides. Although such insects as house flies, mosquitos, and lice constitute the primary problems of insect control, it was decided to undertake the present research on *Drosophila melanogaster* because of the relative ease of making genetic analyses with this insect and because *Drosophila* can be reared with greater economy and efficiency in the laboratory. The work was begun using DDT, since this is the best known and most widely used of the newer residential insecticides.

The first item on the agenda was the development of resistant strains, and to date the work has been concentrated on this aspect of the problem. First, however, it was necessary to develop a technique for administering measured doses of insecticide. For a number of reasons an aerosol treatment was decided on. The DDT is dissolved in tributyrin; an aerosol is produced in a nebulizer and carried at a controlled rate of flow into a flask containing the flies to be treated. Treatments are measured by the time that the flow is continued. The treated flies are then shaken into a glass cylinder with open ends which are capped with voile. After standing for twenty-four hours the flies are separated into live and dead, and counted. In order to prevent death from starvation and desiccation during the twenty-four hours, a strip of photographer's sponge soaked in enriched *Drosophila* medium is suspended in each cylinder on a wire rack. Untreated flies, or flies treated with tributyrin alone, show a mortality of about 0.5%.

Considerable time and effort have been expended in developing this technique, but it still has imperfections. Chief among them is the fact that mortality figures for the same line and the same dose show large fluctuations from treatment to treatment and from day to day. This variability has been cut down to some extent but still remains troublesome.

Somewhat similar variation in results, however, characterizes all other methods of treating with insecticides, and the present technique has the advantage that large numbers of flies can be treated with a minimum of work.

In order to produce resistant lines, survivors from among the treated flies are used as parents to produce another generation. These flies are in turn treated, their mortality measured, and the survivors saved to propagate another generation. Two separate stocks have been used as progenitors of the selected lines: a laboratory Oregon-R stock and a wild stock collected in a grocery store in Syosset, N.Y., in the summer of 1952. Within each stock lines are being carried at three levels of selection: one in which the parents are a single pair from among the survivors of a treatment giving high mortality (95%-99%), another in which from four to ten pairs are used as parents from a treatment giving a similarly high mortality, and a third in which the parents are all the survivors of a treatment giving approximately 50% mortality. In the third case flies can be treated and selected in every generation. In the first and second, however, where the number of parents is small, treatment and selection can be carried out only in alternate generations when the number of offspring is sufficient to make treatment and selection feasible. So far as possible within each stock and at each level of selection, two separate lines are carried in the hope that we may discover whether the same stock exposed to the same type of selection always reacts in the same way. In all, ten separate lines are being carried, as shown in Table 1.

TABLE 1

Line	Selected Lines and Program of Selection			Generations Treated
	Original Stock	Flies Used as Parents	Approximate Mortality	
ORS-2	Oregon-R	Single pair	96-99%	Alternate
ORS-3	"	" "	" "	"
ORS-105	"	4-10 pairs	90-99%	"
ORS-1001	"	All Survivors	50%	Every
SyS-1	Syosset	Single pair	96-99%	Alternate
SyS-2	"	" "	" "	"
SyS-102	"	4-10 pairs	90-99%	"
SyS-103	"	" "	" "	"
SyS-1001	"	All Survivors	50%	Every
SyS-1002	"	" "	" "	"

The fluctuations in percentage of mortality at the same dose result in a high variance for any group of similar treatments. This means that averages have high standard errors and it is difficult to demonstrate statistically significant differences between mortalities of different generations, of different lines, or between any one selected line and the unselected stocks. It is therefore impossible as yet to show clearly any increase in resistance in any one line. One can obtain, however, a general picture of the results of the experiment to date by comparing the average mortalities of each of the

different lines with the average mortalities of the unselected stocks. This is done in Table 2. Disregarding statistical significance, if the average mortality of a selected line at a given dose is below that of the corresponding unselected stock, the comparison is labeled minus, if above, plus. It can be seen from the table that the lines stemming from the Syosset stock appear to have developed a distinctly increased resistance. Those lines stemming from the Oregon-R stock exhibit no clear difference in resistance from the unselected controls.

TABLE 2

Comparison of Mortality Figures for Selected Lines with Mortality Figures for Unselected Control Stocks at Five Different Time-Doses of DDT Aerosol.

+ =mortality of selected line above that of control.

- =mortality of selected line below that of control.

Line	Genera- tion	4 Min.	8 Min.	16 Min.	24 Min.	32 Min.
ORS-2	10	-	+	+	-	-
ORS-3	10	-	+	+	-	-
ORS-105	12	+	+	+	-	±
ORS-1001	10	-	+	+	-	±
SyS-1	8	-	-	-	-	-
SyS-2	10	-	-	-	-	-
SyS-102	10	+	-	-	-	-
SyS-103	10	-	-	-	-	-
SyS-1001	10	-	-	-	-	-
SyS-1002	9	-	-	-	-	-

It can be concluded that different stocks respond differently to selection for resistance. But the fact that the Oregon-R lines show no clear increase does not necessarily mean that they will not develop it under further selection. Even in the Syosset lines, resistance has developed slowly. Four generations earlier there was no clear evidence of increased resistance in the Syosset lines. This gradual increase indicates that resistance is a complex genetic character resulting from the interaction of numerous factors. One can say that if there are single genes which produce striking changes in resistance, none has been uncovered in the ten lines subjected to selection.

The program of treatments and selection is being pushed as rapidly as possible and every effort is being made to standardize the treatments and cut down the variances of the mortality figures. It is hoped that as selection proceeds, the development of resistance will become clearer and that it will be possible to demonstrate its statistical significance.

REPORTS OF SUMMER INVESTIGATORS

Abramson, H. A., 133 East 58th Street, New York, N.Y., **Goldfarb, A. R.**, Chicago Medical School, Chicago, Ill., and **Ames, E.**, Cold Spring Harbor, N. Y.—Previous experiments to isolate in purified form the cause of ragweed hay fever and asthma were continued. Absorption spectra of ragweed pollen extracts prepared by new electrophoretic methods were studied. Pollen granules extracted by 90% methyl alcohol served as a source of new biologically active material. A new colorless material hitherto not found in ragweed but biologically active was found after removal of most of the pigments. Biological activity of the essentially pigment-free new preparation is identical with a preparation containing all of the pigment.—In addition to our studies on the cause of allergy, the manner in which epinephrine alleviates the symptoms of skin allergies was studied by following the blanching effect of epinephrine on the human skin. The relationship between concentration of epinephrine and time of blanching was established.

Bernheimer, Alan W., College of Medicine, New York University, New York, N. Y.—Two problems were investigated. The first was a survey of the occurrence and distribution of hemagglutinins among higher fungi, principally Basidiomycetes. Saline extracts of the fruiting bodies of 70 species were studied for the presence of agglutinins for human erythrocytes of blood groups A, B, and O. Examination of the extracts revealed the presence of agglutinins in 15 and hemolysins in 6 species. The agglutinins and hemolysins proved in all instances to be nonspecific in that they did not permit differentiation of the ABO blood groups. The 70 fungus extracts are also being studied for other properties. It has been found, for example, that some of them contain substances capable of inhibiting streptolysin S, a hemolytic toxin produced by pathogenic strains of streptococci. The second problem investigated concerns the origin of hemagglutinins present in the hemolymph of the larvae of certain insects. It has been suggested (*Science*, 1952, 115, 150) that the insect agglutinins may be associated with the presence of parasites in the larvae. In order to test this idea, the hemolymph of unparasitized tomato caterpillars (*Protoparce sexta* reared from eggs under conditions which excluded parasites) was compared to hemolymph of *Protoparce sexta* larvae naturally infected with hymenopteran parasites. Hemagglutinin was found to be present in the hemolymphs of both parasitized and unparasitized larvae. Related observations were also made on normal and parasitized (*Habrobracon juglandis*) examples of *Ephestia kuhniella*. The findings with both *Protoparce* and *Ephestia* larvae, indicate that the hypothesis postulating a relationship between parasitism and presence of hemagglutinins should be abandoned.

Fox, Allen S., Ohio State University, Columbus, Ohio.—Immunogenetic analysis of Schultz's co-isogenic Oregon-R stocks of *Drosophila melanogaster* (including Ore-R, cv Ore-R, f Ore-R, rb Ore-R, v Ore-R, y Ore-R) was initiated. Conventional precipitin-absorption techniques

yielded results which indicated that the antigenic differences among these stocks is quantitative rather than qualitative. The Oudin technique (antigen diffusion into serum-agar) was employed in an attempt to resolve these differences. Four antigenic components were demonstrated to be present in all of the stocks, but in differing amounts. Mathematical extension of Fick's law of diffusion led to the development of methods for the estimation of relative concentrations and diffusion coefficients of individual components in each stock. This work was performed with the assistance of Arthur Chovnick and Natalie Barish.

Glass, Bentley, Department of Biology, The Johns Hopkins University, Baltimore, Md.—The summer was devoted entirely to writing and editing. In addition to the major task of editing Volume II of "A Symposium on Phosphorus Metabolism" (Johns Hopkins Press) and writing the included summary of 90 pages, a paper was written in collaboration with C.C. Li of the Graduate School of Public Health, University of Pittsburgh, on "The dynamics of interracial mixture—an analysis based on the American Negro."—The proximity of the Brookhaven National Laboratory enabled some experimental work to be done there during the course of the summer.

Granick, S., The Rockefeller Institute for Medical Research, New York, N. Y.—The summer was spent primarily in writing a review on "The metabolism of some metals concerned in hematopoiesis," for the symposium on the biochemistry of hematopoiesis held at the Second International Congress of Biochemistry in Paris.

Hotchkiss, Rollin D., Marmor, J., and Evans, Audrey, The Rockefeller Institute for Medical Research, New York, N. Y.—Biochemical characters of *Pneumococcus* are little known, principally because the growth of this species of bacteria occurs best, and is usually followed, in rather complex media containing peptones and rich tissue extracts. It would be very desirable to have control of biochemical properties of these bacteria in order to investigate whether these properties can be inheritably transferred from one strain to another by the process known as transformation. To this end, several simplified and relatively inexpensive media were developed and tested for pneumococcal growth. Some of these proved to be very useful in giving growth that is dependent upon compounds of the folic acid series, or upon known added sugars.

Maramorosch, Karl, The Rockefeller Institute for Medical Research, New York, N. Y.—Part of the summer was spent in preparing for publication two papers representing experimental work carried out at the Rockefeller Institute. These were: (1) Recovery of aster-yellows and corn-stunt viruses from nonvector leafhoppers, (2) Studies on the nature of the specific transmission of aster-yellows and corn-stunt viruses.

Mayr, Ernst, The American Museum of Natural History, New York, N. Y.—During the summer of 1952 three chapters were written of a book,

"Animal Species and Evolution." A study was made of the local species of fireflies (*Photuris*), their ecology, and the possible function of the light flashes as isolating mechanisms. Samples of snails of the genus *Cerion* were measured in preparation for a study on geographic variation and hybridization of these snails in the Bahamas.

Sandow, Alexander, Department of Biology, Washington Square College of Arts and Science, New York University, New York, N. Y.—The mainspring of my work at the Laboratory was the writing of a review of the monograph "The Rheology of the Cross Striated Muscle Fiber with Particular Reference to Isotonic Conditions" by F. Buchthal and E. Kaiser (Det Kgl. Danske Vidensk. Selskab, Biol. Medd. 21, 7, 318 pp., 1951), which has since been published in the *Journal of Neurophysiology*, 15, 513-514, 1952. In connection with this work I made a general study of rheology, especially as related to biological structure and activity. Although this reading was done in special reference to muscle, it has given me much broader perspectives, for rheological factors play a role in processes as diverse as the flow of blood in circulation and the behavior of chromosomes in cell division.

Szybalski, W., Biological Laboratory, Cold Spring Harbor, N. Y., and **Nelson, Thomas C.**, Vanderbilt University, Nashville Tenn.—The observation of one of us (W.S.) that the radiation-resistant strain B/r of *Escherichia coli* was about 40 times more resistant than strain B to the nitrofurans derivatives, furadroxyl and furacin (Eaton Labs.), and that the drug-resistant strains were radiation resistant, was studied in detail. Thirty independently isolated strains of B/r showed the same property, and all twenty-seven independently isolated strains of B, resistant to furadroxyl, were also radiation resistant. This indicates that both toxic agents select the same class of mutants. The mutation rate of strain B to furadroxyl resistance (measured at 0.4 mcg/ml of furadroxyl, the inhibitory concentration for strain B being 0.1 mcg/ml) was 3×10^{-7} per bacterium per generation, as measured by the second method of Luria and Delbruck. This was considerably lower than the mutation rate of strain B to the radiation-resistant B/r, as determined from survival curves following multiple ultraviolet irradiation. However the majority of putative ultraviolet-resistant survivors were phenotypically and not genotypically resistant, thus resulting in approximately equal mutation rates to resistance to radiation and drug exposure. Strains B/r and K-12, (both lysogenic and lambda sensitive) showed similar inhibitory thresholds of about 4 mcg/ml of furadroxyl. Selection in furadroxyl-containing medium resulted in mutants of strains B/r and K-12 of even greater resistance. Resistance to furadroxyl developed in clear-cut large steps with wide plateaus, convenient for use as genetic markers. This pattern is intermediate between the penicillin and streptomycin types of Demerec. It might be expected that multistep mutants to furadroxyl resistance would be more resistant to ultraviolet radiation than strains B/r and K-12. This was not found to be true—Subsequent studies by one of us (T.C.N.) have shown that four

resistance steps in the sexually reproducing strain K-12 (with inhibitory concentrations of 4-6, 20-30, 60-65, and 80-90 mcg/ml of furadroxyl) behave as if they were determined by very closely linked alleles, adjacent to the locus responsible for streptomycin resistance.

COURSE ON BACTERIOPHAGES

June 23 — July 12, 1952

Instructor: A. H. Doermann, Oak Ridge National Laboratory.

Assistant: Mary Baird Hill, Oak Ridge National Laboratory.

The three-week course on method and current research in the field of bacterial viruses was given for the eighth consecutive year. The laboratory syllabus was supplemented with three new experiments dealing with the following topics: (1) estimation of intracellular bacteriophage; (2) mapping genetic loci in bacteriophage; (3) lysogenesis. The eighteen students enrolled in the course are listed below:

S. M. Beiser, Ph.D., USPHS Tuberculosis Research Laboratory, New York, N.Y.

Thomas J. Bird, University of Pennsylvania, Philadelphia, Pa.

Elizabeth M. E. Burgi, Cornell University, Ithaca, N.Y.

Rita H. Cota, Lehigh University, Bethlehem, Pa.

John Clifton Davis, University of Pennsylvania, Philadelphia, Pa.

Solon Arthur Ellison, D.D.S., College of Physicians and Surgeons, Columbia University, New York, N.Y.

Russell A. Eversole, Hopkins Marine Station, Stanford University, Pacific Grove, Calif.

Lillian B. Fly, University of Miami, Miami, Fla.

Charles O. Gitterman, Ph.D., Merck and Company, Rahway, N.J.

Thomas Clifford Nelson, Ph.D., Vanderbilt University, Nashville, Tenn.

Don T. Parker, University of Wisconsin, Madison, Wis.

Howard A. Schneider, Ph.D., Rockefeller Institute, New York, N.Y.

Josephine See, Radcliffe College, Cambridge, Mass.

Mildred D. Southwick, Ph.D., Vassar College, Poughkeepsie, N.Y.

Franklin W. Stahl, University of Rochester, Rochester, N.Y.

Helen Van Vunakis, Ph.D., Johns Hopkins University, Baltimore, Md.

M. Jeanne Whallon, Camp Detrick, Frederick, Md.

Haim Yaniv, Ph.D., Weizmann Institute of Science, Rehovoth, Israel.

In connection with the course, a series of five lectures on bacteriophage problems was given by some of the leading investigators in this field. The speakers and their topics are listed below:

M. Delbruck—Photoreactivation in bacteriophage.

A. D. Hershey—Independent functions of viral protein and nucleic acid in growth of bacteriophage.

C. Levinthal—Precursors of bacteriophage investigated by electron microscopy.

S. Mudd—Electron microscopy of virus-infected bacteria.

N. Zinder—Transduction in *Salmonella*.

COURSE ON BACTERIAL GENETICS

July 16 — August 5, 1952

Instructors: V. Bryson and M. Demerec, in collaboration with Waclaw Szybalski, Jessie Hanson, E. L. Labrum, and I. Galinsky.

Assistants: Helen Deiches and Miriam Schwartz.

For the third time, a course on selected methods in bacterial genetics, initiated in the summer of 1950, was offered to advanced graduate and post-doctoral students. The course emphasized the newer methods used in the study of heredity in bacteria, and some of the recent results of work in this field. Sixteen students took the course and in addition two auditors attended the lectures and seminars. The following students and auditors were enrolled:

Students:

H. Baer, Ph.D., Tulane University, New Orleans, La.
Arthur Brown, Ph.D., State University of New York, Brooklyn, N.Y.
Elizabeth Burgi, Cornell University, Ithaca, N.Y.
Russell A. Eversole, Hopkins Marine Station, Pacific Grove, Calif.
Lillian B. Fly, University of Miami, Miami, Fla.
Paula Gottdenker, Newark Beth Israel Hospital, Newark, N.J.
Philip E. Hartman, University of Pennsylvania, Philadelphia, Pa.
Mary A. Medill, University of Pennsylvania, Philadelphia, Pa.
Helen N. Miller, Amherst College, Amherst, Mass.
Helene Nathan, Burroughs Wellcome, Inc., New York, N.Y.
Noel R. Rose, Ph.D., University of Buffalo, Buffalo, N.Y.
Arthur K. Saz, Ph.D., National Institutes of Health, Bethesda, Md.
Franklin W. Stahl, University of Rochester, Rochester, N.Y.
Helen Van Vunakis, Ph.D., Johns Hopkins University, Baltimore, Md.
Richard Weindling, Ph.D., Lederle Laboratories, Pearl River, N.Y.
H. Yaniv, Ph.D., Weizmann Institute of Science, Rehovoth, Israel.

Auditors:

Morton Klein, Ph.D., Temple University, Philadelphia, Pa.
Julius Marmur, Ph.D., National Institutes of Health, Bethesda, Md.
In connection with the course, the following series of lectures and seminars was given by students and summer research workers.
M. A. Medill—Erickson's criticism of the Luria-Delbruck fluctuation test.
A. Brown—Eagle's experiments on adaptation of bacteria to drug resistance.
M. Demerec—Analysis of the action of the different mutagenic agents.
W. Szybalski—Methods of studying mutation rate.
Arthur Saz—Review of the problem of bacterial transformation.
A. Brown—Freeman's work on the relation of bacteriophage to virulence in *Corynebacterium diphtheriae*.
T. Nelson—Bacterial recombination.
J. Wainright—Problems of enzyme action.
W. Maas—Biochemical genetics.

COURSE ON THE CYTOLOGY OF MICROORGANISMS

Instructor: Edward D. DeLamater, in collaboration with Mary E. Hunter and Sydney Yaverbaum, University of Pennsylvania, Philadelphia, Pa.

This three-week course dealt particularly with techniques for the production of cytological preparations of various microorganisms of genetical interest. Opportunity was afforded for making and studying such preparations. The following topics were taken up: staining of bacteria, yeasts, fungi (*Neurospora*), and blue-green algae for nuclear structure and for mitochondria, using various methods (Feulgen, Piekarski-Robinow, DeLamater, aceto-orcein); study of mitosis in bacteria (*Bacillus megaterium*, *Micrococcus cryophilus*); use of tetrazoles for study of mitochondria in bacteria and yeast; phase-contrast microscopy for the study of microorganisms.

The twelve students enrolled in the course are listed below:

Natalie Barish, Ohio State University, Columbus, Ohio.
Everett C. Bracken, Vanderbilt University, Nashville, Tenn.
Lillian B. Fly, University of Miami, Miami, Fla.
Elsa Granick, New York, N. Y.
Aviva Jabotinsky, Weizmann Institute of Science, Rehovoth, Israel.
Norma M. Keigler, University of Maryland, College Park, Md.
Philip G. Miles, Indiana University, Bloomington, Ind.
Joseph Y. Peary, Sc.D., Alderson-Broadbush College, Philippi, W. Va.
Robert A. Roosa, University of Connecticut, New London, Conn.
Josephine See, Radcliffe College, Cambridge, Mass.
Franklin W. Stahl, University of Rochester, Rochester, N.Y.
H. Yaniv, Ph.D., Weizmann Institute of Science, Rehovoth, Israel.

NATURE STUDY COURSE

July 7 — August 8, 1952

Instructor: Pauline James, Department of Biology, Texas College of Arts and Industries, Kingsville, Texas.

Assistant: Mrs. Ruth Moore, Memphis, Tennessee.

The five-week Nature Study Course offered students an opportunity to observe the numerous natural phenomena that continually exist all around them. They were encouraged to make careful observations in the field and to participate in the different activities. Every effort was made to acquaint the students with as many varied forms of nature as possible and to create in each student a basic understanding and appreciation of man's relation to his environment and his complete dependence upon it.

The location of the Biological Laboratory within easy access to many different ecological situations, varying from spring-fed fresh-water streams and lakes to salt-water beaches and brackish swamps, as well as open fields and heavily wooded hills, allowed opportunity for unlimited field work. All classes spent much time in the field in addition to working in Wawepex Laboratory, from which the course was directed.

The students were divided into four age groups. The thirteen Beginners, six and seven years of age, met on Monday and Wednesday from 9:00 a.m. until 11:00 a.m.; and the seventeen Juniors, eight and nine years old, met on Tuesday and Thursday from 9 a.m. until 11:00 a.m. The twelve Intermediates, aged ten and eleven, met on Tuesday and Thursday from 2:00 p.m. until 4:00 p.m.; and the five Seniors, aged twelve or over, on Monday and Wednesday from 2:00 p.m. until 4:00 p.m.

The field activities of the Beginner group were limited to nearby areas within easy walking distance of the Laboratory. Efforts were made to bring the children into contact with as many types of living things as possible and to help them form habits of accurate observation. Frequent opportunity was given for sharing experiences with other youngsters of their own age. When weather conditions made it unwise to leave the laboratory, this group showed great interest in such activities as making spore-prints of fungi, mounting leaf specimens that they had previously collected, studying animals in the laboratory, and working with the Bird Chart.

The youngsters in both the Junior and Intermediate groups took part in all field work, and as usual showed keen interest and enthusiasm. Some collections were made, but more detailed studies were carried on in the field and in the laboratory. Most of these students were intensely interested in marine life, and a number of trips were made to the beach for studying and collecting specimens to set up individual aquaria in the laboratory. The microscope proved to be a fascinating asset in studying the many organisms found in fresh-water ponds and lakes. In setting up fresh-water and marine aquaria, and woodland and marsh terraria, students learned the need for understanding the interrelations that exist in the natural habitat.

The small Senior group was made up chiefly of teen-aged boys with inexhaustible interest and enthusiasm. Much of their time was spent on

the study of fresh-water vertebrates, particularly the turtle group. Since this class was small, it was possible to take several automobile trips to outlying areas of especial interest. One of these trips was made to the "pine barrens" located in the central part of Long Island where there was opportunity to study an entirely different type of habitat. On a more local trip the boys discovered a bumble bee nest under a log and, after returning to the laboratory for equipment, were able to collect the entire colony. This "find" proved to be one of the most fascinating of the entire course. The bees were taken to the laboratory and placed in a glass container, where they could be fed and observed by students in each of the classes.

Staff members of the New York State Fish Hatchery, located near the Laboratory grounds, kindly conducted the different classes on tours of the hatchery, explaining the various activities carried on there. The reasons for restocking streams, and the methods used, proved to be of great interest, as did the inspection of growing trout. The Intermediate class was fortunate enough to visit the hatchery at the time a specially equipped truck was being loaded with fingerling trout for shipment upstate, and was thus able to observe each step in the procedure.

Classes also visited the Roosevelt Bird Sanctuary at Oyster Bay, where Mr. James Callaghan, the director, demonstrated and explained purposes of the exhibits in the Trailside Museum. He then took the youngsters along the Nature Trail, where they were able to observe some of the methods used to attract birds. The older students were especially interested in the exhibits, and after close inspection returned to Wawepex Laboratory and adapted some of the ideas to their own demonstrations.

The Nature Study course closed on August 8 with a public exhibition of the activities of the different groups during the five-week period. The youngsters had shown great interest in preparing their exhibits for their parents and friends, and eagerly pointed them out on the day of the demonstration. At 3:00 p.m., students and visitors alike were shown the movie "Birds on the Home Front" photographed by Dr. A. A. Allen of Cornell University. The movie was followed by a short series of Kodachrome slides showing some of the field activities of the students. Refreshments were served by the Laboratory.

The following students were enrolled in the course:

Alexander, Anne	Gerbino, Jason
Biesele, Megan	Granick, Lee
Buck, John L.	Hart, Chip
Buckley, Sally	Keil, Judy
Carley, William	Lyon, Stephen C.
Cleaveland, Peter	Melzig, Ricky
Cooke, Stephen	Miller, Carol Anne
Crary, Edith I.	Miller, Joyce
Cummings, Tabby	Montgomery, David
Deegan, Jimmy	Morris, Andrew

Murphy, John
Nicholas, Mary
Osborn, Oliver S.
Page, Jane
Palfrey, John
Pierce, Elizabeth
Pivnick, Carol
Radsch, Tom
Rippere, Kenneth
Rippere, Lawrence
Romaine, Gary
Roosevelt, Alexandra
Ross, Charles
Ross, Joe

Schieffelin, Julie
Schneider, Ann M.
Shemin, Louise
Stone, Charles
Storey, William
Tittler, Robert
Vacquier, Victor
Valens, Tom
Warner, Bradford
Warner, Miner H.
Warren, Margaret
Warren, Virginia
Werner, Roger

COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY

Current volume: XVII (1952). The Neuron. About 340 quarto pages.

Table of contents listed below:

INTRODUCTION

- Bodian, D.—Introductory survey of neurons.
Tobias, J.M.—Some optically detectable consequences of activity in nerve.
Frankenhaeuser, B.—The hypothesis of saltatory conduction.
Tasaki, I.—Conduction of impulses in the myelinated nerve fiber.

PROPERTIES OF NERVE AXONS

- Hodgkin, A. L., and Huxley, A. F.—Movement of sodium and potassium ions during nervous activity.
Brink, F., Bronk, D.W., Carlson, F.D., and Connelly, C.M.—The oxygen uptake of active axons.
Lorente de No, R.—Observations on the properties of the epineurium of frog nerve.
Monnier, A. M.—The damping factor as a functional criterion in nerve physiology.
Shedlovsky, T.—Electromotive force from proton transfer reactions. A model for bioelectric phenomena.
Therman, P. O.—Electrotonic potentials and excitability changes in nerve.

PERIPHERAL ORIGINS OF NERVOUS ACTIVITY

- Hunt, C. C.—Muscle stretch receptors; peripheral mechanisms and reflex function.
Hartline, H.K., Wagner, H.G., and MacNichol, E. F., Jr.—The peripheral origin of nervous activity in the visual system.
Davis, H., Tasaki, I., and Goldstein, R.—The peripheral origin of activity with reference to the ear.

THE NEURON SOMA

- Wiersma, C. A. G.—Neurons of Arthropods.
Ottoson, D., and Svaetichin, G.—Electrophysiological investigations of the frog retina.
Eccles, J. C.—The electrophysiological properties of the motoneurone.
Woodbury, J. W., and Patton, H. D.—Electrical activity of single spinal cord elements.

CORTICAL AND SPINAL NEURONS

- Chang, Hsiang-Tung.—Cortical neurons with particular reference to the apical dendrites.
Lloyd, D. P. C.—Electrotonus in dorsal nerve roots
Bernhard, C. G.—The cord dorsum potentials in relation to peripheral source of afferent stimulation.

SPINAL CORD AND SYMPATHETIC GANGLIA

Skoglund, C. R.—Factors that modify transmission through the spinal cord.
Larrabee, M. G., and Bronk, D. W.—Metabolic requirements of sympathetic neurons.

JUNCTIONAL TRANSMISSION

Bullock, T. H.—The invertebrate neuron junction.
Fatt, P., and Katz, B.—Some problems of neuro-muscular transmission.
Kuffler, S. W.—Neurons in the retina: Organization, inhibition and excitation problems.

APPENDIX

Karreman, G., and Landahl, H. D.—On the mathematical biology of excitation phenomena.

PREVIOUS VOLUMES

- *Vol. 1 (1933) Surface Phenomena, 239 pp.
 - *Vol. II (1934) Growth, 284 pp.
 - *Vol. III (1935) Photochemical Reactions, 359 pp.
 - *Vol. IV (1936) Excitations, 376 pp.
 - *Vol. V (1937) Internal Secretions, 433 pp.
 - *Vol. VI (1938) Protein Chemistry, 395 pp.
 - *Vol. VII (1939) Biological Oxidations, 463 pp.
 - *Vol. VIII (1940) Permeability and the Nature of Cell Membranes, 285 pp.
 - Vol. IX (1941) Genes and Chromosomes, 315 p.p.
 - *Vol. X (1942) The Relation of Hormones to Development, 160 pp.
 - Vol. XI (1946) Heredity and Variation in Microorganisms, 314 pp.
 - Vol. XII (1947) Nucleic Acids and Nucleoproteins, 279 pp.
 - Vol. XIII (1948) Biological Applications of Tracer Elements, 220 pp.
 - Vol. XIV (1949) Amino Acids and Proteins, 217 pp.
 - Vol. XV (1950) Origin and Evolution of Man, 425 pp.
 - Vol. XVI (1951) Genes and Mutations, 521 pp.
- *Out of print.

LABORATORY STAFF

- * Adams, Mark H. — Bacteriologist, Instructor
- § Binder, Robert G. — Research Assistant
- * Bryson, Constance — Technical Assistant
- Bryson, Vernon — Geneticist
- Corey, Perl Roy — Carpenter
- Cosillo, Gloria — Research Assistant
- Deiches, Helen L. — Research Assistant
- * DeLamater, Edward D. — Cytologist, Instructor
- § Dittman, Ilse — Research Assistant
- * Doermann, August H. — Bacteriologist, Instructor
- Elliot, Arthur H. — Laborer
- Elliot, Dorothy W. — Technical Assistant
- Farrington, Margaret — Technical Assistant
- Franzese, Eleanor — Clerical Assistant
- Fricke, Dorothy N. — Research Assistant
- Gardner, Henry — Technical Assistant
- * Garth, Clara S. — Research Assistant
- Geronimus, Lippman H. — Bacterial Physiologist
- * Haworth, Barbara Jane — Research Assistant
- Hershey, Harriet D. — Research Assistant
- * Hill, Mary B. — Assistant Instructor
- * Hunter, Mary E. — Assistant Instructor
- James, Ina Pauline — Nature Study Course Instructor
- § Kaufmann, Bobbie T. — Research Assistant
- King, James C. — Research Associate
- Klem, Dorothy V. — Secretary
- * Kremp, Fred W. — Research Assistant
- Lowell, Francis — Superintendent of Grounds
- Lowell, Lillian — Technical Assistant
- Madden, Carol V. — Research Assistant
- * Mayr, Christa — Technical Assistant
- * Marbourg, Nina — Cook
- Merlino, Aldo — Laborer
- Merlino, Joseph — Laborer
- § McGunnigle, Edward C. Jr. — Research Assistant
- § Meany, Carol — Research Assistant
- * Paget, Oliver — Research Assistant
- Reddy, William — Laborer
- § Riecke, Lillian A. — Technical Assistant
- § Rosenblum, Eugene D. — Bacteriologist
- § Ross, Agnes — Technical Assistant
- * Schwartz, Miriam — Research Assistant
- Stuard, Barbara J. — Research Assistant
- Szybalski, Waclaw T. — Bacteriologist
- Treanor, Ellen T. — Maid
- * Turner, Nellie — Cook

- * Turner, Harry — Assistant Cook
- Varro, Alice — Dining Hall Manager
- * Wade, Evelyn — Assistant Instructor
- Wallace, Bruce — Geneticist
- * Yaverbaum, Sydney — Assistant Instructor
- * Summer and Temporary
- § Resigned during the year.

SUMMER RESEARCH INVESTIGATORS

- Abramson, Harold A.—Cold Spring Harbor, New York
- Baer, Harold—Tulane University, New Orleans, Louisiana
- Benesch, Reinhold—Northwestern University, Chicago, Illinois
- Bernheimer, Alan W.—New York University College of Medicine, New York, N. Y.
- Chovnick, A.—Ohio State University, Columbus, Ohio.
- DeLamater, Edward D.—University of Pennsylvania, Philadelphia, Pa.
- Evans, Audrey—The Rockefeller Institute for Medical Research, New York, N. Y.
- Fox, Allen S.—Ohio State University, Columbus, Ohio
- Glass, H. Bentley—The Johns Hopkins University, Baltimore, Maryland
- Goldfarb, A. Roberts—The Chicago Medical School, Chicago, Illinois
- Granick, S.—The Rockefeller Institute for Medical Research, New York, N. Y.
- Harris, E. Huntington—New York City
- Hotchkiss, Rollin D.—The Rockefeller Institute for Medical Research, New York, N. Y.
- Hunter, Mary Elizabeth—University of Pennsylvania, Philadelphia, Pa.
- Maramorosch, Karl—The Rockefeller Institute for Medical Research, New York, N. Y.
- Mayr, Ernst—The American Museum of Natural History, New York, N. Y.
- Nason, Alvin—McCullum-Pratt Institute, The Johns Hopkins University, Baltimore, Maryland
- Nelson, Thomas C.—Vanderbilt University, Nashville, Tennessee
- Sager, Ruth—The Rockefeller Institute for Medical Research, New York, N. Y.
- Sandow, Alexander—Washington Square College of Arts and Sciences, New York, N. Y.
- Shemin, David—College of Physicians and Surgeons, Columbia University, New York, N. Y.
- Tittler, Irving—Brooklyn College, Brooklyn, New York
- Wolken, Jerome J.—The Rockefeller Institute for Medical Research, New York, N. Y.

REPORT OF THE SECRETARY

A meeting of the Executive Committee of the Board of Directors was held at Cold Spring Harbor on September 19, 1952, with five members present. The meeting was called by President Ames to consider the purchase of the 22½ acres of Jones Estate property situated on the west shore of Cold Spring Harbor between two parcels belonging to the Long Island Biological Association. The great desirability of obtaining this property, in order to protect the rest of the Association's holdings, was discussed, and possible sources of the necessary funds were reported. By unanimous vote the Director of the Laboratory was empowered to negotiate a definite option on this property.

A meeting of the Executive Committee was held on January 22, 1953, at the home of the President. After a discussion of finances related to the completion of the purchase of the Jones property, the Treasurer was empowered to take preliminary steps toward the sale of the Association's hilltop property. The Laboratory budget proposed by Dr. Demerec for 1953 was discussed in detail. Plans were considered for the dedication ceremonies of the new Lecture Hall. An invitation to the Association to join the National Society for Medical Research was discussed, and it was agreed to accept this invitation.

The 65th meeting of the Board of Directors was held on February 1, 1953, in the new Lecture Hall at Cold Spring Harbor, with sixteen members present. President Ames gave the background for the action of the Executive Committee in purchasing the Jones property, which was made possible by the cooperation of the Carnegie Institution of Washington in purchasing half of the estate. The actions and considerations of the Executive Committee were approved and confirmed. The report of the Treasurer on the affairs of the Association and the financing of the new property was accepted and approved. Dr. M. Demerec, Director of the Laboratory, reported on its activities, including the research program, plans for the use of the new Lecture Hall, and the organization of the forthcoming Symposium on "Viruses." President Ames outlined the special activities planned for the next six months, including a letter from the President to the community, the dedication of the new Lecture Hall, and a lecture by Dr. Robert Cushman Murphy. The proposed budget for 1953 was discussed and approved.

A meeting of the Executive Committee was held on June 4, 1953, at the home of President Ames. The following topics were discussed: survey of land in connection with a possible sale; finances; nominations for Directors of the class of 1957; and the annual appeal for funds.

E. Carlton MacDowell, Secretary.

MAIN AND COMPANY

Certified Public Accountants
New York, U. S. A.

Long Island Biological Association,
Cold Spring Harbor, L. I., N. Y.

We have made an examination of the accounts of the Long Island Biological Association for the year ended April 30, 1953. Our examination was made in accordance with generally accepted auditing standards, and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the accompanying balance sheet and statements of income and expense and net worth, and supporting schedule, together with the note thereon, present fairly the position of the Long Island Biological Association at April 30, 1953 and the results of its operations for the year ended on that date.

Main and Company
Certified Public Accountants

New York, N. Y.,
June 8, 1953.

LONG ISLAND BIOLOGICAL ASSOCIATION
BALANCE SHEET
APRIL 30, 1953
ASSETS

General and Endowment Fund

Cash:

In banks	\$ 5,280.65		
On hand	100.00	\$ 5,380.65	

Investments (market value \$21,951.98—Note "A")			21,755.13
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Accounts receivable:

Josiah Macy, Jr. Foundation	\$ 231.40		
United States Atomic Energy Commission	4,030.88		
United States Department of the Army: Chemical Corps	11,277.04		
Office of Surgeon General	3,533.26		

United States Department of the Navy: Office of Naval Research	715.68		
Miscellaneous	1,165.82	20,954.08	

Land, buildings and equipment,
at cost or appraisal values:

Land	\$102,141.51		
Improvements to land	2,898.01		
Buildings	101,265.00		
Land and buildings leased from Wawepex Society	49,700.00		
Equipment	57,940.32	313,944.84	\$362,034.70

Special Funds

Cash in bank		\$ 927.12	
Investments (market value \$15,494.93)		15,710.00	16,637.12

Total	\$378,671.82
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NOTE "A": Includes securities having a book value of \$21,681.13, with a market value of \$21,873.38, held by The Hanover Bank as collateral on a demand loan of \$12,400.00.

NOTE "B": In accordance with the Association's established practice, the above balance sheet does not include the inventory at April 30, 1953 of the published volumes of the Association's yearly Symposia of Quantitative Biology, nor has any depreciation or amortization on buildings and equipment been recorded on the Association's records. Additions and improvements to buildings and equipment have been charged against current operations in conformity with the Association's usual practice.

LIABILITIES AND NET WORTH

General and Endowment Fund

Liabilities:

Bank loan (Note "A")	\$ 12,400.00	
Accounts payable	3,230.24	
Accrued payroll	549.17	
Special grants and contracts:		
The Jane Coffin Childs Memorial Fund for Medical Research	\$ 405.27	
National Tuberculosis Association	.76	406.03
Total Liabilities	\$ 16,585.44	
Reserve for Scientific research	3,000.00	
Endowment Fund:		
Dr. William J. Matheson Bequest	20,000.00	
Net worth	322,449.26	\$362,034.70

Special Funds

Blackford Memorial Fund:			
Principal		\$ 5,000.00	
Charles Benedict Davenport Memorial Fund:			
Principal	\$4,934.75		
Unexpended income	657.75	5,592.50	
Charles Benedict Davenport, Junior, Fund:			
Principal		1,037.12	
Temple Prime Scholarship Fund:			
Principal	\$2,500.00		
Unexpended income	142.50	2,642.50	
Dorothy Frances Rice Fund:			
Principal	\$2,265.80		
Unexpended income	99.20	2,365.00	16,637.12
Total			\$378,671.82

LAND, BUILDINGS AND EQUIPMENT

April 30, 1953

Land:

Purchased with funds raised through public subscription	\$69,466.52	
Land purchased from Estate of Mary E. Jones	15,674.99	
Henry W. deForest land	12,000.00	
Airlie land	5,000.00	\$102,141.51

Improvements to land:

Pipe line	\$ 1,860.39	
Road	746.64	
Light and telephone poles	290.98	2,898.01

Buildings:

Airlie building	\$ 5,000.00	
Blackford Hall *	19,000.00	
Cole Cottage	2,105.00	
Davenport Laboratory	8,500.00	
Henry W. de Forest building	15,000.00	
Reginald G. Harris House	8,500.00	
Dr. Walter B. James Laboratory	13,500.00	
George L. Nichols Memorial Laboratory	13,700.00	
Williams House	11,300.00	
Urey Cottage	2,660.00	
Machine shop and garage	2,000.00	101,265.00

Land and buildings leased from
Wawepex Society under lease
expiring in 1979:

Land		\$13,500.00	
Buildings:			
Hooper House	\$13,200		
Jones Laboratory	10,000.00		
Osterhout Cottage	5,500.00		
Wawepex Laboratory	7,500.00	36,200.00	49,700.00

Equipment:

General	\$38,577.27	
Biophysics	16,849.90	
Physiology	2,513.15	57,940.32

Total

\$313,944.84

* Built on land leased from Wawepex Society.

STATEMENT OF NET WORTH

For the Year Ended April 30, 1953

Balance, May 1, 1952	\$327,871.84
Add:	
Excess of expense over income for the year ended April 30, 1953	5,422.58
	\$322,449.26

STATEMENT OF INCOME AND EXPENSE

For the Year Ended April 30, 1953

Income:

Contributions:

Dues and contributions	\$ 5,357.50	
Carnegie Corporation (grant for publication of Annual Symposia)	6,000.00	
Wawepex Society	1,650.00	
John D. Jones Scholarship	500.00	\$13,507.50

Symposia:

Book sales	\$20,303.15	
Registration fees	125.00	20,428.15

Dining Hall		9,571.75
Rooms and apartments		12,502.28
Research fees		11,466.92
Interest and dividends on investments		951.67

Other income:

Summer course tuition	\$ 3,270.00	
Nature study course	240.12	
Beach permits	135.00	
Annual distribution from Walter B. Jones Fund	165.00	
Miscellaneous	3.00	3,813.12

Total income	\$72,241.39
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Expense:

Symposia:

Publication of annual Symposia on Quantitative Biology	\$21,184.40	
Expense of Participants and lecturers	4,507.82	\$25,692.22

Dining Hall		10,383.64
Rooms and apartments		3,561.05
Research expenses		1,697.44
Summer course expense		4,011.09
Loss on sale of investments		125.47
Interest on loan		118.14
Distribution of John D. Jones Scholarship		445.00
Buildings and grounds maintenance		
Salaries	\$10,384.56	
Materials and supplies	7,625.88	
Heat, light and water	3,155.21	
Real estate taxes	688.34.	21,853.99

General and administrative:		
Salaries	\$ 5,985.01	
Insurance	1,592.67	
Printing and stationery	1,132.26	
Telephone, telegraph and postage	262.40	
Other	803.59	9,775.93

Total expense		<u>77,663.97</u>
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Excess of expense over income		<u>\$ 5,422.58</u>
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SUSAN COOPER