Meetings

Molecular Biophysics: International Summer School

The main impetus for biophysics comes from biology, and particularly from that part of biology which has been steadily progressing toward the molecular level—a level which is describable only in physicochemical terms. Biology, molecular biology, biochemistry, and molecular biophysics form a logical sequence between the description of living systems and the physical characterization of the molecular entities responsible for them. Molecular biophysics interacts most strongly with its "nearest neighbor" biochemistry, and the relation between the two is analogous to that between chemical physics and chemistry.

These relationships were reflected by the program of the International Summer School on Molecular Biophysics held at Squaw Valley, California, 17-28 August 1964, in which studies ranged from the biological level to detailed molecular properties. A review of protein biosynthesis and the cell machinery responsible for it was given by Gros (Centre National de la Recherche Scientifique, Paris). Rich (M.I.T.) elaborated on certain details, particularly in regard to the role of the ribosomal particles, and continued with a discussion of structural features of nucleic acids and proteins as revealed by analysis of x-ray diffraction patterns. Schachman (University of California) and Katchalski (Weizmann Institute, Rehovoth) concentrated on proteins and model compounds—conformational stability, thermodynamics of solution, electrochemical properties, and the basis for higher order structure (secondary, tertiary, and so forth). Electronic properties of biomolecules were discussed by B. Pullman (Sorbonne) on the basis of indices arising from molecular orbital theory. A large number of physicochemical properties, including radiosensitivity, photochemical effects, reactive sites, and the mutagenic and carcinogenic effects of hydrocarbons, may be described from this standpoint.

Weber (University of Illinois) and Tinoco (University of California) discussed absorption and fluorescence spectra of proteins in solutions, polarization, rotatory dispersion, and the relationship of optical properties to conformation. A. Pullman (CNRS) summarized molecular orbital methods in conjugated systems. Hirschfelder (University of Wisconsin) concentrated on intermolecular forces, and McConnell (Stanford) described various types of collective excitations in ordered molecular aggregates. Certain photochromic effects resulting from configurational transitions were discussed by Douzou (Laboratoire de Biophysique, Paris). Scrocco (Instituto di Chimica Fisica, Pisa) discussed electronic properties derivable from nuclear quadrupole resonance spectroscopy, while Weissbluth (Stanford University) gave analogous discussions for Mössbauer spectroscopy in proteins containing iron and for spin-resonance spectroscopy of the triplet state in amino acids. Griffith (University of Manchester, England) continued with spin-resonance spectroscopy of iron compounds. The program also included a number of seminars, including one on information theory and memory, led by Griffith, and one on the molecular basis for radiation damage, led by Kaplan (Stanford). Jehle (George Washington University) conducted a seminar on the relation between specificity and London forces, and a seminar on the molecular aspects of muscle contraction was conducted by Morales (University of California).

From the discussions at this meeting it was apparent that there still exists a wide gap between molecular biology and biochemistry and, of course, an even wider gap with respect to molecular biophysics; physicochemical explanations of biological phenomena have barely begun. Another difficulty is that there is no physical theory of macromolecules, which are now treated either as crystals or as collections of semi-independent small molecules; both approximations are useful, but both have shortcomings. Also, physical methods used in molecular biophysics are based on concepts drawn largely from thermodynamics and quantum mechanics. These problems make this an immensely exciting field, particularly to those who have a physical orientation.

B. Pullman was the director of the Summer School which was sponsored jointly by NATO and the U.S. Office of Naval Research. Approximately 150 conferees attended, of whom more than one-fourth came from outside the United States. The proceedings will be published.

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DNA Replication and Recombination

A symposium on the mechanisms of DNA replication and recombination was held during the annual meeting of the American Society for Microbiology in Washington, D.C., in May 1964. The four participants—Sidney Brenner (Cambridge, England), Karl Lark (Kansas State University), Frederick Forro (Yale University), and Matthew Meselson (Harvard University)—all presented work done with the enteric bacterium *Escherichia coli* and its viruses.

Meselson's contribution to the symposium was presented as his acceptance speech for the Eli Lilly Award in Microbiology. He discussed his experiments, begun with Jean Weigle (California Institute of Technology), with the bacteriophage λ which infects *E. coli*; in these experiments the bacterial cells were mixedly infected with two strains of λ which differed in a number of genetic markers. The phages had previously been grown in a medium containing heavy isotopes of carbon and nitrogen and then used to infect bacteria in light medium. When the infected cells lysed they liberated progeny phage particles of several sharply defined densities: a few in which both DNA strands of the phage chromosome had been conserved (heavy-heavy), a very large number

of particles containing only DNA synthesized during the infection (light-light), and a few with exactly intermediate density (heavy-light), as expected to result from semiconservative replication of heavy-heavy DNA.

Meselson pointed out that, if two heavy-heavy chromosomes recombine by a crossover in the middle of the chromosome, and if crossing over consists of breakage and reunion of double-stranded DNA molecules, there should be produced a recombinant chromosome containing 100 percent heavy DNA. If a heavy-heavy and a heavy-light chromosome recombine in this manner, a recombinant chromosome containing 75 percent heavy DNA will result. Similarly one would also expect to find recombinant phages containing 50 percent and 25 percent heavy DNA.

Using the technique of density gradient centrifugation in cesium chloride, which Meselson played a major role in developing, he was able to show that genetically recombined phages of the predicted densities could be recovered. These results firmly establish that genetic recombination can occur by breakage and reunion, leaving the recently popular model of recombination by "copy-choice" still to be substantiated by experiment. The results also show that genetic map distance, as measured by the probability of crossing over, is at least approximately proportional to molecular length. Finally, Meselson established that the bond holding together the DNA fragments contributed by two different parents is a stable one, since it can survive a second cycle of infection.

Brenner traced the development of the "replicon" hypothesis first proposed in 1963 by himself and F. Jacob. The replicon was defined as the unit of replication; in an *E. coli* cell, for example, three different replicons may be present at the same time: the bacterial chromosome, the sex factor, and a temperate phage such as λ. The sex factor (F) and λ are capable of replicating autonomously, or in a state of integration with the chromosome. A replicon replicates sequentially from one point only; another cycle of replication cannot begin until the current cycle is completed.

These facts suggest that each replicon has in its structure a special recognition element which is also the starting point for replication. This element, called the replicator, will start a cycle of replication only if it receives a signal to do so. Since different replicons in the same cell can be under independent controls, replicators must be highly specific.

From experiments on cells mixedly infected with two different phages, it can be inferred that control is positive: that is, the replicator must be turned on by the action of a specific initiator substance (rather than acting continuously unless turned off by a repressor). Thus a replicon must possess the following elements of a control system: a structural gene which produces a gene product (the initiator) and a replicator with which the initiator combines to activate a cycle of replication.

Brenner then elaborated further evidence in support of this model, including a description of temperature-sensitive mutants of F which fail to replicate autonomously at high temperatures, but do so when integrated with the chromosome. The ability of the mutant F to replicate at high temperature is restored by putting into the same cell a wild-type sex factor. A diffusable factor controlling replication in a positive manner must thus be produced by the wild-type F: this is the postulated initiator.

Finally, Brenner showed how the replicon model can be extended to explain the transfer of DNA from cell to cell by conjugation. According to the model, replication occurs at a specific site on the bacterial membrane. As a replicon passes through this site, it is replicated; growth of a transverse septum from the same site ensures that the two replicas are segregated into the two daughter cells. The sex factor, F, is presumed to determine the formation on the cell surface of a specific receptor for attaching to F^- cells, the receptor being directly opposite the point where F is attached to the inner membrane. Replication of F in a conjugating cell then leads, in an unknown manner, to transfer of one of its own replicas. If F is integrated with another replicon, such as the chromosome, then transfer of the entire integrated structure occurs.

Lark described some experiments which bear directly on the nature of the substances which play a role in the regulation of DNA replication. The general approach used by Lark and his collaborators has been to pulse-label the DNA with H^3-thymine for a small fraction of a generation, and at some later time to shift the density of the DNA precursors in the medium so that all DNA made after the shift can be separated and measured in the ultracentrifuge as hybrid material. The rate at which radioactivity appears in the DNA of hybrid density then reveals, among other things, the fraction of cells in which DNA replication was proceeding along the segment of the chromosome labeled by the H^3 pulse.

For example, if the cells are starved of required amino acids, they continue to synthesize DNA only until the current cycle of replication has been completed. On restoration of the amino acids replication begins at the same point in every cell. (This point is the "origin" in Lark's terminology, and essentially corresponds to the "replicator" of Jacob and Brenner.) If a pulse of H^3-thymine is given when the amino acids are restored, and several generations later the density shift is carried out, radioactivity appears in the hybrid DNA at the linear rate predicted if the cells have become randomized during the intervening period—for example, 50 percent of the radioactivity is incorporated into hybrid when 50 percent of the DNA has become hybrid. On the other hand, if the replication cycles are aligned by amino acid starvation just prior to the density shift, the bulk of the radioactivity is incorporated when only 10 percent of the DNA has become hybrid. Thus, amino acid starvation stops DNA replication at the same point on the chromosome in every cell, each time it is carried out.

By means of such experiments, together with experiments which measure the overall rate of DNA synthesis after different treatments, the following points have been established: (i) Thymine starvation of a thymine-less auxotroph brings about the premature initiation of a new cycle of DNA replication on one of the two replicas of the chromosome already present. The new cycle, which commences as soon as thymine is restored, starts at the same "origin" as that which exists after amino acid starvation. After restoration of thymine most cells replicate their chromosomes from two points: the growing point which existed when DNA replication was halted by thymine deprivation, and the origin. (ii) Amino acid starvation can prevent the premature initiation of DNA replication caused by thymine starvation. (iii) The premature initiation is inhibited by chloramphenicol or by fluorouracil, while the reinitiation which occurs after amino starvation is resistant to these agents.

From these results two proteins are inferred to play a role in the regulation of DNA replication. One of these, which is formed during thymine starvation, may be the initiator postulated by Jacob and Brenner; its formation seems to be specifically blocked by an inhibitor which contains thymine. The other, which is synthesized even in the presence of chloramphenicol, may be a structural protein necessary for the attachment of the DNA to the cell surface layers as called for by Jacob and Brenner's model.

Forro described yet another experimental system for studying DNA replication in vivo. Forro and his associates label the DNA of *E. coli* with H^3-thymine and then carry out radioautography of clones derived from single labeled cells. The segregation of labeled DNA among daughter cells grown on nonradioactive medium provides some insight into the organization and mode of replication of DNA within cells. Experiments were also described in which the radioautography was carried out on clones arising from zygotes that had received DNA from labeled males.

The data presented by Forro are consistent with a model of semiconservative replication, the units of replication having a molecular weight of 2 to 3 $\times$ 10^9. In many cases, a dispersion of label in the clone was observed, which can be explained by random crossing over between sister chromosomes with a frequency of about 0.5 per chromosome per generation. The transfer experiments with Hfr cells indicate that two-stranded DNA is transferred; in the case of $F^+ \times F^-$ crosses, many clones showed only a single labeled unit, as if only one of the two transferred strands had been labeled. Finally, a correlation was shown between the amount of chromosome transferred as measured genetically and as measured by radioautography.

The material presented by Meselson, Brenner, Lark, and Forro was summarized by E. A. Adelberg, who pointed out that all of the work presented was carried out in vivo, and that the models inferred have far outrun the ability of experiments in vitro to demonstrate the existence and nature of the postulated substances (enzymes, initiators, replicators, attachment sites) which act to control DNA replication and recombination.

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Winter Gordon Research Conferences

The Winter Gordon Research Conferences will be held from 25 January to 5 February 1965 in Santa Barbara, California, at the Miramar Hotel and at the Santa Barbara Biltmore Hotel. The purpose of the Gordon Research Conferences is to stimulate research in universities, research foundations, and industrial laboratories. This purpose is achieved by an informal type of meeting consisting of scheduled lectures and discussion groups. Sufficient time is available to stimulate informal discussions among the members of each conference. Meetings are held in the morning and in the evening, Monday through Friday, with the exception of Friday evening. The afternoons are available for recreation, reading, or participation in discussion groups as the individual desires. This type of meeting is a valuable means of disseminating information and ideas to an extent that could not be achieved through the usual channels of publication and presentation at scientific meetings. It is hoped that each conference will extend the frontiers of science by fostering a free and informal exchange of ideas among persons actively interested in subjects under discussion. The Summer Conferences are held in New Hampshire [*Science* **143**, 1203 (1964)].

Registration and reservations. Attendance at the conferences, limited to approximately 100, is by application. Individuals interested in attending the Conferences are requested to send their applications to the office of the director. *Applications must be submitted in duplicate on the standard form, which may be obtained from the office of the director.* The applications will be reviewed by the Conference Committee. This committee in selecting the participants will distribute the attendance as widely as possible among the institutions and laboratories represented by the applications. A registration card will be mailed to those selected. Advance registration by mail is required; this is completed when the registration card with a deposit of $25 is received in the office of the director. A registration card not accompanied by the $25 deposit will not be accepted. This advance deposit is not required of scientists from foreign countries.

A fixed fee of $125 has been established for resident conferees and covers registration, double room with bath, City of Santa Barbara room tax, meals, and gratuities for five conference days. There will be an additional charge for a single room and for rooms occupied more than the five conference nights (Sunday through Thursday). This fee was established to encourage attendance for the entire conference and to increase the Special Fund that is available to the Conference Chairmen for assisting participants who attend the conference wholly or in part at their own expense.

The participants are expected to live at the conference location because one of the objects of the conference is to provide a place where scientists can get together informally to discuss scientific research. All participants are urged to attend the conference for the entire week. Under special circumstances conferees will be permitted to stay at locations other than the site of the Conference. Such nonresident conferees will be charged a registration fee of $60.

Conferees living at the conference location who will pay all or part of the fixed fee as a personal expense may request a reduction of $25 in the fixed fee. *Application for this special fee must be made at the conference office during the conference.*

Accommodations are available for wives who wish to accompany their husbands, and for children 12 years of age and over. All such requests should be made at the time the attendance application is submitted. The charge for room and meals for a guest is $75.

Cancellation. The $25 deposit is forfeited if an approved application for attendance at the conference is cancelled.

Attendance. Requests for application forms for attendance at the Conferences, or for additional information, should be addressed to W. George Parks, Director, Gordon Research Conferences, University of Rhode Island, Kingston.

Miramar Hotel

Electrochemistry: Electrode Processes

Richard P. Buck and Ernest Yeager will serve as *chairman* and *vice chairman*, respectively.

25 January. Roger Parsons, "The structure of the double layer at electrodes"; David M. Mohilner, "Comparative double layer studies"; James