CHEMICAL BIOLOGY

Collaboration between biology and chemistry at Caltech has already resulted in some impressive discoveries. Now a new grant promises to put the program on a long-term basis.

THE ROCKEFELLER FOUNDATION last month made a conditional grant of $1,500,000 to the Institute for research in chemical biology—the condition being that the Institute match the Foundation's $1,500,000 in a period of three years.

This means that if the Institute can raise approximately $100,000 every two months for the next three years—from individuals, corporations or foundations—the Rockefeller Foundation will contribute an equal amount toward the support of chemical biology at Caltech.

This new grant is actually a continuation and an extension of support provided by the Rockefeller Foundation for several years. Present work in chemical biology here is being conducted in part on a $700,000, seven-year Rockefeller grant, available at the rate of $100,000 a year.

Chemical biology is, of course, no new branch of science. It is merely the name given to that work in chemistry which is of biological interest—and to that work in biology in which the chemical approach is used to solve biological problems.

Though this collaboration between chemistry and biology is certainly not unique to Caltech, it is nevertheless in full and vigorous operation here, and is proving to be an increasingly productive field of research.

From the chemical side, Caltech's chemical biology program includes:

1. Organic chemistry—the chemistry of the compounds of carbon, which occurs in practically all of the substances which constitute living matter.

2. The principles of molecular structure, as these apply to compounds of biological importance—particularly the proteins and the nucleic acids. These are key substances in all living systems. They are enormously complex. They have never been synthesized, and their structure is not known, but they are essential to the progress of biology.

Proteins form a vital part of the protoplasm of all plants and animals. Their presence in cells and tissues (and therefore in man's food materials) is essential to the continuance of life.

Nucleic acid is considered to play an important part in the synthesis of protein, with which it usually occurs combined. According to the most recent studies (page 11) it may be the substance out of which genes are made. It may also be the key to reproduction.

3. Immunochemistry—studies of the structure and action of antigens and antibodies.

4. Enzyme chemistry—attempts to discover and isolate enzymes, the catalysts responsible for many of the chemical reactions of living organisms.

5. Disease in relation to molecular abnormalities. This unique field of research has developed from the discovery four years ago in the Caltech chemistry laboratories, that some forms of anemia are based upon abnormalities of the hemoglobin molecule.

From the biological end the Caltech chemical biology program covers:

1. The physiology of plants and animals.

2. Biochemistry—the chemical reactions which take place in living organisms.

3. Certain chemical aspects of embryology (such as the mechanism of fertilization).

4. Chemical genetics—studies of the genes, the units of heredity, and what they do in relation to the development of form and function in an organism.

5. Immunogenetics—the investigation of how genes are related to the antigens that are of importance in blood groups, skin grafting, and immunity to disease.

6. Bio-organic chemistry—the chemistry of naturally occurring compounds.

7. Virology—studies of viruses, the smallest known entities that can reproduce themselves.

8. Some aspects of plant and animal ecology.

In general this program involves an attempt to uncover basic principles rather than to attack specific practical problems. The researchers are trying to determine the structure of genes and the mechanism of their action rather than to develop commercially profitable mutants; to obtain a fundamental understanding of viruses and antibodies rather than to prepare an antiserum for a particular disease; to learn the basis of the physiological activity of drugs in terms of their molecular structure rather than to find a new bacteriostatic substance.

Nevertheless, practical discoveries are often made incidentally in the course of fundamental investigations. In fact, the Caltech workers hope that in the course of this fundamental research new ideas will be developed which will provide the basis for clinical research on such medical problems as those presented by neoplastic, cardiovascular, and virus diseases.

Several impressive discoveries have taken place in chemical biology in recent years.

The structure of proteins

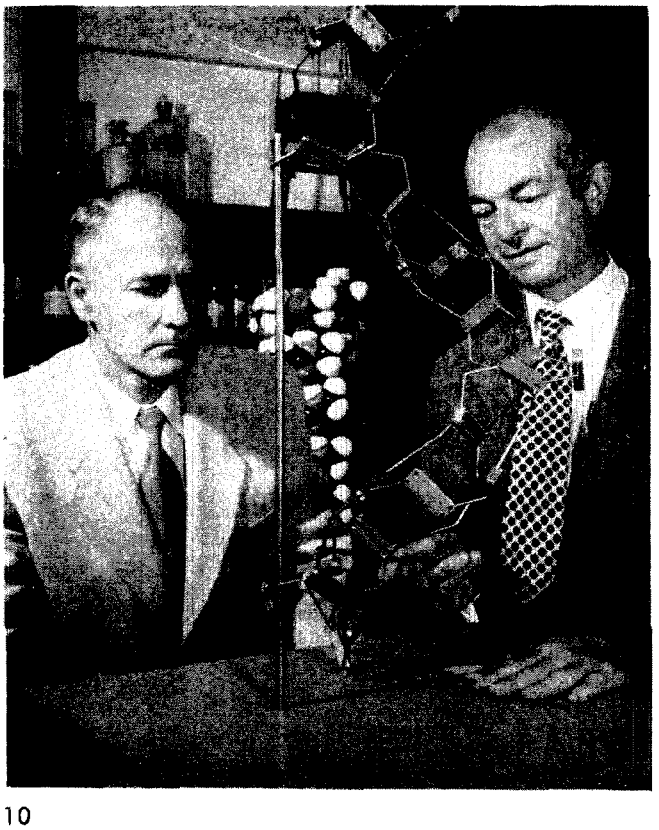
In 1951 Dr. Linus Pauling, chairman of the Caltech Division of Chemistry and Chemical Engineering, and Dr. Robert B. Corey, Professor of Structural Chemistry, reported their discoveries of the essential atomic structure of several proteins—including those found in bone, muscle, and red blood cells.

One of the most important problems in the field of biochemistry is to find out how proteins, the principal building blocks of the body, are put together.

The major components of all living cells are proteins, fats, carbohydrates, salt and water. Though all of them are essential, the proteins among these are responsible for many of the activities which we associate primarily with living things—and in this respect, they may be considered more important than any of the other components of living cells.

Some of the most important proteins include hair, silk, wool, horns, fingernails and feathers. The major components of skin and muscle are proteins; so are the major components of hemoglobin and the antibodies found in the blood. In addition, both the viruses and the genes either contain proteins or are closely associated with them.

Altogether, there are thousands of different kinds of proteins in the human body. Unlike the molecules of most other chemicals, which consist of a score or two of individual atoms, protein molecules are made up of thousands—sometimes millions—of individual atoms,



George W. Beadle, chairman of the Caltech Division of Biology, and Linus Pauling, chairman of the Division of Chemistry and Chemical Engineering. Pauling is pointing out details of bonding in a proposed protein structure.

Dr. Renato Dulbecco, Associate Professor of Biology. His new technique for studying animal viruses made it possible to isolate, for the first time, genetically pure strains of the three known types of polio virus.

each occupying a specific place in the architecture of the molecule.

The first great advance toward an understanding of protein structure was made in 1900 when Emil Fischer, a German, found that a protein molecule is composed of simpler substances known as amino acids (of which there are 24 in all), and that the amino acids, in turn, are linked together into larger groups known as peptides, and the peptides are linked together into even larger groups known as polypeptides.

The problem of determining the structure of proteins then became one of finding the sequence of various amino acids in the chain and the way in which the chain is coiled.

Instead of trying to study the complicated proteins directly, Pauling and Corey, some fifteen years ago, began to investigate the crystal structure of the amino acids, of simple peptides, and of other simple substances related to proteins. In this way they were ultimately able to obtain enough structural information to permit the precise prediction of reasonable configurations of the structure of several proteins.

Virus research

In 1952 Dr. Renato Dulbecco, then a Senior Research Fellow in Biology (now Associate Professor), developed a new technique for studying those viruses which attack animal tissue (as compared with those which attack only plants, or bacteria). These are the viruses which cause such diseases as smallpox, shingles, influenza and poliomyelitis. Formerly, animal viruses could be studied only by the slow and expensive process of infecting monkeys or (at less cost) chicken embryos.

Dulbecco's new technique is to grow a single layer of animal tissue cells in a nutrient medium in a small dish and then to introduce a weak suspension of virus particles. If a single virus attacks a tissue cell it will multiply and produce a small visible area of dead cells. Thus the number of virus particles in the original suspension can be counted and the progeny from any single virus can be "bred" for further study.

This technique is analogous to the "plaque count" technique so widely used for study of the viruses that attack bacteria.

The importance of this development has already been demonstrated. Last year, applying the plaque technique to polio virus, Caltech researchers were able to isolate for the first time genetically pure strains of the three known types of polio virus. This means that it is now possible to start intensive studies of the development and hereditary properties of that virus.

Nucleic acid

In 1953, J. D. Watson, then at the Cavendish Laboratory in Cambridge (and now Senior Research Fellow in Biology at Caltech), and F. H. C. Crick proposed a molecular structure for desoxyribonucleic acid (DNA). This chemical is found largely in the chromosomes, and recently has come to be thought of prime importance in living systems. Various types of biological experimentation indicate a close relationship—if not identity—with the gene itself, the unit of heredity.

The Watson-Crick structure consists of two (not one, as had previously been proposed) polynucleotide chains helically coiled around a common axis. A polynucleotide is a long chain molecule formed by the regular union of nucleotides (units containing sugar, phosphate, and purine or pyrimidine bases).

The DNA structure has four bases; two of these—adenine and guanine—are purines; and two—thymine and cytosine—are pyrimidines. The two chains are held together transversely by hydrogen bonds between bases in such a way that guanine is bonded to cytosine and adenine to thymine. The phosphate residues are on the outside of the helix.

The DNA structure is of particular interest because it indicates how it might carry out the essential operation required of genetic material—that of exact self-duplication. The feature that appears to have special biological significance is the complementary nature of the two components of the double helix. The structure presumes that specificity is determined by base composition and order; when the specificity of one chain is fixed, that of the other is determined in a complementary way. Presumably during nucleic acid biosynthesis the two complementary components of the helix separate and each directs the synthesis, not of another chain exactly like itself, but rather of a complementary counterpart.

Chemistry at Caltech

Research in chemistry at Caltech began in 1913—the year that Arthur A. Noyes, then Acting President of the Massachusetts Institute of Technology and Director of its Research Laboratory of Physical Chemistry, became associated with this institution. The first unit of the Gates Chemical Laboratory was constructed in 1916, the second unit in 1927, and the Crellin Laboratory in 1937.

For six years Dr. Noyes divided his time between Caltech and MIT. In 1919 he began to spend full time here, and teaching and research in chemistry expanded vigorously. Dr. Noyes, a physical chemist, concentrated on the inorganic aspects of the science, and aspiring chemists came from all over the country to study under him.

Among these was Linus Pauling, a graduate of Oregon State Agricultural College. After three years of advanced study under Noyes, Pauling was so interested in the physical aspects of chemistry that he considered becoming an atomic physicist. On a National Research Fellowship he spent a year in Munich, studying theoretical physics under Arnold Summerfeld. In the following year he studied with Niels Bohr in Copenhagen and Erwin Schroedinger in Zurich.

But chemistry was still his chief interest. In 1931, when he was 30 years old, he become a full professor at Caltech, and when Dr. Noyes died in 1936, Pauling was chosen to succeed him as chairman of the Division of Chemistry and Chemical Engineering.

Under Pauling the division began to expand its studies in organic chemistry. With the support of several grants and an endowment fund of $1,000,000 from the Rockefeller Foundation, the field of organic chemistry was soon as strong as inorganic chemistry at Caltech. And, under Pauling's influence, it concentrated on the organic chemistry of substances of biological importance, such as antibodies and hemoglobin.

Biology

Changes were taking place in the Division of Biology at Caltech, too. Work in biology got under way here in 1928, when the first unit of the William G. Kerckhoff Laboratories of the Biological Sciences was built (the second being added in 1938).

Thomas Hunt Morgan came from Columbia University to organize the Division of Biology at Caltech. The presence of the famous geneticist here attracted students and faculty interested in this branch of biology. Among these was George W. Beadle, a graduate of the University of Nebraska, with a Ph.D. from Cornell University, who came to Caltech as a National Research Fellow. Beadle worked in Dr. Morgan's laboratory from 1930 to 1936, went to Stanford University for 10 years, then returned to Caltech in 1945 as chairman of the Division of Biology.

In the years when Pauling was becoming interested in the biological aspects of chemistry, Beadle was concerned with the chemical aspects of biology. At Stanford, his research with the bread mold, *Neurospora*, did much to establish the chemical nature of gene action—and to encourage the development of the now thriving field of chemical genetics.

It was inevitable that, with Beadle and Pauling in charge, the Divisions of Chemistry and Biology at Caltech would work together closely. In 1946, in fact, shortly after Beadle became chairman of Biology, he and Pauling outlined their first joint program of research on the fundamental problems of biology and medicine.

This program has been supported, to date, by the Rockefeller Foundation's $700,000 seven-year grant, as well as by a number of grants from foundations, private sponsors, government agencies, and other organizations.

Gifts and bequests of the late Norman W. Church have now provided a fund of approximately $1,000,000 for the construction of a new chemical biology laboratory (*E&S*—February 1953) adjacent to the Crellin and Kerckhoff buildings, and with connections planned to both of them. Construction of the Norman W. Church Laboratory of Chemical Biology should get under way this year.

To date, $1,500,000 has been authorized for the construction of the Church Laboratory—though the cost of building will probably be closer to $2,000,000. When funds can be found for the purpose, it is also planned to build a 90 x 50 foot connection between the Kerckhoff and Church Laboratories. The estimated cost of this wing is $600,000. It would contain a general stockroom for the Division of Biology and, in addition to laboratories for general use, specialized laboratories for the virus research that is now being carried on partly in

James D. Watson, Senior Research Fellow in Biology. With F. H. C. Crick, he has proposed a molecular structure for desoxyribonucleic acid (DNA) — a chemical which is closely related to, if not identical with, the gene. A model of the DNA structure is in the lower right hand corner of this picture; Watson is examining a possible structure for another form of nucleic acid — ribosenucleic acid (RNA).

inadequate space in the Kerckhoff Laboratories, and partly in space borrowed from the Huntington Memorial Hospital Medical Research Institute.

These proposed additions to the physical plant, however, must come from a source other than the new Rockefeller grant—and other than the matching $1,500,000 which the Institute hopes to raise. These funds are urgently needed for increasing costs of research and training programs, normal salary increases, and a modest increase in activities.

Most important of all, the new Rockefeller grant will be used for long-term projects. If the chemical biology program at Caltech is to be effective, its support must be on a long-term basis. In order to attract high-calibre faculty men it is necessary to offer tenure. On the average, this means that support should be available for a period of 15 to 25 years. Short-term support, like that provided by the National Institutes of Health, the National Science Foundation, the Office of Naval Research, and the Atomic Energy Commission, cannot be used safely to underwrite tenure appointments. Short-term support, besides, is usually designated for fairly specific activities.

Support from the Rockefeller Foundation, besides being long-term, can be used catalytically for supporting ventures in their speculative beginning stages, and for supporting non-fashionable work in areas which are important, but in which project funds are not available. At Caltech, as at similar institutions, experience has shown that a laboratory engaged in basic research—where the turn of a given investigation and its needs cannot be foreseen far in advance—must have flexibility in the use of funds for effective operation.

Experience over the past seven years, during which time the chemical biology program has existed in its present form, indicates that if a capital sum of $3,000,000 is added to present funds, the future of the program should be assured for a period of 15 to 25 years.