Electron Transport and Other Problems

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During the summer of 1954 the time seemed ripe to expand the activities of the Institute in the realm of enzyme chemistry and to initiate a systematic research and educational program in this field. In October 1954, under the aegis of the Biochemistry Department, the Enzyme Division was set up with the writers and Miss Norma Zastrow as its initial members.

The numerous problems involved in creating suitable facilities for the large scale isolation of enzymes, in instrumentation used in the study of their mode of action, and in providing trained personnel have been met with help from several sources. With generous support from institutional funds, an excellent laboratory for large scale isolation was added to the existing nucleus of laboratory space and equipment, and the unit was equipped to handle most problems encountered in the isolation, assay, and detailed investigation of enzymes. The Research Committee of the American Heart Association agreed to transfer the established investigatorship of Dr. Singer, and further provided a long-term grant-in-aid in support of the contemplated program. The National Heart Institute, U. S. Public Health Service, intent on expanding an evident interest in enzyme chemistry and intermediary metabolism in this area, has provided generous long-term support of research starting in October 1954. Further extramural support of the program has come from a contract between the Institute and the Office of Naval Research, U. S. Navy, involving research in the general area of biological oxidations. These research grants have provided funds for two post-doctoral fellowships, occasional visiting investigators, two research assistants, and for additional capital equipment and supplies.

The two fellowships have been held by Dr. Vincent Massey, who came here in October 1955 from the University of Cambridge, and Dr. Antonio Giuditta, of the Stazione Zoologica, Naples, Italy, who joined the group in 1956 upon the receipt of a Fulbright Travel Award. Since May, 1957 the position vacated by Miss Zastrow has been occupied by Dr. R. Ringler, a graduate of Michigan State University.

The scope of the activities of the group has been greatly increased as a result of collaboration with other scientists in the Detroit area and with visiting scientists who have worked in the Division for varying periods. In the first category mention should be made of a collaborative program with Dr. Caroline Hebb of the Detroit Institute of Cancer Research on the adaptive development of enzymes concerned with electron transport. Visiting scientists who have worked in the enzyme laboratory have included Professor Enzo Boeri, University of Ferrara, Ferrara, Italy; Dr. Francisco J. S. Lara, University of Sao Paulo, Ribeirao Preto, Brazil (Rockefeller Fellow); Miss M. G. P. J. Warringa of the Netherlands National Defense Research Council Laboratories, Rikswijk, Holland (Fulbright Fellow); and Mr. Oliver Smith, graduate student at the Department of Microbiology, Western Reserve University School of Medicine.

The two main activities of the enzyme group have been research and the training of specialists in enzyme chemistry.

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Recognizing that successful solution of the major problems in the field of enzyme chemistry is greatly facilitated by the collaboration of investigators of varied training and background, the majority of the investigative work has represented the voluntary cooperation of several individuals in the group in the broad areas of biological oxidations and electron transport mechanisms. Reduced to its simplest terms, the aim of these efforts is to elucidate the chemical machinery whereby the energy residing in the chemical structure of foodstuffs is converted to a form which the living cell can utilize for its manifold activities. World-wide interest in this problem during the past three decades has resulted in a virtually complete mapping of the intricate pathways whereby individual sugar, fat, amino acid, and nucleic acid molecules are degraded to CO₂, water, and nitrogenous end products and are synthesized from the latter. Furthermore, the individual enzymes concerned with each step have been isolated and purified in many cases and obtained in crystalline or homogeneous form in others. While these accomplishments unquestionably represent a major triumph of modern biochemistry, some of the crucial problems involving the transformation of chemical energy during oxidations in the living cell remain quite obscure. Thus, while it has been known for almost 30 years that the oxidation of succinate to fumarate is a key step during the “terminal oxidative cycle” (Krebs cycle) of all foodstuffs, knowledge of how the energy of this chemical transformation is trapped in a utilizable form has been virtually nil. The oxidation involves the loss of a pair of hydrogen atoms and, therefore, of a pair of electrons, in the conversion of succinate to fumarate, and both pairs end up as water after union with O₂, the ultimate cellular oxidant. The union of hydrogen atoms with O₂ is not a direct one, but proceeds by an intricate pathway, involving many enzymes (including the so-called cytochrome system). The purpose of an intricate step-wise oxidation is to permit the gradual release of energy, in contrast to a wasteful, direct, explosive step of low efficiency. It is this “electron-transport” pathway and the enzymes that catalyze it that hold the secret of biological energy generation. It is to the study of this pathway and of its enzymes that the major efforts of the group have been devoted since its inception.

The succinic dehydrogenase system, referred to above, has not been unique as an area of metabolism which has defied the efforts of many able biochemists to unravel its mode of action. Rather, it is the prototype of the electron transport machinery and it may be safely predicted that its understanding will permit broad generalizations which may ultimately lead to the full understanding of the steps between the absorption of foodstuffs and the utilization of their chemical energy for muscular contraction, secretion, growth and other processes.

No account of a chemical transformation in a living system is complete, however, until the action of the enzyme, the catalytic agent which brings about the change, is explained on a molecular and electronic level. The elucidation of the mode of action of enzymes in this regard is in its infancy since knowledge of the structure of proteins, a prerequisite for a rational explanation of enzyme action, is all too scarce. Hopeful signs of progress have been made with some of the simpler hydrolytic and oxidative enzymes. An altogether different level of complexity is encountered in the enzymes of electron transport, which often have several non-protein “prosthetic
groups" (metals and vitamin derivatives) playing a role in the catalysis. Much of the current and future work of the group is aimed in this direction.

In difficult problems of this type the indirect route is sometimes the fastest. Thus, a comparison of the mode of action of homologous oxidative enzymes from many cells: mammalian tissues, plants, aerobic and anaerobic bacteria has served as a powerful tool in the elucidation of the role of the various components.

Lastly, attention may be called to the fact that this type of study has not only fundamental interest to the biologist intent on understanding the machinery of living processes but also some very practical implications. The "trace substance hypothesis", the working hypothesis of the majority of biochemists, holds that most or all substances capable of eliciting major biological effects in trace amounts (many drugs, poisons, hormones, toxins) act directly or indirectly by affecting enzymes. The succinic dehydrogenase system is a good example of an enzyme system which is profoundly affected in vitro and in vivo by a number of trace substances. The elucidation of the mode of action of these agents on the individual enzymes is an integral part of the effort of the group.

Another aspect of the program of the enzyme group involves the training of postdoctoral fellows and visiting scientists in both general enzyme chemistry and in specialized aspects thereof. This is accomplished partly by means of frequent research conferences, partly by a recently inaugurated departmental seminar program in which we have been fortunate in obtaining the participation of noted speakers from other institutions.