The Mitochondrial System

IN THE early 1940s the belief was fairly general that the individual enzyme was the only catalytic unit to be reckoned with. The discovery by Krebs of the citric acid cycle initiated studies in several laboratories which led to the conclusion that the full complement of enzymes necessary for carrying out the cycle was associated with particles common to all types of animal cells. Two developments that followed in rapid succession helped clarify the biological significance of particle-bound enzymes. In 1946 the hypothesis was advanced that these particles were the structural units of an organized, integrated complex of enzymes (the cyclophorase system), which implemented the citric acid cycle and ancillary reactions, and the operational principles of which appeared to be unlike those obtaining for the soluble, isolated enzymes that presumably originated from the complex. For example, the enzyme complex showed no requirement for added coenzymes, and it catalyzed processes such as oxidative phosphorylation and the complete oxidation of pyruvic acid and fatty acids, which then could not be duplicated with soluble enzymes. In 1948, the structural unit of the complex was identified independently by Lehninger and Potter as the mitochondrion.

A new unit of enzyme chemistry thus emerged—a mosaic of more than a hundred enzymes linked together to form a huge macromolecule. Three developments helped prepare the way for the successful reconstruction of integrated activity in nonmitochondrial systems. In order, they were the demonstration by Lipmann and his group of the key role of coenzyme A in a variety of reactions involving transfer of acyl groups; the studies by Barker and Stadtman of fatty acid oxidation and synthesis in a cell-free soluble extract of Cl. Kluyverii-studies, which have adumbrated many of the reaction principles that apply to the mitochondrial system; and, finally, the recognition of heart muscle as the tissue of choice for solubilizing the fragile enzymes of mitochondria.

The Symposium on Phosphorus Metabolism, held at The Johns Hopkins University in 1951, marked the end of the period in which certain reaction sequences could be studied only at the mitochondrial level. As a result of work in four different laboratories (Cohen, Ochoa, Racker, and Green), all the known integrated activities of mitochondria have now been duplicated in nonmitochondrial systems. These activities include synthesis of citrulline from ornithine, synthesis of citrate from pyruvate and oxalacetate, oxidative phosphorylation, and the complete oxidation of pyruvate and fatty acids. There are several features characteristic of these reactions. They all require an energy source provided either by ATP or by some oxidative reaction. This "energizing" reaction involves the activation of the substrate through the intermediation of coenzyme A. The activated substrate (CoA-linked) is then transferred from one enzyme to another and undergoes reaction without at any time being in equilibrium with the corresponding nonactivated molecules. Such a reaction sequence calls for the intimate collaboration of a group of enzymes and thus again, even in soluble extracts, the catalytic unit for the over-all reaction is no longer the individual enzyme but a team of enzymes. As work along these lines is continued, we may anticipate further clarification of the significance of the organizational features of the mitochondrial unit.

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SCIENCE, founded in 1880, is published each Friday by the American Association for the Advancement of Science at the Business Press, 10 McGovern Ave., Lancaster, Pa. Entered as second-class matter at the Post Office at Lancaster, Pa., January 13, 1948, under the Act of March 3, 1879. Acceptance for mailing at the special rate postage provided for in the Act of February 28, 1925, embodied in Paragraph (d-2) Section 34.40 P. L. & R. of 1948.

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Annual subscriptions, $7.50; single copies, $.25; foreign postage, outside the Pan-American Union, $1.00; Canadian postage, $.50. Special rates to members of the AAAS.

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