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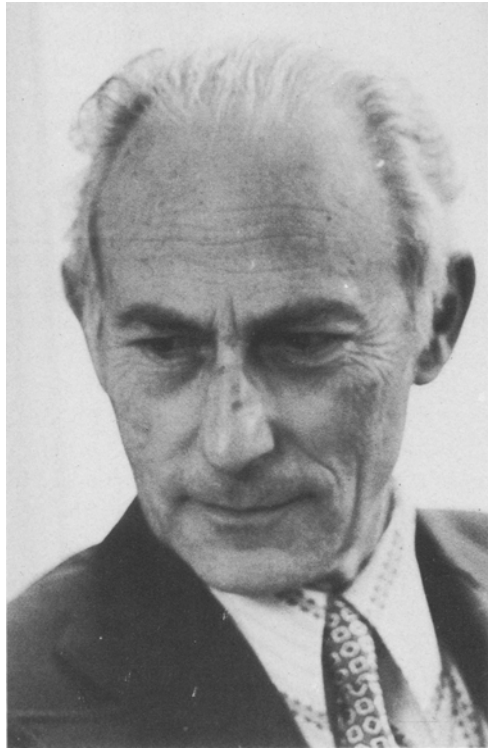
David E. Green: A Personal Recollection

David Green was a remarkable person. Endowed with a keen intellect, an insatiable curiosity about Nature, a vivid imagination, and boundless energy, he pursued a career devoted entirely to research. Over a period of four decades, he and his colleagues published nearly 700 journal articles and reviews covering a broad spectrum of enzymology and bioenergetics, and he was the author, co-author, or editor of eight books. A legion of postdoctorals and visiting investigators received training in his laboratory. History will surely record that he was one of the giants of 20th-century biochemistry.



David E. Green, 1910–1983

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David was born in 1910 in New York City and received the B.A. and A.M. degrees from the Washington Square campus of New York University. Introduced to biology by two inspirational teachers, Robert Chambers and Leonor Michaelis, he soon perceived that the budding area of enzymology afforded a unique opportunity to bring the quantitation and rigor of chemistry to an otherwise descriptive science. He was particularly fascinated by the power of enzymes to catalyze reactions with great speed in aqueous media and at ordinary temperatures. Since Cambridge University was one of the major centers of enzymology at that time, he went there for further training and received a Ph.D. in 1934 under the supervision of Malcolm Dixon. This was followed by six additional years as the recipient of a prestigious Beit postdoctoral fellowship. Cambridge offered many attractions. Gowland Hopkins, the Professor of Biochemistry, had assembled a number of outstanding scientists who set high standards for scholarly achievement. Despite his youth, David's quick mind and skill at the bench soon made him one of the leaders of this group. The opportunity to work full-time in the laboratory, with freedom to follow whatever leads seemed interesting, caused him later to recall the Cambridge experience as the "Golden Years" of his professional career. Most important, during his stay in England he met Doris Cribb, the future Mrs. Green, whose companionship meant so much to him in all the years that followed.

Now a full-fledged enzymologist, David Green returned to the United States on the eve of World War II. After a brief appointment in the Department of Biological Chemistry at Harvard, he was invited to Columbia to set up an Enzyme Chemistry Laboratory. This unit, committed entirely to research, soon attracted a number of postdoctorals and substantial grant support. As it turned out, the operation was a trial run for things to come. In 1948, he moved to the University of Wisconsin as Director of a newly created Institute for Enzyme Research. This post provided an ideal environment for David's creativity and temperament. In turn, he brought to the University additional visibility in the field of enzymology. During the following 35 years, he provided leadership, programs, and facilities for the research efforts of a multitude of postdoctorals and visiting investigators. Today, scientists from all over the world acknowledge their indebtedness to David for training received in the Institute.

The research accomplishments of David Green are perhaps best viewed in the context of the various phases of his career. At Cambridge, Harvard, and initially at Columbia, the emphasis was upon soluble enzymes. He was a pioneer in the purification and characterization of a wide range of pyridinoproteins (e.g., lactate, α-glycerophosphate, and β-hydroxybutyrate dehydrogenases), flavoproteins (xanthine oxidase, aldehyde oxidase, and L-amino acid oxidase), and several pyridoxal- and thiamine-containing proteins. In the field of coenzyme-linked enzyme systems, he was an acknowledged leader.

The second phase began during the final period at Columbia and continued through the formative years of the Enzyme Institute at Wisconsin. Wishing to undertake something more challenging than soluble enzymes, David turned to the murky world of enzymatic activities available only as insoluble preparations. The first paper in this new direction, concerned with the complete oxidation of pyruvate to carbon dioxide and water, utilized well-washed particulate fractions from rabbit kidney and liver. The enzymes catalyzing the two separate aspects of this process (i.e., metabolism of the carbon skeleton and transfer of reducing equivalents to oxygen) were present in remarkably constant proportions in various preparations. This suggested the existence of a physical and functional complex, named the "cyclophorase system," rather than a random collection of enzymes. The properties of enzymes in this complex also appeared to be different from those of solubilized counterparts. Opposition to these ideas arose from some who thought that the Krebs cycle was being rediscovered, or from others who believed that enzymes should be studied only in soluble form. David dismissed the former charge as groundless, and disagreed strongly with the latter philosophy. Subsequent work in various laboratories established the mitochondrion as the subcellular locus of the citric acid cycle and electron transport enzymes (as well as those responsible for fatty acid oxidation and oxidative phosphorylation) and, in confirming and extending these observations, David eventually replaced the term "cyclophorase" by "mitochondrial" in describing the operational systems.

The third and most productive phase was marked by expansion of the Institute, both physically and programmatically. This led in turn to the formation of research teams, each under the supervision of one of David's senior associates. Credit for the formidable accomplishments that emerged during this period is shared among these individuals, who played major roles in both the planning and execution of the programs, and the Director, who provided funds, facilities, advice, and inspiration. The research centered about isolation of components of the mitochondrial system and elucidation of their mechanisms of action. This effort was facilitated by the development of an assembly line of skilled technicians and multiple banks of centrifuges for preparing large quantities of mitochondria. Methods were devised for comminution of the particulates to yield, for example, ETP (the electron transfer particle) and PETP (the phosphorylating ETP). Electron microscopy became a routine tool in the laboratory for visualization of mitochondria and derived particles and for correlation of structure and function. Solubilization of individual components was achieved, often through the clever use of organic solvents. The multi-component and multi-functional aspects of the pyruvate and α-ketoglutarate oxidases were delineated. Fatty acid oxidation and synthesis systems were resolved into sets of soluble enzymes. The electron transport systems for the NADH $\rightarrow$ O_2 and succinate $\rightarrow$ O_2 sequences were

systematically disassembled, characterized, and reconstituted. Outstanding accomplishments in this latter program included resolution of these systems into four discrete complexes, the discovery of Coenzyme Q, and clarification of the roles of nonheme iron and copper as redox components.

In the final phase of his career, although still occupied with projects carried over from the previous period, David grappled with the problem of energy transduction, the cornerstone of bioenergetics. Oxidative phosphorylation had been examined by many investigators using a variety of experimental approaches, but the mechanism had remained elusive. Phosphorylated intermediates were postulated but not found, and attention had shifted to more esoteric possibilities. The striking morphological changes shown by mitochondria in various states of energization, a phenomenon studied extensively in the Institute, had suggested that redox-induced conformational motion might be the driving force for synthesis of ATP. Mitchell's chemiosmotic mechanism, which David admired for its conceptual boldness (although he disagreed with some of its implications), clarified the thermodynamic portion of the puzzle by identifying proton gradients, produced vectorially by the flow of reducing power from NADH to oxygen, as the energy source. Nevertheless, the molecular mechanism by which ADP and P_i are united, during recycling of protons through the ATPase complex, still remains obscure. In his effort to solve the problems of bioenergetics, David turned away from the experimental approach, which had served him well, to the world of hypotheses and models. He hoped that the latter would lead to unifying concepts, accounting both for the known data and providing a realistic basis for planning future experiments. It was, as he remarked on several occasions, probably unwise to trade the comfortable role of an experimentalist for the hazardous life of a theorist, but this transition was prompted by his impatience with the low yield of information accruing from the tedious isolation and characterization of mitochondrial components. Influenced by his experience in enzymology, he reasoned that the principles embodied in the catalytic activities of single enzymes would be recapitulated in the multi-enzyme sequences involved in energy transduction. In an extended series of papers, he attempted to formulate, in specific detail, concepts which he perceived in shadowy outline. It was a heroic process, marked by continued reorientation and by the replacement of one hypothesis by another. This unusual approach evoked criticism—some justified, some not. The initial publications probably erred in attempting to assign precise spatial and temporal relationships to the putative components of energy-transducing systems. However, the concept that every process in bioenergetics must occur in paired and coordinately linked steps may well turn out to be David's most important contribution.

David Green's achievements received due recognition from the scientific community. He was the first recipient (1946) of the Paul Lewis Award in

Enzyme Chemistry, and he was elected to membership in the National Academy of Sciences and the American Academy of Arts and Sciences. Much in demand as a speaker at Symposia and seminars, he traveled extensively in the United States and abroad. He particularly enjoyed coming to La Jolla as a Visiting Professor in the Department of Biochemistry at Scripps Clinic and Research Foundation. On those occasions, he would roam through the department, chatting with postdoctorals about their research projects. The young investigators greatly appreciated his interest and enthusiasm, and they profited from his perspective and insights.

David's spectacular scientific accomplishments and forceful presence at meetings made him one of the best-recognized figures in biochemistry. His personal side was less visible. Stoical in the face of adversity or illness, he bore the latter with such courage that few even of his close friends knew of its seriousness. Although self-assured and jovial on the surface, he was really a rather shy and private person. To understand David, it was essential to recognize that research was the central focus of his life. Its progress occupied most of his waking moments and dominated his conversations. He was constantly planning new experiments, reviewing data with colleagues, and writing papers. Except for his immediate family, he had few other interests. It was a matter of supreme indifference to him who was playing in the World Series or the Super Bowl, and the vicissitudes of the University of Wisconsin football team left him unmoved. Both in his own institution and nationally, he studiously avoided committees and politics. Hobbies were nonexistent, except for ice-skating and ballroom dancing. In the latter activity, he and Doris excelled. La Jollans will long remember their virtuoso performances at the Beach and Tennis Club. David had a repertoire of knowledge in many areas other than science, and his shrewd insight and witty comments led to particularly lively discussions. As a writer and speaker, he combined eloquence with clarity. Many of his colleagues today are grateful for the time he spent attempting to pass along these skills. Although combative in scientific forums and publications, his attacks were never directed against individuals—only against experiments or conclusions with which he did not agree. To his friends, he was a warm and extremely kind person, always anxious to be helpful with advice or material assistance. As an outstanding scientist, his contributions will be greatly missed. As a person, he will be missed even more.

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