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In Memory of

Albert Lester Lehninger

Albert Lester Lehninger

1917–1986

With the death of Albert Lester Lehninger on March 4, 1986, the field of biochemistry lost a towering figure. During his career of 40 years he helped to shape the new discipline of bioenergetics and the scientific lives of many of its leaders. He was a renowned teacher and the author of *Biochemistry*, perhaps the single most influential and successful textbook of biochemistry ever written. He was a member of the Board of Editors of *The Journal of Membrane Biology* since its beginning. The Journal owes much to his foresight and wisdom. It has lost one of its pillars.

Albert Lehninger was born on February 17, 1917, in Bridgeport, Connecticut. In 1935 he entered nearby Wesleyan University as an English major and devoted himself to the writing of stories and poetry, a talent he was later to exploit in science. At Wesleyan his interests soon changed to chemistry, where he was introduced to the exciting developments then occurring in the new field of biochemistry. Lehninger was inspired by the monumental work of Otto Warburg in Berlin on the "Wasserstoffubertragende Fermente" (hydrogen-transporting enzymes) and the equally exciting work of Hans Krebs in Sheffield on the tricarboxylic acid cycle. This interest led him to embark upon a combined career in Medicine and Biochemistry at the University of Wisconsin, where he received the Doctor of Philosophy degree in the Department of Physiological Chemistry. His dissertation research under Edgar J. Witzemann was concerned with the metabolism of acetoacetate and the oxidation of fatty acids by disrupted liver preparations. He abandoned the medical studies and then joined the wartime research effort of the Plasma Protein Fractionation Program master-minded by E.J. Cohn. At this time he became aware of the early papers on oxidative phosphorylation, which appeared in the early 1940's. These discoveries seized his imagination and from then on the mechanisms of energy capture and transduction in cells became the central themes of his scientific life.

In 1945 Lehninger moved from Wisconsin to the University of Chicago where he assumed the titles of both Assistant Professor of Biochemistry and Assistant Professor of Surgery. The latter title signified his close association with the laboratory of Charles Huggins (Nobel Prize in Physiology and Medicine, 1966) which later became known as the Ben May Laboratory for Cancer Research. Although they never published jointly, Huggins profoundly influenced Lehninger's scientific career. Following their first meeting, Huggins summarized his impressions succinctly to one of the writers: "He looks like a racehorse to me." And a racehorse he was! During the ensuing six years at Chicago, Albert Lehninger and his first students, Eugene P. Kennedy (now Hamilton Kuhn Professor of Biological Chemistry at Harvard Medical School) and Morris E. Friedkin (now Professor of Biology at University of California, San Diego), provided two of the most fundamental and significant generalizations of contemporary biochemistry. Lehninger and Kennedy made the landmark discovery that mitochondria contained virtually all of the organized oxidative activity of the cell. They demonstrated that these subcellular particles had the capacity to catalyze the complete oxidation of fatty acids to CO_2 and H_2O, and thus possessed all of the enzymatic components for the β-oxidation of fatty acids, the tricarboxylic acid cycle, and the electron transport system. Lehninger and Friedkin showed that electron transport from NADH to oxygen is an immediate and direct energy source for oxidative phosphorylation.

His imaginative work on fatty acid oxidation and oxidative phosphorylation attracted world-wide attention, and in 1952 Lehninger was invited to as-

sume the DeLamar Professorship and Directorship of the Department of Physiological Chemistry (now Biological Chemistry) at the Johns Hopkins University School of Medicine at the early age of 35. He served as Director of the department until 1978 when he was honored by appointment as University Professor of Medical Science at Johns Hopkins, a position which was especially created for him. At Johns Hopkins he built up a distinguished faculty, and innovative teaching and graduate programs. In 1958 the first NIH training grant specifically designated for graduate study was awarded to the Johns Hopkins School of Medicine with Albert Lehninger as its Program Director. Lehninger's perception of the important issues of high caliber medical and graduate education enabled him to play a leading role in the academic affairs of the Johns Hopkins University.

Lehninger's most important scientific contributions centered on two themes: (1) discovery of the major role of the mitochondrion in respiratory metabolism and in compartmentation of metabolism in the cell, and (2) discovery of some of the main features of oxidative phosphorylation and other energy-coupling mechanisms associated with the electron transport chain. His career began with the basic observations that led to the discovery in 1948 that the entire complex of enzymes catalyzing the Krebs tricarboxylic acid cycle, electron transport and oxidative phosphorylation, and oxidation of fatty acids are localized in the mitochondria. He was the first to show that oxidative phosphorylation of ADP is coupled to the flow of electrons along the respiratory chain from NADH to oxygen. Although thermodynamic analysis had predicted this to be the case as early as 1939, it was not until 1951 that Lehninger proved it experimentally with the recognition that oxidative phosphorylation takes place *within* the mitochondria and that the membrane presents a permeability barrier to the entry of NADH and other reduced coenzymes. His discovery that NADH cannot pass through the membrane of intact mitochondria established that NADH formed by glycolysis does not directly enter the mitochondria and indicated that some other pathway was required, one that would necessarily be of crucial importance in the integration and regulation of glycolysis and respiration. This work ushered in a new era in our understanding of cell metabolism and later led to the recognition that many other metabolites, such as tricarboxylic acid cycle intermediates, and coenzymes, such as ATP and Coenzyme A, are compartmented into separate pools.

Lehninger was among the first to consider ion transport as an important means of energy conservation by mitochondria. Early work in his laboratory revealed a very rapid incorporation of K^+ and Ca^{2+} ions into respiring mitochondria and submitochondrial vesicles. He and his colleague, Carlo S. Rossi (now Professor of Biological Chemistry at the University of Padua), carried out a classical study of the stoichiometric relationship between the number of Ca^{2+} ions transported into the mitochondrial matrix and the number of electrons flowing from substrate to oxygen. The capacity for stoichiometric coupling between electron transport and ion transport so demonstrated gave much impetus to the chemiosmotic coupling hypothesis of Mitchell, which was proposed in 1961 but not given much serious consideration until the mid 1960's, when ion transport became widely accepted as an important mitochondrial activity.

In 1963 Lehninger observed that accumulation of Ca^{2+} and phosphate by isolated mitochondria leads to formulation of electron-dense insoluble deposits in the mitochondrial matrix. These amorphous deposits of calcium phosphate were postulated by Lehninger to be involved in biological calcification processes. Based upon these and other lines of evidence he formulated a general hypothesis of biological calcification.

Albert Lehninger's more recent work focused on the number of H^+ ions ejected by electron transport during mitochondrial respiration. Whereas the chemiosmotic hypothesis postulated two H^+ ions ejected per pair of electrons per energy-conserving site, Lehninger and his colleagues, with more refined methods, established that each energy-conserving site ejects 4 H^+ ions to the medium. These experiments, together with stoichiometric data on H^+ ion movements during ATP synthesis and membrane transport processes gave important insights into the role of H^+ ion transport in oxidative phosphorylation and in ATP-dependent reversal of electron flow.

During his long career Lehninger received many honors which included membership in the National Academy of Sciences, the American Philosophical Society, and the American Academy of Arts and Sciences. He held honorary Doctor of Science degrees from Wesleyan University, University of Notre Dame, Acadia University (Nova Scotia), Memorial University of Newfoundland, University of Paris Val de Marne, Catholic University of Louvain, and an honorary Doctor of Medicine degree from the University of Padua. He delivered numerous distinguished lectureships and received the Paul-Lewis Award in Enzyme Chemistry in 1948, the Remsen Award of the American Chemical Society in 1969, the Premio La Madonnina of the City of Milan, Italy, in 1976, and the Passano Foundation Award in 1986.

He was frequently called upon to serve on important decision-making bodies at the national level. He served on the Councils of the National Academy of Science and the Institute of Medicine.

He was appointed in 1975 by President Ford to the President's Panel on Biomedical Research mandated by an act of Congress. He served as president of the American Society of Biological Chemistry in 1972-3 and was a member of the Scientific Advisory Committee of the Massachusetts General Hospital. In 1975 he was elected vice-president of the American Philosophical Society. He was also a member of the Editorial Boards of many important journals, including the *Journal of Biological Chemistry, Physiological Reviews, Journal of Biophysical and Biochemical Cytology, Biochemistry*, and the *Journal of Membrane Biology*.

Among Lehninger's most widely-known achievements was the writing of a comprehensive biochemistry text, which was first published in 1970 with the second edition appearing in 1975. This book, a monumental accomplishment, was generally recognized as the outstanding textbook of biochemistry worldwide. It may well represent the last time that a single author can successfully write a comprehensive account of general biochemistry suitable for undergraduates, medical students, and graduate students. Lehninger was the author of two other excellent monographs of major importance: *The Mitochondria* (1964) and *Bioenergetics* (1965, 1971). All of these books have been translated into many foreign languages.

In many ways Albert Lehninger was a very private person, but where science was concerned there were no boundaries in sharing from the depth and breadth of his scientific insight. He was a gentleman; he was a gentle man.

M. Daniel Lane
Paul Talalay
Baltimore, Maryland