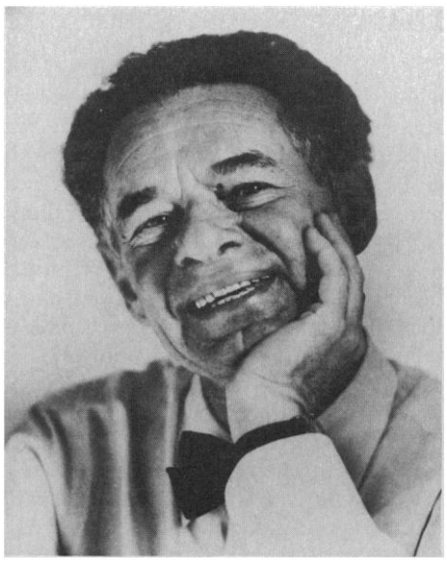
A Figure in Biochemistry

The Roots of Modern Biochemistry. Fritz Lipmann's Squiggle and Its Consequences. HORST KLEINKAUF, HANS VON DÖHREN, and LOTHAR JAENICKE, Eds. De Gruyter, Hawthorne, NY, 1988. xii, 994 pp., illus. $249.25. From a meeting, Berlin-Dahlem, 1987.

To those who, like me, did not know him personally but had heard him speak at large and small meetings and had read transcripts of discussions at other meetings, Fritz Lipmann has always seemed a mystery. His talks were nearly unintelligible, and his pronounced accent was the least of the problems. A coherent message was seldom transmitted to the audience, and responses to questions tended not to be incisive. We are told in our youth, and generally find it to be true, that clarity of expression accompanies clarity of thought. How could a man whose expression, at least on formal public occasions, was frequently disjointed and ineffective be responsible for the fundamental contributions that Lipmann had made and was continuing to make?

The mystery was not cleared up by his autobiography, *Wanderings of a Biochemist*, published in 1971, or by his autobiographical chapter in the 1984 volume of *Annual Review of Biochemistry*. These writings show that it was not by chance that Lipmann's scientific wanderings repeatedly brought him, at just the right times, into just those research areas that allowed him to elucidate new types of metabolic activation; for 40 years his explicit criterion in choosing problems for investigation was the likelihood that chemically activated intermediates were involved. But the writings were of no help in reconciling his public image with the magnitude of his scientific contributions. Thus the appearance of a memorial volume containing papers by many of Lipmann's close associates aroused anticipation. But this book, too, does nothing to dispel the mystery. Instead, it confirms that the paradox was real, and apparently more striking the better one knew Lipmann. Former associates note that he was not a gifted speaker, frequently becoming inaudible or omitting words and phrases, that he was unwilling or unable to follow a complicated argument, and that in general his personal characteristics differed from those expected for a scientist of such stature. Thus rather than supplying an explanation, the book gives us fascinating and more intimate glimpses of one of the most complex scientists of our time.

The book results from a memorial meeting that was held in Berlin in 1987. Its 90 papers and 994 pages are divided into five sections, of which the first, entitled Fritz Lipmann (1899–1986) and consisting of 138 pages, is the part of greatest interest. This section contains a brief reminiscence by Lipmann's wife of 55 years, a reprint of the autobiographical chapter from *Annual Review of Biochemistry*, and 12 papers on various aspects of Lipmann's life. In addition to its information on the development of Lipmann's career, this section has much of interest to anyone who is interested in the history of metabolic biochemistry.

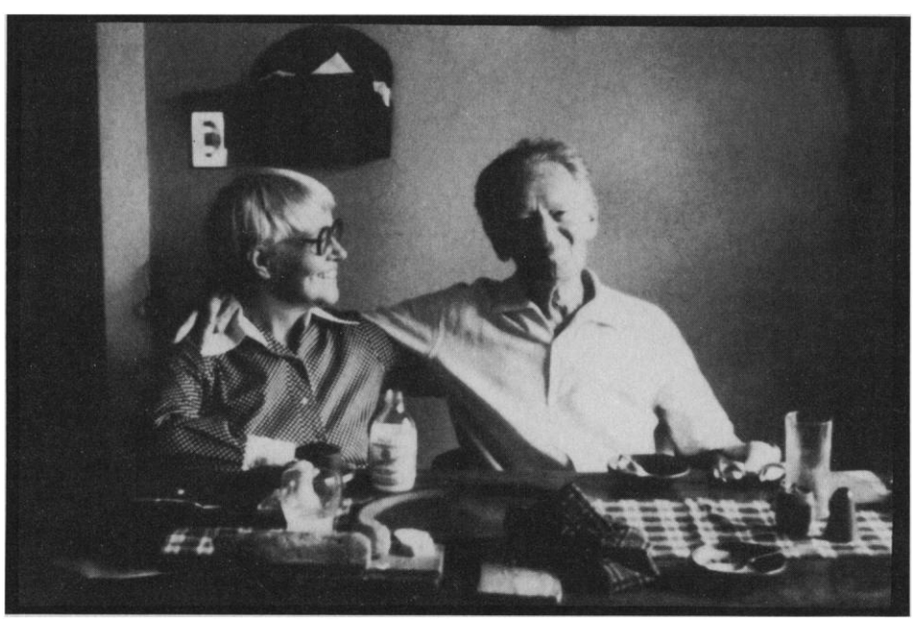


Fritz Lipmann. [From *The Roots of Modern Biochemistry*]

The 76 papers in the other four sections—Biochemistry Comes of Age (which contains some papers on topics of historical interest), Molecular Biology Sharpens Its Tools, Functional Dynamics, and Evolution—are less closely related to Lipmann, although some of them contain interesting personal reminiscences. At a single-session memorial service, visitors sign a register. At a more extended memorial meeting of this type it is an unfortunate tradition that signatures are not acceptable; each participant must contribute a manuscript. Most of the authors in this case recognized the ceremonial nature of the occasion and, wisely, merely provided brief abstracts of current research projects.

When he moved permanently to America just before the outbreak of the Second World War, Lipmann was 40 years old. He had made some solid research contributions in rather scattered areas but had not done anything especially noteworthy. In later years he liked to point out that, in contrast to the generally held belief that scientists are most creative in their early years, his important contributions had been made during his 40s and later.

Soon after arriving in the United States, Lipmann wrote his famous article for the first volume of *Advances in Enzymology*, one of the most important papers in the history of metabolic biochemistry. It contains the first statement of the importance of chemical



"The Lipmanns at lunch time in their country home (1985)." [From *The Roots of Modern Biochemistry*]

activation of key intermediates that serve as group donors: "groups, such as phospho-, acetyl-, and amino-, are brought by metabolic mechanisms intermediately into positions from which they can easily be carried into desired places." Examples and corollaries of this generalization that underlie the organization of metabolism were discussed, among them the central role of ATP: by virtue of formation of ATP from ADP in catabolic sequences and of ADP from ATP in energy-requiring processes, the ATP-ADP couple serves as the central energy-transducing system by which metabolic sequences are functionally interrelated; thus biological energy transfer is stoichiometric and quantized.

To emphasize the metabolic importance of activation, which he compared to the use of such organic reagents as acetyl chloride, Lipmann spoke of "biologically interesting linkages designed to transfer groups with loss of energy," which are " 'weak' linkages based on the usual chemical nomenclature," as energy-rich bonds and proposed that they be distinguished by the special symbol ~. That symbol and some ambiguous statements about "concentration" of energy in such bonds were promptly adopted by biochemists. They proved a mixed blessing. On the one hand, by emphasizing the central role of ATP, they established the pervasive interdependence of sequences and the quantized nature of those relationships, and thus contributed importantly to the development of a functional view of metabolism. On the other, they led to wide acceptance in biochemistry and biology of such chemically illiterate concepts as bonds into which energy can be packed and which release energy on cleavage. Since cleavage of any bond necessarily requires, rather than releases, energy, that terminology confused students and estranged metabolic chemistry from mainstream chemistry for several decades. That estrangement was as unnecessary as it was unfortunate, since if defined appropriately the ~ symbol could have emphasized the importance of activation and quantization in metabolism without doing violence to the fundamental meaning of activation. In this book Slater remarks rather condescendingly that although the discussion of energy-rich bonds "upset the chemists somewhat, since it seemed to run counter to their concepts of bond energy," biochemists always clearly understood that it referred to the standard Gibbs free energy of hydrolysis of the bond. If Slater really believed that in 1987, he should have reread nearly any biochemistry textbook, or nearly any review treatment of metabolic energetics, published between about 1945 and 1970.

From 1941 onward, Lipmann's interests were focused on metabolic activation. His research group discovered the carbamoyl donor carbamoyl phosphate and the sulfate donor PAPS, and (in the work for which he received the Nobel Prize) contributed to the discovery of coenzyme A, which is involved in the activation of acyl groups. It was his curiosity as to the mode of activation of amino acids for formation of peptide bonds that led to the very important contributions to understanding of protein biosynthesis that his group made during the last decades of his career.

Several contributors to this volume mention the strangely parallel careers of Lipmann and Hans Krebs. Born within a few months of each other, both attended medical school. They met at the beginning of their research careers in the Kaiser Wilhelm Institute laboratories at Berlin-Dahlem, where Lipmann worked with Meyerhof and Krebs with Warburg. Both left Germany to escape the Nazis, Krebs going to Britain and Lipmann to the United States. Their research careers were complementary. Krebs's most important contributions were the discovery of the urea cycle (and with it the concept of metabolic cycles) and the citrate cycle. Lipmann's most important contribution was the concept of the importance of metabolic activation, with emphasis on the role of ATP, which in aerobic cells is regenerated primarily as a consequence of Krebs's citrate cycle. He discovered the donor of carbamoyl groups to the urea cycle and contributed to the discovery of the donor of acetyl groups to the citrate cycle. They shared the Nobel Prize in 1953.

It is the contrast between the temperaments of Lipmann and Krebs that intrigues several of the authors of this volume. Krebs was hard-driving, highly organized, logical, quick-witted, and fluent in lectures and discussions—all characteristics to be expected in a major scientist. Lipmann seemed the opposite in all these respects. These two men, so different in temperament, were the most important metabolic biochemists of their generation. One could not ask for a better illustration of the wide range of personal characteristics that may underlie high achievement in science.

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