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The Power of Phosphate: Making and Breaking Bonds across the Atlantic, 1927–1946

ABSTRACT

This paper concerns the development of a central tenet of modern biochemistry: that cellular metabolism coordinates biological energy supply through the cyclical making and breaking of "energy-rich" phosphate bonds. This interpretation of intermediary metabolism was comprehensively set forth in two review articles published nearly simultaneously (though independently) in early 1941 by German biochemist Fritz Lipmann and Danish biochemist Herman Kalckar. Lipmann and Kalckar first met in the early 1930s in Copenhagen, where they were in frequent contact until 1939, when both left Denmark. Despite the similar claims advanced in Lipmann's and Kalckar's reviews, the two men's presentations differed substantially with respect to their descriptions of "energy-rich" phosphate bonds and their target audiences. In order to explore the circumstances behind these divergences, this paper utilizes a "parallel lives" approach. By analyzing Lipmann's and Kalckar's lives in parallel, particular institutional contexts emerge as having been especially significant in shaping their differing interpretations of the power of phosphate bonds. The period

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The following abbreviations are used: CCP, Carl F. Cori Papers, Bernard Becker Medical Library Archives, Washington University in St. Louis; FLP/RAC, Fritz Albert Lipmann Papers, FA123, Rockefeller Archive Center, Sleepy Hollow, NY; HKC, Herman M. Kalckar Collection, Howard Gotlieb Archival Research Center at Boston University; NBPC/NBA or NBSC/NBA, Niels Bohr Private Correspondence or Niels Bohr Scientific Correspondence, Niels Bohr Archive, Copenhagen, Denmark; NOW/BBAW, Nachlass Otto Heinrich Warburg, Archiv der Berlin-Brandenburgischen Akademie der Wissenschaften, Berlin, Germany; ALPP, Ava Helen and Linus Pauling Papers (MSS Pauling), Oregon State University Special Collections and Archives Research Center, Corvallis, Oregon; RFR/RAC, Rockefeller Foundation Records, Rockefeller Archive Center, Sleepy Hollow, NY.

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that Lipmann spent in muscle researcher Otto Meyerhof's laboratory (1927–30) conditioned his physiological interpretation of the role of phosphate bonds in cellular energy metabolism. Kalckar's time at California Institute of Technology (1939–40)—where he was in regular communication with chemists such as Linus Pauling—played the most significant role in his decision to present the power of phosphate bonds from a chemical perspective. Ultimately, an examination of the life stories behind Lipmann's and Kalckar's 1941 reviews illuminates how older physiological perspectives were combined with recent advances in theoretical chemistry to explain how energy flows through living organisms.

KEY WORDS: phosphate bonds, energy metabolism, émigré biochemists, cellular bioenergetics, muscle physiology, review articles, parallel lives, simultaneous discovery

INTRODUCTION

This paper investigates how perspectives from the chemical and physiological sides of biology were combined to focus the attention of researchers interested in understanding the nature of metabolic energy upon "energy-rich" phosphate bonds, such as those present in the well-known molecule adenosine triphosphate (ATP).[1] The term "energy-rich" phosphate bond was introduced broadly into biochemistry by two review articles published independently and nearly simultaneously in 1941 by German biochemist Fritz Albert Lipmann (1899–1986) and Danish biochemist Herman Moritz Kalckar (1908–91). In their reviews, both authors concluded that the greater part of the energy derived from cellular oxidation/reduction reactions was transformed into a specific type of phosphate bond, which served as the main unit of energy that living cells used to power energy-requiring chemical reactions. By representing the critical link between catabolic (degradative) and anabolic (biosynthetic) intermediary metabolism, Lipmann and Kalckar's formulation of the concept of the "energy-rich" phosphate bond served to unify all vital processes in energetic and biochemical terms.[2]

The overlaps between Lipmann's and Kalckar's personal and professional trajectories are striking. Both were born in Europe into middle-class Jewish

1. "Bioenergetics" was not widely used to describe the field of research concerned with biological energy transformations until at least the mid-twentieth century. I thus use the phrase "biological energy studies," or some variation thereof, in this paper. For a history of bioenergetics, see John N. Prebble, *Searching for a Mechanism: A History of Cell Bioenergetics* (Oxford: Oxford University Press, 2019).

2. On the history of intermediary metabolism, see Frederic Lawrence Holmes, *Between Biology and Medicine: The Formation of Intermediary Metabolism* (Berkeley: Office for History of Science and Technology, University of California at Berkeley, 1992).

families. Both studied medicine but chose not to practice, opting instead to pursue graduate work in physiology and chemistry.[3] The two men first met in the 1930s in Copenhagen, where they worked within the same circle of scientists and communicated regularly about their shared interest in phosphate metabolism. In 1939, Lipmann and Kalckar (separately) left Copenhagen for the United States, just before the outbreak of World War II in Europe.[4] Although they were destined for opposite ends of the country (Kalckar for California and Lipmann for New York), their respective first months in America were marked by key interactions with Carl F. Cori, one of the country's most prominent investigators of carbohydrate and phosphate metabolism. After moving across the Atlantic, Lipmann and Kalckar reflected on their previous work in Copenhagen, and independently reached the same biochemical generalization: cellular metabolism operates via the cyclical making and breaking of "energy-rich" phosphate bonds. Both decided to communicate this interpretation in a synthetic review article, and these two reviews were published within about a month of each other in early 1941.[5] In the immediate aftermath of their publication, the two reviews were quickly understood by other scientists—and their authors themselves—to be proposing very similar ideas. Lipmann and Kalckar later viewed their review articles as a shared experience that connected them to one another.[6] This connection strengthened Lipmann and Kalckar's friendship, which was sustained over the years through visits and correspondence.[7] Kalckar once expressed to Lipmann,

3. Fritz Lipmann, "A Long Life in Times of Great Upheaval," *Annual Review of Biochemistry* 53, no. 1 (1984): 1–33, on 1–4; Herman M. Kalckar, "Autobiographical Notes from a Nomadic Biochemist," in *Selected Topics in the History of Biochemistry, Personal Recollections, III*, ed. G. Semenza and R. Jaenicke, vol. 37, Comprehensive Biochemistry (Amsterdam: Elsevier, 1990), 101–76, on 169–74.

4. On the impact of National Socialism on Jewish chemists and biochemists, see Ute Deichmann, "The Expulsion of Jewish Biochemists from Academia in Nazi Germany," *Perspectives on Science* 7, no. 1 (1999): 1–86; Ute Deichmann, "Chemists and Biochemists during the National Socialist Era," *Angewandte Chemie International Edition* 41, no. 8 (2002): 1310–28.

5. H. M. Kalckar, "The Nature of Energetic Coupling in Biological Syntheses," *Chemical Reviews* 28, no. 1 (1941): 71–178; Fritz Lipmann, "Metabolic Generation and Utilization of Phosphate Bond Energy," in *Advances in Enzymology and Related Subjects*, ed. F. F. Nord and C. H. Werkman, vol. 1 (New York: Interscience Publishers, 1941), 99–162.

6. Fritz Lipmann, "Fifty Years of ATP," in *From Cyclotrons to Cytochromes: Essays in Molecular Biology and Chemistry*, ed. Nathan O. Kaplan and Arthur Robinson (New York: Academic Press, 1982), 283–89, on 286.

7. See, for example, Kalckar to Lipmann, 6 Aug 1959, Box 13, Folder 4, FLP/RAC.

"[Y]ou are a subtle and wise friend and know my past."[8] As their friendship endured, their professional lives continued to intersect; in 1961, Kalckar assumed Lipmann's recently vacated research post at Massachusetts General Hospital, where he was "to take over the 'Lipmann Lab.'"[9]

That the two reviews were cited together in the biochemical literature almost immediately after their independent publication suggests that Lipmann and Kalckar were seen by their contemporaries as having made a "simultaneous discovery" of sorts.[10] But a close examination of the two papers reveals that their authors actually wrote them for different audiences and made quite distinct claims about "energy-rich" phosphate bonds. Kalckar crafted his review primarily for an audience of chemists and drew on recent developments in theoretical chemistry to explain the special properties of these bonds. Lipmann, on the other hand, composed his review for a much more biologically oriented audience, and focused his writing on the physiological purpose or function of the bonds within cellular metabolism. Cases of simultaneous discovery, Buhm Soon Park has argued, can illuminate much about "the borderland where two or more disciplines overlap," especially when "different routes" are taken "to a common destination."[11] Indeed, an analysis of Lipmann's and Kalckar's divergent approaches to the "energy-rich" phosphate bond highlights the disciplinary fluidity of the developing field of biological energy studies in the years leading up to World War II. Further, the underlying similarity of their approaches—the review article format—allowed both men the flexibility to construct the "energy-rich" phosphate bond across disciplinary boundaries.[12] The central

8. Kalckar to Lipmann, 18 Oct 1955, Box 8, Folder 5, FLP/RAC.

9. Kalckar to Lipmann, 12 Sep 1961, Box 16, Folder 16, FLP/RAC.

10. Thomas S. Kuhn, "Energy Conservation as an Example of Simultaneous Discovery," in *The Essential Tension: Selected Studies in Scientific Tradition and Change* (Chicago: University of Chicago Press, 1977), 66–104.

11. B. S. Park, "The Contexts of Simultaneous Discovery: Slater, Pauling, and the Origins of Hybridisation," *Studies in History and Philosophy of Science Part B: Studies in History and Philosophy of Modern Physics* 31, no. 4 (2000): 451–74, on 472, 452.

12. On the diversity and flexibility of review as a genre, see: Eugene Garfield, "Reviewing Review Literature, Part 1, Definitions and Uses of Reviews," in *Essays of an Information Scientist*, vol. 18 (Philadelphia: ISI Press, 1987), 113–16; Anthony M. Woodward, "The Roles of Reviews in Information Transfer," *Journal of the American Society for Information Science (Pre-1986); New York* 28, no. 3 (1977): 175–79; Anthony M. Woodward, "Review Literature: Characteristics, Sources and Output in 1972," *Aslib Proceedings* 26 (1974): 367–76; A. A. Manten, "Scientific Review Literature," *Scholarly Publishing* 5 (1973): 75–89; Scott Adams, "The Review Literature of Medicine," in *Bibliography of Medical Reviews*, vol. 6, "Culmination" (Washington, DC: US Department of Health, Education, and Welfare, Public Health Service, 1961).

claim of this paper is that the two review articles, by virtue of their conceptual overlap and their different disciplinary orientations, unified perspectives from the physiological and physicochemical sides of biology to elevate the "energy-rich" phosphate bond to a special status in cellular energy metabolism.

The differing and independent approaches that Lipmann and Kalckar took to explaining the "energy-rich" phosphate bond may be somewhat surprising given their intertwined lives in the 1930s and early 1940s. In order to understand how the two men's common base of knowledge about phosphate metabolism was refracted through their personal experiences to yield divergent presentations of the "energy-rich" phosphate bond in 1941, this paper utilizes a "parallel lives" approach.[13] When Lipmann's and Kalckar's lives are considered in parallel, it becomes clear that their distinct institutional contexts, before they met and after they both left Copenhagen, played significant roles in how they viewed and communicated the power of phosphate bonds in their review articles.

The remainder of this paper progresses as follows. The first section provides an overview of the state of research into biological energy at the end of the 1920s through a discussion of Lipmann's time in muscle researcher Otto Meyerhof's laboratory (1927–30), the place where Lipmann was initially exposed to the possibility that phosphate compounds might be connected to biological energy transformations. The second section follows Lipmann to Copenhagen, where he first met Kalckar, and where both men carried out research projects on the connections between carbohydrate and phosphate metabolism. The third section traces Kalckar's and Lipmann's 1939 departures from Copenhagen and situates them within their new American intellectual ecosystems (Pasadena and then St. Louis for Kalckar, New York for Lipmann). This section also describes—to the extent that the available sources allow—the immediate factors that contributed to the genesis of their respective review articles. The fourth and fifth sections offer a compare-and-contrast analysis of the contents of Kalckar's and Lipmann's reviews. The sixth section describes the dissimilar receptions the two review papers received among different scientific communities. The conclusion offers some reflections on scientific mobility and the genre of review articles.

13. S. S. Schweber, "John Herschel and Charles Darwin: A Study in Parallel Lives," *Journal of the History of Biology* 22, no. 1 (1989): 1–71. Following Schweber, I do not use "parallel lives" to literally mean never intersecting, but rather as a useful framework to systematically compare life stories (paying special attention to divergences) in order to understand how similar experiences and outlooks can nevertheless result in different accounts of the same phenomenon.

FROM LACTIC ACID TO PHOSPHATE

In 1927, Lipmann began working in Otto Meyerhof's laboratory, then located on the first floor of the Kaiser Wilhelm Institute (KWI) for Biology at Berlin-Dahlem.[14] In addition to Lipmann, other researchers in Meyerhof's laboratory in the late 1920s included Germans Karl Lohmann and David Nachmansohn, Spaniard Severo Ochoa, and American Dean Burk.[15] On the top floor of the KWI for Biology was the laboratory of cell physiologist Otto Warburg, with whom the young Hans A. Krebs had been working since 1926.[16] Lipmann, who had completed his medical training and spent the following three years studying chemistry, had come to Meyerhof's laboratory to perform research for his doctoral thesis in chemistry.[17]

When Meyerhof accepted Lipmann into his laboratory, Lipmann remembered that Meyerhof "asked . . . if I had any problem to work on and I was ashamed to say that I hadn't. I had to get a problem from him."[18] Meyerhof had been studying topics related to energy transformations in muscle for about a decade.[19] Initially trained in medicine, Meyerhof eventually switched to physiological research, which he conducted at the University of Kiel from 1913 to 1924.[20] Meyerhof had developed an interest in biological energy transformations as early as 1913, and after several years of research on other physiological topics he decided to pursue this subject through an investigation of muscle metabolism, in which lactic acid was known to play a role.[21] From

14. Fritz Lipmann, *Wanderings of a Biochemist* (New York: Wiley-Interscience, 1971), 6.

15. David Nachmansohn, "Biochemistry as Part of My Life," *Annual Review of Biochemistry* 41, no. 1 (1972): 1–30, on 5.

16. Lipmann, *Wanderings* (ref. 14), 6. Hans Krebs, *Otto Warburg: Cell Physiologist, Biochemist and Eccentric*, trans. Hans A. Krebs and Anne Martin (Oxford: Clarendon Press, 1981), v.

17. Lipmann, "A Long Life" (ref. 3), 4–5.

18. Hans A. Krebs and Fritz Lipmann, "Dahlem in the Late Nineteen Twenties," in *Lipmann Symposium: Energy, Regulation and Biosynthesis in Molecular Biology*, ed. Dietmar Richter (Berlin; New York: Walter de Gruyter, 1974), 7–27, on 20.

19. For Meyerhof's work, see Marcel Florkin, *A History of Biochemistry, Part III. History of the Identification of the Sources of Free Energy in Organisms*, ed. Marcel Florkin and Elmer H. Stotz, vol. 31, Comprehensive Biochemistry (Amsterdam: Elsevier, 1975). For the history of muscle contraction, see Dorothy M. Needham, *Machina Carnis: The Biochemistry of Muscular Contraction in Its Historical Development* (Cambridge: Cambridge University Press, 1971).

20. David Nachmansohn, "Otto Meyerhof: A Tribute on His 65th Birthday (April 12, 1949)," *Biochimica et Biophysica Acta* 4 (1950): 1–3, on 1.

21. David Nachmansohn, Severo Ochoa, and Fritz A. Lipmann, "Otto Meyerhof: 1884–1951," *Science* 115, no. 2988 (1952): 365–68, on 365; W. M. Fletcher and F. Gowland Hopkins, "Lactic Acid in Amphibian Muscle," *The Journal of Physiology* 35, no. 4 (1907): 247–309.

about 1919 to 1922, Meyerhof developed a system from his Kiel laboratory for studying how muscle generated contraction energy from the breakdown of the carbohydrate glycogen (a storage form of glucose) to lactic acid. In his investigations, Meyerhof utilized isolated frog muscles.[22] This choice of research material contributed to Meyerhof's physiological approach to lactic acid metabolism in muscle; he aimed to capture the dynamics of this substance during the different phases of muscle activity (rest, electrically stimulated contraction, and recovery), and in different gaseous environments (aerobic, anaerobic). During these years, Meyerhof coordinated his quantitative biochemical findings with the results of British biophysicist A. V. Hill, who had been conducting measurements of heat changes in muscle during its different phases of activity. The two received the 1922 Nobel Prize in Physiology or Medicine for their work on muscle. Together, Meyerhof's and Hill's results suggested that anaerobic lactic acid formation from glycogen was the chemical process most closely connected to the energetics of muscle contraction, and that during oxidative muscle recovery, most of this lactic acid was converted back into glycogen, while a fraction of it was oxidized.[23]

Meyerhof had moved to the KWI for Biology at Berlin-Dahlem in 1924. There, he continued his research program on energy transformations in muscle and the role of lactic acid therein.[24] But things had started to change when Lipmann arrived in 1927. That year, two separate laboratories isolated an unstable, phosphorus-containing organic compound from muscle and obtained evidence that this compound—which went by various names, including "phosphagen," "phosphocreatine," and "creatine phosphate"—was involved in the energetics of muscle contraction.[25] As Lipmann later explained, the function of this new phosphate compound "had . . . to be reconciled with [the]

22. On the history of frog muscle as experimental material, see Frederic L. Holmes, "The Old Martyr of Science: The Frog in Experimental Physiology," *Journal of the History of Biology* 26, no. 2 (1993): 311–28.

23. A. V. Hill, "The Mechanism of Muscular Contraction," *Physiological Reviews* 2, no. 2 (1922): 310–41; Otto Meyerhof, "Über einige Probleme der Muskelphysiologie," *Naturwissenschaften* 12, no. 50 (1924): 1137–40.

24. Otto Meyerhof, "Recent Investigations on the Aerobic and Anaerobic Metabolism of Carbohydrates," *The Journal of General Physiology* 8, no. 6 (1927): 531–42.

25. Philip Eggleton and Grace Palmer Eggleton, "The Inorganic Phosphate and a Labile Form of Organic Phosphate in the Gastrocnemius of the Frog," *Biochemical Journal* 21, no. 1 (1927): 190–95; Philip Eggleton and M. G. Eggleton, "The Significance of Phosphorus in Muscular Contraction," *Nature* 119, no. 2988 (1927): 194–95; Cyrus H. Fiske and Y. Subbarow, "The Nature of the 'Inorganic Phosphate' in Voluntary Muscle," *Science* 65, no. 1686 (1927): 401–3.

well-documented role of lactic acid formation as a source of energy for the muscle."[26] The same year, another phosphate compound, "adenylic acid," now known as adenosine monophosphate (AMP), was isolated from muscle extracts.[27] From 1927 onward, Meyerhof and his coworkers—especially Karl Lohmann—turned their attention to calorimetric analyses of phosphate compounds.[28] Meyerhof and Lohmann measured the heat of hydrolysis of phosphagen (phosphocreatine) and reported that this value was a great deal higher than that for other phosphate compounds.[29] Lohmann taught Lipmann, who investigated the role of phosphocreatine in frog muscle contraction as one of his first jobs in Meyerhof's laboratory, how to work with phosphate compounds:

> From Lohmann I learned about the handling of phosphate derivatives. He had developed a masterful technique for distinguishing the various compounds through the modes by which their phosphates could be released, primarily distinguishing them by rates of acid hydrolysis.[30]

Lipmann's early work on phosphocreatine, assigned to him by Meyerhof, "did not yield a much wanted understanding of" its function in muscle contraction.[31] Lipmann then moved on to a project on the mechanism of fluoride's inhibition of glycolysis, which became the basis for his doctoral thesis.[32] Lohmann, meanwhile, through his new techniques, isolated "pyrophosphate" (PP) in 1928, and in 1929 identified a novel phosphate compound, which he initially called "adenylpyrophosphoric acid"; it later became

26. Fritz Lipmann, "Discovery of Creatine Phosphate in Muscle," *Trends in Biochemical Sciences* 2, no. 1 (1977): 21–22, on 21. See also Herman Kalckar, "Exit Lactic Acid, Enter 'Phosphorylium,'" *Trends in Biochemical Sciences* 5, no. 2 (1980): 56–57.

27. Gustav Embden and Margarete Zimmermann, "Über die Bedeutung der Adenylsäure für die Muskelfunktion. I. Mitteilung: Das Vorkommen von Adenylsäure in der Skelettmuskulatur," *Zeitschrift für physiologische Chemie* 167, no. 1–3 (1927): 137–40.

28. On Meyerhof's work with Lohmann, see Eberhard Hofmann, "Otto Meyerhof und Karl Lohmann—Wegbereiter der heutigen Biochemie im Schatten ihrer Zeit," *Acta Historica Leopoldina* 55 (2010): 331–82. English translation available in Otto Meyerhof Biographical File, Box 1747, Office of Alumni Records, Biographical Records, 1750–2007, UPF 1.9AR, University Archives and Records Center, University of Pennsylvania, Philadelphia, PA.

29. O. Meyerhof and K. Lohmann, "Über den Ursprung der Kontraktionswärme," *Naturwissenschaften* 15, no. 32 (1927): 670.

30. Lipmann, *Wanderings* (ref. 14), 7, 8–9.

31. Lipmann, "A Long Life" (ref. 3), 5.

32. Lipmann, *Wanderings* (ref. 14), 9.

known as adenosine triphosphate, or ATP.[33] During his first couple of years in Meyerhof's laboratory, Lipmann thus witnessed the proliferation of reports of new muscle-derived phosphate compounds, gained experience in phosphate chemistry, and saw the increasing recognition that phosphate compounds may have a role to play in the energetics of muscle contraction.

In late 1929, Meyerhof was preparing to move his laboratory (and all his laboratory workers) from Berlin to Heidelberg, where he had been offered the directorship of the physiological section of the newly built KWI for Medical Research.[34] Right before his move, Meyerhof unexpectedly received a preprint of a research article, "Investigations into Muscle Contractions without Lactic Acid Formation," from its author, Danish physiologist Einar Lundsgaard.[35] *Biochemische Zeitschrift* published Lundsgaard's article soon thereafter (early 1930).[36] By injecting isolated frog muscles with monoiodoacetic acid (which prevented lactic acid formation), Lundsgaard observed that these "poisoned" muscles were still able to achieve a number of contractions upon electrical stimulation.[37] From these results, Lundsgaard concluded that lactic acid formation from glycogen must not be directly connected to the energetics of muscle contraction.[38] Additionally, Lundsgaard determined that when the "poisoned" muscles were made to contract, phosphagen (phosphocreatine) was completely broken down, which indicated that this phosphate compound was more immediately involved in furnishing energy for muscle contraction than was lactic acid.[39] Lundsgaard fashioned the following hypothesis, which relegated lactic acid to an indirect role in muscle energetics: phosphagen breakdown (to creatine and phosphate) directly supplied the muscle with

33. Karl Lohmann, "Über das Vorkommen und den Umsatz von Pyrophosphat in Zellen. I. Mitteilung: Nachweis und Isolierung des Pyrophosphats," *Biochemische Zeitschrift* 202 (1928): 466–93; Karl Lohmann, "Über die Pyrophosphatfraktion im Muskel," *Naturwissenschaften* 17, no. 31 (1929): 624–25. In 1929, Fiske and Subbarow also reported the identification of what was later determined to be the same substance. Koscak Maruyama, "The Discovery of Adenosine Triphosphate and the Establishment of Its Structure," *Journal of the History of Biology* 24, no. 1 (1991): 145–54.

34. Severo Ochoa, "The Pursuit of a Hobby," *Annual Review of Biochemistry* 49 (1980): 1–31, on 6.

35. David Nachmansohn, *German-Jewish Pioneers in Science, 1900–1933* (Berlin, Heidelberg, New York: Springer-Verlag, 1979), 279–80.

36. Einar Lundsgaard, "Untersuchungen über Muskelkontraktionen ohne Milchsäurebildung," *Biochemische Zeitschrift* 217 (1930): 162–77.

37. Ibid., 177.

38. Ibid., 165–166.

39. Ibid., 170.

contraction energy, while the formation of lactic acid afforded energy for the resynthesis of phosphagen.[40]

Lundsgaard's findings were in direct opposition to the Meyerhof school. As Lipmann remembered: "When this startling news reached us in Meyerhof's laboratory, it was very upsetting to our group which looked upon glycolytic lactic acid as the link between metabolic energy generation and muscle contraction."[41] Severo Ochoa, who was also working with Meyerhof in Heidelberg at the time, recalled that Meyerhof at first "received Lundsgaard's results with skepticism."[42] That summer (1930), Lundsgaard came to Heidelberg to demonstrate his experiments in person.[43] It was in Heidelberg that Lipmann and Lundsgaard "first met and became friends."[44] Working closely with Meyerhof, Lipmann, and others, Lundsgaard repeated his experiments, confirmed his previous findings, and expanded his claims.[45] One of Lipmann's last projects in Meyerhof's laboratory was a corroboration of Lundsgaard's argument that phosphagen (phosphocreatine) breakdown coincided with muscle contraction.[46] Lundsgaard's results and the Meyerhof laboratory's confirmation and acceptance of them constituted the final stage of what A. V. Hill called "The Revolution in Muscle Physiology" in 1932.[47] Lundsgaard's work had prompted a widespread recognition among muscle researchers that phosphate compounds were the key energetic substances powering muscle contraction, but whether their energetic functions extended beyond muscle was an open question. Even as Meyerhof's approach became more biochemical in nature throughout the 1930s, he continued to ask "how the chemical activities might accomplish physiological functions," according to William Bechtel's analysis of Meyerhof's later work.[48] From his foundational three-year period

40. Ibid., 175.

41. Fritz Lipmann, "Einar Lundsgaard," *Science* 164, no. 3877 (1969): 246–47, on 247.

42. Ochoa, "Pursuit" (ref. 34), 6.

43. Ibid.

44. Lipmann, "Einar Lundsgaard" (ref. 41), 246.

45. Einar Lundsgaard, "Weitere Untersuchungen über Muskelkontraktionen ohne Milchsäurebildung," *Biochemische Zeitschrift* 227 (1930): 51–83.

46. Fritz Lipmann, "Über den Tätigkeitsstoffwechsel des fluoridvergifteten Muskels," *Biochemische Zeitschrift* 227 (1930): 110–15.

47. A. V. Hill, "The Revolution in Muscle Physiology," *Physiological Reviews* 12, no. 1 (1932): 56–67.

48. William Bechtel, "Building Interlevel Theories: The Discovery of the Embden-Meyerhof Pathway and the Phosphate Cycle," in *Foundations of Biology*, ed. Paul Weingartner and Georg Dorn (Vienna: Verlag Hölder-Pichler-Tempsky, 1986), 65–97, on 66.

in Meyerhof's laboratory, Lipmann thus took away not only an appreciation for the role of phosphate compounds in biological energy transformations but also a commitment to understanding the physiological function of biochemical reactions within living organisms.

CONNECTING IN COPENHAGEN

In the early 1930s, Lipmann and Kalckar became acquainted in Copenhagen, where they both lived until 1939. In 1932, Lipmann arrived in Copenhagen to begin working in the laboratory of Danish biologist Albert Fischer, who had recently been appointed director of a newly constructed Biological Institute co-funded by the Rockefeller Foundation and the Carlsberg Foundation of Denmark.[49] Lipmann resided in an apartment directly above the new laboratory building on Tagensvej.[50] This placed him in the immediate vicinity of Einar Lundsgaard's laboratory, located within the University of Copenhagen's Institute of Medical Physiology.[51] Lipmann of course knew Lundsgaard from Meyerhof's laboratory, and during the 1930s, the two men "saw each other a great deal" in Copenhagen.[52] After visiting Meyerhof's laboratory in Heidelberg and other laboratories in London, Lundsgaard returned to his native Denmark in the summer of 1931.[53] There, Lundsgaard continued to work

49. Before arriving in Copenhagen, Lipmann worked briefly with Albert Fischer in Berlin, and then spent a year with P. A. Levene at the Rockefeller Institute for Medical Research (RIMR) in New York City. Lipmann, *Wanderings* (ref. 14), 20, 23. Albert Fischer, initially trained in medicine in Copenhagen, had studied tissue culture techniques with Alexis Carrel at the RIMR in the early 1920s. See Leif Rasmussen and Denys N. Wheatley, "The Biological Institute of the Carlsberg Foundation: International Centre for Cell Biology for 50 Years," *Cell Biology International Reports* 7, no. 12 (1983): 1071–79, on 1072. The Carlsberg Foundation, founded in 1876 by Danish brewer J. C. Jacobsen, was created as a way to direct funds from the Carlsberg Brewery to further scientific research in Denmark. See Birger Trolle, "The Origins of the Laboratory and Its Background in the Carlsberg Brewery," in *The Carlsberg Laboratory 1876|1976*, ed. H. Holter and K. Max Møller (Copenhagen: The Carlsberg Foundation; Rhodos Publishing House, 1976), 16–23.

50. Freda Hall Lipmann, "Life with Fritz," in *The Roots of Modern Biochemistry: Fritz Lipmann's Squiggle and Its Consequences*, ed. Horst Kleinkauf, Hans von Döhren, and Lothar Jaenicke (Berlin & New York: Walter de Gruyter, 1988), 3–8, on 5. Lipmann, "A Long Life" (ref. 3), 13.

51. Lipmann, *Wanderings* (ref. 14), 27.

52. Lipmann, "Einar Lundsgaard" (ref. 41), 246.

53. Lundsgaard to Hill, 8 Jul 1931, A. V. Hill Papers, AVHL II 4/56, Churchill Archives Centre, Churchill College, Cambridge, UK.

on the energetics of muscle contraction, and in April 1934 he became director of the University of Copenhagen's Institute of Medical Physiology.[54] That year, a medical graduate named Herman M. Kalckar joined the institute to begin his doctoral work in Lundsgaard's laboratory.[55] Kalckar had studied medicine in Copenhagen, where he obtained a medical degree in 1933 and subsequently completed an internship year.[56] Although Lundsgaard was Kalckar's official research advisor, Lundsgaard became increasingly busy with his new administrative duties. Lipmann, by contrast, was available, and Kalckar often turned to him for mentorship and advice.[57] This initial student-mentor relationship between Kalckar and Lipmann eventually grew into a friendship.

In the second half of the 1930s, both Lipmann and Kalckar pursued research projects on the connections between carbohydrate and phosphate metabolism. One of Lipmann's main lines of research at Fischer's institute was pyruvic acid metabolism, which interested Lipmann because pyruvate was believed to be the metabolic branching point between glycolysis (which produced lactate via reduction) and respiration (which yielded acetate and carbon dioxide via oxidation).[58] Lipmann utilized dried lactic acid bacteria for his experiments, which he carried out by adding to the bacteria extracts of animal organs and a cofactor given to him by Lohmann. Lipmann observed that the enzyme-catalyzed dehydrogenation of pyruvic acid to acetic acid and carbon dioxide was blocked when he removed phosphate from the reaction. Upon re-addition of inorganic phosphate, the reaction resumed.[59] Further, Lipmann determined that if he added adenylic acid (AMP) to the reaction, it gained phosphoryl groups, eventually yielding adenosine polyphosphate (ATP).[60] Lipmann observed this phosphorylation in the presence and in the absence of oxygen.[61] For Lipmann, these unexpected results indicated that (1) inorganic phosphate was required for pyruvic acid dehydrogenation; (2) there was likely

54. "Lundsgaard, Dr. Einar," Fellowship Recorder Cards, FA426, Box 10, RFR/RAC.

55. "Personal Data—H. M. Kalckar," FA386b, Series 713, Subseries 713.D, Box 5, Folder 60, RFR/RAC.

56. Ibid.

57. Kalckar, "Autobiographical Notes" (ref. 3), 103.

58. Lipmann, *Wanderings* (ref. 14), 28.

59. Fritz Lipmann, "Pyruvic Acid Dehydrogenation, Vitamin B_1 and Cocarboxylase," *Nature* 140, no. 3531 (1937): 25.

60. Fritz Lipmann, "Coupling between Pyruvic Acid Dehydrogenation and Adenylic Acid Phosphorylation," *Nature* 143, no. 3616 (1939): 281.

61. Ibid.

a phosphorylated intermediate somewhere in the reaction sequence; and (3) pyruvic acid dehydrogenation was "coupled" to phosphorylation, at least in this bacterial system.[62] Lipmann guessed that the phosphorylated intermediate in this reaction was probably acetylphosphate, and demonstrated that synthetic acetylphosphate could phosphorylate adenylic acid during bacterial metabolism.[63] He proposed that acetylphosphate served as an "active acetate" intermediate that could transfer phosphoryl groups to other molecules.[64] Moreover, Lipmann believed that the "coupling" between these metabolic oxidation-reduction reactions and phosphorylation might be indicative of a more general mechanism whereby the extraction of energy from the breakdown of carbohydrates was linked to phosphorylation. Over the course of the 1930s, Meyerhof had also been developing a similar theory that phosphorylation was the key to energetic "coupling."[65] With his time in Meyerhof's laboratory likely in mind, Lipmann suggested that this coupling could explain how muscle tissues were furnished with contraction energy: "A new source of phosphorylation energy appears which can be utilized both aerobically and possibly anaerobically. The skeletal muscle and to a still greater extent the heart muscle are probably supplied with energy from this source."[66]

Lipmann was especially helpful when Kalckar expressed an interest in biological phosphorylation, and suggested he "study the newer literature on carbohydrate and phosphate metabolism in isolated mammalian tissue extracts or tissue particle preparations."[67] Kalckar chose to study mammalian kidney cortex extracts. He observed that if glucose was added to kidney cortex tissue pulp, the glucose was phosphorylated under aerobic conditions but not under anaerobic conditions.[68] Kalckar, who was studying a completely different system than Lipmann, nevertheless reached a similar conclusion—that there existed "a coupled reaction between oxygen consumption and phosphorylation."[69] After noticing that including fumaric acid or malic acid in the

62. Ibid. Fritz Lipmann, "Role of Phosphate in Pyruvic Acid Dehydrogenation," *Nature* 144, no. 3643 (1939): 381–82.

63. Lipmann, "Role of Phosphate" (ref. 62).

64. Ibid.

65. Bechtel, "Building Interlevel Theories" (ref. 48), 84–87.

66. Lipmann, "Coupling" (ref. 60), 281.

67. Kalckar, "Autobiographical Notes" (ref. 3), 105.

68. Herman Kalckar, "Phosphorylation in Kidney Tissue," *Enzymologia* II (1937): 47–52.

69. Ibid., 51.

reaction resulted in increased phosphorylation, Kalckar suggested that malate (an intermediate in Hans Krebs's recently elucidated citric acid cycle) was oxidized (via oxaloacetate) to pyruvate, which then served as "a phosphate acceptor" in the system.[70] Kalckar identified the phosphorylated product as phosphopyruvic acid (now known as phosphoenolpyruvic acid, or PEP).[71] Like Lipmann's description of acetylphosphate, Kalckar too had identified a phosphorylated intermediate generated in connection with oxidative processes. The Copenhagen experiments of Lipmann and Kalckar offered evidence from a bacterial system and a kidney-based system, respectively, that oxidation-reduction reactions involving carbohydrates were energetically coupled to phosphorylation. In the late 1930s, Lipmann and Kalckar maintained an active dialogue about their related experiments, as evidenced by their citations to each other's papers and acknowledgments at the end of Kalckar's publications, for example: "I wish to thank Professor Lundsgaard and Dr. F. Lipmann for several interesting and important discussions."[72] The two also presented their findings at the weekly colloquia of the Carlsberg Laboratory, which were attended by Lundsgaard and protein chemist K. U. Linderstrøm-Lang, a mutual friend of Lipmann and Kalckar.[73]

THE GOSPEL OF PHOSPHORYLATION

In early 1939, Lipmann's and Kalckar's paths diverged. Back in March 1938, Kalckar had applied for a Rockefeller Foundation postdoctoral fellowship to travel to the United States for further study.[74] Following the January 1939 defense of his doctoral thesis, "Phosphorylations in Animal Tissues," based on several years of work in Lundsgaard's laboratory, Kalckar left Copenhagen for

70. Herman Kalckar, "Formation of a New Phosphate Ester in Kidney Extracts," *Nature* 142, no. 3602 (1938): 871; Herman Kalckar, "The Nature of Phosphoric Esters Formed in Kidney Extracts," *Biochemical Journal* 33, no. 5 (1939): 631–41, on 636–40.

71. Kalckar, "Formation" (ref. 70).

72. Kalckar, "Phosphorylation" (ref. 68), 52.

73. H. M. Kalckar, "Recollections of Carlsberg Colloquia 1934–38," in *The Carlsberg Laboratory 1876|1976*, ed. H. Holter and K. Max Møller (Copenhagen: The Carlsberg Foundation, Rhodos Publishing House, 1976), 322–24.

74. "Personal History Record Submitted in Connection with Application for a Fellowship in Natural Science," Fellowship Files, FA244, Series 713, Subseries 713.E, Box 424, Folder 6184, RFR/RAC.

the United States, arriving in New York on February 9, 1939.[75] Kalckar's ultimate destination was California Institute of Technology (Caltech), where he had been accepted for a position in Henry Borsook's laboratory.[76] After spending some time in New York, Kalckar began his westward journey, making stops along the way to visit friends and colleagues. For example, on February 17, 1939, Kalckar met friend and fellow Copenhagener Niels Bohr in Princeton, New Jersey.[77] Through his connections to Bohr, Kalckar likely kept informed of developments in 1930s theoretical physics. Continuing westward, Kalckar stopped in St. Louis, where he visited the laboratory of husband-and-wife biochemist team Carl and Gerty Cori, who had been working on phosphorylation and carbohydrate metabolism as well.[78] During this visit, Kalckar helped the Coris replicate his Copenhagen kidney experiments.[79]

Kalckar reached Pasadena, California, on March 1, 1939.[80] During his time at the Kerckhoff Biological Laboratories, Kalckar was surrounded not only by biologists such as T. H. Morgan (who had founded Caltech's Biology Division in 1928), Henry Borsook (who Morgan had hired in 1929 to head the Biochemistry Unit), and physicist-turned-biologist Max Delbrück but also by some of America's leading chemists, including Linus Pauling (the head of Caltech's Chemistry Division) and Charles D. Coryell.[81] Pauling, in particular, became an important interlocutor for Kalckar in discussions about the

75. "Personal Data—H. M. Kalckar," FA386b, Series 713, Subseries 713.D, Box 5, Folder 60, RFR/RAC; "Kalckar, Dr. Herman Moritz" Fellowship Recorder Cards, FA426, Box 10, RFR/RAC.

76. "Kalckar, Dr. Herman Moritz" Fellowship Recorder Cards, FA426, Box 10, RFR/RAC.

77. See Kalckar to Bohr, 11 Feb 1939, Series I, Folder 429, Item 1, NBPC/NBA; and Bohr to Kalckar, 13 Feb 1939, Series I, Folder 429, Item 2, NBPC/NBA. I thank Rob Sunderland of the NBA for providing translations from the original Danish. On Bohr's time in Princeton, see John Archibald Wheeler, "Fission in 1939: The Puzzle and the Promise," *Annual Review of Nuclear and Particle Science* 39, no. 1 (1989): xiii–xxviii.

78. Both Coris were born in Prague but settled in the United States in 1922. They worked at the State Institute for the Study of Malignant Disease in Buffalo, New York, until 1931, at which point they moved to Washington University School of Medicine in St. Louis. See Carl F. Cori, "The Call of Science," *Annual Review of Biochemistry* 38 (1969): 1–21.

79. Kalckar, "Autobiographical Notes" (ref. 3), 113.

80. Ibid., 114.

81. On the history of Caltech's Biology and Chemistry Divisions, see Lily E. Kay, *The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the Rise of the New Biology* (Oxford: Oxford University Press, 1993). The chemists worked next door at the Crellin and Gates Chemical Laboratories. See Herman M. Kalckar, "Biological Phosphorylation, ^{32}P, and Fifty Years of ATP," in *From Cyclotrons to Cytochromes: Essays in Molecular Biology and Chemistry*, ed. Nathan O. Kaplan and Arthur Robinson (New York: Academic Press, 1982), 291–97, on 292.

implications of recent developments in physics and chemistry for biology.[82] Having spent the previous dozen years engaging with quantum mechanics—part of this time on the ground in Europe in the midst of its development—Pauling had begun to formulate a program of "quantum chemistry," in which recent developments in quantum mechanics were brought to bear on electronic and structural analyses of atoms and molecules.[83] The culmination of these efforts, Pauling's landmark monograph, *The Nature of the Chemical Bond and the Structure of Molecules and Crystals*, was published in 1939, the very same year that Kalckar arrived at Caltech.[84]

Borsook, for his part, was interested in biological thermodynamics and worked closely with Hugh M. Huffman to establish a research program that aimed to gather thermodynamic data from various biochemical reactions (especially protein synthesis).[85] After arriving at Caltech in the early 1930s, Huffman could often be found in the basement laboratory of the biology building—known to Caltech workers as the "crematorium"—where chemicals were burned and thermodynamic data obtained.[86] At Caltech, Kalckar was thus able to immerse himself in thermodynamic studies of molecules of biological importance.

Kalckar brought a conviction, nurtured by years in Copenhagen with Lundsgaard and Lipmann, that the key to thermodynamic transformations in living organisms resided in phosphate bonds. "Yet," Kalckar remembered, "in California in 1939, no one cared very much about phosphorylation and I was therefore zealous to preach the 'gospel of phosphorylation.'"[87] Kalckar

82. Mary Jo Nye, "Physical and Biological Modes of Thought in the Chemistry of Linus Pauling," *Studies in History and Philosophy of Science Part B: Studies in History and Philosophy of Modern Physics* 31, no. 4 (2000): 475–91.

83. Kostas Gavroglou and Ana Simões, *Neither Physics nor Chemistry: A History of Quantum Chemistry* (Cambridge, MA: MIT Press, 2012).

84. Linus Pauling, *The Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry* (Ithaca, NY: Cornell University Press, 1939). This monograph was based on a series of papers that Pauling had published in the *Journal of the American Chemical Society* earlier in the decade.

85. Norman H. Horowitz, "Henry Borsook, 1897–1984," *Engineering and Science* 47, no. 5 (1984): 24.

86. "Bulletin of the California Institute of Technology" 41, no. 137 (1932): 1–252, on 24; Kalckar, "Autobiographical Notes" (ref. 3), 115.

87. Herman M. Kalckar, "Lipmann and the 'Squiggle,'" in *Current Aspects of Biochemical Energetics: Fritz Lipmann Dedicatory Volume*, ed. Nathan O. Kaplan and Eugene P. Kennedy (New York, London: Academic Press, 1966), 1–8, on 2.

spread his message through a series of seminars that he gave to Caltech's Biochemical Unit at Borsook's invitation.[88] One of the main purposes of these seminars, in Kalckar's view, was to integrate ideas and findings from different disciplines. As Kalckar wrote to new acquaintance Carl Cori, "I have given 5–6 seminars on [*sic*] Cal. Tech. trying to unify different fields: thermodyn. problems, diff. types of fermentations & recent discoveries of biolog. imp. phosphate esters."[89] Kalckar's experiences leading these seminars, in addition to the considerable time he spent conducting a wide-ranging study of relevant literature—including "the fundamentals of structural chemistry"—became the basis for Kalckar's review article.[90] In terms of experimental work, Kalckar had originally planned to obtain the "thermal data of P-esters," but after finding this idea "impracticable," he turned his attention to the development of a propionic acid bacterial system for studying dehydrogenase enzymes.[91] Kalckar was inspired to begin working with bacteria after spending July and August at Stanford's Hopkins Marine Station at Pacific Grove, where he participated in C. B. van Niel's famous course, "General Microbiology."[92] By January of 1940, Kalckar reported to Cori that "[b]esides the exp. work I have in the last months been absorbed in the study of free energy data."[93]

Meanwhile, in early 1939, Lipmann was still working in Denmark. But conditions were becoming ominous in Europe, especially for Lipmann, a German Jew. Looking to leave Europe quickly, Lipmann reached out to Dean Burk, who had visited him in Copenhagen and with whom he had overlapped in Meyerhof's laboratory, for advice on finding a position in America.[94] Burk happened to have openings for two researchers to join him in the laboratory of Vincent du Vigneaud at Cornell Medical College in New York City, where Burk was to begin a temporary appointment. Burk offered Lipmann one of these positions, and Lipmann set sail for New York with his

88. Kalckar, "Autobiographical Notes" (ref. 3), 114.

89. Kalckar to Cori, 8 Jan 1940, FC050-S02-B01-F78, CCP.

90. Ibid.; Kalckar to Cori, 5 Feb 1940, FC050-S02-B01-F78, CCP.

91. Kalckar to Cori, 29 Sep 1939, FC050-S02-B01-F78, CCP; Kalckar to Cori, 8 Nov 1939, FC050-S02-B01-F78, CCP.

92. Ibid.; "Kalckar, Dr. Herman Moritz" Fellowship Recorder Cards, FA426, Box 10, RFR/RAC. On van Niel and his course, see Susan Barbara Spath, "C.B. van Niel and the Culture of Microbiology, 1920–1965" (PhD dissertation, University of California, Berkeley, 1999).

93. Kalckar to Cori, 8 Jan 1940, FC050-S02-B01-F78, CCP.

94. Lipmann, "A Long Life" (ref. 3), 13, 15–16.

wife in July 1939, just a couple of months before the outbreak of World War II in Europe.[95]

Shortly after arriving in New York, Lipmann traveled to Long Island to take part in the Seventh Cold Spring Harbor Symposium on Quantitative Biology on the theme of "Biological Oxidations."[96] There, Lipmann had the opportunity to present his work on pyruvic acid metabolism in detail.[97] Burk was also in attendance and delivered a talk on the Pasteur Effect.[98] While at Cold Spring Harbor, Lipmann met Carl Cori in person and spoke with him about Kalckar and his work.[99] Cori had multiple exchanges with Lipmann during the meeting, according to the discussion transcripts printed at the end of their two papers.[100] Remaining at Cold Spring Harbor for the rest of the summer after the meeting had concluded, Lipmann and Carl and Gerty Cori had many opportunities for further discussion.[101] Lipmann wrote to the Coris later that fall, recalling fondly "the days in C.Sp.H., when we stood on [*sic*] the blackboard—discussing."[102]

Upon his return to New York City in the fall, Lipmann began his new research position in du Vigneaud's laboratory as part of Dean Burk's group, which focused on D-amino acids and cancer. Unfortunately for Lipmann, "there was no interest in phosphate compounds in du Vigneaud's laboratory at all," according to Mildred Cohn, who worked there with

95. Lipmann, *Wanderings* (ref. 14), 35. Lipmann's Copenhagen friend, Linderstrøm-Lang, also played a role in securing Lipmann this position by recommending Lipmann to Vincent du Vigneaud. Fritz Lipmann, "Recollections of Linderstrøm-Lang," *Trends in Biochemical Sciences* 5, no. 6 (1980): III–IV, on IV.

96. Eric Ponder, "Front Matter," *Cold Spring Harbor Symposia on Quantitative Biology* 7 (1939): v. Although Lipmann was not listed as a presenter on the draft program of March 1939, it is probable that he was a last-minute addition once it became clear that he would be coming to the United States. See "Tentative Program for Symposium on Biological Oxidations," enclosed with Ponder to Cori, 4 Mar 1939, FC050-S02-B02-F46, CCP.

97. Fritz Lipmann, "An Analysis of the Pyruvic Acid Oxidation System," *Cold Spring Harbor Symposia on Quantitative Biology* 7 (1939): 248–59.

98. Dean Burk, "A Colloquial Consideration of the Pasteur and Neo-Pasteur Effects," *Cold Spring Harbor Symposia on Quantitative Biology* 7 (1939): 420–59.

99. Cori to Kalckar, 22 Aug 1939, Box 1, Folder 1, HKC.

100. See Lipmann, "An Analysis" (ref. 97); Carl F. Cori, "Enzymatic Breakdown and Synthesis of Carbohydrate," *Cold Spring Harbor Symposia on Quantitative Biology* 7 (1939): 260–68.

101. Gerty T. Cori to Eric Ponder, 25 Mar 1939, FC050-S02-B02-F46, CCP; Lipmann, "A Long Life" (ref. 3), 16.

102. Lipmann to Carl and Gerty Cori, 16 Nov 1939, FC050-S02-B01-F95, CCP.

Lipmann.[103] Lipmann did, however, correspond about phosphorylation with Kalckar (who had been in California for about six months), as evidenced by the following remark in a letter from Kalckar to Cori: "I have got [*sic*] some letters from Lipmann . . . The acetyl-phosphate seems to be very promising."[104] Kalckar later characterized Lipmann's letter describing acetylphosphate as "electrifying" and as having "inspired" his own review.[105] For Lipmann, acetylphosphate was likewise a critical impetus to begin theorizing on the generalized role of phosphate bonds in energy metabolism. Although Lipmann was working on cancer-related problems with Burk, he found time to follow up on the pyruvic acid experiments he had conducted before he left Copenhagen. In mid-May of 1940, Lipmann reported in a short letter to the editors of the *Journal of Biological Chemistry* that he had obtained evidence that the phosphorylated intermediate acetylphosphate did indeed seem to be *metabolically* generated in the course of pyruvic acid oxidation.[106] Recall that in Copenhagen, Lipmann had been able to determine only that synthetically prepared acetylphosphate could phosphorylate adenylic acid. Lipmann's brief letter of May 1940 appears to be the first time he mentioned, in published literature, the phrase "energy-rich phosphate bond," which would become the centerpiece of his 1941 review. Referring to the acetylphosphate intermediate, Lipmann wrote, "Since pyruvic acid was found to promote adenylic acid phosphorylation, any such intermediate must contain an energy-rich phosphate bond."[107]

Around the time that Lipmann sent this letter to the editors, he and his wife traveled to Vermont for a vacation.[108] Their destination was a lakeside cottage, where Lipmann remembered having sufficient undisturbed time "to meditate on the metabolic appearance of a compound like acetyl phosphate."[109] Deep

103. Mildred Cohn, Interviewed by Leon Gortler at the University of Pennsylvania, Philadelphia, PA, 15 Dec 1987 and 6 Jan 1988, Oral History Transcript #0080, Science History Institute, 1–119, on 52.

104. Kalckar to Cori, 8 Nov 1939, FC050-S02-B01-F78, CCP.

105. Kalckar, "Autobiographical Notes" (ref. 3), 114, 121. While there is not much evidence for Kalckar's claim, he did discuss Lipmann's acetylphosphate work at length in his review.

106. Fritz Lipmann, "A Phosphorylated Oxidation Product of Pyruvic Acid," *Journal of Biological Chemistry* 134, no. 1 (1940): 463–64.

107. Ibid., 463.

108. Freda Hall Lipmann remembered this vacation as having taken place in summer of 1940, rather than in spring of 1940, as Lipmann himself remembered it. Lipmann, "Life with Fritz" (ref. 50), 6; Lipmann, "A Long Life" (ref. 3), 16.

109. Lipmann, "A Long Life" (ref. 3), 16.

thinking led to writing, and in this Vermont lakeside cottage, Lipmann began to draft an essay that would become his 1941 review.[110] Also around this time, New York–based biochemist F. F. Nord asked Lipmann to contribute an essay on the Pasteur effect to a new review series he was working to establish, to be called *Advances in Enzymology and Related Subjects*.[111] But seeing the potential to develop the material he had first drafted at the Vermont cottage into a review on the biological role of phosphate bonds, Lipmann proposed this topic instead, and Nord accepted.[112]

While Lipmann was settling into a new life on the east coast, Kalckar was still out west and had decided to compose a review article on the energetics and thermodynamics of biological syntheses. This was at the suggestion of Linus Pauling, who promised to help place it in *Chemical Reviews*.[113] But as Kalckar's time at Caltech on the Rockefeller Foundation's dime was quickly running out, he needed to make plans about where he would go next. Kalckar was monitoring the situation in his home country very closely, noting to Cori in November 1939 that he and his wife were receiving "regular mail from Denmark where the situation of course is very serious but still not hopeless."[114] Luckily, Carl Cori issued Kalckar an invitation to join his laboratory in St. Louis.[115] Kalckar was eager to accept, pending an extension of his Rockefeller Foundation fellowship.[116] By mid-October of 1939, Carl Cori had leveraged his status and connections to put in a good word for Kalckar with the Rockefeller Foundation, which subsequently notified Kalckar of a six-month extension.[117] Kalckar updated Niels Bohr about his decision to go to St. Louis: "I am very happy with this arrangement," Kalckar wrote, "as Cori is the most important man in the area of modern metabolic chemistry . . . in the U.S."[118] By not returning home to Copenhagen in February 1940, Kalckar, who was Jewish, avoided getting caught in the Nazi invasion of Denmark that occurred

110. Ibid., 17.

111. Lipmann, *Wanderings* (ref. 14), 37. On *Advances,* see J. H. Quastel, "Advances in Enzymology and Related Subjects," *Nature* 152, no. 3857 (1943): 368–370, on 368.

112. Lipmann, *Wanderings* (ref. 14), 37.

113. Kalckar, "Autobiographical Notes" (ref. 3), 117.

114. Kalckar to Cori, 8 Nov 1939, FC050-S02-B01-F78, CCP.

115. Cori to Kalckar, 22 Aug 1939, Box 1, Folder 1, HKC.

116. Kalckar to Cori, 29 Sep 1939, FC050-S02-B01-F78, CCP.

117. See Cori to Hanson, 19 Oct 1939, FC050-S02-B01-F65, CCP; and Kalckar to Cori, 8 Nov 1939, FC050-S02-B01-F78, CCP.

118. Kalckar to Bohr, 10 Dec 1939, Folder 160, Item 1, NBSC/NBA. I thank Rob Sunderland of the NBA for providing an English translation from the original Danish.

just a couple of months later (April 1940).[119] Kalckar and his wife left California by train, destined for the Cori laboratory, which Kalckar later termed "the 'Phosphate Center.'"[120] During this long journey, Kalckar recalled that he "sat up most of the night on the train to St. Louis writing page after page of the review for Linus Pauling."[121] From St. Louis, Kalckar wrote to Berlin cell physiologist Otto Warburg and friend Niels Bohr, informing both of his impending review article.[122]

While Kalckar notified multiple scientists that he was writing his review article, there is no evidence—surprising as it may be—that he informed Lipmann. An opportunity to confide in Lipmann may have come around November 1940, when Kalckar notified Otto Warburg of a visit he had made to Lipmann in New York, likely the first face-to-face meeting between the two friends since Copenhagen: "I visited Lipmann in N.Y.; he still remains the most interesting person I have met."[123] Kalckar later claimed to have been unaware of Lipmann's review paper until several months after it was published.[124] And it is unlikely that anyone in du Vigneaud's laboratory (except an unnamed "younger colleague" who assisted Lipmann with his English and perhaps Dean Burk) knew of Lipmann's review either.[125] Mildred Cohn stated categorically that she "certainly wasn't aware that he was writing that paper."[126] Descriptions of Lipmann's personality suggest that he had a reserved disposition, and was therefore unlikely to have disseminated his beliefs about phosphorylation around New York City; Lipmann's wife, for example, once wrote that Lipmann had "an aura of quietness about him."[127] Further testimony from Mildred Cohn suggests that Lipmann may have struggled to

119. Due to the war, Kalckar stayed with the Coris until 1943, and in the United States until 1946. Kalckar, "Autobiographical Notes" (ref. 3), 116–19.

120. Kalckar to Cori, 24 May 1941, C050-S02-B01-F78, CCP.

121. Herman M. Kalckar, "50 Years of Biological Research—from Oxidative Phosphorylation to Energy Requiring Transport Regulation," *Annual Review of Biochemistry* 60, no. 1 (1991): 1–38, on 12.

122. Kalckar to Warburg, 22 Nov 1940, Nr. 484, NOW/BBAW; and Kalckar to Bohr, 4 Dec 1940, Folder 160, Item 2, NBSC/NBA. I thank Rob Sunderland of the NBA for providing an English translation from the original Danish.

123. Kalckar to Warburg, 22 Nov 1940, Nr. 484, NOW/BBAW.

124. Kalckar, "Autobiographical Notes" (ref. 3), 115.

125. Lipmann, *Wanderings* (ref. 14), 37. Given that Lipmann and Burk worked in Meyerhof's laboratory together, and that Lipmann made use of Burk's thermodynamic data in his review, it is possible that Burk knew of Lipmann's publishing plans.

126. Cohn, Interview (ref. 103), 51.

127. Lipmann, "Life with Fritz" (ref. 50), 3.

communicate his ideas to others; she saw him as "completely intuitive," even "inarticulate."[128] When questioned, Lipmann "couldn't tell you how he arrived at his conclusions. It was as though it [*sic*] came to him from on high."[129] Together, these fragments of evidence tend to confirm Kalckar's claim that Lipmann did not inform him of his review, and although it remains unclear whether Lipmann knew of Kalckar's, the available evidence suggests he did not.[130]

SYNTHESIS AND COUPLING

Kalckar's survey article was published in *Chemical Reviews* in February 1941.[131] One of the earliest articles to appear in *Chemical Reviews* was a 1928 essay by Linus Pauling on the elucidation of the structure of the hydrogen molecule using the tools of quantum mechanics.[132] As the then-editor of *Chemical Reviews*, Gerald Wendt, wrote to Pauling in May of 1928, "Please remember that this is a review journal and that most readers are not familiar with the subject. This does not in any sense mean that the papers should be 'popular' but they should contain a sufficiently broad survey of the field to give background to the reader."[133] Less than a decade later, Pauling found himself on the editorial board of *Chemical Reviews* as the editorial expert in the area of "theoretical physical chemistry."[134]

Although Pauling's three-year term on the editorial board (1936–39) had concluded by the time Kalckar submitted his manuscript, he maintained

128. Cohn, Interview (ref. 103), 51.

129. Ibid.

130. Lipmann's name does not appear in the acknowledgments of Kalckar's review, although those of the following scientists do: Linus Pauling, E. R. Buchman, C. D. Coryell, Henry Borsook, Hugh M. Huffman, C. B. van Niel, C. F. Cori, G. T. Cori, and S. P. Colowick. Kalckar, "Nature of Energetic Coupling" (ref. 5), 171.

131. Kalckar, "Nature of Energetic Coupling" (ref. 5). *Chemical Reviews* was founded in 1924. For its history, see Mary Ellen Bowden, "The Early History of Chemical Reviews: 'Established To Fill a Definite Want,'" *Chemical Reviews* 100, no. 1 (2000): 13–22.

132. Linus Pauling, "The Application of the Quantum Mechanics to the Structure of the Hydrogen Molecule and Hydrogen Molecule-Ion and to Related Problems," *Chemical Reviews* 5, no. 2 (1928): 173–213.

133. Wendt to Pauling, 13 Mar 1928, Linus Pauling Personal Safe, Box 3, Folder 18, ALPP.

134. Ralph L. Shriner, "Chemical Reviews, 1924–1951," in *History of the American Chemical Society, Seventy-Five Eventful Years*, ed. Charles Albert Browne and Mary Elvira Weeks (Washington, DC: American Chemical Society, 1952), 406–09, on 408.

sufficient influence to see that Kalckar's review article was accepted. In late 1939, Pauling wrote to the new editor of *Chemical Reviews*, W. A. Noyes:

> We have had in the Biology Department here for some months a young Dane, Dr. Herman Kalckar, who has been studying diligently the problem of the chemical mechanism of biological syntheses . . . His ideas seem to me and to the other chemists here to be very good. He is now planning to collect the results of his investigations [and literature search] into a summarizing article . . . Would you be interested in publishing it in Chemical Reviews and if so when would you like to have the manuscript? Dr. Kalckar . . . is especially interested in publishing it in a journal like Chemical Reviews which reaches chemists as well as biologists.[135]

Noyes found Kalckar's proposed article to "be very worthwhile."[136] Kalckar finished the review in St. Louis, having sent Pauling writing updates from Missouri.[137] In June 1940, Kalckar apologized for his slow progress, explaining, "in the last two months I have not been in very good spirits for writing."[138] In his letter to Pauling accompanying the final manuscript, Kalckar acknowledged the critical encouragement from Caltech: "I am very glad for your corrections and for Dr. Coryell's extensive examination and excellent suggestions."[139]

Chemists like Pauling and Coryell were Kalckar's intended audience. The beginning of the published review reads: "The purpose of this review is to acquaint *chemists* with the great advances made recently in that branch of biological chemistry which is concerned with the chemical mechanism of cellular respiration and the nature of energetic coupling."[140] For chemists, "energetic coupling"—in the way that Kalckar used the concept—likely would not have conveyed much meaning, as it was predicated on peculiarities of biological thermodynamics. Indeed, Kalckar began by explaining to chemists that the chemical reactions occurring within biological organisms were often

135. Pauling to W. A. Noyes, 20 Dec 1939, Box 279, Folder 279.5, ALPP. The bracketed portion of this quotation was added in handwriting to the typed letter via a caret.

136. W. A. Noyes to Pauling, 27 Dec 1939, Box 279, Folder 279.5, ALPP.

137. See, for example, Kalckar to Pauling, 20 Mar 1940, Linus Pauling Correspondence, Box 70, Folder 70.5, ALPP.

138. Kalckar to Pauling, 13 Jun 1940, Linus Pauling Correspondence, Box 70, Folder 70.5, ALPP. Here, Kalckar was, perhaps, referring to his anxieties about the war and the fate of his family in his home country.

139. Kalckar to Pauling, 11 Oct 1940, Linus Pauling Correspondence, Box 70, Folder 70.5, ALPP.

140. Kalckar, "Nature of Energetic Coupling" (ref. 5), 72. Emphasis added.

much more complex than those that could be studied in laboratories.[141] One such reaction was biological synthesis, or the creation of complex biological molecules from simpler ones.

"Synthesis"—in many senses of the word—was the central thematic of Kalckar's review. Kalckar first sought to disabuse chemists of their assumptions about the meaning of the word "synthesis," as it did not mean the same thing to them as to biologists. Whereas organic chemists typically employed the word "synthesis" to indicate "the conversion of one substance into another more complex substance, regardless of thermodynamic concept," for biologists the term had a more specific thermodynamic meaning, almost always connoting "an increased free energy (positive ΔF) of some of the members of a given system."[142] In other words, biological syntheses did not occur spontaneously, but required an input of energy. To remain consistent with the laws of thermodynamics, biological syntheses, Kalckar explained, had to be "coupled," or linked, to reactions that produced the energy they required.[143] Adding another layer of complexity to the discussion, Kalckar informed his readers that another type of coupling needed to be factored in as well—that between oxidation/reduction reactions and phosphorylation, which he and Lipmann had studied in Copenhagen.[144] The principal aim of Kalckar's review was to synthesize available biochemical evidence for these two types of coupling, in order "to understand chemically how the energy of respiration and fermentations can be utilized for biological syntheses."[145]

The muscle metabolism work of Meyerhof et al. and Lundsgaard, with which Kalckar opened his review, was one of the most well-studied examples of both kinds of coupling.[146] Drawing on Meyerhof's heat values, Kalckar argued that "the pyrophosphate [PP] linkages in the adenine polyphosphates [e.g., ATP] represent 11,000 calories," whereas "[t]he free energy of ordinary

141. Ibid.

142. Ibid., 74.

143. Using the newly introduced terminology of Charles D. Coryell, Kalckar re-expressed this point more succinctly by writing that "exergonic" reactions were always coupled to "endergonic" reactions in biological systems. Ibid., 75. Coryell introduced the terms "exergonic" and "endergonic" to refer to negative and positive values for ΔF, respectively, suggesting that the older terms "exothermic" and "endothermic" be used to refer only to negative and positive values for changes in heat (ΔH), respectively. See Charles D. Coryell, "The Proposed Terms 'Exergonic' and 'Endergonic' for Thermodynamics," *Science* 92, no. 2391 (1940): 380.

144. Kalckar, "Nature of Energetic Coupling" (ref. 5), 74.

145. Ibid., 73.

146. Ibid.

phosphoric esters" was "about 1000 to 2000 calories."[147] In order to explain the different thermodynamic properties of these two groups of phosphate compounds, Kalckar argued for the broad applicability and explanatory power of the concept of chemical resonance. Pauling's impact on Kalckar's thinking is particularly apparent here. Resonance theory was a key part of the way in which Pauling "translated" quantum mechanics for chemists, and his promotion of the theory and flair for presentation appear to have made quite an impact on Kalckar, if not directly, then certainly through Coryell.[148] Kalckar wrote in his review that his understanding of structural chemistry had been informed by G. N. Lewis's 1923 *Valence and the Structure of Atoms and Molecules* and, of course, by Pauling's 1939 *The Nature of the Chemical Bond*.[149] "A study of these two monographs," Kalckar wrote, "supplemented by discussions with Dr. Coryell, has led the author of this review to believe that the modern concepts of structural chemistry will actually be able to account for the thermodynamic properties of biological redox systems in general and phosphoric esters in particular."[150] After first describing the inverse relationship between chemical energy and stability (i.e., high energy = low stability and low energy = high stability), Kalckar explained that chemists had begun to assess molecular stability through resonance structures (the more possible resonance structures, the more stable the molecule). Extending this generality to the specific case of phosphate esters, Kalckar argued that "[t]he phosphoric esters which are rich in energy" suffered from a lack of added resonance stability due to a phenomenon that he called "opposing resonance."[151] Kalckar identified two resonance structures (labeled "Type A" and "Type B" in figure 1) that were not electronically possible because they opposed each other. In other words, the organic group on the left side of the phosphate ester and the phosphate group on the right side were "each making demands on the same atom [the middle oxygen] for the independent resonating systems."[152] Kalckar argued that the "instability of the ester in connection with the very high stability of the

147. Ibid., 125.

148. Buhm Soon Park, "Chemical Translators: Pauling, Wheland and Their Strategies for Teaching the Theory of Resonance," *The British Journal for the History of Science* 32, no. 1 (1999): 21–46; Kalckar, "Autobiographical Notes" (ref. 3), 115.

149. Gilbert Newton Lewis, *Valence and the Structure of Atoms and Molecules* (New York: The Chemical Catalog Company, Inc., 1923); Pauling, *Nature of the Chemical Bond* (ref. 84).

150. Kalckar, "Nature of Energetic Coupling" (ref. 5), 83.

151. Ibid., 127–128. In his discussion of "opposing resonance," Kalckar cited a "[p]ersonal communication from C.D. Coryell," on 128.

152. Ibid., 128.

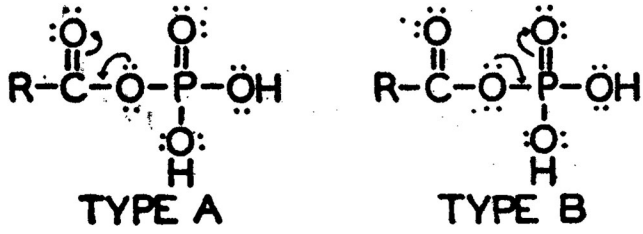


FIGURE 1. Kalckar's depiction of "opposing resonance." Reprinted with permission from H. M. Kalckar, "The Nature of Energetic Coupling in Biological Syntheses," *Chemical Reviews* 28, no. 1 (1941): 128. Copyright 1941 American Chemical Society.

hydrolyzed product is responsible for the large liberation of free energy when this kind of phosphoric ester is hydrolyzed."[153] Kalckar, therefore, mobilized the theoretical and structural chemistry he had been exposed to while at Caltech in order to shed new light on "energy-rich" phosphate esters and their general role in energy metabolism.

Phosphate compounds were also at the center of another main argument of Kalckar's review: the need for greater collaboration between life and physical scientists. Kalckar claimed that "[t]he recent revolutionary progress in our understanding of the coupling between oxidations and phosphorylations has led to new problems, particularly in the field of physical chemistry."[154] In particular, Kalckar suggested that more chemists should take up physical studies of biological molecules to understand how their chemical structures enabled energy to be stored and transferred.[155] He ended his review by proclaiming, "it would be a very great advantage for biological sciences if physicists and physical chemists would pay more attention to the fundamental well-defined chemical reactions which are the driving forces behind the various manifestations of life."[156] Kalckar's review thus argued both for the "energy-rich" phosphate bond as an important energetic unit in biological syntheses,

153. Ibid., 128–129. For more on Kalckar's application of resonance theory to biological molecules, see H. M. Kalckar, "The Function of Phosphate in Cellular Assimilations," *Biological Reviews* 17, no. 1 (1942): 28–45; Herman M. Kalckar, "Mesomeric Concepts in the Biological Sciences," in *Currents in Biochemistry*, ed. David E. Green (New York: Interscience Publishers, 1946), 229–40.

154. Kalckar, "Nature of Energetic Coupling" (ref. 5), 167.

155. Ibid., 167–168.

156. Ibid., 168.

and for the formation of closer disciplinary connections between biologists and physical chemists.[157]

THE POTENTIAL OF THE SQUIGGLE (~)

Lipmann's review appeared in the inaugural volume of *Advances in Enzymology* (February 1941).[158] In contrast to Kalckar, Lipmann wrote his review primarily for an audience of biochemists and physiologists, who sought to understand both the functional significance of biological energy transformations and their chemistry within the cell. While Kalckar used the terminology of theoretical chemistry he had picked up at Caltech, Lipmann largely neglected orthodox chemical and thermodynamic jargon. Rather, Lipmann sought to establish a new discourse for biological energy through the creation of new terms and notations.

Lipmann began his review by explicitly arguing that through the work of Meyerhof and colleagues, "[t]he biochemistry of the energy-rich phosphate bond was, in fact, herewith opened."[159] Although it was initially by studying muscle that researchers recognized the potential for phosphate compounds to be connected to energy generation, transfer, and utilization, there was no expectation that other tissues would use energy in the same way. As Lipmann wrote: "The metabolism of muscle is an almost unique case in nature of a straightforward utilization of chemical energy. Here the need of organization into a uniform type is understandable. In all other cells the energy problem is much more complex."[160] This difficulty notwithstanding, Lipmann marshaled evidence for the general role of phosphate bonds in all biological energy systems: "More and more clearly it appears," wrote Lipmann, "that in all cells a tendency exists to convert the major part of available oxidation-reduction energy into phosphate bond energy."[161] Generalization of "phosphate bond energy" beyond muscle was thus a major goal of Lipmann's review.

157. Although one of Kalckar's final sections was called "The significance of phosphorylation in living cells," he did not put forth a comprehensive physiological explanation of the function of phosphorylation, but instead explored whether results obtained from cell extracts could also be considered valid for living cells.

158. Lipmann, "Metabolic Generation" (ref. 5).

159. Ibid., 100.

160. Ibid., 102.

161. Ibid.

Lipmann adopted three strategies in his review to argue that "phosphate bond energy" is the common and uniform source of energy throughout the biological world: (1) the coining of new terms/the repurposing of old terms; (2) the creation of a new symbol; and (3) the construction of a new vision of the cell. First, Lipmann decided that the available chemical language was not sufficient for his purposes. He advanced the new term "group potential" in the early pages of his review, distinguishing his approach from that of researchers who used "the usual chemical nomenclature."[162] Chemists, Lipmann explained, typically differentiated between "weak" and "strong" chemical linkages—or bonds—according to the following criteria. Bonds considered to be "weak" were characterized as having a tendency to break and to release a large amount of energy upon this cleavage. "Weak" bonds, therefore, quite easily facilitated the transfer of functional groups from one molecule to another. "Strong" bonds, by contrast, could be thought of as more or less opposite in each of these respects. In Lipmann's estimation, this terminology focused chemists' attention away from another related feature of chemical bonds that was of substantial biological importance: the potential energy housed within the bond before it was broken. It was this latter characteristic of chemical bonds that Lipmann associated with his new term "group potential." As Lipmann explained:

> Now, very often the biochemist and likewise the synthetic organic chemist is not interested to talk so much about the weakness of the linkage by which a group is bound as about the energy accumulated in the linkage. Instead of emphasizing the negative, the escape of energy through cleavage, he wants to emphasize the positive, the largeness of the energy present in the linkage before cleavage, which determines the *group potential*, the escaping tendency of the group.[163]

What Lipmann called "energy-rich" bonds had high group potentials, whereas "energy-poor" bonds had low group potentials. "Such clarification," Lipmann wrote, "seems desirable since useful terms like energy-rich linkage and group potential will be unfamiliar to workers used to the common nomenclature."[164]

In addition to coining new terms such as "group potential," Lipmann also used a common chemical term, "bond energy," in a way highly unconventional for chemists. "Bond energy," as it appeared throughout his 1941 review,

162. Ibid.
163. Ibid., 102–03, emphasis in original.
164. Ibid., 103.

reversed the then-accepted meaning of the term. Chemists had been in the habit of using the term "bond energy" to indicate the *input* of energy needed to break a bond. In this orthodox formulation, a high bond energy value indicated a strong (stable) bond. Lipmann, however, deployed the term "bond energy" to indicate the potential energy "stored" within a bond, or the energetic *output* available from the breakage of a bond. In the context of Lipmann's usage, a high bond energy value meant a weak (unstable) bond.[165] After the publication of his review, Lipmann remembered that "chemists were outraged by what they felt was a misuse of the term *bond energy*."[166]

The second strategy that Lipmann adopted was to reinforce his new usage of the term "bond energy" through the creation of a novel symbol, ~, which came to be known as the "squiggle." Lipmann used ~ to indicate his notion of an "energy-rich" bond, that is, a bond with high group potential. "Energy-poor" bonds (low group potential), in turn, were assigned the standard straight-line bond symbol, –. Following his explication of these new terms and symbols, Lipmann put them to use in an analysis of phosphate bonds. There existed, Lipmann argued, two basic types of phosphate bonds: one rich in energy and high in group potential, the other poor in energy and low in group potential. Like Kalckar, Lipmann compiled and analyzed the then-available phosphate bond thermodynamic data from various sources (especially from the work of Meyerhof and colleagues), and was able to estimate that the group potential of "energy-poor" phosphate esters was likely somewhere in the range of 2,000–4,000 calories, whereas that of "energy-rich" phosphate esters was likely in the range of 9,000–11,000 calories.[167]

A third and final strategy that Lipmann deployed—which differentiated his review considerably from Kalckar's—was to articulate a vision of the cell within which his claims about the energetics of phosphate bonds could be situated. Lipmann described his approach as "tak[ing] wholeheartedly the 'inside viewpoint' of the cell."[168] This was important, Lipmann argued, because "[c]hemical reactions occurring in living cells are part of cell procedures. A procedure implies purpose and design, and to approach the understanding of cell procedures their purposefulness has to be taken into consideration."[169] Lipmann's invocation of the language of "purpose" here

165. Lipmann, *Wanderings* (ref. 14), 37; Lipmann, "Fifty Years of ATP" (ref. 6), 288.
166. Lipmann, *Wanderings* (ref. 14), 37, emphasis in original.
167. Lipmann, "Metabolic Generation" (ref. 5), 103–110.
168. Ibid., 148.
169. Ibid.

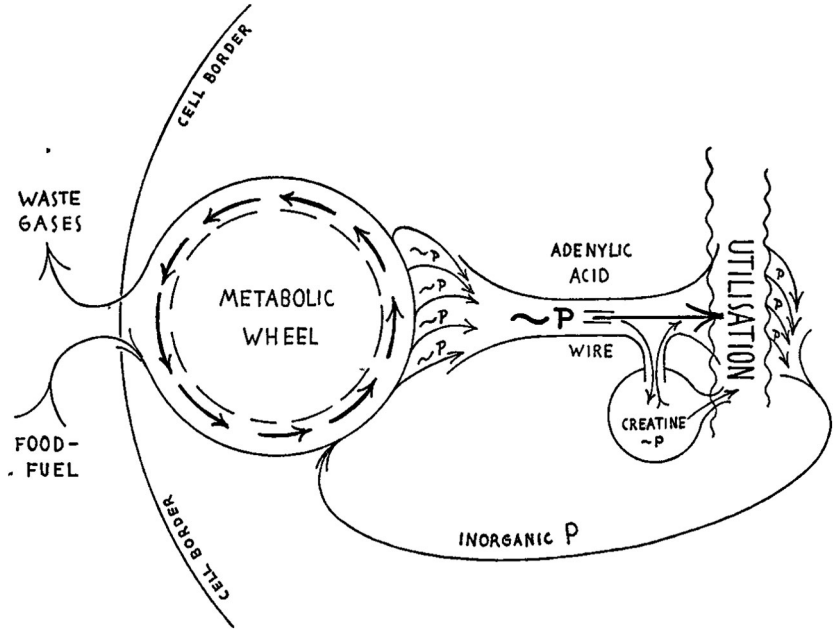


FIGURE 2. Lipmann's "Metabolic Wheel." Reprinted with permission from Fritz Lipmann, "Metabolic Generation and Utilization of Phosphate Bond Energy," in *Advances in Enzymology and Related Subjects*, ed. F. F. Nord and C. H. Werkman, vol. 1 (New York: Interscience Publishers, 1941), 122. Copyright © 1941 by Interscience Publishers, Inc.

is very reminiscent of Meyerhof's approach to biological energetics. And in placing more significance in biological function than in the chemical reactions themselves, Lipmann identified his main audience as biological scientists, a group distinct from the chemists that Kalckar was trying to reach. For biologically oriented thinkers, Lipmann outlined and illustrated (see figure 2) the following steps through which the ~ ph cycle coordinated all of cellular metabolism:

> (1) introduction of inorganic phosphate into ester linkage, (2) generation of energy-rich phosphate bonds (~ph) by oxidation-reduction, (3) the taking over and distribution of ~ph by cell catalysts (e.g., adenylic acid), (4) utilization of ~ph and the regeneration of inorganic phosphate.[170]

The consideration of Lipmann's depiction of "energy-rich" phosphate bonds as functional units within the cell (figure 2) alongside Kalckar's representation

170. Ibid., 121–122.

of the same bonds as "opposing resonance" structures (figure 1) reveals the essence of the two men's divergent approaches. For Lipmann, the role of "energy-rich" phosphate bonds in energy metabolism could not be understood outside of the physiological context of the biological cell. For Kalckar, the structural and chemical properties of these bonds were sufficient to infer their biological significance.

THE SQUIGGLE AS BIOCHEMICAL "SLANG"

In the immediate aftermath of the publication of Lipmann's and Kalckar's reviews, other scientists began to link the two papers together via their shared claims about "energy-rich" phosphate bonds. Max Delbrück, for example, was one of the earliest to cite Lipmann's and Kalckar's reviews together in a paper presented in the summer of 1941.[171] Although the two reviews were quickly connected to one another in the scientific literature, Lipmann's contribution received much more criticism than did Kalckar's. Lipmann remembered that he "had many bad hours over being told that this was all wrong and that there was nothing like energy-rich phosphates or energy-transferring molecules."[172] Disapproval of Lipmann's arguments and terminology came mostly from chemists, one of whom wrote to Lipmann suggesting that he "rapidly retract all that nonsense."[173]

This criticism of Lipmann's ideas contributed to his increasing uncertainty about the future. Lipmann's wife recalled that Lipmann's "two years [in New York] were not happy," and that "[a]s the time neared the end, things really looked black" in terms of finding a position.[174] In early May of 1941, Lipmann expressed this insecurity to Cori: "Have only two months left with money, and nothing being done really."[175] Lipmann asked Cori if he might correspond with the Rockefeller Foundation on his behalf to seek support.[176] Cori subsequently wrote to C. B. van Niel, asking if there might be any suitable openings available for Lipmann out west. Cori described Lipmann as

171. M. Delbrück, "A Theory of Autocatalytic Synthesis of Polypeptides and Its Application to the Problem of Chromosome Reproduction," *Cold Spring Harbor Symposia on Quantitative Biology* 9 (1941): 122–26.

172. Lipmann, "Fifty Years of ATP" (ref. 6), 288.

173. Ibid.

174. Lipmann, "Life with Fritz" (ref. 50), 6.

175. Lipmann to Cori, 6 May [1941], FC050-S02-B01-F95, CCP.

176. Ibid.

"somewhat shy and sensitive" but possessing "sterling qualities" and a "lovable personality."[177] Kalckar also suggested Lipmann to van Niel, who was scouting for someone to study "the P metabolism of the cell nucleus." [178] Lipmann clearly had the support of his friends, but an opportunity arose to stay on the east coast as "an advising biochemist."[179] As Lipmann communicated to Cori: "Until just a week ago, everything was still uncertain . . . Now, finally another possibility appeared in Massachusetts General Hospital in Boston. And there I am going to be from July."[180]

In late spring of 1941, Kalckar was still working with the Coris in St. Louis but was also visiting different laboratories on the east coast to learn how to work with isotopes.[181] Kalckar ran across Lipmann's review article while at Columbia: "Some time [*sic*] in May 1941 I found in the library of the Department of Biochemistry at P and S, volume 1 of *Advances in Enzymology*, the monumental article by Fritz Lipmann on bioenergetics."[182] Kalckar felt a great deal of sympathy for his friend's take on biological energy and phosphate bonds. On his trip to Boston, Kalckar met Lipmann at his new laboratory at Massachusetts General Hospital and was eager to discuss these issues and to "listen to his thoughts."[183] Kalckar believed that Lipmann had intended "phosphate bond energy" and his other invented terms as useful heuristics for biologically oriented chemists, as a kind of biochemical "slang."[184] Kalckar also claimed that Lipmann's intended audience was indeed more physiologically aligned than his had been:

> In 1941 Lipmann decided that in order to make physiologists and biochemists aware of the new problem it would be necessary to express the gospel of phosphorylation in a clever slang: "phosphate bond energy," "energy-rich bond" or "~," "group potential"!—and to disregard the purity and austerity of classic thermodynamics.[185]

177. Cori to van Niel, 13 May 1941, FC050-S02-B02-F87, CCP.

178. Kalckar to Cori, 24 May 1941, FC050-S02-B01-F78, CCP.

179. Lipmann to Cori, 13 Jun 1941, FC050-S02-B01-F95, CCP.

180. Ibid.

181. Kalckar, "Autobiographical Notes" (ref. 3), 120. On the various uses of radioisotopes in biology, see Angela N. H. Creager, *Life Atomic: A History of Radioisotopes in Science and Medicine* (Chicago: University of Chicago Press, 2013).

182. Kalckar, "Autobiographical Notes" (ref. 3), 121.

183. Ibid., 122.

184. Ibid., 121.

185. Kalckar, "Lipmann and the 'Squiggle'" (ref. 87), 3.

By contrast, Kalckar's time at Caltech had discouraged him from using any chemically dubious phrases or terms.[186] Even after publishing his review, Kalckar remained fervent about reaching California's academic chemists. He wrote to Linus Pauling in March of 1941 to ask whether Caltech's one hundred reprints of his review could be circulated "to a number of chemists (see enclosed list) at California Institute of Technology and at some other universities in California."[187]

In September 1941, "A Symposium on Respiratory Enzymes" was held at the University of Wisconsin-Madison.[188] Taking place in the months following the publication of Lipmann's and Kalckar's reviews, this conference was attended by the two friends, in addition to Otto Meyerhof (who had fled Europe for America the previous year), Carl Cori, Dean Burk, Severo Ochoa, and coeditors of *Advances in Enzymology* F. F. Nord and C. H. Werkman. The role of phosphate bonds in intermediary carbohydrate metabolism was a prominent area of discussion among the participants. Both Meyerhof and Cori integrated Lipmann's terminology into their contributions to the symposium—"Intermediate Carbohydrate Metabolism" and "Phosphorylation of Carbohydrates," respectively—but neither cited Kalckar's review paper (though both referred to his experimental work). This indicates that Meyerhof and Cori, two of the most prolific biological energy researchers of the prewar period, likely found Lipmann's physiological presentation of the power of phosphate bonds more impactful (or perhaps more useful) than they found Kalckar's chemical formulation.

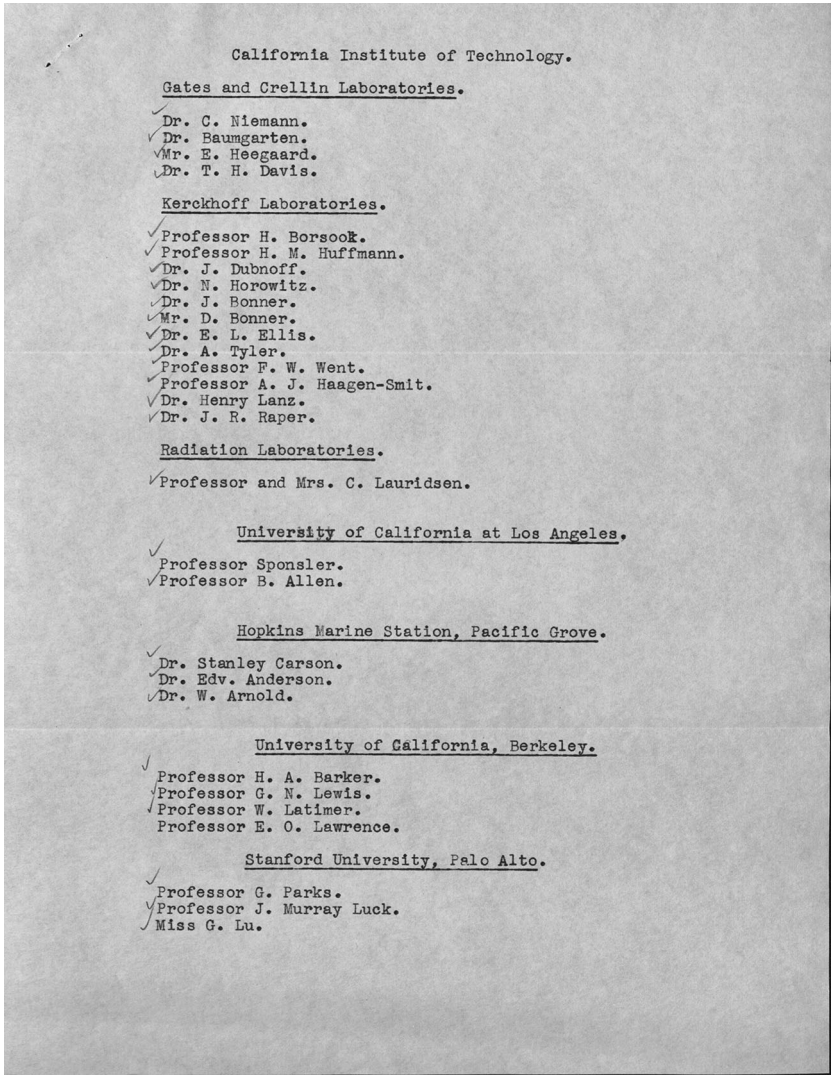
Over the subsequent years, however, Lipmann's concept of the "energy-rich" or "high-energy" phosphate bond continued to attract disapproval. Some authors critiqued the physicochemical basis of the "high-energy" phosphate bond, but like Kalckar, argued that the "terminology . . . is convenient and vivid."[189] Others were more pointed in their remarks, stating forcefully that the "concept of 'energy-rich' phosphate bonds . . . is irreconcilable with

186. Ibid., 2.

187. Kalckar to Pauling, 29 Mar 1941, Box 70, Folder 70.5, ALPP.

188. P. W. Wilson, ed., *A Symposium on Respiratory Enzymes* (Madison: University of Wisconsin Press, 1942). Just a few months earlier, Carl Cori had reviewed Lipmann's contribution favorably. See Carl F. Cori, "Review: Advances in Enzymology," *Science* 94, no. 2429 (1941): 67–68.

189. Terrell L. Hill and Manuel F. Morales, "On 'High Energy Phosphate Bonds' of Biochemical Interest," *Journal of the American Chemical Society* 73, no. 4 (1951): 1656–60, on 1659.



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Stanford University, Palo Alto.

Professor G. Parks.
Professor J. Murray Luck.
Miss G. Lu.

FIGURE 3. List of California chemists to whom Kalckar wanted reprints of his *Chemical Reviews* article sent. Enclosed with Herman M. Kalckar to Linus Pauling, March 29, 1941, Box 70, Folder 70.5, ALPP. Reprinted with permission from the Oregon State University Special Collections and Archives Research Center, Corvallis, Oregon.

physicochemical principles."[190] Kalckar's review was much less polarizing than Lipmann's, though Kalckar's use of "opposing resonance" did initially come

190. R. J. Gillespie, G. A. Maw, and C. A. Vernon, "The Concept of Phosphate Bond-Energy," *Nature* 171, no. 4365 (1953): 1147–49, on 1147.

under some scrutiny as researchers questioned whether this concept was actually a satisfactory chemical explanation for the special energetic properties of "energy-rich" phosphate bonds.[191] As biochemist Peter Oesper explained in 1950, "there has not yet appeared any clear explanation as to why certain phosphate compounds contain more energy than do ordinary ester phosphates."[192] For Oesper, Kalckar's initial 1941 presentation of "opposing resonance" had not been well described, and was possibly not as widely significant as Kalckar had originally suggested.[193] By 1960, however, the concept of "opposing resonance" became generally recognized as "playing a more or less important role in all types of energy-rich phosphates."[194]

Lipmann's biochemical slang, in spite of the physicochemical critiques, caught on among biochemists, in part due to its incorporation into reference works and pedagogical materials. For example, an entry on "Phosphate Bond Energy" (authored by Lipmann) was included in the 1943 *Dictionary of Biochemistry and Related Subjects*.[195] Lipmann's squiggle notation, in particular, was used in biochemistry textbooks for decades to come. Even critics of Lipmann's ideas acknowledged the widespread usage of the squiggle in teaching resources. In 1992 biology professor Richard D. Storey noted that "[t]he celebrated squiggly line (~) showing the putative high energy rich bonds of ATP . . . remains in many well-subscribed biology textbooks today," even as he disparaged Lipmann's squiggle as an example of a common "textbook error" in descriptions of cell bioenergetics.[196]

Over the years, Lipmann occasionally responded to his detractors through his writings. In 1960, for instance, Lipmann revived one of the original arguments of his review—biological specificity—in defense of his 1941 terminology:

> Chemical and biological definitions are becoming more and more confluent. In this situation, terminologies occasionally need a mutual adjustment for which some common sense has to be used. Cellular chemistry is part of

191. Terrell L. Hill and Manuel F. Morales, "Sources of the High Energy Content in Energy-Rich Phosphates," *Archives of Biochemistry* 29 (1950): 450–51.

192. Peter Oesper, "Sources of the High Energy Content in Energy-Rich Phosphates," *Archives of Biochemistry* 27 (1950): 255–270, on 255.

193. Ibid.

194. Bernard Pullman and Alberte Pullman, "Electronic Structure of Energy-Rich Phosphates," *Radiation Research Supplement* 2 (1960): 160–81, on 163.

195. William Marias Malisoff, ed., *Dictionary of Bio-Chemistry and Related Subjects* (New York: Philosophical Library, Inc., 1943), 403–06.

196. Richard D. Storey, "Textbook Errors & Misconceptions in Biology: Cell Energetics," *The American Biology Teacher* 54, no. 3 (1992): 161–66, on 162–63.

> a technology of a very special kind and this aspect often deviates from interests of pure chemistry. Thus, the term "energy-rich" bond and the ~ sign in the biological sense describe energy units in cellular metabolism. Their acceptance and wide use by biologically minded chemists shows the need for this type of description in the context of cellular chemistry.[197]

Nearly two decades after the first appearance of his review paper, Lipmann still believed that his insights about phosphate bonds were most effective when situated within the biological cell.

CONCLUSION

After the war, Lipmann remained in the United States, and Kalckar returned for a while to Copenhagen.[198] Learning of Kalckar's impending departure, Lipmann wrote to him in 1946:

> Dear Kalckar: I wanted to write you a specially [nice] farewell letter and finding myself rarely in the right frame of mind and being anyway very [lazy], I see it is now more than a week ago that I received your letter telling that you are definitely leaving now. From my extensive experience as a wandering Jew, I have developed a great appreciation of the good of really belonging somewhere and it is with some envy that I see you going back. There is something to it to speak a language you really understand & speak and to feel rightly at home. It eats on you in the long run otherwise. To me your leaving marks in a way the end of a period in my life—maybe you understand what I mean—and I had hoped to say goodbye to you, having some errand in N.Y., but it did not [work] out."[199]

197. Fritz Lipmann, "Attempts toward a Formulation of Biological Use of Energy in Terms of Group Potentials," in *Molecular Biology: Elementary Processes of Nerve Conduction and Muscle Contraction*, ed. David Nachmansohn (New York: Academic Press, 1960), 37–47, on 37.

198. While back home in Copenhagen, Kalckar became the postdoctoral advisor of James D. Watson, who travelled to Denmark so that Kalckar could teach him biochemistry. This pairing did not work out, however. Kalckar, who makes a cameo in Watson's *The Double Helix*, was described by Watson as difficult to understand, absent from the lab, and on the brink of divorce. See James D. Watson, *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*, ed. Gunther S. Stent, A Norton Critical Edition, with Text, Commentary, Reviews, Original Papers (New York: Norton, 1980), 17–31.

199. Lipmann to Kalckar, 15 Jan 1946, Box 1, Folder 3, HKC. The bracketed words in this quotation indicate handwriting that was difficult to read. Other German émigré scientists of Lipmann's generation shared similar sentiments related to the loss of their native German language, as described in Michael D. Gordin, *Scientific Babel: How Science Was Done before and after Global English* (Chicago: University of Chicago Press, 2015), 201–10.

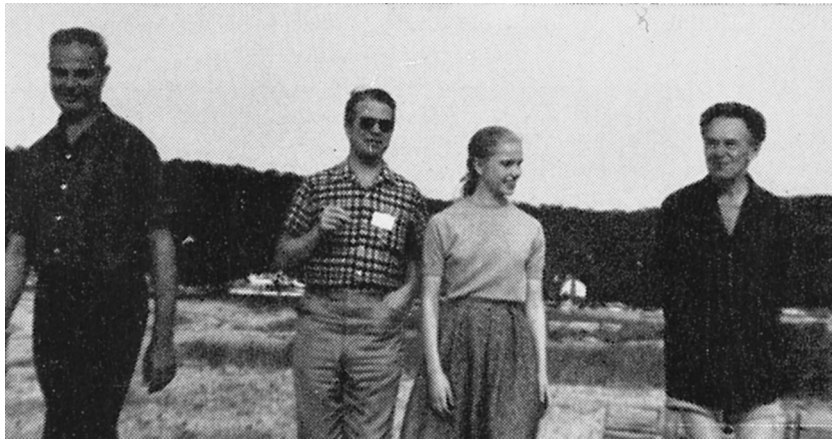

FIGURE 4. Lipmann and Kalckar together at the 1961 Cold Spring Harbor Symposium on Quantitative Biology. Left to right: Herman Kalckar, Ole Maaløe, Miss Maaløe, Fritz Lipmann. Courtesy of Cold Spring Harbor Laboratory, New York.

Perhaps Kalckar did understand what Lipmann meant. The two friends had been bonded together through their common interest in phosphate bonds—and through their shared experiences of being European Jews in the 1930s—for nearly a dozen years. For most of this time, Lipmann and Kalckar had lived lives of great uncertainty and instability. As European émigré scientists, they had spent many years moving from temporary position to temporary position, often wondering how they would support themselves financially. Indeed, itinerancy became the main framework through which they later understood their own lives; the titles of Lipmann's and Kalckar's main autobiographical writings are *Wanderings of a Biochemist* and "Autobiographical Notes from a Nomadic Biochemist," respectively.[200] Having lived through such turbulent times in which they experienced firsthand the fragility of personal and professional bonds, it is no wonder that Lipmann and Kalckar did all they could to forge new bonds in place of those that had broken.

The parallel consideration of Lipmann's and Kalckar's itinerant lives brings into view certain commonalities that help to elucidate the circumstances behind their "simultaneous discovery" of "energy-rich" phosphate bonds: their similar research programs and close connections to Einar Lundsgaard in Copenhagen, their timely interactions with Carl Cori once they had reached the United States, and that phosphorylation did not seem to be a topic of

200. Lipmann, *Wanderings* (ref. 14); Kalckar, "Autobiographical Notes" (ref. 3).

interest in their immediate new American academic environments, to name a few. But certain differences, particularly with regard to formative institutional contexts, also stand out. For Lipmann, who was nearly a decade older than Kalckar, the formative period was the three years he spent at the end of his twenties in Meyerhof's laboratory. There, Lipmann was at the epicenter of the rapidly changing knowledge about biological energy, muscle contraction, and phosphate compounds. He was also exposed to Meyerhof's physiological way of thinking about energy transformations, and this prioritization of biological purpose pervades his 1941 review. The formative period for Kalckar also began during his late twenties, when he studied with Lundsgaard and Lipmann in Copenhagen, and extended into his early thirties when he moved to Caltech. In California, Kalckar's thinking about phosphate bonds was shaped by his interactions with Pauling, Coryell, and Borsook. His reliance on theoretical chemistry in his 1941 review demonstrates clearly the importance of this institutional context.

If Lipmann explained the role of "energy-rich" phosphate bonds by looking back toward older physiological traditions, Kalckar described the same bonds with an eye toward the future potentialities of recent developments in theoretical chemistry. Lipmann's and Kalckar's review articles "d[id] not merely provide information on what [wa]s known and accepted," but rather interpreted the same body of published work through different disciplinary lenses to ultimately advance "new knowledge claims" about phosphate bonds.[201] The review genre's synthetic nature allowed Lipmann and Kalckar to reflect upon their personal and professional histories, while its flexibility provided opportunities for each to move the field of biological energy metabolism in new directions (even when their unstable work situations might have restricted their experimental output in this area). In the end, the life stories behind Lipmann's and Kalckar's reviews shed a great deal of light on how the power of phosphate bonds was translated for and made legible to both biological and physicochemical audiences.

201. Christiane Sinding, "Literary Genres and the Construction of Knowledge in Biology: Semantic Shifts and Scientific Change," *Social Studies of Science* 26, no. 1 (1996): 43–70, on 57.

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