KALCKAR, HERMAN MORITZ (b. Copenhagen, Denmark, 26 March 1908; d. Cambridge, Massachusetts, 17 May 1991), biochemistry, enzymology, molecular biology.

Kalckar’s biochemical contributions were multifaceted. His initial work opened an investigative pathway to what has come to be called oxidative phosphorylation. As a mature investigator, he utilized his laboratory to play a significant role in the rapidly evolving field of enzymology, and Kalckar introduced innovative ways of measuring enzymatic activity. A significant part of his enzymological work focused on galactose metabolism, and he was one of the first investigators to clarify the nature of the genetic disorder galactosemia. Like many twentieth-century biochemists, Kalckar did not restrict his work to any single organism or tissue, and he contributed equally to the understanding of microbial physiology and human diseases.

Early Life and Education. Kalckar was the middle of three sons and described his early family life as “a middle-class, Jewish-Danish family—Danish for several generations.” While not financially wealthy, his family life was intellectually rich and allowed Kalckar’s “interest in the humanistic disciplines” to develop and thrive. His businessman father, Ludvig, had an avid interest in the theater and described seeing the 1879 world premiere of Henrik Ibsen’s A Doll’s House. His mother, Bertha Rosalie (née Melchior), was fluent in both German and French and introduced Kalckar to writers such as Gustave Flaubert, Marcel Proust, Johann Wolfgang von Goethe, Heinrich Heine, and Gotthold Ephraim Lessing. Although the family members were “mainly free-thinkers” and his father was primarily secular, his mother was more observant and encouraged some religious education. Thus, Kalckar learned “a minimum of Hebrew” at the Copenhagen main synagogue (Kalckar, 1991, p. 2).

Kalckar attended the Østre Borgerdyd Skole, located a short distance from home, which he described as “interesting and rewarding” and having an “Athenian flavor,” a characteristic that arose from the headmaster, a world-renowned Greek scholar. His early scientific education also benefited from “a formidable and passionately devoted teacher in mathematical physics,” who significantly influenced Kalckar’s decision to pursue a career in research and teaching. The Danish Nobel Prize–winning (Physiology or Medicine, 1920) physiologist August Krogh shaped Kalckar’s biological interests by some human physiology demonstrations. Kalckar commented that Krogh was “the only physiologist in the 1920s who took an active interest in introducing the principles of human physiology to Danish high school boys.” The demonstrations were apparently elaborate, as Krogh used a number of research instruments from his own research program (Kalckar, 1991, pp. 2–3).

Kalckar’s younger brother, Fritz, was a physicist and a student/colleague of Niels Bohr. Herman Kalckar also knew Bohr and was close friends with the Bohr family (his son Niels Kalckar was named after Bohr). In 1937 Fritz Kalckar died from a status epilepticus attack while in California. The Bohr family provided personal comfort to the Kalckar family, and Niels Bohr gave a eulogy at Fritz’s cremation service (Kalckar, 1991, p. 8). The close Bohr friendship may explain the intense chemical focus that Kalckar brought to biological problems.
Kalckar

In 1933 Kalckar completed medical studies at the University of Copenhagen and the following year began graduate studies in the Department of Physiology. His research mentor was Ejnar Lundsgaard. In the early 1930s, Lundsgaard revolutionized the way physiologists understood cellular energetics by demonstrating that phosphocreatine was involved in muscle contraction. Several simultaneous events happened when Kalckar joined Lundsgaard’s lab. The biochemist Fritz Lipmann was forced to leave Germany, and Lundsgaard offered him a position in Copenhagen. Also, Lundsgaard became physiology department chair, and thus his time was more restricted. Consequently, Lipmann became Kalckar’s primary mentor and encouraged him to read “the newer literature on carbohydrate and phosphate metabolism in isolated phosphorylation tissue extracts or tissue particle preparations” (Kalckar, 1991, p. 5).

Kalckar began his research career at an important period in biochemistry’s history. Eugene Kennedy observed that the central question facing many biologists at the time was: “How is energy captured by the oxidation of sugars and other foodstuffs linked to the reduction of molecular oxygen?” (1996, p. 151). Kalckar very indirectly set about to address this question and decided to study phosphate and carbohydrate metabolism in kidney cortex extracts.

His use of kidney cortex tissue seems a bit surprising because many workers at the time (including Hans Krebs) were working with minced pigeon breast muscle. Kalckar stated that one reason for his choice of tissue was his mentor’s interest in carbohydrate transport in the kidney, a process thought “to be driven by phosphorylation-dephosphorylation cycle in the membrane.” Thus, Kalckar “set out to scout for a really vigorous phosphorylation system that could drive” carbohydrate transport in the kidney cortex (Kalckar, 1969, p. 171). Later, Kalckar explained that in order to study pigeon tissue he would have to train himself to decapitate pigeons, however he “greatly preferred to avoid killing animals, probably from a lack of courage.” He was fortunate to obtain fresh cat and rabbit kidneys from the weekly physiology department perfusion experiments (Kalckar, 1991, p. 6).

Using Otto Warburg’s manometric technique and apparatus, Kalckar began to measure relationships between oxygen utilization and phosphorylation in minced kidney tissue. Few modern investigators can appreciate the multitude of difficulties associated with this experimental approach, which required measuring changes in extremely small volumes of gases. The apparatus was standard biochemical equipment for much of the twentieth century; nevertheless, Efraim Racker half jokingly referred to the apparatus as “nystagmus inducing” (1965, p. 19). Regardless, Kalckar’s choice of this experimental approach was important, because in the Warburg apparatus the minced tissue was continuously exposed to high oxygen levels.

Kalckar noted that his “studies on phosphorylation and respiration in kidney cortex extracts turned out to be rewarding” (1991, p. 6). Prior to his work, researchers were investigating various pathways whereby carbohydrates are oxidized to products such as lactic acid. These oxidations involved a number of phosphorylation reactions and produced a phosphorylated compound, ultimately identified as adenosine triphosphate (ATP). Referred to as “glycolysis,” these reactions occurred in the absence of oxygen. While a variety of phosphorylated compounds were produced in addition to ATP, the role of phosphorylation was not understood; most biochemists believed that the phosphate group somehow made the compound more “fit” for reaction.

In a series of papers published between 1937 and 1939, Kalckar established that in kidney cortex tissue slices these phosphorylation reactions were “coupled” with oxygen consumption. In these experiments, Kalckar suspended minced kidney cortex in phosphate buffer, which was then incubated with various carbohydrates in a Warburg apparatus. At various times O₂ consumption was manometrically determined and inorganic phosphate (Pᵢ) was chemically measured. In the presence of O₂, Pᵢ levels were significantly reduced, whereas under anaerobic conditions no Pᵢ was consumed. Carbohydrate (e.g., glucose) was also required for Pᵢ consumption. The process, which Kalckar referred to as “aerobic phosphorylation,” was the first direct demonstration that carbohydrate oxidation was directly “coupled” to carbohydrate phosphorylation (Kalckar, 1937; 1939; 1969, pp. 171–172); the process, later referred to as oxidative phosphorylation, is fundamental to life, and Kalckar’s work helped establish the basic phenomenon and opened the way to its systematic exploration (Kennedy, 1996).

Early Career. Kalckar completed work for his PhD in 1939 and in January received a Rockefeller research fellowship to spend a year at the California Institute of Technology (Caltech). After a brief visit in London, Kalckar spent much of February in St. Louis visiting Carl and Gerty Cori’s Washington University laboratory, which was then doing some of the most innovative biochemical work in the United States. The Cori lab had, unsuccessfully, tried to reproduce some of Kalckar’s published work. Kalckar noted that in their technique, which involved “the old-fashioned Meyerhof extract technique, using test tubes,” the tissue extracts were static. In Kalckar’s technique, using the Warburg manometer, the tissue extract was vigorously shaken and thus highly aerated. Kalckar worked with the Coris’ graduate student, Sidney...
Colowick, and quickly demonstrated that when the cortex extracts were shaken, oxidative phosphorylation was easily observed (Kalckar, 1991, p. 10).

In early March 1939, Kalckar arrived in Pasadena, where he and his wife Vibeke Meyer rapidly became involved in the Caltech intellectual and social community, which included Max Delbrück, Linus Pauling, and two Bonner brothers, James and David. The Delbrück friendship, which had initially begun with a brief Copenhagen meeting, became lifelong. The Bonner brothers introduced Kalckar to various members of the Caltech faculty, and helped Herman and Vibeke settle into an American life by arranging housing and the purchase of a car.

Most likely at Delbrück’s encouragement, Kalckar attended Cornelius B. van Niel’s popular microbiology course taught at Pacific Grove. Van Niel was responsible for introducing numerous American scientists to the complexity of the microbial world. As a student of Albert Jan Kluver, van Niel spread the gospel of biochemical unity, which Kluver expressed in the aphorism, “From the elephant to the butyric acid bacterium it is all the same!” (Kamp et al., 1959, p. 20). The Pacific Grove experience “may have planted a seed that led later to Kalckar’s interest in microbial molecular biology” (Kennedy, 1996, p. 153). Throughout his career, Kalckar, like many of his contemporaries, frequently turned to bacterial systems to address questions unresolvable in more complex biological systems.

The Pauling connection proved especially valuable. Most likely from his familiarity with Bohr’s atomic concepts, Kalckar was influenced by the potential impact of Pauling’s chemical ideas on biological problems. At Pauling’s encouragement, Kalckar wrote an extensive review in which he developed many of our modern concepts of bioenergetics, including the notion that oxidation reactions are “coupled” to phosphorylation reactions via ATP (Kalckar, 1941).

Although not widely appreciated at the turn of the twenty-first century, Kalckar’s 1941 Chemical Reviews paper influenced the way many scientists thought about the energetics of life processes. One reason for this lack of appreciation perhaps lies in the fact that Fritz Lipmann also published a similar paper, in which he developed the “high energy bond” concept, in 1941. While the Kalckar paper was influential in shaping scientists’ views about bioenergetics, the Lipmann paper was more frequently cited. Nevertheless, Kalckar viewed his relationship with Lipmann as collaborative, stating: “While Lipmann was preaching the gospel of phosphorylation and the ‘high energy phosphate bond’ on the eastern seaboard ... I was beginning my missionary work at the same time in the ‘Pacific triangle’—Caltech, Berkeley, and Stanford” (Kalckar, 1992, p. 43).

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The outbreak of World War II, and German occupation of Denmark, stranded the Kalckars in the United States. Because of his earlier visit in the Cori lab, in 1940 Kalckar received an appointment as research fellow in the Pharmacology Department at Washington University, and he and Vibeke moved to St. Louis. Kalckar resumed work with Colowick studying phosphorylation reactions in muscle tissue. The work was important in terms of Kalckar’s scientific maturation for two reasons: first, he began to focus more on individual enzymatic reactions, even partially purifying the responsible protein, than he had previously; second, he and Colowick discovered the enzyme myokinase (now called adenylate kinase), which catalyzed the reversible reaction:

\[
\text{ATP} + \text{AMP} \rightleftharpoons 2 \text{ADP} \quad (\text{Reaction 1})
\]

Because many biochemical processes led to adenosine monophosphate (AMP) production, the enzyme was important in helping replenish cellular levels of ATP. Shortly after the collaboration began, Colowick was drafted to do war research, and Kalckar finished the myokinase characterization by himself.

In 1943 Oliver Howe Lowry invited Kalckar to join his lab at the New York Public Health Institute as a research associate. The appointment helped advance Kalckar’s enzymology research in part because, as Paul Berg commented, Kalckar “developed a whole new approach to being able to use enzymes in a novel way” (2000, p. 26). The lab had a new, and relatively rare, Beckman DU ultraviolet spectrophotometer, and Kalckar rapidly became a virtuoso of the instrument, using it to develop a number of novel enzyme assay techniques. The work culminated in a series of three papers on purine metabolism enzymes (Kalckar, 1947a, b, c). All three papers were highly cited (3,200 citations in 2006), and the third paper was recognized as a “Citation Classic” in 1984. In a brief commentary on the paper, Kalckar noted that the paper’s popularity most likely arose from its potential clinical applications such as diagnosing diseases such as arthritis urica or Lesch-Nyhan syndrome, a serious inborn metabolic error in infants (Kalckar, 1984).

Return to Denmark. When the war ended, Lundsgaard arranged for Kalckar to return to Copenhagen in 1946 where he ran the new Cytofysiologisk Institute, funded by the Rockefeller Foundation, Lederle Laboratories, as well as the Danish Carlsberg Foundation. His research focused primarily on the enzymology of nucleoside and nucleotide metabolism, and the lab rapidly became a magnet attracting numerous bright young biochemists from around the world, including Americans such as Paul Berg, Morris Friedkin, Walter McNutt, Günter Stent, and James Watson.
Shortly after his return to Copenhagen, Kalckar's marriage to Vibeke dissolved. He married Barbara Wright, a developmental biologist and American postdoctoral fellow in his lab. Three children, Sonja, Nina, and Niels, were born of this marriage (Kennedy, 1996).

In early 1950, Kalckar suggested that such nucleotides as uridine diphosphate (UDP), UDP-glucose, or UDP-galactose were involved in the conversion of glucose-1-P to galactose-1-P, and his laboratory began to focus on galactose metabolism in microbial and animal tissues, a research program that dominated the rest of his career.

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Return to the United States. Bernard Horecker, at the National Institutes of Health (NIH), invited Kalckar to come to Bethesda, Maryland, as a visiting scientist in 1952; later the appointment was made permanent in the National Institute of Arthritis and Metabolic Diseases. At the NIH, Kalckar expanded his research program on galactose metabolism and developed an interest in the genetic disease, galactosemia. The disease, which is characterized by liver enlargement, kidney failure, and mental retardation, occurs because of galactose (formed from the milk component lactose) accumulation. In untreated infants, mortality is as high as 75 percent. The prevailing view on galactosemia in 1952 is summarized in Reactions (2) through (4).

\[
\text{Lactose (in milk) } \rightarrow \text{ Glucose + Galactose (Reaction 2)}
\]

\[
\text{Galactose + ATP } \rightarrow \text{ Galactose-1-P (Gal-1-P) (Reaction 3)}
\]

\[
\text{Gal-1-P } \rightarrow \text{ Glucose-1-P (Reaction 4)}
\]

Reaction 3 is catalyzed by an enzyme called an "epimerase," and investigators speculated that galactosemia arose from a defect in this enzyme (which would lead to galactose accumulation via reversal of Reaction 3).
For a variety of reasons, Kalckar suspected another enzyme was defective; he thought the enzyme blocked was Galactose-1-P uridyl transferase (GALT), which catalyzes Reaction 5:

$$\text{Gal-1-P} + \text{UDP-glucose} \rightarrow \text{UDP-galactose} + \text{Glucose-1-P}$$ (Reaction 5)

If this enzyme was not functioning, Gal-1-P would accumulate leading to galactose build up through reversal of Reaction 3. Although galactosemia is relatively rare, Kalckar’s associates were able to identify several afflicted individuals and obtain blood samples from them. If Kalckar’s hypothesis was correct, the analysis should show two features. First, individuals with the disease should have decreased levels of GALT. Second, epimerase levels in afflicted individuals should be normal. Both features were observed in blood samples from galactosemia patients when compared with normal subjects (Kalckar, et al., 1956a and b).

In addition to a rich scientific environment, the NIH community offered personal advantages. Unlike many institutions at the time, the NIH had no official prohibitions regarding employing scientific couples; thus Kalckar’s wife, Barbara Wright, also had a staff appointment. The environment was both intellectually and socially rewarding. Other married couples working at the NIH at the same time included: Thressa and Earl Stadtman; Marjorie and Evan Horning; and Martha Vaughan and Jack Orloff (Park, 2002).

In 1958 William McElroy offered Kalckar a full professorship in biology at Johns Hopkins University, where his biochemical interests in galactose metabolism continued. Perhaps reflecting the long-term influence of van Niel’s course, his research focus shifted to bacterial systems.

While at Hopkins, Kalckar suggested (in a Nature paper) that the effects of isotope fallout from nuclear weapons testing could be measured by analysis of strontium-90 levels in children’s deciduous teeth (Kalckar, 1958). The proposal was both important and original and elicited numerous state and local organizations to collect teeth for analysis; the data did indeed show a correlation between isotope levels and nuclear testing. Arguably the resulting program helped encourage public sentiment to ban atmospheric nuclear weapons testing.

In 1961 Kalckar moved again, to the Harvard Medical School where he was Henry S. Wellcome Research Biochemist and headed the Massachusetts General Hospital Biochemical Research Laboratory, a position previously held by Fritz Lipmann. His research program continued to focus on bacterial galactose utilization, however it tended to become more physiologically oriented (Wellcome Trust, 1963, p. 16). He became interested in cellular sensory and signaling processes. For example, in collaboration with Winfried Boos, he isolated a galactose binding protein in Escherichia coli that played an important role in cellular galactose transport. Later work demonstrated that the same protein played an important role in E. coli’s chemotactic response to galactose.

The Boston move also had significant personal ramifications for Kalckar: his marriage to Barbara Wright dissolved; he renewed a friendship with Agnete Fridericia, whom he had known as a student in Copenhagen. Kalckar commented that their “cheerful conversations during the 1960s, most of it in Danish, changed [his] life”; in 1968, he and Agnete were married (Kalckar, 1991, p. 27).

Kalckar retired as head of the Biochemical Research Laboratory in 1974 but remained at Massachusetts General as visiting professor. In 1979 he was appointed as a distinguished research professor in the Boston University chemistry department, a position that permitted him to continue his research work for the rest of his life (Kennedy, 1996, p. 159).

In a scientific career that spanned almost six decades of the twentieth century, Herman Kalckar witnessed many fundamental changes in biochemistry. Although urease had been crystallized in 1926, in 1934—when Kalckar began his graduate studies—some biochemists were still debating the nature of enzymes. At his death, after having been a founder of modern bioenergetics and enzymology, he was studying the genes responsible for enzyme action. These achievements received numerous recognitions: he was elected to the National Academy of Sciences, the Royal Danish Academy, and the American Academy of Arts and Sciences; he received honorary degrees from Washington University, the University of Chicago, and the University of Copenhagen.

On a personal level, Kalckar often appears enigmatic. On the one hand, Eugene Kennedy noted “The sweep of his intellect was very broad, his spirit was open and generous, and he had a wonderful sense of humor” (Kennedy, 1996, p. 160). Former associates speak fondly of exciting scientific discussions, which might be interrupted to talk about art, music, even Nordic mythology. As his work on strontium-90 levels in children’s teeth suggests, Kalckar was passionately concerned about social issues like the spread of nuclear weapons and weapons testing.

However, Kalckar was equally known for his peculiar way of talking, which some hearers found unintelligible. He would, for example, often begin an argument with a conclusion and work backward to the premises. Boos, his former associate, referred to this speech mode as a “language” he called “Kalckarian”: a language that Kalckar occasionally used to avoid conversations he found uninteresting.
Boos further observed that Kalckar divided the scientific world into two types. The Apollonian was a capable technician, who accumulated data to tell clear, logical stories, a perspective Kalckar found boring and lacking any sense of humor. The Dionysian, however, was more interested in the answers, even if they come in a dream, than in the logic and proof of the answer. For Boos, Kalckar “was the archetype of a Dionysian” (Boos, 1991, p. 8).

The term Dionysian can be used in another sense, related to the Roman incarnation of Bacchus, the God of wine and other pleasures. In this view, an individual is open to all that life offers and is not bound in a single worldview; Kalckar seems to fit this image as well. Science was one of life’s rich rewards; good music, good friends, a cornucopia of human experiences were equally valuable.

**WORKS BY KALCKAR**


**OTHER SOURCES**


**NEW DICTIONARY OF SCIENTIFIC BIOGRAPHY**


KAMMERER, PAUL (b. Vienna, Austria-Hungary, 17 August 1880; d. Puchberg am Schneeberg, Lower Austria, 23 September 1926), zoology, heredity, evolution.

The main goal of Kammerer’s research was to demonstrate the modifying power of the environment and the heritability of acquired characteristics, using the...