

Current Comments

To Remember Sir Hans Krebs: Nobel, Friend, and Adviser

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I was deeply saddened to hear of the death on November 22, 1981, of my friend and colleague, Sir Hans Krebs.¹ Krebs received the 1953 Nobel prize for his discovery of the citric acid cycle²—widely known as the Krebs cycle. He had become a good friend, although we never met in person. A longtime member of the *Science Citation Index*[®] (*SCI*[®]) editorial advisory board, Krebs was a wonderful source of moral and scientific support to me during the many years that it took for *SCI* to gain acceptance. He was also a regular reader of these essays and often suggested topics for my consideration. He occasionally contacted me with some kind words about an essay he particularly admired. And I will always cherish a letter he wrote in reaction to an essay memorializing my mother.³ This helps to explain how I could feel so close to a colleague through correspondence. I know that *Current Contents*[®] (*CC*[®]) readers everywhere have these kinds of friendships because science is so dependent upon written communication.

The impact of Krebs's work upon biochemistry was recently attested to by his longtime collaborator, biochemist Sir Hans Kornberg, University of Cambridge. In the pages of *New Scientist*, Kornberg wrote: "Of all the biochemists whose work has given us insight into the molecular events that characterize living matter, Sir Hans Krebs was indisputably

among the greatest."⁴ Kornberg will soon begin writing an official memoir of Krebs for the Royal Society of London. Those interested in Krebs's life and work will also find Krebs's recently published autobiography rewarding.⁵

Krebs was born August 25, 1900, in Hildesheim, a small town in the northern part of Germany. His mother was the former Alma Davidson and his father, Georg, an otolaryngologist. Hans was educated at the Hildesheim Gymnasium Andreanum. He intended to follow his father in a medical career and pursued his education in many universities, as was the custom of the day. Moving freely from one setting to the next, Hans studied at the Universities of Göttingen, Freiburg, Munich, and Berlin from 1918 to 1923. In 1924, he interned at the Third Medical University Clinic in Berlin. He received his medical degree from the University of Hamburg in 1925.⁵

According to Hermann Blaschko, the Oxford pharmacologist who profiled Krebs for his eightieth birthday *fest-schrift* issue of *FEBS Letters*, Hans was noticed by physician Bruno Mendel while interning in Berlin.⁶ It was Mendel who recommended Hans to Otto Warburg at the Kaiser Wilhelm Institute for Biology at Berlin-Dahlem. Warburg was an acclaimed scientist in his own right, who would win the Nobel prize in 1931 for his research into the respiratory enzyme.^{7,8} In his 1953 Nobel prize lecture,



Hans Krebs

Krebs acknowledged Warburg's influence. He stated that he learned more from Warburg than from any other single teacher,⁹ and eventually published a biography of his mentor.¹⁰

Although he had proved himself in the laboratory, Hans continued to seek a medical career. He obtained a position at the Municipal Hospital at Altona, a suburb of Hamburg, in 1930. In 1931, he became privatdocent of internal medicine at the University of Freiburg. (A privatdocent is a teacher who receives payment directly from students' fees.⁵)

At Freiburg, Hans also found time for laboratory work. He collaborated with a student, Kurt Henseleit, to produce the classic paper that demonstrated how ammonia is converted to urea in animals.¹¹ This paper immediately established Krebs's reputation. In Blaschko's analysis, "It gave the answer to an important unsolved problem, that of the site and of the mechanism of urea biosynthesis in the mammalian body. It also demonstrated a physiological role for arginase, an enzyme that had been known for some time. The most important features of the work were the discovery of the catalytic role of ornithine [an amino acid found in bird urine] and

the proposal of the 'urea cycle.'"⁶ Joseph S. Fruton, Yale University, stated that the paper "marked a new stage in the development of biochemical thought."¹²

As Krebs told *CC* readers in a *Citation Classic* commentary, the paper also reported some new methodologies. These concerned the use of tissue slices to study metabolism, and a new saline solution with which to preserve them.¹³ Ten years earlier, Krebs had written: "The use of tissue slices which I had learned in Otto Warburg's laboratory, so it seemed to me, opened up an entirely new kind of approach to many problems of metabolism."¹⁴ The saline solution "proved superior to all earlier plasma saline substitutes."¹³ It is for this solution, he believed, that the paper is so highly cited—more than 2,400 explicit citations between 1961 and 1981. This is remarkable considering its 1932 publication date. We'll only know its impact for the previous 30 years when we compile the *SCI* for that period.

About the time of the publication of the urea cycle paper, the Nazis came to power in Germany. Because he was a Jew, Hans lost his university position. However, he had several offers from institutions in England. He was able to emigrate before the situation for Jews in Germany worsened.⁵ In the *Citation Classic* mentioned earlier, he pointed out that his coauthor Henseleit also suffered under the Hitler regime. "Having been associated with me and not being a Nazi, he was told that in the 'Third Reich' he had no future in academic medicine." Henseleit eventually became a successful practicing internist in Friedrichshafen in south Germany, where he died in 1972.

His reputation secured through his outstanding publications, Krebs accepted an invitation from Sir Frederick Gowland Hopkins to come to the de-

partment of biochemistry at the University of Cambridge. Hopkins had won the Nobel prize in 1929 for his pioneering work on vitamins. Supported by the Rockefeller Foundation, Hans continued the work on amino acid metabolism that he had begun at Freiburg. This led to an appointment to the position of university demonstrator in biochemistry at Cambridge.¹⁵

In 1935, Krebs moved to the University of Sheffield to become lecturer in pharmacology. At Sheffield, he did his most acclaimed work. He discovered, with William A. Johnson, a graduate student, the mechanism for the synthesis of citric acid from oxaloacetic acid and pyruvic acid, one of the major steps in cell metabolism.²

While much was known about cell metabolism before this work, Hans supplied much missing information and was able to organize the body of knowledge into a workable whole.⁶ To understand the significance of this discovery, one has to understand a little about cell metabolism.

Cell metabolism can be viewed as the way energy is released from foodstuffs and converted to chemical energy that is useful to the body. In animals, this is done by stepwise oxidation, or removal of electrons, from food materials. The electrons are then fed into a chain of carriers that ultimately leads to their combination with oxygen to form water, and the concomitant synthesis of the compound that is the carrier of chemical energy, adenosine triphosphate (ATP).

The cycle discovered by Krebs describes how the two-carbon product of metabolism, acetyl coenzyme A, is broken down, and its electrons removed in small steps. The cell condenses this two-carbon compound with the four-carbon intermediate oxaloacetic acid to form the six-carbon acid, citric acid. It is the oxidation of citric acid that not only

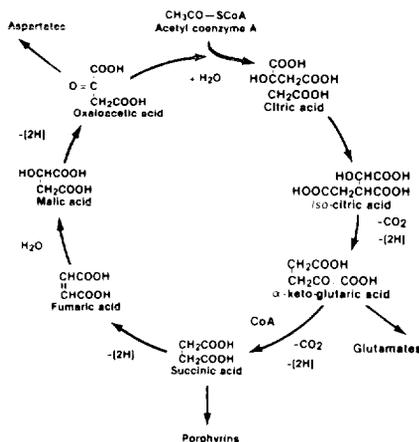
leads to the re-formation of oxaloacetic acid, but allows packets of electrons to be released in small steps that can be strictly controlled. Figure 1 presents an illustration of the Krebs cycle.

As Krebs explained in his Nobel prize lecture, "Of major significance was another new observation. Citrate was not only broken down at a rapid rate but was also readily formed in muscle and in other tissues."⁹ The Krebs cycle, according to E. Hammarsten, Karolinska Institute, Sweden, explains "two simultaneous processes: the degradation reactions which yield energy, and the building-up processes which use up energy."⁹ Krebs's work also showed how ATP is formed and used in cell metabolism. The Krebs cycle is also sometimes called the tricarboxylic acid cycle.

The paper reporting the Krebs cycle was published in 1937 in *Enzymologia*,² but not before it was rejected by *Nature*. As *Nature* recently acknowledged, Krebs cherished the rejection slip for the article that reported his Nobel prizewinning work.¹⁶ We have no way of knowing how often this paper was cited before the appearance of *SCI*, but it was cited explicitly only about 30 times in the past 20 years. It is undoubtedly a good example of the "obliteration phenomenon." The Krebs cycle is now common wisdom in biochemistry.

Besides being a period of great professional accomplishment, the late-1930s was a period of personal satisfaction as well. In 1938, Hans married Margaret Cicely Fieldhouse of Wickersley, Yorkshire. They had two sons, Paul and John, and a daughter, Helen.⁵ A patriot in his new homeland, Krebs made many contributions to British life during World War II. He supervised research for the British Medical Research Council on the human nutritional requirements for vitamin A and ascorbic acid.¹⁷ As a result of his research, the official recom-

Figure 1: The Krebs cycle. The cycle begins with acetyl coenzyme A, an end product of the metabolic breakdown of amino acids, carbohydrates, and fatty acids. Coenzyme A is a catalyst, and is regenerated in the formation of the next intermediate compound, citric acid. A series of reactions occurs, during which two carbon atoms are lost, the end product being oxaloacetic acid. Oxaloacetic acid combines with acetyl coenzyme A, which is converted to citric acid, and the cycle begins anew. Each turn of the cycle liberates eight hydrogen atoms. These in turn are incorporated into ATP, from which the body draws energy.



mended dietary requirement for ascorbic acid was reduced from 70 mg per day to 30 mg. Hans is credited with helping to develop the national wholemeal loaf that "kept the English people well-nourished through the war years despite food shortages."¹⁸

After the war, Krebs returned to his research. In 1945, he was appointed the first professor of biochemistry at the University of Sheffield and the honorary director of the Medical Research Council Unit for Research in Cell Metabolism. He received more honors, and in 1947, he was elected a Fellow of the Royal Society of London. In 1953, he won the Nobel prize for his discovery of the citric acid cycle. He shared the \$33,840 cash award with Fritz A. Lipmann,¹⁹ although the two were not collaborators. Earlier that same year, Krebs received the Lasker Health

Award.²⁰ It is significant that Krebs and Lipmann both were among the 1,000 most-cited contemporary authors for their publications from 1965 to 1978.²¹

At Sheffield, Hans continued his research on the oxidation of carbohydrates by microorganisms as well as animal tissues.⁵ He also discovered a number of new analytical techniques. His experiments on the accumulation of glutamic acid within isolated tissue slices were important in adding to our understanding of metabolic chemical reactions.¹⁷ Glutamic acid is an amino acid which mammals can synthesize themselves.

Krebs was a magnet for students and endeavored to teach them all he knew.¹⁸ An editorial in *Nature* pointed out, "At one stage, more than a dozen British chairs of biochemistry were occupied by his students. He was a giant eager that his shoulders should be used by younger people."¹⁶

In 1954, when Sir Rudolph Peters retired from the Whitley chair of biochemistry at Oxford University, Hans was appointed to the post. The Medical Research Council Unit moved to Oxford with him.¹⁵ That same year, Krebs received the Royal Medal of the Royal Society of London.²² At Oxford, his laboratory continued the study of metabolic regulation. In 1958, Krebs received one of the highest honors his adopted country could bestow when he was knighted.

After 13 years at Oxford, Sir Hans Krebs retired from the Whitley chair, but he continued his work with his close collaborators L.V. Eggleston, R. Hems, Patricia Lund, and D.H. Williamson. He set up the Metabolic Research Laboratory in the Radcliffe Infirmary, Oxford, in 1967.

In recent years, Krebs studied, among other things, ways to preserve the liver for long periods after removal for transplantation to other humans. He was also

Table 1: The most-cited papers of Hans Krebs in which he appears as first author.

**Total
Citations
1961-81**

Bibliographic Data

- 2492 **Krebs H A & Henseleit K.** Studies on urea formation in the animal organism. *Hoppe-Seylers Z. Physiol. Chem.* 210:33-66, 1932.
- 581 **Krebs H A.** Body size and tissue respiration. *Biochim. Biophys. Acta* 4:249-69, 1950.
- 418 **Krebs H A, Bennett D A H, de Gasquet P, Gascoyne T & Yoshida T.** Renal gluconeogenesis. *Biochem. J.* 86:22-7, 1963.
- 315 **Krebs H A.** The Croonian lecture, 1963. Gluconeogenesis. *Proc. Roy. Soc. London Ser. B* 159:545-64, 1964.
- 265 **Krebs H A & Hems R.** Some reactions of adenosine and inosine phosphates in animal tissues. *Biochim. Biophys. Acta* 12:172-80, 1953.
- 187 **Krebs H A & Eggleston L V.** The role of pyruvate kinase in the regulation of gluconeogenesis. *Biochem. J.* 94:3c-4c, 1965.
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- 105 **Krebs H A, Gascoyne T & Notton B M.** Generation of extramitochondrial reducing power in gluconeogenesis. *Biochem. J.* 102:275-82, 1967.
- 103 **Krebs H A & Eggleston L V.** 55. The oxidation of pyruvate in pigeon breast muscle. *Biochem. J.* 34:442-59, 1940.

interested in diseases known as "inborn errors of metabolism." Thus his interests came full circle, back to research with direct application to medicine.⁶

Over the years, Krebs compiled an impressive citation history. His work has been cited more than 11,000 times since 1961. A bibliography of the most-cited papers in which he appears as first author is presented in Table 1. Hans

once commented to me about his own citedness and about the fact that many most-cited articles are cited for their methodology. "Oddly enough," he said, "the only paper of mine ever rejected outright by an editor was a purely methodological one. It was a paper on the handling of biological material for metabolic experiments. The editor believed, I think wrongly, that results are more im-

portant than methods. The frequent quotation of methods papers unequivocally demonstrates the usefulness of such papers."²³

When budgetary considerations prompted governments in the US and Britain to cut back on science-related spending, Krebs became concerned with the issue of waste in science. In 1970, he told the American Philosophical Society that "casual and ineffectual use of research facilities means irresponsible wastefulness. In view of the unavoidable financial stringencies it is essential to deploy the limited resources effectively."²⁴ He also pointed out that on visits to laboratories "one is liable to see valuable space, equipment, and personnel involved in work which over many years has produced nothing tangible. This sterile research and pretension of doing research have been called 'occupational therapy for university staff.'"²⁴

He suggested that universities allocate resources more effectively. "There is too great a tendency to regard all staff members of a science department as equal in respect to their abilities in teaching, research, and administration and to give them an equal share of the various departmental responsibilities. They are of course very unequal, and duties and facilities should be distributed according to ability and inclinations."²⁴

Krebs also continued to edit *FEBS Letters*, along with Kornberg and others. In the issue dedicated to Krebs's eightieth birthday, the editors noted, "There is nothing that his friends can offer him that will be more to his liking than the demonstration that they have profited from his teaching and by his example."²⁵

The example he set was one of excellent science, innovative methods, and care for his fellow scientists. Much has been said about the atmosphere in his laboratories. "For those eager to work there was no better place to go to. He always created an air of cheerful activity around him," Blaschko said.⁶ E.A. Evans and K. Burton, both of whom had worked with Krebs, wrote that the atmosphere in his Sheffield laboratory was "one of unusual harmony as well as intellectual stimulation. This is due in no small measure to Krebs' personal and intellectual qualities...."¹⁷ They also praised his ability to plan the exact necessary experiment and efficient use of time and facilities.

Up until his last days, Krebs remained interested in both biochemistry and other aspects of the world around him. He sent me a copy of a manuscript on juvenile delinquency. In this piece, published in Unesco's *New Horizons of Human Knowledge*,²⁶ he argued that an inadequate understanding of fundamental biological principles is one of the causes of juvenile delinquency.

It is always difficult to sum up the life of an extraordinary and prolific scientist. The task is even more difficult if his interests outside of science were wide-ranging. Although I can only envy the intimacy others shared in working in his laboratory, I feel that I was privileged to know him in a special way. I was fortunate to have his support during some trying times. But undoubtedly, a real measure of his life is that humanity profited vastly from the work of this giant.

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