Carl and Gerty Cori and Carbohydrate Metabolism

September 21, 2004

A National Historic Chemical Landmark

American Chemical Society
SCIENCE THAT MATTERS

"My grandfather, that is, my mother's father, toward the end of his life became diabetic and he said to his daughter, who was a doctor, 'Find me a cure."

Tom Cori, *Living St. Louis*, a production of KETC in St. Louis, Missouri.

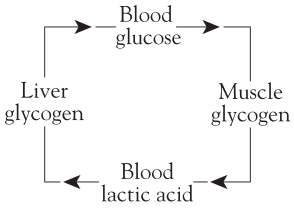
glucose

The "Cori cycle"

Carl and Gerty Cori spent more than three decades exploring how the human body metabolizes glucose. It was known in the 1920s that faulty sugar metabolism could lead to diabetes, and it was also known that insulin kept the disease in check. The effect of insulin on blood sugar levels had been observed, but scientists did not understand the biochemical mechanism behind insulin's effect or how carbohydrates were metabolized.

Sugar metabolism supplies energy for life's activities. The human body is unable to make the slightest muscular movement without burning sugar. In the 19th century the great French physiologist, Claude Bernard, discovered glycogen, the starch-like substance found in muscles and the liver. Glycogen is the polymeric storage form of glucose and when energy is needed glycogen is converted by the body into glucose. This mechanism keeps the glucose level in the blood constant even though the supply is uneven.

The interplay between glucose and glycogen is at the heart of what is known as the "Cori cycle." The Coris found that insulin increased the oxidation of glucose and its conversion to glycogen in muscle, as well as in the liver. Epinephrine, or adrenaline, worked in reverse, decreasing muscle glycogen and liver glycogen. Since other researchers had established that muscle glycogen does not contribute significantly to blood glucose, the Coris concluded that muscle glycogen must form an intermediate substance which then circulates through the blood to the liver. The Coris theorized – and eventually demonstrated – that this intermediate was lactic acid and was integral to the "cycle of carbohydrates," or the "Cori cycle," which they depicted in 1929:



The "Cori ester" and the synthesis of glycogen

In the 1930s the Coris found a new intermediate of glycogen breakdown, which they demonstrated to be glucose-1-phosphate, known as the "Cori ester." Working with Sidney Colowick, the Coris established the compound's structure and discovered the enzyme that catalyzed its formation, which they named phosphorylase. In addition, the Coris demonstrated that the reversal of the phosphorylase-catalyzed reaction produced glycogen, the first time a biological macromolecule had been synthesized in a test tube. The Coris, in collaboration with Arda Green, crystallized the enzyme glycogen phosphorylase from muscle and investigated its chemical properties.

The Coris' path-breaking research resulted in their sharing the Nobel Prize in Physiology or Medicine in 1947 with Bernardo Houssay of Argentina. The Nobel committee cited the Coris "for their discovery of the course of the catalytic conversion of glycogen" and Houssay "for the discovery of the importance of the anterior pituitary hormone for the metabolism of sugar."

European backgrounds

Carl Cori and Gerty Radnitz shared much in common. Both were born in 1896; both came from families that were Austrian in origin but had lived in Prague for generations. When they met in their first year of medical school, they found other things they had in common: a love of research and an enthusiasm for mountain climbing.

Yet their backgrounds were very dissimilar. Carl came from a Catholic family with a history of university professors on both sides. When Carl was two years old his family moved to Trieste, then part of the Austro-Hungarian Empire. Summers were spent with his extended family in the Tyrolean Alps, where the young Carl Cori developed a lifelong love of mountaineering.

Gerty Radnitz was Jewish. Her father was a chemist who devised a method for refining sugar and became a successful manager of sugar refineries. Her mother, a cultured woman, was a friend of Kafka. The oldest of three sisters, Gerty was educated at home until ten, when she was sent to a private school.

Carl Cori and Gerty Radnitz first met in 1914 – at the beginning of World War I – when they entered Carl Ferdinand University in Prague to study medicine. In 1916 Cori was drafted into the Austrian army. Carl's experiences in a barracks that served as a hospital for infectious diseases left him gloomy about the ability of doctors to control disease. Disease was rampant, and, as he wrote, "the influenza epidemic with its high mortality rate among the poorly nourished soldiers and civilians and the inability to be of any help came as a great shock to me."

At the end of the war, Carl and Gerty were reunited. They received their medical degrees in 1920. That same year the young couple was married in Vienna, where they were pursuing postdoctoral studies. Carl Cori wrote

many years later that "life in Vienna had its compensations," but in fact it also had its deprivations, and Gerty developed symptoms of xerophtalmia, a condition caused by vitamin A deficiency. Because of the difficulty of life in Europe and because Gerty, as a Jew and a woman, had trouble finding an academic position, the Coris decided to immigrate to the United States.

Buffalo and St. Louis

Carl Cori accepted a position as a biochemist at the State Institute for the Study of Malignant Disease in Buffalo, New York, in 1922. Gerty Cori joined him six months later, taking a position as an assistant pathologist. The two were never apart again professionally. At the beginning of their tenure at the Institute, the Coris encountered opposition to their working together. Gerty Cori was told she would lose her job if she strayed from her laboratory in the Pathology Department. Soon, however, their colleagues came to understand and respect the Coris' wish to work together.

In 1931 Carl Cori was offered the chairmanship of the pharmacology department at the Washington University School of Medicine in St. Louis. In 1946 Carl switched departments, becoming chairman of biological chemistry. The years in St. Louis were productive and rewarding for the Coris. They were able to collaborate on research, doing seminal work in the mechanism of glycogen utilization. And they liked St. Louis, so much so that they turned down prestigious offers from Harvard, Berkeley, and the Rockefeller Institute. The Coris were supportive of the many scientists who flocked to their laboratory in St. Louis to study and work with them. All were invited to take part in the daily brown-bag lunches in the library, where the conversation included current research interests but also might touch on a raft of non-scientific subjects.

Most visitors were impressed by the depth of their interests and knowledge. They had many friends in St. Louis, a modern house and a garden in which they divided the labor; she grew the flowers, he raised the vegetables. The Coris read widely. Gerty was interested in history, biography, and modern fiction, while her husband was knowledgeable in archaeology, poetry, and art. Carl was also a poet and fluent in German, French, Italian, and English.

The final years

The excitement of receiving the Noble Prize in 1947 was overshadowed by the knowledge that Gerty Cori had developed an incurable and fatal illness, myelosclerosis, which leads to anemia. She suffered for ten years. Carl later wrote that "she bore [the disease] with great fortitude and without letup in her scientific interests." She continued her research almost until the end, working on the enzymatic lesions in different forms of glycogen storage disease and describing with Joseph Larner a new enzyme they called "the debrancher." Gerty Cori died in 1957.

In 1960 Carl Cori married Anne Fitzgerald-Jones. The two shared many common interests, including archaeology, art, and literature. After retirement in 1966 from Washington University, Carl was appointed visiting professor of Biological Chemistry at Harvard Medical School. Cori's research focused on the relation of mutations of an enzyme, glucose-6-phosphatase, to metabolic diseases. In this work he began collaborating with a noted geneticist Salomé Glüecksohn-Waelsch of the Albert Einstein College of Medicine in New York. Cori and Glüecksohn-Waelsch published their first joint paper in 1968 and the last in 1983, when Carl became too ill to continue research. Carl Cori died in 1984.

A truly collaborative relationship

It was a truly collaborative relationship, as relatives and former colleagues testify. David Kipnis says: "They were a remarkable pair. Gerty would have flights of fancy. She'd come up with extraordinary ideas. Cori had the ability to put them into concrete questions to answer. And therefore, as a team, they were extraordinary." Their son Tom says his mother had the ideas; then they both would go into the laboratory to execute the idea or disprove it. Their closeness extended beyond their scientific endeavors; as Mildred Cohn relates, they complemented each other intellectually: "She would start a sentence, he would finish it." Carl Cori summed up the nature of their partnership in his remarks at the Nobel banquet in 1947: "Our collaboration began 30 years ago when we were still medical students at the University of Prague and has continued ever since. Our efforts have been largely complementary, and one without the other would not have gone as far as in combination."

National Historic Chemical Landmark

The American Chemical Society designated the research of Carl and Gerty Cori on the metabolism of carbohydrates at Washington University School of Medicine a National Historic Chemical Landmark on September 21, 2004. The plaque commemorating the event reads:

Beginning in the 1920s, Carl and Gerty Cori conducted a series of pioneering studies that led to our current understanding of the metabolism of sugars. They elucidated the "Cori cycle," the process by which the body reversibly converts glucose and glycogen, the polymeric storage form of this sugar. They isolated and purified many of the enzymes involved in glucose metabolism. The work of the Coris advanced understanding of glycogen breakdown in cells and of metabolic regulation. Building on their work, others developed improved techniques to control diabetes. The Coris were awarded a Nobel Prize in 1947.

About the National Historic Chemical Landmarks Program

The American Chemical Society, the world's largest scientific society with more than 159,000 members, has designated landmarks in the history of chemistry for more than a decade. The process begins at the local level. Members identify milestones in their cities or regions, document their importance, and nominate them for landmark designation. An international committee of chemists, chemical engineers, museum curators, and historians evaluates each nomination. For more information, please call the Office of Communications at 202-872-6274 or 800-227-5558, e-mail us at nhclp@acs.org, or visit our web site: www.chemistry.org/landmarks.

A nonprofit organization, the American Chemical Society publishes scientific journals and databases, convenes major research conferences, and provides educational, science policy, and career programs in chemistry. Its main offices are in Washington, DC, and Columbus, Ohio.

Acknowledgments

Photo Credits: Bernard Becker Medical Library, Washington University School of Medicine.

Written by Judah Ginsberg

In addition to consulting the standard reference works on the Coris and their writings, the author interviewed scientists who worked in the Coris' laboratory at Washington University at one time or another. He wishes to thank the following people who shared their memories of Carl and Gerty Cori: Dr. Barbara H. Brown, Professor Emerita, Washington University School of Medicine; Dr. David H. Brown, Professor Emeritus, Washington University School of Medicine; Dr. Mildred Cohn, Benjamin Rush Professor Emerita, Department of Biochemistry and Biophysics, University of Pennsylvania School of Medicine; Dr. David Kipnis, Distinguished University Professor of Medicine, Professor of Molecular Biology and Pharmacology, Washington University School of Medicine. Also thanks to Tom Cori, who shared memories of his parents with me. Both Drs. Brown and Drs. Cohn and Kipnis read drafts of this brochure, and it is better for their insights on the Coris and their research. Dr. Ernest J. M. Helmreich, Professor Emeritus, University of Wurzberg kindly answered a long string of questions from me by email. In addition, Dr. Carl Frieden, Wittcoff Professor and Head, Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine read a draft and made several key suggestions regarding carbohydrate metabolism. Thanks also go to Paul Jones and Frankie Wood-Black of the National Historic Chemical Landmarks Committee for their editorial comments. Needless to say, any remaining errors are mine alone.

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