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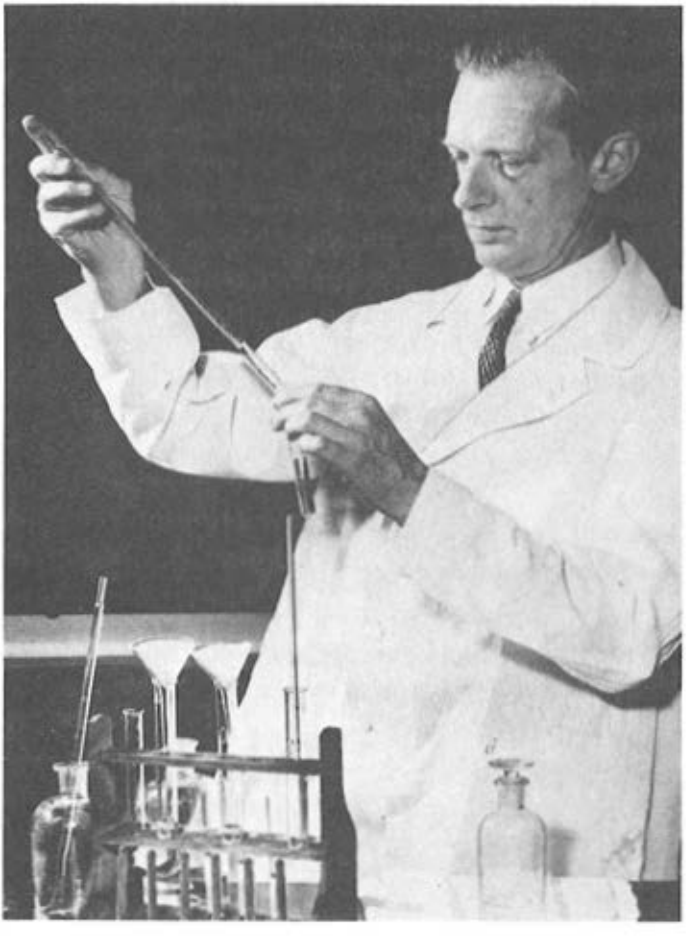
CARL FERDINAND CORI

1896—1984

A Biographical Memoir by

MILDRED COHN

Biographical Memoir



Carl F. Cori

Archives, Washington University School of Medicine

CARL FERDINAND CORI

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BY MILDRED COHN

UNRAVELING THE glycolytic and glycogenolytic pathways was a remarkable feat and a testament to the imagination and ingenuity of all those who participated. Carl and Gerty Cori contributed an essential part and in so doing were among the pioneers who showed that biochemical investigations of isolated enzyme systems could lead to an understanding of physiological processes. From their discovery of the first product of glycogen breakdown, glucose-1-phosphate, the Coris went on to isolate and crystallize the enzyme phosphorylase that catalyzed the reaction—the first of a class of reactions in which inorganic orthophosphate reacts to yield an organic phosphate ester.

Glycogen phosphorylase proved a treasure trove for biochemistry. By reversal of the phosphorylase reaction, it was shown that a macromolecule could be synthesized in a cell-free system. The enzyme was further found to exist in two interconvertible forms, though one was inactive in the absence of adenylic acid, which acted as an effector. The next generation of scientists trained in the Cori laboratory, using the Coris' fundamental discoveries, probed still further and discovered the two most widespread metabolic regulatory mechanisms: the cyclic AMP system and phos-

phorylation-dephosphorylation of enzymes accompanied by a cascade system of control.

EUROPE (1896–1922)

Carl Cori never regretted leaving Europe at the age of twenty-five to come to the United States and grew to be thoroughly at ease with the language, institutions, and customs of his chosen country. Yet he was, and would always be, a product of his cultured European background.

Carl Ferdinand Cori was born in Prague (then part of the Austro-Hungarian empire) on October 19, 1884. When he was two the family moved to Trieste, where his father took over as director of the Marine Biological Station. Carl spent his formative early years in Trieste, and his autobiographical essay, "The Call of Science" (1969), paints the picture of a happy childhood in a cultured and international milieu. In Trieste, Carl came into contact with a variety of ethnic groups. He was soon fluent in Italian, and the racial tolerance he developed there proved to be life long. Educated at the classical gymnasium from 1906 to 1914, furthermore, he obtained a grounding in Latin and Greek he would never forget.

Just as important, however, was the informal education he received at the Marine Biological Station. During field trips on the motorboat "Adria," his father, who captained the boat, lectured on the geology, botany, and early cultural history of the coastal region in addition to its oceanography and marine biology. Renowned for his own broad erudition in biology, archaeology, and history, the younger Cori attributed his abiding interest in them to his experiences on these field trips.

Summers with his extended family in the Austrian Tyrol rounded off Carl's education by giving him a love of mountaineering and music. His only rebellion, he records, was

a certain penchant for practical jokes aimed at embarrassing his parents. His reference to a crystal of permanganate in the chamber pot, for example, caused consternation for a visiting maiden aunt with hypochondriac tendencies.

Carl's family boasted illustrious scientists and academics on both sides. Ferdinand Lippich, his maternal grandfather and professor of mathematical physics at the German University of Prague, had (in addition to making theoretical contributions to physics) developed the polarimeter as a precision instrument. Wilhelm Lippich, his great-grandfather, had been an anatomist at the University of Padua and a professor in Vienna. His uncle Friedrich Lippich was professor of chemistry in Prague, while his father, Carl I. Cori, was one of Europe's leading zoologists and marine biologists. Prominent scientists, furthermore, were frequent visitors to the house, and it is hardly surprising that young Carl chose to embark on a scientific career.

In 1914, at the age of seventeen, he entered the Carl Ferdinand University (the German university of Prague) to study medicine—at that time the customary route to a research career in the life sciences. He was fortunate to find there an intelligent and charming fellow student, Gerty Radnitz, who shared his interest in science and love of the outdoors. In 1916, while still medical students, they published their first joint research paper. Later, Gerty became Carl's wife and was, until her death in 1957, his dedicated scientific collaborator.

During World War I, in his third year at the university, Carl was drafted into the Austrian army. He was first stationed in a bacteriology laboratory, where—after a severe bout of typhoid fever he ascribed to his own carelessness—he taught himself a meticulous technique for handling pathogens. Later he served in a hospital for infectious diseases near the Italian front. Because of his knowledge of Italian,

he was charged with caring for civilians as well as soldiers. While he could help some patients with the drugs then available, he found tuberculosis, malaria, pellagra, scurvy, and typhoid rampant in this poorly nourished population. His inability to help the victims of an influenza epidemic shocked him. This, along with the experience of a long and dangerous retreat amid a mass of undisciplined soldiers, made him skeptical about the practice of medicine and strongly averse to war ever after.

Cori returned to Prague in 1918, completed his clinical studies, and was awarded the M.D. degree. He and Gerty were married in Vienna, where both had gone to do postdoctoral work, in August 1920. He divided his laboratory work between the university's Pharmacology Institute and its internal medicine clinic but found his experiences in the latter so discouraging that he had no desire to continue in clinical medicine. The alternative—a career devoted entirely to research—was attractive both to him and to Gerty. Unfortunately, the postwar devastation in Austria made it highly unlikely that they would find paid positions; one could hardly get enough to eat. Gerty Cori, working at Karolinen Children's Hospital, developed symptoms of xerophthalmia from the inadequate diet provided for her there.

Fortunately, Carl Cori's research on the mechanism of seasonal variation of vagus action in the frog heart (1921) caught the attention of H. H. Meyer, who had just retired from the Pharmacology Institute. In the summer of 1921, Dr. Gaylord, director of the State Institute for the Study of Malignant Diseases (now the Roswell Park Memorial Institute) in Buffalo, New York, asked Meyer to suggest a biochemist for his institution. Meyer recommended Cori, who was interviewed for the position but was so certain that nothing would come of it that he accepted a position with

Otto Loewi in the Pharmacology Department of the University of Graz.

Cori stayed at Graz only six months, during which he learned a great deal. Loewi's enthusiasm and originality coupled with his wide knowledge of all aspects of biomedical science made him an invaluable mentor. It was during this intellectually stimulating period that Cori first thought of a way to study intestinal absorption, and the fate of sugar, in general, in the animal body. But other aspects of the Graz experience were decidedly unpleasant. To be eligible for employment at the university, Cori had had to prove his Aryan descent, and despite his scientific stature, Otto Loewi's future there was questionable. Living conditions and research facilities were woefully inadequate. When Gaylord offered Cori the position in Buffalo, therefore, both he and Gerty Cori welcomed the opportunity to leave Europe. Carl left early in 1922, and Gerty joined him six months later.

BUFFALO, NEW YORK (1922–31): STATE INSTITUTE FOR THE STUDY OF MALIGNANT DISEASES–ROSWELL PARK MEMORIAL INSTITUTE

In Buffalo, Cori initiated his life's work on carbohydrate metabolism and its regulation. Obliged to do routine laboratory tests for the hospital affiliated with the Institute, he used the opportunity to hone his analytical skills. His first paper on carbohydrate metabolism was published in 1922; in the ensuing decade, he published some eighty papers. After some initial problems in 1922–23 (1969,1), Gerty Cori, who had a position in the Institute's pathology department, was allowed to collaborate with Carl, and the majority of those eighty papers are joint publications. In the following discussion no attempt will be made to assess individual contributions because it was the work of two peers speak-

ing with one inseparable voice. As Carl Cori stated (1947,1): "Our efforts have been largely complementary; and one without the other would not have gone so far as in combination."

Regulation of Glucose Concentration in the Blood

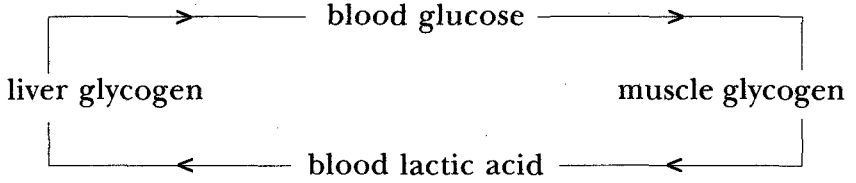
The question the Coris wanted to answer was: What regulates blood glucose concentration? Their initial experiments were physiological, designed to determine the amount of sugar absorbed in the alimentary tract by measuring the unabsorbed sugar left in the gut of a rat after it had ingested a known amount (1925,5). This was followed by experiments with a new method devised to determine the glycogen content of liver and carcass separately.

But in order to assess changes in glycogen concentration after sugar ingestion or hormone administration, a control value had first to be established. It was found that the glycogen concentration was fairly constant in rats fasting for twenty-four to forty-eight hours. Higher and more uniform glycogen concentrations, furthermore, could be obtained by giving an amount of glucose that could be absorbed completely in three hours.

Having established conditions and analytical methods that were reproducible, it was then possible to do balance studies to determine the fate of the absorbed glucose in fasted rats and the influence insulin and epinephrine had on that fate. The researchers found that insulin increased oxidation of glucose and conversion to muscle glycogen but decreased conversion to liver glycogen (1926,1, 1928,1). Epinephrine, on the other hand, decreased muscle glycogen and increased liver glycogen (1928,2,3). Since it was known that muscle glycogen does not contribute glucose to blood, the Coris concluded that another intermediate must be formed from muscle glycogen and circulated through

the blood to the liver to become the precursor of liver glycogen. Since it was known that lactic acid was formed when glycogen disappeared in muscle, the Coris postulated—and later demonstrated—that lactate was the intermediate in the "cycle of carbohydrates" (1928,2,3).

The "cycle of carbohydrates," which the researchers represented in the diagram given below (1929,1):



came to be known as the "Cori cycle." This scheme derived from research on the circulation of carbohydrate material in the intact animal was a milestone in the elucidation of carbohydrate metabolism and, along with other insights on blood homeostasis, helped clarify the action of epinephrine on blood glucose. Yet equally important were the reliable—and reproducible—techniques developed by the Coris to detect and quantify even small changes in liver glycogen, on which their research depended.

Influential Publications

During his stay at the Institute in Buffalo, Carl Cori also published a number of papers dealing with cancer. In 1923, Otto Warburg found that tumors display higher aerobic and anaerobic glycolysis than normal tissue. But Warburg's studies were carried out in vitro, and the Coris were the first to demonstrate that tumors in intact animals also showed abnormally high formation of lactic acid from glucose (1925,4).

In 1931, Cori wrote a masterly review on mammalian carbohydrate metabolism (1931,4). With more than 100

pages and some 500 cited references, the review included a critical evaluation of the literature, a summary of the pioneering work Carl and Gerty Cori had accomplished, and an indication of the direction of their future research on the mechanism of glycogenolysis. It established Carl Cori as a leader in the field and influenced the study of carbohydrate metabolism for many years to come.

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS (1931–45)

In 1931, Carl and Gerty Cori moved to St. Louis, where Carl became the chairman of the Pharmacology Department at Washington University and Gerty was given a position in the department, albeit with a token salary. In addition to his research, however, Cori was now expected to organize a department, equip a research laboratory, and spend considerable time teaching medical students. Understandably, there was a hiatus in the publication of papers.

During the last phase of the Buffalo period, however, the Coris had started working with isolated muscle preparations rather than intact animals. From balance-studies with epinephrine, they had concluded that the formation of a precursor of lactate from glycogen that accumulates in muscle is accompanied by the disappearance of inorganic phosphate (1930,5). They had developed a method, furthermore, for detecting hexose monophosphate simultaneously as both hexose and phosphate (1931,3). These experiments were a prelude to their important discovery of glucose–1–phosphate, for it was in St. Louis that their research progressed in the direction of biochemistry.

Phosphorylase—The Cori Ester

To study the concomitant disappearance of glycogen and phosphate, the Coris decided to use minced skeletal muscle

from frogs. When the water extracted, muscle dispersions were incubated anaerobically in phosphate buffer, and they observed that—unless boiled muscle extract were added—only small amounts of hexose monophosphate were produced. In the first striking result from these experiments, they identified 5'-adenylic acid as an obligatory activator of the reaction (1936,4; 1938,1)—a finding that foreshadowed the idea that the allosteric activation of appropriate enzymes regulates metabolic processes.

At the 1935 International Physiological Congress in Moscow, the Coris presented their results on the formation of hexose monophosphate from the reaction of glycogen with stoichiometric amounts of phosphate in rat and frog muscle. Subsequently investigating the reaction in muscle extracts on his own, J. K. Parnas confirmed that, simultaneous with the cleavage of glycogen, phosphate disappears—a reaction he characterized with the term "phosphorolysis."

Because there was a large discrepancy in their analytical results for hexose monophosphate between phosphate- and reducing-power determinations, the Coris postulated the formation of a hitherto unknown phosphorylated, nonreducing precursor of hexose-6-phosphate. Having isolated this product as a crystalline brucine salt, they tentatively assigned it the structure of glucose-1-phosphate. They adduced, together with S. P. Colowick, final proof of this structure by synthesizing α-glucose-1-phosphate (1937,2), and it subsequently came to be known as the "Cori ester."

Discovery of the Cori ester bore the hallmark of the Coris' meticulous approach to scientific problems. Their success depended first and foremost on reliable methods of analysis whose results could be quantified—as seen in their analysis of phosphorylated hexose. They took particular care, furthermore, with the design of their experiments—as exemplified by the series that led to their identification of the

activator 5'-AMP. Add to this the element of luck, for the muscle dispersions the Coris' chose as a medium allowed glucose-1-phosphate to accumulate. In intact muscle, the presence of Mg^{2+} causes the enzyme phosphoglucomutase (1938,3) to convert glucose-1-phosphate to glucose-6-phosphate, so that its concentration is nineteen times that of glucose-1-phosphate at equilibrium. But happily for the Cori experiments, in their method of muscle preparation, much of the Mg^{2+} was "washed out." They suggested that, contrary to earlier notions, blood glucose in the liver is regulated by the sequential action of three enzymes: glycogen phosphorylase, phosphoglucomutase, and glucose-6-phosphatase—a sequence confirmed by their later work (1939,1).

The Coris named their new-found enzyme, which catalyzed the formation of glucose-1-phosphate from glycogen and inorganic phosphate, "phosphorylase," consistent with Parnas's term "phosphorolysis" for the reaction. This new intermediate in glycogenolysis, furthermore, was novel in two ways. First, it was the first known example of the esterification with inorganic orthophosphate at the reducing group of a hexose. It was also evidence of a phosphorolytic cleavage of glycogen by the enzyme.

Their 1936 discovery launched the Coris full-fledged into enzymology. Seeking to synthesize glycogen, they reversed the phosphorylase reaction, adding a small amount of glycogen when they observed a lag in its production (1939,3). This established the need of a primer in polysaccharide synthesis and produced as a product a large, starch-like polysaccharide (1940,2). For the first time, researchers working with a cell-free preparation had synthesized a macromolecule—an exciting demonstration that contradicted the long-held notion that the biosynthesis of macromolecules required energy-metabolism and could, therefore, occur only in intact cells.[1]

It would be difficult to overestimate the conceptual impact of the Coris' biosynthesis of glycogen. Because of their success, subsequent investigators used biochemical approaches to investigate how macromolecules are synthesized, approaches that served them well.

Polysaccharides and Phosphorylase a *and* b

In 1942–43, the Coris collaborated with Arda Green to publish a series of brilliant papers laying the groundwork in two important areas: 1) the structure, biosynthesis, and characterization of polysaccharides; and 2) the characterization of phosphorylase *a* and *b* and their role in metabolic regulation.

The Coris' purification and crystallization of muscle phosphorylase (1942,1) made large quantities of the polysaccharide it produced available for study, enabling them to investigate the synthesis and chemical structure of the product formed from glucose-1-phosphate. The polysaccharide formed in the phosphorylase reaction was not glycogen (a branched polysaccharide) but rather an unbranched polysaccharide similar to amylase. The necessity of adding liver or heart muscle extract to phosphorylase to induce the formation of glycogen led the Coris—in an ingenious series of experiments—to infer the existence of another enzyme, in addition to phosphorylase, in the formation of branched polysaccharides (1943,2).

In this same period they were investigating how phosphorylase activity was regulated in some detail. Describing, with Arda Green, two forms of muscle phosphorylase, *a* and *b*, they found that the *b* form was active only in the presence of 5'-AMP (1943,1). The formation of *b* from *a*, furthermore, was demonstrated to be enzyme-catalyzed. The researchers named this PR (prosthetic-group removing) enzyme, but 5'-AMP—the presumptive prosthetic group—

was not found in phosphorylase *a*. Establishing that the *a* form contained four times as much phosphate as the *b* form, the Coris postulated, with their usual astuteness, that interconversion plays a significant role in metabolic regulation, since the inactive form is found in resting muscle, while the active form is found in contracting muscle (1974,1).

WASHINGTON UNIVERSITY, ST. LOUIS (1945–66)

With the end of World War II, Carl Cori left the Pharmacology Department to become chairman of the Biochemistry Department, and scientists from all over the world flocked to St. Louis to work with the Coris. From 1946 to 1960 I, too, was privileged to be in Carl Cori's department. Both Coris trained young scientists, and they were consistently supportive, treating us with respect, offering encouragement, and expressing appreciation.

Though we were somewhat in awe of the breadth and depth of Carl Cori's knowledge, our daily departmental luncheons in the library were much enlivened by his wit. One of those rare individuals to whom all products of the human intellect are accessible, he was equally at home discussing archeology, music, or botany. He spoke only when he had something to say, was both logical and precise, and was, therefore, always listened to with great respect. Cori was intellectually and personally so compelling that even occasional contact with him left a tremendous impression. His direct, unornamented approach to the pursuit of his scientific objectives could make him seem aloof, even austere, but he was never solemn, and his high spirits often gave rise to a wonderful gaiety.

Cori's linguistic ability was legendary, and his scientific writing was exemplary in its economy and rigor. His psychological insight was uncanny. On one occasion, after an hour with a prospective graduate student, he discussed the

student with me and predicted the kind of scientific career the student would have. Twenty years later, his prediction had been completely confirmed.

Cori's philosophy regarding the way to run a small department was to gather a group in which everyone would work on different aspects of the same general subject—in the case of his Biochemistry Department, carbohydrate metabolism. Some might be interested in the physical properties of enzymes or in their detailed mechanisms of action, others might be interested in more physiological effects of hormonal regulation, but all would benefit from interaction with each other. Under Cori, this system proved particularly effective, but whether it would have been so under anyone else's leadership is questionable.

The Coris lived with their son, Tom, born in 1936, in a pleasant house of modern design in a suburb of St. Louis. There they particularly indulged in gardening, a hobby Carl Cori pursued actively throughout his life. They extended hospitality to members of the department and visiting scientists and to their many non-scientist friends, who included sociologists, artists, and musicians. In the Cori home, the welcome was always warm and the conversation animated and intellectually stimulating.

In 1947, the Coris were awarded the Nobel Prize for Physiology or Medicine, which they shared with Dr. Bernardo Houssay of Argentina. Dr. Houssay was cited "for his discovery of the importance of the anterior pituitary hormone for the metabolism of sugar," while Carl and Gerty Cori were cited "for their discovery of the catalytic conversion of glycogen." The announcement of the award engendered great excitement and joy in the laboratory and among their friends everywhere. Gerty Cori was the first American woman to receive the Nobel Prize and the third from anywhere in the world, having been preceded only by Marie Curie and

Irène Joliot Curie. But 1947 was also the year that brought the devastating news that Gerty Cori was suffering from an incurable form of anemia, the disease that led to her death a decade later. Gerty's zeal was undaunted, and, if possible, her dedication to science was even more inspiring than it had been before her illness.

In 1956, their associates over the years at Washington University published a tribute to the Coris in a special issue of *Biochimica Biophysica Acta* entitled *Enzymes and Metabolism: A Collection of Papers Dedicated to Carl F. and Gerty T. Cori on the Occasion of Their 60th Birthday.* Contributors included five future Nobel laureates—C. de Duve, A. Kornberg, L. F. Leloir, S. Ochoa, and E. W. Sutherland—and the volume included many important and elegant papers. Several treated subjects particularly close to the Coris' interest, including Sutherland et al.'s treatment of phosphorylase *a* and *b* conversion; Krebs and Fischer's paper on the conversion of phosphorylase *b* to *a*; and Ochoa, Grunberg-Manago, and Ortiz's paper on a new enzyme, polynucleotide phosphorylase.

In addition to the 1947 Nobel Prize, Carl Cori received many other awards and honors. Among them were the Lasker Award of the American Public Health Association; the Squibb Award of the American Society for Endocrinology, which he shared with Gerty Cori; and the Willard Gibbs Medal of the American Chemical Society. He received honorary degrees from many universities, including Cambridge (England), Granada (Spain), Monash (Australia), and Trieste (Italy).

Cori was also elected to many prestigious intellectual academies and societies, including the American Academy of Arts and Sciences, the National Academy of Sciences (1940), and the American Philosophical Society. He was also a member of many foreign academies and societies, including the

Royal Society (London), the National Academy of Medicine (France), and the Royal Danish Academy of Sciences.

Glycogen Structure and the Regulation of Carbohydrate Metabolism

Because his research focused on enzymes from 1945 on, it was fitting that Cori head a department of biochemistry. But to him enzymes were always a means to understand the metabolic pathways in the cell. In his research he first attempted to isolate and characterize the mechanism of action of enzymes during glycogenolysis and glycolysis, then sought to understand the regulation of carbohydrate metabolism by hormones. Together with M. W. Slein, the Coris isolated and crystallized glyceraldehyde-3-phosphate dehydrogenase from rabbit muscle (1945,3); tightly bound NAD was found in the crystalline enzyme (1948,4). (J. Harting and S. Velick later elucidated this enzyme's mechanism of action, an example of substrate-level oxidative phosphorylation.) Next, with L. Berger, M. W. Slein, and S. P. Colowick, they isolated, from yeast, pure hexokinase, the enzyme that catalyzes the formation of glucose-6-phosphate from glucose and ATP, the first step in glucose utilization (1946,3). In 1948, Gerty Cori, J. F. Taylor, and A. A. Green crystallized aldolase. A year later, Carl Cori and V. Najjar purified phosphoglucomutase, which converts glucose-1-phosphate to glucose-6-phosphate, and investigated its mechanism of action (1949,1,3).

In 1951, Gerty Cori and J. Larner described a new enzyme they called "the debrancher." This was an amylo-1,6 glucosidase, and it catalyzed the hydrolysis of the 1,6 glucosyl bonds at the branch points in glycogen. Now—with the combined activities of phosphorylase and the debrancher enzyme—glycogen could be almost completely degraded in the presence of phosphate to produce glucose-1-phos-

phate from the α-1-4 linkages, and glucose from the α-1-6 linkages, respectively. It was possible, consequently, to decipher the structure of branched polysaccharides. As degradation with both enzymes proceeded and fewer branch points remained, glycogen was found to produce a decreasing amount of glucose, suggesting a tree-like, branched structure as a model for glycogen structure.

Hand in hand with the Coris' studies of the properties of the enzymes, they continued to research the problem of metabolic regulation. After demonstrating with Sutherland that insulin preparations brought about glycogenolysis in liver slices, Cori, Sutherland, Haynes, and Olsen isolated the impurity in the insulin preparations, which proved to be glucagon, the glycogenolytic factor in insulin preparations (1949,3). Cori and Sutherland subsequently showed that glucagon and epinephrine increase the rate of conversion of phosphorylase *b* to *a*, thereby controlling the rate of glycogenolysis in liver (1951,2). In the mid-fifties, Sutherland (with Wisolait) and Krebs (with Fischer), both trained in Cori's laboratory, proved that the conversion of phosphorylase *b* to *a* involved phosphorylation of the enzyme—Sutherland working with the liver enzyme and Krebs with the muscle enzyme. Sutherland's studies led to his discovery of cyclic AMP formation, while Krebs's work led to the elucidation of the complex cascade of regulating enzymes involved in the conversion of *b* to *a*.

The Action of Insulin

From his experiments with rat-muscle extracts, Cori concluded that insulin could increase glucose utilization by overcoming the inhibitory effects of adrenocortical fractions. He also suggested that insulin's first site of action was at the hexokinase-catalyzed reaction: glucose + ATP→ glucose-6-phosphate + ADP by reversing the inhibitory ef-

fects of anterior pituitary and adrenocortical factors. This proved difficult to reproduce, however, and—after a good deal of research by a number of investigators—a consensus evolved that insulin acts first by affecting the permeability of muscle cells to sugars. This was confirmed some ten years later by Cori and Helmreich, who presented evidence that insulin increases the permeability of muscle to glucose.

Although Cori's attempt to establish the direct effect of insulin on the enzyme level was unsuccessful, the Coris' studies on phosphorylase, as well as later studies by Sutherland and others, validated the idea of explaining hormone action by proceeding experimentally from the whole cell to the pure, isolated enzyme. It should be noted that, to this day, the mechanism of insulin action is not completely understood.

Using intact diaphragms from rats, Cori and M. Krahl were able to show that glucose uptake in the diaphragms of diabetic rats was stimulated in the presence of insulin (1947,2). In later studies, they showed that insulin strongly affects the uptake of pentose (1957,2) and 2-deoxyglucose (1960). These in vivo studies demonstrated, furthermore, that hexokinase in diaphragm muscle from diabetic rats is inhibited.

Glycogen-storage Diseases

Throughout the fifties the Coris also investigated the nature of glycogen-storage diseases, and Carl Cori continued this research into the sixties. They were the first to pinpoint the defects in glycogen-storage diseases on the molecular level. Von Gierke's disease, for instance, is characterized by very low levels, or the complete absence, of the enzyme glucose-6-phosphatase in the liver (1952,2). This enzyme catalyzes the breakdown of glucose-6-phosphate to glucose, and, in its absence, glycogen cannot yield blood glucose. The Coris conducted further studies on glycogen

storage disease in collaboration with B. Illingworth (1956,2), which were continued after Gerty Cori's death (1959,1, 1965,1).

THE LATER YEARS: BOSTON (1966–84)

At the end of the difficult decade of Gerty Cori's illness, which culminated in her death in 1957, Carl Cori was emotionally drained. Fortunately; this period was succeeded by a happy marriage in 1960 to Anne Fitzgerald-Jones, with whom he shared many interests in archeology, art, and literature. Carl Cori's wit and grace flourished in this last period of his life in the warm atmosphere of his and Anne Cori's home. After his retirement from the chairmanship of the Biochemistry Department of Washington University in 1966 at the age of 70, the couple moved to Boston.

Carl Cori left an indelible mark on Washington University by the example of his high standards and the outstanding productivity of his group. W. H. Danforth, a former Cori postdoctoral fellow who became chancellor of Washington University, acknowledged the strong influence Carl Cori, whose advice was often sought and heeded, on the university.

Enzyme Synthesis and Gene Expression

In 1966, Cori was appointed visiting professor of Biological Chemistry at Harvard Medical School and occupied a laboratory at Massachusetts General Hospital. He remained active in research until his final illness in 1983 and formed many deep friendships in Boston, as attested by the number of people who attended his memorial service held there.

Concerned about metabolic regulation for more than forty years, Carl Cori now struck out in a new direction—the study of the regulation of enzyme synthesis at the level of gene expression. This work was a collaborative effort with the eminent geneticist Salomé Glüecksohn-Waelsch of the Albert Einstein College of Medicine.

They investigated radiation-induced mutations in mice in which deletions in the chromosome region that included the albino locus served as a marker (1968,2). Because of the suppression of glucose-6-phosphatase, these deletions proved lethal in homozygous mutant mice (1968,2, 1969,2, 1970,1), since this liver enzyme (which the Coris had found to be deficient in von Gierke's glycogen-storage disease) is essential for the maintenance of blood sugar levels. The mutants manifested multiple biochemical defects (1973,1), including a deficiency of tyrosine aminotransferase and certain blood plasma proteins (1976,5). These multiple biochemical abnormalities, and the lack of gene-dosage effect in heterozygotes, suggested the involvement of other genes besides structural ones.

Yet, with many enzymes being synthesized normally, it was clear that this was not a defect in the general mechanism of protein synthesis. As it continued (1981,1, 1983), this research produced a striking result: unequivocal evidence that the structural genes for several of the missing enzymes were completely normal, but that regulatory genes were deleted. The DNA of the structural genes is encoded to specify the structure of the protein, but the regulatory gene determines the expression or non-expression of the structural gene. Furthermore, the Glüecksohn-Waelsch and Cori group's experiments demonstrated by experiments hybridizing mutant mouse liver cells and normal rat hepatoma cells that the regulatory genes for glucose-6-phosphatase and tyrosine aminotransferase were deleted from chromosome 7, and that structural genes are on other chromosomes.

This work broke new ground in demonstrating that both structural and regulatory genes are essential for the synthesis of individual proteins in a mammal, a phenomenon previously only known to occur in bacteria and yeast. It is impressive that Carl Cori in his ninth decade was making

significant contributions to a problem at the frontier of molecular biology. His mind continued to absorb new knowledge and use it creatively to the end of his life.

Cori was often called upon to write review articles, and this did not cease during his years in Boston. He also wrote a considerable number of historical articles in this period, and philosophical treatises on the relation between science and the humanities. In addition to an autobiographical essay, he wrote articles about scientists he had known, including Francis Schmitt, Earl Sutherland, James Summer, Embden, and Gerty Cori. He ended his own memoir with:

> The frontiers of physics, astronomy and biology, and the instrument of their study, the human mind, fill one with wonder as to the great creations of art and architecture, past and present. From these, and from contact with nature, love and friends, spring the joy of living and the understanding of sorrow and of the human predicament. Humanism may be as important to mankind as competence in a particular field of science.

Carl Cori was an eminently civilized man.

THE BEST SOURCE for Carl Cori's early life is his autobiographical essay, "The Call of Science," which appeared in *Annual Review of Biochemistry.* Other excellent sources include Herman M. Kalckar's historical account of the Coris's contributions in "Selected Topics in the History of Biochemistry: Personal Recollections," *Comprehensive Biochemistry* 35 (1983); a biographical memoir for the *American Philosophical Society Yearbook* (1985), by John T. Edsall; and the very detailed biographical memoir in *Biographical Memoirs of Fellows of the Royal Society,* 32 (1986), by Philip Randle.

NOTE

1. L. F. Leloir and his collaborators subsequently showed that, in vivo, a different enzyme—glycogen synthetase—catalyzes the formation the α-1,4 glucosidic bond from UDP-glucose in the biosynthetic pathway of glycogen.

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