# INTRODUCTION

## CARL F. AND GERTY T. CORI

by

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CARL FERDINAND CORI and GERTY THERESA CORI—*née* RADNIZ—were born in Prague, Czechoslovakia, then a part of the Austrian-Hungarian Empire, in 1896. CARL was the son of a Professor of Zoology. He attended secondary school in Trieste while GERTY studied in Tetschen and in Prague. They were students at the Medical College of the German University of Prague, graduated as medical doctors in 1920, and were married that same year, thus starting a successful scientific association which has lasted 35 years.

The initiation to their career took place in the University Clinics. CARL was Instructor of Medicine in Prague from 1919 to 1920 and assistant in Vienna from 1920 to 1921. GERTY was Demonstrator in Medicine at Prague from 1917 to 1919 and Assistant of the Children's Hospital at Vienna from 1920 to 1922.

In 1921 CARL started his scientific career as Assistant of Pharmacology at Graz in OTTO LOEWI's Institute. In 1922 they decided to leave for the United States of America in order to obtain better possibilities for their scientific work and they became American citizens in 1928.

CARL CORI worked from 1922 to 1931 as biochemist of the State Institute for the Study of Malignant Diseases in Buffalo, N.Y. GERTY was assistant in Pathology from 1922 to 1925 at the same Institute. In 1930–1931 CARL became assistant professor of Physiology at the University of Buffalo.

In 1931 CARL was appointed Professor of Pharmacology and in 1942 of Biochemistry at the School of Medicine of Washington University in St. Louis, Missouri. GERTY was research fellow and associate from 1931 to 1944, Associate professor from 1944 to 1947 and Professor of Biochemistry from 1947 to date, in the same department.

Their first interests were in the field of Internal Medicine and from 1920 to 1921 GERTY published papers on the thyroid and on splenectomy in cases of thrombopenia; at that time, CARL carried out work on the action of nerve stimulation on the isolated heart.

Their medical and physiological training gave them the background to correlate biochemical phenomena with the processes of physiological or pathological integration in the entire organism. At the State Institute for the Study of Malignant Diseases in Buffalo they carried out studies on the biological action of X-rays, carbohydrate

metabolism of tumors and the effect of ovariectomy on mammary tumors of the mouse. The choice of their problems was influenced by several circumstances, such as the interest aroused by the studies of carbohydrate metabolism of tumors, the discovery of insulin, and their finding complete freedom for research and adequate means for work at the Institute.

They studied the fate of ingested sugars in the whole animal. They fed rats a known quantity of sugar and placed them in respiratory chambers—this enabled them to determine how much of the sugar was oxidized to carbon dioxide and water. At the end of the experimental period, the whole animal was analyzed for carbohydrate. In this way they found that about half of the absorbed sugar was stored as glycogen in liver and muscles and that some of the sugar was converted to fat and stored as such. These methods were applied to the study of the influence of hormones, particularly insulin and epinephrine, on carbohydrate metabolism. They found that insulin led to increased combustion of glucose. At the same time a large quantity was converted to muscle glycogen and this was balanced by a decreased deposition of glycogen in the liver. This effect was also obtained in the absence of the adrenals. With epinephrine, glycogen deposition was decreased, glucose mobilization was increased and peripheral oxidation was diminished thus producing hyperglycemia. They observed that lactic acid was produced from muscle glycogen, so that its concentration in blood increased. This lactic acid was then utilized in the liver for the formation of glycogen. The latter then gave rise to blood glucose which was again transformed into muscle glycogen. This process has been known as the "Cori cycle".

A derivation of these studies led to the determination of the minimal amounts epinephrine which when injected continuously in the veins produced threshold effects on the blood pressure, blood lactic acid, blood sugar and basal metabolism in man and other animal species. These studies also gave rise to classical investigations on the rate of intestinal absorption of sugars, alcohol and lactic acid. The selective absorption of some sugars was described and many factors which modify the absorption were studied.

In 1931 CARL CORI published in *Physiological Reviews* a classical paper entitled "Mammalian Carbohydrate Metabolism". It was at this time that the CORIS moved to Saint Louis and this coincided with a change in the orientation of their research. Up to then, they had studied on the whole body, the changes in glucose concentration, its oxidation to $CO_2$ and its conversion to glycogen and fat. In order to gain a deeper understanding of the transformations of the glucose molecule they started to work on isolated enzyme systems. While working with minced, washed frog muscle they found that by incubation in a solution containing phosphate and traces of adenylic acid a hitherto unknown sugar phosphate was formed. They isolated and identified this compound as α-glucose-1-phosphate, and confirmed its structure by chemical synthesis. Since then this sugar phosphate has been widely known as the "Cori ester".

The next step was the discovery and study of the enzyme (phosphoglucomutase) which catalyzes the reversible conversion of glucose-1-phosphate to glucose-6-phosphate. Their interest in this enzyme was again aroused in 1949 when LELOIR and his group discovered that glucose-1,6-diphosphate is the coenzyme of phosphoglucomutase. Not only did they confirm this work but found that the same mechanism of phosphate migration took place in the interconversion of 2- and 3-phosphoglyceric acid. In this case, the coenzyme is 2, 3-diphosphoglyceric acid.

tists have published papers which were the result of the stimulating atmosphere of the Saint Louis laboratories.

Besides the Nobel Prize in Medicine for 1947, they have been awarded many other prizes: the Midwest Award of the American Chemical Society in 1947; the Squibb Award (American Society of Endocrinology) in 1947. In addition CARL CORI received the Lasker Award (American Public Health Association), 1946; the Sugar Research Foundation Award 1947 and 1950; the Willard Gibbs Medal (American Chemical Society) 1948. GERTY CORI was awarded the Garven Medal (American Chemical Society) 1948; the Sugar Research Prize (National Academy of Sciences) 1950; the Borden Award (Association of American Medical Colleges) 1951 and the St. Louis Award, 1948.

As recognition of their brilliant work, may honors were bestowed upon them: CARL received honorary degrees from the Universities of Western Reserve (1947), Yale (1947), Boston (1948), Cambridge (1949), and GERTY from Boston University (1948), Smith College (1949), Yale (1951), Columbia (1954), and Rochester (1955). They are members of the U.S. National Academy of Sciences, the American Philosophical Society, the American Society of Biological Chemists, the Harvey Society, American Chemical Society, American Society of Arts and Sciences, and Sigma Xi. CARL CORI is also a Foreign Member of the Royal Society and a member of the American Society of Pharmacology and Experimental Therapeutics, The American Association for the Advancement of Science, and the Society of Experimental Biology and Medicine.

The research work of the CORIS bears proof of their imagination, experimental rigor and critical judgement. A vast general culture and a thorough training in Medicine, Physiology and Pharmacology gave them an integrated view of the relations between the chemical changes studied *in vitro* with the behavior of isolated tissues and the entire organism under normal or pathological conditions. Their discoveries have permanent historical importance and have led to fundamental advances in our knowledge of cell physiology. Apart from their scientific achievements, the high human value of their personalities have won the CORIS the friendship and admiration of all those who have the privilege of knowing them. The continuity and perseverance of their work have progressively enlightened the most fundamental mechanisms of biochemical processes.

*Highlights of three decades of work in the CORIs' laboratory*

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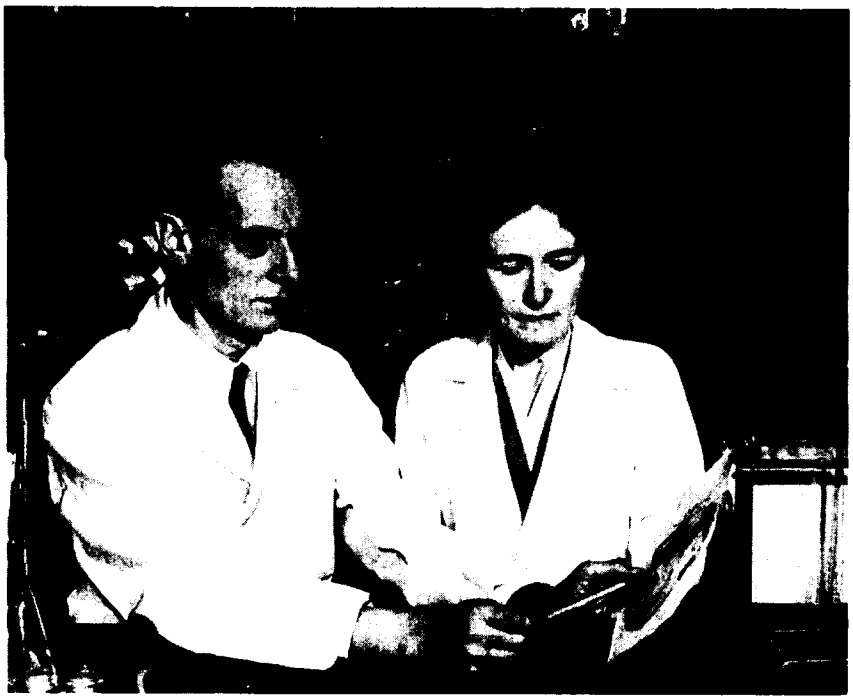
| 1923 | Sugar content of liver and its relation to glycogen synthesis and glycogenolysis (first joint publication). |
| 1925–30 | Muscle-liver lactic acid production-glycogen synthesis cycle ("Cori cycle"); selective intestinal absorption of sugars. |
| 1930–37 | Studies of effects of insulin and epinephrine on carbohydrate metabolism. |
| 1936–37 | Phosphorolysis of glycogen; discovery and isolation of glucose-1-phosphate. |
| 1938 | Discovery of phosphoglucomutase; isolation of phosphorylase. |
| 1939 | First enzymic synthesis of a polysaccharide; elucidation of mechanism of glycogenolysis in liver. |
| 1940 | Coupling of succinate oxidation with phosphorylation. |
| 1941 | Enzymic conversion of glucose to glycogen in the test tube. |
| 1941 | Discovery of myokinase; isolation of fructose-1-phosphate and inorganic pyrophosphate. |
| 1942 | Crystallization of muscle phosphorylase. |
| 1943–44 | Discovery of polysaccharide branching factor (later named amylo-1,4 → 1,6-transglucosidase). |
| 1943–45 | Elucidation of mode of action of phosphorylase and of over-all reversible conversion glucose-1-phosphate ⇌ glycogen + phosphate; discovery of phosphorylases *a* and *b* and their interrelation. |
| 1945 | Crystallization of muscle triosephosphate dehydrogenase. |
| 1946 | Isolation of pure yeast hexokinase; crystallization of muscle aldolase. |
| 1947 | Discovery of specific hexokinases and hormone effects on hexokinase. |
| 1948 | Isolation of hyperglycemic-glycogenolytic factor; crystallization of phosphoglucomutase. |
| 1948 | Discovery of diphosphopyridine nucleotide pyrophosphatase; discovery of bound diphosphopyridine nucleotide in triose phosphate dehydrogenase. |
| 1949 | Crystallization of muscle glycerophosphate dehydrogenase; mechanism of cleavage of phosphate esters studied with $^{18}O$. |
| 1950 | Discovery of control of phosphorylase by epinephrine and hyperglycemic-glycogenolytic factor. |
| 1951 | Discovery of amylo-1,6-glucosidase; enzymic analysis of polysaccharide structure. |
| 1951–53 | Mechanism of reaction catalyzed by triosephosphate dehydrogenase. |
| 1952 | Studies on molecular pathology; pathogenesis of glycogen storage disease. |
| 1953–55 | Enzymic interconversion of phosphorylases *a* and *b* and its physiological significance; studies of tissue permeability; enzymic synthesis of hyaluronic acid. |



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The isolation of glucose-1-phosphate had a number of consequences. The enzyme which leads to the formation of this ester from glycogen (phosphorylase) was discovered in 1938 and crystallized in 1942. It was found in all animal tissues which contain glycogen and in plant tissues containing starch. Phosphorylase was found to be involved in several physiological processes. For the first time, liver glycogenolysis could be explained by the successive action of phosphorylase, phosphoglucomutase and glucose-6-phosphatase. The synthesis of glycogen *in vitro* was an accomplishment at that time. The conversion of glucose to glycogen was achieved *in vitro* by hexokinase, phosphoglucomutase and phosphorylase, in the presence of adenosinetriphosphate and glucose. Phosphorylase can break or make an α-1-4-glycosidic bond at the terminal (non-reducing end) of a glycogen or starch chain. The interaction of inorganic phosphate with the terminal glucosidic bond results in the formation of glucose-1-phosphate and the loss of one chain unit. Thus, phosphorylase catalyzes the reversible polymerization of polysaccharides (polysaccharide phosphorylase).

Two types of phosphorylase were extracted from muscle. One which is active *per se* (phosphorylase *a*) and another which requires trace amounts of adenylic acid (phosphorylase *b*). The conversion of *a* to *b* was found to be catalyzed by an enzyme which was named the P.R. enzyme (prosthetic group removing or, in more recent usage, phosphorylase rupturing). Furthermore, many studies were carried out on the physiological changes of phosphorylase activity and especially, on the action of hormones (insulin).

On mixing crystalline muscle phosphorylase and glucose-1-phosphate no reaction was found to take place. However, when traces of starch or glycogen were added, polysaccharide synthesis began immediately. Therefore, the enzyme did not initiate the formation of a polysaccharide chain, it only added glucose units to a pre-existing chain. Polysaccharide phosphorylase was found to catalyze the synthesis or breakdown of straight-chain polysaccharides. When phosphorylase acts in conjunction with amylo-1,4→1,6-transglucosidase (brancher) the product is glycogen or amylopectin, depending on the ratio of the two enzymes. A separate enzyme, amylo-1,6-glucosidase, hydrolyzes 1,6 linkages once they have been exposed by preceding phosphorylase action. Polysaccharides, such as glycogen and amylopectin, are multibranched, tree-like substances, the structure of which can be studied by enzymatic analysis. Such analysis led to a complete understanding of the structure of glycogen.

Four different types of glycogen storage diseases were recognized. Two with normal and two with abnormal glycogen. The pathological accumulation of polysaccharide was found to be due to a deficiency of glucose-6-phosphatase in the cases with normal glycogen (liver and kidney storage), and attributed to alterations of other enzymes (branchers or debranchers) in the cases with abnormal glycogen.

For their remarkable discoveries of the processes of "catalytic metabolism of glycogen" the Nobel Prize of Physiology and Medicine was awarded in 1947 to the CORIS, shared with me for "the discovery of the importance of the pituitary anterior lobe on sugar metabolism". After 1947, the researches of the CORIS in the same field, developed in a most remarkable way.

Several other enzymes concerned with carbohydrate metabolism were investigated in the Department of Biochemistry of Washington University. D-Glyceraldehyde-3-phosphate dehydrogenase was crystallized from muscle and its composition and mode of action were carefully studied (1945–48). Aldolase was crystallized from rabbit muscle. Glucagon, the hyperglycemic-glycogenolytic factor, was separated from insulin and obtained from dog gastric mucosa (1948–49). Studies on hexokinases and on the formation of fructose-1-phosphate were carried out (1951). The uptake of glucose by isolated rat diaphragm was studied and it was found that in diabetic animals the utilization of glucose is lower than in normals.

The mechanism of action of hormones has been one of the main interests of the CORIS. Over a period of 20 years they carried out several studies on the pituitary. In 1936 they observed that the marked decrease in glycogen and the lowering of blood sugar in hypophysectomized rats occurred with a concomitant increase in the rate of glucose oxidation. In 1945 they studied the action of hormones on hexokinase and observed that some pituitary extracts inhibit this enzyme *in vivo* and *in vitro* and that insulin counteracts this inhibition. Adrenocortical extracts greatly intensified the inhibitory effect of added or previously injected pituitary extracts. It has not been determined as yet which is the active pituitary substance and on the other hand, the *in vitro* effects do not explain the increased sensitivity of hypophysectomized animals to insulin. Further studies will be necessary in order to clarify the action of hormones on hexokinase and the other actions of the pituitary extracts and insulin.

The CORIS have not only carried out personal work of extraordinary originality and significance but they have also inspired and directed one of the most active centers of biochemical research. Their laboratory was and still is the point of attraction of all workers interested in carbohydrate metabolism and more than sixty first class scien-