ISSN:2249-5347
IJSID
International Journal of Science Innovations and Discoveries
An International peer Review Journal for Science

Nobel Prize in Medicines 1947



Carl Ferdinand Cori **Gerty Theresa Cori, née Radnitz** **Bernardo Alberto Houssay**

The Nobel Prize in Physiology or Medicine 1947 was divided, one half jointly to Carl Ferdinand Cori and Gerty Theresa Cori, née Radnitz "for their discovery of the course of the catalytic conversion of glycogen" and the other half to Bernardo Alberto Houssay "for his discovery of the part played by the hormone of the anterior pituitary lobe in the metabolism of sugar"

The teaching body of the Caroline Institute has decided to award one half of the 1947 Nobel Prize for Physiology or Medicine to Professor Carl Cori and Dr. Gerty Cori «for their discovery of the course of the catalytic conversion of glycogen», and the other half to Professor Bernardo Houssay «for his discovery of the part played by the hormone of the anterior pituitary lobe in the metabolism of sugar».

The work of these prize-winners is within the same centrally important sphere, namely the metabolism of sugar in the body. They have elucidated the enzymatic reactions between glucose and glycogen, and have shown how these reactions are controlled by physiological factors. Faulty sugar metabolism may lead to diabetes, with its universally known symptoms. Everyone now knows, too, that in the majority of cases it has been

possible to keep this disease in check by insulin since its discovery by Banting and MacLeod, to whom the Nobel Prize was awarded in 1923. It would be a grave mistake, however, to believe that this brilliant discovery unravelled the immense complex of problems concerning sugar metabolism. Certainly it is long known that insulin decreases the blood sugar level, but until recently the mechanism of this effect was veiled in mystery.

The task of sugar metabolism is to supply energy for the activities of life. One cannot make the slightest muscular movement without the combustion of an appropriate amount of sugar. It is readily understandable that one of our most urgent tasks is to elucidate this branch of metabolism. A clear light has been thrown on previously obscure points in our knowledge, by the discoveries for which the prizes are awarded this year.

Ninety years ago the great French physiologist, Claude Bernard, discovered that the liver and muscles contain a starch-like substance, which he called glycogen, the «sugar former». Every molecule of glycogen consists of a large number of grape sugar molecules, which are united together to be stored up in that form until they are needed. When needed, the glycogen disintegrates again into grape sugar, or glucose, to use a more scientific name. In this way the glucose content of the blood can be kept fairly constant in spite of an uneven supply. The credit for having revealed how the interplay between the glucose and the glycogen takes place falls to Professor and Doctor Cori. From the works of Robison and Embden in the 1920's it was known that the sugar in living cells and tissues, e.g. in yeast and in muscle, appears under certain circumstances bound to phosphoric acid. Closer analysis showed that in these combinations the phosphoric acid was bound to the sixth in the chain of the six carbon atoms of the sugar molecule.

After a great deal of preliminary work during the years 1932-1936, Professor Cori and his wife showed that if ground-up muscle was washed with water, the washed residue could still promote the disappearance of free phosphoric acid, which, as could be expected, was due to its being bound to sugar. But the washing had effected a change; the sugar phosphoric acid then formed exhibited certain singular properties. The Cori's were soon able to prove by means of crystallization and determination of the constitution of the new

compound that the characteristic properties of this phosphoric acid ester, the so-called Cori ester were due to the fact that phosphoric acid was linked to the first carbon atom of the sugar instead of to its sixth. A layman would probably think that such a detail could only be of interest for hairsplitting specialists; but the grain of mustard seed may grow up into a great tree, if it is sown in suitable soil. From this apparently insignificant startingpoint the Cori's and their co-workers, in a long series of masterly studies, have thrown clear light on the previously unknown interplay between glucose, phosphoric acid and glycogen. The reason why the Cori ester is found only in washed muscle is that with the washing water an enzyme is removed, i.e. a protein substance with a special catalytic effect, which moves phosphoric acid from one end of the sugar molecule, the 1-position to the opposite, the previously known 6-position.

An enzyme crystallized by the Cori's and Green, phosphorylase, plays a chief part in the mechanism. It is met with in many different tissues and can be prepared from, e.g., muscle, liver or yeast. If the phosphorylase is allowed to act on glycogen in the presence of phosphoric acid, the whole glycogen molecule is split up, with the simultaneous appearance of glucose molecules bound to phosphoric acid. This substance is indeed the Cori ester. The same process may, however, also proceed in the opposite direction, so that glycogen is formed from the Cori ester. The direction of the reaction is determined by the relative amounts of the components. For glycogen synthesis to start, a small amount of glycogen must be present as a nucleus upon which to build. Thus, if under extreme conditions it should happen that all the glycogen were broken down, the individual in question would lose for all time the capacity to form glycogen. Such a thing cannot happen, however, thanks to an ingenious protective mechanism discovered by the Cori's. When the glycogen supply threatens to come to an end, an enzyme intervenes, which for the time being inactivates the glycogen-splitting phosphorylase and thus preserves the last traces of the glycogen. Nature's wealth of invention is truly amazing!

For a chemist, synthesis is the definite proof of how a substance is built up. Professor and Doctor Cori have accomplished the astounding feat of synthesizing glycogen

in a test tube with the help of a number of enzymes which they have prepared in a pure state and whose mode of action they have revealed. This synthesis would be impossible by methods of organic chemistry alone, since the six carbon atoms of the various glucose molecules might conceivably be bound to one another in a chaotic mass of combinations. The Cori enzymes made this synthesis possible, because the enzymes favour certain modes of linkage. In spite of this, the difficulties were formidable; the first isolated phosphorylases formed unbranched compounds resembling starch, and only with the help of further enzymes were the branched chains characteristic of glycogen obtained.

Blood and tissues contain free glucose. The chemical changes in metabolism are always initiated by its being coupled to phosphoric acid, which is transferred from a nitrogenous phosphoric acid compound usually called ATP. The reaction is promoted by the enzymehexokinase. Two years ago a great sensation was aroused in the scientific world when the Cori's, together with Price, Colowick and Slein, announced that this hexokinase reaction was promoted by insulin but checked by another hormone in extracts from the anterior lobe of the pituitary gland, the hypophysis. The experiments have been confirmed and extended this year. This discovery is of fundamental significance. We have long known that the secreting organs - the pituitary gland, the thyroid gland, the accessory thyroid glands, the suprarenal glands, the pancreas, the sex-glands, and a number of others - exercise a decisive influence on our vital functions. But the perpetual question, which we meet already in Luther's catechism: «How does it take place?» has remained unanswered until the discovery - published by Cori's Institute - that hormones intervene chemically in the hexokinase reaction. A wide new field of physiology was thereby linked up with the domain of chemistry. In the near future it will be possible to express a further part of the mystical «vital force» in chemical formulae.

This latest work of the Cori's is directly connected with the discovery of the effect of the hypophysis on the utilization of sugar by Professor Bernardo A. Houssay, who has also been awarded a prize. The hypophysis, or the pituitary gland, is a small secreting gland at the base of the brain, where it lies sunk in a bony hollow in the most sheltered spot in the

whole body. Its importance justifies its sheltered position, but its size is far from impressive: that of a bean in man, a pea in the dog, and a radish seed in the toad Bufo marinus.

People sometimes cite, more or less jokingly, the statement by Cartesius, the famous philosopher, that the soul lies in the pineal gland. Now it does so no more than in any other individual organ, but if Cartesius had chanced, instead, to guess at the hypophysis, which looks much the same and is situated immediately in front of the pineal gland, he would have been nearer the truth, for in spite of its diminutive size the hypophysis exercises a number of vital functions and occupies a commanding position in relation to the other endocrinous glands. By means of its hormones the hypophysis controls the thyroid, the sex glands and the cortex of the suprarenal glands; it regulates the formation of milk and the growth of the whole body. By means of extremely beautiful experiments Houssay has shown that it also plays a prominent role in the conversion of sugar.

It was the discovery of insulin which aroused Houssay's interest in the hypophysis. As early as in the 1880's the great French research worker, Pierre Marie, had found that the excretion of sugar in the urine was a regular symptom in acromegalia, which is due to a disturbance in the function of the hypophysis, and therefore a connection between the function of the hypophysis and the metabolism of sugar might be suspected.

Houssay has worked chiefly with dogs and a large kind of toad, Bufo marinus, which is plentiful in the Argentine. In many series of experiments the hypophysis, or sometimes only its anterior lobe, was removed by operation. In the case of dogs, especially, the operation calls for highly developed technical skill if the result is not to be «the operation was successful, but the patient died». Houssay then found that the animals which had been operated on were abnormally sensitive to insulin and died with symptoms of bloodsugar deficiency from doses which were quite harmless for normal animals. In conformity with this, the glycogen content in the liver was abnormally low. A corresponding pathological picture is met with in the case of Simmond's disease in man. Dogs and toads exhibited the

same kind of reaction, as have all the rest of the vertebrates hitherto investigated. This proves that Houssay had discovered a universal biological mechanism.

The discovery that a daily implantation of anterior lobe of hypophysis from toads on the operated animals protected the latter from the dangerous effect of insulin, was also of immense importance.

Thus the hormone of the anterior lobe of the hypophysis was clearly antagonistic to the hormone of the pancreas, insulin. This was confirmed and illustrated by a further series of ingenious experiments. Davidoff and Cushing had observed already in 1927 that if diabetes was provoked in dogs by the removal of a part of the pancreas, the symptoms were moderated if part of the hypophysis was also taken away. However, these experiments were not entirely conclusive, since as a rule the diabetes provoked in this way may disappear spontaneously. Houssay and Biasotti obtained definite elucidation by means of a more radical procedure. The whole hypophysis was first removed and subsequently the pancreas. For three whole days after the latter operation no sugar appeared in the urine, which is always the case if the pancreas is removed from an animal which still has its hypophysis.

In 1931, in the course of their work on the growth hormone of the hypophysis, H. M. Evans and his co-workers in U.S.A. found that the extract which naturally was still impure - provoked diabetes if injected into animals. At the same time and independently of Evans, Houssay and his co-workers arrived at similar results. After injections of extract from the anterior lobe of the hypophysis, the diabetes persisted, in many cases for months, and this was found to be due to injury to the insulin-producing cells in the pancreas.

The active factor in the hypophysis is so extremely sensitive that all the preparations must be made at a low temperature, if they are not to be spoiled. Therefore a number of research workers, who were less careful than Houssay on this point, did not at first succeed in confirming his results. It may be added that the Cori's had to grapple with the same difficulties in the preparation of their extract of hypophysis, which to some extent confirms that both groups of workers were dealing with the same active substances.

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A short description of the most important results of many years of scientific work can never give a complete idea of the days and nights of labour which is most frequently fruitless. Diligence and patience are indispensable components in the mental equipment of the research worker. These alone seldom or never lead to pioneer discoveries, however, because it is impossible to deal thoroughly and systematically with all the conceivable alternatives, at least in the case of biological problems. The possibilities are all too many. Intuition is the indispensable lode-star, promising new goals to be reached by a labyrinth of paths, the majority of which are blind alleys.

In work characterized by unremitting diligence, brilliant skill, and masterly acumen, today's prize-winners in physiology or medicine have shown themselves to possess all the qualities of the great research worker in natural sciences. They have thrown light on previously undreamt of connections between the inaccessible world of the enzymes and the hormones. The task of the doctor to prevent, heal or alleviate disease demands a knowledge of the functions of the body; this year's prize-winners have opened new fields in which Ernest Starling's happy expression «The physiology of today is the medicine of tomorrow» will prove its truth.

Professor Carl Cori and Doctor Gerty Cori. During the past decade the scientific world has followed your work on glycogen and glucose metabolism with an interest that has gradually increased to admiration. Since the discovery of glycogen by Claude Bernard ninety years ago, we have been almost totally ignorant of how this important constituent of the body is formed and broken down. Your magnificent work has now elucidated in great detail the extremely complicated enzymatic mechanism involved in the reversible reactions between glucose and glycogen. Your synthesis of glycogen in the test tube is beyond doubt one of the most brilliant achievements in modern biochemistry. Your discovery of the hormonal regulation of the hexokinase reaction would seem to lead to a new conception of how hormones and enzymes cooperate.

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In the name of the Caroline Institute I extend to you hearty congratulations on your outstanding contribution to biochemistry and physiology.

Professor Houssay. That great philanthropist, Alfred Nobel, had a great personal interest in physiology. Few things gave him so great a pleasure as being able to witness the brilliant development of this science in the nineteenth century. In the development of physiology, Professor Houssay, you have played a very active part, particularly regarding the work which you have brought into prominence and which is now to be honoured by the Nobel Prize.

The hypophysis is a small gland, but its importance is not related to its size, since it regulates many of our most important functions. Amongst these functions, which you have studied and analysed in a clear and striking manner, is the dominant role the gland plays in our metabolic processes.

On behalf of the Caroline Institute I congratulate you on receiving the Nobel Prize which is presented to you today, and which is a sure sign that your name will ever remain engraved in the annals of physiology.

Professor Carl Cori and Doctor Gerty Cori; Professor Houssay. I now have the honour of asking you to accept the prize from the hands of His Majesty our gracious King.

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http://www.nobelprize.org/nobel_prizes/medicine/laureates/1947/press.html