

## Chemistry

### 3. Research on Sugar Nucleotides Brings

#### Honor to Argentinian Biochemist

One day in Buenos Aires some 20 years ago, a young and inexperienced biochemist in despair asked Luis Leloir, "But how do you know, Dire,\* what experiment to do next, where to direct your research?" Back came this answer: "Oh, you just take hold of one end of the line and keep pulling, little by little." Leloir has pulled quite a bit by now, bringing in one discovery after another. We will pull on another rope, that of memory, and see what comes to the surface. A vivid remembrance is that of the day when, attracted by a small newspaper ad offering a fellowship, I went to see the director of the Instituto de Investigaciones Bioquímicas, Fundación Campomar. The imposing name referred to a small and rather dilapidated one-story house, transformed into a laboratory. On a small patio, a slightly built man wearing a grey and rather shabby duster was gassing test tubes with hydrogen sulfide. He introduced himself as Leloir, and without interrupting his polluting task said amiably: "Go ahead and talk if you please. While I am working I will listen to you." This lack of ceremony was applied equally to the young applicant and to famous visitors.

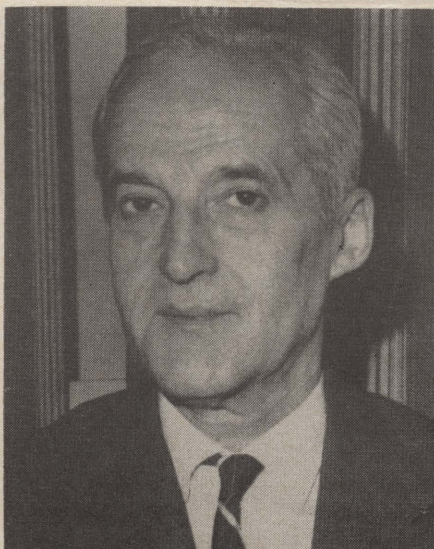
Indeed, it is characteristic of Leloir that he talks to everybody in the same courteous, unassuming way—the mark of a gentleman—and that his experiment must go on at all times—the mark of a worker. His rare demonstrations of anger occur only when someone shows bad manners or wastes his time with useless talk. The serenity that Leloir displays at all times and his quiet sense of humor have been a powerful influence in maintaining a calm atmosphere and in soothing bad tempers in the laboratory. His Spartan use of words does not make it easy for a student or a fellow to work with him. Yet, in his brief encounters with the Dire, the disciple will be surprised again and again by the penetrating remark which abruptly opens unexpected vistas and makes him swear under his breath, "How the hell does he do it . . . ?"

Frugality does not stop with words. One rainy day water leaked into the library of the decaying quarters which

housed the Institute. The roof was never fixed—it was too costly; but Leloir built a system of gutters of waterproof cardboard *inside* the library to catch the seeping water and lead it away from the books into strategically placed pans. Such ingenious and, above all, money-saving inventions were greatly encouraged in the laboratory, and several homemade apparatus and gadgets still in use bear the mark of Leloir's craftsmanship. This parsimony brought one important point home: One should not be discouraged by dearth of material means and unexpected difficulty should be a challenge to one's ingenuity and resourcefulness.

Luis Leloir comes from an old Argentine family, but he was born in 1906 in Paris when his family was on a brief visit to France. He grew up and was educated in Buenos Aires and studied medicine at Buenos Aires University. It is said that a man of genius usually shows a wide range of interests, and that he leaves his mark in more than one field. This is especially true of Leloir. After completing his internship in 1932, he briefly engaged in endocrinological research under the guidance of Bernardo A. Houssay, who, in later years, received a Nobel prize in medicine.

Attracted by the burgeoning science of biochemistry, in 1935 Leloir went to Cambridge, England, where Sir Frederick Gowland Hopkins directed the Institute of Biochemistry. After his



Luis Leloir

return to Buenos Aires, he worked from 1937 to 1944 in the Institute of Physiology of the medical school, studying the oxidation of ethanol and, later, of fatty acids. It may come as a surprise to some readers that Leloir and Muñoz were the first to obtain reproducibly an enzymatic system capable of oxidizing fatty acids *in vitro*. This important discovery was not followed up, and Leloir joined a team that was studying renal hypertension under the leadership of Eduardo Braun-Menendez. This work culminated in the discovery of the hypertensive peptide angiotensin. Leloir had a principal role in establishing the mechanism by which angiotensinogen is transformed into angiotensin by the enzyme renin.

Perón's access to power in Argentina led to the disbanding of the group at the Institute of Physiology, and Leloir spent 1945 and 1946 in the United States.

Back in Buenos Aires, and with the help of his former teacher, Professor Houssay, he obtained the support of a businessman, Jaime Campomar, to establish a private institute for biochemical research. The Institute was dedicated in November 1947, and on that day began a most fruitful period for Leloir and his associates. The initial group included, in addition to Leloir, Ranwel Caputto, Carlos Cardini, Naum Mittelman, Alejandro Paladini, and Raul Trucco. The atmosphere of the laboratory was that of a closely knit family. The oppressive political environment contributed to the cohesiveness of the group and imparted a feeling of pioneering effort to what might otherwise have been an ivory-tower situation. Those days will not be easily forgotten by the participants.

The goal initially set by the group was to discover how milk sugar, or lactose, was synthesized. The problem was first attacked from the opposite direction, that is, by studying the degradation of lactose by yeast. This approach gave unexpected dividends. The first steps, a hydrolysis of lactose to glucose and galactose, followed by phosphorylation of galactose in the unusual 1-position, were quickly established. The further transformation of galactose 1-phosphate into glucose 6-phosphate required heat-labile enzymes and two heat-stable cofactors. One of the latter was identified as glucose 1,6-diphosphate and found to act as a coenzyme for phosphoglucomutase, the enzyme that catalyzes the conversion of glucose 1-phosphate into

\* "Dire," short for director, is the affectionate appellation used by Leloir's co-workers.

glucose 6-phosphate, thus providing Leloir and his group with their first big achievement. After purification, the structure of the second heat-stable co-factor was established in a remarkable tour de force. The substance turned out to be uridine diphosphate glucose (UDPG), the first sugar nucleotide. The discovery of this new type of substance and of its function in sugar interconversion and in the biosynthesis of complex carbohydrates is the basis for the present Nobel award.

The mechanism by which UDPG participates in the conversion of galactose 1-phosphate to glucose 1-phosphate was established by Kalckar and his co-workers and by Leloir himself. The uridylyl group is enzymatically transferred from UDPG to galactose 1-phosphate, thus giving rise to UDP-galactose. An epimerase converts this nucleotide back into UDP-glucose, and the cycle is restarted. Thus, the role of sugar nucleotides as substrates for monosaccharide interconversion was established.

The initial successes of Leloir's group brought some fame and some welcome financial assistance. The Rockefeller Foundation was the first to help. Of great importance was a grant made by the National Institutes of Health in 1951 and continued until last year, when restrictions in foreign aid forced its cessation.

New sugar nucleotides, UDP-acetylglucosamine and GDP-mannose, were isolated from yeast in Buenos Aires, and soon many others were found in different laboratories. In 1961 40 sugar nucleotides were listed in a review article, and the number now is probably close to 100. The inability to find a function for the new compounds initially caused some despair in the Institute, but indications were already accumulating that these substances might participate in glycosyl transfer reactions. The first confirmation was provided in 1953 by the discovery of Dutton and Storey that UDP-glucuronic acid served as a precursor of glucuronic acid conjugates. During the same year in Buenos Aires the first disaccharide, trehalose phosphate, was synthesized enzymatically from UDP-glucose and glucose 6-phosphate with the use of a preparation from yeast. Shortly thereafter Leloir and his associates reported the enzymatic formation of sucrose and sucrose phosphate. The pathway was now clearly indicated, and soon the synthesis of the first polysaccharide, chitin, was an-

nounced by Glaser and Brown, thus providing a function for the elusive UDP-acetylglucosamine. By now the field was expanding in an exponential fashion, and in a few years there were many new examples of the sugar nucleotides' two main functions, namely (i) serving as substrates for enzymes which interconvert monosaccharides, and (ii) acting as donors in glycosyl transfer reactions, thus leading to the formation of glucosides, di- or oligosaccharides, and homo- or heteropolysaccharides. For Leloir this new phase culminated in the discovery of the mechanism of glycogen synthesis, a function previously assigned to phosphorylase. Again, UDP-glucose was the precursor. That was the last discovery to be made in the old house. Soon thereafter Perón's dictatorship was overthrown, and the new government, more benevolent toward science, provided the Institute with much larger premises. The day we left the old lab, Leloir said in a prophetic voice: "We will remember with regret the happy days we spent here!" He was right: in the new building there were no leaking roofs to fix.

The staff of the laboratory rapidly expanded, partly because of the larger space available and partly as a result of an agreement with the School of Science of the University, which increased the number of positions. Leloir himself was appointed Professor Extraordinarius and later was made

chairman of the department of biochemistry, a position he recently relinquished to have more time for his research.

Leloir has received many prizes and other honors in recent years, and a continual stream of invitations has caused him to travel with relative frequency. Coming from a family of private wealth, Leloir has donated all of his prize money as well as his professor's salary and many collections of journals to the Institute. Indeed, he is as generous with his own money as he is parsimonious with that of others.

Despite his new activities and the increase in administrative problems resulting from the expansion of the Institute, Leloir has not for a single day interrupted his experiments. New projects dealing with different glycogen synthetases, then the discovery of ADP-glucose as the precursor of starch in plants, and more recently studies on the structure and formation of particulate glycogen have kept him busy. You will find him there, at his laboratory bench.

The world is made richer by the presence of persons like Leloir. With his example he taught many of us a style of life and, with his work, he has enlarged the horizon of human adventure.

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## Science Funds: NSF Survey Probes Effects of Shifts in Federal Aid

A report released 15 October by the National Science Foundation provides the first broad scale picture of what has happened to the financing of academic research and science education in this period of decelerating federal support. Titled "Impact of Changes in Federal Science Funding Patterns on Academic Institutions,"\* the report confirms the existence of a financial recession in university science activ-

ities. And it clearly points out that private institutions are the hardest hit. But it also provides ground for believing that, in general, the situation is appreciably short of the cataclysm routinely depicted by many leaders of the scientific community in recent years. In any case, though interpretations may widely differ, the report—actually a summary that will be expanded upon in a publication probably early next year—becomes at once a basic document for discussing the financial health of science in the universities. (Medical schools, perhaps the most financially

\*NSF 70-39, 8 pages, available without charge from the National Science Foundation, Office of Economic and Manpower Studies, Washington, D.C.