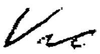
Special Issue

Dedicated to Raymond Urgel Lemieux

16 June 1920 – 22 July 2000

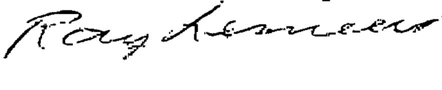
University of Alberta – Photo Services



For fifty years, I have shared the excitement of unravelling Nature's secrets in collaboration with the world chemical community. My research was mainly in the realm of complex carbohydrate molecules and their functions in the guidance of natural processes. The collaborations I received from my students and colleagues were most precious and necessarily based in the great body of chemical knowledge to which you have importantly contributed.

My active participation in research has had to end and it seemed appropriate to prepare the attached review. In fact, I am proud that I could end my career with the novel concept of hydrophobicity and look forward to seeing how well it will survive.

With compliments

 [1]

Before the mid-1950s, carbohydrate chemistry was considered to be the refuge, the last remnants of classical organic chemistry, strewn with empirical observations, bizarre test reactions, and the reputation of uncrystallizable substances. It was a field of its own, removed from the mainstream of organic chemistry. The schools of Haworth in England and Hudson and Wolfrom in the United States provided the systematic accumulation of knowledge in this field. The quantum leap was provided by Ray Lemieux.

This *In Memoriam* Special Issue of *Synlett* for Ray Lemieux celebrates the field of carbohydrate chemistry. Over the past half century, he has been singularly responsible for elevating this obscure, highly specialized, and introverted discipline into the mainstream of organic chemistry. In fact, we need not proceed much further into the 21st Century to recognize the significant imprint of the research of Ray Lemieux on the fields of chemistry, biology, and medicine.

Formal Studies to Research in the "boondocks"[2]

Raised in Edmonton, Alberta, in "an Irish-French-Ukrainian ghetto where the main challenge was to avoid associations that could lead to reform school", Ray fell under the spell of Ruben Sandin, the legendary teacher at the University of Alberta who enticed budding chemists to continue graduate work with one-sentence letters of recommendation. Rube sent Ray to Clifford Purves at McGill's Pulp and Paper Institute for his initial confrontation with the strange world of carbohydrates. As his Ph.D. studies ended in 1946, Ray learned about the work Melvin Wolfrom at Ohio State University on the structure of streptomycin, just discovered to be a carbohydrate and, with Purves' recommendation, took up postdoctoral work, which immersed him in the new field of amino sugar antibiotics and led to the establishment of the absolute stereochemistry correlation of sugars and amino acids and, in future independent work, to a multitude of papers on methodologies based on anomeric stereocontrol.

In 1953, working in the humble ("boondocks") surroundings of the Prairie Regional Laboratories in Saskatoon, Saskatchewan, Lemieux demonstrated his appreciation of the profound impact of ongoing work in physical organic chemistry and conformational analysis by the first synthesis of sucrose, a monumental achievement which initiated the flow of contributions in synthetic carbohydrate chemistry from his laboratories. During these studies, his keen sense of observation in a laboratory refrigerator cleanup led to the discovery of an oxidation reagent which bears his name.

"*. . . you never learn much by talking to people who are doing the same thing you are*."[3]

After moving to the University of Ottawa in 1954, Ray heard a lecture on NMR and wondered if steric effects would cause axial and equatorial oriented hydrogens to have different chemical shifts. In collaboration with Schneider and Bernstein, true masters of the "machine", a 40 MHz spectrum showing low-field signals with large and small spacings due to anomeric α and β hydrogens was recorded in early morning hours when "city line voltage was more constant and the street traffic was relatively quiet". This landmark 1957 contribution, which forever changed how structural proof is viewed, also laid the experimental foundation for the Karplus relationship between the viscinal coupling constant and the torsion angle and for the use of time-averaged coupling constants to estimate conformer populations. In the same period, initially only published in a thesis and communicated at two conferences, the anomeric effect was discovered constituting a fundamental stereoelectronic effect of widespread occurrence both in affecting stabilities of molecules in the ground and transition states which has had pervasive impact in mechanistic, synthetic, and theoretical chemistry.

In the 1960–1965 period, with the acquisition of a powerful 60 MHz NMR instrument, several other major exciting events occurred in the Lemieux labs: analysis of the NMR spectra of dioxalanes showed the requirement that geminal and vicinal coupling constants bear opposite signs, results which necessitated revision of the view based on theoretical calculations; the absolute configuration of detrarotatory 1-deuerioethanol was established which has had significant influence in the field of biosynthesis; and the reverse anomeric effect was postlated, thereby predicting the "coiling" of oligosaccharides (now possible with a laptop), and providing a rational basis of the stereoelectronic effect in oxygen and nitrogen heterocycles.

"*. . . answers to questions of basic importance . . .*"

In the early 1970s, Lemieux, seeking to understand enzyme-catalyzed transformations of carbohydrates, began his systematic work on synthesis, conformational analysis and receptor binding properties of oligosaccharide determinants. Concurrently, initial insight into the structures of complex oligosaccharides and evidence on critical messenger substances in cell-cell recognition and glycoprotein biosynthesis and transport was being obtained. He entered this field at a time when further progress was frustrated by lack of materials for study and the most direct solution, the synthesis of these complex molecules, had not been attempted for lack of required synthetic methods. Even the construction of a simple disaccharide was a hurdle and the synthesis of a trisaccharide was a major challenge.

Taking advantage of his appreciation of the anomeric effect and the emerging structural elucidation techniques, Lemieux discovered new pathways for glycosylation and solved the long-standing problem of the controlled, stereospecific formation of the glycosidic linkage. Among the new methods, glycosylations based on the oximino-chloride-, the phthalimido- and the halide-ion methods are truly landmark achievements and provided the required weapons to attack the problem of complex oligosaccharide synthesis. In particular, the halide-ion glycosylation, first announced at a Gordon Conference in 1968, rendered possible the first practical synthesis of biologically significant trisaccharide antigenic determinants and set the foundation for research in other laboratories. In characteristic fashion, Ray conquered these outstanding problems by logical and persistent stages which, as we now observe with hindsight, is establishing the power of modern carbohydrate chemistry in solving central problems in enzymology and immunology and a diverse array of biomedical applications now collectively referred to as glycobiology.

Following Pasteur's Dictum

With brilliant insight, Lemieux proposed that the synthetic trisaccharides could be used as artificial antigens. As Ray wrote retrospectively, his first encounter with blood group chemistry was the reading of Maurice Stacey's "Chemistry of Mucopolysaccharides and Mucoproteins" in the year he obtained his Ph.D. degree. Synthesizing the oligosaccharides bearing "linker-arms" allowed their covalent attachment to appropriate carrier molecules. Furthermore, he recognized that attachment to solid supports would provide biospecific absorbents. The most exciting development occurred when immunization experiments with these antificial antigens raised antibodies specific for the carbohydrate determinants. Isolation of the carbohydrate-specific antibodies was followed by production of antibodies specific for human blood-group determinants which allowed, for the first time, the use of totally synthetic ologosaccharides for detecting and recognizing the corresponding naturally-occurring substances on cell and tissue surfaces. With the availability of synthetic material, determination of blood type no longer required "real" blood.

Access to synthetic oligosaccharides in quantity triggered the next logical step to establish their conformational properties. As Lemieux anticipated earlier, the relative orientations of contiguous sugar residues in oligomeric structures is governed by a stereoelectronic effect which he verified using ^{13}C- enriched model glycosides and, subsequently, by molecular modeling and calculations. Always aiming for wide scope and applicability, he devised predictive regimens for establishing the conformational properties of complex oligosaccharides. The knowledge gained led to investigations on the binding of human blood-group specific determinants to antibodies and lectins. To elucidate the structural features which affect oligosaccharide recognition and binding by protein receptors, over one hundred tri- and tetra-saccharide analogues were synthesized in the Lemieux laboratories based on which, contrary to reasonable expectation that protein-carbohydrate interactions are governed by hydrogen-bonding, he proposed that binding is governed by hydrophobic properties of oligosaccharide surfaces and their configurational and conformational properties. In his final triumph, he postulated the source of the binding energy between proteins and carbohydrate epitopes ("How water provides the impetus for molecular recognition in aqueous solution"),[1] a question of central significance to understanding carbohydrate absorption from aqueous media into the active sites of enzymes and other receptor sites. Characteristically, this research was far ahead of its time and can be taken to the next discovery stage only by the very recently evolving technology.

"*The necessary number of mistakes were made*."

Starting with an early interaction with Bristol laboratories, Lemieux founded R & L Molecular Research Ltd. in 1962 and, with his "feet wet" and the firm belief in the development of the university as an instrument to serve the Canadian economy, established Raylo Chemicals Ltd. and Chembiomed (now Synsorb Biotech). Although experiencing a "shallow learning curve", Lemieux refers to this as a resounding successful experiment. The companies, with business in custom synthesis and monoclonal antibodies and immunoadsorbents respectively, have become commercially successful and have played a significant role in teaching the university and the local government about high technology.

"*My proudest achievement is my family*"

At Ohio State University, Ray met a graduate student, Virginia McConaghie, whom he married in 1948, an event he called the real beginning of his career. The obvious pride in his five daughters and one son is revealed in the photographs[2] and in conversations in which, with a twinkle in his eye, and especially in a bar, he delighted in relating their accomplishments. Equally revealing of Ray is the dedication to his seventeen grandchildren.

The contributions of Ray Lemieux to organic chemistry, spanning structural and synthetic chemistry, NMR – based methods for stereochemical assignments, stereoelectronic concepts, and molecular recognition, have uniquely contributed to the emergence of carbohydrate chemistry as a magnificent field of intellectual and practical consequences with profound influence in areas bridging chemistry to biology and medicine.

Fortuitously, this Special Issue appears fifty years after the disclosure of the monumental synthesis of sucrose. The diversity of papers in this issue, ranging from former students and collaborators, to the new generation of carbohydrate chemists, and to chemists in unrelated fields of research, attest to the legacy of Ray Lemieux. Ray would have broken into a broad grin, given generous credit, and expressed excitement for discoveries on the horizon.

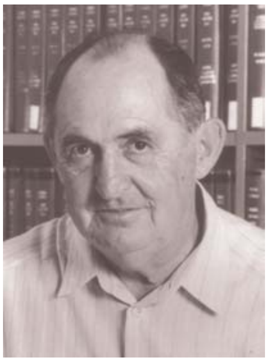
Victor Snieckus[3,4]

(1) Reproduced from the cover of a reprint, Lemieux, R. U. *Acc. Chem. Res.* **1996,** *29*, 373 sent by Ray to colleagues worldwide.
(2) Selected quotes are extracted from Lemieux, R. U. *Explorations with Sugars. How Sweet It Was,* Volume in the Series *Profiles, Pathways and Dreams. Autobiographies of Eminent Chemists*, Seeman, J. I. Ed., American Chemical Society, Washington, DC. 1990.
(3) I am indebted to Bill Ayer, David Bundle, Bert Fraser-Reid, and Ole Hindsgaul, distinguished former students and colleagues of Ray Lemieux for providing memoirs, articles, and biographies which give deeper insight into the rich life and career of this most outstanding Canadian chemist of the 20th century. Fraser-Reid, B. *Can. J. Chem.* **2000**, *80*, August issue, xii. Hindsgaul, O.; Bundle, D. R. *Bioorg. Med. Chem.* **1996**, *4*, 1795; Bundle, D. R. *Biorg. Mems. Fell. R. Soc. Lond.* **2002**, *48*, 251. I am particularly grateful to Ole Hindsgaul for invaluable assistance in the invitation of contributors and in the refereeing process and Karin Fodor whose sharp recall memory allows us to enjoy the shown photo.
(4) Parts of this editorial are based on my nomination letter for a prize that Ray Lemieux did not receive. If Ray would have been present during my final undergraduate year at the University of Alberta when I failed to characterize a simple sugar unknown in the qual organic lab, my career would probably have taken a different path.

Biographical Sketch

Raymond Urgel Lemieux

16 June 1920 – 22 July 2000



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Education

B.Sc. (Honors Chemistry), University of Alberta, 1939–1943; Ph.D. McGill University, 1943–1946; Postdoctoral Fellow, Ohio State University, 1946–1947.

Professional Career

Assistant Professor, University of Saskatchewan, l947–1949; Senior Research Officer, Prairie Regional Laboratory, National Research Council, l949–1954; Professor and Chairman, Dept. of Chemistry, Vice-Dean, Faculty of Pure and Applied Science, University of Ottawa, l954–196l; Professor of Organic Chemistry, 1961–1981;Chairman, Division of Organic Chemistry 1966–1973, 1981–1983; University Professor, 1981–2000; University Professor Emeritus, 1985–2000, University of Alberta; Co-founder, President and Research Director, l963–1976, R & L Molecular Research Ltd., Edmonton; Founder, President and Research Director, l966–1976, Raylo Chemical Ltd.; President, 1977–1978, Honorary Member, Board of Directors, 1986–1991, Chembiomed Ltd.

Medals and Prizes (selected)

National: First Award, Division of Organic Chemistry, Chemical Institute of Canada (CIC),1954; Louis Pariseau Medal, Association Canadienne Francaise pour l'Advancement des Sciences,1961; Palladium Medal, CIC, 1964; Izaak Walton Killam Award, The Canada Council, 1981; Sir Frederick Haultain Prize, Government of Alberta, 1982; Medal of Honour, Canadian Medical Association, 1985; Canada Gold Medal for Science and Engineering, First Recipient, 1991; E. C. Manning National Award of Distinction, 1992; PMAC Health Research Foundation Medal of Honour, 1992. *International*: C. S. Hudson Award, American Chemical Society, 1966; Haworth Medal, The Chemical Society, England, 1978; Tishler Award Lecture, Harvard University, 1983; Rhône-Poulenc Award, Royal Society of Chemistry, 1989; King Faisal International Prize in Science, 1990; "Albert Einstein" World Award of Science, 1992; Wolfe Prize in Chemistry, 1999.

Honorary Degrees

Thirteen from the major *Canadian Universities* over the period 1967–1993; Docteur, Université de Provence, France, 1972; Doctor of Philosophy, University of Stockholm, Sweden, 1988.

Distinctions (selected)

Canadian: Fellow, CIC, 1954; Fellow, Royal Society of Canada, 1955; Centennial of Canada Medal, 1968, Officer of the Order of Canada, 1968; Honorary Fellow of the Canadian Society for Chemistry, 1986; Le Sueur Award of The Society of Chemical Industry, 1989; Alberta Order of Excellence, 1990; Honorary Fellow of the CIC, 1992; Great Canadian Award, 1993; Special Alberta Science and Technology Foundation Award – "Alberta Pioneer", 1993; Induction to University of Alberta Alumni Wall of Recognition, 1994; Companion of the Order of Canada, 1994; *Foreign*: Fellow of the Royal Society of London, 1967.

Distinguished Lectures (selected)

Canada: C. B. Purves Lectures, McGill University, 1969; J. W. T. Spinks Lecturer, University of Saskatchewan, 1977; Armes Lectures, University of Manitoba, 1979; W. J. Chute Memorial Lecturer, Dalhousie University, 1980; C. I. L. Distinguished Lecturer, Acadia University, 1980; A. R. Gordon Distinguished Lecturer, University of Toronto, 1982; J. K. N. Jones Memorial Lecturer, Queen's University, 1982; C. I. L. Distinguished Lectureship, Simon Fraser University, 1983; Conferencier Barré, University of Montreal, 1983; University Lecturer in Chemistry, University of Ottawa, 1990. *International*: Karl Folkers Lecturer, University of Illinois, 1958; Karl Pfister Lecturer, MIT, 1968; Fred Smith Lectures, University of Minnesota, 1978; Karl Pfister Lecturer, MIT, 1981; Distinguished Visiting Lecturer, James Cook University, Australia, 1983; Leopold Ruzicka Centennial Symposium, Swiss Chemical Society, 1987; Seville Academy of Science, Spain, 1989; Alfred Burger Lecturer for 1990–1991, University of Virginia, 1990; First Cytel Lecture, Scripps Research Institute, La Jolla, CA, 1992; 1st Decennium Symposium, King Faisal International Prizes in Medicine and Science, London, U.K., 1992; Nieuwland Lecturer, University of Notre Dame, Notre Dame, IN, 1993; Korea Lectureship in Organic Chemistry, Korea, 1993.

Named Lectures

The Lemieux Lectures, University of Ottawa, inaugurated in 1972; The Raymond U. Lemieux Lectures on Biotechnology, University of Alberta, inaugurated in 1987; The R.U. Lemieux Award for Organic Chemistry, Canadian Society for Chemistry, inaugurated in 1992.