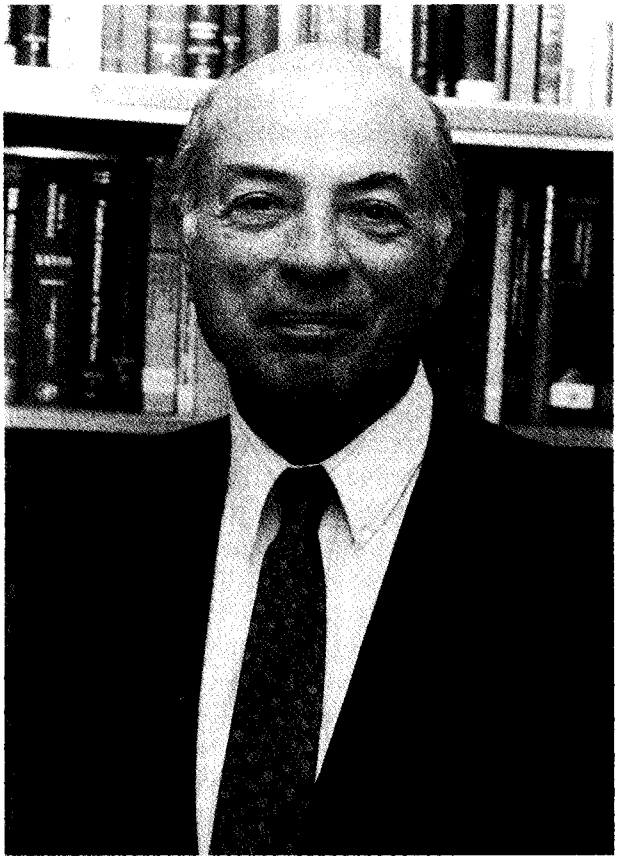

Professor Nathan Sharon

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PROFESSOR NATHAN SHARON

Nathan Sharon was born on November 4, 1925, in Brisk, Poland, and in 1934 emigrated to what was then Palestine. After graduation from High School in Tel Aviv in 1943, he enrolled as a student at the Hebrew University in Jerusalem, where he was awarded the M.Sc. degree in 1950. However, already in 1949, he started as Research Assistant in the Dairy Research Laboratory at the Agricultural Research Station in Rehovot, where he first became acquainted with *Bacillus subtilis* (later classified as *Bacillus licheniformis*), an organism which was to keep him busy again in the future. In 1950, he began work on his Ph.D. thesis under the guidance of Aharon Katzir (Katchalski) on the chemical interactions between sugars and amino acids. Thus, Sharon was introduced into the field of carbohydrate–protein interactions at a very early stage of his scientific career. Although after his doctoral studies he did not pursue the chemical aspects of such interactions, this topic became, in one form or another, the main subject of his research activities and the area in which his major contributions were made.

Sharon was awarded his Ph.D. degree in 1953 and the following year was appointed Research Assistant in the Department of Biophysics at the Weizmann Institute of Science in Rehovot, which was to be his scientific home until this day and Head of which he became in 1973. In the 1950's, the Department was headed by Ephraim Katzir (Katchalski) who did there his pioneering work on the chemical synthesis of poly-α-amino acids and their use as protein models. Sharon investigated the action of proteolytic enzymes, in particular pepsin, on a variety of such homo- and hetero-polymers.

The years 1956–1958 were spent at the Biochemical Research Laboratory and at the Laboratory for Carbohydrate Research, Massachusetts General Hospital and Harvard Medical School in Boston, first with Fritz Lipmann, and then with Roger W. Jeanloz. In the laboratory of the latter, Nathan Sharon became interested in amino sugars and compounds containing amino sugars, both from the chemical and biological point of view. He continued work on these problems upon his return to Rehovot and during his second stay with Jeanloz in 1962–1963. By now, the importance of amino sugars in the structure of bacterial cell walls was becoming clear and Sharon helped to elucidate the correct structure of the repeating disaccharide unit of the glucosamine–muramic acid polymer backbone. In this work, hen egg-white lysozyme was utilized as a specific degradative enzyme, and its successful employment encouraged Sharon to broaden his efforts in this field on his return to Israel. A series of investigations performed under his aegis by a number of young students in his laboratory clarified the mechanism of action of the enzyme on natural and synthetic substrates. They showed the orientation of the substrate in the active site and the importance of "fit" and "strain" on the catalysis of hydrolysis and transglycosylation by the enzyme, employing a variety of biochemical and physicochemical techniques. Other lysozymes, in addition to that from hen eggs, were also investigated in comparative studies. Concurrently, a very

successful collaboration was set up with David C. Phillips in Oxford who was elucidating the three-dimensional structure of the enzyme.

At the same time, chemical work in Sharon's laboratory confirmed the structure of the diamino sugar he had discovered in *B. licheniformis* as 2-acetamido-4-amino-2,4,6-trideoxy-D-glucose. Its synthesis was achieved together with the first unequivocal synthesis of L-fucosamine.

Sharon's involvement with lectins, the field with which he is most closely identified, is an excellent example of the unpredictability of scientific research. It started in the early 1960's in the course of studies on soybean proteins, initiated by E. Katchalski under a project supported by the U.S. Department of Agriculture. The purpose of the project was to provide knowledge leading to improved utilization of soybean proteins in human nutrition, thereby contributing to the elimination of the threat of global famine. In contemplating how to attack the problem, Sharon saw that he could combine his interest in carbohydrates with the aim of the new project. He chose to concentrate on the hemagglutinin known to be present in soybeans, not only because of its possible deleterious effect on the nutritional properties of raw soybeans and soybean oil meal, but also because earlier work indicated that it may be a glycoprotein. At the time, glycoprotein research was in its infancy, and nothing was known about the occurrence of such compounds in plants.

Nathan Sharon soon proved that soybean agglutinin is indeed a glycoprotein, and thus demonstrated for the first time that plants contain glycoproteins. Subsequently, he established the detailed structure of its carbohydrate unit and showed it to be identical in all respects with that of the *N*-linked $Man_9GlcNAc_2$ unit found in animal glycoproteins, thus providing strong evidence for the evolutionary conservation of such structures.

In 1970, Sharon established that the hemagglutinin activity of soybean agglutinin is specifically inhibited by *N*-acetyl-D-galactosamine and that it, therefore, belongs to the rapidly growing class of carbohydrate-specific, cell-agglutinating proteins known as lectins. Aware that an understanding of the molecular basis of lectin–carbohydrate interactions requires a thorough knowledge of the lectins as protein molecules, Nathan Sharon, together with his students and colleagues, turned his attention to the systematic investigation of the molecular properties of soybean agglutinin as well as other lectins. Their interest in the interaction of lectins with cells was prompted by reports in the literature that certain lectins preferentially agglutinated malignantly transformed cells, and by the increasing awareness of the key role that cell surface sugars may play in growth and differentiation, in interactions of cells with their environment, as well as in a variety of pathological processes. Sharon realized that the sugar specificity of lectins could make them excellent cell surface probes, capable of giving new insights into the structure and function of the cell surface.

Studies carried out in Sharon's laboratory led to the development of a new, simple, and widely used method for the identification and fractionation of cells from the immune system by lectins (mainly peanut agglutinin, another lectin isolated and thoroughly characterized in Sharon's laboratory, and soybean agglutinin) according to carbohydrate markers expressed on their surfaces. The method made it possible, for the

first time, to isolate mouse and human immature thymocytes with minimal contamination by functional mature thymocytes. This was of great value for studies of the route of T-cell maturation, an important problem in modern immunological research. In addition, the receptor for peanut agglutinin became a common marker of immature cells. Perhaps the most important and exciting development has been the successful application of the method to the isolation, by means of soybean agglutinin, of human bone marrow cells suitable for transplantation across histocompatibility barriers in numerous cases of children born with severe combined immunodeficiency and, more recently, also for leukemic patients. In May 1986, Yair Reisner, whose work in Sharon's laboratory laid the foundations of the method and who developed its clinical applications at the Sloan-Kettering Institute, New York, was on the team of Robert Gale, invited by the Soviet Government in an attempt to save the lives of the lethally irradiated victims of the Chernobyl accident. Both of the two surviving transplanted victims received bone marrow that had been treated with soybean agglutinin. And so, by a long and circuitous path, a soybean protein has been harnessed to the saving of human lives, albeit not from starvation as originally envisaged.

Parallel with his studies on plant lectins, Nathan Sharon turned his attention to bacterial surface lectins. Since the 1950's, it has been known that the adherence of many gram-negative bacteria to eukaryotic cells is specifically inhibited by D-mannose and methyl α-D-mannopyranoside. In 1977, Sharon, together with David Mirelman from his own Department and Itzhak Ofek from Tel Aviv University, suggested that bacteria possess surface lectins by which they bind to D-mannose units on other cells. Subsequently, he isolated the D-mannose-specific lectin from *Escherichia coli*, where it appears in long, filamentous proteins, named fimbriae (or pili). Nathan Sharon studied carefully the specificity of the lectin and showed preferential binding to oligomannose and hybrid units that are typical constituents of animal cell surface glycoproteins. Together with Ofek, he demonstrated the role of the lectin in infectious disease by showing that it is possible to block experimental *E. coli* infection by simple sugars such as methyl α-D-mannopyranoside. They also demonstrated that bacterial surface lectins mediate the adherence of the bacteria to the host phagocytes, that results in the killing of the bacteria, a mechanism which they named lectinophagocytosis. This is analogous to opsonophagocytosis, in which recognition between phagocytes and their targets is mediated by antibodies or complement, or both. An early step in these processes is activation of the phagocytes by the bound bacteria, as evidenced by the appearance of an oxidative burst. Nathan Sharon showed that activation of human granulocytes by *E. coli* possessing D-mannose-specific surface lectins involves the phospholipid-dependent protein kinase C and that, in this respect too, lectinophagocytosis is similar to opsonophagocytosis. Although the occurrence of lectinophagocytosis *in vivo* has not yet been demonstrated, it may serve as a defence mechanism against microbial infection in sites poor in opsonins, such as the renal medulla or the peritoneal cavity of patients undergoing peritoneal dialysis. Lectinophagocytosis could thus be the answer to the long-standing enigma of how phagocytosis occurs without opsonins.

Nathan Sharon has done research and lectured at a number of U.S. and European Universities. He was Visiting Professor at the University of California in Berkeley and

in Santa Barbara, at Oxford University, and at The College de France in Paris; he was a Scholar-in-Residence of the Fogarty International Center and a Distinguished Visiting Scientist at the National Institutes of Health, Bethesda. He is on the editorial board of several journals, is a Member of the Nomenclature Committee of the International Union of Biochemistry, and has been active in the organization of numerous international scientific meetings, most recently as President of the Organizing Committee of the Xth International Symposium on Glycoconjugates (Jerusalem, 1989). He is a member of the Ciba Foundation's Scientific Advisory Panel, was Chairman of the Federation of European Biochemical Societies (1980–1981), and President of the International Glycoconjugate Organization (1988–1990). Sharon's achievements have brought him many other honors, among which is The Weizmann Prize in Exact Sciences from the City of Tel Aviv, Honorary Membership of the American Society of Biological Chemists, the Datta Lectureship Award of the Federation of European Biochemical Societies, the Olitzki Prize (Israel Society for Microbiology), the Bijvoet Medal (Utrecht University), and Docteur Honoris Causa, Université René Descartes, Paris. He has published more than 400 scientific papers, six of which have been selected as Citation Classics in "Current Contents", and "The Scientist" ranked him 260 among "Citation Superstars 1973–1984". In addition to his scientific endeavors, an activity very close to his heart is communicating science (in Hebrew) to the Israeli general public, which has included editing a weekly radio program of science news, a bimonthly science magazine, and a weekly science column in a leading Israeli newspaper. His clarity of exposition and gift of explaining things in a simple manner has made him a much soughtafter author of numerous invited review articles, both in the area of lectins and of glycoproteins.

Sharon's extensive research activities and contagious enthusiasm have attracted many students and scientists from different countries, too many to be mentioned in the space of a short appreciation. His conviviality and social graces, with the assistance of his charming and talented wife Rachel, have won him many friends throughout the world. He has a hobby that has become his "trademark" — almost as much as lectins and carbohydrates. We refer, of course, to swimming. Usually early in the morning, whether at home, before the start of a long working day, or before the first session at an International Meeting, Nathan is at the pool where, he claims, his best ideas are born. It does not matter that the water temperature may often be considered "freezing" by most people, especially if the meeting is being held somewhere in Northern Europe. This persistence encourages a few other "crazy souls" nearby, including one of the authors of this appreciation. Sharon also takes part in the annual 4-kilometer swim across the Southern tip of the Sea of Galilee. Another of Sharon's hobbies is stamp collecting. In this, he is greatly aided by his far-flung correspondence and the stream of reprint requests from all over the world.

Together with all his friends and collegues, we offer Nathan Sharon our best wishes and, if we may end with a local saying — may his physical energy continue to match his intellectual vigor "ad me'a v'esrim" (until 120).

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HAROLD FLOWERS