Ephraim Katzir, whose creative research in the 1940s had a seminal impact on the development of protein science, died on May 30, 2009 at the age of 93. His pioneering research as a graduate student at The Hebrew University of Jerusalem led to a new field of science—the design, construction, and application of synthetic polypeptides as models of natural proteins. Ephraim also played major roles in the founding of the Weizmann Institute of Science and the establishment of the State of Israel of which he was the fourth President (1973–1978).

The Katchalski family emigrated from Poland to Palestine in 1922 when Ephraim was six, and his older brother, Aharon, was nine. Both brothers had a deep interest in science, graduating from The Hebrew University of Jerusalem. Ephraim’s fascination with the flora around Jerusalem led him to study biology, but he switched to the newly opened Department of Theoretical and Macromolecular Chemistry, where he conducted his groundbreaking Ph.D. research with Max Frankel. Their studies on the polycondensation of α-amino acid esters to form polypeptides of glycine and alanine resulted in two papers in 1942 (1, 2). But Ephraim, dissatisfied with the use of amino acid esters, looked for other derivatives to make the desired polymers.

That search led him to the α-N-carboxyl amino acid anhydrides synthesized by Leuchs in 1906, launching a new direction for research on proteins. The resulting paper was originally rejected by a Journal of the American Chemical Society editor who was not convinced that a polymer was produced. Months elapsed before it was resubmitted with additional evidence and finally published in October of 1947 (3). The editor had difficulty fathoming the reason for this delay, not knowing that Ephraim was deeply involved as an Officer of the Haganah in the War of Independence leading to the establishment of the State of Israel in 1948. During that turmoil, both Katchalski brothers received invitations to join the new Weizmann Institute of Science. Ephraim founded the Department of Biophysics and was its head for many years, while Aharon formed the Department of Polymers, which he headed until his death at the hands of terrorists at Ben Gurion Airport in May of 1972. Largely as the result of the creative research of the Katchalski brothers, the Weizmann Institute of Science became internationally renowned and was the launching pad for many talented students who earned international reputations.

**Polypeptides as Models**

A flood of papers followed Ephraim’s poly-\(\text{L}\)-lysine article. Better methods for removing blocking groups from side chains were discovered, and a variety of polypeptides such as poly-\(\text{L}\)-histidine, poly-\(\text{L}\)-aspartic acid, and poly-\(\text{L}\)-proline were synthesized along with different copolymers. These macromolecules became the subject of research in physical chemistry laboratories throughout the world. They served as models for optical rotation, circular dichroism, infrared spectroscopy, and x-ray diffraction studies aimed at determining the structure of polypeptide chains in proteins and analyzing conformational changes. Tests of theories of the helix-coil transition were based on experiments with polyamino acids of varying molecular weights and compositions. Experiments on the “melting” of helical polypeptides to form random coils were relevant to ongoing investigations of protein denaturation. The exciting demonstration by Ephraim and his colleagues of the cis and trans configurations of the peptide bonds in...
poly-l-proline played a major role in elucidating the structure of collagen. Their accompanying analysis of the conformations of the polymer in solution demonstrating both right-handed and left-handed helices proved invaluable in much later research on the kinetics of protein folding. The striking discovery that certain amino acids had a propensity to form α-helices, whereas others preferred β-parallel or anti-parallel pleated sheets, had a major impact on research aimed at predicting and determining the structures of proteins. Studies on highly charged polypeptides were crucial in the development and testing of theories of polyelectrolyte behavior. Synthetic polypeptides also were of value in initial investigations of the genetic code, when it was shown that the product of cell-free synthesis using polyuridylate as messenger RNA corresponded to the poly-l-phenylalanine that had been synthesized earlier by chemical means.

An outgrowth of the synthesis of linear polypeptide chains was the construction of multichain polyamino acids and polypeptidyl proteins with polypeptide chains attached covalently to free amino groups. Through these methods, the Katchalski group synthesized polytyrosyl gelatin, and the demonstration of its antigenicity led to an outstanding research program on the formation of synthetic antigens in the laboratory of one of Ephraim’s first students, Michael Sela.

Immobilized Enzymes
During the time he was studying synthetic polypeptides, Ephraim started constructing “water insoluble enzymes” that were fully active catalytically. In 1960, he published a paper titled “A Water-insoluble Trypsin Derivative and Its Use as a Trypsin Column” (4) with Atara Bar-Eli. Such columns, they noted, could be “employed repeatedly to induce specific chemical changes in relatively large amounts of substrates.” In preparing this column, Katchalski and Bar-Eli used trypsin to initiate the polymerization of N-carboxy-l-tyrosine anhydride to form water-soluble, fully active polytyrosyl trypsin. It was then coupled to a diazotized copolymer of p-aminocephylalanine and leucine, leading to the insoluble product used as a trypsin column. This imaginative adaptation of the various techniques developed in Ephraim’s laboratory was the start of a major international activity leading to industrial processes. For his contributions in the development of immobilized enzymes, Ephraim was awarded the first Japan Prize in 1985.

Education and Training
While deriving a strong sense of aesthetic pleasure from his own research, Ephraim also enjoyed involvement with students and protégés. To pay his debt to teachers who helped shape his aspirations, he developed an extramural scientific program for children on Israeli university campuses. He also co-edited a popular science magazine called Madah (Science) aimed at a youthful audience.

Ephraim loved to teach, and it showed; he literally radiated enthusiasm in his lectures. His thoughtful and creative scientific research attracted many trainees, and he delighted in their development as independent investigators. Ephraim always considered these individuals as a second family, and he was particularly proud that three former students became department heads at the Weizmann Institute: Avraham Patchornik (Organic Chemistry), Michael Sela (Chemical Immunology), and Izchak Steinberg (Chemical Physics).

Service to the Nation
Ephraim had a strong sense of national responsibility, which was reflected in the number of positions he assumed in government activities. This included service as Chief Scientist of the Israel Defense Ministry and Chairman of the National Council for Research and Development and the Council for the Advancement of Science Education.

In May 1973, the Israeli Knesset elected Ephraim the fourth President of the State of Israel. It was then that he adopted the Hebrew name Katzir, as his brother Aharon had done earlier. His term in office was a difficult one, since it began some four months prior to the outbreak of the Yom Kippur war and a year after the tragic murder of Aharon, who was the original designee to be President. The presidency of Israel is an honorific and ceremonial position wherein the incumbent symbolizes moral rather than political leadership for the nation. Ephraim fulfilled that role admirably; he was responsive to the needs of the people of Israel, who found in their President a deep resonance with their concerns, their pain, their joys, their achievements, and their dreams.

Post-presidency Research
Following his presidential term of office, Ephraim returned to science at both the Weizmann Institute, as an Institute Professor, and the University of Tel Aviv, where he founded the Department of Biotechnology. In the 1980s, Ephraim...
played a major role in the development of biotechnology that catapulted Israel into the forefront internationally.

In his later years at Weizmann, Ephraim investigated molecular mechanisms of protein interactions between specific proteins and peptides selected from a random peptide library. This approach contributed to a more precise definition of the structural requirements for the binding of a neurotoxin (bungarotoxin) in the nervous system. He also led a group that developed a theoretical protein-protein recognition algorithm (docking) that successfully predicted the structure of the complex between β-lactamase and the protein inhibitor BLIP, before it was experimentally determined. Clearly, the novelty of Ephraim's research continued to the end.

Honors and Legacy
Ephraim received many honors including membership in the Israel Academy of Sciences and Humanities, the Royal Society of London, the U.S. National Academies, and the Académie des Sciences in France. He received the Rothschild and Israel Prizes in Natural Science, the Linderstrøm-Lang Gold Medal, the Engineering Foundation's International Award in Enzyme Engineering, and he was appointed to France's Order of the Legion of Honor.

In addition to his scientific legacy, there are the memories that we will always treasure: the warm humaneness, the unfailing generous spirit, the intellectual honesty and generosity, the insatiable curiosity, the possession of an inner strength rarely encountered, and the unflagging enthusiasm for life. The protein science community has lost an outstanding researcher, a selfless supporter of the scientific enterprise, and an inspirational educator.

His own words provide a beautiful summary of his career:

“...I have had the opportunity to devote much of my life to science. Few activities can be more rewarding than conducting research that leads to a better understanding of the phenomena of life and nature, and indeed my work in all its aspects—research, teaching, collaboration with colleagues, and promotion of scientific activities—has brought me great personal fulfillment.

“Yet, my participation over the years in activities outside science has taught me that there is life beyond the laboratory. I have come to understand that if we hope to build a better world, we must be guided by the universal human values that emphasize the kinship of the human race—the sanctity of human life and freedom, peace between nations, honesty and truthfulness, regard for the rights of others, and love of one’s fellows.”

Below, as a tribute to Ephraim we offer thoughts and reflections from several of his friends and colleagues.

I was one of Ephraim’s first Ph.D. students. He has been a great teacher and a close friend for the past 59 years. His contribution to science and to the State of Israel has been enormous.

His original development of polyamino acids and water-insoluble enzymes has been among his many important contributions to science worldwide. His optimism in the future of science and its role in the progress of humanity has been paramount, notwithstanding tragedies in his family.

Characteristic of him, were his warm heart, kindness, sense of humor, and desire to help others.

Michael Sela
W. Garfield Weston Professor of Immunology
Weizmann Institute of Science

It was a wonderful period for us to be graduate students with Ephraim in what was then the newly established Biophysics Department at the Weizmann Institute. Ephraim was a true scholar. He showed true respect for other people’s opinion and ideas, often expressing his own opinion in Yiddish to clarify his point.

Ephraim’s schedule for a work day was interesting and unusual. The day usually started with a meeting with one of the students very early in the morning, studying a subject that often was completely unrelated to the student’s research. To an outsider, he probably looked like a checkmate game master who played a simultaneous game against a group of student players.

Scientific writing was done at night, often in a small group, with the involved partners in the famous Ephraim’s style, which involved checking and rechecking every word until Ephraim was satisfied, regardless of the tired eyes of the participants. (He never seemed to get tired himself.)

It was certainly a privilege to be associated with Ephraim. His death is a sad loss to all of us.

Izchak Steinberg
Professor Emeritus of Neurobiology
Weizmann Institute of Science

I knew Ephriam as a friend and a scientific collaborator. I first met him at a Proteins Gordon Conference in the 1950s, where I heard his brilliantly delivered and exciting
lecture on polyamino acids. Later, in December 1959, on a return trip from a summer lecture course in Melbourne, Australia, I stopped at the Weizmann Institute to visit Ephraim and deliver a lecture in his biophysics department. In 1963, Ephraim graciously accepted me in his laboratory during my sabbatical leave from Cornell, and I have been a steady visitor to the Weizmann Institute almost every year since then, including another sabbatical leave there in 1970.

During all these years, I had very close scientific contact with Ephraim, with much give and take on scientific issues, on Israeli politics, and other topics, either in his office or in his home on the campus. We had many overlapping scientific interests and challenged each other with problems at the frontier of our field. This relationship continued even in his home in Jerusalem when he became President of the State of Israel. As President, Ephraim convened many scholarly discussion groups, to which he invited me. It was there that I met many of university intellectuals and Israeli government officials and benefited from wide-ranging discussions there.

Ephraim was the father of the field of polyamino acids, including his studies of the synthesis and physical and biological properties of these biopolymers. He had a vivid imagination that enabled the field to make leaps of progress at many stages of its development. His international stature as a scientist brought honor and fame to the Weizmann Institute and to the State of Israel. I am very pleased to have known him and am saddened only in never again being able to drop into his home on the campus for coffee and exciting discussions.

Ephraim taught a course in biophysics in 1962 that included laboratory experiments. The course was given at The Hebrew University of Jerusalem, where I completed my M.Sc. thesis, and the laboratory experiments were conducted at The Hebrew University of Jerusalem and the Weizmann Institute. The course opened my eyes to macromolecules, mainly polyamino acids. It was a fascinating time in macromolecular biochemistry because polyamino acids were the only pure molecules that mimicked proteins and whose properties could be studied in a precise manner. I therefore came to the conclusion that one could utilize polyamino acids also as models for enzymes, so I moved to the Weizmann Institute where the action was. I wanted to generate a model enzyme, so I, together with Israel Pecht, generated a complex between Cu(II) and polyhistidine and proved that this complex indeed behaved as an oxidative enzyme. Ephraim was immensely impressed with this finding because it was a proof that polyamino acids can mimic enzymes. He therefore hooked me up with Arieh Berger, a great enzymologist at the Department of Biophysics, with whom I finished my Ph.D.

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Ephraim was my postdoctoral mentor from 1971 to 1972. He gave me the greatest time of my life, scientifically speaking, as his office was always open to me, and his mind was always receptive to discussing scientific ideas. I think Ephraim’s great success as a scientist was embodied in the four enduring lessons I learned from him: 1) words matter; 2) use synthetic chemistry to study biological problems; 3) know and love your system; and 4) build a team. Ephraim lived these lessons and imparted them to his colleagues and students. His legacy will endure in the lives of those he touched and in the greater context of science in Israel.

Jeffrey M. Becker
Professor and Head, Microbiology Department
University of Tennessee, Knoxville

Ephraim was my postdoctoral mentor. I remember him as a passionate advocate for basic research who taught his students a love of science and a tremendous respect for careful systematic investigation. He always urged us to see the big picture and to pursue important problems. In that respect, he added greatly to the biochemical sciences in peptide synthesis, enzymology, protein chemistry, biotechnology, and immunology. He was my teacher, my supporter, and ultimately, a dear friend. I and his other students will miss him terribly.

Ephraim emulated the importance of hard work to scientists. He led a large group of scientists and was also involved in many aspects of Israeli society. These included advocacy for applications of scientific research in the industrial sector, and science policy vis-à-vis the security of Israel and its impact on the economy. Given his enormous responsibilities, he needed to find a way to provide access to the young scientists that he trained into his late 1980s. One way he did this was working literally around the clock. I remember writing papers with him through the night, from 1 am to 6 am. How did he do this? He took brief naps to regenerate his strength and then plowed ahead. He was truly a force to behold.

Fred Naider
Distinguished Professor of Chemistry and Biochemistry, College of Staten Island
The City University of New York

During my last meeting with Ephraim, he was really very tired, but he took my hand, looked in my eyes, and asked me how will we, at the Weizmann Institute and in Israel at large, succeed in recruiting excellent, top candidates for faculty positions. “Getting bright people is so important for our future,” he added. That was two hours before his death.

Benny Geiger
Dean, Faculty of Biology
Department of Molecular Cell Biology
Weizmann Institute of Science

Ephraim was an excellent scientist, teacher, and human being. His door was always open. Whenever I had a problem or results I did not fully understand, I went to him. During our discussions, everything became clear. He was also a great lecturer. Three days before he passed away, I visited him, and he told me that the most important thing is to take care of young scientists.

Meir Wilchek
Professor of Biological Chemistry
Weizmann Institute of Science

Ephraim achieved the almost unbelievable; while remaining for his entire adult life totally immersed in science, breathing it 24–7, he managed also to leave an unforgettable signal imprint on the Israeli society at large. He did this not only by training scores of students and postdocs, many of whom are the backbone of Israeli science, but also by serving in key positions on the national scene. These included the chief scientist of the Ministry of Defense, head of various government committees, and, ultimately, the President of the State of Israel. I will particularly remember him for being a very wise, highly influential, and broad-minded mentor with a terrific sense of penetrating humor.

Yadin Dudai, Professor
Weizmann Institute of Science

Cyril M. Kay is an emeritus professor of Biochemistry at the University of Alberta, and Howard K. Schachman is a professor of Molecular and Cell Biology at the University of California, Berkeley.

REFERENCES