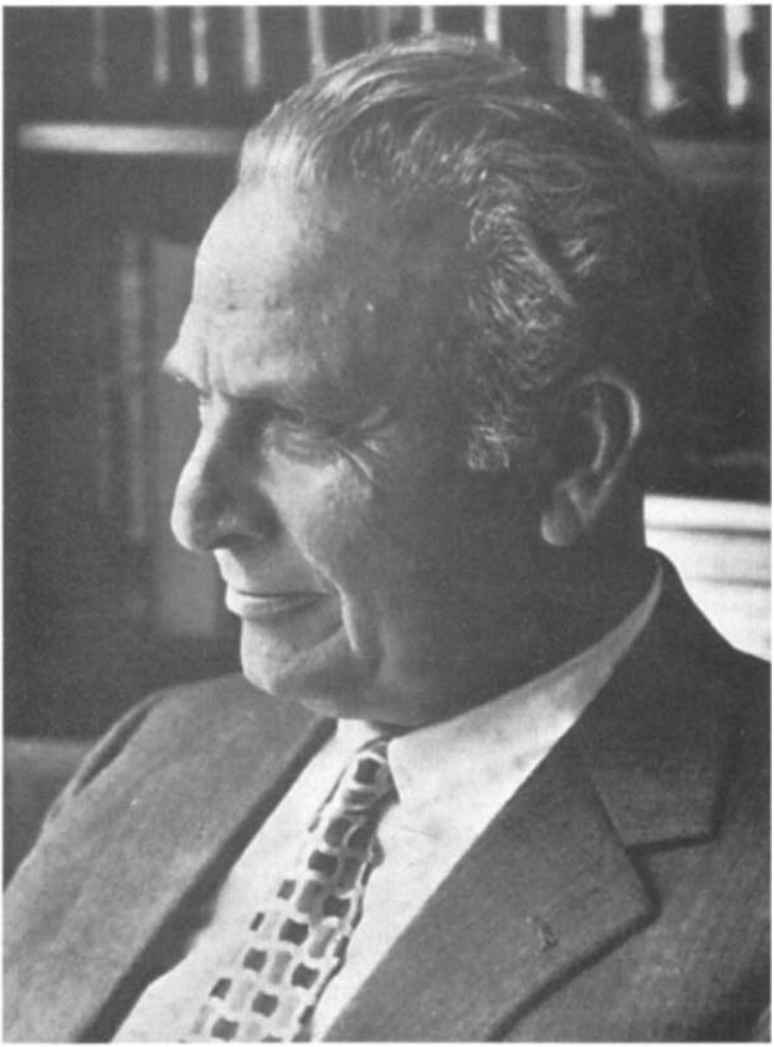

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MY LIFE IN AND BEYOND THE LABORATORY

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ABSTRACT

Ephraim Katchalski-Katzir grew up in Israel at a time when the State was coming into being, and like many of those of his generation, participated in its creation and defense. He received his scientific education at the Hebrew University of Jerusalem and thereafter at the Polytechnic Institute of Brooklyn, Columbia University, and Harvard University. During and after the establishment of the State, he acted as scientific consultant to the defense leadership, and continued throughout his career to advise the Government of Israel on research and development. His public activities culminated in his election in 1973 as President of the State of Israel.

As one of the founders of the Weizmann Institute of Science, he headed the Department of Biophysics for many years. His research

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included the study of poly-α-amino acids as protein models, immobilized enzymes, and polymers as chemical reagents. He also carried out theoretical and experimental work on the determination of distance distributions and conformational fluctuations in proteins by nonradiative energy-transfer techniques.

Introduction

I was born in Kiev, in the Ukraine. In 1922, when I was six years old and my brother Aharon nine, the family emigrated to Palestine from Poland. Our first home was in Tel Aviv, then a tiny city taking shape on the sand dunes adjacent to ancient Jaffa. After a year we moved to Jerusalem, and Aharon and I went to the prestigious Gymnasium, where we were lucky enough to be taught by inspiring teachers. Both of us showed special aptitude for the natural sciences, and we decided to continue our studies at the newly established Hebrew University of Jerusalem on Mount Scopus.

Aharon entered the university with the first group of biology students in 1930. I started two years later and very soon realized that I wanted to spend my life in research and teaching. But in high school I had realized that, like all those of my generation, I would have to play my part in activities that had nothing to do with learning but were bound up with the national renaissance. Growing up in Palestine under the British mandate, and especially on the university campus, I was caught up in the ideological and political ferment of that time. Jews were returning to their ancient homeland after 2000 years, filled with the desire to build a democratic state in which we could determine our own future, revive our original language, and revitalize our culture. We were ready to forge a new society, which would be based on the principles of social justice defined by our biblical prophets and would offer a high quality of life enriched by fine moral and spiritual values. In this exhilarating atmosphere, we felt inspired to do our best, and we threw ourselves with great enthusiasm into activities aimed at fulfilling the Zionist dream.

The local Arab population, however, angered by the increasing Jewish presence and the progress in building, agriculture, and other enterprises, had resorted to terrorist attacks against the Jews. Clearly we had to protect ourselves, and this we did by joining the illegal Jewish defense organization, the *Haganah,* which later became the Israel Defense Forces.

Thus, while still a student, I already had quite a clear idea of my goals in life. As well as attempting to do some original research, I felt that I must play my part in raising a new generation of Israeli scientists

and help create the physical and intellectual conditions in which science and technology could flourish in this region. I would also do what I could to help establish the State of Israel and to contribute to its security and its social and economic development. I have been lucky enough to spend my life in pursuit of these goals, with some success and considerable satisfaction. In 1973, I became the fourth President of the State of Israel. After serving in this capacity for five years, I was happy to return to my first love, scientific research, and to take up again my work at the Weizmann Institute of Science and embark on new activities at Tel Aviv University.

Not many of my scientific colleagues, I think, have lived through the birth pangs of a new state, or felt the need to throw themselves into a wide range of operations in the national interest, or served as their country's president. Perhaps I may therefore be excused if, while describing my scientific activities, I also give some account here of my life outside science. As this brief survey indicates, I have participated fully, and with great satisfaction, in the most significant areas of life in my country. At the same time, while I have come up against almost insurmountable difficulties, I have been fortunate enough to derive enormous pleasure and fulfillment from my chosen path of research and teaching in the life sciences.

Study and Work at the Hebrew University of Jerusalem

The international tone of Israeli scientific endeavor was set in the early years of the Hebrew University by the excellent teachers, some of them world-famous scientists, who had made their way to Palestine from the great centers of learning in England, Europe, and the United States. After years of solitary research before regular teaching activities started at the university, they were delighted that at last they had someone to teach. We were a small group of students, and they treated us as their friends and future scientific heirs, as they did their best to endow us with all their accumulated knowledge. Professors and students roamed the country together, exploring and recording its flora and fauna, geology, water, and mineral resources.

Our mathematics teacher was Binyamin Amira, who set up the Institute of Mathematics at the university and grew roses in his spare time. Shimon Samburski, professor of physics, gave lectures of extraordinary lucidity. Moshe Weizmann, Chaim Weizmann's younger brother, taught us organic chemistry. I remember him as a rather eccentric character, with an unfortunate tendency to let things slip out of his fingers. We took to hiding the glass utensils, which in those days were hard to replace. Leo Picard, who taught us geology and paleontology, intro-

duced me to a completely new field of knowledge. I remember his handing me a book in English, with instructions to be ready to discuss it with him after two weeks. I had to study day and night, but in the end I had a good idea of English and the geology of the Dead Sea.

A teacher I admired greatly was the Romanian botanist Tchorna Reiss. She used to write her lectures in English and I translated them into Hebrew for her. I remember going with her to Lake Huleh to study its plankton, which I described in my first scientific publication. Alexander Eig, head of the Department of Botany, unlike our other teachers, had not studied at a European center of learning, but was instead self-taught. He was a splendid botanical ecologist with an astonishing knowledge of the plants of Israel. He would take us into the Judean Desert on long field trips, pointing out plant societies and describing their struggles against each other for survival. My second scientific paper, written together with my friend Gideon Orshan, was on plants in the Judean Desert.

Michael Evenari introduced us to a new field of study, plant physiology. Both Aharon and I were enthralled by the subject. Gladly putting aside classification and collection and memorization of details, we tried instead to fathom the secrets of biological processes and the physical and chemical mechanisms that cause them. We also became close friends of the zoologist Shimon Bodenheimer, with whom Aharon wrote in Hebrew a small book about the butterflies of Israel, called *Children of the Sun*. I can still remember my brother running after butterflies and hardly ever catching one.

I soon found myself under the spell of the biological sciences, with botany, zoology, and bacteriology as my major subjects. I was enchanted by the beauty and complexity of living organisms and the intricate ways in which they function. In trying to understand their behavior, however, I soon realized that I would first have to learn chemistry, physics, and mathematics, and so I spent some years in the study of the exact sciences before returning to living organisms. Here my interest was attracted by the large molecules, the macromolecules of the cell, which play a most important role in determining life processes. I was fascinated by the lectures of my biochemistry professor, Andor Fodor, who introduced me to the world of biopolymers. It was particularly intriguing to realize that proteins not only constitute the basic building blocks of elaborate cellular structures, but also act as molecular machines that carry out a multitude of complex reactions within cells and tissues.

The research for my MSc and PhD degrees was done in the Department of Theoretical and Macromolecular Chemistry, headed by the late

Max Frankel. Aharon was by then Frankel's laboratory assistant and was using potentiometric techniques to investigate the interaction of amino acids and peptides with aldehydes and sugars. Understandably, he persuaded me that for my master's thesis I should prepare salt-free basic trifunctional amino acids and investigate their electrochemical properties. These amino acids were not available on the market, so I had to prepare them from red blood cells. For about a year I collected blood from the slaughterhouse, separated and hydrolyzed the red cells, and isolated the basic amino acids lysine, arginine, and histidine from the hydrolysate by means of an elaborate electrophoretic technique. I needed amino acids for my doctoral research as well and was greatly relieved to discover that purchasing them had become possible. But they were expensive, and Prof. Frankel kept a watchful eye on the supplies. Aharon and I overcame this obstacle by quietly emptying the bottles and refilling them with talcum powder. Years later, when I was working at the Weizmann Institute, rumors reached me of an uproar at the Hebrew University—Frankel's amino acids were no longer dissolving in water!

We also kept a low profile regarding our activity with the *Haganah*. I became an officer in this underground organization and for a while commanded a field unit, but was mainly involved, with Aharon and others, in the establishment of the scientific research team that later became the Israeli army's research and development unit. At night we would sneak into the laboratory and manufacture various materials, including tear gas. Occasionally traces of our labors lingered until morning, and sometimes even Frankel himself would shed a tear without knowing why. From our acquaintance with him we knew that he would not take kindly to the underground use of the laboratory, and we preferred not to burden him with our secret. Thus, we had to be doubly secretive about *Haganah* affairs, keeping our activities from the British on the one hand and from the university authorities on the other.

One of the most useful books I came across during my graduate studies was *Proteins, Amino Acids and Peptides,* by Cohn & Edsall (6a), which made me realize that in order to know something about proteins, I would first need to understand the structure and properties, in the solid state and in solution, of various high-molecular-weight polypeptides. Because we were working in a department of macromolecular chemistry, Aharon and I decided to acquaint ourselves with the theoretical and practical information available on synthetic and native polymers, about which we knew very little. We spent many pleasant hours together in a small grove of trees outside the laboratory, poring over whatever articles on polymer chemistry we could lay our hands on,

and soon we could practically recite by heart the pioneer works of Hermann Staudinger, Herman Mark, Kurt Meyer, and Paul Flory. Within a year we became the experts on macromolecules in Palestine, and within another year or two found ourselves leading the field in the Middle East. However, we felt completely isolated from the mainstream of scientific activity in Europe and the US. Naturally there was a certain satisfaction in having one's own theories uncontaminated by those of others, but this feeling was rapidly superseded by the need to exchange ideas with colleagues working in related areas.

Staudinger, Meyer, and others had suggested that synthetic high-molecular-weight compounds might serve as useful models in the study of biopolymers. This idea caught my attention. I thought if I could prepare synthetic high-molecular-weight polypeptides consisting of a single or a few amino acid residues, a study of their properties might contribute to the elucidation of the structure-function relationships in proteins. This seemed worth a try.

At the start, I believed it would be possible to prepare amino acid polymers by polymerizing the corresponding amino acid esters. Although I had some success in synthesizing polyglycine and poly-L-alanine by this technique (11, 12), I soon realized that amino acid esters, both in the solid state and in solution, tend to yield diketopiperazines rather than polyamino acids. While perusing the literature in search of a more suitable monomer, I came across Abderhalden's Handbook (1), which contained a description of the work of Leuchs carried out in 1908. After synthesizing *N*-carboxyglycine anhydride by cyclization of *N*-carbomethoxyglycyl chloride, Leuchs had found that *N*-carboxyglycine-anhydride readily gives off carbon dioxide to yield what he called an anhydroglycine. Suspecting that this product was in fact a linear polyamino acid, I decided to synthesize some additional *N*-carboxy-α-amino acid anhydrides, study their polymerization, and characterize the corresponding amino acid polymers obtained. As I was particularly interested in preparing a high-molecular-weight, water-soluble polyamino acid, I decided to start with the synthesis of poly-L-lysine. This polypeptide was finally obtained by polymerization of ϵ,*N*-carbobenzyloxy-α,*N*-carboxy-L-lysine anhydride to yield poly-ϵ,*N*-carbobenzyloxy-L-lysine, after removal of the protecting group by suitable means (36, 37). Removal of the protecting group was extremely difficult, and after many attempts I discovered, together with my first PhD student, Izhak Grossfeld, that it could be done with PH_4I. At first we assumed that the benzyl groups of the benzyloxycarbonyl residue are reduced by the liberated PH_3; however, because all of us wept copiously during synthesis, we realized that benzyl iodide was evolving as

a result of the HI liberated. Many years later, these findings led Arieh Berger and Dov Ben Ishai in my laboratory at the Weizmann Institute to develop the classic technique for removal of the benzyloxycarbonyl-protecting groups with HBr in glacial acetic acid.

When we sent in our first paper on the synthesis of poly-L-lysine to the *Journal of the American Chemical Society*, it was rejected by the editor, who was not convinced that a polymer had actually been produced. More hard work in the laboratory yielded evidence that persuaded even the most skeptical editor that what we had was indeed a high-molecular-weight, water-soluble polymer of L-lysine. I felt wonderful that we now had our model, which we would be able to use to understand the properties of some of the basic proteins, such as protamines and histones. The technique we developed opened the way for the preparation of linear homopolymers of other bi- and trifunctional amino acids, in which the steric configuration of the amino acid monomer was always retained during polymerization.

Transfer to the Weizmann Institute of Science

In the meantime, our work at the Hebrew University was coming to an end, as our proposed research budgets, each amounting to about $30 a year, were beyond the means of the university's treasury. Both Aharon and I were therefore in a receptive mood when Chaim Weizmann, the distinguished organic chemist who in 1948 became the first President of the State of Israel, invited us in 1946 to join the academic staff of a new scientific center to be named after him.

The planning committee of the new Weizmann Institute of Science was headed by Herman Mark, who in 1947 invited me to spend some time in his world-famous Polymer Center at the Polytechnic Institute of Brooklyn. On the way to Brooklyn, I took the opportunity to spend a couple of months at Columbia University, where the eminent biochemist David Rittenberg, himself a member of the planning committee of the Weizmann Institute, had offered to act as my mentor. From him I learned the new techniques in which isotopically labeled compounds are used to identify and characterize intermediate metabolites. Rittenberg was aware of my work on poly-L-lysine and drew my attention to a recently published short note by Robert Woodward and CM Schramm in the *Journal of the American Chemical Society* (74), describing the synthesis of a copolymer of L-leucine and DL-phenylalanine by copolymerization of the corresponding *N*-carboxyamino acid anhydrides in benzene. Because of the extremely high viscosity of the resulting solution, Woodward & Schramm had assumed that their copolymer was of extremely high molecular weight, within the limits

1,000,000–15,000,000. When I got hold of their solution, I realized that the authors had erred in their conclusion, as addition of a few drops of formic acid dramatically reduced the viscosity of their polymer in benzene solution. The apparent high viscosity was therefore the result of polypeptide association. This short publication, "Synthesis of protein analogs," nevertheless gave me considerable satisfaction, as the title clearly showed that Woodward & Schramm thought, just as I did, that poly-α-amino acids would be useful as simple high-molecular-weight models for proteins.

At Columbia and Brooklyn I had my first encounters with well-equipped scientific laboratories, and they were indeed splendid places in which to become acquainted with the new theoretical and experimental developments in polymer science. My teachers at Brooklyn were Herman Mark himself, Fred Eirich, and Turner Alfrey. With their help, and thanks to the tools that were placed at my disposal, I showed conclusively, together
Elson, that the high-molecular-weight compounds I had synthesized in Jerusalem were in fact amino acid homopolymers.

Herman Mark organized the purchase of the first sophisticated scientific equipment for the Weizmann Institute—an ultracentrifuge, an electron microscope, an electrophoretic apparatus, and an X-ray diffractometer. Palestine at that time (1947) was in turmoil, with the British preparing to leave and our leaders girding themselves for the declaration of the State of Israel. Rather than risk shipping our precious hardware to Rehovot, Mark had it temporarily installed in the laboratories at Brooklyn. He even suggested running the Weizmann Institute as part of the Brooklyn Polytechnic until things settled down, an offer I naturally declined, and within a short time the equipment and I were home in Rehovot.

This was at the beginning of May 1948. Most of my colleagues were by now involved in intensive on-campus research and development activities for the *Haganah*. Other types of research were virtually at a standstill. Aharon and I threw ourselves into whatever had to be done, drawing on all our professional expertise to assist in the defense of the new state. It was painfully clear to all of us that, much as we might aspire to careers in basic research, survival was the first necessity.

The State of Israel was established on May 14, 1948. On the same day, the new State was invaded by five Arab armies and found itself fighting for its existence. I was put in charge of the Israeli army's science corps, and until the end of the war we carried out military research, laying the foundations for *Hemed*, the army's scientific defense unit. With most of the scientists at the Institute in uniform, we felt we

were racing against the clock. Day and night the laboratories were in use, and the formerly tranquil campus resounded with the test explosions of new weapons. What we lacked in arms experience we made up for in motivation and a talent for innovation, and this work prepared the way for Israel's future defense industry. The physicists among us—Saul Meiboom, Ephraim Frei, Gideon Yekutieli, and others—helped to develop rockets and electronic systems, while the chemists, including David Vofsi, Yehuda Mazur, Felix Bergmann, and Israel Dostrovsky, worked on the development of modern explosives and propellants. At the same time, because some of the American scientists who were supposed to take charge of departments at the Institute were jittery about coming to Israel, Aharon was asked to be temporary head of the Department of Polymers and I was made acting head of the Department of Biophysics. These two appointments soon became permanent.

Shortly afterwards, in 1951, at the invitation of John Edsall, I first came to Harvard University and its Medical School as a Visiting Scientist and have maintained close contacts with my colleagues there ever since. The department at that time was headed by Edwin Cohn. It took a while, I remember, to become familiar with the Harvard scene and style. After some months, having acquired the courage to come up with my own proposals for research, I would talk them over with John Edsall, who unfailingly encouraged my efforts. Next I would call on Larry Oncley, who unfailingly discouraged them: he would assure me that my ideas could not work, or had already been tried without success. My next sounding-board was Edwin Cohn, who would enthusiastically collar me and deliver lengthy monologues on his own projects. At Harvard I established lasting friendships with Elkan Blout, Paul Doty, Bob Woodward, and Konrad Bloch, all of whom encouraged me to continue with my original research and offered useful critical comments.

Poly-α-Amino Acids as the Simplest Protein Models

Once I had settled into my new quarters at the Weizmann Institute, I continued to extend my work on polyamino acids as protein models. With my colleagues and students I synthesized several other polyamino acids (39) including poly-L-arginine (45), poly-L-histidine (55), poly-L-aspartic acid (3), poly-L-tyrosine (38), poly-L-serine (5, 50), poly-L-cysteine (59), poly-L-proline (4), and poly-L-hydroxyproline (49). We also synthesized amino acid copolymers and multichain polyamino acids (62, 64); in the latter, a suitable polypeptide backbone, such as polylysine, serves for the attachment of several polypeptide chains, resulting in branched macromolecules.

By this time, numerous other groups were also preparing polyamino acids and studying their properties. Within two decades, the 1950s and 1960s, it was possible to clarify the mechanism and kinetics of polymerization of *N*-carboxyamino acid anhydrides (7, 40), determine the α-helical conformation of some of the polyamino acids in the solid state and in solution (39), detect β-parallel and antiparallel pleated sheets of polyamino acids, and induce helix-coil transitions in the solid state and in solution under appropriate conditions (31). Collaboration between experimentalists and theoreticians facilitated the successful correlation of the macromolecular conformations of polyamino acids in solution with their hydrodynamic properties, optical properties, dipole moments, and nuclear magnetic properties (33, 46, 52, 72).

I was particularly intrigued by the behavior of poly-L-proline in solution (34, 72). Hydrodynamic and optical rotatory studies showed that poly-L-proline can attain two different macromolecular forms in solution. Form I ($[\alpha]_D \approx -50°$), which is stabilized in poor solvents such as pyridine and aliphatic alcohols, is characterized by a right-handed helix with all peptide bonds in the *cis* configuration. Form II ($[\alpha]_D \approx -540°$), which is stabilized in good solvents such as formic acid and water, is a left-handed helix with all peptide bonds in the *trans* configuration. A series of acid-catalyzed *cis-trans* isomerizations of peptide bonds cause the transformation of the poly-L-proline I helix into the poly-L-proline II helix and vice versa. Because collagen contains a high percentage of proline, finding that the X-ray diffraction spacing of poly-L-proline II and of stretched collagen shows striking similarity was particularly gratifying (8, 61). The predicted conformations for polyglycine II and poly-L-proline II were very useful in the derivation of the structure of collagen by Ramachandran & Kartha (56) and Rich & Crick (57), who proposed that collagen fibers consist of three polypeptide chains of the polyglycine II and poly-L-proline II type coiled about each other in a triple-stranded rope. Our group found that an ordered sequence polymer of the structure H(Pro·Gly·Pro)$_n$OH forms, in the solid state and in solution, a collagen triple helix (9) and thereby proved that the replacement of every third proline residue in poly-L-proline with a glycine residue, leading to the appearance of a CONH group per tripeptide unit, is sufficient to stabilize a collagen-like structure.

In Rehovot, I also investigated the biological properties of polyamino acids (32, 63). To my delight, poly-L-lysine and other homopolyamino acids and amino acid copolymers turned out to be excellent models for investigation of the mechanism of enzymatic protein hydrolysis and transpeptidation. Much of this work was done in the late 1940s. I still remember the excitement with which I followed the rapid hydrolysis

of poly-L-lysine by trypsin, using the cumbersome old Van Slyke apparatus. We showed that the specificity of an enzyme acting on a high-molecular-weight polypeptide is often strikingly different from that observed in the presence of low-molecular-weight peptides. Partial hydrolysis of poly-L-lysine yields, as expected, a mixture of lysine oligomers. These were separated chromatographically and investigated immunologically by my former student Arieh Yaron, in Herb Sober's laboratory at the US National Institutes of Health (75, 77). Uptake of these oligomers by *Escherichia coli* was studied by Charles Gilvarg of Princeton University, then a visiting scientist at the Weizmann Institute (16). By using a lysineless mutant of *E. coli,* Gilvarg showed that *E. coli* readily takes up all oligomers up to tetralysine, but no higher, and that these oligomers permit growth of the lysine auxotroph.

In our experiments with a prolineless mutant of *E. coli,* my coworker Sara Sarid observed that the organism can grow on a synthetic medium in which poly-L-proline is substituted for L-proline (60). Clearly, the polymer was being hydrolyzed by an unknown enzyme. Further investigations by Arieh Yaron of the cleavage of various synthetic proline-containing oligo- and polypeptides (76) led to the identification and characterization of a novel enzyme, amino-peptidase P, which subsequent studies showed to be present in other prokaryotes and in eukaryotes.

Poly-L-lysine itself found many additional applications both in our department and in other laboratories. Together with Chana Shalitin, I showed, for example, that poly-L-lysine inhibits multiplication of bacteriophages (66, 67), apparently by interaction with the phage DNA. Earlier, in collaboration with Leah Bichowsky-Slomnicky and Ben Volcani (35), I used polylysine and other polypeptides to investigate the surface charge and agglutination of bacteria, the mechanism of action on bacteria of antibiotic peptides such as gramicidin S, and the mechanism of blood clotting.

An important outgrowth of the studies on synthetic polyamino acids was the development in my laboratory of techniques for the preparation of polypeptidyl proteins (proteins to which polypeptide chains are covalently attached via amide bonds to the free amino groups of the protein). The synthesis of polytyrosyl gelatin and the demonstration that it is antigenic (65), in contrast to the unmodified protein, led in 1960 to the preparation by Michael Sela and Ruth Arnon, then in my department, of the first fully synthetic antigen. In this compound, tyrosine and glutamic acid residues are attached to a multi-poly-DL-alanyl poly-L-lysine. I vividly remember our immunological experiments, in which guinea pigs injected two or three times with polytyrosyl gelatin went into ana-

phylactic shock—a most unpleasant experience for the guinea pigs and a sobering demonstration to me of how careful one should be in treating living beings with synthetic or even native polymers. Nevertheless, the way was opened for the fundamental and extensive studies of Sela and his coworkers on the chemical and genetic basis of antigenicity. Some of the polypeptidyl enzymes we prepared retained full enzymatic activity. This finding was the basis for our subsequent preparation of a great variety of immobilized enzymes.

Knowledge of the properties of synthetic polypeptides played a decisive role in the work that led in 1961 to the cracking of the genetic code. In their first paper on the subject, Marshall Nirenberg & JH Matthei identified the poly-L-phenylalanine, produced enzymatically in a cell-free system in the presence of polyuridylate used as messenger, with the poly-L-phenylalanine we had synthesized in Rehovot in 1955. As it happens, Michael Sela was at the NIH when Nirenberg was working on the code, and he had informed Nirenberg that the normally insoluble poly-L-phenylalanine could be dissolved in acetic acid saturated with HBr. Soon afterward, Nirenberg & Ochoa identified other homo- and heteropolyamino acids as part of the effort to decipher the genetic code: Poly A was found to code for poly-L-lysine, poly-C for poly-L-proline, and poly-G for polyglycine.

Immobilized Enzymes

My interest in enzyme-polymer conjugates was aroused by the growing body of data indicating that many of the enzymes embedded in organelles or biological membranes within cells act as heterogeneous catalysts. I thought an interesting experiment would be to artificially immobilize enzymes and study their properties, especially their kinetic characteristics, under controlled conditions. Moreover, I felt that such immobilized enzymes could be utilized in the construction of novel enzyme reactors of use in the laboratory, the clinic, and industry.

My first paper on a water-insoluble enzyme was published in 1960 (2), when I described the preparation of a water-insoluble trypsin derivative and its use in a trypsin column. The method involved preparation of a polytyrosyl trypsin derivative containing tyrosyl peptide side chains by means of the polymerization of *N*-carboxy-L-tyrosine anhydride with trypsin (17) and coupling of the resulting water-soluble derivative with a diazotized copolymer of *p*-amino phenylalanine and leucine to yield the required water-insoluble trypsin. The trypsin column showed high activity towards benzoyl-L-arginine methyl ester, poly-L-lysine, and other well-known synthetic and native trypsin substrates. Of particular interest

water-insoluble trypsin remained practically unaltered in dilute HCl at 2°C. Immobilization prevented autodigestion, and blocking of the ϵ-amino groups of the enzyme led to a marked decrease in the number of peptide bonds susceptible to trypsin.

These encouraging results prompted us to prepare other immobilized enzymes (30) such as immobilized chymotrypsin (23), urease (58), papain (68), alkaline phosphatase (20), and carboxypeptidase (69), in each case by covalent binding of the enzyme via nonessential side groups to water-insoluble carriers.

Soon after our first experiments with immobilized enzymes, I developed a simple equation, based on the well-known Michaelis-Menten relation, describing the activity of an enzyme column (29). The product yield is, as expected, a function of enzyme and substrate concentrations, height of column, and rate of flow. This simple approach was soon superseded by a more careful analysis of the mode of action and kinetics of immobilized enzymes acting as heterogeneous catalysts, taking into account the rate of diffusion of substrate towards the catalyst, the rate of catalysis, and the diffusion of product from the catalyst into the surrounding medium (23).

Growing interest in immobilized enzymes led to the development by various groups of novel enzyme immobilization techniques in which enzymes were adsorbed or covalently bound to organic or inorganic carriers, or entrapped in gels, fibers, or microcapsules, and systems in which enzymes remained in solution but functioned in a limited space enclosed by an ultrafiltration membrane (6). In a novel enzyme immobilization technique that I developed together with my collaborators at Tel Aviv University's Biotechnology Center, immobilized monoclonal antibodies were used as carriers to combine with their corresponding enzyme antigen (70). With this technique, immobilization did not result in any loss of enzymatic activity.

Thus, we could, within a relatively short period, obtain a great variety of immobilized enzymes as well as enzyme reactors of various types (53), which opened the way for the use of immobilized enzymes in the food, pharmaceutical, and chemical industries.

Another aspect of my work in this field involved the preparation and study of enzymes immobilized in artificial membranes. In 1965, my collaborators and I succeeded in preparing a stable papain membrane on a collodion matrix by adsorbing papain on a collodion membrane and then cross-linking the papain with a cross-linking agent (22). The pH dependence of the enzyme membrane's activity on the concentration of the substrate benzoyl arginine ethyl ester differed from that of crystalline papain. This anomalous behavior was caused by lowering

of the local pH within the membrane as a result of the release of acid by the enzymatic hydrolysis of the ester substrate. This latter finding showed that enzymatic reactions within a membrane, leading to accumulation of a product, might alter the environment in which the enzyme acts, and thus lead to an unexpected activity pattern. The availability of papain-collodion membranes enabled us to analyze in detail the kinetic behavior of enzymes immobilized in artificial membranes and calculate the concentrations of substrate and product within the various membrane regions (19, 21).

In attempting to elucidate the function of different carriers on the mode of action of enzymes, we observed that polyelectrolyte carriers markedly affect the pH activity profile of the enzymes to which they are attached (51). In the case of trypsin bound to a copolymer of maleic acid and ethylene, for example, at low ionic strength and with benzoyl-L-arginine ethyl ester serving as the substrate, the pH activity profile was displaced by approximately 2.5 pH units towards more alkaline pH values when compared with native trypsin under similar conditions. At high ionic strength, however, the pH activity curve of the polyelectrolyte-surrounded enzyme shifted to more acid pH values approaching the pH activity of the native enzyme. These findings could be explained in terms of the effect of the electrostatic potential of the polyelectrolyte carrier on the local concentration of H^+ ions in the microenvironment of the bound enzyme molecules. Obviously, then, the microenvironment surrounding an enzyme within an artificial or native membrane might strongly affect its mode of action (44).

In a theoretical analysis of the kinetic behavior of a two-enzyme membrane carrying out a consecutive set of reactions, we showed that, under suitable conditions, the rate of production of the end product at the first stage of the reaction is markedly higher for an immobilized enzyme system than that predicted for the corresponding homogeneous system (18).

The first industrial use of immobilized enzymes was reported in 1967 by Chibata and coworkers of the Tanabe Seiyaku Company in Japan, who developed columns of immobilized *Aspergillus oryzae* aminoacylase for the resolution of synthetic racemic DL-amino acids into the corresponding optically active enantiomers. Around 1970, two other immobilized systems were launched on a pilot plant scale. In England, immobilized penicillin acylase, also referred to as penicillin amidase, was used to prepare 6-amino-penicillanic acid from penicillin G or V, and in the US, immobilized glucose isomerase was used to convert glucose into fructose. These successful industrial applications prompted extensive research in enzyme technology, leading to a steady in-

crease in the number of industrial processes based on sophisticated immobilized enzyme reactors.

The use of immobilized enzymes in industry is now well established (73). I still chuckle when I recall the comment of my good friend, the late Ernst Chain, who told me that I was wasting my time modifying pure, well-characterized enzymes and transforming them into heterogeneous catalysts of no use whatsoever. Happily, he was more successful as a scientist than as a prophet. The intermediate compound 6-amino penicillanic acid, which he employed in the preparation of the semisynthetic penicillin derivatives used as oral antibiotics, is now prepared worldwide by means of an immobilized enzyme process; its estimated production in 1992 was 7500 tons. In the same year, 15,000 tons of acrylamide were produced from acetonitrile by use of immobilized nitrile hydratase, and the production of high-fructose corn syrup from glucose by immobilized glucose isomerase reached 8 million tons (33a).

The Japanese were somewhat more appreciative of my efforts than Professor Chain. In 1985 I was awarded the first Japan Prize for my work on immobilized enzymes.

Polymers as Chemical Reagents

In preparing enzyme-polymer conjugates in which enzymes are bound covalently to polymeric carriers, one needs to prepare chemically active polymers. Not surprisingly, therefore, my group began to think about the possible use of polymers as chemical reagents. Polymers of the type *P*-A that contain the covalently bound group A, which readily reacts with a low-molecular-weight reagent B, can be used to synthesize compound A-B according to the equation:

$$P - A + B \rightarrow A - B + P.$$

At the end of the reaction the insoluble polymer can be removed by filtration or centrifugation. The filtrate should thus contain only A-B and unreacted B. The most suitable polymers *P*-A for use as chemical reagents contain relatively large amounts of A, are highly stable when stored, and possess appropriate mechanical properties. Furthermore, the reactivity of a polymer can be markedly modified by the introduction of suitable neighboring side chains.

To examine the possible use of chemically reactive polymers in acylation reactions, we prepared insoluble high-molecular-weight active polyesters of acetic acid and benzoic acid by allowing the corresponding chlorides to react with cross-linked poly-4-hydroxy-3-nitrostyrene. Treatment of the chemically reactive polymer with amines or carboxy-blocked peptides yielded the corresponding acetyl or benzoyl amides

or peptide derivatives (13). The successful preparation of active esters of N-blocked amino acids of the above polymer type led to the development of a novel technique for peptide synthesis, enabling the high-yield synthesis of bradykinin and other linear and cyclic peptides (14, 15).

My student and collaborator Avraham Patchornik (54) further developed the use of polymers as chemical reagents. I have no doubt that in due course some of these chemically reactive polymers will be used extensively in organic synthesis.

Effect of Microenvironment on Enzyme Action

The availability of artificial membranes containing immobilized enzymes led us to consider the role of the microenvironment in determining the mode of action of enzymes that are immobilized, singly or as multienzyme complexes, within native or synthetic membranes. In analyzing the influence of the microenvironment on enzyme activity, one can distinguish between effects attributable to the matrix and effects resulting from the enzymatic reaction itself. Our observations in this connection were summarized in a detailed review (44). In considering the effects of various types of biological microenvironments, we took as our reference the model systems consisting of artificial well-characterized membranes in which enzymes are embedded.

Determination of Distance Distributions and Conformational Fluctuations by Nonradiative Energy-Transfer Techniques

As a polymer chemist, I was interested in the behavior of synthetic polymers in solution. Because many of the characteristics of linear polymer solutions are determined by their chain length and flexibility, I thought that partially ordered or flexible structures in peptides and globular proteins should also be described in terms of intramolecular distance distributions and rates of transitions and that these could be determined by a time-resolved long-range dynamic nonradiative energy transfer technique based on Förster's theory (10). First, with Izchak Steinberg, I analyzed the role of diffusion in nonradiative energy transfer as well as in fluorescence quenching and chemical reactions (71). Together with Elisha Haas, we then searched for model oligopeptides in which we could use the energy-transfer technique to determine the distribution of end-to-end distances as well as the Brownian motion of the ends of oligopeptide chains in solution. We synthesized a homologous series of oligopeptides, each consisting of four to nine N^5-(2-hydroxyethyl)-L-glutamine residues and containing at its ends a fluores-

cent donor and a fluorescent acceptor of electronic excitation energy. The chromophores naphthalene and dansyl, used as donor and acceptor, respectively, fulfilled the conditions necessary for energy transfer according to the Förster mechanism. The kinetics of fluorescence decay of the donor in a highly viscous glycerol solution enabled the derivation of the characteristic end-to-end distribution function between the donor and acceptor (26). Subsequent analysis of the fluorescence decay curves of these oligopeptides in solvents of low viscosity enabled the estimation of the apparent diffusion rate of the molecular ends relative to one another (25, 41).

The nonradiative energy-transfer technique was subsequently extended by Elisha Haas and his students to different proteins specifically labeled with a fluorescent donor and fluorescent acceptor, enabling them to determine intramolecular distances as well as intramolecular dynamics in various proteins such as pancreatic trypsin inhibitor (24) and phosphoglycerate kinase (27). Further theoretical and experimental developments have yielded new information on the denaturation and renaturation of proteins and can be expected to elucidate the mechanisms by which proteins fold during their biosynthesis on ribosomes, as well as the preferential folding of peptide hormones upon binding to their corresponding receptors.

Education and Teaching

As a scientist and a teacher, I have always thought it important to make young people aware of the achievements of modern science and technology and their relevance for everyday life. Early in my career I started to arrange for schoolchildren to meet each week on the university campus with scientists who shared their enthusiasm for experimental work and who often stimulated those young imaginations. This was the beginning of the move towards extramural scientific activities for children and youths. Over the years these programs have become an integral feature of all of Israel's institutes of higher learning, with the support of the Ministry of Education and the active participation of thousands of pupils and of the hundreds of PhD students who serve as instructors. At the Weizmann Institute, thanks to the devoted efforts of my friend, the late Amos de Shalit, an international science summer camp has become a prestigious annual event for scientifically gifted high school seniors, and a science village for schoolchildren was recently opened on campus.

My interest in popularizing science in Hebrew also led me to coedit, together with the late Shlomo Hestrin, one of the first Israeli popular

science journals, *Mada,* on which a whole generation of youngsters was raised.

From the early 1950s, several unusually talented young men and women came to work with me and my group in the Department of Biophysics at the Weizmann Institute. Having received such inspiring guidance from my own teachers, and in view of my strong desire to help educate young Israeli scientists, I was more than ready to invest time and effort in nurturing these gifted young people. As a result, instead of concentrating strictly on my own specific research interest, I found myself moving in a number of directions, exploring different—though related—ideas with my students. My aim was to guide each of my students into an area that would enable him or her to tackle specific problems in my laboratory and eventually form independent research groups in which they could continue working on projects of their own. Some of my students went on to achieve remarkable success, which gave me enormous satisfaction. Our collaborations would often continue even after they had left my team and begun work in other disciplines. At one point, former students of mine headed no less than three scientific departments at the Weizmann Institute: Organic Chemistry (Avraham Patchornik), Chemical Immunology (Michael Sela), and Chemical Physics (Izchak Steinberg).

Aharon, My Brother

Of all those who have touched my life, the one who had the greatest personal influence on me was my brother. Aharon Katzir-Katchalsky was known to the world as a distinguished scientist. But to me he was my much-loved, much-admired, older brother—my closest friend and colleague, my guide and leader into the world of polymer research. The work we did together in Prof. Frankel's laboratory in the 1930s launched us on a scientific collaboration that continued for more than 30 years, until his untimely death at the hands of terrorists at Ben Gurion Airport in May, 1972.

Aharon's major scientific interest was in proteins and nucleic acids, and he devoted himself to elucidating the characteristic properties of these most important biopolymers. He developed new approaches to understanding the processes occurring in the living cell. His work on polyelectrolytes, nonequilibrium thermodynamics, and transport phenomena in living organisms, and his extension of network theory from the biological point of view are well known (47).

The scientific group established by Aharon at the Weizmann Institute won the esteem and admiration of scientists throughout the world. His colleagues in Israel and abroad were impressed by his strikingly original

ideas and inspired by his enthusiasm and broad-mindedness. He sought to bridge the gap between scientific understanding and ethical insight. Fascinated by all living organisms, in particular by human beings, he believed that "the understanding of living organisms would provide man with a better understanding of himself" and that such understanding would "suggest relationships between human biology and ethical behavior."

After Aharon's death, a group of distinguished scientists from many parts of the world met at my home. We decided to set up a Center in his name, for the promotion of activities in physical biology, macromolecular science, and other scientific areas that fell within his wide-ranging interests. The Aharon Katzir-Katchalsky Center furthers international scientific cooperation through the organization of scientific meetings, lectures that emphasize the impact of scientific and technological advances on human society, and a program that helps young Israeli scientists participate in study courses given abroad. By involving myself in these activities, of which he would have thoroughly approved, I feel that I am continuing my dialogue with my brother.

Serving My Country as State President

As I became more involved in science, I increasingly felt that the academic community had a moral duty to participate in matters of public concern. Because of this sense of obligation, as well as my lifetime involvement with social activities in Israel, in 1966 I accepted the invitation of Prime Minister Levi Eshkol to head a committee charged with advising the government on the organization of its future activities in science and technology. An important result of our work was the appointment, in several government ministries, of Chief Scientists charged with promoting applied research in governmental institutions, in institutes of higher learning, and in industry itself. Our recommendations prompted a marked increase in cooperation between these three sectors. They also led to a dramatic increase in government spending on applied research, leading to a surge in innovative science-based activities, especially in industry and agriculture.

My ongoing involvement as an adviser in government-related activities included participation in various bodies, such as the National Councils for Education and for Research and Development, and a committee that recommended the legal framework covering the rights and obligations of engineers and technicians. In 1967, during the period that culminated in the Six Day War, I served as Chief Scientist of the Defense Ministry. In view of my close association with all sectors of Israel's government and its prime ministers in the course of the above activities,

I was not entirely surprised when Prime Minister Golda Meir approached me to stand for President. I was clearly being offered a unique opportunity to place whatever talents I might possess at the service of my country. In May, 1973, I became the fourth President of the State of Israel and embarked on one of the most interesting periods of my life.

The President is elected by the Knesset, Israel's parliament, for a five-year term. Israelis look to their President for moral rather than political leadership and choose an individual noted for intellectual activities rather than political experience. Running the country is the responsibility not of the President but of the prime minister and his/her cabinet. The President's function, on the other hand, is to represent the state and the people. He therefore serves, both at home and abroad, as a symbol of the State of Israel.

This description may suggest that being President is a rather pleasant pastime, not overly arduous, and requiring not much more than gracious behavior on official occasions. Nothing could be further from the truth. On becoming President, I frequently found myself thinking of my mentor, Chaim Weizmann. A visitor had once asked him how he spent his time as President, to which Weizmann had replied: "Oh, I'm kept very busy—I symbolize and symbolize all day long." I soon came to understand exactly what he had meant. Symbolizing the state means not only supporting it in its successes but also defending it in its failures. It means being a source of moral strength and inspiration, acting sometimes as a father figure and always as an example. It means raising the national morale in times of trouble. I found that symbolizing my country and representing its people was by no means an easy task.

In Israel, the President is relatively accessible to the public, and one of the most demanding—and satisfying—aspects of my office was my contact with hundreds of people from all walks of life who came to *Beit Hanassi,* the presidential residence, to share their ideas and feelings with their President. In the reception rooms, surrounded by the images and symbols of our ancient past and our national rebirth, people talked to me about the lives they wanted to lead, the country they hoped to build, and the state and society to which they would be proud to belong. They talked of their dreams of peace with our Arab neighbors and their hopes for tranquillity within our own borders, echoing the vision of the prophet Isaiah, whose words are inscribed on the frieze framing the ceiling of the President's study: "Nation shall not lift up sword against nation, neither shall they learn war any more."

My involvement, in the course of my presidential duties, with individuals and families in distress reaffirmed my belief in the power of the

President to act as a positive feature in the people's lives. A President who has the humanity and compassion to use his influence wisely may find the means of helping afflicted people in a way that could determine the future course of their lives. I should perhaps mention, however, that with all their esteem for the President, Israelis are not in the habit of indulging any self-importance the President might feel. I well remember being invited to address a lunch-time meeting of the Israel Association of Architects and Engineers, and asking the chairman how long I was expected to talk. "You're the President, sir," he replied. "You can talk for as long as you like. We're leaving at 2 o'clock."

When I accepted the presidential nomination, I realized that I would have to give up my scientific activities for a few years. As any scientist will appreciate, this sacrifice was quite difficult. I expected that I would miss my work in the laboratory, and my fears turned out to be fully justified. I kept up as far as possible with the literature and attended scientific meetings whenever they could be accommodated in my schedule. I also took advantage of my office to promote science and higher education. All too rarely my colleagues, presumably mindful of my other activities and reluctant to make demands on my time, would approach me to review a scientific article. To their astonishment they usually received my comments within a day or two, never realizing with what relish I had fallen upon the work.

Two of the most momentous events in Israel's modern history occurred when I was President. I refer to the Yom Kippur War and the visit of President Anwar Sadat of Egypt to Jerusalem. The first of these occurred six months after I entered office, and the second shortly before I left it, so that the period of my presidency was in one sense defined by those two events.

The Yom Kippur War started on October 6, 1973, when Egypt and Syria launched a surprise attack while Jews were at prayer on Yom Kippur, the holiest day in the Jewish calendar. From the military point of view, Israel gained an impressive victory, but at very great cost. We lost more than 2500 soldiers; many more were wounded and hundreds taken prisoner.

Towards the end of the war, Henry Kissinger appeared on the scene, attempting to mediate between Israel and Egypt, Syria, and Jordan. He covered a good deal of mileage during his trips back and forth between Sadat in Cairo, Assad in Damascus, Hussein in Amman, and Golda Meir in Jerusalem. Progress was slow and the discussions never-ending. I once asked Kissinger whether his earlier experience as a professor of political science at Harvard was of any use to him in his present role as mediator. "Most decidedly," he replied. "As a member

of the university senate I often had to sort out differences between obstinate professors who had a talent for presenting an argument in the most lucid and convincing way." As an afterthought he added, "To tell the truth, compared with that my work in the Middle East is child's play."

It was not, however, until Anwar Sadat came to Jerusalem in November 1977 that the way was opened to peace with one of our erstwhile enemies. The visit came at very short notice and took us all by surprise. Its direct outcome was the peace treaty between Egypt and Israel, signed at Camp David in Washington on March 26, 1979. Twelve years passed before other Arab leaders were ready to follow Sadat's courageous example. The Madrid Peace Talks, held under the auspices of the US and Russia, and later the talks held in Oslo, raised a new spirit of optimism and hope for peace in the region. As a result of these talks, a peace agreement was finally signed in 1994 between the Prime Minister of Israel, Yitzhak Rabin, and the chairman of the Palestine Liberation Organization, Yasser Arafat, and autonomous rule was established, as a first step, in Gaza and Jericho. As I write, King Hussein of Jordan has declared his willingness to meet with the Israeli Prime Minister to negotiate peace. There is also hope of future negotiations with Syria. Thus it seems that the process started by the far-sighted Egyptian leader might lead in time to an enduring peace settlement and a new era of cooperation in the Middle East. Enormous potential benefits for the entire region can be expected to follow, given the advanced scientific and technical expertise of Israel, the vast natural resources of some of the Arab states, and the strong motivation of the Palestinian Arabs to improve the conditions of their lives. Thus, the vision of the early Zionist leaders, and our own dreams, may yet become a reality.

Back to Science

When my term of office ended, I was happy to return to the Weizmann Institute, where I enjoyed having the time to think, design research programs, and plan experiments. Also, after a break of some years, I felt ready to move on to new science-related projects. During my presidency I had decided that upon my return to the world of science I would give high priority to the promotion of biotechnological research in Israel. Accordingly, since 1978 I have divided my time between the Department of Biophysics at the Weizmann Institute and the Department of Biotechnology, which I set up at Tel Aviv University. In 1986 I headed a government-appointed committee for biotechnology, which presented some far-reaching recommendations aimed at promoting and

supporting research and development in the rapidly growing fields of agricultural, marine, pharmaceutical, and industrial biotechnology.

Because of my conviction that Israel needs a large work force trained to operate in an increasingly high-tech labor market, I agreed to serve as World President of ORT, a Jewish organization established in Russia about 100 years ago as the Organization for Rehabilitation and Training, and today involved in large-scale vocational training at its schools in Israel and abroad. During my term of office, from 1985 to 1990, I helped to establish the first ORT international college in Israel at Carmiel, where young Israelis—Jews, Arabs, and Druze—live and study together with their counterparts from many countries. I am confident that the new college will turn out superbly trained technicians who are well able to take their place in a modern society. I have also involved myself in a move to introduce college education leading to a first degree in the liberal arts or the vocational disciplines. Students wishing to study further could then proceed to a university. Israel's universities are bursting at the seams, and a sensible solution would be to modify the higher-education infrastructure by restricting the universities to students particularly interested in research or especially well suited to creative academic life, while at the same time offering all high school graduates access to the highest educational level to which they may aspire.

Back in the laboratory, the focus of my own scientific interest was now on the factors determining the specificity of antibodies, enzymes, and receptors, and I succeeded in engaging the interest of some of my colleagues in the study of the mode of action of these proteins on a molecular level. Together we developed and used monoclonal antibodies to study protein conformation and conformational alterations, employed peptide libraries to identify peptides that bind to monoclonal antibodies and receptors, and used the findings of crystallographers and theoreticians to explore the interactions between different proteins.

Elucidation of the three-dimensional structure of antibodies and some of the antigen-antibody complexes assured me that it would soon be possible to understand, on a molecular level, interactions between a given antibody and the corresponding epitope on a protein antigen. Furthermore, one could reasonably assume that any conformational alteration occurring at such an epitope would be accompanied by a marked change in its characteristic binding to the corresponding monoclonal antibody (42). Our first observation that monoclonal antibodies can be used as macromolecular probes to detect conformational changes induced in proteins by heat or by adsorption onto solid sup-

ports was made at Tel Aviv University during a study of interactions of monoclonal antibodies with lactate dehydrogenase (28). Our group also investigated the interaction of monoclonal antibodies raised against native hen egg white lysozyme (HEL) with the enzyme after its partial reversible denaturation by heating (48). Here, too, the use of different monoclonal antibodies made it possible to demonstrate conformational changes in the enzyme upon heating.

Libraries of synthetic peptides, as well as those consisting of filamentous bacteriophages displaying peptides fused to the minor viral coat protein PIII, are useful tools in the identification of peptides that bind specifically to antibodies and receptors. I therefore decided, together with my collaborators at the Weizmann Institute, Sara Fuchs, Avner Yayon, and David Givol, to use a random phage epitope library in the search for peptides that inhibit the binding of basic fibroblast growth factor to its receptor (78) and the binding of antibody 5.5 to the nicotinic acetylcholine receptor (1a). We found well-characterized inhibitory hexapeptides in both cases. The hexapeptide (DLVWLL) detected in the case of monoclonal antibody 5.5 mimicked a conformation-dependent binding site of the acetylcholine receptor. Bioactivity of the peptide was demonstrated in vivo in hatched chickens by inhibition of the myasthenia gravis–like symptoms caused by injection of monoclonal antibody 5.5.

While continuing to utilize peptide libraries to elucidate the binding specificity of antibodies and receptors, I am trying to clarify the meaning of biological specificity on a molecular level. Some of my ideas on molecular recognition, and those of my colleagues Doron Lancet and Amnon Horovitz, are recorded in an article to be published shortly in a book commemorating the 100th anniversary of the formulation of Emil Fischer's lock-and-key theory. In that article we discuss the meaning of biological specificity as revealed by a single receptor as well as by systems comprised of a repertoire of receptors, the geometric fit between proteins and their ligands, and additivity and nonadditivity in protein-ligand interactions (49a).

A theoretical study of protein recognition reveals that the association of proteins with their ligands involves intricate inter- and intramolecular interactions, solvation effects, and conformational changes. Because of such complexity, we do not yet have a comprehensive and efficient way to predict the formation of protein-ligand complexes from the structure of their free components. With some assumptions, however, such predictions become feasible. One simplifying approach is based on geometric considerations. I was attracted to this approach, as the three-dimensional structure of most protein complexes reveals a close

geometric match between contiguous parts of the protein and ligand surfaces. Indeed, the shape and other physical characteristics of the surfaces largely determine the nature of the specific molecular interactions in the complex. In many cases, the three-dimensional structure of the components in the complex closely resembles that of the molecules in their free, native state. Geometric matching thus seems to play an important role in determining the structure of a complex.

Together with my colleagues at the Weizmann Institute, I developed a geometrically based algorithm for predicting the structure of a possible complex between molecules of known structures. Our algorithm is relatively simple and straightforward and relies on the well-established correlation and Fourier transformation techniques used in the field of pattern recognition (43). The algorithm was tested and validated in analyses of the α-β hemoglobin dimer, tRNA synthetase-tyrosinyl adenylate, aspartic proteinase-peptide inhibitor, and trypsin-trypsin inhibitor. The correct relative positions of the complexes within these molecules were successfully predicted.

Concluding Remarks

Like all those of my generation who were a part of that sublime moment in Jewish history, the re-establishment of a Jewish homeland, I feel privileged not only to have witnessed the fulfillment of an ancient dream, but also to have played some part in making it a reality. At the same time, 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, promotion of scientific activities—has brought me great personal fulfillment. Looking back over the years, I can see that my simple protein models, the poly-α-amino acids, have contributed to a better understanding of the secondary structure of proteins and were useful as the first fully synthetic antigens. My work on the transformation of enzymes into heterogeneous catalysts, the immobilized enzymes, has found extensive use in the pharmaceutical, chemical, and food industries. By extension of Foŕster's theory on nonradiative energy transfer, we were able to work out a way to measure relatively long distances between amino acid residues of a protein or peptide, as well as to determine conformational fluctuations in those molecules. Finally, monoclonal antibodies and peptide libraries continue to be employed as useful tools in the elucidation of protein specificity. If I add to this my contribution to the development of the Weizmann Institute and the establishment of the Biotechnology Center at

Tel Aviv University, my part in raising a new generation of life scientists, and my services as scientific adviser to the Government of Israel, I feel that I have not wasted my life.

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.

Moreover, as a scientist I am keenly aware of the power of scientific tools and of their awesome potential both for the good of humankind and for its destruction. The rapid progress of science and technology will continue to raise complicated moral questions. There are no simple answers, and the choices we make will inevitably depend on what we value.

I am still working at the Weizmann Institute. It is here that I was guided, as a young man, by Chaim Weizmann, distinguished scientist and remarkable leader of his people. When he opened the first Knesset in 1949 as first President of the State, he expressed his philosophy in words that I, as fourth President, chose to repeat 24 years later in my own inaugural speech: "All my life I have labored to make science and research the basis of national endeavor, but I have always known full well that there are values higher than science. The only values that offer healing for the ills of humanity are the supreme values of justice and righteousness, peace and love."

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