

# Reflections

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### My Contributions to Science and Society

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Not too many of my scientific colleagues have lived, as I have, through the birth pangs of a new state or felt the need to throw themselves into a lifestyle that is critical for their own survival and their nation's future. If this sounds dramatic, it is no more and no less than what it was like to be a scientist in the emerging and newly established State of Israel for the larger part of the 20th century when the local Jewish population and many Zionists living abroad were devoting all their energies to achieving statehood and then building and protecting the new state after its creation in 1948. Perhaps I may therefore be forgiven if these reflections on my scientific activities are inextricably interwoven with recollections of my life outside science. I have participated in the most significant events in my country during the historic period of its emergence and development as a dynamic new state. At the same time, I have derived enormous pleasure and fulfillment from my chosen path of research and teaching in the life sciences.

In 1922, when I was 6 years old and my brother Aharon was 9, my family emigrated to Palestine from Poland. Our first home was Tel Aviv, then a tiny city taking shape on the sand dunes adjacent to ancient Jaffa. After a year we moved to Jerusalem. My brother and I were especially drawn to the natural sciences, and after high school we both decided to continue our studies at the new Hebrew University of Jerusalem. I began in 1932, 2 years after Aharon had enrolled in the university's first group of biology students. The ascent to Mount Scopus each day on my motor bike, one of the few motorized vehicles in Jerusalem in those days, was always an exhilarating experience with the Old City in front of me flanked by the mighty Judean desert to the west and the stone-colored new city shining in the east.

Already in high school it was clear to me that, like all those of our generation, we would have to play our 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 the highest moral and spiritual values. In this exhilarating atmosphere, we threw ourselves with great enthusiasm into activities aimed at fulfilling the Zionist dream.

In the 1930s and 1940s the local Arab population, angered by the increasing Jewish presence, often attacked the Jews. 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 had already formed quite a clear idea of my goals in life. I would do what I could to help establish the State of Israel and contribute to its security and its social and economic development. In addition, I would attempt to do some original research while at the same time playing my part in raising a new generation of Israeli scientists and helping to

create the physical and intellectual conditions in which science and technology could flourish in this region. Like Chaim Weizmann, whose life and work served as an inspiration to many young scientists, I believed with all my heart “that science will bring peace to this country, renew its youthful vigor and create the sources for new life, both spiritually and materially.” I have been lucky enough to spend my life in pursuit of my goals, with some success and considerable satisfaction.

### *Study and Work at 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. They treated their small groups of students as their friends and future scientific heirs, doing 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 participated in the setting up of the Institute of Mathematics at the university and grew roses in his spare time. Shimon Samburski taught us physics, and Moshe Weizmann, Chaim Weizmann’s younger brother, taught us organic chemistry. Leo Picard taught us geology and paleontology. I remember him handing me his book in English, dealing with the formation of the Dead Sea, with instructions to be ready to discuss its contents after 2 weeks.

With Tchorna Reiss, a Romanian botanist who asked me to translate her lectures into Hebrew, I spent many hours at the swampy Lake Huleh near the Sea of Galilee, looking for plankton species, which I then described in my first scientific publication. I was captivated by the variety of exquisite unicellular organisms in the lake, the ordered patterns of their lives, and the wonderfully delicate silicon structures that some of them built for themselves.

Alexander Eig, who headed the Department of Botany, was a self-taught expert on botanical ecology with an astonishing knowledge of the plants of Israel. He would take us into the Judean Desert on lengthy field trips, pointing out plant societies and describing their struggles as they competed with one another for survival. I well remember how the desert came to colorful life after a brief rainstorm, with myriads of plant species springing into flower. My enchantment with those unforgettable vistas led me to study the desert flora, and my second publication, together with my friend Gideon Orshan, was on the plants that survive in this arid area. Together with Haim Shifroni, headmaster of the school in Kibbutz Ein Harod, I also published two volumes on organic chemistry, which were used as high school textbooks for many years.

Michael Evenari introduced my brother and me to plant physiology, a new and fascinating field of study. 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 became close friends of the zoologist Shimon Bodenheimer, with whom Aharon wrote a small book in Hebrew about the butterflies of Israel, called *Children of the Sun*. I can still see 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. In trying to learn something about the structure, function, and behavior of these living organisms, however, I realized that I would first have to study chemistry, physics, and mathematics, and so I spent some years in the exact sciences before returning to biology. Here my interest was attracted by the large molecules, the macromolecules of the cell, which play a critical role in determining life processes. I was fascinated by the lectures of our biochemistry professor, Andor Fodor, who introduced me to the world of biopolymers. Most intriguing was the revelation 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 M.Sc. and Ph.D. degrees was done in the Department of Theoretical and Macromolecular Chemistry, headed by the late Max Frankel. Aharon, Frankel’s laboratory assistant, 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 it was now possible to buy them.

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.

One of the most useful books I came across during my graduate studies was *Proteins, Amino Acids and Peptides as Ions and Dipolar Ions* (by Edwin J. Cohn and John T. Edsall, published in 1943), which made me realize that 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 proteins and polypeptides. Aharon and I 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 were the undisputed 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 United States. Naturally there was a certain satisfaction in having one's own ideas 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. Israel's plastics industry did not yet exist, and so the only available polymers were the polyethylene, polystyrene, nylons, and bakelite that we had to purchase for our laboratory. Although it was fascinating to realize that the structurally complicated plastic materials appeared to have multiple potential uses, for example as fibers, fabrics, and kitchenware, it was disappointing to find that they were biologically inert and therefore of no interest to biologists. I therefore set out to transform inert synthetic polymers into biopolymers that would be of biological relevance.

### *Synthesis of Poly-L-lysine*

What interested me was the synthesis of the simplest polymer, composed of repeats of one amino acid only. I assumed that if I could synthesize this macromolecule it might be possible, by studying its properties, to learn something about structure-function relationships in proteins. Also, it seemed to me that by covalently attaching amino acids, peptides, and proteins to selected inert synthetic polymers, it should be possible to endow these polymers with specific biological characteristics. The project seemed to be worth a try.

At the start, I believed it would be possible to prepare amino acid polymers by carrying out well chosen polycondensation reactions of the corresponding amino acid esters. My results with this approach were not particularly impressive, and so I looked around for other amino acid derivatives that might yield the desired polymers. To my great satisfaction, I found that  $\alpha$ -*N*-carboxyl amino acid anhydride, which Leuchs had prepared in 1906 and which can by now be readily prepared by interacting amino acids with phosgene, had yielded a reactive labile monomer that readily yielded the desired polyamino acid in the solid state or in solution. As I was particularly interested in preparing a basic polyamino acid, I decided to start with the synthesis of poly-L-lysine. I believed that the synthesis of this basic polyamino acid would shed new light on the chemical, biophysical, and biological properties of basic proteins such as the protamines and histones, which are found in all cell chromosomes in combination with DNA and seem to protect and regulate the activity of genes during development of the cell. The preparation of poly-L-lysine was finally achieved by polymerization of  $\epsilon$ -*N*-carbonyloxy- $\alpha$ -*N*-carboxy-L-lysine anhydride to yield poly- $\epsilon$ -*N*-carbonyloxy-L-lysine and the removal of the protecting carbonyloxy group with phosphonium iodide, work carried out with my student Izhak Grossfeld. At first we assumed that the benzyl groups of the benzoyloxycarbonyl residue

are reduced by the liberated phosphine; however, as we found ourselves weeping 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 was delighted that we now had our synthetic macromolecule that showed all the characteristics of a high molecular weight polymer, and in the case of poly-L-lysine, of a polyelectrolyte as well. It was also gratifying to find that our poly-L-lysine was readily attacked by trypsin and interacted with viruses, bacteria, cells, and tissues in an interesting biological manner. 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 the new scientific center to be named after him.

The planning committee of the new Weizmann Institute of Science was headed by Ernst David Bergmann, Weizmann's distinguished assistant, and Herman Mark, Head of the Polymer Institute at the Polytechnic Institute of Brooklyn, who in 1947 invited me to spend some time in his world famous Polymer Center. On the way there I spent a few weeks as a Research Fellow at Columbia University with David Rittenberg, learning the new isotopic labeling techniques for identifying and characterizing 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 C. M. Schramm in the *Journal of the American Chemical Society* (1). The title of their work, "Synthesis of protein analogs," gave me considerable satisfaction, as it clearly showed that Woodward and Schramm thought, just as I did, that poly- $\alpha$ -amino acids would be useful as simple high molecular weight models for proteins.

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 temporarily placed in charge of the Israeli army's science corps, and until the end of the War of Independence we carried out military research, laying the foundations for the army's scientific defense unit, *Hemed* (an acronym for *Cheyl Mada* or Science Unit), which was established by Aharon, Yochanan Ratner (from the Technion in Haifa), Ernst David Bergmann (by then head of the Weizmann Institute), and myself. Most of the scientists at the Institute were in uniform, laboratories were in use day and night, 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. We designed and produced various items of defensive equipment.

Just prior to the establishment of the State, Ben-Gurion had taken upon himself the position of unofficial defense minister. I remember that while still in Brooklyn I received a letter from my brother describing his meeting with Ben-Gurion, who had summoned him to hear about *Hemed's* activities and to offer his help. Aharon told him that the unit needed money, whereupon Ben-Gurion reached in his pocket and handed him fifteen English pounds. Aharon was delighted, and wrote that they had hardly known what to do with the unit's new-found wealth!

Nearly 60 years later, *Rafael*, which grew out of *Hemed*, is a billion dollar company producing highly sophisticated military equipment in cooperation with the Israel Defense Forces.

During our War of Independence, some of the American scientists who were supposed to take charge of departments at the Institute became jittery about coming to Israel. Consequently, 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 afterward, 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 garnered 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- $\alpha$ -amino Acids as the Simplest of Protein Models*—After moving to 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, as well as amino acid copolymers and multichain polyamino acids, including branched macromolecules.

By this time, other groups were also preparing polyamino acids and studying their properties: Mark Stahmann in Wisconsin (2), Clement Bamford in England, and Elkan Blout and Paul Doty at Harvard. Some of these synthetic polymers could be drawn into fibers whose conformation, as determined by x-ray analysis, resembles that of silk and wool keratin. The information gathered by Bamford's group at the research laboratory of Cortaulds in Maidenhead, Berkshire on the conformation and conformational transitions occurring in polyamino acids prompted the company to build a pilot plant for the production of poly- $\gamma$ -methyl-L-glutamate fibers and cloth. I still have a piece of cloth made of these fibers, given to me on one of my visits to the British group. Because of the high costs of raw materials and production the project was dropped but not before a film studio had produced a movie starring Alec Guinness in an indestructible white flannel suit made of poly- $\gamma$ -methyl-L-glutamate.

The availability of high molecular weight polyamino acids opened the way to the x-ray analyses of poly- $\gamma$ -benzyl-L-glutamate fibers done by Max Perutz in 1951, which confirmed the predictions of Pauling and Corey in connection with the  $\alpha$ -helical polypeptide backbone. These data as well as the findings of Elliott and Malcolm in 1959 helped John Kendrew and Max Perutz decipher the x-ray patterns of myoglobin and hemoglobin. In addition, polyamino acids synthesized and studied in my laboratory by Arieh Berger, Joseph Kurtz, and Jurgen Engel served as useful models for elucidating the structure of collagen.

With the availability of poly- $\alpha$ -amino acid models it was possible to clarify, during the 1950s and 1960s, the mechanism and kinetics of polymerization of *N*-carboxyl amino acid anhydrides, determine the  $\alpha$ -helical conformation of some of the polyamino acids in the solid state and in solution, detect  $\beta$ -parallel and anti-parallel pleated sheets of polyamino acids, and induce helix-coil transitions in the solid state and in solution under appropriate conditions. Fruitful collaboration between experimentalists and theoreticians like H. Scheraga, J. Schellman, J. R. Tinoko, M. Levitt, and S. Lifson 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 (3).

*Biological Properties of Polyamino Acids*—Meanwhile, in Rehovot during the late 1940s, I concentrated on the study of the biological properties of polyamino acids. 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. 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 with low molecular weight peptides. Partial hydrolysis of poly-L-lysine yielded, 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 National Institutes of Health in the United States. Uptake of these oligomers by *Escherichia coli* was studied by Charles Gilvarg of Princeton University, then a visiting scientist at the Weizmann Institute. By using a lysineless mutant of *E. coli*, Gilvarg showed that *E. coli* readily takes up all oligomers up to tetralysine, but not larger polypeptides, and that these oligomers permit growth of the lysine auxotroph.

In our experiments with a prolineless mutant of *E. coli*, my co-worker Sara Sarid observed that the organism can grow on a synthetic medium in which poly-L-proline is substituted for L-proline. 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 led to the identification and characterization of a novel enzyme, aminopeptidase P, in prokaryotes and eukaryotes.

*Antigenicity of Poly- $\alpha$ -amino Acids*—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, 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 anaphylactic shock. Besides being a nasty experience for the guinea pigs, this was 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 now opened for the fundamental and extensive studies of Sela and his co-workers 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 (4).

*Use of Poly- $\alpha$ -amino Acids in Deciphering of the Genetic Code*—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 and J. H. Matthai identified the poly-L-phenylalanine, produced enzymatically in a cell-free system in the presence of polyuridylylate used as messenger, with the poly-L-phenylalanine we had synthesized in Rehovot. As it happens, Michael Sela was at 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 and 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.

*A Treatment for Multiple Sclerosis*—Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system in which infiltrating lymphocytes, predominantly T cells and macrophages, cause irreversible damage to the myelin sheath. It is thought to be an autoimmune disease associated with an early viral infection. Based on previous clinical information, Michael Sela and Ruth Arnon examined the effect of a copolymer prepared in my laboratory, consisting of L-Ala:L-Glu:L-Lys:L-Tyr (6.0:1.9:4.6:1.0) on rats and mice suffering from experimental allergic encephalomyelitis, an animal model for MS. Their encouraging results led to development of the drug known as copolymer I (Cop-1), termed Copaxone and glatiramer acetate by the industry and widely used today as a therapeutic

vaccine to reduce the rate of progress of MS in patients with the exacerbating-remitting form of this disease.

*Proteins with Glutamine Repeats and Reiteration of Other Amino Acids*—Four neurodegenerative diseases are linked to excessive repeats of glutamine residues near the N terminus of affected proteins. They are Huntington's disease, spinobulbar muscular atrophy, spinocerebral ataxia type 1, and dentatorubral-pallidoluysian atrophy. The more numerous the glutamine repeats, the more severe the disease and the earlier its onset. The repeats tend to lengthen in successive generations of affected individuals, especially in male transmission. These findings prompted Max Perutz and his collaborators to construct molecular models of poly-L-glutamine and study their optical, electron, and x-ray diffraction properties. Their published data disclosed the presence of  $\beta$ -sheets strongly held together by hydrogen bonds, suggesting that glutamine repeats might function as polar zippers by joining specific transcription factors bound in separate DNA segments. In line with these findings an impressive set of data on codon reiteration, published by Green and Wang (5) showed that hydrophobic amino acids, and particularly glutamine, account for a large proportion of the longer reiterants.

It is interesting to note that in vertebrates there are specialized telomeric structures, which are located at the ends of eukaryotic chromosomes and appear to function in chromosome protection, positioning, and replication. The telomeres consist of hundreds or thousands of tandem repeats of the sequence TTAGGG. Remarkably, all immortal cells examined to date show no net loss of telomeric length upon cell division, suggesting that maintenance of telomeres is required in order for cells to escape from replicative senescence.

*Immobilized Enzymes and Other Polymer-Biopolymer Conjugates*—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 it should be feasible to immobilize an enzyme by conjoining it artificially to a non-biological polymer, thereby restricting its free movement, and then to study its properties, especially its kinetic characteristics, under controlled conditions. I believed that the enzyme, once immobilized, could be put to work in novel enzyme reactors, allowing continuous transformation of appropriate substrates into desired products in the laboratory, the clinic, and industry.

My first paper on an immobilized enzyme was published in 1960 (6) when I described the preparation of a water-insoluble trypsin derivative and its use in a trypsin column. Our column indeed showed high activity toward most of the well known synthetic and native trypsin substrates. Of particular interest was the finding that the enzymatic activity of the water-insoluble trypsin remained practically unaltered in dilute HCl at 2 °C. Immobilization prevented autodigestion, and blocking of the  $\epsilon$ -amino groups of the enzyme led to a marked decrease in the number of peptide bonds susceptible to trypsin.

These encouraging results prompted my group to prepare other immobilized enzymes, including immobilized chymotrypsin, urease, papain, alkaline phosphatase, and carboxypeptidase, in each case by covalent binding of the enzyme via non-essential side groups to water-insoluble carriers. Under well specified conditions many of these conjugates showed higher stability than the enzymes from which they were derived so that they could be employed in the design and utilization of enzyme reactors of various kinds (stirred tank reactors, packed bed reactors, fluidized bed reactors, enzyme tubes, and enzyme films).

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 ultra-filtration membrane. 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. With this technique, immobilization did not result in any loss of enzymatic activity. Thus, within a relatively short period, we were able to obtain a great variety of immobilized enzymes as well as enzyme reactors of various types, which opened the way to the use of immobilized enzymes in the food, pharmaceutical, and chemical industries (7). In addition to their more obvious economic and technical advantages, the products of enzymic reactions do not, as a rule, contaminate the environment. Furthermore, thermostable enzymes can be isolated from

thermophilic bacteria, and it is possible to modify the characteristics of the enzyme by the use of modern molecular genetic techniques applied to suitable microorganisms.

The first industrial use of immobilized enzymes was reported in 1967 by Chibata and co-workers 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 (8). In England, immobilized penicillin acylase, also referred to as penicillin amidase, was used to prepare 6-aminopenicillanic acid from penicillin G or V, and in the United States, immobilized glucose isomerase was used to convert glucose into fructose. These successful industrial applications prompted extensive research in enzyme technology, leading to a steady increase in the number of industrial processes based on sophisticated immobilized enzyme reactors.

The use of immobilized enzymes in industry is now well established. 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-aminopenicillanic 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. Many companies produce tons of products, including acrylamide from acetonitrile using immobilized nitrile hydratase and high fructose corn syrup from glucose using immobilized glucose isomerase. 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.

### ***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. While still a student I ran a program of well attended science lectures for the general public, which were held at the Hebrew University and also at newly established settlements (mainly *kibbutzim*) in different parts of the country. 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 were able to stimulate those young imaginations. This was the beginning of the tradition of extramural scientific activities for children and youth. Over the years and throughout the country 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 participation of hundreds of Ph.D. students who serve as instructors and thousands of pupils, many of them new immigrants from culturally disadvantaged backgrounds. Today, some 10,000 children attend courses in astronomy, physics, chemistry, bacteriology, virology, genetics, proteomics, and electronics on our university campuses. 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. Moshe Rishpon, a physicist who ran the Youth Activities Section at the Institute for many years, now presides over a well equipped "hands on" Science Park, which draws many hundreds of children and parents alike.

My interest in popularizing science in Hebrew also led me to coedit, together with the late Shlomo Hestrin, one of the first Israeli Hebrew popular science journals, *Mada (Science)*, 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 motivated by 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 interests, I found myself moving in a number of directions, exploring different (though related) ideas with my students. My aim was to guide each one into an area that would enable him or her to tackle specific problems in my laboratory and eventually form independent research groups. Some of my students went on to achieve remarkable success. 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 depart-

ments at the Weizmann Institute: Organic Chemistry (Avraham Patchornik), Chemical Immunology (Michael Sela), and Chemical Physics (Izchak Steinberg).

### *Serving My Country*

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 high technology industry and space research.

Serving as Fourth President of the State of Israel

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 5-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 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 was a serious sacrifice. 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 6 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 were taken prisoner. The entire country was in mourning.

It was not until Anwar el-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 by President Sadat, Prime Minister Menachem Begin, and American President Jimmy Carter at Camp David near Washington, D. C. 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 United States 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 those 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, Yasir Arafat, and autonomous rule was established, as a first step, in Gaza and Jericho. Also in 1994, Yitzhak Rabin and the Prime Minister of Jordan signed a peace treaty between our two countries in the presence of King Hussein of Jordan and the American President Bill Clinton.

There was a time when I believed, as did many of my friends, that we could find an arrangement with the Palestinians that would allow us to achieve a normal relationship, both nations pursuing their own national, economic, and social aspirations while cooperating on a regional level in matters of concern to us all. I remember with mixed pleasure and sadness the close personal relationship that I developed with President Sadat during his brief but momentous visit to Israel and until his untimely death. This was a valued friendship and one that I had hoped would help establish closer ties between our two countries. It was a bitter disappointment to find that zealots from both sides seemed to have ruined every chance for lasting peace. Sadat was murdered in Egypt by Moslem extremists, and Rabin, whom I greatly respected and admired, was assassinated by a Jewish extremist in Israel.

And yet, even in these difficult and uncertain times, when terrorist outrages occur daily not only in our region but in many places around the world, I have not lost hope. I feel that there is still a chance that in the end the peace seekers among the Israelis, the Palestinians, and the Arab countries in the Middle East will prevail, and a way will be found for all of us to live rather than die together on this tiny piece of the planet.

### ***My Brother Aharon***

My beloved elder brother Aharon was murdered in May, 1972, at Ben-Gurion Airport, by Japanese terrorists supported by local Palestinian groups. Of all those who touched my life, the one who had the greatest personal influence on me was my brother. Aharon was my closest friend and colleague, my guide and leader into the world of polymer research. Together we studied quantum mechanics, statistical mechanics, polymer chemistry, thermodynamics, and biophysics. Our decision to move to the Weizmann Institute was taken jointly, and together we

worked toward promoting science and technology in the early days for the benefit of Israel's Defense Forces and later in the interest of the wider society.

Aharon Katzir-Katchalsky was one of Israel's most gifted scientists and social leaders, a brilliant speaker, an inspiring lecturer, and a prolific writer who did much to popularize science. Among his many accomplishments was the creation of the Israel National Academy of Sciences. His untimely death was mourned by scientists and non-scientists and indeed by citizens in all sectors of the country. All of us felt ourselves bereft by his loss. Abroad, his many distinguished colleagues were horrified by this blow and came together in Israel to set up a Center in his name to promote scientific activities in areas within his wide range of interests. Aharon will long be remembered by the entire scientific community for his outstanding contributions to many spheres of life and science.

### ***Biotechnology in Israel***

When my term as State President ended, I was invited to spend some time at Tel Aviv University before returning to the Weizmann Institute. During my time-out from the laboratory in the 1970s I had kept myself informed of the important advances in the life sciences taking place in the United States, England, and Europe. Particularly impressive was the progress in biotechnology. Therefore, after consulting with colleagues, I decided to try and establish a Department of Biotechnology at Tel Aviv University. It was clear to me that it was only a matter of time before the achievements in genomics and proteomics would have a profound influence on medicine, agriculture, and industry. At that time many young scientists in Israel were interested in research in the basic life sciences, and it seemed to me that it would be good for the economy, as well as for the young scientists, to redirect their work into more practical avenues. With the consent and encouragement of the President of the University, Prof. Yoram Dinstein, I was able to establish a biotechnology department after receiving excellent advice on designing the teaching program and research work from outstanding scientists such as Malcolm Lilly from the United Kingdom and Arnold Demain from the United States.

The Department of Molecular Microbiology and Biotechnology at Tel Aviv University is now well established and is popular with students of biology, chemistry, physics, and mathematics. Several of its graduates are now working in newly established local biotechnology industries or in local ministries concerned with biotechnology. Promising research is under way at Tel Aviv as well as in biotechnology departments that have opened up in other institutes of higher learning.

After persuading the Prime Minister, as well as the Ministers of Commerce and Industry, Science and Technology, of the importance of setting up a biotechnology industry in this country, I was invited to chair a Biotechnology Committee to advise the government on the steps to be taken in this direction. We recommended that generous financial backing be provided for interdisciplinary research and development at the levels of the technical college, the university, and industry in both public and private sectors. The acceptance and application of our recommendations have led to the remarkably successful growth and development of biotechnology in Israel. This, and my unofficial designation as the "father of biotechnology" here, give me an enormous sense of satisfaction.

### ***Research after Retirement***

I have now returned at last to the Weizmann Institute where, as an Institute Professor, I may continue to reside within the Institute's campus and carry out my own research. At present I am particularly interested in protein-protein interactions and phage display techniques.

*Prediction of the Structure of Protein-Protein Complexes*—Almost every process in the living cell is dependent on molecular recognition and the formation of complexes. The latter can be transient or stable assemblies of two or more molecules, with one molecule acting on the other or promoting intra- and intercellular communication, or they can be permanent oligomeric ensembles.

The rapid accumulation of data on protein sequences and protein-protein structures calls for the development of computational methods to process and combine the information. Especially important are the methods designed to predict the structures of molecular complexes and ensembles that cannot be studied by current experimental methods. Transient complexes, for example, are too short-lived for crystallization or NMR spectroscopy.

In the theoretical approach that I developed with my colleges, we employed various grid representations of the complex component molecules and thereafter applied correlation functions to search the solution space and evaluate the putative complex. Our algorithms treat the molecules as rigid bodies, reducing the docking problem to a six-dimensional search through the rotation-translation space. Grid representation of molecules are digitized onto three-dimensional grids, and the surface and interior of the molecules are distinguished from each other by a digital process. For each orientation the correlation functions are calculated via fast Fourier transformations (FFT), thereby allowing all the relative translations to be searched. This simple and straightforward method has appealed to many research groups who adopted and modified this approach. The first era of FFT docking (the bound docking) and the second era of unbound protein-protein docking are described in detail in our recent review article (9).

Further development of the geometric docking procedure has enabled us to incorporate electrostatic complementarity, hydrophobic complementarity, and binding site information in our calculation. The method known as “MolFit,” which we developed to predict the conformation of the complexes formed, proved unequivocally that geometric complementarity appears to be an essential feature for complex formation, even in unbound docking.

*Use of Phage Display Peptide Libraries*—Combinatorial phage display peptide libraries are useful tools for the production of peptide library repertoires from which users can readily select a single peptide that binds specifically with a well chosen desired protein. I chose  $\alpha$ -bungarotoxin ( $\alpha$ -BTX), the highly toxic component of the venom of the snake *Bungarus multicinctus*, as the first protein to be used for testing this technique. I chose this protein because of its relatively low molecular weight, its known three-dimensional structure, and its interesting and important biological characteristics.  $\alpha$ -BTX binds specifically to the nicotinic acetylcholine receptor (AChR) present at the postsynaptic membrane of the neuromuscular junction and serves as a potent antagonist of this receptor. The peptide selected by the phage display peptide for its significant binding with  $\alpha$ -BTX was MRYYESSLKSYPD. We therefore used this “lead peptide” in a novel chemical attempt to prepare peptides with the highest possible binding constant. We achieved this after elucidating the amino acid residues of the lead peptide, which are in close contact with  $\alpha$ -BTX by NMR techniques and then systematically replacing the other free amino acid residues of the peptide by a set of well chosen amino acids. Using this synthetic technique, which we called “systematic residue replacement” (SRR), we obtained a set of peptides that inhibit the binding of  $\alpha$ -BTX at nanomolar concentrations to AChR. X-ray and NMR spectroscopy showed that the high affinity peptides fold into an anti-parallel  $\beta$ -hairpin structure. The homologous loop of acetylcholine binding protein, a soluble analogue of the AChR, showed remarkable similarity. The superposition of the above described complexes indicated that the toxin wraps itself around the binding site loop blocking access of acetylcholine to its binding site. All of the available information led us to conclude that the peptides which bind  $\alpha$ -BTX with high affinity mimic the three-dimensional structure of the binding site of the AChR (10).

In my recent research work, done in collaboration with Fortune Kohen, Roni Kasher, and other colleagues, the phage display technique enabled us to synthesize peptides that showed some estrogen-like activity when tested under appropriate conditions. The experimental approach adopted in this case is based on the ability to identify, by the use of the phage display peptide library, a peptide that binds specifically to a monoclonal antibody recognizing estrogen (11).

### **Looking Ahead**

I have always thought of Israel as a pilot plant state in which dedicated people can explore all kinds of imaginative and creative possibilities aimed at improving society and the state. I feel certain that in the years to come we will continue to operate as a testing ground, drawing on the fruits of science and technology to determine the best and most satisfying ways of living in a country geared to the future. The highest standards of health care, educational practice, and cultural and recreational facilities will flow from research and development in the natural sciences, as well as in automation, computer science, information technology, communication, transportation, and biotechnology. I believe it is possible to create such a pilot plant state by encouraging the development of science-based high technology industry and agriculture. Once it gains momentum, this core of activity will contribute significantly to the economic growth and prosperity of the country. In this pilot plant state, I would like to see a free, pluralistic

society, a democracy whose citizens live by the rule of law, and a welfare state in which public services are efficiently handled. Great emphasis will be laid on excellence in science and research, literature, and the arts, thus enriching the intellectual and cultural life of every citizen.

We Jews are eternal optimists. We have always believed, even in the depths of our despair, that the Messiah will come, even if he tarries a little. I am sure that ultimately we will create our model society geared for life in the twenty-first century and founded on the great moral and ethical tenets that we have held sacred since ancient times.

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