Supramolecular Structure and Function 7

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Preface

This volume represents a collection of lectures delivered by outstanding specialists in the fields of biophysics and of related scientific disciplines during the 7th International Summer School on Biophysics held in Rovinj, Croatia from 14 to 25 September 2000 under the title *"Super molecular Structure and Function"*.

This scientific-educational event was organized by the Ruder Boskovic Institute of Zagreb, Croatia with substantial material and intellectual support of a number of national and international institutions including the Croatian Biophysical Society (CBS), the International Union of Pure and Applied Biophysics (IUPAB), the International Centre for Genetic Engineering and Biotechnology (ICGEB) and the UNESCO Venice Office – Regional Office for Science and Technology for Europe (UVO-ROSTE).

The seventh edition of the series of International Summer Schools on Biophysics, which was started in 1981, attracted more than 120 young researchers and post-graduate students coming from 27 countries of Europe, Asia, Africa and Latin America.

Twenty-five outstanding experts in pure and applied biophysics presented the most advanced knowledge of this very interdisciplinary area of science during their lectures and round tables. It was commonly acknowledge that the Summer School achieved great success and fully reached its objectives.

The success of the Rovinj Summer School was also due to the constantly growing attention being paid by scientific communities to younger generations of scientists, thanks also to the major outcomes of the World Conference on Science "Science for the Twenty-first Century: A New Commitment" held by UNESCO and ICSU in Budapest, Hungary in June 1999.

It is believed that the knowledge on the most recent and advanced developments in biophysics presented at the School will be of great help for young scientists, who are beginning their professional careers in current and future research work in their home countries. The School could also serve as an important case of the most appropriate modality of the sharing and use of scientific knowledge.

The Organizers of the International Summer School on Biophysics also thought that the publication of this volume and its distribution within the scientific community would also serve towards the objectives of expanding, sharing and providing easy access to scientific knowledge as it was proclaimed during the World Conference on Science.

The publication of the volume is due to the substantial financial support provided by the UNESCO Venice Office – Regional Office for Science and Technology for Europe (UVO-ROSTE) as well as by the intellectual efforts of Prof. Greta Pifat-Mrzljak from the Ruđer Bošković Institute – initiator of the series of International Schools on Biophysics and also Chairperson of the 7th School held in Rovinj in 2000.

Organizing Committee

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Aspects of the Evolution of Biophysics: Polyelectrolytes and the Weizmann

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To provide a haven for Jewish refugee scientists fleeing Nazi wrath as well as a laboratory for Chaim Weizmann, the Manchester chemist and Zionist leader, the Sieff Institute, devoted to chemistry and microbiology, was established in 1933 in Rehovot, Palestine. The Institute was small and modest consisting of a main building, an excellent library established round the nucleus of books previously belonging and donated by the Jewish German scientist Fritz Haber, whose name it carried, some sheds for industrial research and a small cafeteria. Next to it was situated the Agricultural Research Station already established in 1921, to provide basic research and testing facilities for the dedicated tillers of the then barren soil.

The driving force leading the fledgling Institute in its timid initial steps was Ernst Bergmann, an organic chemist previously of Berlin, a devoted and faithful collaborator of Weizmann. During World War II the importance of the small research Institute gained considerably as a result of the services it was able to provide to the Allied Forces, cut off from regular channels of supply of some critical items. When Nazi Germany was vanquished and peace restored the future looked bright. The idea was conceived to present Weizmann, who was also the first President of the newly born State of Israel, with a birthday gift, a modern broadly oriented research Institute, bearing his name.

In June of 1946 a scientific symposium was held in Rehovot, to commemorate laying of the cornerstone for what was planned to become the "Institute of Physics and Physical Chemistry". A little volume "Trends in Modern Science" (1949) summarized the conference. In the preface Weizmann states that this was "the first time that a group of "Palestinian" (!)

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scientists met a group of distinguished visitors from abroad", hoping that these interchanges would be repeated as the "Palestinian" scientists had both much to offer and much to absorb. In his words, written in December 1948, Weizmann believes that "only science can lead the world back to sanity; the scientists and scientific institutions educating coming generations are responsible for the direction in which our civilization will develop". Also, from now on the Jewish student, the Jewish scholar, after having been a guest everywhere, a host nowhere, could finally be host to Jewish and non-Jewish students and scholars. Among the participants at this founding meeting were Louis Fieser, Ernst Bergmann, Saul Adler, Judah Quastel, Bernhard Zondek, David Rittenberg, Ladislaus Farkas, Herman Mark, Franz Ollendorf, Chaim Pekeris and Yizhak Elazari-Volcani, indicating a healthy mixture of chemistry, biology, medicine, physical chemistry, polymers, physics, mathematics and agricultural science.

Though plans had been made a few years earlier, the creation of the State of Israel and new currents in the march of Science brought about an almost complete change in emphasis in the development of the Institute. The scientific committee formed in 1944 to plan the Institute of Physics and Physical Chemistry consisted of Bergmann, Fieser, W.P. Hohenstein, Mark, Pekeris, Quastel, Rittenberg and Kurt G. Stern. Hohenstein, Pekeris and Stern were planning to leave the U.S.A. and settle in Rehovot to lead the Polymer, Applied Mathematics and Biophysics Departments. Stern and Hohenstein did not take up their positions at the Institute. Pekeris arrived in 1949 and set up the Department of Applied Mathematics, whereas Polymers and Biophysics were entrusted to my teacher Aharon Katchalsky, and his brother Ephraim Katchalski-Katzir respectively. Ephraim became well-known for his pioneering studies on the polymerization of amino acids and the use of the resulting polypeptides in biology (Katchalski-Katzir, 1995). His original ideas and work attracted many collaborators from Israel and abroad. Michael Sela, Ephraim's student, extended the use of synthetic polypeptides into chemical immunology, and founded a department at the Institute carrying this name (Sela, 1998).

Early in the 1950's the new building, now called the Ziskind building, became the central feature of a much broader budding Weizmann Institute and a temporary, extended or permanent abode for a large number of activities hardly envisaged by the founding fathers. I have already mentioned Applied Mathematics, Polymers and Biophysics, the latter moving into the Ullman building in 1963. Experimental Biology, led by Isaac Berenblum, the noted cancer scientist, stayed briefly in it in its initial stages until moving into the Wolfson building in 1952. Israel Dostrovsky explored the mineral resources of the southern desert of our country, the Negev, exploited the use of isotopes in chemical kinetics, and set up processes of water distillation to isolate oxygen isotope ^{18}O-rich water, a product still very much in demand today. Isotopes moved into the new building of Nuclear Sciences in 1958. Joe Jaffe headed the Infrared Optics laboratory which came into full swing with the operation of its giant infrared spectrometer in the basement of the Physics building in 1958. Gerhard Schmidt pioneered X-ray crystallography and solid state chemistry, and eventually moved in 1964 into the enlarged Sieff building, the Bergmann Institute. Benny Volcani, who had discovered the existence of life in the Dead Sea in the late 1930's in the form of a variety of microorganisms, continued for a while the tradition of the Sieff Institute in microbiology, and left for the States in the 1950's. Intensive activity was engendered by Pekeris who moved into geophysical research, search of oil and construction of digital computers which were a novelty in the world and unheard of in Israel. They were still running on electronic tubes before the days of the transistor and the microchip, and huge air-conditioning facilities and raised floors had to be constructed to provide the cooling capacity for the Weizac and the Golem computers.

I will, in the following, restrict my attention to the activities of the Polymer Department, with which I have been associated from its beginnings in 1949. I will emphasize a number of aspects, which made it so valuable to us. Its name is purely historical, but its activities transcended the limited significance its name might imply. Yet the concept of a polymer, or a macromolecule, is basic in the creation of life, be it on functional or on structural grounds, and it is no accident that the description of the DNA double helix structure by Watson and Crick in 1953 also emphasized its fundamental informational nature. It created the science of molecular biology, which has dominated modern science ever since.

The unique shape and content which the Polymer Department assumed owed much to the presence of Aharon but also to the inspired group of young students who gathered around him (Figure 1). Already at the Hebrew University in Jerusalem, and although trained in botany and zoology on Mount Scopus, in a University recently founded and still very limited in scope, he visualized a new class of charge-carrying polymers, polyelectrolytes, broadly significant in both biology and in the physical sciences. Initial studies of Aharon with Max Frankel were devoted to the interaction of amino acids and peptides with sugars in aqueous solution, leading to Aharon's doctoral thesis in 1939, at the young age of 25. Later Aharon supervised Nathan Sharon's doctoral thesis (1953) on aldose amino acid interactions. Nathan went on to lifelong intensive studies of carbohydrates and proteins and lectins (Sharon, 2000).

The name polyelectrolytes had been coined by Ray Fuoss in 1947, and in 1951 Ray became the first distinguished scientific visitor to visit the

Figure 1. Aharon Katchalsky, members and visitors to the Polymer Department at the front entrance of the Ziskind Building, Rehovot, 1965. Photo courtesy of Weizmann Institute Archives.

Polymer Department, attracted by our initial publications in this exciting new field. Structure in biology is heavily dependent on proteins, carbohydrates and nucleic acids, and diverse aspects of function relate to electrostatic charges spread on these macromolecules. This represented a basic and far-reaching thrust into the big unknown and provided tremendous stimulation towards an early understanding of biological structure and function, before X-ray crystallography, nuclear magnetic resonance, protein sequencing and many other superb tools of modern science became available. Werner Kuhn and Paul Flory had worked out the rules for the behavior of macromolecular chains in solution due to Brownian motion, and could relate these to hydrodynamic and thermodynamic manifestations, and sedimentation in the ultracentrifuge. Alex Silberberg came to us from Kuhn's laboratory and extended his studies on theoretical and experimental aspects of polyelectrolyte behavior. Alex and his students early discovered an interesting phenomenon distinguishing polymethacrylic acid, our major polyelectrolyte material in these days, from polyacrylic acid, which had been studied by Werner Kern, a student of Herman Staudinger. When solutions of polymethacrylic (not polyacrylic) acid were stirred rapidly, clear solutions gelled into solid-like material which would recover their liquid form after a while, demonstrating an important structural principle related to hydrophobic interactions deriving from the additional methyl group absent in polyacrylic acid. It was given the name negative thixotropy by the authors. My doctoral thesis (1952) guided by Aharon, on polyelectrolytes, molecular and macroscopic systems, emphasized the transition from polyelectrolyte solutions to mechano-chemistry, the transformation of chemical energy into mechanical work, resulting from crosslinking of molecular polyelectrolyte chains. This then provided the basis for my future work (Eisenberg, 1990a,1990b).

In my post-doctoral studies with Fuoss at Yale University in 1952 I would deepen my understanding in electrolyte behavior and statistical mechanics. Indeed, the Chemistry Department at Yale, with Kirkwood, Onsager, Fuoss, Sturtevant, Harned and Owen was the most sophisticated institution then dealing with these problems. Upon returning to the Polymer Department in 1953 I extended my work on simple electrolyte conductance performed during my stay at Yale, to the design of conductance cells useful in the study of ion condensation in polyelectrolyte solutions.

The first method which Aharon and Pnina (Spitnik) Elson had actually used in polyelectrolyte research was potentiometric titration. It is quite clear that as protons are removed from a polycarboxylic acid, an electrostatic field arises, which increases with increasing dissociation (pH). It becomes increasingly difficult to remove protons, the acid gets weaker and weaker, and the potentiometric titration of the polyacid is different from that of a simple acid: that is the theory in a nutshell. For further advances consult later work (Biophysics and other topics, 1976).

Great ideas in science and other human activities must be viewed in the context of the times in which they were created. In final analysis specificity and fine tuning are responsible for the precise functioning, preservation and replication of the biological machine, yet an understanding of the basic principles grafting function on structure cannot be easily dispensed with. Thus, early steps comprised physical analysis in solution, strongly affected by electrostatic charges, hydrogen bonds, and related factors creating difficulties in the determination of molecular weights, shapes of expanded "worm-like" coils, conductance, potentiometric behavior, surface interactions in solutions - studied by Israel Miller in the Polymer Department - and suspensions of natural and synthetic macromolecules. Viscosity was strongly shear-dependent in solutions of polyelectrolyte chains expanded by the repulsion of electrostatic charges, and we created special devices and approaches to overcome these problems. Classical rules devised to interpret the behavior of non-ionic macromolecules in the analytical ultracentrifuge, or the scattering of light or of X-rays were extended by Ed Casassa and myself, during my stay between 1958 and 1960 at the Mellon Institute in Pittsburgh then headed by Flory, by devising a theory for the thermodynamics of charged synthetic polyelectrolyte and biological multicomponent systems (Eisenberg, 1990a, 1990b).

Early excitement generated by the "kibbutznik" Shneior Lifson in developing theoretical approaches to understand the precise details of polyelectrolyte behavior was dampened by the realization of the enormous difficulties, persisting today, facing the solution of this problem (Lifson, 1997). No good theory was available, and is not available to the present day, for the determination of polyelectrolyte dimensions. Theories based on the expansion of coils all overestimated the force of repulsion and yielded fully stretched macromolecules, which was not confirmed from simple experiments (Eisenberg, 1976). Shneior and Aharon started to work on a model which, they felt, though it would not be useful to determine dimensions, would be useful for calculating potentiometric titration, ion-binding, conductance, osmotic pressure and so forth. This model states that for relatively short distances along the chain it is possible to assume a rod-like shape and calculate the distribution of counter-ions surrounding a cylinder with equally spaced oppositely charged co-ions. This model of polyelectrolyte behavior, later extended by Zeev Alexandrowicz to include simple salts, and known as the cell model, has maintained itself in one form or another to the present day. Already in 1963 Shneior, long the house theoretician of the Polymer Department, established the Department of Chemical Physics at the Institute, to deal with more spiritual aspects of the behavior of matter.

It was a well known and accepted concept in the early days of polyelectrolyte research that viscosity was an important method in the study of polyelectrolyte expansion with increasing charge and decreasing salt concentration. However viscosity was strongly shear dependent and the use of capillary viscometers was not leading to correct and reliable results. In a joint study with Jean Pouyet I was exposed to the Vallet Couette viscometer in Charles' Sadron Centre de Recherches sur les Macromolecules in Strasbourg and decided to design and build a Couette viscometer with electrostatic restoring force in the Polymer Department, covering a wide range of rates of shear, without using the classical delicate galvanometer suspension wire. I was fortunate to collaborate with Ephraim Heini Frei, then Head of our Electronics Department, on the original design of our precision rotation viscometer with electrostatic restoring torque, first reported at the founding session of the Israel Physical Society in 1954, and dedicated to Albert Einstein on his 75th birthday. In the construction of this instrument we also received valuable advice from our physicist friend Saul Meiboom, who later became one of the early pioneers in NMR research.

With the help of the instrument (Figure 2) we could determine viscosities of synthetic polyelectrolytes and of biological macromolecules such as DNA

Figure 2. Heini Eisenberg operating the Couette viscometer with electrostatic restoring force in the Polymer Department, Rehovot, 1955. Photo by Schleissner Photography, Rehovot.

and RNA, correctly extrapolated to zero rates of shear. Valuable information thus became available.

Polyelectrolyte chains connected in three-dimensional networks created, as already mentioned, mechano-chemical systems, capable of transforming chemical energy reversibly into mechanical work. Though far from leading to a correct interpretation of muscle contraction, which is still a hot topic of research to date, conceptual advances contributed to a better understanding of biological motion. Much interest was generated on the significance of polyelectrolyte behavior when the Watson-Crick DNA double helix was discovered, including subtle distinctions in the behavior of double and single-stranded polynucleotide chains. Next attention veered to irreversible thermodynamics, essential in the maintenance of the processes of life, and in particular to the behavior of biological membranes, in the work of Ora Kedem and Aharon (Figure 3).

Activities described above cut strongly across the disciplines of chemistry, physics and biology. Excitement was high and we were in the front-line of explosive research in a number of connected disciplines.

Continuous visual and audial exchange was generated around the blackboard in the Polymer Library. A continuous flow of visitors on short- and long-term visits led to frequent lectures in the overcrowded library filled to the brim, including occupation of the top of the bookshelves. Long-lasting associations were created across the continents, the big cupboards in the office filled with doctoral theses and enormous numbers of reprints. It was

Figure 3. Aharon Katchalsky lecturing on irreversible thermodynamics in the Polymer Department. Photo courtesy of Weizmann Institute Archives.

science at its best, with no artificial boundaries between the various disciplines. In the quest for knowledge and understanding of the laws of nature separation into divided compartments was meaningless (Eisenberg 1972).

In April 3-6,1956, we organized the first IUPAC International Congress in Israel, in Rehovot and in Jerusalem, on polymers and polyelectrolytes which did much to focus world-wide attention on our activities and interests. Outstanding scientists from the world over came to attend this meeting in a country which had come into existence only a few years before. To name just a few J.J. Hermans and J.Th.G. Overbeek came from Holland, Charles Sadron, Michel Magat and Henri Benoit from France, Paul Doty, Herman Mark, Ray Fuoss, Terrell Hill and Herbert Morawetz from the U.S.A.(Jim Watson of recent DNA fame was also there participating in the discussions), Arthur Peacocke from the UK, V.A. Kargin and V.N. Tsvetkov from the then Soviet Union, Michel Mandel and G. Smets from Belgium, Fumio Oosawa and A. Wada from Japan, Anton Peterlin from then Yugoslavia. Sadron brought his whole Laboratory from Marseilles to Haifa in an Israeli passenger boat. Little did they realize that this was the week of Pesah (Passover) and they were served only Matzot, no bread, on this trajectory. However this did not discourage their enthusiasm. The meeting was extremely successful and eighty papers were published in the J.Polymer Sci. in 1957 (IUPAC, 1957).

Involvement with polymers, with polyelectrolytes, with fibers and with membranes led to a number of applied activities and interactions with industry and agriculture. With funds raised from the US Government we set up a versatile facility for plastics testing, extrusion, molding and literature search. Saul Gassner manufactured novel plastic mini-devices, not yet available at that time, advised the fast growing plastics industry and developed invisible freely breezing plastic coatings to protect oranges and other fruit. Eventually in 1970 the Plastics Laboratory became the independent Plastics Department, under the guidance of David Vofsi.

Aharon moved more deeply into the problems of the origin of life - trying to mimic prebiotic synthesis by polymerizing with Mela Paecht amino acids and nucleotides by heterogenous catalysis on mineral surfaces, such as swollen montmorillonite clays, - and into philosophical aspects of science. He was killed on May 30, 1972, in the main hall of Lydda Airport, together with many other innocent passengers, by a Japanese, hired by an Arab terrorist group - returning home from a meeting with Manfred Eigen in Göttingen. The senseless death of Aharon was a heavy blow to Israeli science. However a broad range of activities continued unabated even though the Department was weakened by the departure of the membrane group to establish an independent Membrane Department, led by Ora Kedem, in 1974. Symposia in memory of Aharon continue to be organized at regular intervals (Eisenberg, 1977).

Additional ways of expression, communication and knowledge interchange, meetings in which members of the Polymer Department participated or which they organized were Edmund de Rothschild Schools in Molecular Biophysics, sponsored by Bernard Pullman, the Institut de Biologie Physico-Chimique in Paris, on biomembranes and intracellular structures, DNA and chromatin, and modern aspects of halophilism. Aharon Klug was a regular teacher and participant, Morton Bradbury, Roger Kornberg, Harold Weintraub, Gary Felsenfeld, Richard Dickerson, Ken Van Holde, Pete Von Hippel, Pat Dennis, Rainer Jaenicke, Janos Lanyi, Dieter Osterhelt, Hans Günther Wittmann, Wolfram Zillig, Joel Sussman, Ada Yonath and many others. Aharon was a founder of the International Union of Pure and Applied Biophysics (IUPAB), and we were able, with Israel

Pecht, to organize the very successful 9th International Biophysics Congress in 1987 24-29 August in Jerusalem (Eisenberg, 1988; Eisenberg and Navon, 1988).

Interests in the Polymer Department continued to range over a wide spectrum, in step with the advancing frontiers of biophysical sciences. A shift of emphasis gradually developed, progressing from the fundamental study of synthetic charge-carrying polyelectrolytes to the investigation of more complex biological macromolecules, enzymes from halophilic bacteria surviving at extremely high saturated salt concentrations in the Dead Sea, nucleic acids and chromatin (Eisenberg, 1990b). A highly sophisticated laboratory for small angle X-ray scattering, of major use in biology and chemistry, was established and conducted by Ellen Wachtel and Reuven de Roos. Our Department became a unique place in the scientific world in which joint ultracentrifuge, elastic and inelastic light scattering, X-ray scattering and neutron scattering experiments, by collaboration with Joe Zaccai in Grenoble, could be undertaken on important biological macromolecular systems.

Glycoproteins represent a major secretion of the mucous membrane, the study of which was actively pursued by Alex on a physiological, biochemical and physico-chemical basis. Another related field of their study was concerned with the biorheology of epithelial mucus, blood, fibrin clotting and platelet aggregation. The study of macromolecular structures and complexes, from the theoretical as well as the experimental points of view, and attempts towards understanding relations between structure and function remained major aims in the activities of the Department.

Polymer science, long a field pioneered by physical chemists such as Kuhn, Flory, Bruno Zimm, Walter Stockmayer, "Geheimrat" Mark, an old friend and supporter of the Department, and many others, underwent a rediscovery process in the hands of pure physicists, as exemplified by Sam Edwards and by Pierre-Gilles de Gennes. As a matter of fact de Gennes, invited by Shlomo Alexander to Rehovot in 1966 for a solid state physics meeting, was all excited having quite recently discovered the existence of polymer science and spent many exhilarating afternoons and evenings with Alex, myself and other members of our Department, to strengthen his grip on this fourth state of matter. The lecture he delivered at the physics meeting dealt with polymers, and not with Solid State Physics. Later, in his Nobel lecture, de Gennes stressed the impact of polymer science on biological phenomena. In 1977 Jacob Klein, product of the new Polymer Physics trend, joined the Polymer Department, and extended his novel approach in the evaluation of forces on the Ångstrom scale by synthetic polymers absorbed on mica surfaces in solution. He could also find new uses for the antiquated van der Graaf generator in Nuclear Physics, for the study of solid polymers in thin layers. Jacob became the last head of the Polymer Department. Sam Safran, expert in the theory of colloids and surfaces, came from the USA to join the Department. Jacob Anglister introduced multi-dimensional NMR protein structural studies into Israel. Ed Trifonov who came in 1977, coined the term, now universally accepted, of DNA 'bendability', and is expert on manifold aspects of the genetic code, a field he calls Gnomics. Ed is continuously surrounded by recent immigrants from the former Soviet Union and tries hard to create conditions suitable for their successful absorption into the Israeli life and culture.

In October 1991 the Department was disbanded in a broad organizational move at the Institute and its members were transferred into the two newly founded Departments of Structural Biology and Materials and Interfaces. However this is another story which I may narrate at another future occasion.

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